

INTRODUCTION TO COENZYME Q10

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Coenzyme Q10 (CoQ 10) or ubiquinone is essentially a vitamin or vitamin-like substance. Disagreements on nomenclature notwithstanding, vitamins are defined as organic compounds essential in minute amounts for normal body function acting as coenzymes or precursors to coenzymes. They are present naturally in foods and sometimes are also synthesized in the body. CoQ10 likewise is found in small amounts in a wide variety of foods and is synthesized in all tissues. The biosynthesis of CoQ10 from the amino acid tyrosine is a multistage process requiring at least eight vitamins and several trace elements. Coenzymes are cofactors upon which the comparatively large and complex enzymes absolutely depend for their function. Coenzyme Q10 is the coenzyme for at least three mitochondrial enzymes (complexes I, II and III) as well as enzymes in other parts of the cell. Mitochondrial enzymes of the oxidative phosphorylation pathway are essential for the production of the high-energy phosphate, adenosine triphosphate (ATP), upon which all cellular functions depend. The electron and proton transfer functions of the quinone ring are of fundamental importance to all life forms; ubiquinone in the mitochondria of animals, plastoquinone in the chloroplast of plants, and menaquinone in bacteria. The term "bioenergetics" has been used to describe the field of biochemistry looking specifically at cellular energy production. In the related field of free radical chemistry, CoQ10 has been studied in its reduced form (Fig. 1) as a potent antioxidant. The bioenergetics and free radical chemistry of CoQ10 are reviewed in Gian Paolo Littarru's book, *Energy and Defense*, published in 1994(1).

HISTORY

CoQ10 was first isolated from beef heart mitochondria by Dr. Frederick Crane of Wisconsin, U.S.A., in 1957 (2). The same year, Professor Morton of England defined a compound obtained from vitamin A deficient rat liver to be the same as CoQ10(3). Professor Morton introduced the name ubiquinone, meaning the ubiquitous quinone. In 1958, Professor Karl Folkers and coworkers at Merck, Inc., determined the precise chemical structure of CoQ10: 2,3 dimethoxy-5 methyl-6 decaprenyl benzoquinone (Fig. 1), synthesized it, and were the first to produce it by fermentation. In the mid-1960's, Professor Yamamura of Japan became the first in the world to use coenzyme Q7 (a related compound) in the treatment of human disease: congestive heart failure. In 1966, Mellors and Tappel showed that reduced CoQ6 was an effective

antioxidant (4,5). In 1972 Gian Paolo Littarru of Italy along with Professor Karl Folkers documented a deficiency of CoQ10 in human heart disease (6). By the mid-1970's, the Japanese perfected the industrial technology to produce pure CoQ10 in quantities sufficient for larger clinical trials. Peter Mitchell received the Nobel Prize in 1978 for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory, which includes the vital protonmotive role of CoQ10 in energy transfer systems (7,8,9,10).

In the early 1980's, there was a considerable acceleration in the number and size of clinical trials. These resulted in part from the availability of pure CoQ10 in large quantities from pharmaceutical companies in Japan and from the capacity to directly measure CoQ10 in blood and tissue by high performance liquid chromatography. Lars Ernster of Sweden, enlarged upon CoQ10's importance as an antioxidant and free radical scavenger (11). Professor Karl Folkers went on to receive the Priestly Medal from the American Chemical Society in 1986 and the National Medal of Science from President Bush in 1990 for his work with CoQ10 and other vitamins.

COENZYME Q10 DEFICIENCY

Normal blood and tissue levels of CoQ10 have been well established by numerous investigators around the world. Significantly decreased levels of CoQ10 have been noted in a wide variety of diseases in both animal and human studies. CoQ10 deficiency may be caused by insufficient dietary CoQ10, impairment in CoQ10 biosynthesis, excessive utilization of CoQ10 by the body, or any combination of the three. Decreased dietary intake is presumed in chronic malnutrition and cachexia(12).

The relative contribution of CoQ10 biosynthesis versus dietary CoQ10 is under investigation. Karl Folkers takes the position that the dominant source of CoQ10 in man is biosynthesis. This complex, 17 step process, requiring at least seven vitamins (vitamin B2 - riboflavin, vitamin B3 - niacinamide, vitamin B6, folic acid, vitamin B12, vitamin C, and pantothenic acid) and several trace elements, is, by its nature, highly vulnerable. Karl Folkers argues that suboptimal nutrient intake in man is almost universal and that there is subsequent secondary impairment in CoQ10 biosynthesis. This would mean that average or "normal" levels of CoQ10 are really suboptimal and the very low levels observed in advanced disease states represent only the tip of a deficiency "ice berg".

