Coenzyme Q10: A Novel Cardiac Antioxidant

Debasis Bagchi, Ph.D., FACN[1]

Introduction

The heart is the most susceptible of all the organs to premature aging and free radical oxidative stress.[1-4] Clinical research has clearly documented the role of oxidative stress and free radical-induced tissue injury and the progression of numerous degenerative diseases, particularly cardiovascular disease.[1-4] This may be the result of acute ischemia-reperfusion injury, endothelial damage of hyperhomocysteinemia, as well as chronic oxidative damage secondary to lipid peroxidation.[2,4]

Coenzyme Q10: History and Development

Coenzyme Q10, a lipid soluble benzoquinone, has been demonstrated to possess excellent antioxidant and membrane stabilizing properties in the cardiac tissues[5]. Coenzyme Q10 was first isolated in pure form by Professor F. L. Crane and his group at the University of Wisconsin in 1957.[6] The well known medicinal chemist Dr. Karl Folkers re-isolated coenzyme Q10 from beef muscle, characterized and elucidated its structure, and synthesized the pure compound by fermentation.[7,8] He further demonstrated that this compound is no way less than an essential vitamin supplement for the maintenance of cardiovascular and immunological health.[7-9] In 1960, Dr. Folkers hypothesized that Coenzyme Q10 was essential to the body's production of energy in the form of adenosine triphosphate (ATP).[7,8] Furthermore, Dr. Folkers established his hypothesis that all vitamins as well as Coenzyme Q10 are components of the enzyme or antioxidant complexes involved in respiration and are absolutely essential for human life.[8]

1.Pharmaceutical & Administrative Sciences, Creighton University School of Pharmacy & Allied Health Professions, 2500 California Plaza, Omaha, NE 68178

Coenzyme Q10 has been used as nutritional supplements for humans in Japan since the mid-1960s to treat cardiovascular dysfunctions. Their results were overwhelming positive. It is now distributed in Japan under the name of "ubidecarenone," and has become one of the top six pharmaceuticals consumed in Japan. Today, a large fraction of Japanese include Coenzyme Q10 in their nutritional regimen. Later, Coenzyme Q10 was introduced in the United States as a nutritional supplement.

Coenzyme Q10: Occurrence and Chemistry

Coenzyme Q10 is a naturally occurring nutrient which occurs in beef muscle, beef heart and eggs.[10] Unfortunately, these items are also high in cholesterol and saturated fat. Coenzyme Q10 occurs in lesser quantities in spinach, grains, beans and specific oils. With aging, the body loses its ability to assimilate and synthesize sufficient Coenzyme Q10 from foods. Since, the supplementation of Coenzyme Q10 is usually inadequate from natural sources, researchers and doctors recommend Coenzyme Q10 as the preferred source of supplementation. Bliznakov has demonstrated[9] that aged mice exhibit an abnormally low content of Coenzyme Q10 in the thymus and the size of the thymus is abnormally small. However, with Coenzyme Q10 supplementation, the shrinking of the thymus was reduced and the average lifespan of the mice was significantly extended.[7,8] Folkers *et al.*[7,8] studied eight aging patients under treatment with Coenzyme Q10 for heart and blood vessel disease, diabetes and cancer. The study revealed that after the patients received Coenzyme Q10, seven of the eight showed an elevated increase in

antibody levels.[7] Similar findings were demonstrated by the researchers of the Osaka University Medical School, Japan.[7-11] Furthermore, it has been demonstrated by Scientists that people afflicted with cancer and heart disease have an alarmingly low supply of Coenzyme Q10.[5-10] Thus, it is very important to supplement Coenzyme Q10. In an article published by the Linus Pauling Institute of Science and Medicine, it has been stated that supplementation of Coenzyme Q10 strengthens the heart, even without exercise; normalizes blood pressure; elevates energy levels, and contributes to life extension. Other studies have indicated that supplementation of Coenzyme Q10 can replenish depleted Coenzyme Q10 stores, increase stamina and energy, and heighten the effectiveness of the immune system.

