Application of Coenzyme Q10 in Clinical Practice

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Abstract

Coenzyme Q10 (CoQ10) is naturally produced by the body and is an important factor in aerobic cellular respiration. This substance plays key roles in cellular energy production in mitochondria and is a potent antioxidant. The productivity of CoQ10 declines during the aging process. The heart, liver and kidneys have the highest energy requirements, thus these organs have the highest concentrations of CoQ10. Significant decreases in levels of CoQ10 are observed in various diseases such as diabetes, congestive heart failure, myocardial infarction, and cancer. Emerging evidence supports that administration of CoQ10 may have beneficial effects at the mitochondrial level. This review will emphasize the cellular mechanisms of CoQ10 and the administration of CoQ10 in different clinical disease states.

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INTRODUCTION

Coenzyme Q10 is a lipid-soluble substance that is naturally produced by all cells in the human body. In 1957 Drs. Crane and Morton isolated the molecule subsequently identified as CoQ10, and in the following year, its chemical structure was determined by Dr. Karl Folkers and associates at Merck.[1] In the next decade international research identified two significant attributes of CoQ10: its critical role in the electron transport system, and powerful antioxidant properties. Coupled with the commercial production of CoQ10, and its availability over-the-counter, the ever expanding knowledge of physiologic & pathophysiologic processes has produced widespread interest, research, and usage of CoQ10.

Coenzyme Q10 is an essential component in mitochondrial bioenergetics and is needed for optimal cell functions. As an antioxidant, it protects cells and tissues from oxidative damages caused by reactive oxygen species (ROS). There are two forms of CoQ10 that are present in the body: ubiquinone and ubiquinol.[2] Ubiquinone is the fully oxidized form of CoQ10. Ubiquinol is the completely reduced form that can be converted from ubiquinone by CoQ10 reductases including NADH-cytochrome b_5 reductase and NAD(P)H: quinone reductase 1.[3, 4] The majority of CoQ10 that is circulating in the body is ubiquinol, functioning as an active and potent antioxidant. The normal plasma levels of CoQ10 in a healthy adult range from 0.68 to 1.1 μmol/L, which is maintained principally by endogenous synthesis, and to a lesser extent by the ingestion of foods containing CoQ10.[5] However, the biosynthesis of CoQ10 and its efficiency gradually diminish in aging. The levels of CoQ10 may be depleted in many acute or chronic diseases. The deficiency of CoQ10 often leads to alterations in mitochondrial energy production and increased free radical damage due to the reduced scavenging capacity. Supportive evidence for taking dietary CoQ10 supplements for numerous disease conditions is rapidly growing. It has been reported that CoQ10 is one of the common dietary supplements that are consumed by patients for the therapeutically beneficial effects in treating various diseases and conditions, such as congestive heart failure,[6, 7] diabetes,[8, 9] or cancers.[10]

The purpose of this article is to: 1) review the anatomy of the mitochondria and the roles of CoQ10 in mitochondria bioenergetics and its antioxidant property; 2) present

evidence of its clinical usages in various diseases/conditions, including diabetes, congestive heart failure, acute myocardial infarction reperfusion injury, statin therapy, cancer, and migraine.