HMG-CoA reductase inhibitors used to treat elevated blood cholesterol levels by blocking cholesterol biosynthesis also block CoQ10 biosynthesis(13). The resulting lowering of blood CoQ10 level is due to the partially shared biosynthetic pathway of CoQ10 and cholesterol. In patients with heart failure this is more than a laboratory observation. It has a significant harmful effect which can be negated by oral CoQ10 supplementation(14).

Increased body consumption of CoQ10 is the presumed cause of low blood CoQ10 levels seen in excessive exertion, hypermetabolism, and acute shock states. It is likely that all three mechanisms (insufficient dietary CoQ10, impaired CoQ10 biosynthesis, and excessive utilization of CoQ10) are operable to varying degrees in most cases of observed CoQ10 deficiency.

TREATMENT OF HEART DISEASE WITH COENZYME Q10

CoQ10 is known to be highly concentrated in heart muscle cells due to the high energy requirements of this cell type. For the past 14 years, the great bulk of clinical work with CoQ10 has focused on heart disease. Specifically, congestive heart failure (from a wide variety of causes) has been strongly correlated with significantly low blood and tissue levels of CoQ10 (15). The severity of heart failure correlates with the severity of CoQ10 deficiency (16). This CoQ10 deficiency may well be a primary etiologic factor in some types of heart muscle dysfunction while in others it may be a secondary phenomenon. Whether primary, secondary or both, this deficiency of CoQ10 appears to be a major treatable factor in the otherwise inexorable progression of heart failure.

Pioneering trials of CoQ10 in heart failure involved primarily patients with dilated weak heart muscle of unknown cause (idiopathic dilated cardiomyopathy). CoQ10 was added to standard treatments for heart failure such as fluid pills (diuretics), digitalis preparations (Lanoxin), and ACE inhibitors. Several trials involved the comparison between supplemental CoQ10 and placebo on heart function as measured by echocardiography. CoQ10 was given orally in divided doses as a dry tablet chewed with a fat containing food or an oil based gel cap swallowed at mealtime. Heart function, as indicated by the fraction of blood pumped out of the heart with each beat (the ejection fraction), showed a gradual and sustained improvement in tempo with a gradual and sustained improvement in patients' symptoms of fatigue, dyspnea, chest pain, and palpitations. The degree of improvement was occasionally dramatic with some patients developing a normal heart size and function on CoQ10 alone. Most of these dramatic cases were patients who began CoQ10 shortly after the onset of congestive heart failure. Patients with

more established disease frequently showed clear improvement but not a return to normal heart size and function.

Internationally, there have been at least nine placebo controlled studies on the treatment of heart disease with CoQ10: two in Japan, two in the United States, two in Italy, two in Germany, and one in Sweden (17,18,19,20,21,22,23,24,25). All nine of these studies have confirmed the effectiveness of CoQ10 as well as its remarkable safety. There have now been eight international symposia on the biomedical and clinical aspects of CoQ10 (from 1976 through 1993 (26,27,28,29,30,31,32,33)). These eight symposia comprised over 300 papers presented by approximately 200 different physicians and scientists from 18 different countries. The majority of these scientific papers were Japanese (34%), with American (26%), Italian (20%) and the remaining 20% from Sweden, Denmark, Germany, United Kingdom, Belgium, Australia, Austria, France, India, Korea, Netherlands, Poland, Switzerland, USSR, and Finland. The majority of the clinical studies concerned the treatment of heart disease and were remarkably consistent in their conclusions: that treatment with CoQ10 significantly improved heart muscle function while producing no adverse effects or drug interactions.

It should be mentioned that a slight decrease in the effectiveness of the blood thinner, coumadin, was noted in a case by a Norwegian clinician (34). This possible drug - CoQ10 interaction has not been observed by other investigators even when using much higher doses of CoQ10 for up to seven years and involving 25 patients treated with coumadin concomitantly with CoQ10 (this is still, as of this date, unpublished data).

The efficacy and safety of CoQ10 in the treatment of congestive heart failure, whether related to primary cardiomyopathies or secondary forms of heart failure, appears to be well established (35,36,37,38,39, 40,41,42). The largest study to date is the Italian multicenter trial, by Baggio et al., involving 2664 patients with heart failure (43).

The most recent work in heart failure examined the effect of CoQ10 on diastolic dysfunction, one of the earliest identifiable signs of myocardial failure that is often found in mitral valve prolapse, hypertensive heart disease and certain fatigue syndromes (44,45). Diastolic dysfunction might be considered the common denominator and a basic cause of symptoms in these three diagnostic groups of disease. Diastole is the filling phase of the cardiac cycle. Diastolic function has a larger cellular energy requirement than the systolic contraction and, therefore, the process of diastolic relaxation is more highly energy dependent and thus more highly dependent on CoQ10. In simpler

terms, it takes more energy to fill the heart than to empty it. Diastolic dysfunction is a stiffening' of the heart muscle which interferes with the heart's ability to function as an effective pump. It is seen early in the course of many common cardiac disorders and is demonstrable by echocardiography. This stiffening returns towards normal with supplemental CoQ10 in tempo with clinical improvement.

