Statins are among the most commonly prescribed medications and are used for the reduction of cholesterol levels in patients with dyslipidemia or those who are at a high-risk of experiencing a cardiovascular event. However, some patients experience statin-induced adverse effects including mild myalgia to rhabdomyolysis. Statin-induced myopathies may be misdiagnosed for other disorders. Skeletal muscle adverse effects occur because statin therapy is postulated to interfere with the production of coenzyme Q10 (CoQ10). This issue of CLIPS briefly summarizes an article that reviews current published trials to assess the efficacy of CoQ10 supplementation on statin-induced myalgia. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Background

- Statin intolerance is defined 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.”
- In order for statin-intolerance to be established in the patient, other comorbid conditions that may cause muscle pain, fatigue, or soreness must be ruled out. For example, hypoparathyroidism with hypocalcemia may cause myopathy with elevated creatine kinase (CK) levels.
- Coenzyme Q10 is predominately found in the heart, liver, kidney and brain and is largely recognized as a food supplement.
- Approximately 0.5 g must be produced or ingested daily for physiologic function.
- Coenzyme Q10 is a cofactor in the mitochondrial respiratory chain, serves as an antioxidant to inactivate free radicals after reduction in the body to ubiquinol, and may promote tissue metabolism.
- Possible benefits of CoQ10 supplementation include: enhanced 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 factors.
- Statins interfere with the production of coenzyme Q10 by inhibiting HMG-CoA reductase, which is responsible for the production of fat-soluble substances and other substances, including CoQ10.
- Polymorphisms in the SLCO1B1 gene, which encodes the protein responsible for hepatic uptake of statins, and the coenzyme Q2 gene (important in the synthesis of CoQ10) may be associated with the etiology of statin-induced myopathy.

Methods

- Literature searches were conducted in MEDLINE, Cochrane Library, Scopus, and EMBASE databases. Searches were limited to randomized controlled trials investigating the efficacy of CoQ10 in reducing statin-induced myopathy in adults published between November 1, 1987, and May 1, 2014.
- Studies were included if they were randomized, placebo-controlled, parallel or crossover trials, enrolled patients 18 years and older, the intervention group received CoQ10 and the comparison group received placebo, and they contained data regarding the measurement of CK or measures of the severity of myopathic pain.
- The efficacy of CoQ10 supplementation on statin-induced myopathy was measured by significant reductions in plasma creatine kinase (CK) activity and statistically significant effect on muscle pain. Muscle pain severity was evaluated using the short-form McGill Pain Questionnaire, pain severity score, pain interference score, and a visual analog scale for pain, weakness, cramps, tiredness, and myalgia score.

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Methods (continued)

- Studies were excluded if no data were presented regarding myopathy-associated circulating measures of plasma CK activity or severity of myopathic pain; the study was not conducted in statin-treated individuals; the study was not designed to assess the impact of CoQ10 on myopathy; no numerical values were provided; the study did not include a control group; did not have adequate details of study methods; or the study was an ongoing trial.

Results

- A total of 1607 articles were identified and six studies were included in the meta-analysis.
- Trials were conducted in the United States, Slovakia, Japan, New Zealand, and Norway, including a total of 276 patients.
- Patients received either CoQ10 at doses of 100 to 300 mg/day or placebo for 30 days to 12 weeks among studies.

Effect of CoQ10 Therapy on Plasma CK Activity

- Of the 5 studies containing data regarding CK activity with CoQ10 supplementation, 226 patients were randomized to receive either CoQ10 (100-400 mg/day) or placebo. The number of participants in each trial ranged from 32 to 60.
- In total, 118 patients were given CoQ10 supplementation and 108 patients received a placebo.
- Compared to the placebo group, CoQ10 therapy did not significantly modify plasma CK activity (mean difference, 11.69 U/L; 95% CI, -14.25 to 37.63 U/L; p=0.38).
- Sensitivity analysis showed that I² ranged from 0% to 30%, where larger values indicate increasing heterogeneity.
- Meta-regression analysis did not show any dose-effect association between observed changes in plasma CK activity and administered doses of CoQ10.
- A potential for publication bias was observed as evidenced by funnel plot curves.

Effect of CoQ10 Therapy on Muscle Pain

- Of the 5 studies containing data regarding myalgia response with CoQ10 supplementation, 253 patients were randomized to receive either CoQ10 (100-400 mg/day) or placebo. The number of participants in each trial ranged from 32 to 76.
- A total of 134 patients were given CoQ10 supplementation and 119 patients received a placebo.
- Compared to the placebo group, CoQ10 therapy had a statistically significant reduction in muscle pain in 2 out of 5 studies, while there was no significant effect on muscle pain in the remaining 3 studies (standardized mean difference, -0.53; 95% CI, -1.33 to 0.28; p=0.20).
- Sensitivity analysis showed that I² ranged from 70% to 92% suggesting there was increased heterogeneity among the studies.
- Meta-regression analysis did not show any dose-effect association between assessed myalgia ratings and administered doses of CoQ10.

Summary

- Supplementation of CoQ10 can have several benefits previously discussed and studies show that doses of 50-1200 mg/day are safe and well tolerated.
- There were several limitations to the current study including the small sample size of the studies included; there were differences in design, duration, and dose of CoQ10; and no criteria was used for USP designation for CoQ10 to ensure content uniformity among the studies.
- In the current meta-analysis, there was a lack evidence to prove that CoQ10 supplementation of doses 100 mg to 400 mg daily was an effective option for the treatment of statin-induced myopathy.