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Primary and secondary coenzyme Q10 deficiency: the role of therapeutic supplementation

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Coenzyme Q10 (CoQ10) is the only lipid-soluble antioxidant that animal cells synthesize de novo. *It is found in cell membranes and is particularly well known for its role in the electron transport chain in mitochondrial membranes during aerobic cellular respiration. A deficiency in either its bioavailability or its biosynthesis can lead to one of several disease states. Primary deficiency has been well described and results from mutations in genes involved in CoQ10 biosynthesis. Secondary deficiency may be linked to hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), which are used for the treatment of hypercholesterolemia. Dietary contributions of CoQ10 are very small, but supplementation is effective in increasing plasma CoQ10 levels. It has been clearly demonstrated that treatment with CoQ10 is effective in numerous disorders and deficiency states and that supplementation has a favorable outcome. However, CoQ10 is not routinely prescribed in clinical practice. This review explores primary as well as statin-induced secondary deficiency and provides an overview of the benefits of CoQ10 supplementation.*

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INTRODUCTION

Coenzyme Q10 (CoQ10) has been reported to have a wide range of therapeutic effects.[1] The mechanism(s) underlying these therapeutic benefits are not yet fully understood. In addition to showing potential as an antioxidant and functioning as a cofactor in the mitochondrial respiratory chain, CoQ10 has been suggested to have gene regulatory properties that might account for its effects on overall tissue metabolism.[1]

Despite reports of its safety, its efficacy in various disease states, and its deficiency in a number of conditions, CoQ10 supplementation is not widely prescribed in clinical practice. Potential reasons include a lack of understanding about the critical role of CoQ10, ignorance of the detrimental effects associated with CoQ10 deficiency, and the fact that CoQ10 is a nutraceutical rather than a patentable drug.

Primary deficiency of CoQ10 has been attributed to mutations in enzymes involved in CoQ10 biosynthesis. Secondary deficiency has been described in several settings, including hypercholesterolemic patients on statin therapy. Statins are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which plays an important role in regulating the production of mevalonate. Mevalonate is a key precursor in the metabolic pathway of cholesterol, dolichol, and CoQ10 synthesis. Therefore, correction of hypercholesterolemia with statins may result in a concomitant reduction in the production of the other end products like CoQ10 and dolichol.

The objectives of this review are to provide a brief overview of primary and secondary CoQ10 deficiencies; to consider CoQ10 biosynthesis and pharmacokinetics and how endogenous CoQ10 production is affected by statin therapy; and to discuss the role of CoQ10

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supplementation in the prevention of statin-induced side effects on skeletal muscle.

WHAT IS COENZYME Q10?

CoQ10 is naturally present in most aerobic organisms, from bacteria to mammals.[2] In higher organisms such as humans, this molecule has 10 isoprenoid units in its side chain, hence the name CoQ10.[3] It is a lipid-soluble molecule located in the hydrophobic domain of the phospholipid bilayer of virtually all cellular membranes.[4,5] CoQ10 is the only endogenously synthesized lipid with a redox function in mammals and exhibits broad tissue and intracellular distribution.[6] It is also the only known lipid-soluble antioxidant that can be synthesized *de novo* by animal cells. CoQ10 can be regenerated from its oxidized product, which is formed during the course of the antioxidant activities of CoQ10, through unique enzymatic mechanisms present in animal cells.[7] Although the chemical structure of CoQ10 is similar to that of vitamin K, CoQ10 is not considered a vitamin because it is synthesized *de novo* in the body.[8]

Cells generally rely on biosynthesis for their supply of CoQ10. Endogenous levels are subject to regulation by physiological factors that are related to the oxidative activity of the organism.[7,9] Para-hydroxybenzoic acid from the amino acid tyrosine is the first aromatic precursor in the biosynthetic pathway of CoQ10 in humans and constitutes the quinoid ring structure of the CoQ10 molecule. The tail, consisting of 10 isoprenoid units, is derived from the mevalonate pathway.[10] Endogenous CoQ10 levels are determined by both the rate of production and the rate of consumption in the body. These levels can be altered in a number of disease states, among which cardiovascular disease and degenerative muscle disorders have been well studied in humans.[6,11,12]