It is important to note that in all of the above clinical trials, CoQ10 was used in addition to traditional medical treatments, not to their exclusion. In one study by Langsjoen et al (46), of 109 patients with essential hypertension, 51% were able to stop between one and three antihypertensive drugs at an average of 4.4 months after starting CoQ10 treatment while the overall New York Heart Association (NYHA) functional class improved significantly from a mean of 2.40 to 1.36. Hypertension is reduced when diastolic function improves. In another study(39), there was a gradual and sustained decrease in dosage or discontinuation of concomitant cardiovascular drug therapy: Of 424 patients with cardiovascular disease, 43% were able to stop between one and three cardiovascular drugs with CoQ10 therapy. The authors conclude that the vitamin-like substance, CoQ10, "may be ushering in the new era of cellular/biochemical treatment of disease, complementing and extending the systems-oriented, macro and microscopic approach that has served us well to this point".

FREQUENTLY ASKED QUESTIONS

Over the past several years, there has been a steady increase in public interest and awareness of nutritional supplements and vitamins. Along with this accelerated interest has come an understandable explosion in the number and complexity of questions raised by patients about vitamins in general. By and large, these questions are quite difficult to answer. I personally am frequently asked the following questions:

1. What is CoQ10?

It is a fat-soluble vitamin-like substance present in every cell of the body and serves as a coenzyme for several of the key enzymatic steps in the production of energy within the cell. It also functions as an antioxidant which is important in its clinical effects. It is naturally present in small amounts in a wide variety of foods but is particularly high in organ meats such as heart, liver and kidney, as well as beef, soy oil, sardines, mackerel, and peanuts. To put dietary CoQ10 intake into perspective, one pound of sardines, two pounds of beef, or two and one half pounds of peanuts, provide 30 mg of CoQ10. CoQ10 is also

synthesized in all tissues and in healthy individuals normal levels are maintained both by CoQ10 intake and by the body's synthesis of CoQ10. It has no known toxicity or side effects.

2. Should I take CoQ10?

This question can be asked in two ways. First, should a reasonably healthy person take CoQ10 to stay healthy or to become more robust? At present I do not believe anyone knows the answer to this question. Second, should a person with an illness such as congestive heart failure take CoQ10? As with any change in nutrition, diet, medication, or even activity, CoQ10 should be discussed with one's physician. As improvement in heart function occurs, a patient should have regular medical follow up with particular attention to concomitant drug therapy. The attached references will provide detailed information on the clinical use of CoQ10 and can be obtained from any good medical library.

3. What is the dosage of CoQ10?

The dosage of CoQ10 used in clinical trials has evolved over the past 20 years. Initially, doses as small as 30 to 45 mg per day were associated with measurable clinical responses in patients with heart failure. More recent studies have used higher doses with improved clinical response, again in patients with heart failure. Most studies with CoQ10 involve the measurement of the level of CoQ10 in blood. CoQ10 shows a moderate variability in its absorption, with some patients attaining good blood levels of CoQ10 on 100 mg per day while others require two or three times this amount to attain the same blood level. All CoQ10 available today in the United States is manufactured in Japan and is distributed by a number of companies who place the CoQ10 either in pressed tablets, powder-filled capsules, or oil-based gelcaps. CoQ10 is fat-soluble and absorption is significantly improved when it is chewed with a fat-containing food. Published data on the dosage of CoQ10 relates almost exclusively to the treatment of disease states. There is no information on the use of CoQ10 for prevention of illness. This is an extremely important question which, to date, does not have an answer.

4. If CoQ10 is so effective in the treatment of heart failure, why is it not more generally used in this country?

The answer to this question is found in the fields of politics and marketing and not in the fields of science or medicine. The controversy surrounding CoQ10 likewise is political and economic as the previous 30 years of research on

CoQ10 have been remarkably consistent and free of major controversy. Although it is not the first time that a fundamental and clinically important discovery has come about without the backing of a pharmaceutical company, it is the first such discovery to so radically alter how we as physicians must view disease. While the pharmaceutical industry does a good job at physician and patient education on their new products, the distributors of CoQ10 are not as effective at this. This education is very costly and can only be done with the reasonable expectation of patent protected profit. CoQ10 is not patentable. The discovery of CoQ10 was based primarily on support from the National Heart Institute of NIH (National Institute of Health) at the Institute for Enzyme Research, University of Wisconsin.

