The Role of Coenzyme Q10 in Clinical Medicine: Part II. Cardiovascular Disease, Hypertension, Diabetes Mellitus and Infertility

by Alan R. Gaby, M.D.

Abstract:

This review discusses the role of coenzyme Q10 (CoQ10) in cardiovascular disease, hypertension, diabetes mellitus, and infertility. Deficiencies of CoQ10 have been documented in patients with heart disease. Administration of CoQ10 has been shown to prolong survival and improve quality of life in patients with cardiomyopathy. In patients with congestive heart failure, CoQ10 ameliorated symptoms, reduced the number of hospitalizations and appeared to increase the survival rate. Treatment with CoQ10 may also reduce the number of anginal attacks in patients with stable angina pectoris. CoQ10 has been shown to prevent adriamycin cardiotoxicity and to reduce the incidence of postoperative cardiac dysfunction in patients undergoing heart surgery. Several studies indicate that CoQ10 may also have a role in the treatment of essential hypertension. This nutrient may be of value for patients with diabetes mellitus or male infertility, but additional studies are needed in these areas. CoQ10 status may be adversely affected by treatment with certain cholesterol-lowering drugs, beta blockers, tricyclic antidepressants, and phenothiazines.

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Part I of this two-part article reviewed the relationship between coenzyme Q10 (CoQ10) and immune function, periodontal disease, gastric ulceration, obesity, physical performance, allergy, and muscular dystrophy. Part II discusses the effect of CoQ10 on cardiovascular disease, hypertension, diabetes mellitus, and infertility, as well as reviewing drug interactions with CoQ10.

Cardiovascular Disease - General Aspects

Enhancing myocardial function is an important, though frequently overlooked component of the overall prevention and treatment of cardiovascular disease. CoQ10 plays a key role in energy production, and is therefore essential for all energy-dependent processes, including heart-muscle contraction. CoQ10 deficiency has been documented in patients with various types of cardiovascular disease. It is not clear whether a decline in CoQ10 levels is a primary cause or a consequence of heart disease. However, given the fundamental involvement of CoQ10 in myocardial function, it is not unlikely that CoQ10 deficiency would exacerbate heart disease

and that correction of such a deficiency would have therapeutic value.

In addition, CoQ10 has been shown to be a potent antioxidant. In one study, ubiquinol-10, the reduced form of CoQ10, protected human low density lipoproteins (LDL) more efficiently against lipid peroxidation than did vitamin E.[1] Since oxidation of LDL is believed to be an initiating factor in the development of atherosclerosis, CoQ10 appears to be a preventive factor.

CoQ10 Deficiency in Cardiac Disease

Circulating levels of CoQ10 were significantly lower in patients with ischemic heart disease[2] and in those with dilated cardiomyopathy (mostly New York Heart Association [NYHA] functional class III or IV) than in healthy controls.[3] In another study, CoQ10 levels in myocardial tissue (estimated by enzymatic methods) were low in approximately 75% of patients undergoing cardiac surgery. Concentrations of CoQ10 declined progressively in both blood and myocardial tissue with increasing severity of heart disease.[4] Myocardial deficiencies of CoQ10 were also found in the majority of patients with aortic stenosis or insufficiency, mitral stenosis or insufficiency, diabetic cardiomyopathy, tetralogy of Fallot, atrial septal defects and ventricular septal defects.[5] In patients with cardiomyopathy and myocardial deficiency of CoQ10, oral administration of 100 mg/day of CoQ10 for 2-8 months resulted in an increase in myocardial CoQ10 levels ranging from 20-85%.[6] These findings suggest that CoQ10 deficiency is common in patients with various types of cardiovascular disease, and that oral administration of CoQ10 can increase tissue levels of this nutrient.

Treatment of Cardiomyopathy

In one study, 126 patients with dilated cardiomyopathy (98% of whom were in NYHA functional class III or IV) received 100 mg/day of CoQ10 for periods of up to 66 months. After 6 months of treatment, the mean ejection fraction increased from 41% to 59% ($p < 0.001$), and remained stable thereafter with continued treatment. After 2 years, 84% of the patients were still alive and at 5.5 years, 52% were alive.[7] These survival rates are considerably better than the published survival statistics of patients given conventional therapy (i.e., 2-year survival rate of 50% for symptomatic cardiomyopathy and 1-year survival rate of 50% for decompensated cardiomyopathy).

