

Coenzyme Q10 and Statin-Induced Mitochondrial Dysfunction

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ABSTRACT

Coenzyme Q10 is an important factor in mitochondrial respiration. Primary and secondary deficiencies of coenzyme Q10 result in a number of neurologic and myopathic syndromes. Hydroxyl-methylglutaryl coenzyme A reductase inhibitors or statins interfere with the production of mevalonic acid, which is a precursor in the synthesis of coenzyme Q10. The statin medications routinely result in lower coenzyme Q10 levels in the serum. Some studies have also shown reduction of coenzyme Q10 in muscle tissue. Such coenzyme Q10 deficiency may be one mechanism for statin-induced myopathies. However, coenzyme Q10 supplements have not been shown to routinely improve muscle function. Additional research in this area is warranted and discussed in this review.

INTRODUCTION

Coenzyme Q10 was discovered in 1957 by Dr. Fred Crane. During the past 50 years, coenzyme Q10 has been found to be a key component in mitochondrial bioenergy transfer. Its enzymatic processes facilitate electron transfer in the generation of adenosine triphosphate (ATP). It has also been shown to have important antioxidant properties. Physiologic concentrations of coenzyme Q10 do not fully saturate the mitochondrial receptors. Accordingly, even a small increase in the coenzyme Q10 concentration of mitochondrial membranes can lead to an increase in mitochondrial respiration.¹ This observation may be

the biochemical mechanism by which exogenous coenzyme Q10 administration has in some studies improved mitochondrial myopathies and cardiomyopathies. A diagram of the key role that coenzyme Q10 plays in mitochondrial membrane generation of ATP is shown in Figure 1. Mitochondrial complexes I through V are specialized protein complexes found in the inner mitochondrial membrane that facilitate the transfer of electrons in the mitochondrial utilization of oxygen. Note that this crucial cofactor, coenzyme Q10, lies at the intersection of electron transfers from both the citric acid cycle and in the reaction as nicotinamide adenine dinucleotide (NADH) is reduced to NAD⁺.

Coenzyme Q10 is a lipid compound with 10 isoprenoid units and is widely distributed in the human body. It is a lipophilic inner mitochondrial membrane cofactor that is used to shuttle electrons in the formation of ATP.² The compound is synthesized in a number of reactions from mevalonic acid, whose production itself is inhibited by hydroxyl-methylglutaryl coenzyme A (HMA CoA) reductase inhibitors (Figure 2). Coenzyme Q10 has been shown to inhibit oxidation of proteins, DNA, and lipids in its reduced form, ubiquinol. Coenzyme Q10 in the serum is largely found bound to the lipoprotein transport of low-density lipoprotein (LDL) cholesterol and does not circulate in any appreciable concentration as an unbound form. Dietary supplementation of coenzyme Q10 increases levels of its reduced form within the circulating lipoproteins and inhibits LDL peroxidation. This inhibition of LDL peroxidation may play a key role in its antiatherogenic effects.¹ Typical serum concentrations of coenzyme Q10 in values for healthy individuals are in the 0.8 to 1 µg/mL range. The half-life in human plasma is 30 to 35 hours.³

DEFICIENCY STATES OF COENZYME Q10

Multiple studies have shown that statins can decrease coenzyme Q10 levels. A portion of this decrease is related to the decrease in the levels of its lipoprotein transport carriers, which is induced by the therapeutic effect of the statins.⁴ Animal studies have revealed depletion of both tissue and blood levels of coenzyme Q10 after statin therapy in the dog model, hamster model, squirrel monkeys, and minipigs.⁴ In humans, exposure to atorvastatin, 80 mg for 14 to

