

Review Article

The role of Coenzyme Q₁₀ in statin-associated myopathy

Sanjay Kalra¹, Navneet Agrawal², Bharti Kalra¹, Amit Sharma¹, Ritu Kamboj¹

¹Bharti Hospital, Karnal, India

²Medical College, Gwalior, India

Corresponding author:

Sanjay Kalra, Bharti Hospital, Karnal, India

Tel: 091 184 2268484, Fax: 091 184 2267885, E-mail: brideknl@gmail.com

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Statins, or 3-hydroxyl-3-methylglutaryl coenzyme HMG-CoA reductase inhibitors, are cholesterol-lowering drugs which are frequently used in the primary and secondary prevention of coronary artery disease. Current research and recommendations support and encourage more extensive use of these drugs.

However, statin usage is limited by many factors, including a high incidence of statin-associated myalgia and myopathy. This review focuses on the use of Coenzyme Q₁₀ in statin-associated myopathy.

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INTRODUCTION

Statins, or 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are potent drugs which have pleiotropic effects, including the lowering of cholesterol. The mechanism of

action of these drugs has been well researched.

Associated with their beneficial clinical effects, however, are certain adverse events, including muscle-related complaints. Statin-associated myalgia typically affects 5% of patients, myopathy affects 0.1 %, while rhabdomyolysis occurs in 0.01 % of

statin users (1). Studies also suggest that myalgia is among the leading causes of statin discontinuation (1).

The incidence of statin-induced rhabdomyolysis is higher in practice than in controlled clinical trials, from which high-risk subjects are excluded. Accepted high-risk factors for development of myopathy include age; renal, hepatic and thyroid dysfunction; hypertriglyceridemia; exercise; Asian race; and perioperative status (2).

Statin-induced myopathy is a heterogeneous condition with multiple pathophysiologic causes. It may be due to the mechanism of action of the drug per se; interactions with other drugs; or genetic, metabolic or immunological vulnerabilities. Statin use may unmask latent conditions such as hypovitaminosis D-related myopathy or hypothyroid myopathy.

Muscle metabolism is adversely impacted by statin therapy through various mechanisms. These include altered fatty acid oxidation, increased myocyte protein degradation via atrogen-1 and ubiquitin-proteasome pathways (3), or autoimmune mechanisms. Statins also reduce sarcolemmal cholesterol and GTP while increasing intracellular lipids (occasionally leading to lipid myopathy), and myocellular phytosterols, and at the same time cause mitochondrial dysfunction by reducing intramuscular coenzyme Q₁₀ (CoQ₁₀) (4).

The lack of CoQ₁₀ has been postulated to be an etiologic factor for statin-associated myopathy. CoQ₁₀, a 1,4 benzoquinone with a 50-carbon isoprenoid side chain which was first isolated from beef heart mitochondria in 1957, is present in the body in both the reduced (ubiquinol CoQ₁₀ H₂) and oxidized (ubiquinol CoQ₁₀) forms. Oxidized CoQ₁₀ is reduced to CoQ₁₀ H₂ in the mitochondria by flavoenzymes including mitochondrial succinate dehydrogenase and NADH dehydrogenase. CoQ₁₀ is lipophilic and is transported in

lipoprotein particles in the circulation. CoQ₁₀ is an essential cofactor in mitochondrial oxidative phosphorylation, and is necessary for ATP production. CoQ₁₀ acts as a mobile electron carrier transferring electrons from complex I (NADH coenzyme Q reductase) to complex III (cytochrome bc₁ complex) or from complex II (succinate dehydrogenase) to complex III. The reduced form of CoQ₁₀ is also an antioxidant, and is the only endogenously synthesized lipophilic antioxidant (5).

CoQ₁₀ is a natural, fat-soluble quinone localized in hydrophobic parts of cell membranes, and is obtained from dietary fat (meat) or from endogenous synthesis (5). It is involved in mitochondrial oxidative phosphorylation, protection against free radical induced oxidative stress (6), and regeneration of vitamin C and E (7, 8).

CoQ₁₀ deficiency is associated with a large variety of diseases including infantile-onset multi-systemic diseases, encephalomyopathies with recurrent myoglobinuria, cerebellar ataxia, pure myopathy, heart failure, Parkinson's disease, and malignancy (5,9). It affects children more often than adults. While mutation in CoQ₁₀ biosynthetic genes, CoQ₂ and PDSS 2 have been identified in CoQ₁₀-deficient children, the molecular basis of adult -onset CoQ₁₀ deficiency is undefined (9).

In statin-induced myopathy, however, the enzymatic basis of CoQ₁₀ deficiency is gradually becoming better understood. Statins block production of farnesyl pyrophosphate, an intermediate in the production of CoQ₁₀, thus creating a CoQ₁₀ deficiency, which adversely affects mitochondrial function.

The effect on mitochondrial CoQ is also noted in the Hep G2 cell line treated with simvastatin. High concentrations of simvastatin lead to cell death, DNA oxidative damage, and reduced ATP

synthesis in Hep G2 cells. CoQ₁₀ supplementation reduces cell death and DNA oxidative stress, and increases ATP synthesis. Workers suggest that CoQ₁₀ deficiency plays a role in statin-induced hepatopathy as well (10).

