Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins


Coenzyme Q10 (ubiquinone, CoQ10) is an essential component of the mitochondrial electron transport chain. Synthesis of CoQ10 requires the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the same enzyme that is blocked by statins for the treatment of hypercholesterolemia. Consequently, treatment with statins may reduce the synthesis of CoQ10, which in turn may affect oxidative phosphorylation and mitochondrial adenosine triphosphate (ATP) production. Previous studies have demonstrated a 25% to 50% reduction in CoQ10 levels associated with statin treatment, which is accompanied by an increase in the lactate/pyruvate ratio, indicating dysfunction of the mitochondrial respiratory system. It has been speculated that drug-induced CoQ10 depletion and consequent impairment of muscle energy metabolism may be, at least in part, responsible for the development of myopathy and myalgia that is sometimes reported by patients receiving treatment with statins.

In order to determine whether supplementation with CoQ10 may reduce muscle symptoms in patients treated with statins, these investigators randomised 32 patients reporting muscle symptoms (pain alone or with other symptoms such as fatigue or weakness) with statin treatment to supplementation with CoQ10 (100 mg/day) or vitamin E (400 IU/day). Myopathic pain and interference with daily activities were assessed using the Brief Pain Inventory before and after 1 month of treatment. Vitamin E was chosen to control for the antioxidant effects of CoQ10.

Statin usage was similar in the two groups. After 30 days, pain intensity was reduced by 40% in the CoQ10 group and unchanged in the vitamin E group (p<0.001 for comparison of pain change between groups). Sixteen of 18 patients in the CoQ10 group and only 3 of 14 patients in the vitamin E group reported a reduction in pain, described as a decrease in pain, ache, burning sensation and overall muscle fatigue. Interference with daily activities was reduced by 38% in the CoQ10 group and unchanged in the vitamin E group. Plasma creatine kinase concentrations did not change during the 30 day treatment period and were similar in the two groups at baseline and at the end of treatment.

**Reviewer's comment**

Important points from this small randomized, double-blind study show that CoQ10 supplementation reduces muscle pain by 40%.

The authors compare the raised lactate / pyruvate ratio, which occurs in mitochondrial myopathies with that associated with statin treatment, suggesting that ultimately **mitochondrial dysfunction** may be the cause of myopathic symptoms.

Also CK levels are not well correlated with myopathic symptoms and should be considered poor markers - a normal CK associated with severe symptoms is common.

In high-risk vascular patients, in whom statin therapy is crucial, CoQ10 supplementation may assist in maintaining long-term statin compliance.
Letter: Statins, Coenzyme Q10, and cachexia: What’s the link?


This letter was written in response to the publication of the study summarized above and describes results of the authors’ own animal studies which support the findings of Caso and colleagues.

Rats bearing the AH-130 hepatoma experience profound muscle loss due to the actions of tumour necrosis factor alpha and other pro-inflammatory cytokines, and are used as a model for the study of cancer cachexia. These rats were given simvastatin, which prevented spleen enlargement, thereby confirming its anti-inflammatory activity. However, not only did simvastatin not prevent muscle wasting, it exacerbated muscle loss. The authors propose that the reduction in CoQ10 synthesis associated with inhibition of HMG CoA reductase may have been responsible for the increase in muscle loss. They further propose that oxidative stress, also associated with CoQ10 deficiency, may also induce cell apoptosis.

CoQ10 is reduced in diseases, such as muscular dystrophies and neurogenic atrophies, that are characterized by muscle wasting. In tumour bearing rats, cachexia can be prevented by exercise and this is associated with an increase in CoQ10 concentrations. These observations, taken together, provide supporting evidence for the role of CoQ10 deficiency in disease- and drug-associated myopathies. The authors suggest that CoQ10 supplementation may have a valuable role to play in improving survival and quality of life in patients with a variety of different diseases associated with muscle wasting and loss of function, including heart failure and cancer.

Reviewer’s comment

In this edition, I have included a letter from investigators in Italy which makes for thought-provoking reading into the complex biology and controversies about statins and CoQ10.

As clinicians we will not always get answers from randomized clinical trials, and will have to narrow / bridge the gap between laboratory / research on the one hand and bedside management on the other; often we are compelled to carefully examine the basic science and apply what we can to clinical situations.