Coenzyme Q10: Bioavailability and Health Benefits

The human body is made of trillions of cells. Each individual cell performs various vital biochemical functions of the body. Thus, without the production of energy at the cellular level, life cannot exist. Coenzyme Q10 acts as the catalyst that allows the body to produce energy at the cellular level. This energy enhances the immune system, the body's primary line of defense against disease. Without adequate enhancement, the immune system can no longer prevent illness. Coenzyme Q10, also known as ubiquinone, is a naturally occurring substance that is essential component of the mitochondrial respiratory chain where aerobic energy is produced.[5-8] It is an important regulator of the cardiovascular system. Nutritional researchers describe coenzyme Q10 as a restorative for homeostasis in the heart and blood vessels.[9-11]

Coenzyme Q10 is indispensable to biochemical mechanisms of bioenergetics, and it has a specific role as an antioxidant,[5-11] Coenzyme Q10 has demonstrated a hematological activity for the human and has shown an influence on the host defense system. Coenzyme Q10 potentiates transplasma membrane electron transport system which influences healthy tissue regeneration, cell growth and viability.[12,13] The human species is not genetically adapted to survive past middle age, and it appears that supplementation of Coenzyme Q10 and other antioxidants is required to ensure a more healthy, elderly population.[8-11] Coenzyme Q10 has been identified to have a profound beneficial effects in the following areas.[8-11]

1) Acts as a novel antioxidant
2) Enhances stamina, endurance and energy levels
3) Helps to reduce body weight
4) Normalizes blood pressure
5) Attenuates immune function
6) Protects against cardiovascular dysfunction
7) Reverses periodontal disease
8) Increases effectiveness of various chemotherapeutic agents and anti-malarial drugs

Coenzyme Q10: Recent Clinical Observations

The cardioprotective abilities of Coenzyme Q10 have been extensively documented. Furthermore, the following data and knowledge have recently been gathered from biochemical, biomedical and clinical research on Coenzyme Q10:

Coenzyme Q10 Supplementation Protects Lipoprotein Lipids, and Induces Energy Conserving and Free Radical Scavenging Properties in Humans.[14,15]

Coenzyme Q10 supplementation to 22 human volunteers resulted in a higher plasma level of reduced Coenzyme Q10, significant decrease in hydroperoxide level and a decreased lipid peroxidation level, but sparing of other plasma antioxidants (i.e. vitamin C and vitamin E) was not observed. Coenzyme Q10 has been shown to protect lipoprotein lipids against free radical-induced oxidative damage. Low density lipoproteins (LDL) isolated from Coenzyme Q10 supplemented volunteers

are more resistant to oxidative damage induced by free radicals. Coenzyme Q10 has been demonstrated to protect isolated enzymes and erythrocyte membrane bound enzymes from the inactivating effect of free radicals. Following Coenzyme Q10 supplementation, all the three LDL subfractions namely LDL_1 LDL_2 and LDL_3, had significantly increased Coenzyme Q10 levels. Thus, Coenzyme Q10 endowment in the subfractions of LDL affects their oxidizability, and have important implications for the treatment of diseases. Coenzyme Q10 has also been demonstrated to protect very low density lipoprotein (VLDL) against free radical induced injury. These data have important implications for the development of new strategies for daily supplementation of Coenzyme Q10 for the amelioration of the energy decline that occurs in mitochondrial disease and during the human aging process.

Breast Cancer and Regression of Metastases with Coenzyme Q10 Therapy[16]:

Coenzyme Q10 has been shown to overt complete regression of the tumors in five cases of breast cancer. Conventional protocol of this therapy included a daily oral dosage of 390 mg of Coenzyme Q10 during the complete trials over 3-5 years. The numerous metastases in the liver of a 44-year-old patient disappeared and no signs of metastases were found elsewhere following treatment with Coenzyme Q10. A 49-year-old patient, on a dosage of 390 mg of Coenzyme Q10, revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma on one breast, after lumpectomy and 390 mg of Coenzyme Q10 therapy, showed no cancer in the tumor bed or metastases.