In addition to its antioxidant function, CoQ10 is a redox-active lipid that functions as a cofactor in the electron transport chains of mitochondria and plasma membranes.[13] CoQ10 is also indispensible for the maintenance of the bioenergetics of skeletal and heart muscle. It plays a central role in normal cell respiration and function, and thus a deficiency in its availability or endogenous production disrupts normal cellular functions. Such cellular disruption may lead to abnormal patterns of cell division and may produce an oncogenic response.[14] It is therefore not unexpected that a number of pathological conditions respond favorably to supplementation with CoQ10. In 2010, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies [15] evaluated the health claims about CoQ10. The claimed effects included, among others, "energy production," "muscle function," and "energising by stimulating the obtainance of adenosine triphosphate from the cellular energetic processes." The Panel concluded that a cause-and-effect relationship could not be established between the consumption of CoQ10 and contribution to normal energy-yielding metabolism. The Panel also mentioned that a small number of subjects included in one of the studies did show some changes in muscle energy metabolism in response to CoQ10 supplementation, but the relevance of these results to the claimed effect was thought to be unclear.

CoQ10 DEFICIENCY

The importance of CoQ10 in living organisms is illustrated by the number of reports describing genetic disorders in which CoQ10 synthesis is impaired. Deficiency of CoQ10 occurs in either a primary or a secondary form (Table 1).

In 1989, Ogasahara et al.[16] described the first patients with CoQ10 deficiency, presumably of the primary form, as it was shown that familial mitochondrial myoencephalopathy resulted from a tissue-specific defect in CoQ10 biosynthesis. Primary deficiency is caused by mutations in genes involved in the biosynthesis of CoQ10[17] (Table 2)[16,18–22] and was recently identified as a heterogeneous group of autosomal recessive conditions with a clinical spectrum that encompasses at least five major phenotypes,[4] including the following: 1) encephalomyopathy, characterized by recurrent myoglobinuria, brain involvement, and ragged red fibers; 2) severe infantile multisystemic disease; 3) cerebellar ataxia; 4) Leigh syndrome with growth retardation, ataxia, and deafness; and 5) isolated myopathy. In most of these conditions, patients responded well to CoQ10 supplementation.[4,23]

Secondary deficiency of CoQ10 includes all nonprimary forms of deficiency. It may occur as a result of mutations in genes not directly involved in the biosynthesis of CoQ10 (Table 1) and has been associated with conditions such as cerebellar ataxia, pure myopathy, and cardiofaciocutaneous syndrome.[24] Secondary deficiency may also occur as a result of dietary insufficiency or the use of certain pharmacotherapeutic agents such as statins.

Table 1 **Causes of primary and secondary CoQ10 deficiencies.**

Type of CoQ_{10} deficiency	Cause
Primary	Mutations in genes involved in CoQ10 biosynthesis
Secondary	Impairment in biosynthesis of CoQ10 Insufficient dietary CoQ10 Excessive endogenous utilization of CoQ10

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Table 2 **Summary of gene mutations associated with CoQ10 deficiency.**