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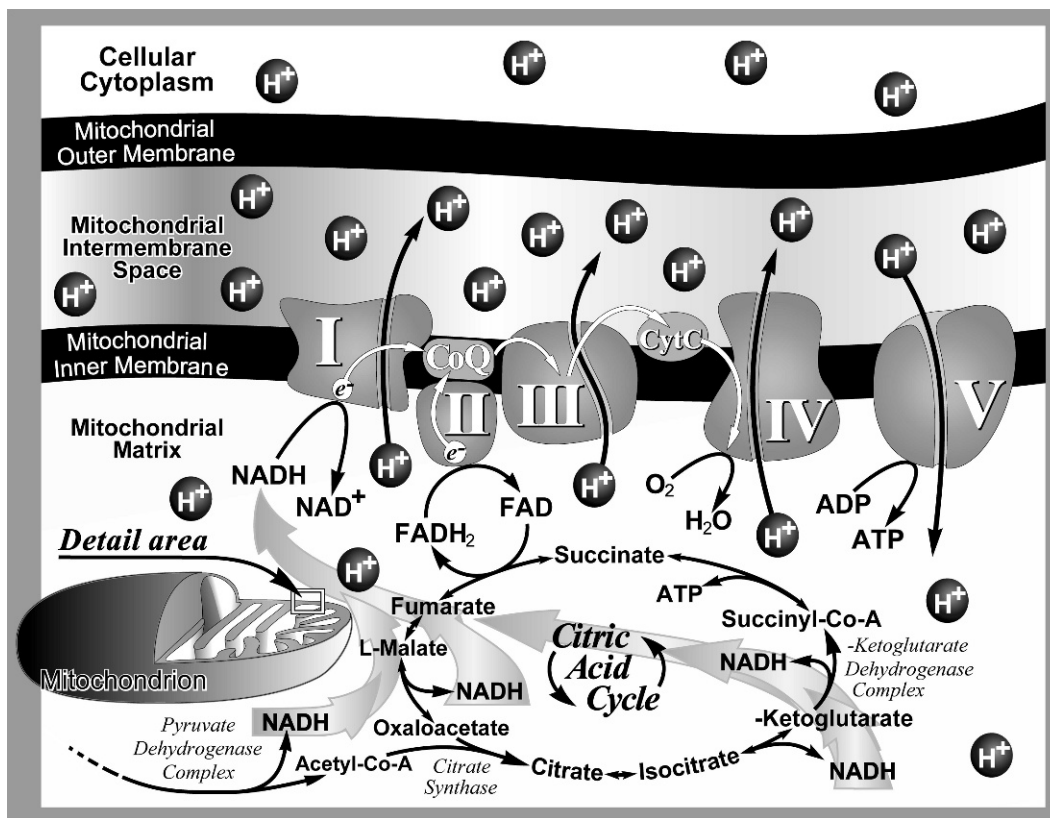


Figure 1. Mitochondrial energy production. (Reproduced with permission from Steve Fowkes, www.ceri.com/mito.htm.)

30 days, caused a significant reduction in coenzyme Q10 levels of 34 subjects both at day 14 and at day 30. Baseline levels of coenzyme Q10 decreased from 1.26 to 0.67 $\mu\text{g}/\text{mL}$ at 14 days and to 0.62 $\mu\text{g}/\text{mL}$ at

30 days.⁵ Simvastatin, 20 mg daily, and pravastatin, 20 mg daily, have also been associated with a 40% reduction in coenzyme Q10 levels.⁶ Lamperti et al⁷ found muscle coenzyme Q10 levels that were at least 1 standard deviation below the mean in 9 of 12 patients who had statin-induced myopathy or elevated creatinine phosphokinase (CPK) levels. High-dose statin therapy resulted in decreased mitochondrial function in those patients who had low levels of ubiquinone in muscle.⁸

Although serum levels of coenzyme Q10 routinely decrease with statin therapy, not all studies confirm the potential mitochondrial dysfunction induced by statins. In humans, Laaksonen et al⁹ found no change in high-energy phosphate levels and coenzyme Q10 levels in muscle biopsies from patients before and after treatment with simvastatin, 20 mg/d for 6 months. The results did not differ from the muscle biopsy findings of matched controls taken at the same time.⁹

Aging appears to play an important role in causing low levels of coenzyme Q10.⁴ Older animals may be particularly affected by statin-induced coenzyme Q10 deficiency. Diebold et al¹⁰ found that mitochondrial conversion from adenosine diphosphate to ATP decreased by 45% in cardiac mitochondria in 2-year-old guinea pigs when compared with younger