In another study, 88 patients with cardiomyopathy received 100 mg/day of CoQ10 for periods of 1-24 months. Significant improvements in at least two of three cardiac parameters (ejection fraction, cardiac output and NYHA class) were seen in 75-85% of the patients. Approximately 80% of the patients improved to a lower (i.e., more favorable) NYHA functional class.[8]

In a double-blind, crossover trial, 19 patients with cardiomyopathy (NYHA classes III and IV) received 100 mg/day of CoQ10 or a placebo, each for 12 weeks. Compared with placebo, CoQ10 treatment significantly increased cardiac stroke volume and ejection fraction. Eighteen patients reported subjective improvement in tolerance for physical activity while taking CoQ10.[9]

Congestive Heart Failure

The potential of CoQ10 as a treatment for congestive heart failure (CHF) was suggested as early as 1967 by Japanese researchers.[10] In 1976, these same investigators administered 30 mg/day of CoQ10 to 17 patients with CHF. All of the patients improved, and 9 (53%) became asymptomatic after 4 weeks of treatment.[11]

In an open trial of 34 patients with refractory NYHA class IV CHF, administration of 100 mg/day of CoQ10 resulted in sustained

improvement in cardiac function in 28 cases (82%). The survival rate after two years was 62%, compared with an expected two-year survival rate of less than 25% for similar patients.[12]

In another study, 12 patients with advanced CHF who had failed to respond adequately to digitalis and diuretics received 100 mg/day of coenzyme Q10 for 7 months. Two-thirds of the patients showed definite clinical improvement after a mean treatment period of 30 days. In these patients, dyspnea at rest disappeared and energy level and tolerance for activity increased. Objective improvements included decreased hepatic congestion, reductions in heart rate and heart volume, and a decline in systolic time intervals (suggesting improved myocardial performance). Withdrawal of coenzyme Q10 was followed by severe clinical relapse, with subsequent improvement upon resumption of treatment.[13]

In a large multicenter trial of 1,113 CHF patients, 50-150 mg/day of CoQ10 was given for 3 months (78% of the patients received 100 mg/day). The proportion of patients with improvements in clinical signs and symptoms were as follows: sweating, 82.4%; jugular reflux, 81.5%; cyanosis, 81%; pulmonary rales, 78.4%; edema, 76.9%; palpitations, 75.7%; vertigo, 73%; arrhythmia, 62%; insomnia, 60.2%; dyspnea, 54.2%; nocturia, 50.7%; and enlargement of the liver area, 49.3%.[14]

The results of these uncontrolled studies were confirmed more recently in a double-blind trial. Some 641 patients with CHF (NYHA classes III or IV) were randomly assigned to receive placebo or CoQ10 (2 mg/kg/day) for one year. Conventional therapy was continued in both groups. The number of patients requiring hospitalization during the study for worsening heart failure was 38% less in the CoQ10 group than in the placebo group ($p < 0.001$). Episodes of pulmonary edema were reduced by about 60% in the CoQ10 group, compared with the placebo group ($p < 0.001$).[15]

Angina

Twelve patients with stable angina pectoris were randomly assigned to receive 150 mg/day of CoQ10 or a placebo, each for 4 weeks, in a double-blind crossover trial. CoQ10 treatment significantly increased exercise tolerance on a treadmill (time before onset of chest pain), and significantly increased the time until ST-segment depression occurred. Compared with placebo, there was a 53% reduction in the frequency of anginal episodes and a 54% reduction in the number of nitroglycerin tablets needed during CoQ10 treatment; however, these differences were not statistically significant.[16]

These results suggest that CoQ10 is a safe and effective treatment for angina pectoris. Although the amelioration of anginal attacks was not statistically significant, the magnitude of the effect was large. It would therefore be worthwhile to perform a similar study with a larger number of patients.