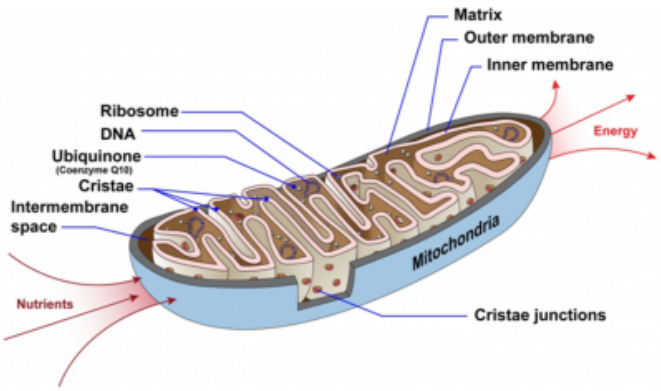
MITOCHONDRIA AND COENZYME Q10

ANATOMY OF MITOCHONDRIA

The structure of a mitochondrion is unique as it contains two double-layer phospholipid membranes.[11] Figure 1 presents the structural characteristics of a mitochondrion and illustrates CoQ10 or ubiquinone. The two double-layer phospholipid membranes are the outer and inner membrane respectively, which are embedded with proteins and enzymes. Similar to the membranes of other organelles, the outer membrane of the mitochondrion encloses the whole organelle. Relatively large internal channels are formed by many integral proteins in the outer membrane to allow passage of molecules. Distinguished from the outer membrane, the mitochondrial inner membrane forms many folds known as cristae. The surface area of the inner membrane is increased substantially, thus enhancing the productivity of cellular respiration. The outer and inner membranes divide the mitochondrion into two compartments, the intermembrane space and the mitochondrial matrix. The area between the outer and inner membranes is called the intermembrane space. The mitochondrial matrix is the compartment enclosed by the inner membrane. There are various enzymes, mitochondrial ribosomes, deoxyribonucleic acid (DNA), and granules within the matrix. Coenzyme Q10 or ubiquinone is located on the electron transport chain in the inner membrane, a key component in adenosine triphosphate (ATP) production.

Figure 1

Figure 1. Anatomic Structure of a Mitochondrion Illustrating Ubiquinone (Coenzyme Q10).



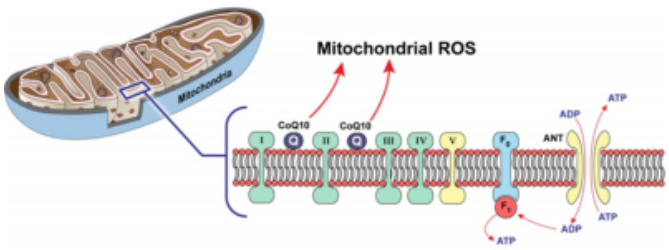
DNA: deoxyribonucleic acid

THE ROLES OF COENZYME Q10 IN MITOCHONDRIAL ATP AND ROS PRODUCTION

The uniqueness of the mitochondrion in the cells result from its essential function in the survival and apoptosis of cells.[12] Adenosine triphosphate, the primary molecular energy required for vital organs like the brain, heart, lungs, skeletal muscles, and kidneys, is mainly generated in the mitochondria by converting digested nutrients such as proteins, lipids, and carbohydrates via oxidative phosphorylation. Oxidative phosphorylation begins when carbohydrates are metabolized into glucose and then into pyruvate in the cytoplasm via glycolysis. The pyruvate is transported into the mitochondrion and formed into acetyl CoA where it enters the citric acid cycle, resulting in NADH and FADH2. This process decreases equivalents utilized for transporting electrons. Figure 2 demonstrates the key roles of CoQ10 in mitochondrial bioenergetics and mitochondrial ROS reduction involving the five mitochondrial complexes (I, II, III, IV, and V) in the electron transport chain. As shown in Figure 2, the electron transport chain is located on the mitochondrial inner membrane. Complexes I and II are the sites for oxidation of NADH and FADH2, respectively. Coenzyme Q10 is located between complexes I, II and III, and functions as an electron transporter. Electrons generated during oxidation are transported by CoQ10 from complexes I and II to complex III. In complex III, electrons are transferred to cytochrome c. In complex IV, oxygen receives electrons from cytochrome c, generating water. An electrochemical gradient is created during electron transport as the protons being pumped across the inner membrane into the intermembrane space from the matrix. At complex V, ATP synthase utilizes the energy from the electrochemical gradient to condense a molecule of inorganic phosphate with adenosine diphosphate (ADP), resulting in generation of ATP. To fully utilize ATP, vital organs must have the capacity to adjust the ATP synthesis to meet metabolic requirements. In the heart, this is accomplished through an energy transfer process called the creatine kinase energy shuffle. During this mechanism, creatine kinase catalyzes the high-energy bond in ATP to form phosphocreatine. Smaller than ATP, phosphocreatine rapidly diffuses from the mitochondria to the myofibrils, whereby myofibrillar creatine kinase catalyzes the reformation of ATP from phosphocreatine. Functioning as an energy buffer, the levels of phosphocreatine decreases when cardiac metabolic demands increase, maintaining ATP levels.

Figure 2

Figure 2. Key roles of CoQ10 in mitochondrial bioenergetics and mitochondrial ROS reduction.



CoQ10: coenzyme Q10; ROS: reactive oxygen species; ATP: adenosine triphosphate; ADP: adenosine diphosphate; ANT: Adenine Nucleotide Translocase.