Muscular Dystrophies and Neurogenic Atrophies with Coenzyme Q10 Therapy[17,18]

Clinical trials were conducted with 27 patients, ranging from 7-69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and the Welander disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored. Coenzyme Q10 was shown to definitely improve the physical performance of these patients. In retrospect, a dosage of 100 mg was too low, although effective and safe. Clinicians recommended that patients suffering from these muscle dystrophies and the like should be treated with Coenzyme Q10 indefinitely. Coenzyme Q10 was also found to be therapeutically beneficial in the improvement in soleus muscle function in animals.

Retinal Degeneration and Coenzyme Q10 Supplementation[19]

Coenzyme Q10 can improve mitochondrial functionality in the brain and skeletal muscle of patients with retinitis pigmentosa (retinal degeneration disease). Oral supplementation of Coenzyme Q10 (100 mg/day) to the patients with retinitis pigmentosa resulted in a larger brain energy reserve capacity.

Human Seminal Fluid and Coenzyme Q10 Therapy[20]

Clinical data suggest a pathophysiological role of Coenzyme Q10 in human seminal fluid and a molecular defect in the spermatozoa of varicocele or infertile patients. Coenzyme Q10 measurement in seminal fluid may represent an important examination in infertile patients. Coenzyme Q10 supplementation has been suggested as a possible treatment of dyspermic patients.

The Activities of Coenzyme Q10 on Immune Response:[21,22]

The blood levels of IgG and T_4-lymphocytes increased significantly following supplementation of Coenzyme Q10 and vitamin B_6 to humans. Increases of

IgG and T_4-lymphocytes levels indicate boosting of the immune system. The increasing ratios of T_4/T_8 lymphocytes in the human following treatment with Coenzyme Q10 constitute a rationale for new clinical trials on treating patients with AIDS, ARC and diverse malignancies with Coenzyme Q10

These findings definitely warrant the importance of daily supplementation of Coenzyme Q10 to humans, which has a broad spectrum of nutritional and therapeutic potential.

Coenzyme Q10: New Findings

The major target of free radicals include lipids, proteins and biological macromolecules, antioxidant enzymes and DNA. Since various cardiac disorders are associated with oxidative stress, we have recently evaluated[23] ethanol-induced oxidative stress and DNA damage in cultured cardiac cells *in vitro*, and determined the protective ability of Coenzyme Q10. In a recent study, we have isolated and cultured cardiac cells from fertile chicken eggs, and assessed the concentration-dependent cardioprotective ability of Coenzyme Q10 in ethanol-induced enhanced lipid peroxidation and DNA damage in cultured cardiac cells. Lipid peroxidation was determined based on the formation of thiobarbituric acid reactive substances (TBARS), while DNA damage was determined by quantitating DNA fragmentation. Ethanol-induced enhanced production of free radicals including superoxide anion and hydroxyl radicals, were determined by cytochrome c reduction and HPLC assay, and the protective ability of Coenzyme Q10 was assessed. Furthermore, ethanol-induced changes in cell morphology and modulation of intracellular oxidized states in cultured cardiac cells were measured by laser scanning confocal microscopy. DNA fragmentation and laser scanning confocal microscopic techniques have recently been considered as markers of apoptopic cell death. Our results indicate that Coenzyme Q10 can significantly ameliorate ethanol-induced oxidative stress and pathophysiology in cultured cardiac cells.

