Coenzyme Q10 Supplementation and Heart Failure

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the Western world. Oxidative stress appears to play a pivotal role in atherosclerosis. Coenzyme Q10 (CoQ10), one of the most important antioxidants, is synthesized de novo by every cell in the body. Its biosynthesis decreases with age and its deficit in tissues is associated with degenerative changes appearing in the course of aging. CoQ10, also known as ubiquinone, ubiquinol, and ubidecarenone, is a lipid-soluble benzoquinone with 10 repeated isoprenyl units in the side chain (Figure 1). CoQ10 is a naturally occurring, ubiquitous, fat-soluble quinone in eukaryotic cells and is available in the United States as an over-the-counter nutritional supplement. It has been used for 35 years as adjunctive therapy for various cardiovascular disorders. CoQ10, which refers to both the oxidized and reduced forms of the redox pair (as ubiquinone and ubiquinol), is an obligatory component of the mitochondrial electron transport chain for ATP synthesis. Tissues generally synthesize CoQ10 from farnesyl diphosphate and tyrosine. Iron, magnesium, and vitamin B₆ are cofactors for CoQ10 biosynthesis. CoQ10 can be obtained from dietary sources of meat, fish, vegetables, and fruits. A typical Western diet provides 3 to 5 mg of CoQ10 daily, of which approximately two-thirds is derived from meat and poultry. However, total absorption of CoQ10 is thought to be less than 10%. Tissues with high energy requirements, such as the heart, kidney, liver, and skeletal muscle, contain high amounts of CoQ10.

COENZYME Q10 AS A PRIMARY ANTIOXIDANT

One function of CoQ10 is as an antioxidant. Its reduced form, ubiquinol, protects membrane phospholipids and mitochondrial membrane proteins, as well as DNA, from free-radical-induced oxidative damage. Not only can ubiquinol act to remove oxygen radicals, but it can also reduce tocopheryl radicals and semidehydroascorbate back to tocopherol and ascorbate, respectively. The ubiquinone formed in this process is reduced back to ubiquinol in the electron transport chain by metabolic supply of NADH or NADPH. These antioxidant functions for CoQ10 take on much larger significance with the evidence that CoQ10 is present in all cellular membranes, not just mitochondria. Ubiquinol has also been reported to protect LDL from oxidation.
Circulating Plasma Values, Dosage, and Formulation of Coenzyme Q10

In the circulation, CoQ10 is mainly carried by lipoproteins, mostly in LDL particles, where it is predominantly in its reduced form. HDL also contains small amounts of CoQ10. The circulating concentrations of CoQ10 may be useful to assess its status and also to monitor response to CoQ10 supplementation. The mean plasma CoQ10 concentration (total) in healthy subjects is reported to be approximately 1.1 μM. However, the circulating CoQ10 status does not necessarily reflect tissue status, which may explain the discrepancy in clinical improvement observed in patients with apparently normal plasma values. The dosage of CoQ10 employed in treating CVD patients generally ranges from 100 to 200 mg/d. Furthermore, being a lipophilic substance, the efficacy of absorption of orally administered CoQ10 is poor. CoQ10 supplementation leads to an increase in plasma CoQ10 concentration, the extent of which depends on the dosage, duration, and the type of formulation. A solubilized formulation of CoQ10 has been shown to have increased bioavailability.

Coenzyme Q10 and Its Deficiency in Tissues in Disease

Myocardial tissues of CVD patients are reported to be deficient in CoQ10. Littarru et al. first reported its deficiency in heart disease. These authors reported that 75% of cardiac surgery patients had decreased CoQ10 in blood and in myocardium with increased disease severity. Furthermore, Folkers et al. reported low myocardial CoQ10 in patients with aortic and mitral wall disease, diabetic cardiopathy, and congenital valvular defects. Later, the same group of investigators reported that, compared with people with less-severe heart failure (class I and II), people with more-severe heart failure (class III and IV) had lower plasma and myocardial CoQ10, suggesting an increased risk of a CoQ10 deficiency as heart disease worsens.

