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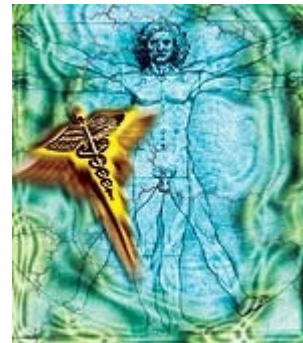
REPORT

Innovative Research and Applications for CoQ10

By Kurt J. Samson

In 1983, the Life Extension Foundation introduced coenzyme Q10 (CoQ10) to the United States. Over the past 21 years, hundreds of studies have confirmed the safety and effectiveness of CoQ10 supplementation for health disorders ranging from neurological aging to heart disease.

Yet the US medical establishment and federal drug regulators have been hesitant to embrace these findings, reserving opinion until more large-scale trials are completed. With several major studies under way, CoQ10 could be on the cusp of broader acceptance across a range of medical disciplines.



Understanding CoQ10

Ubiquinone, commonly referred to as coenzyme Q10, was originally so named because of its omnipresence in virtually every cell of the human body. According to Dr. Karl Folkers, a pioneer in the CoQ10 fermentation synthesis, CoQ10 should be properly renamed “vitamin Q,” and thus take its rightful place in the pantheon of essential nutrients.

Two main theories have been set forth as to how CoQ10 assists in achieving optimal health and regeneration from illness. First is its ability to increase the amount of energy available to those parts of the body whose cells most require it, including the heart, brain, kidneys, and skeletal muscles, among others. Second, many of the benefits derived from CoQ10 are thought to be a result of its potent antioxidant effects, as it scavenges dangerous free radical oxygen species that normally harm the body.

Dr. Folkers' quest and legacy are being carried on by dozens of researchers whose efforts are continuing to bring information about CoQ10 to the forefront of academic medicine. A number of encouraging studies were published by respected medical and scientific journals in 2003 and early 2004. Life Extension surveyed the literature and herein presents some of the most significant highlights.

CoQ10 and Kidney Failure

In the *Journal of Nutritional and Environmental Medicine*, CoQ10 research pioneers Drs. Ram Singh and Adarsh Kumar reported the results of a very well-designed trial indicating CoQ10 might have a powerful role as adjunctive therapy in patients with end-stage kidney disease—in some cases even reducing or averting the need for dialysis.¹

In a randomized, double-blind, placebo-controlled trial, the researchers found CoQ10 treatment decreased progression and reversed renal dysfunction in a majority of patients with end-stage disease, many of whom were able to discontinue dialysis over the course of the 12-week trial. The report followed up on a pilot study the scientists published in 2000 involving a smaller number of subjects.

End-stage kidney disease produces marked organ contraction and progressive dysfunction, with corresponding increases in levels of serum creatinine and blood urea nitrogen. Levels of toxic waste products accumulate in the blood because the kidneys cannot clear them from the body.



A cell showing the nucleus (with DNA) and the cytoplasm with organelles, including smooth and rough endoplasmic reticulum, ribosomes, Golgi complex, mitochondria, lysosomes, and centrioles. Endocytotic and exocytotic vesicles are included in the cell's plasma membrane.



A patient undergoing hemodialysis.

Dr. Singh and his colleagues documented significantly lower levels of serum creatinine and blood urea nitrogen in the CoQ10-treated patients, with increases in creatinine clearance and urine output regardless of patient dialysis or baseline status. More significantly, only half the number of CoQ10 patients required dialysis at the end of the study when compared to subjects receiving placebo.

The researchers also reported considerable increases in the antioxidant vitamins E and C and beta-carotene in treated subjects, while plasma levels of oxidative stress such as thiobarbituric acid reactive substances, diene conjugates, and malondialdehyde all fell dramatically.

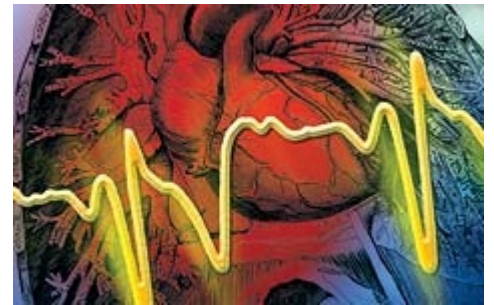
Although one in five patients did not respond, the researchers concluded that CoQ10 supplementation improves renal function in end-stage patients regardless of dialysis status, and can delay or avert the need for dialysis. They suggested that higher doses than those used in their study (180 mg per day) might result in even greater improvement and response in others.