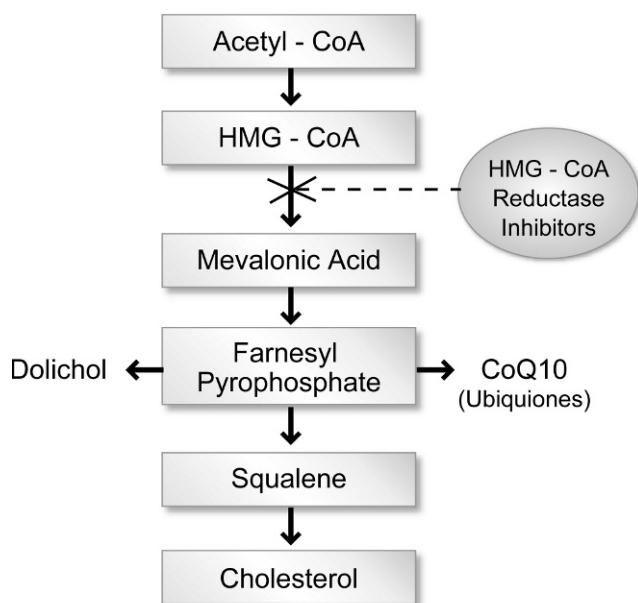


Figure 2. Role of hydroxyl-methylglutaryl coenzyme A reductase inhibitors on coenzyme Q10 synthesis.

animals treated with lovastatin. In humans, aging may cause increased demands for coenzyme Q10. A study of the contractile force of myocardial trabecular tissue in humans noted a significantly lower coenzyme Q10 content in the tissue in patients older than 70 years. This lower coenzyme Q10 content of the tissue was associated with a significantly reduced contractile performance in vitro, which was reversed by pretreatment with coenzyme Q10.¹¹ Differences in the contractile strength between young and senescent myocardial tissue from rats were similar.¹¹ The study concluded that pretreatment with coenzyme Q10 improved the tolerance of the senescent myocardium to aerobic stress by improving ATP generation within the affected mitochondria as well as through its antioxidant role as a free radical scavenger.

Exercise may also induce a relative coenzyme Q10 deficiency because of increased demands on the mitochondria for ATP production. Oxidative stress as found in testing after vigorous exercise may cause depletion of muscle levels of coenzyme Q10. Such exercise results in increased uptake of coenzyme Q10 by the muscles.¹²

Finally, several primary deficiency states of coenzyme Q10 exist that result in encephalopathies, severe infantile multisystem disease, Leigh syndrome, myopathies, and cerebellar ataxia.^{2,5} Such coenzyme Q10 deficiency results from an autosomal recessive disorder with a clinically heterogeneous phenotype.

EFFECTS OF COENZYME Q10 SUPPLEMENTATION

Clearly, the biochemistry of coenzyme Q10 is an integral part of mitochondrial function. Deficiency states have been associated with multiple pathologic conditions. However, study results have been mixed on the clinical efficacy of coenzyme Q10 administration.

Studies Showing a Benefit of Coenzyme Q10 Administration

Mizuno et al¹³ found that coenzyme Q10 administration improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials. In this double-blind, placebo-controlled trial, 17 healthy volunteers were randomized to either placebo or 100 mg or 300 mg of coenzyme Q10 for 8 days. Total coenzyme Q10 levels at baseline were 0.54 $\mu\text{g/mL}$. Supplementation with 100 mg/d of coenzyme Q10 resulted in a total serum level of 2.08 $\mu\text{g/mL}$. Supplementation with 300 mg/d of coenzyme Q10 resulted in a serum level of 3.11 $\mu\text{g/mL}$. After 30 minutes of exercise on a bicycle ergometer, the group randomized to 300 mg/d of coenzyme Q10 showed a statistically significant

improvement in measures of fatigue using a visual analog scale.

A study of 18 male Japanese kendo athletes demonstrated that coenzyme Q10 supplementation decreased exercise-induced muscle injury as measured by CPK levels. These athletes were treated with 300 mg/d of coenzyme Q10 or placebo in a double-blind, randomized manner. Coenzyme Q10 levels at baseline were near 1 $\mu\text{g/mL}$ and increased fourfold in the treated group, and CPK elevations in the treated group were statistically lower by approximately 50% than those in the nontreated group after 5 days.¹⁴

In a double-blind crossover trial of 25 Finnish top-level cross-country skiers, a statistically significant improvement was noticed in multiple measures of physical performance. After administration of 90 mg of coenzyme Q10 per day, plasma levels in the treated group rose from 0.8 to 2.8 $\mu\text{g/mL}$.¹⁵ The peak inspired oxygen consumption ($\dot{V}\text{O}_2\text{max}$) increased by 1.6 mL/kg per minute ($P = 0.02$), the anaerobic threshold increased by 2.4 mL/kg per minute ($P = 0.003$), and aerobic threshold increased by 2.6 mL/kg per minute ($P = 0.001$). Additionally, 94% of the athletes, versus only 33% in the placebo group, thought that coenzyme Q10 had improved their performance in recovery time. No significant differences were noticed in lactic acid clearance.