As shown in Figure 2, mitochondrial ROS are also produced during electron transport and are natural byproducts of normal oxygen metabolism. Reactive oxygen species are a group of highly reactive molecules that contain oxygen and unpaired electrons. During the process of transporting electrons in the mitochondria, superoxide (O_2^-) is generated as electrons are added to oxygen (O_2). Superoxide is then converted by superoxide dismutase (SOD2) to hydrogen peroxide (H_2O_2), which can be further reduced to hydroxyl radicals (OH^-).[12] The extent of ROS formation can be significantly influenced by the functional activity of the mitochondria. For example, higher mitochondrial membrane potential and lower concentrations of ADP can lead to greater production of ROS. Hydroxyl radicals can directly and indirectly damage DNA, lipids, and proteins by oxidation. As the only endogenously synthesized lipid soluble antioxidant, the reduced form of CoQ10 (ubiquinol) can effectively protect not only lipids from peroxidation but also proteins from oxidation by reducing the initiating free radicals and preventing propagation. It can also interfere with DNA oxidation, especially mitochondrial DNA.[13] The potent antioxidant property of ubiquinol presents a strong defensive mechanism against oxidative damage for all cells.

With aging or various diseases, there is a significant decrease in either the biosynthesis of CoQ10 or its productivity in mitochondrial bioenergetics and scavenging ROS. Consequently, with low levels of CoQ10 there is a corresponding energetic deficiency and excessive formation of ROS with low levels of CoQ10. These abnormalities can be substantially ameliorated by exogenous CoQ10 supplementation. Excessive ROS can activate apoptotic pathways and lead to apoptosis or programmed cell death when too much damage is caused to its mitochondria.[14]

When the production of ROS exceeds the capacity of the antioxidant system to counterbalance, damage to protein, DNA, and lipids occurs. Oxidation of the mitochondrial outer membrane by ROS can induce mitochondrial dysfunction by destroying the membrane potential, leading to the release of cytochrome c from the mitochondria. The releasing of cytochrome c can initiate apoptotic pathway.

MITOCHONDRIAL FUNCTION AND COQ10 IN AGING

The functions of the mitochondria and the productivity of CoQ10 are affected by aging and various age-related diseases. Mitochondria are continuously undergoing dynamic changes in morphology by fusion and fission, which are the two important processes to maintain mitochondrial integrity, including electrical and biochemical connectivity, modulating cellular redox status, turnover of mitochondria, and apoptosis. However, alterations in the outer and inner mitochondrial membrane including peroxidation of lipids and decreases in fluidity of the membranes were observed as one of the multidimensional changes of the aging process.[15] The biosynthesis of both CoQ10 and its reductases also deteriorate as a result of aging, limiting the conversion of ubiquinone to ubiquinol. The production of ATP is thus significantly reduced with aging, resulting in the deficiency of cellular energy. Deficits in energy at the cellular level could induce various disease processes such as cardiovascular disease and diabetes; the consequent increase in ROS production can further damage mitochondrial DNA, creating a vicious cycle.[16]

CLINICAL USAGE OF COQ10 IN VARIOUS DISEASES/CONDITIONS

There have been numerous clinical trials specifically examining CoQ10 in various diseases. Since the first clinical trials were first conducted approximately 45 years ago, about 3,450 (averaging about 77 per year) randomized clinical trials have been conducted world-wide relating CoQ10 to oxidative stress and/or cellular energetics. The quality of many of these clinical trials varies based upon design, subject selection, type of CoQ10, dosing, etc. Despite the abundant number of clinical trials, national clinical guidelines have not included CoQ10 in the armamentarium of therapy. There may be several reasons why CoQ10 may not be used in clinical practice. The first relates to the clinicians' knowledge concerning the complexities of CoQ10 and the optimal dosage to be used with various diseases. The second relates to a communication barrier between research scientists and clinicians who provide

patient care.

The following section is a discussion of six disease processes/conditions that illustrates the current potential usage of CoQ10 in clinical medicine: Diabetes mellitus, congestive heart failure (CHF), reperfusion injury, statins, cancer, and migraine.