Cardiovascular Advances

CoQ10 has been shown to be effective against chronic inflammation of the arteries and heart muscle tissue resulting in cardiac myopathy. In addition, studies by Japanese and Australian re-searchers, as well as by scientists in the US and elsewhere, have consistently shown the supplement's effectiveness against congestive heart failure and in preventing secondary cardiac events after patients have suffered an initial heart attack.

In Molecular Cell Biology, Drs. Singh and Kumar published the results of another randomized, double-blind, placebo-controlled study showing CoQ10's benefits in combating atherosclerosis, increasing survival, and reducing the risk of subsequent cardiac events in heart attack patients, including those taking lipid-lowering drugs.²

The scientists reported that among 73 patients receiving 120 mg per day of oral CoQ10 for one year after a first heart attack, the treated subjects suffered significantly fewer cardiac events than their untreated counterparts (24.6% vs. 45%). The CoQ10 group had a nearly 50% lower incidence of non-fatal heart attacks (13.7% vs. 25.3%) and significantly fewer deaths than the untreated patients.

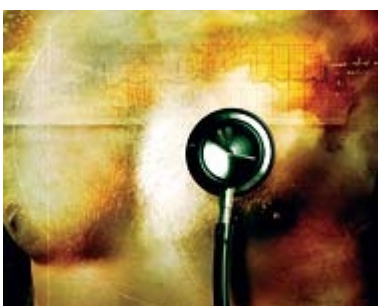


Further, the researchers found plasma levels of vitamin E and protective high-density lipoprotein (HDL) were significantly higher in CoQ10 patients, and thiobarbituric acid reactive substances, malondialdehyde, and diene con-jugates were lower than in the control group. According to Dr. Singh, it is important to note, with respect to concern over statin therapy and CoQ10 supplements, that half of the patients in each group were taking lovastatin.

Last year, Danish scientists at Copenhagen University Hospital's Heart Center, led by noted re-searcher Dr. Svende Aage Mortensen, announced the launch of a large, two-year multinational trial to "establish the future role of CoQ10 as part of a maintenance therapy in patients with chronic heart failure."³

The double-blind, multi-center trial will review morbidity and mortality data on patients with chronic heart failure taking supplemental CoQ10. In announcing the study design and endpoints in the journal *Biofactors*, which dedicated an issue to papers presented at the Third Conference of the International CoQ10 Association, Dr. Mortensen noted that double-blind, placebo-controlled trials have demonstrated the benefits of the bioenergetic antioxidant in more than 1,000 patients. Improved exercise capacity, reduced hospitalizations, and significant improvements in various hemodynamic parameters have been the "overwhelming experience," he writes, with only three of 13 studies showing neutral results.

"Thus, based on the available con-trolled data, CoQ10 is a promising, effective, and safe approach to chronic heart failure," Dr. Mortensen concluded.



Dr. Mortensen also participated in a study examining serum concentrations of CoQ10 in 99 healthy male subjects taking daily 30-mg or 100-mg supplements for one month, compared with matched controls receiving placebo.

In this randomized, double-blind trial, he and Czech scientists at the Medical Faculty Hospital in Prague ascertained the median baseline serum level of CoQ10. Supplementation with 30 mg of CoQ10 resulted in an increase in the baseline concentration of CoQ10 of 44%, while an increase of 108% was noted in the group that received 100 mg of CoQ10. These changes were significantly higher in both groups of subjects supplemented with CoQ10 compared to the group that received placebo, regardless of baseline CoQ10 levels, age, or

body weight.

Late last year, Japanese scientists at the University of Kyoto's Graduate School of Medicine add-ed further evidence that CoQ10 protects the heart muscle against acute viral myocarditis, a life-threatening infection of the heart walls.⁴

Dr. Chiharu Kishimoto and colleagues infected mice with a strain of encephalomyocarditis virus in order to measure the degree of oxidative damage and DNA injury, using thioredoxin expression and 8-hydroxy-2'-deoxyguanosine in the myocardium to measure CoQ10's benefits. The scientists found survival was about three times higher in treated mice, with significantly increased levels of CoQ10 in the heart muscles and a marked decrease in serum creatine kinase (a marker of heart muscle damage). Further, the up-regulation of myocardial thioredoxin indicating DNA damage was considerably lower in treated mice. The researchers concluded that pretreatment with CoQ10 (supplementation) can reduce the severity of viral myocarditis as well as oxidative stress and DNA damage in the myocardium.

