

## The Benefits of Coenzyme Q10 as A Nutritional and Medicinal Supplement

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### Abstract

Coenzyme Q10 or ubiquinone is an antioxidant can be found in many plant and animal cells. Patients with some chronic diseases such as congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, and hypertension are Co enzyme Q10 deficient. Deficiency of coenzyme Q10 has been observed in patients after coronary revascularization. Studies have showed that Coenzyme Q10 is involved in the production of ATP and therefore is beneficial in preventing cellular damage during ischaemia-reperfusion injury. The clinical benefits are mainly due to its ability to improve energy production, antioxidant activity, and membrane stabilizing properties. Several studies showed that coenzyme Q could be useful in patients with congestive heart failure, angina pectoris, cardiomyopathy, coronary artery disease and in the preservation of myocardium. Strong evidence has now emerged supporting the role of oxidative stress and defective energy metabolism in the pathogenesis of many neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer disease (AD). There is, therefore, a robust scientific rationale for testing this agent as a potential neuroprotective therapy. Levels of CoQ10 in the brain and other tissues in humans and animals have been shown to decline with age, further suggesting a potential therapeutic role in age-related neurodegenerative disorders. Moreover, the substantianigra, in which cell death results in the disabling motor symptoms of PD, has the lowest CoQ10 content within the brain. Here we review the most important clinical trials in neurodegenerative disease, their scientific underpinnings, and their implications for the future of treatment of patients suffering from neurodegenerative disease.

**Keywords:** Co-enzyme Q10; antioxidant; CVD; Aging; supplement

### Introduction

Coenzyme Q10 is a fat soluble compound which can be found in almost all cell membranes [1]. Mammals can synthesize ubiquinones; consequently, coenzyme Q10 cannot be considered an essential nutrient such as vitamin [2]. It's called ubiquinone because of the ubiquitous presence of these compounds in living organisms. One of the critical features in the biochemical functions of ubiquinones is the ability of the benzoquinone head group of coenzyme Q10 to accept and donate electrons is a Coenzyme Q10 can exist in three oxidation states.

The presence of coenzyme Q in the inner mitochondrial membrane is required for the conversion of energy from carbohydrates and fats to the form of energy used by cells (ATP). As part of the mitochondrial electron transport chain, coenzyme Q accepts electrons from reducing equivalents generated during fatty acid and glucose metabolism and then transfers them to electron acceptors [2]. Coenzyme Q then transfers protons outside the inner mitochondrial membrane, creating a proton gradient across that membrane releasing energy which is used to form ATP [1].

Symptoms of coenzyme Q10 deficiency have not been reported in the general population, so it is generally assumed that normal biosynthesis and a varied diet provides sufficient coenzyme Q10 for healthy individuals [3]. It has been estimated that dietary consumption contributes about 25% of plasma coenzyme Q10, but there are currently no specific dietary intake recommendations for coenzyme Q10

from the Institute of Medicine or other agencies [4]. Studies have not proved which dietary consumption has an impact on tissue coenzyme Q10 levels. Oral coenzyme Q10 supplementation has been shown to improve neurological and muscular symptoms in some patients with primary coenzyme Q10 deficiency [5]. Coenzyme Q10 levels have been found to decline gradually with age in a number of different tissues, but it is unclear whether this age-associated decline constitutes a deficiency. Decreased plasma levels of coenzyme Q10 have been observed in individuals with diabetes, cancer, and congestive heart failure [4]. Lipid lowering medications that inhibit the activity of HMG-CoA reductase, a critical enzyme in both cholesterol and coenzyme Q10 biosynthesis, decrease plasma coenzyme Q10 levels although it remains unclear whether this has clinical or symptomatic implications [6].