Amadio et al¹⁶ studied 18 basketball players following administration of 100 mg/d of coenzyme Q10 for 40 days; they noted an 18% improvement in $\dot{V}\text{O}_2\text{max}$ in the athletes. In 2008, Cooke et al¹² found that coenzyme Q10 supplementation at 200 mg/d resulted in significantly increased coenzyme Q10 serum concentrations, which correlated with $\dot{V}\text{O}_2\text{max}$ and treadmill time to exhaustion. There was also a significant correlation of serum coenzyme Q10 levels with muscle tissue levels of coenzyme Q10. This finding was present in both trained and untrained individuals. The study enrolled 22 trained athletes who had been exercising 8 hours per week in the course of 9 workouts per week for at least 2 years. The 19 untrained individuals who enrolled had not engaged in regular exercise for the past year.

Studies have also shown a benefit of coenzyme Q10 administration in the mitochondrial function of heart muscle. A randomized, multicenter study of 322 patients with congestive heart failure comparing patients receiving 2 mg/kg of coenzyme Q10 with those receiving placebo showed a significant decrease in hospitalization for heart failure. After 1 year, 73 patients in the treatment group versus 118 patients in the control group required hospitalization for heart failure.¹⁷ Statistically significant declines in pulmonary edema, cardiac asthma, and arrhythmias were also noted.

Studies Showing No Benefit of Coenzyme Q10 Administration

Other studies have not shown a clear benefit of coenzyme Q10 administration. In a study of 11 trained male triathletes, those receiving three daily doses of 100 mg of coenzyme Q10 did not significantly improve time to exhaustion.¹⁸ The trial was designed as a double-blind, crossover trial consisting of two 4-week periods of treatment separated by a 4-week washout between the 2 treatment periods. However, the study was confounded by the fact that other nutrients were also administered to the group receiving coenzyme Q10, including cytochrome C, inosine, and vitamin E. Additionally, the placebo that was administered, dicalcium phosphate, may have had an influence on the athletic performance of the control group. Finally, the coenzyme Q10 dose of only 100 mg three times daily may have been somewhat low. Coenzyme Q10 levels were not evaluated in this study; it is not known whether therapeutic levels were obtained from the dose of coenzyme Q10 that was administered.

A randomized, double-blind, placebo-controlled, crossover study of 11 young athletes and 8 older athletes receiving 120 mg of coenzyme Q10 per day failed to show any significant difference in $\dot{V}O_2\text{max}$ following treatment with coenzyme Q10.¹⁹ The study consisted of two 6-week treatment periods separated by 4-week washout.

Finally, the mixed results of the studies are underscored by a 2003 review by Rosenfeldt et al,²⁰ who found 6 studies showing improvement in exercise capacity with coenzyme Q10 supplementation and 5 studies showing no improvement. In the most recent extensive review, Marcoff and Thompson²¹ concluded that, given the conflicting nature of the studies, there is insufficient evidence to routinely recommend coenzyme Q10 therapy for statin-induced myopathy. However, they concluded that this therapy could be strongly considered, particularly considering the possible benefit and its low potential for side effects. They called for more research into this topic.

MEASUREMENTS OF MITOCHONDRIAL FUNCTION

The studies measuring activity of coenzyme Q10 on mitochondrial function have used a number of end points. Many studies have used $\dot{V}O_2\text{max}$ as a measure of oxygen consumption. Some studies have used muscle biopsy and endomyocardial tissue to assess in vitro contractile ability with and without coenzyme Q10 availability. Phosphorus 31 and magnetic resonance spectroscopy have also been used to assess ATP activity. A study evaluating the effect of 100 mg

of coenzyme Q10 on muscle energy metabolism, using magnetic resonance spectroscopy in middle-aged, postpolio patients showed a significant benefit.²² Magnetic resonance spectroscopy has been used in a variety of settings to assess mitochondrial dysfunction in a number of human mitochondrial diseases.²

Muscle biopsy can allow for a number of sophisticated DNA, biochemical, and pathologic studies. Its use is more limited because of its more invasive nature.