Arrhythmias

Twenty-seven patients with ventricular premature beats (VPB's) and no evidence of organic heart disease received a placebo for 3-4 weeks, followed by 60 mg/day of coenzyme Q10 for 4-5 weeks. The reduction in VPB's was significantly greater after CoQ10 than after placebo. The beneficial effect of CoQ10 was seen primarily in diabetics, in whom the mean reduction in VPB frequency was 85.7%. A significant reduction in VPB's also occurred in 1 (11%) of 9 otherwise healthy patients and in 4 (36%) of 11 patients with hypertension.[17]

Prevention of Adriamycin Toxicity

The clinical value of adriamycin as anti-cancer agent is limited by its toxicity,

which includes cardiomyopathy and irreversible heart failure. Adriamycin-induced cardiotoxicity is believed to be caused, at least in part, by a reduction in CoQ10 levels and by inhibition of CoQ10-dependent enzymes. In rats treated with adriamycin, administration of CoQ10 restored the levels of this nutrient to normal and prevented adriamycin-induced morphologic changes in the heart.[18] Treatment with CoQ10 also prevented adriamycin-induced cardiotoxicity in rabbits.[19]

Cancer patients receiving adriamycin had lower myocardial levels of coenzyme Q10 than did controls. The magnitude of CoQ10 depletion was directly related to the severity of cardiac impairment.[20] To determine the effect of CoQ10 supplementation on adriamycin cardiotoxicity, 7 patients receiving adriamycin were also given 100 mg/day of CoQ10, beginning 3-5 days before adriamycin was started. Another 7 patients (control group) received adriamycin without CoQ10. Cardiac function deteriorated significantly in the control group, whereas patients given CoQ10 had little or no cardiotoxicity, even though the cumulative dose of adriamycin in the CoQ10 group was 50% greater than that in the control group.[21] Despite the small number of patients in this study, the results are highly encouraging. Since administration of CoQ10 does not appear to affect the antitumor activity of adriamycin,[22] CoQ10 prophylaxis seems appropriate for all patients receiving adriamycin.

Protection During Cardiac Surgery

Postoperative low cardiac output is a major cause of early death following cardiac surgery. Fifty patients undergoing cardiac surgery for acquired valvular lesions were randomly assigned to receive 30-60 mg/day of CoQ10 for 6 days prior to surgery or to a control group that did not receive CoQ10. Postoperatively, a state of severe low-cardiac output developed in 48% of the patients in the control group, compared with only 12% of those in the CoQ10 group. These results suggest that preoperative administration of CoQ10 increases the tolerance of the heart to ischemia during aortic cross-clamping.[23]

Mitral Valve Prolapse

Cardiac performance was evaluated using an isometric hand grip test in 194 children with symptomatic mitral valve prolapse. Prior to treatment, all patients had an abnormal hand-grip test. Sixteen children received 2 mg/kg/day of CoQ10 or a placebo for 6 weeks, in a single-blind trial. Hand grip strength became normal in 7 children receiving CoQ10 and in none of the placebo-treated patients.[24]

Note that the relevance of this study to the treatment of mitral valve prolapse in adults is questionable, and hand grip may not be a reliable test of cardiac function. Furthermore, impaired cardiac function is not typical of mitral valve prolapse in adults and the symptoms associated with this condition do not appear to be caused by diminished cardiac function. While the symptoms associated with mitral valve prolapse may respond to magnesium supplementation,[25] the role of CoQ10 in the treatment of this disorder is unclear.

Hypertension

Enzymatic assays revealed a deficiency of CoQ10 in 39% of 59 patients with essential hypertension, compared with only 6% of healthy controls. In animal models of hypertension, including spontaneously hypertensive rats, uninephrectomized rats treated with saline and deoxycorticosterone, and experimentally hypertensive dogs, orally administered CoQ10 significantly lowered blood pressure.[26-29]

Twenty-six patients with essential hypertension received coenzyme Q10, 50 mg

twice a day. After 10 weeks of treatment, mean systolic blood pressure decreased from 164.5 to 146.7 mm Hg and mean diastolic blood pressure decreased from 98.1 to 86.1 mm Hg ($p < 0.001$). The fall in blood pressure was associated with a significant reduction in peripheral resistance, but there were no changes in plasma renin activity, serum and urinary sodium and potassium, and urinary aldosterone. These results suggest that treatment with CoQ10 decreases blood pressure in patients with essential hypertension, possibly because of a reduction in peripheral resistance.[30]