Symptoms	Gene mutated	Gene product	Function of the gene product	Reference
Familial mitochondrial encephalomyopathy caused by CoQ_{10} deficiency	No genetic analyses performed			Ogasahara et al. (1989)[16]
Severe Leigh syndrome, nephritic syndrome, and CoQ10 deficiency	*PDSS2*	Polyprenyl diphosphate synthase subunit 2	Subunit of decaprenyl diphosphate synthase, the first enzyme in the biosynthetic pathway of CoQ10	López et al. (2006)[18]
Primary CoQ10 deficiency in two siblings with infantile form of CoQ10 deficiency	*COQ2*	Para-hydroxybenzoate-polyprenyl transferase	Second enzyme in the biosynthetic pathway of CoQ10	Quinzii et al. (2006)[19]
Multisystem disease with early-onset deafness, encephaloneuropathy, obesity, livedo reticularis, and valvulopathy	*PDSS1*	Polyprenyl diphosphate synthase subunit 1	Enzyme responsible for the elongation of the prenyl side chain of CoQ	Mollet et al. (2007)[20]
Progressive neurological disorder with cerebellar atrophy, developmental delay, and hyperlactatemia	*CABC1*, also known as *ABC1* or *COQ8*	Chaperone activity of bc1 complex in *Schizosaccharomyces pombe*; (ABC1)-like	Putative protein; function remains unknown, thought to be involved in regulation of CoQ10 biosynthesis	Mollet et al. (2008)[21]
Poor feeding, hypothermia, increased tone, and lactic acidosis at 6 h of age. Development of an intractable seizure disorder accompanied by severe global developmental delay with cerebral and cerebellar atrophy	*COQ9*	CoQ9 protein	Unknown; likely involved in an enzymatic modification step of the benzoquinone ring in the CoQ10 biosynthetic pathway	Duncan et al. (2009)[22]

Secondary deficiency has been linked to a mutation in the *APTX* gene, which encodes aprataxin.[25] The protein product is involved in the repair of double-stranded DNA, and lack of this product is known to cause ataxia-oculomotor-apraxia 1.[26,27] This supports the hypothesis proposed by DiMauro et al.[28] that different clinical variants of CoQ10 deficiency encompass both primary and secondary forms of deficiency. It was therefore suggested that patients presenting with the ataxic form of CoQ10 deficiency should also be examined for other gene defects associated with autosomal recessive cerebellar ataxias.[28] Secondary CoQ10 deficiency is usually not correlated with disease duration, severity, or progression.[29] Gempel et al.[30] described pathogenic mutations in the electron-transferring-flavoprotein dehydrogenase (*ETFDH*) gene in seven patients from five unrelated families. Patients presented with pure myopathy manifesting as proximal myopathy with exercise intolerance and increased serum creatine kinase (CK) and lactate levels, and CoQ10 deficiency was demonstrated in muscle. A response to CoQ10 supplementation was reported in these patients. Mevalonate kinase is a proximal enzyme of cholesterol synthesis and is responsible for the conversion of mevalonate to mevalonate-5-phosphate. Deficiency of mevalonate kinase has been shown to lead to reduced CoQ10 synthesis, which has been associated with the clinical progression of a disease characterized by increased lipid peroxidation, cerebellar atrophy, cataract development, and myopathy with increased CK activity.[31] As CoQ10 deficiency is potentially treatable, early detection is important. Duncan et al.[22] suggested that the identification of mutations in genes involved in CoQ10 deficiency could allow prenatal diagnosis and treatment from birth.

PHARMACOKINETICS, BIOAVAILABILITY, AND SAFETY

The absorption of CoQ10 is enhanced in the presence of lipids. As a lipophilic substance, CoQ10 follows the same absorption process in the gastrointestinal tract as lipids. The mechanism of CoQ10 uptake appears to be similar to that of vitamin E.[8] Following absorption, CoQ10 is incorporated into chylomicrons and is transported to the systemic circulation via the lymphatic system.[32]

CoQ10 has a remarkable safety profile that shows a low rate of adverse events. A large number of clinical trials have been conducted using a range of CoQ10 doses. Adverse gastrointestinal effects, including nausea, could not be causally related to the active ingredient because no dose-response relationship could be defined. Adverse effects were found to be no more common at daily intakes of 1,200 mg than at 60 mg.[33] The "observed safe level" risk assessment method suggested that CoQ10 is safe at intakes of up to 1,200 mg/day and that this level could subsequently be identified as the observed safe level.[33]

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Much higher levels (up to 3,000 mg/day)[34–36] have been tested without adverse effects and may be safe, but the data for dose concentrations above 1,200 mg/day are not adequate to confidently support product safety.[33] CoQ10 has been implicated in a decreased International Normalized Ratio in patients on warfarin therapy.[37] Engelsen et al.,[38] on the other hand, found changes in prothrombin time and International Normalized Ratio levels to be of no significance in patients on stable, long-term warfarin therapy who received 100 mg of CoQ10 for 4 weeks.

