Therapeutic implication of coenzyme Q10 during statin therapy: pros and cons

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Abstract

Coenzyme Q10 (CoQ10) is a vitamin-like substance, and a natural intermediate of electron transport chain (ETC) of mitochondria which can accepts and donates electrons from complex I and complex II. CoQ10 shares a biosynthetic pathway with cholesterol and dolichol thus it can be a potential target of the widely available lipid-lowering drugs. The lipid lowering drugs such as statins, are widely administered to individuals who have high cholesterol levels.

This article reviews the a) clinical benefits of CoQ10 b) association between administration of statin and CoQ10 deficiency and c) involvement of CoQ10 in statin-associated myopathy.

Keywords: Coenzyme Q10, mitochondria, cholesterol, lipid-lowering drugs, myopathy.

1. Introduction

Coenzyme Q10 (CoQ10) is a naturally occurring quinine which was first isolated from the beef heart mitochondria in 1957 (1) and its structure was identified in 1958 (2). It is a lipid soluble compound present in blood and all cellular membranes of human (3, 4) with highest concentrations in heart, kidney and liver (5). CoQ10 is found in different organelles but at highest amounts is available in mitochondria (6). CoQ10 in humans and most mammals is the most predominant form of coenzyme Q (7). It is present in both oxidized (ubiquinone) and reduced forms (ubiquinol) but the major form in the body is ubiquinol (5, 8). A benzoquinone ring of CoQ10 is derived from tyrosine or phenylalanine and a polyrenyl chain is an intermediate from the mevalonate pathway (9, 10). In multiple steps (11) several enzymes catalyze methylation, carboxylation, and hydroxylation of intermediates to produce CoQ10 (12). Acetyl-CoA is a precursor of cholesterol, coenzyme Q10 and dolichol. CoQ10 synthesis is initiated in the rough endoplasmic reticulum and the final condensation takes place in the Golgi apparatus (13). The biosynthesis of CoQ10 is divided into three steps: (a) synthesis of the benzoquinone center, (b) formation of the isoprenoid side chain and (c) the condensation of these two structures (14). The major regulatory step of CoQ10 synthesis is 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, an enzyme common to the cholesterol biosynthetic pathway (15). Within the inner mitochondrial membrane CoQ10 accepts electrons from mitochondrial complexes and also it accepts electron from $\beta$-oxidation of fatty acids to reduce complex III (16, 17). At the same time it transfers protons to the outside of the mitochondrial membrane (18).
HMG-CoA reductase is a transmembrane protein and the rate-controlling enzyme of the metabolic pathway that produces cholesterol and the other isoprenoids. In humans this enzyme is thus the target of the widely available cholesterol-lowering drugs such as statins. Statins including pravastatin, lovastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin are the most widely prescribed lipid-lowering drugs which are able to inhibit HMG-CoA reductase, and they are used to lower serum cholesterol as a means of reducing the risk of cardiovascular disease (19-21). Statins have HMG-CoA reductase inhibitory properties (22-24) and also they reduce coenzyme Q10 production (25-28).

2. Clinical advantages of CoQ10

Pre-clinical and clinical safety data sheets have shown that CoQ10 does not cause serious adverse effects in humans and experimental animals. These studies include acute, sub-acute, sub-chronic and chronic toxicity tests. CoQ10 also does not show any reproductive side effects and genotoxicity (29).

CoQ10 is found at high level in organs with high-energy requirements or metabolic activity such as heart, kidney, liver and muscle (20). CoQ10 deficiency is associated with impaired energy metabolism in Huntington’s disease and the other mitochondrial dependent disorders (30). It has also been reported that CoQ10 is significantly low in mitochondria of Parkinson patients (31). CoQ10 has been used to improve sperm immobility, endothelial dysfunctions, in type 2 diabetic patients and to reduce blood pressure (Table 1) (32-36). Administration of coenzyme CoQ10 were found to be effective in treating of breast cancer (37) and it may have potential therapeutic effects in hepatocellular carcinoma (38). However, to fill this knowledge gap, more proper clinical trial studies are required (39). It has also been reported that CoQ10 can regulate cell growth and inhibit apoptosis (3).