In a separate series of experiment, we have assessed the *in vivo* cardioprotective ability of Coenzyme Q10.[24] Since ischemia and reperfusion are associated with the development of oxidative stress and lipid peroxidation, and free radical scavengers/antioxidants have been shown to be beneficial for ischemic myocardium, we hypothesized that stimulation of Coenzyme Q10 may protect hearts from ischemia-reperfusion injury. To test this hypothesis, a group of adult pigs were fed Coenzyme Q10-supplemented diet for four weeks, while another group of pigs were fed regular diets for the same period of time. Normothermic regional ischemia was induced for 60 minutes by LAD occlusion followed by 60 minutes of reperfusion. The effects of Coenzyme Q10 were evaluated by measuring left ventricular functions and creatine kinase (CK) and malondialdehyde (MDA) releases as well as by assessing the infarct size. Coenzyme Q10 improved the systolic and diastolic function in the postischemic hearts and reduced CK and MDA release suggesting lowering of tissue injury and oxidative stress. Infarct size of the LAD region was also reduced by Coenzyme Q10 supplementation. Measurement of Coenzyme Q10 in hearts revealed an increased amount of Coenzyme Q10 in mitochondria in the Coenzyme Q10-supplemented animals compared to that of control. The results of this study demonstrated an increased amount of Coenzyme Q10 in mitochondria in the Coenzyme Q10-supplemented animal in concert with reduced formation of malondialdehyde, a presumptive biomarker for lipid peroxidation, and improved post-ischemic ventricular recovery. Thus, Coenzyme Q10 salvaged the pig hearts from ischemia reperfusion injury by reducing the oxidative stress. Furthermore, Coenzyme Q10 supplementation has been

demonstrated to upregulate ubiquitin gene expression in the cardiac tissues of Coenzyme Q10-supplemented animals. The size of the three different transcripts are UbA 1.3 kb, UbB 2.5 kb and UbC 3.5 kb. Upregulation of ubiquitin gene expression in the hearts of Coenzyme Q10-supplemented animals definitely predicts a superior cardioprotection through Coenzyme Q10 supplementation.

Coenzyme Q10: Mechanism of Cytoprotection

Coenzyme Q10 possesses antioxidant and as well as excellent membrane stabilizing properties.[10] Through its antioxidant capacity, Coenzyme Q10 would act as an oxygen radical scavenger whenever oxygen free radicals are generated. In addition, exogenous Coenzyme Q10 has been shown to be inhibitory to the cellular phospholipases responsible for degrading cell membranes.[11] Exogenous administration of Coenzyme Q10 has been shown to be a potent blocker of lipid peroxidation.[5] Coenzyme Q10 is a potent antioxidant and in its reduced form, ubiquinol, acts as a free radical scavengers.

Bioenergetic mechanisms have established that heart failure is caused by predominant deficiency or systemic dysfunctions of Coenzyme Q10. It can also enhance cardiac functional recovery by reducing intracellular Ca^{2+} overloading,[25] It has been reported that Coenzyme Q10 therapy reverses the myocardial Coenzyme Q10 deficiency in patients with ischemic heart disease.[26] Evidence also exists that myocardial Coenzyme Q10 is deficient in patients with congestive heart failure and that the supplementation of Coenzyme Q10 benefits such patients.[27] In a recent study, Weber *et al.*[28] demonstrated that following a supplementation of Coenzyme Q10 for one week the total amount of plasma Coenzyme Q10 increased significantly while the redox status (reduced CoQ10/total CoQ10) remained constant. The levels of lipid peroxidation decreased significantly during the first two weeks of Coenzyme Q10 administration. The decrease of lipid peroxidation and the presence of the majority of the orally supplemented Coenzyme Q10 in the reduced form in plasma seem to strengthen the antioxidant role of Coenzyme Q10 in blood plasma.[28] Two different mechanisms of Coenzyme Q10 antioxidant function are known to exist:

1. It may act independently as chain-breaking antioxidants, providing hydrogen atoms to reduce peroxyl and/or alkoxyl radicals; and/or
2. A redox interaction may exist between Coenzyme Q10 and another lipid soluble antioxidant such as alpha-tocopherol, in its one-electron oxidized form, vitamin E phenoxyl radical.