Healthy subjects generally have 95% of their plasma CoQ10 in a reduced form. Importantly, coronary artery disease (CAD) patients have been reported to have a lower plasma ratio of reduced to oxidized CoQ10 compared with controls, suggesting that CAD patients were exposed to higher levels of oxidative stress. It is important to mention that the determination of this CoQ10 ratio may be compromised by the susceptibility of reduced CoQ10 to oxidation, which could result in erroneous conclusions, possibly accounting for the negative findings in other studies described later in this review.

Kontush et al. reported significantly decreased levels of plasma CoQ10 in 38 hyperlipidemic and 30 healthy subjects, with a negative correlation noted between plasma triglyceride and CoQ10. Hanaki et al. measured the ratios of total cholesterol (TC) to HDL-cholesterol (TC/HDL-C) and LDL-cholesterol to CoQ10 (LDL-C/CoQ10) in 245 control subjects and 72 patients (38 men and 34 women) who had ischemic heart disease or evidence of ischemic changes on electrocardiography. A greater difference in LDL-C/CoQ10 (43%) than TC/HDL-C (17%) was reported between the patients and the normal subjects. Thus, the LDL-C/CoQ10 ratio was suggested to be a sensitive indicator of atherosclerosis risk.

Oxidative stress also plays an important role in vascular disease in diabetes. Hasegawa et al. reported decreased ubiquinol levels in diabetics (n = 11 type 2 diabetes mellitus with diabetic duration of 6.5 ± 1.5 y) compared with control subjects (n = 4). Recently, Lim et al. measured plasma CoQ10 concentrations (ubiquinol as well as ubiquinone) in 60 subjects with normal glucose tolerance (fasting plasma glucose < 5.5 mmol/L), 63 subjects with impaired fasting glucose (fasting plasma glucose 5.6–6.9 mmol/L), and 69 subjects with type 2 diabetes mellitus (fasting plasma glucose > 6.9 mmol/L). These authors report a stepwise reduction in the plasma ubiquinol fraction from normal glucose tolerance (NGT) compared with impaired fasting glucose (IFG) and diabetes mellitus (DM) (DM vs. IFG vs. NGT; P = 0.001). In contrast, the plasma ubiquinone/ubiquinol ratio significantly increased from normal glucose tolerance to impaired fasting glucose to diabetes mellitus (DM vs. IFG vs. NGT; P = 0.01).

COENZYME Q10 AND ITS ROLE IN CARDIOVASCULAR DISEASE

CoQ10 has some inconsistent beneficial effects in many disease states. Most of the consistent evidence for a positive outcome with regard to CoQ10 therapy is in congestive heart failure (CHF) patients.
Coenzyme Q10 and Its Role in Cardiomyopathy and Heart Failure in Adults

A significant correlation has been reported between myocardial tissue ATP content and systolic and diastolic left ventricular indices in heart disease. Patients with dilated and restrictive cardiomyopathy demonstrate low blood and myocardial concentrations of CoQ10, which may explain the underlying energy deficiency in the heart muscle, related impaired heart function, and the possible benefit of supplemental CoQ10 in improving the efficiency of energy production in human heart tissue. There is clear-cut evidence to show that CoQ10 acts at the mitochondrial level to improve the efficiency of energy production in human heart tissue. This is demonstrated by CoQ10 localization and relative abundance in the mitochondria and the fundamental role of CoQ10 in mitochondrial bioenergetics.

The inotropic action of CoQ10, which increases the contractile force of the heart to improve cardiac output, has also been suggested as another interesting role of CoQ10 in aiding heart function in heart failure. It is suggested that supplemental CoQ10 may also improve utilization of oxygen at the cellular level, and possibly benefit patients with coronary insufficiency.