### Antioxidant functions

In its reduced form, CoQ10 H2 is an effective and important fat-soluble antioxidant [1]. This form has been found effective in inhibiting lipid peroxidation when cell membranes and low-density lipoproteins (LDL) are exposed to oxidizing conditions outside the body (*in vivo*). Moreover, the formation of oxidized lipids and the consumption of alpha-tocopherol (the most active form of vitamin E) are suppressed while CoQ10 H2 is present [4]. Coenzyme Q10 also protected membrane proteins and DNA from the oxidative damage that accompanies lipid peroxidation in isolated mitochondria [2].

### Lysosomal function

The main function of Lysosomes is the digestion of cellular debris. The digestive enzymes within lysosomes function optimally at an acid pH. Relatively high concentrations of coenzyme Q10 are found within lysosomal membranes that separate those digestive enzymes from the rest of the cell contain. Studies show that coenzyme Q10 plays a significant role in transportation of protons across lysosomal membranes to maintain the optimal pH [3].

## Disease Prevention

### Cardiovascular disease

Oxidative modification of low-density lipoproteins (LDL) in arterial walls is thought to represent an early event leading to the development of atherosclerosis. Reduced coenzyme Q10 (CoQ10 H2) inhibits the oxidation of LDL in the test tube (*in vitro*) and works together with  $\alpha$ -TOH to inhibit LDL oxidation by reducing the alpha to back to alpha-TOH. In the absence of a co-antioxidant, such as CoQ10 H2 (or vitamin C), alpha-TOH can, under certain conditions, promote the oxidation of LDL *in vitro* [4]. Supplementation with coenzyme Q10 increases the concentration of CoQ10 H2 in human LDL [7]. Studies in apolipoprotein E-deficient mice, an animal model of atherosclerosis, found that coenzyme Q10 supplementation with supra-pharmacological amounts of coenzyme Q10 significantly inhibited the formation of atherosclerotic lesions [8]. Interestingly, co-supplementation of these mice with alpha-TOH and coenzyme Q10 was more effective in inhibiting atherosclerosis than supplementation with either alpha-TOH or coenzyme Q10 alone [9].

### Aging

Aging process is caused by oxidative damage of cell structures by reactive oxygen species (ROS) leading to functional declines [10]. ATP production generate ROS byproduct by mitochondria which may damage mitochondria over time, if not neutralized by antioxidants causing mitochondria to function less efficiently and to generate more damaging ROS in a self-perpetuating cycle. The important roles that Coenzyme Q10 plays are in mitochondrial ATP synthesis and as an antioxidant in mitochondrial membranes. It was shown that tissue levels of coenzyme Q10 decline with age [9]. Aging is characterized in a decline in energy metabolism in liver, heart, and skeletal muscle tissues. It has been proposed that age-associated declines in tissue coenzyme Q10 levels may play a role in this decline [11]. In recent studies, lifelong dietary supplementation with coenzyme Q10 increased tissue concentrations of coenzyme Q10 but did not increase the lifespan of rats or mice [11,12].

## Disease Treatment

### Mitochondrial encephalomyopathies

Mitochondrial encephalomyopathies represent a diverse group of genetic disorders resulting from numerous inherited abnormalities in the function of the mitochondrial electron transport chain. Coenzyme Q10 supplementation has resulted in clinical and metabolic

improvement in some patients with various types of mitochondrial encephalomyopathies [13]. Neuromuscular and widespread tissue coenzyme Q10 deficiencies have been found in a very small subpopulation of individuals with mitochondrial encephalomyopathies [14]. In those rare individuals with genetic defects in coenzyme Q10 biosynthesis, coenzyme Q10 supplementation has resulted in substantial improvement [15]. It is not clear whether coenzyme Q10 supplementation might have therapeutic benefit in patients with other mitochondrial disorders; a phase III clinical trial investigating that question is currently under way [16].