Proof-of-principle clinical studies are needed to confirm the role of CoQ10 supplementation in health, particularly in patients with heart failure, cancer, Alzheimer's disease, Parkinson's disease, and Huntington's disease, as well as in patients on statin therapy. When designing these studies, it is essential to ensure that supplementation has a biological effect and that plasma CoQ10 levels are increased sufficiently to elicit a therapeutic response.[39] Although reasonable correlations between ingested dose and increased plasma concentration have been documented, plasma levels of CoQ10 may not always reflect tissue status. Nevertheless, measurement of plasma concentration has been suggested to provide a good indication of overall nutritional status and serves as a guide to dosing.[8]

Dietary contribution of CoQ10, estimated to be 3–5 mg per day, is minimal. The body relies on endogenous synthesis of this coenzyme.[40] Normal levels of endogenous CoQ10 range between 0.55 mg/L and 1.87 mg/L (mean: 0.99 ± 0.3 mg/L).[41] Deficiency is not expected to occur in healthy individuals because endogenous production is usually sufficient. However, in individuals with primary deficiency of CoQ10 or in those on statin therapy, the dietary contribution becomes more important and, in some cases, even crucial. Due to the small contribution of CoQ10 from diet, supplementation is the easiest way to increase CoQ10 levels to meet physiological requirements.

In order to obtain optimal results following supplementation, it is of the utmost importance that the supplementation protocol is efficacious. Measurement of plasma concentrations may play a very important role in monitoring therapeutic efficacy. Optimal bioavailability also plays a major role in ensuring accurate and effective treatment for various conditions.[42] The aim of formulation technology is to ensure better bioavailability, and the available formulations range in complexity from simple to multifaceted.[42] The bioavailability of the crystalline form of CoQ10 is low and inconsistent in humans due to the poor solubility and high molecular weight of this form. Results from CoQ10 supplementation studies are often difficult to compare because the bioavailability of the CoQ10 formulation(s) used varies between studies. Variables that affect absorption include the type of formulation, the dose administered, the dosing interval, and whether the supplement is taken with or without food.[42] In a study by Molyneux et al.,[39] the Q-Gel® preparation (Tishcon, Westbury, New York) was used in a concentration-response study to obtain further insight into the efficacy of CoQ10 supplementation. The concentration-response data suggested that 200 mg of CoQ10 in the form of Q-Gel® is the maximum single oral dose for effective supplementation, indicating that a saturation of the absorption transport system may occur at higher single doses. The study provided evidence that 200-mg doses twice daily increased plasma levels more effectively than a single 400-mg dose.[43] Significantly better plasma absorption of CoQ10 can be achieved by administering a 300-mg dose as ten 30-mg capsules rather than three 100-mg capsules.[39]

In order to provide a means to measure CoQ10 concentrations in clinical practice, Lu and Frank[44] developed an assay to determine total CoQ10 concentrations in human plasma and serum using high-performance liquid chromatography with electrochemical detection. They suggested that the availability of laboratory methods to determine accurate plasma CoQ10 concentrations may help to establish therapeutic ranges for clinical use and to increase awareness of alternative medical therapy, perhaps leading to improved patient care.[44] Today, many laboratories offer CoQ10 plasma and serum analyses, allowing clinicians access to these services.

FINDINGS OF MUSCLE STUDIES IN HUMANS

Studies of CoQ10 in muscle in humans were reported by Linnane et al.[1] Samples of the vastus lateralis were obtained during the course of a clinical trial that evaluated the effect of CoQ10 administration on patients undergoing hip replacement. In a comparison of gene and protein expression patterns and of muscle fiber differences between placebo- and CoQ10-treated subjects, CoQ10 was found to regulate the expression of numerous genes. The study found 47 genes to be upregulated, including the following: 1) the glutamate receptor protein *GluR5*, 2) the fibroblast growth factor receptor *N-SAM*, (3) protein kinase C-epsilon, and (4) guanylyl cyclase (involved in the synthesis of cGMP). Among the 68 genes that were found to be downregulated, the following were highlighted: (1) the TTF-1 interacting peptide 20 (*TIP-20*), (2) the TR3 orphan receptor, (3) the gene-regulator hZFH helicase, and (4) the major group rhinovirus receptor. Furthermore, muscle fiber types in vastus lateralis were demonstrated to change following administration of CoQ10. A decrease in type I fibers and an increase in type II fibers were observed. The changes were all the more striking because the overall fiber composition following CoQ10

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administration in older subjects became more reminiscent of the fiber composition of the muscle of younger subjects.