DIABETES MELLITUS

Diabetes mellitus is a disease with multiple metabolic abnormalities, principally through the axis of inflammation and oxidative stress with associated mitochondrial dysfunction.[17] Hyperglycemia associated ROS affects the endothelium of all blood vessels with activation of the hexosamine pathway, leading to endothelial dysfunction by impairing endothelial nitric oxide synthase activity. Hyperglycemia can also induce atherogenic mechanisms such as low density lipoprotein (LDL) cholesterol oxidation, facilitating foam cell formation in macrophages. In addition, hyperglycemia associated ROS increases monocyte adhesion, diabetic vascular smooth muscle cell migration and proliferation, and stimulates the expression of plasminogen activator inhibitor-1 and proinflammatory cytokines, as well as the secretion of platelet derived growth factor.[18] Administration of CoQ10 has been found to prevent high glucose-induced oxidative stress in human umbilical vein endothelial cells.[19]

Diabetes affects virtually all organ systems and the most common complication of diabetes is diabetic neuropathy, which occurs in at least half of all diabetics.[20] Although treatments of diabetic neuropathy have historically focused on glycemic control, recent studies report that supplementation of CoQ10 and its analogues (idebenone and mitoquinone) at higher doses improves neurologic function.[21] Another common complication in diabetic patients is diabetic retinopathy, which occurs in the setting of dysfunctional retinal mitochondria, and consequent impaired capacity of ATP generation, with accompanying decreased defense against ROS.[22] Decreased retinal CoQ10 could be a critical factor, as there is known to be a significant age-associated decrease (as much as 40%) in retinal CoQ10 in older patients with diabetes.[23] Since CoQ10 is unique in its role in the electron transport system synthesis of ATP as well as a potent scavenger for ROS, CoQ10 has been utilized in treating diabetic retinopathy, administered alone or in combination with other antioxidants. Only a few studies have demonstrated that in diabetic patients with retinopathy, CoQ10 consistently improved vision initially and the improvement was sustained over long-term treatment with CoQ10.[24, 25] However, there are several publications indicating that CoQ10 plays an antiapoptotic role in corneal fibroblasts,[26, 27] provides retinal protection,[28] and may be a promising ophthalmic drug to protect lens epithelial cells.[29]

CONGESTIVE HEART FAILURE

There are two major types of CHF: 1) systolic heart failure and 2) diastolic heart failure. Systolic heart failure (SHF), which until recently was the predominant form of heart failure, occurs when there is decreased myocardial contractility, with the left ventricular ejection fraction < 50% and accompanying symptoms of pulmonary congestion. In diastolic heart failure (DHF), the left ventricular contractility is "normal" with ejection fraction ≥ 50%, but there is abnormal diastolic filling in the setting of symptomatic pulmonary congestion.

There are many different underlying causes of SHF; the most prevalent cause in the U.S. is preceding myocardial injury from underlying coronary artery disease (CAD). Conversely, DHF is significantly more heterogeneous regarding the underlying pathophysiologic processes, including infiltrative, viral, hypertrophic, and inflammatory cardiomyopathies. Despite the varied underlying processes, the principle underpinning of DHF is impaired cellular energetics.[30] Impairment of mitochondrial function in turn results in increased ROS, causing mitochondrial injury, which can further aggravate mitochondrial dysfunction. The current focus of DHF management is to reduce the risk factors such as diabetes, dyslipidemia, obesity, inactivity, and sleep apnea. However, these measures do not directly address the deficiency of cellular energetics.

CoQ10 has been investigated as an adjunctive agent in the treatment of both systolic and diastolic heart failure over the past 20 years. Research has demonstrated its effectiveness in increasing ejection fraction in patients with cardiomyopathy from 44% to 60% after six months[31] and decreasing incidence of serious complications of CHF such as hospital re-admission, cardiac asthma, and pulmonary edema.[32] Administering 100 mg of CoQ10 twice daily was found to help reduce exercise induced elevation of pulmonary artery pressure and pulmonary capillary wedge pressure in patients with serious heart failure.[33] Keogh et al. conducted a double-blind, placebo-controlled randomized clinical trial of CoQ10 in Class II-III SHF patients. Subjects taking CoQ10 had a significant improvement in exertional cardiac function.[34]

Molyneux et al. found that the serum CoQ10 level was an independent predictor of mortality in chronic heart failure patients. They reported that the optimal CoQ10 serum concentration was 0.73 µmol/l for prediction of mortality.[35] Maes, et al. reported that lower CoQ10 levels were associated with depression, and increased risk for CAD and CHF.[36] The low achieved CoQ10 level with oral doses of ubiquinone prompted Langsjoen & Langsjoen to administer ubiquinol, the reduced form of CoQ10, to seven patients with severe systolic dysfunction. The serum level increased from 1.6 µg/ml to 6.5 µg/ml, with an accompanied improvement of mean left ventricular ejection fraction (LVEF) from 22% to 39%.[37] In that same year, Harinstein et al. demonstrated similar improvements in 11 patients who received micronutrients including CoQ10.[38] All subjects had viable but hibernating myocardium whose mean LVEF improved from 17% to 59%. To further examine the effect of CoQ10 and other micronutrient supplements, Fumagalli et al. investigated the peak oxygen consumption in patients with stable CHF.[39] The experimental group received CoQ10 and creatine supplements in this double blind randomized control trial. At 8 weeks, the experimental group had significantly increased peak oxygen consumption compared to the control group.

