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Coenzyme Q_{10}: A Vital Therapeutic Nutrient for the Heart with Special Application in Congestive Heart Failure

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ABSTRACT—Vitamin coenzyme Q_{10} is a critical adjuvant complementary therapy for patients with congestive heart failure, especially when traditional medical therapy is unsuccessful. The following case studies, with systolic and/or diastolic dysfunction, demonstrate the effectiveness of coenzyme Q_{10} in improving quality of life, as well as survival.

Introduction

COENZYME Q_{10} (CoQ_{10}) or "Ubiquinone," so named for its ubiquitous nature, is a fat-soluble compound that functions as an antioxidant and coenzyme in the energy-producing metabolic pathways. The chemistry, therapeutics, and clinical applications of this compound have appeared in mainstream textbook cardiology.[1] (Table 1). As an antioxidant, the reduced form of CoQ_{10} inhibits lipid peroxidation in both cell membranes and serum low-density lipoproteins, and also protects proteins and DNA from oxidative damage.[2,3] CoQ_{10} also has membrane stabilizing activity as well as recently discovered platelet effects.[4] The bioenergetic activity of this compound, however, is probably its most important function.

Bioenergetics is the study of energy transformations in living organisms, used in the field of biochemistry, to reference cellular energy. Every cell must have a way of obtaining energy. Such oxygen-based production of energy occurs in the mitochondria, where CoQ_{10} acts as an essential component of the electron transport among reduced nicotinamide adenine dinucleotide (NADH), succinate dehydrogenases, and the cytochrome system.[1,2] In the subsequent series of redox reactions involving oxidative phosphorylation pathways, adenosine triphosphate (ATP) is synthesized. Since all cellular function depends on an adequate supply of ATP, CoQ_{10} is an essential component of life itself.

The biosynthesis of CoQ_{10} is a complex process requiring at least seven vitamins and multiple trace elements. CoQ_{10} is found in relatively high concentrations in the heart, liver, and kidney, and in lower concentrations in the brain and colon.

Although CoQ_{10} can be synthesized in the body, situations may occur in which the body's capacity to produce CoQ_{10} is insufficient to meet its requirements. Therefore, some patients may be deficient in this vitamin. For example, in patients receiving total parenteral nutrition, plasma levels of CoQ_{10} may undergo a 50% reduction in just one week.[5] Significantly decreased plasma levels of CoQ_{10} have been noted in a wide variety of diseases involving metabolically active cells, such as those found in the heart,[6] as well as in an overactive thyroid gland.[7]

CoQ_{10} levels in organs may also decrease with advancing age.[1] Thus, CoQ_{10} deficiency may be caused by an insufficient dietary intake of CoQ_{10}, impairment in CoQ_{10} synthesis, an excessive utilization by tissues, or a combination of any of these factors.

Although CoQ_{10} has been shown to be clinically effective in the treatment of coronary artery disease,[8] toxic cardiomyopathy, and hypertension,[9] for the past two decades many clinical studies on CoQ_{10} have focused on congestive heart failure (CHF) and cardiomyopathy. A strong correlation between low blood and tissue levels of CoQ_{10} and the severity of heart failure has been repeatedly confirmed.[6] Functional CoQ_{10} deficiencies were also reported in hypertrophied ventricles resulting from increasing aortic valve pressure gradients due to aortic stenosis.[10]

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Table 1.—History and Time Line for Coenzyme Q_{10}	
1957	CoQ_{10} first isolated from beef heart by Frederick Crane.
1958	Karl Folkers at Merck Phamaceuticals determines the precise chemical formula.
Mid 1960s	Professor Yamamura of Japan is first to use coenzyme Q_7 (related compound) in CHF.
1972	Dr. Littarru (Italy) and Dr. Folkers (USA) document a Q_{10} deficiency in human heart disease.
Mid 1970s	Japanese perfected industrial technology of fermentation to produce pure coenzyme Q_{10} in significant quantities.
1976	CoQ_{10} is placed on formulary in Japanese Hospitals.
1978	Peter Mitchell receives Nobel Prize for CoQ_{10} and energy transfer.
1980s	Enthusiasm for CoQ_{10} leads to marked increase in number and size of clinical studies around the world.
1985	Dr. Per Langsjoen in Texas reported in double blind studies the profound effectiveness Q_{10} has in cardiomyopathy.
1990s	Explosion of use of coenzyme Q_{10} in health food industry.
1992	Q_{10} placed on formulary at Manchester Memorial Hospital, Manchester, Connecticut.
1996	Ninth International Conference on coenzyme Q_{10} in Ancona, Italy—Scientists and physicians report on a variety of medical conditions improved by Q_{10} administration. Blood levels of at least 2.5 μg/mL and preferably higher required for most medicinal purposes.
1996-97	Gel-Tec, a division of Tischon Laboratories, under the leadership of Raj Chopra, develops the "Bio Solv process," allowing for greater bioavailability of supplemental Q_{10} in the body.
1997	CoQ_{10} appears in textbooks of mainstream cardiology.