Discontinuation of statin therapy following an acute myocardial infarction: a population-based study


In clinical trials, the use of statins has been shown to significantly reduce cardiovascular morbidity and mortality, including the incidence of fatal and non-fatal myocardial infarctions (MI) and strokes. Despite numerous guidelines recommending the use of statins, their use in clinical practice is variable and adherence to treatment is poor. Fewer than two thirds of patients are taking their statin 1 year after the initial prescription.

Previous studies have indicated that in patients who have had a MI, discontinuation of statin therapy has a short-term adverse effect on survival. This study was designed to investigate the longer term impact of changes in statin usage after MI. It was a population-based, cohort study of patients who had survived for at least 90 days after a first MI. The patients were divided into 4 groups according to their statin use: 1) non-users, who had never used statins, either before or after the MI (n=2124); 2) Users, who had been taking statins before and after the MI (n=2026); 3) Starters, who had not been on statin therapy before the MI, but started taking statins after the MI (n=5652), and 4) Stoppers, who stopped taking their statin after the MI (n=137). The groups were compared for all-cause mortality between 90 days and 1 year after the MI.

After adjustment for baseline differences, compared to never using a statin, stopping statin therapy was associated with an increased risk of all-cause mortality (hazard ratio, HR 1.88, CI95%: 1.13-3.07) and starting a statin was associated with a significant health benefit (HR 0.72, CI95%: 0.57-0.90). Patients who were users of statins also demonstrated a health benefit, but this did not reach statistical significance (HR 0.84, CI95%: 0.66-1.09).
To see whether this pattern extended to other cardioprotective medication, a similar analysis was used for aspirin and beta-blockers and, to serve as a control, also for proton pump inhibitors (PPI). Although a significant health benefit was observed in patients who started aspirin or beta-blockers after the MI, there was no apparent adverse effect on all cause mortality in patients who stopped these treatments after the MI. There was no difference between PPI groups.

The results suggest that withdrawal of statin therapy may be associated with a rapid loss of anti-inflammatory and vasculoprotective effects, resulting in a biological rebound phenomenon. Physicians should take extra care with drug discontinuation after MI and increase awareness among patients of the potential for adverse outcomes associated with stopping treatment.

**Reviewer’s comment**

This interesting study from Montreal raises the question of biological atherosclerosis rebound, which may potentially worsen outcomes.

Remarkable differences in survival are noted in those that stop statins after an AMI. More data (including animal data) is required to document the extent of atherosclerosis progression / rebound following statin discontinuation.

Within limits, patients should be encouraged to continue statin use, aided with supplements such as CoQ10, unless severe side-effects supervene or there is no prospect of statin tolerance at all.

**Treatment of statin adverse effects with supplemental Coenzyme Q10 and statin drug discontinuation**


These investigators identified 50 patients who were actively taking statin drug therapy at the time of their first visit to a cardiology clinic, and each of whom was experiencing one or more adverse effects related to the statin. In each of the patients, the statin was discontinued and supplemental CoQ10 was started at an average dose of 240 mg/day. The patients were followed up for an average of 22.4 months (84% followed up for >12 months and 51% followed up for >24 months). The average duration of statin use at discontinuation was 28 months. The prevalence of statin-related adverse effects at baseline and at the latest follow-up visit was 64% and 6% for myalgia, 84% and 16% for fatigue, 58% and 12% for dyspnoea, 8% and 4% for memory loss, and 10% and 2% for peripheral neuropathy. The timing of resolution differed among the adverse effects. Fatigue and myalgia rapidly improved by 3 months, whereas memory loss and peripheral neuropathy improved more slowly over 6-12 months with some patients having residual symptoms after that time. No adverse events related to statin withdrawal were observed.

The authors conclude that, where necessary, discontinuation of statin therapy with supplemental CoQ10 is safe and is associated with improved quality of life.

**Reviewer’s comment**

This study is particularly interesting since statins were discontinued and patients were supplemented with CoQ10.

The authors report no adverse consequences of statin discontinuation, with 84% of patients followed up for more than 1 year; “we saw no cases of myocardial infarction or stroke”.

This study contrasts with that of Daskalopoulou (*Eur Heart J* 2008; 29: 2083-2091), reviewed above, where survival was considerably different in the statin stoppers.

We need more refined biologic markers to monitor atherosclerosis progression, regression and rebound.

However, this study can be criticized for its two simultaneous interventions (stopping statins in all and supplementing CoQ10 in all patients).
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