In an experiment by Linnane et al.[45] that was aimed at addressing the problem of mitochondrial bioenergy decline in tissues of aged rats, CoQ10 was found to be effective in re-energizing skeletal muscle. The question arose as to how CoQ10 could possess such extensive effects and act as a gene regulator when it is membrane localized. In a later study, the authors suggested that a broad-based cellular redox function might be responsible for CoQ10's comprehensive effects.[1] They proposed that CoQ10 plays an important role in the manipulation of the redox potential, or redox poise. This manipulation leads to changes in the subcellular membrane potential, which then result in differential regulation of subcellular membrane activities and compartments. Different subcellular redox poises and the modulation thereof were suggested to result in wide-ranging metabolic changes. It has further been suggested that the generation of superoxide anion by reactions involving CoQ10, which then leads to H_2O_2 formation, could play a major role in cellular regulation, with H_2O_2 acting as a second messenger in the regulation of gene and protein expression.[1]

STATINS AND CoQ10 SUPPLEMENTATION

An important breakthrough in the treatment of hypercholesterolemia was the introduction of statin drugs,[46] which are highly efficacious and have good short-term tolerability.[47] Statins reduce the production of cholesterol in the body by interfering with the production of mevalonate (Figure 1) via inhibition of the enzyme HMG-CoA reductase. Introduced in 1987, this group of drugs is regarded as the most effective in the management of elevated low-density lipoprotein cholesterol.[48] Efficacy in reducing cardiovascular events in coronary heart disease patients with moderate and mild low-density lipoprotein cholesterol elevations has been well established.[48] The long-term use of statins is expanding. Although these agents have been reported to be well tolerated,[49] the occurrence of muscle-related complications necessitates further investigation into their overall safety. After its association with around 100 rhabdomyolysis-related deaths, cerivastatin was removed from the global market in 2001.[50] Even though statins have been reported to be safe and effective drugs in the treatment of hypercholesterolemia, the adverse muscle-related complications associated with their use cannot be disregarded. It is therefore important that clinicians understand the mechanism of action of these drugs as well as their overall effect at a biochemical level. One of the adverse events related to statin use is a reduction in CoQ10 levels secondary to the inhibition of HMG-CoA reductase.

Myalgia and coenzyme Q10

Every year, approximately 1.5 million people on statin therapy are likely to develop muscle-related complications directly related to statin use. These adverse events, also referred to as statin-induced myopathy, manifest as myalgia, myositis, or rhabdomyolysis and are accompanied by an increase in CK concentrations.[51] Myopathy is the term used to refer to any muscle disease, regardless of its etiology.[46] Sathasivam and Lecky[51] suggest there is a lack of consistency in the terminology used in studies describing adverse muscle events associated with statin use and that most studies refer to such events collectively as myalgia. Myalgia is the term used to describe muscle aches or weakness not associated with an increase in CK levels.[52] However, normal CK levels do not exclude statin-induced myopathy.[53]

A reduction in endogenous CoQ10 levels is well described in patients treated with statins. Marcoff and Thompson[54] published a systematic review on the role of CoQ10 in statin-associated myopathy. They reported the earliest observations that statins decrease CoQ10 levels in rats[55] and in humans.[56] They also stated that at least nine observational studies and six randomized controlled trials have demonstrated that statins reduce plasma and/or serum CoQ10 levels by 16–54%.[54] Two studies were highlighted as being exceptions. The first was conducted by Miyake et al.,[57] who reported reduced CoQ10 levels in patients with non-insulin-dependent diabetes mellitus with or without statin administration. The second study, conducted by Bleske et al.,[58] investigated the effect of pravastatin and atorvastatin on CoQ10 plasma levels in 12 healthy individuals in an open-label randomized crossover trial. The authors concluded that routine supplementation with CoQ10 may not be necessary with statin administration, as neither atorvastatin nor pravastatin significantly reduced the synthesis of circulating CoQ10.