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Statin Update

CoQ10 deficiency in muscle cell mitochondria results in poor cellular respiration. Oxidative mechanisms and endothelial cell inflammation are recognized as important factors in coronary heart disease and atherosclerosis. Evidence shows CoQ10 supplementation can improve the circulatory process and prevent such irreversible and often fatal conditions as cardiomyopathy, congestive heart failure, and rhabdomyolysis (muscle wasting induced by statin drug toxicity).⁵

Since their introduction, HMG-CoA reductase drugs (statins) have helped millions of people to lower their cholesterol levels. At the same time, however, studies have shown that statin stalwarts such as Lipitor® (atorvastatin),^{6,7} Zocor® (simvastatin),⁷ Pravacol® (pravastatin),^{7,8} and Mevacor® (lovastatin)^{8,9} can deplete natural levels of CoQ10 throughout the body.

Statins have surpassed hypertension medications in generating revenues for pharmaceutical manufacturers, accounting for an estimated \$16 billion in revenues in 2003. These are powerful drugs, but they also carry the risk of a dose-dependent decrease in the body's production of CoQ10. The FDA does not require statin manufacturers to alert patients and physicians to this potential consequence, even though many recent studies have demonstrated that CoQ10 deficits in statin users can cause cognitive, muscular, cardiovascular, and other problems. Conversely, CoQ10 supplementation can alleviate these issues in many patients, researchers have found.

Statins sold in Canada are required to carry on their labels a precautionary warning expressly stating that such CoQ10 depletion can lead to impaired cardiac functioning in patients with congestive heart failure. The US government requires no such warning, despite an emerging generation of "super-statins" (rosuvastatin, pitavastatin) that may further increase the risk and rate of CoQ10 depletion in patients taking the drugs. Schering-Plough recently introduced Zetia®, a product that quadruples the dose of first-generation statins. The FDA approved another powerful drug, Astra-Zeneca's Crestor®, in August 2003.



Canada's Health Warning on Statins

Canadian health authorities require that statins sold in Canada carry a precautionary warning regarding CoQ10 depletion. Pfizer's Lipitor® contains the following warning:

The Effect on Ubiquinone (CoQ10) Levels

"Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure . . ."

Writing in the November 2003 issue of Smart Money magazine, journalist Eleanor Laise took Pfizer to task for failing to address patients who have suffered memory loss, severe muscle pain, and other symptoms of CoQ10 depletion after taking the company's best-selling statin Lipitor®. She noted that Pfizer has thus far balked at acknowledging any association between statins, CoQ10 depletion, and serious side effects.¹⁰

While drug manufacturers and the FDA have yet to weigh in on the issue, Merck, maker of the popular Zocor®, applied for patents in 1989 and 1990 for CoQ10-simvastatin combination products. The company's 1989 patent application states that a combined statin-CoQ10 product might be effective against not only cardiomyopathy, but also elevated levels of the enzyme transaminase, which reflects liver damage. The company has thus far declined to exercise these patents, and the FDA and other major drug manufacturers have yet to acknowledge the risk of CoQ10 depletion from statins.

According to a Pfizer official quoted in the Smart Money article, the drug company has been unable to document "any specific effect" on the heart muscle during clinical trials, a surprising statement considering that several studies by respected medical researchers at the time Lipitor® was being tested warned of the cardiovascular dangers of CoQ10 depletion.

"The depletion of the essential nutrient CoQ10 by the increasingly popular cholesterol-lowering drugs HMG-CoA reductase inhibitors (statins) has grown from a level of concern to one of alarm," notes Dr. Peter Langsjoen of East Texas University,

in a comprehensive review of animal and human studies of statins and CoQ10 depletion published last year in the journal *Biofactors*.⁶ "With ever higher statin potencies and doses, and with a steadily shrinking target LDL cholesterol, the prevalence and severity of CoQ10 deficiency are increasing noticeably."

Under revised target cholesterol guidelines issued by the National Institutes of Health in 2001, as many as 36 million Americans are now candidates for therapeutic statin intervention, up from 13 million under the old guidelines. Yet the issue of CoQ10 depletion remains unresolved within the regulatory milieu that addresses side effects and warning-label requirements.

“We are currently in the midst of a congestive heart failure epidemic in the United States . . . As physicians it is our duty to be absolutely certain that we are not inadvertently doing harm to our patients by creating a widespread deficiency of a nutrient critically important to heart function,” writes Dr. Langsjoen.