### Cardiovascular Diseases

#### Congestive heart failure

Impairment of the heart's ability to pump enough blood for all of the body's needs is known as congestive heart failure (CHF). Myocardial infarction (MI) may also damage the heart muscle, leading to heart failure [17]. Because physical exercise increases the demand on the weakened heart, measures of exercise tolerance are frequently used to monitor the severity of heart failure [18]. The finding that myocardial coenzyme Q10 levels were lower in patients with more severe versus mild heart failure led to several clinical trials of coenzyme Q10 supplementation in heart failure patients [19]. A number of small intervention trials that administered supplemental coenzyme Q10 (100-300 mg/day of coenzyme Q10 for one to three months) to congestive heart failure patients, in conjunction with conventional medical therapy, have demonstrated improvements in some cardiac function measures [20]. A 2006 meta-analysis of ten randomized controlled trials found that in heart failure patients, the function of left ventricular ejection fraction improved when coenzyme Q10 supplemented (99-200 mg/day for one to six months).

The study also found that coenzyme Q10 supplementation resulted in slight increase in cardiac output (0.28 L/min), but this analysis only included two trials (60 mg/day for one month or 200 mg/day for three months) [21]. A recent study in 236 heart failure patients found that lower plasma coenzyme Q10 levels were associated with a heightened risk of mortality [22]; however, a larger study found that plasma coenzyme Q10 level was a biomarker of advanced heart disease and not an independent predictor of clinical outcomes in heart failure patients [23].

#### Myocardial infarction and cardiac surgery

Myocardial infarction (MI) can deprive the heart muscle from oxygen and become ischemic. Myocardial damage occurring during ischemia-reperfusion found to increase the generation of ROS and is also thought to be an important contributor to pretreatment of animals with coenzyme Q10. The treatment has been found to decrease myocardial damage due to ischemia-reperfusion [24]. Three out of four placebo-controlled trials found that coenzyme Q10 pretreatment (100-300 mg/day for 7-14 days prior to surgery) provided some benefit in short-term outcome measures after CABG surgery [25]. In the placebo-controlled trial that did not find preoperative coenzyme Q10 supplementation to be of benefit, patients were treated with 600 mg of coenzyme Q10 12 hours prior to surgery, suggesting that preoperative coenzyme Q10 treatment may need to commence at least one week prior to CABG surgery in order to realize any benefit [26].

#### Angina Pectoris

Angina pectoris happens when the demand for oxygen exceeds the capacity of the coronary circulation to deliver it to the heart muscle, e.g., during exercise. Five small placebo-controlled studies have examined the effects of oral coenzyme Q10 supplementation (60-600 mg/day) in addition to conventional medical therapy in patients with chronic stable angina. Many studies have shown that coenzyme Q10 supplementation improved exercise tolerance and reduced or delayed electrocardiographic changes associated with myocardial ischemia compared to placebo [27].

#### Blood pressure

Few studies in humans suggest that coenzyme Q10 supplementation could be beneficial in the treatment of hypertension [28]. Two short-term placebo-controlled trials in hypertensive individuals have found that coenzyme Q10 supplementation resulted in moderate blood pressure decreases. The addition of 120 mg/day of coenzyme Q10 to conventional medical therapy for eight weeks in patients with hypertension and coronary artery disease decreased systolic blood pressure by an average of 12 mm Hg and diastolic blood pressure by

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an average of 6 mm Hg, in comparison to a placebo containing B-complex vitamins [29]. In patients with isolated systolic hypertension, supplementation with both coenzyme Q10 (120 mg/day) and vitamin E (300 IU/day) for 12 weeks resulted in an average decrease of 17 mm Hg in systolic blood pressure compared with 300 IU/day of vitamin E (300 IU/day) alone [30]. A 2007 meta-analysis of 12 clinical trials, including 362 hypertensive patients, found that supplemental coenzyme Q10 reduces systolic blood pressure by 11-17 mm Hg and diastolic blood pressure by 8-10 mm Hg [31].