Reduction of endogenous CoQ10 production may lead to long-term deficiency states. It is important that clinicians are aware that the endogenous reduction or even depletion of CoQ10 as a direct result of statin treatment can have consequences beyond muscle-related adverse events. Molyneux et al.[59] investigated the relationship between plasma levels of CoQ10 and the survival of patients diagnosed with chronic heart failure. Deficiency of CoQ10 was identified as a sovereign predictor of mortality in chronic heart failure. Tsivgoulis et al.[60] reported that the use of statins may also unmask neuromuscular disorders in presymptomatic patients. It was suggested that additional diagnostic investigations to detect underlying neuromuscular disorders should be performed if adverse muscle events and elevated serum CK levels persist after discontinuation of statin drugs.

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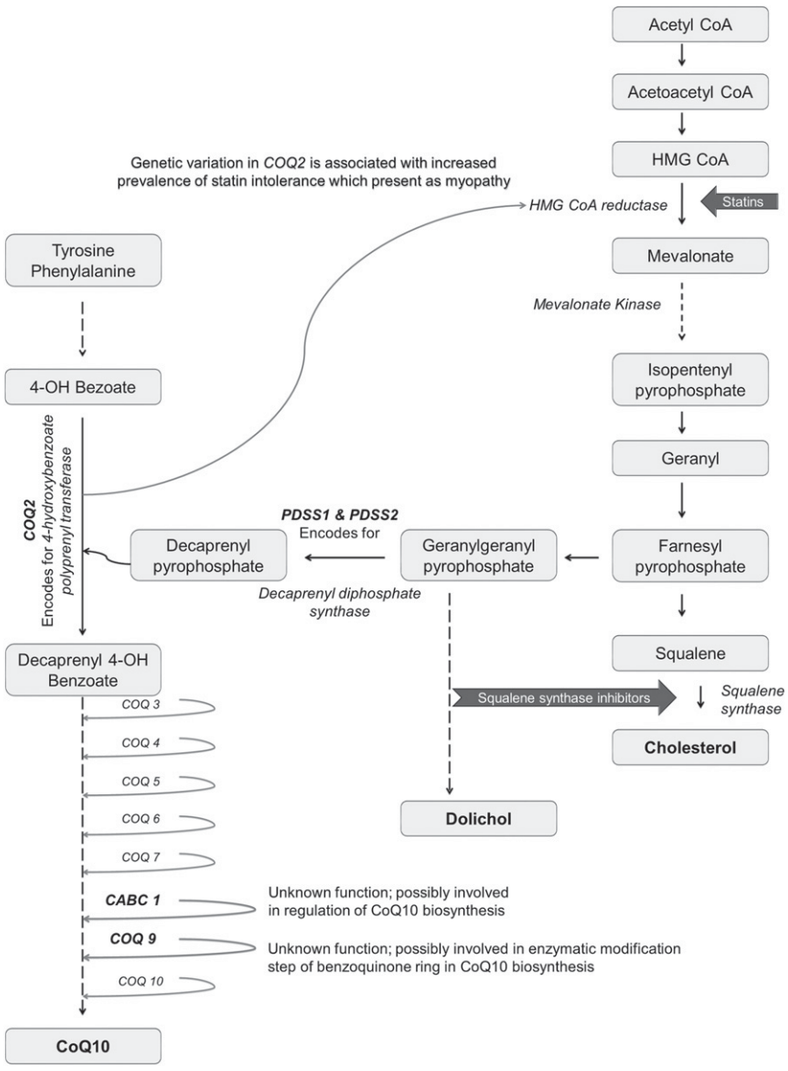