REPERFUSION INJURY

Interruption of arterial blood flow results in tissue hypoxia, with progressive disturbance of cellular processes. The mitochondria are vulnerable in the setting of hypoxemia. However, reperfusion of ischemic tissue results in an overabundance of ROS, often causing irreversible damage to cells.[40] The aged heart has been found to be more vulnerable to reperfusion injury than the middle aged or younger heart.[41]

Numerous subsequent animal and clinical studies on using CoQ10 in preventing reperfusion injury have been conducted over the past 20 years. CoQ10 supplements have been administered before ischemic injury, following the injury, but before reperfusion, or after the injury and reperfusion. Research has demonstrated in animals treated with CoQ10 that there is 30% less myocardial injury following reperfusion injury than control animals.[42] Lekli et al. demonstrated that both CoQ9 and CoQ10 improved left ventricular performance and reduced infarct size and apoptosis.[43] A key factor with reperfusion injury is the opening of the mitochondrial permeability transition pores (mPTP) in the inner mitochondrial membrane, with resultant apoptosis and cell death. Coenzyme Q10 plays a central role in controlling the opening of the mPTP,[44] and the deficiency of CoQ10 is associated with accelerated apoptosis.[45] In addition, administering CoQ10 following reperfusion injury has been shown to assist in the recovery of myocardial function, aerobic efficiency,[46] and higher levels of phosphocreatine and ATP in the myocardium.[47]

In 1990 Julia et al. reported that blood cardioplegia with additional free radical scavengers (superoxide dismutase, catalase, and CoQ10) resulted in the best recovery of systolic shortening and least histochemical damage.[48] A study by Tran et al. found in an acute ischemia-reperfusion injury mouse model, administering CoQ10 decreased superoxide production, reduced infarction size, and normalized mitochondrial dysfunction.[49]

A sentinel study published by Singh et al., in 1998 compared patients with acute myocardial infarction/acute coronary syndrome who were treated with reperfusion therapy using streptokinase. In this double-blinded study, patients received either B complex vitamins or CoQ10. They found that CoQ10 significantly reduced angina pectoris, reduced dysrhythmias, and improved left ventricular function. Thus, they concluded that CoQ10 could be a rapid protective substance to administer to patients within 3 days of acute myocardial infarction.[50] Since this study, there has been no new research specifically on CoQ10 in myocardial infarction patients. However, the research has shifted to investigate ischemic-reperfusion injury and the usage in revascularization surgery patients.

STATINS

Statins or 3-hydroxy 3-methyl glutaryl CoA reductase inhibitors are one class of medications that are frequently prescribed in treating hyperlipidemia. The utility of statins in lowering LDL cholesterol and improving mortality and morbidity is well supported. Statins block the production of mevalonic acid, which is a precursor in the synthesis of CoQ10. Thus, most statins lower serum CoQ10 levels which have been associated with statin-induced myopathies. Low CoQ10 levels are associated with statin-induced low LDL cholesterol, which potentially could place patients at risk, such as the circumstance of septic shock.[51] Okello et al., evaluated patients taking both atorvastatin and CoQ10, as synergists in the interaction on superoxide dismutase, and recommended that CoQ10 be given as a supplement in all patients with underlying CHF.[52] Another study investigated the effects of rosuvastatin in CHF patients. In this study they demonstrated that there was an increased collagen turnover with a decrease in plasma CoQ10 levels.[53] This indicates that

the elevated collagen turnover and/or the reduction in CoQ10 may be associated with increased myocardial fibrosis. However, larger trials are needed to determine the optimum CoQ10 form, dose and frequency of administration.[54]