### **Vascular endothelial function (blood vessel dilation)**

Normal function of the inner lining of blood vessels, known as the vascular endothelium, plays an important role in preventing cardiovascular diseases [32]. Atherosclerosis is characterized with impairment of vascular endothelial function, thus reducing the ability of blood vessels to relax and permit normal blood flow. Patients with elevated serum cholesterol levels and patients with coronary artery disease or diabetes can experience impairment of endothelium-dependent blood vessel relaxation (vasodilation). One placebo-controlled trial found that coenzyme Q10 supplementation (200 mg/day) for 12 weeks improved endothelium-dependent vasodilation in diabetic patients with abnormal serum lipid profiles, although it did not restore vasodilation to levels seen in non-diabetic individuals [33]. Another placebo-controlled study in 23 type 2 diabetics taking statins found that 200 mg/day of coenzyme Q10 for 12 weeks improved flow-mediated dilatation of the brachial artery [34].

However, a placebo-controlled trial in 80 type 2 diabetics found that this supplementation protocol did not improve endothelial function [35]. In another study on individuals with high serum cholesterol levels and endothelial dysfunction who were otherwise healthy, supplementation with 150 mg/day of coenzyme Q10 did not affect endothelium-dependent vasodilation [36]. A prospective, randomized cross-over study of 25 men with endothelial dysfunction found that coenzyme Q10 supplementation (150 mg/day) significantly improved endothelial function, similar to that of a lipid-lowering medication [37]. A randomized, double-blind, placebo-controlled trial on patients with coronary artery disease found that 300 mg/day of coenzyme Q10 for one month improved endothelium-dependent vasodilation [38]. Another randomized, double-blind, placebo-controlled trial in 56 patients with ischemic left ventricular systolic dysfunction reported that 300 mg/day of coenzyme Q10 for eight weeks significantly improved measures of endothelial dysfunction [39]. A 2011 meta-analysis examining the results of five randomized controlled trials, including 194 subjects, found that supplemental coenzyme Q10 (150-300 mg/day for four to 12 weeks) resulted in a clinically significant, 1.7% increase in flow-dependent endothelial-mediated dilation [40].

### **Diabetes mellitus**

Plasma levels of reduced coenzyme Q10 (CoQ10 H<sub>2</sub>) have been found to be lower in diabetic patients than healthy controls when normalized to plasma cholesterol levels [41]. However, supplementation with 100 mg/day of coenzyme Q10 for three months neither improved glycemic control nor decreased insulin requirements in type 1 diabetic compared to placebo [42].

Similarly, 200 mg/day of coenzyme Q10 supplementation for 12 weeks or six months did not improve glycemic control or serum lipid profiles in type 2 diabetics [43].

## **Neurodegenerative Diseases**

### **Parkinson's disease**

Parkinson's disease is characterized by tremors, muscular rigidity, and slow movements because it's considered as degenerative neurological disorder. The causes of Parkinson's disease are not all known so far, but it is thought that decreased activity of complex I of the mitochondrial electron transport chain and increased oxidative stress in a part of the brain called the substantia nigra play a role in development of Parkinson's disease. Coenzyme Q10 is the electron acceptor for complex I as well as an antioxidant, and decreased ratios of reduced to oxidized coenzyme Q10 have been found in platelets of individuals with Parkinson's disease [44]. One study also found higher concentrations of oxidized coenzyme Q10 in the cerebrospinal fluid of patients with untreated Parkinson's disease compared to healthy controls [45]. Additionally, a study of coenzyme Q10 levels in postmortem Parkinson's disease patients found lower levels of total coenzyme Q10 in the cortex region of the brain compared to age-matched controls, but no differences were seen in other

brain areas, including the striatum, substantianigra, and cerebellum [46]. A 16-month randomized placebo-controlled trial evaluated the safety and efficacy of 300, 600, or 1,200 mg/day of coenzyme Q10 in 80 people with early Parkinson's disease [47]. Coenzyme Q10 supplementation was well tolerated at all doses and was associated with slower deterioration of function in Parkinson's disease patients compared to placebo [48]. More recently, a randomized, double-blind; placebo-controlled trial in 106 patients with mid-stage Parkinson's disease reported that 300 mg/day of nanoparticulate coenzyme Q10 for three months had no therapeutic benefit [49]. Another trial found that 2,400 mg/day of coenzyme Q10 for 12 months was not effective in early Parkinson's disease [50]. A phase III clinical trial of coenzyme Q10 (1,200-2,400 mg/day) and vitamin E (1,200 IU/day) supplementation in patients with Parkinson's disease was recently terminated because it was unlikely that such a treatment was effective in treating Parkinson's disease [51].