Figure 1 **Schematic representation of the mevalonate pathway and enzymes involved in the biosynthesis of CoQ10 and cholesterol.**

The notion that CoQ10 has a beneficial effect on adverse muscle effects associated with statin use remains controversial because evidence to support this concept is insufficient. In a double-blind, randomized pilot study, Caso et al.[61] tested the effect of CoQ10 on the degree of muscle pain and its interference with daily activities. Pain intensity was reported to be significantly decreased following supplementation with 100 mg of CoQ10 per day for 30 days. Young et al.,[62] on the other hand, performed a double-blind placebo-controlled pilot study to evaluate whether supplementation with 200 mg/day of CoQ10 could improve statin tolerance and reduce myalgia. The investigators were unable to demonstrate any benefit of CoQ10 supplementation during the 12-week trial.[62]

The mevalonate pathway: why statins reduce endogenous CoQ10 levels

The mevalonate pathway (Figure 1) is responsible for the production of isoprenoids, which constitute a large group of essential molecules involved in various cellular processes. These molecules include, among others, CoQ10, dolichol, and isoprenylated proteins. Isoprenylation of proteins entails the post-translational covalent addition of farnesyl and geranylgeranyl moieties (two downstream products in the mevalonate pathway), which allows proteins to become membrane associated.[63] As a result of the inhibition of HMG-CoA reductase, the subsequent endogenous production of CoQ10 is inhibited. The initial

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part of the mevalonate pathway constitutes a sequence of reactions that forms farnesyl pyrophosphate (F-PP) from acetyl-coenzyme A, the last common substrate for the biosynthesis of CoQ10 and several other end products.[47] Isoprenylated proteins play an important role in cellular functions such as organization of the actin cytoskeleton, signal transduction, and intracellular trafficking.[64] As a direct result of the inhibition of HMG-CoA, the formation of F-PP and geranylgeranyl pyrophosphate (GG-PP) is also inhibited (Figure 1). Baker[65] suggested that statin myopathies may result from impaired protein prenylation and CoQ10 depletion rather than from reductions in membrane cholesterol content. Flint et al.[66] showed that HMG-CoA reductase-induced myotoxicity is a consequence of the inhibition of metabolites of GG-PP rather than of cholesterol itself. Further support of this notion stems from the observation that squalene synthase inhibitors tended not to produce myotoxicity in vitro.[66] Squalene synthase is the enzyme exclusively responsible for conversion of F-PP to squalene. Nishimoto et al.[67] showed that when coadministered with cerivastatin in guinea pigs, the squalene synthase inhibitor lapaquistat acetate almost completely prevented cerivastatin-induced myotoxicity. Lapaquistat acetate is the only squalene synthase inhibitor to date that has progressed to phase II/III clinical trials and for which sufficient efficacy and safety data for clinical development have accumulated.[68,69] Stein et al.[69] reported effective reduction of low-density lipoprotein with the administration of lapaquistat acetate alone and in combination with statins. However, potential hepatic toxicity prevents utilization of the drug in a clinical setting.[69]

There is a significant body of evidence indicating that statins reduce endogenous CoQ10 in animal models and in humans.[47] It is important that prescribing physicians and patients know about this secondary effect associated with statin use and that they are aware that statins might have the potential to impair skeletal muscle and myocardial bioenergetics.[47] It may be useful to routinely monitor plasma CoQ10 levels in patients on statin therapy rather than to postpone monitoring until the appearance of adverse statin-induced effects associated with statin use. The adverse events associated with statin use are triggered by the ability of statins to affect protein modification and synthesis at multiple levels. For instance, interference with signal transduction-associated prenylation and alterations in membrane protein glycosylation may result in growth signal deprivation in muscle fibers. Statins can also affect structural proteins, resulting in increased susceptibility of muscle fibers to mechanical stress.[49] The depletion of F-PP and GG-PP secondary to the inhibition of HMG-CoA reductase by statins may lead to reduced post-translational modification of essential regulatory proteins in mammalian cells, with a direct implication in statin-induced myotoxicity.[66] Such an insult to prenylated proteins may lead to loss of regulation of cellular functions, which in turn may cause suppression of muscle cell biosynthetic activity.[70] Myotoxicity as a result of HMG-CoA reductase inhibition has previously been characterized in vitro by myotubular degeneration, a reduction in protein synthesis, morphologic alterations, and loss of lactate dehydrogenase and adenosine triphosphate.[66,70] Littarru and Langsjoen[47] stated that a decrease in plasma CoQ10 levels in patients on statin therapy often parallels a decrease in cholesterol. It is therefore important that physicians pay particular attention to those cases in which the CoQ10-to-cholesterol ratio drops.[47]