EFFECT OF STATINS ON CoQ₁₀ LEVELS IN CIRCULATION

Statins have been shown to reduce circulating CoQ₁₀ levels in both animal and human studies. The largest trial, of 1049 subjects, reported reductions in plasma CoQ₁₀ levels of 38% after treatment with low (10-20mg/day) doses of atorvastatin (11). This reduction occurs because CoQ₁₀ is transported in LDL ($58 \pm 10\%$ of serum CoQ₁₀), HDL($26 \pm 8\%$), and VLDL \pm LDL ($16 \pm 8\%$) particles(12).

One study (13) has also reported a 12.5% reduction in platelet CoQ₁₀ levels with statin therapy, while other randomized controlled trials (12-17) have demonstrated reductions in plasma/serum levels of 16% to 54%.

The low CoQ₁₀ levels found in platelets and lymphocytes of statin-treated patients, apart from the findings of low plasma LDL in such individuals, suggests a true inhibition of CoQ₁₀ synthesis (17).

The reduction in plasma CoQ₁₀ is seen with simvastatin as well as a combination of ezetimibe and simvastatin, but not with ezetimibe monotherapy (18). The CoQ₁₀ level decrease correlates with decreases in total cholesterol and LDL cholesterol levels.

EFFECT OF STATINS ON CoQ₁₀ LEVELS IN SKELETAL MUSCLE

Statins reduce CoQ₁₀ levels in cardiac muscle and the liver (19, 20), but the effect on skeletal muscle CoQ₁₀ levels is controversial. While some rabbit studies

demonstrate a decrease of 72 % in CoQ₁₀ levels with simvastatin or pravastatin therapies (21), others show no change in skeletal muscle CoQ₁₀ concentrations (22), and yet others report severe muscle lesions (23).

Data from human studies report that low-dose statin treatment does not reduce intramuscular CoQ₁₀ levels (24), while higher doses (simvastatin 80 mg, atorvastatin 40 mg per day) are associated with reduced levels (34 % decrease in the simvastatin-treated group) (25).

Patients with statin-associated myopathy often have low levels of intramuscular CoQ. An open label study of CoQ₁₀ concentration in muscles of patients who developed high serum creatine kinase concentrations while on statins was reported from two tertiary care hospitals. Biopsy showed evidence of mitochondrial dysfunction and nonspecific myopathy in 2 patients each, but was normal in 14 subjects. Ten out of 18 patients had low muscle CoQ₁₀ concentration (26). These low levels may have been a cause of myopathy, or a result of physical inactivity, or could have been associated with the reduced mitochondrial volume (25).

Muscle biopsies done in 4 patients with statin-associated myopathy demonstrated findings of intramuscular lipid, reduced cytochrome oxidase staining, and ragged red fibers, all of which resolved after discontinuing statin treatment in the 3 patients for whom a repeat biopsy was done (27).

EFFECT OF STATINS ON MITOCHONDRIA

Animal studies have shown decreased phosphorylation potential of adenosine diphosphate in cardiac mitochondria in lovastatin-treated guinea pigs (28); decreased mitochondrial respiration in

pravastatin-treated dogs (29) and reduced mitochondrial complex I and IV activity in the diaphragm and psoas major muscles of pravastatin-treated rats (30). These findings correlate with the hypothesis that statins may cause myopathy by acting on the mitochondria. In all these studies, serum CoQ₁₀ concentrations were also reduced.

Electron transport chain dysfunction has been noted in myotoxicity associated with statin use. Skeletal muscle biopsies of patients experiencing myopathy after treatment with simvastatin have shown low CoQ and cytochrome oxidase (complex IV) activity (31).

CoQ₁₀ CO-THERAPY WITH STATINS

Many studies report that CoQ₁₀ administration increases CoQ₁₀ blood levels in statin-treated patients (11,12,19,20), reduces symptoms of statin-induced myopathy in patients given very high doses for cancer (32,33), and successfully treats statin-associated myalgia (34-36).

In an OPD-based study, 50 patients who discontinued statin and started COQ supplementation exhibited improvement in symptoms of fatigue, myalgia, dyspnea, memory loss, and peripheral neuropathy (34).

Other studies, however, show no difference in statin tolerance with or without CoQ₁₀ supplementation (37). This treatment carries no risk, however, and no side effects have been reported by any authors.

Reviewers (38) have noted the contradictory results of many authors, but have not raised any safety concerns regarding CoQ₁₀ use.

LIMITATIONS

Only two randomized trials have reported CoQ₁₀ as a treatment for statin-associated myopathy (36, 37).

The lack of more trials in this interesting field of medicine may be due to the relatively recent advances in the biochemistry of CoQ, the difficulty in assessing intramuscular CoQ levels, or the reliance on 'soft' end points such as pain scores.

However, the main reason, perhaps, is that CoQ is a non-patented or 'orphan' drug, and hence will not find the major pharmaceutical backing required to carry out a large, multicentric trial.

CONCLUSION

The biochemical, physiological, and pharmacological basis of prescribing CoQ₁₀ supplementation in statin-induced myopathy is clear. While most clinical trials suggest beneficial effects, others report variable results.

Limited data have suggested that patients with familial hypercholesterolemia, heart failure, and those aged > 65 years might benefit from CoQ₁₀ supplementation (38).

On the whole, however, CoQ₁₀ supplementation, 200 mg/day, can be tried in patients requiring statin therapy, who develop statin myalgia, and who cannot be satisfactorily treated otherwise. Such treatment would help ensure that myalgic symptoms do not prevent patients from receiving the pleiotropic benefits of statins. More studies are also required to assess the role of CoQ therapy in statin-induced myalgia.

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