Dr. Langsjoen joined Dr. Mark Silver of the Heart Failure Institute at Advocate Christ Medical Center in Oak Lawn, IL, in presenting a study design for determining whether CoQ10 levels might be used to measure myocardial diastolic function as an early marker of ventricular dysfunction.¹¹



They reasoned that statins inhibit HMG-CoA reductase, the rate-limiting step that inhibits cholesterol and CoQ10 synthesis in the liver. Because CoQ10 plays an important role during oxidative phosphorylation in the myocardial cell, evaluating CoQ10 action on ATP might be used as an early-warning indicator of potential heart problems. After a number of baseline cardiovascular and metabolic measurements are established for each subject, the researchers suggest, they would receive oral atorvastatin (Lipitor®) of 20 mg per day for three to six months, with baseline levels repeated after three and six months of treatment. Patients demonstrating reduced measurement of diastolic left ventricular function that worsened during the three to six months of statin therapy would then receive 300 mg per day for three months, with follow-up echocardiogram and blood CoQ10 level measurements. The objective would be to see if CoQ10 supplementation could reverse statin-induced heart failure.



At the University of Texas at Austin’s Biochemical Institute, researcher Dr. Flora Pettit discovered that CoQ10 may be helpful in assessing susceptibility to statin toxicity and determining which patients might benefit from CoQ10 supplementation.

She reported in the journal *Drug Metabolism and Drug Interactions* that even low levels of statins are toxic to human lymphocytes in cell cultures, adding that the patient’s own plasma reversed this toxicity in some instances.¹² Adding CoQ10 to plasma, however, was more effective than plasma alone in reversing cell toxicity in some of these patients, Pettit and colleagues found.

Coumadin® and CoQ10

While some doctors have suggested that CoQ10 might interfere with the effects of the popular blood-thinner warfarin (Coumadin®), a trial by Danish researcher Jyette Engelsen and colleagues, published in the Danish medical journal *Ugeskrift for Læger*, found no association between CoQ10 supplementation (100 mg per day) and the clinical anti-coagulant effect observed in a group of 24 patients on long-term warfarin

treatment.¹³

Moreover, the study’s randomized, double-blind, placebo-controlled, cross-over methodology presents a far more convincing argument that the risk is minimal. Nevertheless, warfarin patients are advised to consult their doctors and frequently monitor their blood test results to assess clotting time (prothrombin time/INR), especially in the first two weeks (something that is already done in most cases, the scientists noted).

Muscular Dystrophy

Muscular dystrophy patients receiving CoQ10 therapy showed significantly less cytogenetic and DNA damage than their untreated counterparts, according to a study by Dr. Lucia Migliore and colleagues at Pisa University in Italy. They compared basal levels of nuclear DNA (nDNA) damage as measured by chromosomal and DNA alterations in leukocytes in 13 patients.¹⁴

The subjects, ranging in age from 29 to 74 and presenting with several forms of muscular dystrophy, were compared with a subgroup of 10 patients who received a two-week course of ubiquinone, a CoQ10 analogue. Untreated muscular dystrophy patients showed an increased level of chromosomal damage (frequency of micronucleated lymphocytes) compared with equally matched individuals receiving CoQ10.

“Patients receiving ubiquinone showed a statistically significant reduction in the frequency of micronucleated cells after therapy, while only a slight decrease was observed in the levels of both primary DNA damage and oxidized bases,” the scientists reported in the January 2004 issue of *Mutagenesis*.



Cancer

Several interesting studies were reported on CoQ10's effects against certain cancers. Studying differences between malignant and non-malignant prostate cancer cells, Dr. Jose L. Quiles and colleagues at the University of Granada, Spain, found that malignant cells respond very differently to coenzyme Q10.¹⁵

CoQ10 supplementation significantly lowered cell growth of the PC3 cancer line without affecting non-malignant cells. The authors noted that if the findings are confirmed, they might present a "novel and interesting" approach using coenzyme Q10 in cancer therapy.

Reproduction

CoQ10 may play a role in the health of sperm cells in fighting male infertility, according to Dr. Antonio Mancini and colleagues at the Institute of Endocrinology at Catholic University of the Sacred Heart in Rome, Italy.¹⁶

In an earlier study, they found CoQ10 was present in seminal fluid and directly correlated to sperm motility in infertile men, with the exception of those with varicocele, a dilation of the pampiniform venous plexus associated with infertility.

A follow-up published in the journal *Metabolism* evaluated distribution of CoQ10 in seminal fluid and plasma in 32 varicocele patients and healthy male controls in an effort to determine whether any metabolic abnormalities played a role in various seminal parameters in varicocele patients.