Pioneering studies on the role of CoQ10 in improving heart function in adult patients with heart failure were first carried out in Japan in the 1960s. Since then, evidence has been accumulating regarding the use of CoQ10 as an adjunct to conventional therapy in adults with cardiomyopathy, CHF, and other forms of heart disease. There have been over 40 controlled trials of the clinical effect of CoQ10 on CVD, a majority of which show benefit in subjective (quality of life, decrease in hospitalizations) and objective (increased left ventricular ejection fraction, stroke index) parameters.

In 1997, Soja and Morensten published a meta-analysis of controlled clinical trials of CoQ10 supplementation and heart disease published during the years 1986–1995. For inclusion in this meta-analysis, a study had to be a double-blinded, placebo-controlled study of CoQ10 treatment in cases of CHF with a prerequisite for the reporting of complete data set. Fourteen potentially eligible published studies were found at that time, but only eight of these clinical trials met the inclusion criteria for a reliable meta-analysis. The remaining six studies were excluded because of a lack of suitable data. The relevant effect parameters investigated in the studies included in the meta-analysis were stroke volume, cardiac output, ejection fraction, cardiac index, end diastolic volume index, systolic time intervals (PEP/LVET), and total work capacity \( W_{\text{max}} \). Seven out of the eight studies documented statistical significant improvement for all of the effect parameters, except the PEP/LVET and \( W_{\text{max}} \), in the CoQ10-supplemented group. For example, the average patient in the CoQ10 group had a better score with regard to stroke volume and cardiac output than 76% and 73%, respectively, of the patients in the placebo group. Based on the clinical trial evidence evaluated in the meta-analysis, it was concluded that CoQ10 had a well-documented basis as an adjunctive treatment of CHF.

However, the validity of this meta-analysis has been recently questioned by Sander et al. on the basis that Soja and Morensten believed that “it was possible to avoid having to reduce and weight the calculated effect sizes.” Thus, Sander et al. cautioned that not weighing effect sizes undermines the validity of the previous meta-analysis. Furthermore, Sander et al. reported that of the eight studies comprising the previous meta-analysis, only one study was neutral. Thus, these authors recently published a new meta-analysis (Figure 2) of double-blinded, prospective, placebo-controlled, parallel, and crossover trials of CoQ10 to evaluate the impact of CoQ10 therapy on ejection fraction and cardiac output. The analysis was based on an updated systematic literature search conducted between 1966 and 2005. Sander et al. found that since the publication of the previous meta-analysis, four additional randomized, controlled trials evaluating the effects of CoQ10 on ejection fraction had been published. Thus, a total of 18 randomized, placebo-controlled CoQ10 trials evaluating CoQ10 treatment in heart failure patients were now available.

In reviewing these studies, the authors excluded one study because none of the specified end points were evaluated; another study was excluded because it was single-blinded; two studies were excluded because coenzyme Q10 was only one component of a proprietary compound; and three studies were excluded due to a lack of data. Of the remaining 11 clinical trials, 10 studies evaluated ejection fraction \( (N = 277) \) and two studies evaluated cardiac output \( (N = 42) \). CoQ10 supplemental doses ranged from 60 to 200 mg/d, and treatment periods ranged from 1 to 6 months. Sander et al. concluded from their analysis that there was a significant 3.7% \( (95\% \text{ CI} 1.59–5.77) \) net improvement in ejection fraction in the patients receiving CoQ10 treatment. A more profound effect \( (6.74\% [95\% \text{ CI} 2.63–10.86]) \) on ejection fraction was found among CoQ10-treated patients not receiving angiotensin-converting enzyme inhibitors. In the CoQ10 group, mean cardiac output increased 0.28 L/min \( (95\% \text{ CI} 0.03–0.53) \). These authors further reported that initially they had made an assumption that patients with a more severe form of heart failure (NYHA class IV) would benefit the most from CoQ10 treatment based on a report by Folkers et al. suggesting greater deficiency of CoQ10 as the disease worsens. However, their disease-severity subgroup analysis did
not support this assumption. Thus, Sander et al.\textsuperscript{24} suggested that compared with progressed heart failure, in which many myocytes may be severely damaged, less diseased hearts may possess more salvageable myocytes that could respond to CoQ10's potent antioxidant properties. Overall, it was concluded from the new meta-analysis that CoQ10 treatment enhances systolic function in chronic heart failure, but its effectiveness may be reduced with concomitant use of current standard therapies.\textsuperscript{24}