Experimental and clinical data provide extensive evidence that CoQ_{10} supplementation in patients with cardiomyopathy and CHF has demonstrated improvements in left ventricular function, ejection fraction, exercise tolerance, diastolic dysfunction, clinical outcome, and quality of life.[11-13] Pretreatment with CoQ_{10} in placebo-controlled trials has been also shown to be effective in preventing left ventricular depression following coronary artery bypass and valvular surgery.[14]

The following case studies will demonstrate how the supplementation of CoQ_{10} was effective in reversing CHF in three critically ill patients who would probably not have survived without the addition of this vital compound. The purpose of this communication is to review CoQ_{10}'s clinical efficacy in the treatment of cardiovascular disease with particular emphasis on CoQ_{10}'s critical role as adjuvant therapy for patients with CHF.

Case Presentations

Case 1.—A 79-year-old female (LG) with a long-standing history of hypertension, LG had been diagnosed with CHF in 1977 at age 60. In 1984 she had experienced her first episode of pulmonary edema, which had been treated with a combination of angiotensin converting enzyme (ACE) inhibition, digoxin, and diuretics. Her ejection fraction (EF) at that time was 35%.

Following a second episode of flash pulmonary edema in 1992, the patient underwent cardiac catheterization that demonstrated a dilated cardiomyopathy and normal coronary arteries.

By October 1994, LG weighed 77 pounds and was suffering from severe end-stage cardiac cachexia (New York Heart Association [NYHA] Class IV). Her ejection fraction at that time had fallen to 10% to 15%, barely enough to support her bed-to-chair existence. CoQ_{10} therapy was initiated at 30 mg three times a day in addition to her conventional therapy.

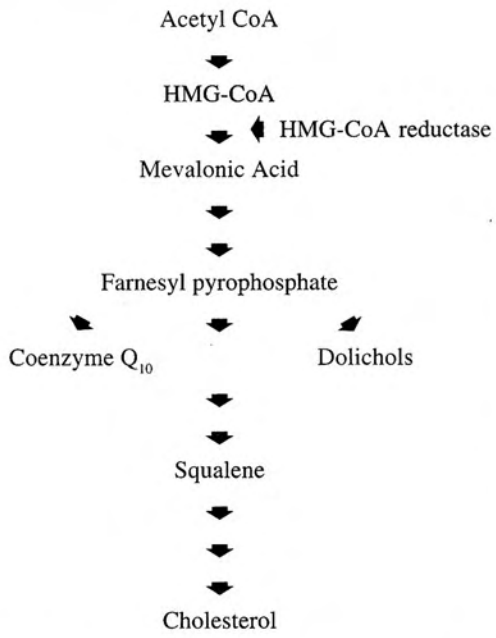
In March 1995, LG was inadvertently started on 300 mg of CoQ_{10} daily. Without realizing it her son had purchased 100 mg instead of her usual 30 mg capsules, more than tripling her dose. Approximately four weeks later, LG experienced a steady and marked improvement in her functional status.

In June 1995, a repeat echocardiogram demonstrated an improvement in her ejection fraction (20%), as well as reduction in both mitral and tricuspid regurgitation which had been previously noted on color-flow and Doppler echocardiographic studies.

By October 1995, LG was shopping and visiting relatives. In January 1996 she fractured her hip, necessitating major surgery for a total hip replacement. She tolerated the surgery well despite her previously compromised cardiac status. She now continues to function at an NYHA Class II status. In addition to her conventional medical therapy, she has been successfully maintained on 300 mg of CoQ_{10} daily.

Case 2.—A second case of refractory CHF on traditional therapy involved a retired male (HD) with a previous history of emphysema, hypertension, anteroseptal myocardial infarction (1982), and surgical repair of an

Figure.—Biosynthetic Pathway of Cholesterol



The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is necessary for the conversion of HMG-CoA to mevalonic acid, an early step in biosynthesis of cholesterol. Because mevalonic acid is also a precursor of coenzyme Q_{10} via a branch of the cholesterol biosynthetic pathway, HMG-CoA reductase inhibitors could reduce serum concentrations of coenzyme Q_{10}.

abdominal aortic aneurysm (1987). He presented with a history of congestive cardiomyopathy over the past few years. He had been hospitalized several times for evaluation of episodes of pulmonary edema complicated by ventricular tachycardia.