CoQ10 can protect cells from oxidative stress (40, 41). It has been shown that free radicals which was produced by ROS producing agents such as nucleoside reverse transcriptase inhibitors (NRTIs) which cause endothelial dysfunction via mitochondrial electron transport chain (ETC) inhibition can be neutralized by using CoQ10 as an antioxidant (42-44). In patients with riboflavin responsive multiple Acetyl-CoA dehydrogenation deficiency, CoQ10 administrations is able to rescue mitochondria from over production of ROS (45). The reduced form of CoQ10, CoQ10H2, is an antioxidant which can protect membranes from the free radicals (46, 47). CoQ10 has been suggested to play a critical role in the maintenance of the other antioxidants such as vitamins C and E (3, 48).

In addition, CoQ10 has been reported to protect PC12 cells from the cisplatin-induced DNA damage and neurotoxicity (49). On the other hand, CoQ10 supplementation seems to be effective against DNA damage (50). CoQ10 supplementation (at a dose of 500 mg/day) has been shown to be effective in relapsing–remitting multiple sclerosis (MS) patients (51) and it can (at 300 mg/day) significantly lowers inflammation of patients with coronary artery disease (CAD) during statins therapy (52).

3. Association between administration of statins and CoQ10 deficiency

Statins administration has been associated with CoQ10 diminution in plasma and muscles of experimental animals and human. In a double-blind controlled study, five healthy volunteers and 30 hyper-cholesterolemic patients were treated with 20 mg/day pravastatin, simvastatin or placebo for 3 months. The results of this study demonstrated that statins could lower plasma CoQ10 lev-
4. Involvement of CoQ10 deficiency in statin-associated adverse effects

Strong evidences supported that mitochondria has central role in the etiology of many diseases including muscular dystrophy, male infertility, Alzheimer, Parkinson, Huntington, neurodegenerative disorders, diabetes, cancer and cardiovascular diseases (53-55). Statin therapy can cause a variety of myopathic complaints and CoQ10 deficiency may be involved in the pathogenesis of mitochondrial-dependent disorders such as muscular dystrophy, male infertility, cardiovascular and the other related diseases (Table 1). Efficacy of coenzyme Q10 supplementation to reduce some degree of muscle pain and neurological symptoms in patient who are under statin therapy has been investigated. The results of clinical studies support the idea that coenzyme CoQ10 supplementation may decreases muscle pain during statin treatment (56) but it is not clear whether CoQ10 deficiency contributes to this symptoms or not (25, 26, 57-63). Although, in an open-labeled
study myopathy has been associated with a mild decrease in muscle CoQ10 concentration (62).

CoQ10 has been used to improve mitochondrial dysfunctions in animal models and human for several years (64, 65). However, the results of CoQ10 supplementation and its effect on mitochondria are in controversial. In some clinical trial studies, CoQ10 supplementation was not able to reverse the primary mitochondrial metabolic defects (66). In contrast, supplementation of CoQ10 in the other studies was useful (25, 58, 67). It is important to indicate that plasma CoQ10 levels are linked with lipoproteins concentrations (35). Limited water solubility of CoQ10 and its relatively large molecular weight leads to be poorly absorbed through oral administration (36). However, this can be improved by using new formulations (37-39).

5. Conclusion

Coenzyme Q10 is a useful drug in treating a variety of disorders and for healing both mitochondrial-dependent or independent symptoms (25, 57, 59, 107). It has been reported that co-administration of statins with CoQ10 couldn’t bypass the mitochondrial metabolic defects (66) whereas in some studies supplementation of CoQ10 were found to be effective (25, 58, 67). In our previous study the bio-energetic functions of mitochondria were improved by supplementation of CoQ10 during statin administration in rats (65). However, a causal link between statin administrated doses and plasma levels of CoQ10 has not been reported so far (25, 26, 59, 108).

Conflict of Interest
None declared.

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