It has now been widely recognized that Coenzyme Q10 (ubiquinone), in addition to its function as a component of the respiratory chain, acts in its reduced form (ubiquinol) as an antioxidant. It has been demonstrated that ubiquinol is the only known lipid soluble antioxidant that is synthesized *de novo* in living cells and for which there exist enzymic mechanisms by which it can be maintained in the reduced state. Ubiquinone, partly in the reduced form, has been shown to occur in various types of cellular membranes as well as in low-density lipoprotein. Ubiquinol has been shown to protect membrane phospholipids and low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) from lipid peroxidation.[29] Ubiquinol is also known to potentiate the effect of vitamin E by regenerating vitamin E from its oxidized form.[30] Exogenous Coenzyme Q10 has been shown to be inhibitory to the cellular phospholipase responsible for degrading cell membranes. In studies with beef heart submitochondrial fractions it has been demonstrated that endogenous ubiquinol prevents lipid peroxidation induced by ascorbate and

ADP-Fe^{3+}, and that this effect is independent of the presence of vitamin E.[31] Supplementation of Coenzyme Q10 has been shown to be a potent blocker of lipid peroxidation in biological systems.[24,31] Coenzyme Q10 is thus a potent antioxidant and in its reduced form, ubiquinol, acts as a free radical scavenger[8-11].

In mitochondria, Coenzyme Q10 acts as a mobile distributor of reducing equivalents between the NADH dehydrogenase, succinate dehydrogenase, and cytochrome b-c_1 segment of the electron transport chain and as participants of the proton motive Q cycle responsible for the transfer of protons across the coupling membrane.[8-12]

Conclusion

These findings indicate a close relationship between oxidative tissue injury, lipid peroxidation and modulation of integral membrane proteins in the mitochondrial inner membrane, and an important role of endogenous ubiquinol in attenuating these effects. The physiological implications of these results may not necessarily be restricted to the inner mitochondrial membrane, because it is well established that protein modification accompanying lipid peroxidation and DNA damage can also occur in other biological membranes and cellular sites, as well as in serum low density lipoprotein (LDL), and that ubiquinol is present in all of these locations and serve as a potent antioxidant.

Thus, Coenzyme Q10 has been identified as a novel antioxidant and a "miracle" nutrient. Because of its ability to boost the human immune system, extensive research continues apace in the fields of myocardial ischemia-reperfusion injury, congestive heart failure, diabetes, transplant surgeries, coronary angioplasty, muscular dystrophies and neurogenic atrophies, retinal degeneration, treatment of dyspermic patients, breast cancer and regression of metastases, AIDS and immune system.

References

1. Bolli R: Oxygen-derived free radicals and myocardial reperfusion injury: An overview. *Cardiovascular Drug Therapy.* 1991; 5: 249-268.
2. Hess ML & Manson NH: Molecular oxygen: Friend or foe. The role of oxygen free radical system in the calcium paradox, the oxygen paradox, and ischemic/reperfusion injury. *J Mol Cell Cardiol* 1984; 16: 979-985.
3. Tosaki A, Bagchi D et al: Comparisons of ESR and HPLC methods for the detection of hydroxyl radicals in ischemic/reperfused hearts. A relationship between the genesis of oxygen-free radicals and reperfusion-induced arrhythmias. *Biochem Pharmacol.* 1993; 45: 961-969.
4. Bagchi D, Das DK et al: Polymorphonuclear leucocytes as potential source of free radicals in the ischaemic-reperfused myocardium. *Europ Heart J* 1990; 11:800-813.
5. Frei B, Kim MC et al: Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. *Proc Nat Acad Sci USA.* 1990; 87: 4879- 4883.
6. Crane FL, Hatefi Y et al: Isolation of a quinone from beef heart mitochondria. *Biochim et Biophys Acta* 1957; 25:220-221.
7. Folkers K: *Biomedical and Clinical Aspects of Coenzyme Q,* Vol. 1. ed. K Folkers and Y Yamamura. New York. Elsevier/North Holland Biomedical Press, 1976.
8. Folkers K, Vadhanavikit S et al: Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with Coenzyme Q10. *Proc Nat Acad Sci USA.* 1985; 62: 901-904.
9. Bliznakov EG: *Biomedical and Clinical Aspects of Coenzyme Q10* Vol. 3. ed. K Folkers and Y Yamamura. New York. Elsevier/North Holland Biomedical Press, 1981.
10. Greenberg SM, Frishman WH: Coenzyme Q10: A new drug for myocardial ischemia? *Medicine Clinical North America.* 1988; 72:243-258.
11. Ozawa T, Sugiyama S: The effect of Coenzyme Q10 on reperfusion injury in canine myocardium. In: *Biomedical and clinical aspects of Coenzyme Q,* Vol. 5. ed. K Folkers and Y Yamamura. Amsterdam. Elsevier Press. 1986: 191-202.
12. Forsmark-Andree P, Dallner G et al: Endogenous Ubiquinol prevents protein modification accompanying lipid peroxidation in beef heart submitochondrial particles. *Free Rad Biol& Medicine.* 1995;19: 749-757.
13. Crane FL, Sun IL et al: Coenzyme Q10, plasma membrane oxidase and growth con-