In December 1994, he complained of chest discomfort at rest, shortness of breath with minimal activity, and dizziness despite treatment with captopril, nitroglycerin paste, furosemide, and ipratropium bromide inhaler.

He was started on a multivitamin/mineral preparation and CoQ_{10} 30 mg three times daily. HD refused angiography. In September 1995, he was admitted for severe CHF. During an episode of flash pulmonary edema, HD required intubation and intravenous drug support with dopamine and high-dose diuretics. Although he was gradually weaned off the ventilator and continued to show slow improvement, HD's functional status remained at Class III-VI status. Echocardiogram showed an EF of 15%. At discharge, CoQ_{10} therapy was increased to 120 mg daily.

Subsequent postdischarge persantine cardiolite stress testing demonstrated old infarction of inferior, anterior, apical, and septal walls with a dilated left ventricle and EF (SPECT) gated wall motion study, estimated at 20%. In late October 1995, his CoQ_{10} dose was increased to 300 mg daily in combination with his usual captopril 50 mg three times daily and furosemide 80 mg twice daily. In December 1995, the patient's quality of life significantly improved. Furosemide was reduced to 40 mg twice daily. Echocardiogram revealed an improved ejection fraction of 25%. HD's quality of life continued to improve, resulting in a residential move to Florida to enjoy the climate. On 300 mg of CoQ_{10} daily, he was functioning at NYHA Class I-II level and was walking long distances on the beach.

Case 3.—A third case of pneumonia and severe CHF involved LH, a 79-year-old female with no known previous medical history. She was admitted to a community hospital with bilateral pneumonia and CHF.

LH required intubation because of pulmonary failure. Her condition continued to deteriorate over the next several days requiring positive end-expiratory pressure and high F_{IO_2} saturation. She was treated with an ACE inhibitor, verapamil, and diuretics. A tracheostomy was performed, but she continued to deteriorate despite conventional medical therapy. The family was notified of her seemingly terminal situation. Her son, a Ph.D. biochemist from California and an expert in CoQ_{10}, asked her doctors to add CoQ_{10} to his mother's treatment. The physicians refused, since it was not in the formulary, and therefore could not be administered. Desperate to find a hospital that would administer CoQ_{10}, her son called me for consultation. LH was then transferred to Manchester Memorial Hospital for conventional as well as CoQ_{10} therapy. On admission, she was on full ventilatory support in a semicomatose state and responded only to commands and painful stimuli.

Initial echocardiographic analysis demonstrated low normal systolic function with an estimated ejection fraction of 50%. Isolated diastolic dysfunction and hypertrophic cardiomyopathy with a subaortic gradient of approximately 30 mmHg were noted. Her pulmonary care was similar to that received at the previous hospital. In addition, LH received 450 mg of CoQ_{10} via nasogastric tube on a daily basis. After 10 days, LH was weaned from the ventilator. Four days later she was discharged to an extended care facility on supplemental oxygen.

She is functioning at a NYHA Class I to II status and is enjoying a good quality of life on ACE inhibitors and 300 mg of CoQ_{10} per day.

Discussion

The efficacy of CoQ_{10} in CHF has been reported in the medical literature. In a study of 126 patients followed for five years on a treatment dosage of 100 mg of CoQ_{10} daily with measured mean blood levels of approximately 2 μg/mL, mean ejection fraction was 41% at the beginning of

the trial and rose to a mean of 59% after six months.[13] After careful scrutiny of individual subjects, it was reported that 71% of the patients achieved a significant improvement in ejection fraction after three months of therapy and 16% in six months. There was an overall improvement in ejection fraction in 87% of the patients. Remarkably, 106 patients had an improvement of one to two NYHA Classes. Only 13% showed no improvement. The study also clearly demonstrated that CoQ_{10} is effective and safe for the treatment of patients with dilated cardiomyopathy for over a period of six years.

In another double-blind placebo-controlled study with a crossover design involving 80 patients, improvements noted with CoQ_{10} as adjunctive therapy were even more significant in terms of exercise capacity and quality of life than those obtained from conventional drug therapy alone.[11]

In a study of cardiac transplantation candidates and CoQ_{10} administration, results indicated that correcting myocardial deficiencies of CoQ_{10} improved myocardial performance.[15] Of 11 transplant candidates, seven patients in Class III-IV improved to Class I-II functional status. In this small, but significant, study CoQ_{10} not only improved quality of life and permitted a longer waiting time for a donor heart, its efficacy and safety justified using the vitamin for patients awaiting cardiac transplantation. In another double-blind controlled trial of 641 patients receiving placebo or CoQ_{10} in a dose of 2 mg per kilogram for one year, there was a 50% reduction in pulmonary edema and a 20% reduction in hospitalization for the CoQ_{10} group *vs* placebo.[12] Perhaps the largest study to date showing the efficacy and safety of CoQ_{10} in the treatment of CHF is the Italian multicenter trial by Baggio et al, involving 2,664 patients with heart failure.[16] Other studies have also shown the positive effect CoQ_{10} has on diastolic dysfunction.