CANCER

Carcinogenesis is a complex and multistage process, which might be activated and stimulated by free radicals. Chemotherapy as one of the mainstay treatments for cancers is known to produce excessive free radicals, causing different side effects. Coenzyme Q10 may have beneficial effects on cancer treatment as it involves in the regulation of intracellular ROS production. However, low plasma levels of CoQ10 are usually found among patients with cancers.[55, 56] Research on breast cancer has demonstrated that CoQ10 has complementing effects on patients who receive tamoxifen treatment, including reduced levels of angiogenic markers and lipids.[57, 58] The results of the study by Bahar et al.[10] showed that CoQ10 could decrease the activity of matrix metalloproteinases 2, which is an important factor in cellular invasion and metastasis, thus possibly preventing the proliferation and metastasis of breast cancer cells. Supplementing CoQ10 to patients with various end-stage cancers such as lungs, breast, kidneys, colon and prostate could potentially improve their survival rates.[59] Studies also found that plasma CoQ10 level is an independent prognostic factor that can be used to estimate the risk for melanoma progression.[60] Furthermore, CoQ10 is found to have cardioprotection for patients who received anthracyclines, thereby reducing the risk of cardiomyopathy induced by anthracyclines.[61]

MIGRAINE

A migraine is a neurological condition in which a person experiences recurrent headaches that often lead to intense throbbing of the head, nausea, vomiting, and photophobia.[62] Migraine attacks may occur for hours to days causing significant pain. Recently, they have discovered a link between migraines and mitochondrial function. When there are variants (polymorphisms) in mitochondrial proteins it can adversely affect oxidation phosphorylation of the cell and thus alter the energy metabolism.[63] Since CoQ10 is an essential component of the electron transport chain, it may play an important role in the prevention and treatment of migraines.

Studies have shown that migraine patients treated with CoQ10 have a significant reduction in the number of days with migraine headaches[64] and frequency of headaches.[65, 66] A study by Boles et al.[67] found that CoQ10 was an effective treatment for cyclic vomiting syndrome which many migraine patients experience. Several of the migraine studies involving CoQ10 have focused on reducing pain and symptoms of pediatric and adolescent patients.[65, 68] A number of the clinical studies related to CoQ10 supplementation for migraines include other combinations of substances such as L-carnitine,[69] riboflavin,[70] and magnesium.[71] CoQ10 at various dosages is an effective prophylaxis treatment for migraines.[72, 73] Future placebo-controlled trials using migraine patients are needed to determine the optimal frequency, dosage and usage of CoQ10.

CONTRADICTORY STUDIES

As with any drug or nutrient being investigated, there are often studies that demonstrate that the substance is not effective. Thus, in the literature investigations have shown that CoQ10 is not therapeutic for various diseases and conditions. However, many times these studies have great variation in experimental design, subject selection, dosage, CoQ10 formulation and method of evaluation. Yet, the overwhelming data support the usage of CoQ10 in clinical practice.

A study by Khatta et al. found in CHF patients that CoQ10 did not affect ejection fraction, peak oxygen consumption, or exercise duration.[74] This was a randomized, double-blind, placebo-controlled trial to investigate the effects of oral CoQ10 (200 mg/d). In this study, 46 subjects with systolic dysfunction were given CoQ10 for 6 months. These researchers found in treatment subjects (mean age = 67 years) the mean serum CoQ10 concentration increased from 0.95 ± 0.62 μg/mL to 2.2 ± 1.20 μg/mL. There are several issues with this study. For example, the standard deviation in the serum CoQ10 was relatively large, which could indicate that the effective dose of CoQ10 at 200 mg/d was subtherapeutic. This could have been related to the type of oral CoQ10 administered in the study since the mean age of the subjects was 67 years old. In other words, the investigators used ubiquinone versus ubiquinol which has greater absorption in older patients. Hence, this could be the reason why the researchers did not observe any effect of oral CoQ10 in this sample.

CONCLUSION

Coenzyme Q10 is an essential factor in mitochondrial bioenergetics, playing a crucial role in transporting electrons in the mitochondria respiratory chain. Additionally, CoQ10

is a highly efficient antioxidant that prevents damage to DNA, proteins, and lipids. Though CoQ10 is naturally produced by all cells in the body, the aging process and various diseases or pathological mechanisms can disrupt the biosynthesis, leading to CoQ10 deficiency. Dietary supplementing of CoQ10 (either ubiquinone or ubiquinol) has promising beneficial effects in a wide variety of diseases and pathophysiologic conditions. The addition of CoQ10 in clinical practice to traditional treatments can lead to improved patient outcomes.

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