Additional Considerations of the Potential Benefits of Coenzyme Q10 Treatment

The largest controlled CoQ10 trial\textsuperscript{25} on adult cardiomyopathy and CHF was reported in 1993 and involved a total of 641 patients. However, this study\textsuperscript{25} was not included in the reported meta-analyses. The trial was a double-blind, placebo-controlled study with NYHA class III and IV patients using a dose of 2 mg CoQ10/kg/d (n = 319) or placebo (n = 322) for 1 year. The findings of this study showed significant improvements in arrhythmias and a reduction in the number of hospital admissions (38% to 61%). Similarly, the episodes of pulmonary edema or cardiac asthma were reduced compared with the control group (20 versus 51 and 97 versus 198, respectively). No differences in death rates were documented. In a follow-up study, the same group of investigators\textsuperscript{32} evaluated cardiac hemodynamics during exercise in CHF patients in a small randomized double-blind, placebo-controlled, crossover trial (n = 6 treated with 150 mg CoQ10/d for 4 weeks). The study showed significant improvements in ejection fraction. The same trends were recorded for the stroke volume and cardiac output. Importantly, this sub-study was part of the meta-analyses reported earlier.\textsuperscript{23,24}

Furthermore, another study\textsuperscript{33} not included in the second meta-analysis reported a significant improvement in volume load ejection fraction, arteriovenous oxygen difference, and quality of life assessment, following the
administration of 100 mg of CoQ10/d or placebo for 3 months in 69 patients with severe chronic cardiomyopathy and CHF. It needs to be emphasized that these clinical trials used CoQ10 as an adjunct to conventional therapy in adult patients. Also, in another controlled trial\(^1\) with 22 heart failure patients (NYHA class II and III) treated with 200 mg of CoQ10/d for 3 months, a marked improvement in left ventricular ejection fraction was demonstrated. In addition, Rosenfeldt et al.\(^17\) reported improved mitochondrial efficiency and increases in mitochondrial tolerance to in vitro hypoxia-reoxygenation stress following preoperative CoQ10 therapy (300 mg/d) or placebo for 2 weeks in 35 patients undergoing cardiac surgery. The study also revealed increased myocardial and cardiac mitochondrial CoQ10 levels in these patients.

A trial\(^3\) with CoQ10 in patients undergoing cardiac valve replacement has also reported significant improvement in postoperative hemodynamics from intravenous and intracoronary CoQ10 treated “round the operative period” (n = 12 each, CoQ10/control group). In that study, plasma malonaldehyde concentration and serum cardiac creatine kinase in the CoQ10 group were significantly lower than in the control group, while erythrocyte superoxide dismutase activity in the CoQ10 group was significantly higher. The authors\(^3\) suggested that CoQ10 treatment plays a beneficial protective role during cardiac valve replacement through its antioxidant properties.

Berman et al.\(^29\) carried out a prospective double-blind study in 27 patients with end-stage heart failure awaiting heart transplantation. The patients were randomly allocated to receive either 60 mg/d of Ultrasome-CoQ10 (a special preparation to increase intestinal absorption) or placebo for 3 months. The study group showed significant improvement in the 6-minute walk test, NYHA functional classification, nocturia, and fatigue and a decrease in dyspnea. However, no significant changes were noted in echocardiography parameters (dimensions and contractility of cardiac chambers) or the levels of atrial natriuretic factor and tumor necrosis factor in blood. Thus, it was concluded that the administration of CoQ10 to heart transplant patients led to a significant improvement in functional status, clinical symptoms, and quality of life, with no objective changes in echocardiogram measurements or atrial natriuretic factor or tumor necrosis factor blood levels. The authors\(^29\) suggested that CoQ10 may serve as an optional addition to the pharmacologic armamentarium of patients with end-stage heart failure. However, the apparent discrepancy between significant clinical improvement and unchanged cardiac status requires further investigation.