Diastolic dysfunction is an early sign of myocardial failure despite the presence of normal systolic function. Since diastolic function requires a larger amount of cellular energy than systolic contraction, more energy is required to fill the heart than to empty it. Such an additional requirement of energy activity makes CoQ_{10} such a reasonable intervention.

As demonstrated in a study of 109 patients with hypertensive heart disease and with isolated diastolic dysfunction, CoQ10 replacement resulted in clinical improvement, lowering of elevated blood pressure, improved diastolic function, and a decrease in myocardial thickness in 53% of the hypertensives.[17] In another study of seven patients with hypertropic cardiomyopathy, six nonobstructive and one obstructive, all patients noted improvement in symptoms of fatigue and dyspnea on an average of 200 mg of CoQ_{10} per day. The mean intraventricular septal thickness and the mean posterior wall thickness both improved significantly. Mitral valve inflow slope by pulsed wave Doppler (E to F slope) showed a nonsignificant trend towards improvement.[18]

Conclusion

Left ventricular function depends on the operational capacity of myocardial cells to generate the energy to expand and contract. Insufficient myocardial contractive forces often contribute significantly to CHF. Literally, heart failure is an "energy-starved heart."

Although there may be several causes of myocardial dysfunction, energy deficiency of cardiac myocytes may play a significant role and probably is the major role in pump failure. It is no longer enough to focus on the fluid retention in pump failure. We need to consider the biochemistry of "pulsation" as well. It is critically important to treat both the molecular and cellular components of the heart when managing CHF.

Therefore, cardiologists must think "bioenergetically." CoQ_{10} has a significant effect upon electron transfer in the respiratory chain and supports intramyocardial energy at the cellular level. Because oxygen-based production of energy takes place in cellular mitochondria, it is not unusual for CoQ_{10} concentrations in myocardial cells to be tenfold greater than those in the brain or colon.

As the heart is one of the few tissues of the body to function continuously in an aerobic mode, the myocardium requires the highest level of ATP support. Thus, any condition that causes a decrease in CoQ_{10} could precipitate a corresponding decrease in oxidative phosphorylation of the mitochondrial respiratory chain, thus making the tissue more susceptible to free radical attack.[19] Since high free radical stress is more pronounced in advancing stages in CHF, the heart becomes even more vulnerable to lipid peroxidation. The antioxidative activity of CoQ_{10} is crucial under these circumstances.

The causes of decreased CoQ_{10} levels in patients with CHF may also arise from the increased consumption of CoQ_{10} secondary to increasing oxidative insult, which may be related to oxidative catabolism of excessive levels of catecholamines. This well-known increase in sympathetic activity that occurs in heart failure may explain the increased incidence of arrhythmias as well as a worsening of heart failure itself.

It has been well-documented by high-pressure (or performance) liquid chromatography* technology that myocardial tissue levels of CoQ_{10} are lower in cases of ad-

*A very sensitive and elegant method by which minute (very small) amounts of a given substance (compound) is separated (by chromatography) and quantitated.

vanced CHF.[6] Since myocardial tissue levels of CoQ_{10} may be restored significantly by oral supplementation, the use of exogenous CoQ_{10} should be considered, not only for its antioxidant and free radical quenching activity, but also for its bioenergetic support.

It is also important to note a subgroup of patients who are vulnerable to CoQ_{10} deficiency; those with CHF and coexistent coronary artery disease who are also on CoQ_{10} depleting agents. Members of this subpopulation treated with HMG-CoA-reductase inhibitors to lower serum cholesterol are at risk for CoQ_{10} depletion. Cholesterol production, as well as endogenous pathways for CoQ_{10} production, are both compromised on HMG-CoA-reductase inhibition. This particular subpopulation of patients may need additional doses of CoQ_{10} to offset the CoQ_{10} depleting effects of these hypercholesterolemic agents.[20] (Fig. 1)

In summary, given the experience of these case studies of patients refractory to conventional CHF management, it is not unreasonable to consider CoQ_{10} therapy as a defense against CHF resulting from long-standing hypertension, ischemia, and diastolic dysfunction. As more controlled double-blinded CoQ_{10} research is performed, cardiologists and other physicians may become more comfortable in utilizing this simple and useful nutritional support for the heart.

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