Noninvasive measures of mitochondrial dysfunction can be performed by blood plasma evaluations of anaerobic metabolism. In mitochondrial dysfunction, ATP production is limited, thereby forcing the muscle fiber to apply anaerobic metabolism, resulting in increased lactate production. Exercise intolerance and fatigue thereby ensue.² Venous lactate-pyruvate ratios have been shown to be clinically helpful in the evaluation of mitochondrial diseases. Chan et al²³ reported that the venous lactate-pyruvate ratio improved after 6 months of supplementation with coenzyme Q10 in patients with mitochondrial myopathies.

Additionally, various exercise testing modalities provide an important method in determining mitochondrial dysfunction. Lactic acid, $\dot{V}O_2\text{max}$, aerobic threshold, and anaerobic threshold levels can be obtained by cardiopulmonary exercise testing and are helpful in diagnosing a variety of cardiopulmonary disorders.²⁴ A number of protocols exist for assessing workload and mitochondrial function using treadmill testing and bicycle ergometry. However, there is no unique mitochondrial dysfunction protocol for exercise testing. The relationship between oxygen utilization by the mitochondria and oxygen uptake by the lungs is shown in Figure 3 and provides the scientific basis for cardiopulmonary exercise testing.

THE ELDERLY POPULATION

Aging has a number of effects on both muscle activity and cardiac activity, including being associated with a steady decline in the absolute heart rate, which can translate into a decrease in cardiac output. Aging is also associated with a gradual decline in $\dot{V}O_2\text{max}$. The elderly also undergo a steady loss of fast-twitch muscle fibers with a relative increase in the proportion of slow-twitch fibers (type 1 fibers).²⁵ Coenzyme Q10 supplementation in rats caused a significant increase in the coenzyme Q10 levels of slow-twitch fibers. Supplementation also reduced exercise-induced muscle injury by enhancing stabilization of the muscle cell membrane.²⁶

Additionally, the elderly appear to be at greater risk for statin-induced myopathies, which can occur in

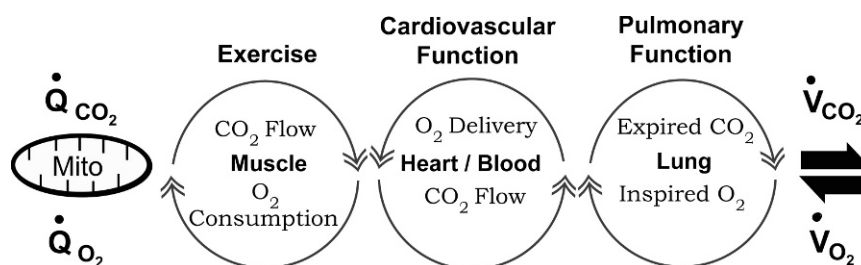


Figure 3. Mitochondrial respiration.²⁴ \dot{Q}_{CO_2} , carbon dioxide production; \dot{Q}_{O_2} , oxygen utilization; \dot{V}_{O_2} , oxygen uptake; \dot{V}_{CO_2} , carbon dioxide output.

up to 11% of these patients. Statins are commonly used medications in the elderly, given the high incidence of medical problems such as diabetes, cerebrovascular disease, and cardiovascular disease in this population.^{27,28}

SUMMARY

Coenzyme Q10 is an important component of mitochondrial biochemistry, allowing for the production of ATP. HMA Co-A reductase inhibitors or statins inhibit one of the key steps in coenzyme Q10 synthesis. These drugs have been associated with a reduction in serum and muscle tissue coenzyme Q10 levels and may play a role in statin-induced myopathy. Given the low risk of toxicity and the potential benefit in treating statin-induced myopathy, a trial of 200 mg of coenzyme Q10 daily should be considered for these patients.

The elderly appear to be more susceptible to coenzyme Q10 deficiency. Athletes, who require the most efficient use of oxygen consumption by mitochondria for athletic performance, are also susceptible to mitochondrial dysfunction due to coenzyme Q10 deficiency. However, study results have been conflicting regarding the uniform effectiveness of coenzyme Q10 supplementation.

A population that would appear to gain the most benefit from coenzyme Q10 supplementation would be that population with all the mentioned characteristics. An elderly population of athletes receiving HMA Co-A reductase inhibitors would appear to be ideally suited to experiencing the greatest benefit from coenzyme Q10 supplementation, given the high risk of mitochondrial dysfunction from coenzyme Q10 deficiencies in this group.

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