In contrast to numerous studies reporting positive results with CoQ10, no improvements were observed in three controlled clinical trials\(^36-38\); all three studies were part of the second meta-analysis.\(^24\) Permanetter et al.\(^36\) demonstrated no possible therapeutic effects of ubiquinone (3 × 33.3 mg or approximately 99.9 mg of CoQ10/d), administered orally in a placebo-controlled, double-blind cross-over study (N = 25) in patients suffering from idiopathic dilated cardiomyopathy. Watson et al.\(^37\) also reported null effects of oral CoQ10 therapy (3 × 33.3 mg or approximately 99.9 mg/d) in 27 patients with left ventricular dysfunction. An oral treatment for 3 months increased plasma levels of CoQ10 to more than twice basal values, but had no positive effects on resting left ventricular systolic function. More recently, Khatta et al.\(^38\) showed null effects of CoQ10 therapy in 46 patients with CHF receiving standard medical therapy. A dose of 200 mg/d of CoQ10 or placebo for 6 months did not affect ejection fraction, peak oxygen consumption, or exercise duration in these patients. The possible reasons for this might be small sample size, severity, and duration of the disease. Also, optimum clinical benefit of coenzyme Q10 requires plasma levels of CoQ10 to be above the normal range so as to enhance its tissue uptake and thus maximize mitochondrial bioenergetics of the heart muscle.

**Coenzyme Q10 and Myocardial Infarction**

The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction or during cardiac surgery. Increased generation of reactive oxygen species when the heart muscle’s oxygen supply is restored (reperfusion) is thought to be an important contributor to myocardial damage occurring during ischemia-reperfusion. Furthermore, acute myocardial infarction is also reported to be associated with CoQ10 deficiency. In this context, a randomized, double-blind controlled trial was carried out in acute myocardial infarction patients allocated to either CoQ10 (120 mg/d; n = 73) or B vitamins (n = 71) for 1 year.\(^39\) The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement, previous coronary artery disease, and elapsed time from symptom onset to infarction at entry in study showed no significant differences between the two groups. This study found that the total cardiac events (24.6% vs. 45.0%), including nonfatal infarction (13.7% vs. 25.3%) and cardiac deaths, were significantly lower in the intervention group compared with the control group. Plasma levels of vitamin E (32.4 vs. 22.1 μM) and HDL cholesterol (1.26 vs. 1.12 mM) increased, whereas thiobarbituric acid reactive substances, malondialdehyde (1.9 vs. 3.1 pmol/L), and diene conjugates were reduced in the CoQ10 group compared with the control group.
with the control group. Fatigue was more common in the control group than the CoQ group (40.8% vs. 6.8%).

**Coenzyme Q10 and Pediatric Cardiomyopathy**

Pediatric cardiomyopathy (PCM) represents a group of rare and heterogeneous disorders that often results in death. While there is a large body of literature on adult cardiomyopathy, the clinical evidence for a potential role of CoQ10 in PCM is based primarily upon data from adult heart failure patients.

Elshershari et al. have demonstrated the potential usefulness of CoQ10 in treating PCM. This appears to be the first such study on the use of CoQ10 in PCM. In this trial, children 2 months to 11 years old with idiopathic dilated cardiomyopathy were first stabilized and then treated with oral CoQ10 at a dose of 10 mg/kg/d as an adjunct to conventional therapy. Overall, there was a highly significant improvement in their cardiac function. The objective measures were significant improvement in fractional shortening (17.3%–30%) and an increase in ejection fraction (41%–60.3%). Although the sample size in this study was small (n = 6), the authors emphasized the importance of the promising findings, which need to be followed up. Thus, based upon the biochemical rationale and a large body of evidence on the clinical benefit in adults with various types of cardiomyopathy and heart failure, and also in children and adults with mitochondrial cytopathies, the outlook for CoQ10 therapy in PCM is promising. Additional studies on the potential usefulness of CoQ10 supplementation as an adjunct to conventional therapy in PCM, particularly in children with dilated cardiomyopathy, are therefore warranted.