### Huntington's disease

Huntington's disease is characterized by selective degeneration of nerve cells known as striatal spiny neurons. With age, symptoms start to develop, such as movement disorders and reduced cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. Coenzyme Q10 supplementation has been found to decrease brain lesion size in animal models of Huntington's disease and to decrease brain lactate levels in Huntington's disease patients [52]. Feeding a combination of coenzyme Q10 (0.2% of diet) and remacemide which is an antagonist of the neuronal receptor that is activated by glutamate (0.007% of diet) to transgenic mice that express the Huntington's disease protein resulted in improved motor performance and/or survival [53].

A 30-month, randomized, placebo-controlled trial of coenzyme Q10 (600 mg/day), remacemide, or both in 347 patients with early Huntington's disease found that neither coenzyme Q10 nor remacemide significantly altered the decline in total functional capacity, although coenzyme Q10 supplementation (with or without remacemide) resulted in a non significant 13% decrease in the decline [54].

### Friedreich's ataxia

Clinically, FRDA is a progressive disease characterized by limb ataxia and CNS abnormalities that result from sensory nerve degeneration [55]. In addition, FRDA patients experience symptoms of hypertrophic cardiomyopathy and diabetes [56]. A pilot study administering coenzyme Q10 (200 mg/day) and vitamin E (2,100 IU/day) to ten FDRA patients found that energy metabolism of cardiac and skeletal muscle was improved after only three months of therapy [57]. The therapy using coenzyme Q10 was effective at preventing the progressive decline of neurological function. Follow-up assessments have shown that cardiac and skeletal muscle improvements were maintained and that FRDA patients showed significant increases in fractional shortening, a measure of cardiac function. [58].

### Cancer

Interest in coenzyme Q10 as a potential therapeutic agent in cancer was stimulated by an observational study that found that individuals with lung, pancreas, and especially breast cancer were more likely to have low plasma coenzyme Q10 levels than healthy controls [59].

### Co enzyme Q10 as sport supplement

At least seven placebo controlled trials have examined the effects of 100-150 mg/day of coenzyme Q10 supplementation for three to eight weeks on physical performance in trained and untrained men. Most found no significant differences between groups taking coenzyme Q10 and groups taking placebos with respect to measures of aerobic exercise performance, such as maximal oxygen consumption ( $VO_{2max}$ ) and exercise time to exhaustion [60]. One study found the maximal cycling workload to be slightly (4%) increased after eight weeks of coenzyme Q10 supplementation compared to placebo, although measures of aerobic power were not increased [61]. Two studies actually found significantly greater improvement in measures of anaerobic [62] and aerobic exercise performance after supplementation with a placebo compared to coenzyme Q10.

### Sources of Co enzyme Q10

#### Biosynthesis

Coenzyme Q10 is synthesized in most human tissues. The biosynthesis of coenzyme Q10 involves three major steps: (1) synthesis of the benzoquinone structure from either tyrosine or phenylalanine, two amino acids; (2) synthesis of the isoprene side chain from acetyl-coenzyme A (CoA) via the mevalonate pathway; and (3) the joining or condensation of these two structures. The enzyme hydroxymethylglutaryl (HMG)-CoA reductase plays a critical role in the regulation of coenzyme Q10 synthesis, as well as the regulation of cholesterol synthesis [1,6].

Adequate vitamin B6 nutrition is essential for coenzyme Q10 biosynthesis because the first step in benzoquinone biosynthesis requires vitamin B6 in the form of pyridoxal 5'-phosphate. A pilot study in 29 patients and healthy volunteers found significant positive correlations between blood levels of coenzyme Q10 and measures of vitamin B6 nutritional statuses [64].