trol. *Molecular Aspects of Medicine.* 1994; 15 Suppl: S1-11.
14. Weber C, Jakobsen TS et al: *Molecular Aspects of Medicine.* 1994; 15 Suppl: S97-102.
15. Alleva R, Tomasetti M et al: *Proc Nat Acad Sci USA.* 1995; 92:9388-9391.
16. Lockwood K, Moesgaard S et al: *Biochem Biophys Res Comm* 1995; 212: 172-177.
17. Folkers K. & Simonsen R: *Biochim et Biophys Acta* 1995; 1271: 281-286.
18. Linnane AW, Degli EM et al: *Biochim et Biophys Acta* 1995; 1271: 191-194.
19. Lodi R, Iotti S et al: *Molecular Aspects of Medicine.* 1994; 15 Suppl: S221-230.
20. Mancini A, Conte B et al: *Molecular Aspects of Medicine.* 1994; 15 Suppl: S 249-255.
21. Folkers K, Morita M et al: *Biochem Biophys Res Comm* 1993; 193: 88-92.
22. Folkers K, Hanioka T et al: *Biochem Biophys Res Comm* 1991; 176: 786-791.
23. Bagchi D, Ghosh S et al: Unpublished Results.
24. Yoshida T, Bagchi D et al: Increased Myocardial tolerance to ischemia-reperfusion injury by feeding pigs with Coenzyme Q_{10}. In: *Myocardial Preservation, Preconditioning, and Adaptation.* ed. DK Das, RM Engelman & KM Cherian. New York. The New York Academy of Sciences. 1996: 414-418.
25. Hano O, Thompson-Gorman SL et al: Coenzyme Q10 enhances cardiac functional and metabolic recovery and reduces Ca^{2+} overload during postischemic reperfusion. *Amer J Physiol,* 1994; 266:H2174-2181.
26. Rouslin W, Millard RW: Canine myocardial ischemia: Defect in mitochondrial electron transfer complex. *J Mol Cell Cardiol*1980; 12: 639-645.
27. Langsjoen PH, Vadhsnavikit S et al: Responses of patients in class III and IV of cardiomyopathy to therapy as a blind and crossover trial with Coenzyme Q_{10}. *Proc Nat Acad Sci USA.* 1985; 82: 4240-4244.
28. Weber C, Sejersgard J et al: Antioxidant effect of dietary Coenzyme Q10 in human blood plasma. *Internat J Vitamin Nutr Res.* 1994; 64:311-315.
29. Stocker R, Bowry VW: Ubiquinone-10 protects human low-density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol. *Proc Nat Acad Sci USA.* 1991; 88: 1646-1650.
30. Mukai K, Kikuchi S et al: Stopped-flow kinetic study of the regeneration reaction of tocopheroxyl radical by reduced ubiquinone-10 in solution. *Biochim et Biophys Acta.* 1990; 1035:77-82.
31. Forsmark P, Aberg F et al: Inhibition of lipid peroxidation by ubiquinol in submitochondrial particles in the absence of vitamin E. *FEBS Letters.* 1991; 285:39-43.