**Coenzyme Q10-Drug Interactions**

**HMG-CoA Reductase Inhibitors (Statins)**

Hypercholesterolemia is a well-known risk factor for coronary heart disease (CHD), and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins have been the most effective means of lowering total cholesterol levels and thereby the risks of CHD. The enzyme HMG-CoA reductase converts HMG-CoA to mevalonate, which constitutes a committed step in the biosynthesis of cholesterol. Mevalonate is also a precursor of CoQ10 and, consequently, statin therapy has been shown to reduce CoQ10 levels, which raises the speculation that a reduction in CoQ10 levels may promote the myopathy that has been associated with statin therapy as a result of mitochondrial damage. This negative outcome has been suggested to be prevented by CoQ10 supplementation. However, studies supplementing CoQ10 to prevent the adverse effects of statin therapy are not definitive and are not recommended at this time. Furthermore, an earlier study reported lowered plasma CoQ10 levels and elevated lactate/pyruvate ratios in patients treated with statin, consistent with mitochondrial dysfunction in these patients.

On the contrary, Bleske et al. reported no difference in CoQ10 levels in 12 healthy volunteers following a 4-week treatment with 20 mg of pravastatin or 10 mg of atorvastatin in a randomized crossover trial. The inclusion of healthy volunteers and the short study period may account for the lack of effects seen in this study. Furthermore, a prospective case-control study has been reported very recently and concluded that although pravastatin lowers plasma CoQ10 concentrations, it does not appear to predict the risk of recurrent CVD events. It is pertinent to note the suggestion that blood CoQ10 concentration should be reported only after normalizing to total lipid or cholesterol levels because CoQ10 circulates with lipoproteins and levels of CoQ10 are highly dependent upon levels of circulating lipids. Given the lipid-lowering effects of statins, it is therefore unclear whether these drugs actually decrease CoQ10 levels independent of a reduction in circulating lipids. Also, very few studies have examined CoQ10 content in target organs; thus, it is not clear whether statin therapy affects CoQ10 concentrations in the body’s tissues. At present, more research is needed to determine whether CoQ10 supplementation might be beneficial for those taking HMG-CoA reductase inhibitors.

**Warfarin**

CoQ10 is structurally related to vitamin K and is postulated to have pro-coagulant effects. Concomitant use of warfarin (Coumadin) and CoQ10 has been reported to decrease the anticoagulant effect of warfarin in at least four cases. Thus, caution is advised for the concomitant use of CoQ10 and warfarin. Blood tests should be performed to monitor and assess clotting time (prothrombin time) frequently, especially in the first 2 weeks.

Additionally, because of CoQ10’s potential hypoglycemic and hypotensive effects, although not discussed in the present review, monitoring is also advised especially when using CoQ10 adjunctively with prescription medications.

**CONCLUSIONS**

As reported by the Task Force on Clinical Expert Consensus Documents Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine, it is clear that, unlike established
therapies such as angiotensin-converting enzyme inhibitors, beta blockers, and aldosterone antagonists, the mortality benefit for CoQ10 is not yet established. The reported consensus further mentioned that one unique formulation of CoQ10 has received FDA orphan drug status for treating mitochondrial disorders. The value of CoQ10 in CVD and with statin use has not been clearly established. Its potential utility appears to be in CHF. However, much further research is required, especially using state-of-the-art techniques such as echocardiography and ventriculography refractory to standard therapy to assess functional outcomes in patients with CHF. Also, future studies looking at long-term outcomes are required to confirm the efficacy of CoQ10 in heart failure patients as adjunctive or alternative therapy to current therapeutic regimens.

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REFERENCES