#### Main dietary Sources

Based on food frequency studies, the average dietary intake of coenzyme Q10 in Denmark was estimated to be 3-5 mg/day [6,7]. Most people probably have a dietary intake of less than 10 mg/day of coenzyme Q10. Coenzyme Q10 and are found in rich resources such as meat, poultry and fish. Other sources can be considered relatively rich including soybean and canola oils, and nuts. Whereas fruits, vegetables, eggs, and dairy products, are considered moderate sources of coenzyme Q10. Cooking methods can affect the level of coenzyme Q10. It was found that frying process of vegetables and eggs can result in 14%-32% loss of coenzyme Q10, but boiling does not alter the content of coenzyme Q10 of these foods. The reason behind that is the combination of temperature and its effect on fatty acid profile.

#### Supplementations

Coenzyme Q10 is sold in the U.S as a dietary supplements without a prescription as a supplement. It is given to adults in the range of 30-100 mg/day, and this amount is higher than normal dietary coenzyme Q10 intake. Therapeutic doses for adults generally range from 100-300 mg/day, although doses as high as 3,000 mg/day have been used to treat early Parkinson's disease under medical supervision [65]. In human, total intestinal absorption is likely to be less than 10% and the rate of absorption decreases with increasing supplemental dose. Because Coenzyme Q10 is fat-soluble, it is best absorbed with fat in a meal. When taking doses higher than 100 mg/day, it is recommended to divide this amount into two or three doses throughout the day [66].

#### Toxicity of co enzyme Q10

There have been no reports of significant adverse side effects of oral coenzyme Q10 supplementation at doses as high as 1,200 mg/day for up to 16 months and 600 mg/day for up to 30 months. In fact, 1,200 mg/day has recently been proposed as the observed safe level (OSL) for coenzyme Q10 [67]. Cases of gastrointestinal disorders were reported, such as nausea, diarrhea, appetite suppression, heartburn, and abdominal discomfort. These symptoms can be by dividing doses higher than 100 mg into two or three daily doses. Because controlled safety studies in pregnant and lactating women are not available, the use of coenzyme Q10 supplements by pregnant or breastfeeding women should be avoided [68].

#### Interactions with Warfarin

Many cases have shown that coenzyme Q10 supplements can interact with warfarin (Coumadin) decreasing the anticoagulant effect of warfarin [69].

#### Interaction with statins: HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors, also known as statins, are widely used cholesterol-lowering medications that may also decrease the endogenous synthesis of coenzyme Q10. Therapeutic use of statins has been shown to decrease blood plasma or serum levels of coenzyme Q10 [70].

However, it has been suggested that blood coenzyme Q10 concentrations should be reported only after normalizing to total lipid or cholesterol levels because coenzyme Q10 circulates with lipoproteins and levels of coenzyme Q10 are highly dependent upon levels of circulating lipids [71]. Given the lipid-lowering effects of statins, it is therefore unclear whether these drugs actually decrease coenzyme Q10 levels independent of a reduction in circulating lipids [72].

### Conclusion

Coenzyme Q10 or ubiquinone is considered as powerful antioxidants and can protect body from the damaging effect of free radicals, which damage cell membranes, alter the biological processes in body causing many degenerative diseases causing death. Studies have demonstrated that free radicals contribute to the aging process, as well as a number of health problems, including heart disease and cancer. Supplementation with Coenzyme Q10 can neutralize free radicals and may reduce or even help prevent some of the damage they cause. Coenzyme Q10 act as an antioxidant and can help in the treatment of heart-related conditions, because it can improve energy production in cells, prevent blood clot formation. Also, coenzyme Q10 can help in prevention and treatment of other diseases such as aging, hypertension, diabetes and neurodegenerative disease such as Parkinson's and Alzheimer's diseases.

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