The researchers reported a significantly higher proportion of CoQ10 in the seminal fluid of varicocele subjects, with high cellular CoQ10 levels correlated with low sperm concentration and motility, suggesting that such patients may be more sensitive to peroxidative damage and therefore reduced energy utilization that might then translate into defective motility. Further, the findings might indicate a possible molecular defect involved in the condition.

Females also demonstrate a reproductive protective benefit. During preeclampsia, a life-threatening disorder affecting about 7% of late-stage pregnancies, women suffer edema, hypertension, and proteinuria. Serum levels of CoQ10 are severely decreased in preeclampsia patients, reported Dr. Enrique Teran, a scientist at the University of Ecuador in Quito.¹⁷

In a study published in the journal *Free Radical and Biological Medicine*, Dr. Teran and his colleagues measured concentrations of CoQ10 in a group of 18 healthy pregnant women, 12 subjects with preeclampsia, and 22 women who were not pregnant or hypertensive. In the normal pregnant women, CoQ10 levels were significantly higher than in nonpregnant women or those with preeclampsia. The mean level of CoQ10 was 1.08 in healthy pregnant women, 0.86 in non-pregnant women, and 0.70 in women with preeclampsia.



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CoQ10 and the Brain

A study conducted by researchers at Columbia University College of Physicians and Surgeons in New York found CoQ10 deficiency in the brains of 17 patients with cerebellar ataxia and/or atrophy, suggesting an ataxic syndrome responsive to therapy with the supplement.¹⁸ The scientists examined the distribution of CoQ10 in different brain regions in animals and in one human subject before and after administering CoQ10 supplements. In experimental rats, the lowest levels of CoQ10 were found in the cerebellum, but the relative proportion was similar in the blood, organs, and tissue.

In the human subject, daily supplementation with CoQ10 increased levels in the blood and liver, but CoQ10 levels in the brain remained low in four brain regions.

Nonetheless, the findings suggest “selective vulnerability” in the cerebellum to CoQ10 depletion and its protective mechanisms, according to Drs. Ali Naini and Salvatore DiMauro.

Macular Degeneration

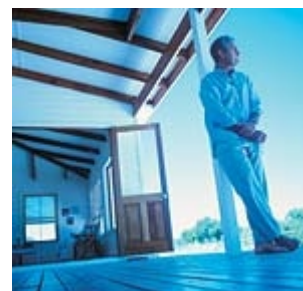
In the journal *Ophthalmologica*, Dr. Janos Feher, a researcher at the University of Rome, Italy, reported that CoQ10 may improve retinal function in patients with age-related macular degeneration by improving the performance of mitochondria in the retinal pigment epithelium.¹⁹

Dr. Feher and associates treated 14 patients diagnosed with early age-related macular degeneration using a preparation that included CoQ10, acetyl-L-carnitine, polyunsaturated fatty acids, and vitamin E. A matched control group received vitamin E alone. A number of tests were then performed at 3, 6, 9, 12, and 24 months.

In patients receiving the CoQ10 mixture, all functions were slightly improved after three months and remained level throughout the two-year study period, while degeneration and visual function among participants in the control group continued to slowly decline.

Parkinson's Disease

In a study of Parkinson's disease patients, 360 mg a day of CoQ10 was administered for only four weeks, producing a mild symptomatic improvement compared to placebo. More important, an established clinical test to measure Parkinson's symptom function showed significantly better improvement of performance in the CoQ10-supplemented patients compared with the placebo group.²⁰



This new study helped to corroborate a report last year that Parkinson's patients consuming 1200 mg a day of CoQ10 showed a 44% reduction in the decline of motor skills, movement, and mental function compared to the placebo group. Those receiving this high-dose CoQ10 also demonstrated an improved ability to perform daily living tasks. This 16-month study was remarkable in that CoQ10 slowed the progression of the disease, something that Parkinson's drugs do not do.²¹

Conclusion

As the many studies outlined in this article show, biomedical researchers are discovering that CoQ10 shows promising effects against disorders as far-ranging as kidney failure, heart disease, muscular dystrophy, and macular degeneration. Despite the ever-growing number of clinical trials attempting to unlock CoQ10's disease-preventing capabilities, widespread acceptance of CoQ10 by mainstream medical practitioners and federal health regulators continues to lag far behind the research findings. As larger and more varied studies of CoQ10 are undertaken and the results disseminated, the day when this critical nutrient gains the attention it deserves appears to be drawing ever nearer.

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