In another study, 109 patients with essential hypertension received coenzyme Q10 (average dose, 225 mg/day) in addition to their usual antihypertensive regimen. The dosage of CoQ10 was adjusted according to clinical response and blood CoQ10 levels (the aim was to attain blood levels greater than 2.0 mcg/ml). The need for antihypertensive medication declined gradually and, after a mean treatment period of 4.4 months, about half of the patients were able to discontinue between one and three drugs.[31] Similar results have been reported by others.[32]

It should be noted that the effect of CoQ10 on blood pressure was usually not seen until after 4-12 weeks of therapy. That observation is consistent with the delayed increase in enzyme activity that results from administration of CoQ10. Thus, CoQ10 is not a typical antihypertensive drug; rather, it seems to correct some metabolic abnormality that is involved in the pathogenesis of hypertension.

Diabetes Mellitus

Diabetes mellitus is a multifactorial disease that is associated with a number of different metabolic abnormalities. The electron transport chain, of which CoQ10 is a component, plays a major role in carbohydrate metabolism. A deficiency of CoQ10 might therefore have an adverse effect on glucose tolerance.

Decreased levels of CoQ10 (measured as total CoQ) were found in rats with experimentally-induced diabetes. Administration of CoQ7 (an analog of CoQ10) partially corrected abnormal glucose metabolism in alloxan-diabetic rats. (Before CoQ10 became commercially available, some therapeutic trials were done with CoQ7. These two compounds are considered to be nutritionally equivalent.)

Thirty-nine diabetics received 120 mg/day of CoQ7 for 2-18 weeks. Fasting blood sugar levels fell by at least 30% in 31% of the patients and the concentration of ketone bodies declined by at least 30% in 59% of the patients. One patient who was poorly controlled on 60 units/day of insulin showed a marked fall in fasting blood sugar and ketone bodies after receiving CoQ7.[33]

Male Infertility

Because sperm production and function are highly energy-dependent processes, CoQ10 deficiency could presumably be a contributing factor to infertility in men. In one study, administration of 10 mg/day of CoQ7 resulted in a significant increase in sperm count and motility in a group of infertile men.[34] Additional research is needed to determine whether CoQ10 therapy has a role in the treatment of infertility.

Drug Interactions

Cholesterol-lowering drugs such as lovastatin and pravastatin inhibit the enzyme 3-hydroxy-3-methylglutaryl(HMG)-CoA reductase, which is required for biosynthesis of both cholesterol and CoQ10. Thus, administration of these drugs might compromise CoQ10 status by decreasing its synthesis. Supplementation of the diet of rats with lovastatin (400 mg/kg of diet) for 4 weeks reduced the concentration of CoQ10 in the heart, liver, and blood.[35] In another study, administration of lovastatin to 5 patients receiving

CoQ10 for heart failure was followed by a reduction in blood levels of CoQ10 and a significant deterioration of clinical status. Some of these patients improved after the dosage of CoQ10 was increased or the lovastatin was discontinued.[36]

These results suggest that people who have low CoQ10 levels and suboptimal cardiac function might develop clinically significant CoQ10 depletion after taking an HMG-CoA reductase inhibitor. Although individuals with high CoQ10 levels and good cardiac function can probably tolerate these drugs better, a case can be made that all patients being treated with HMG-CoA reductase inhibitors should also receive CoQ10 prophylactically.

The beta blockers propranolol and metaprolol have been shown to inhibit CoQ10-dependent enzymes.[37] The antihypertensive effect of these drugs might therefore be compromised in the long run by the development of CoQ10 deficiency. In one study, administration of 60 mg/day of CoQ10 reduced the incidence of drug-induced malaise in patients receiving propranolol.[38]

A number of phenothiazines and tricyclic antidepressants have also been shown to inhibit CoQ10-dependent enzymes. It is therefore possible that CoQ10 deficiency may be a contributing factor to the cardiac side effects that are frequently seen with these drugs. In two clinical studies, supplementation with CoQ10 improved electrocardiographic changes in patients on psychotropic drugs.[39]

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