LINK BETWEEN STATINS AND MUTATIONS IN GENES INVOLVED IN CoQ10 BIOSYNTHESIS

In a study by Oh et al.,[71] 133 patients from a 291-subject sample were found to be intolerant to statin monotherapy. Patients who were intolerant presented with myopathy and at least one of the following: 1) a recommendation to discontinue statins on two or more occasions, 2) an up to threefold elevation of CK levels, or 3) medically diagnosed rhabdomyolysis. The investigators showed that genetic variations in the *COQ2* gene, as defined by two genotypes and a haplotype derived from the two most informative single nucleotide polymorphisms in the gene, were significantly associated with an increased prevalence of statin intolerance. These preliminary pharmacogenetic results support the perception that statin intolerance that manifests primarily through muscle-related symptoms is associated with genetic variation in the *COQ2* gene. Unfortunately, the study did not measure CoQ10 levels in the patients studied. It is also not known whether the genetic alterations that were found affected endogenous CoQ10 production and availability. It is therefore possible that an unidentified relationship exists between statin intolerance and CoQ10 deficiency. One way to address this problem is through a genomic analysis of susceptibility genes, which would reveal the likelihood of a pharmacogenetic link to statin intolerance. This approach may aid in the prevention of muscle-related symptoms through the coadministration of statins and squalene synthase inhibitors.

CONCLUSION

Recommendations for the use of CoQ10 in the clinical setting are based on the documented role of CoQ10 in cellular bioenergetics, the gene regulatory properties of CoQ10, and the potent antioxidant effects of CoQ10.

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Both primary and secondary forms of CoQ10 deficiency have been identified. Given the limited availability of CoQ10 from dietary sources, supplementation is important in the treatment of CoQ10 deficiency, regardless of the cause.

Although there is insufficient evidence at this point to require the routine use of CoQ10 with statin therapy, clinicians should be aware of the secondary CoQ10 depletion that occurs as a result of statin therapy. Moreover, results from the study by Oh et al.[71] open a potentially useful pharmacogenetic approach in which genomic alterations in genes involved in CoQ10 biosynthesis may identify those patients on statins who are predisposed to side effects, which, in turn, should lead to an alteration in the treatment protocol. If genomic analysis could be performed prior to commencement of statin treatment and susceptibility genes be identified, the risk of muscle-related adverse events associated with statin use could potentially be predicted and perhaps prevented with CoQ10 supplementation. Likewise, patients on statins who develop muscle-related side effects could be genotyped to determine the possible existence of a predisposing genetic cause. Statins are considered the drugs of choice in treating patients with hypercholesterolemia. However, the adverse effects associated with statin use should be seen as an opportunity for intervention. The depletion of endogenous CoQ10 can be restored with exogenous supplementation in order to support physiological demands and to maintain tissue bioenergetics. Given its remarkable safety record, CoQ10 should be given due consideration as a prophylactic agent for patients receiving statins for the treatment of hypercholesterolemia. Routine clinical evaluation of plasma CoQ10 levels should be considered in patients on statin therapy with muscle-related symptoms. Solubilized formulations of CoQ10 have previously been reported to be superior to oil dispersions and crystalline forms in their overall bioavailability.[72] In patients in whom CoQ10 depletion is detected, appropriate supplementation should be administered at an optimal dose, using a formulation with proven superior bioavailability, to achieve normal plasma levels. In addition, a pharmacogenetic analysis may provide important information about the potential for statin-induced adverse effects in high-risk patients.

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