THE FUTURE OF COENZYME Q10

In the past 50 years the driving force in medicine has been the development of drugs and procedures to modify the pathophysiology of illness. As viewed from the trenches of medical practice, the advances in drug therapy, although notable and clearly helpful, appear to have reached a plateau. Most of the "new" drugs over the past several years are primarily variants of old drugs. By comparison, the impressive advances made by basic scientists, biochemists, and molecular biologists, are only now beginning to be appreciated by the medical profession, and the enormous potential of these basic science advances has yet to be pursued.

Modern medicine seems to be based on an "attack strategy", a philosophy of treatment formed in response to the discovery of antibiotics and the development of surgical/anesthetic techniques. Disease is viewed as something that can be attacked selectively - with antibiotics, chemotherapy, or surgery - assuming no harm to the host. Even chronic illnesses, such as diabetes and hypertension, yield simple numbers which can be furiously assaulted with medications. Amidst the miracles and drama of 20th century medicine we may have forgotten the importance of host support, as if time borrowed with medications and surgery were restorative in and of itself. Yet, in this age, a patient may be cured of leukemia through multiple courses of chemotherapy and bone marrow transplantation, only to die slowly of unrecognized thiamine (vitamin B1) deficiency(47). Like the vitamins discovered in the early part of this century, CoQ10 is an essential element of food that can now be used medicinally to support the sick host in conditions where nutritional depletion and cellular dysfunction occur. Surely, the combination of disease attacking strategy and host supportive treatments would yield much better results in clinical medicine.

Since CoQ10 is essential to the optimal function of all cell types, it is not surprising to find a seemingly diverse number of disease states which respond favorably to CoQ10 supplementation. All metabolically active tissues are highly sensitive to a deficiency of CoQ10. CoQ10's function as a free radical scavenger only adds to the protean manifestations of CoQ10 deficiency. Preliminary observations in a wide variety of disease states have already been published (48,49,50,51,52,53,54,55,56,57,58).

One of the disease states which has received attention is cancer. Low levels of CoQ10 in the blood of some cancer patients have been noted (59), but overall, there is little data regarding cancer. The best work to date documents a significant reduction in the cardiac toxicity of the chemotherapy drug, Adriamycin (52,53,54). The cardiac toxicity of Adriamycin and related drugs may well relate to free radical generation and this might explain the benefit of CoQ10 in its capacity as a free radical scavenger. The studies on Adriamycin cardiotoxicity were of short duration and did not specifically note any favorable or detrimental effect on the clinical course of the cancer itself. It is reasonable to assume that optimal nutrition (which would include optimal levels of CoQ10) is generally beneficial in any disease state, including cancer.

Another interesting topic is the relationship between the immune system and CoQ10. Immune function is extraordinarily complex and undoubtedly is influenced by numerous nutritional variables. There are some encouraging preliminary data from the study of AIDS patients (50,51). End stage AIDS, like other overwhelming illnesses, has been associated with a significant deficiency in CoQ10. Regarding AIDS and cancer, it would be foolish to make premature statements about future utility of CoQ10, but it is even more foolish to ignore the importance of adequate CoQ10 levels in these disease states. Adequate CoQ10 supplementation (with close attention to plasma CoQ10 levels) is analogous to adequate hydration, and any treatment of critically ill patients should not ignore this easily measured and correctable deficiency.

The antioxidant or free radical quenching properties of CoQ10 serve to greatly reduce oxidative damage to tissues as well as significantly inhibit the oxidation of LDL cholesterol (much more efficiently than vitamin E) (60,61). This has great implications in the treatment of ischemia and reperfusion injury as well as the potential for slowing the development of atherosclerosis. In keeping with the free radical theory of aging, these antioxidant properties of CoQ10 have clear implications in the slowing of aging and age related degenerative diseases. There is epidemiologic evidence in humans that uniformly shows a gradual decline in CoQ10 levels after the age of twenty.

Until recently, attention has been focused on requirements for CoQ10 in energy conversion in the mitochondrial compartment of cells or on the antioxidant properties of CoQ10. New evidence shows that CoQ10 is present in other cell membranes. In the outer membrane it may contribute to the control of cell growth, especially in lymphocytes (the implications are far reaching (62,63,64,65)). The clinical experience with CoQ10 in heart failure is nothing short of dramatic, and it is reasonable to believe that the entire field of medicine should be re-evaluated in light of this growing knowledge. We have only scratched the surface of the biomedical and clinical applications of CoQ10 and the associated fields of bioenergetics and free radical chemistry.

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