

Coenzyme Q10

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Summary

Coenzyme Q10 is a fat-soluble compound primarily synthesized by the body and also consumed in the diet. Coenzyme Q10 is required for mitochondrial ATP synthesis and functions as an antioxidant in cell membranes and lipoproteins. (More information)

Endogenous synthesis and dietary intake appear to provide sufficient coenzyme Q10 to prevent deficiency in healthy people, although tissue levels of coenzyme Q10 decline with age. (More information)

Oral supplementation of coenzyme Q10 increases plasma, lipoprotein, and blood vessel levels, but it is unclear whether tissue coenzyme Q10 levels are increased, especially in healthy individuals. (More information)

Coenzyme Q10 supplementation has resulted in clinical and metabolic improvement in some patients with hereditary mitochondrial disorders. (More information)

Although coenzyme Q10 supplementation may be a useful adjunct to conventional medical therapy for congestive heart failure, additional research is needed. (More information)

Roles for coenzyme Q10 supplementation in cardiovascular diseases, neurodegenerative diseases, cancer, and diabetes require further research. (More information)

Coenzyme Q10 supplementation does not appear to improve athletic performance. (More information)

Although coenzyme Q10 supplements are relatively safe, they may decrease the anticoagulant efficacy of warfarin. (More information)

Although the use of cholesterol-lowering medications known as HMG-CoA reductase inhibitors (statins) decreases circulating levels of coenzyme Q10, it is unclear whether coenzyme Q10 supplementation provides any health benefit to patients taking these drugs. (More information)

Introduction

Coenzyme Q10 is a member of the ubiquinone family of compounds. All animals, including humans, can synthesize ubiquinones, hence, coenzyme Q10 cannot be considered a vitamin (1). The name ubiquinone refers to the ubiquitous presence of these compounds in living organisms and their chemical structure, which contains a functional group known as a benzoquinone. Ubiquinones are fat-soluble molecules with anywhere from one to 12 isoprene (5-carbon) units. The ubiquinone found in humans, ubiquinone or coenzyme Q10, has a "tail" of ten isoprene units (a total of 50 carbon atoms) attached to its benzoquinone "head" (diagram) (2).

Function

Coenzyme Q10 is soluble in lipids (fats) and is found in virtually all cell membranes, as well as lipoproteins (2). The ability of the benzoquinone head group of coenzyme Q10 to accept and donate electrons is a critical feature in its biochemical functions. Coenzyme Q10 can exist in three oxidation states (diagram): (1) the fully reduced ubiquinol form (CoQ10H₂), (2) the radical semiquinone intermediate (CoQ10H[•]), and (3) the fully oxidized ubiquinone form (CoQ10).

Mitochondrial ATP synthesis

The conversion of energy from carbohydrates and fats to adenosine triphosphate (ATP), the form of energy used by cells, requires the presence of coenzyme Q in the inner mitochondrial membrane. 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. At the same time, coenzyme Q transfers protons outside the inner mitochondrial membrane, creating a proton gradient across that membrane. The energy released when the protons flow back into the mitochondrial interior is used to form ATP (2).

Lysosomal function

Lysosomes are organelles within cells that are specialized for the digestion of cellular debris. The digestive enzymes within lysosomes function optimally at an acid pH, meaning they require a permanent supply of protons. The lysosomal membranes that separate those digestive enzymes from the rest of the cell contain relatively high concentrations of coenzyme Q10. Research suggests that coenzyme Q10 plays an important role in the transport of protons across lysosomal membranes to maintain the optimal pH (2, 3).

Antioxidant functions

In its reduced form, CoQ10H₂ is an effective fat-soluble antioxidant. The presence of a significant amount of CoQ10H₂ in cell membranes, along with enzymes that are capable of reducing oxidized CoQ10 back to CoQ10H₂, supports the idea that CoQ10H₂ is an important cellular antioxidant (2). CoQ10H₂ has been found to inhibit lipid peroxidation when cell membranes and low-density lipoproteins (LDL) are exposed to oxidizing conditions outside the body (*ex vivo*). When LDL is oxidized *ex vivo*, CoQ10H₂ is the first antioxidant consumed. Moreover, the formation of oxidized lipids and the consumption of alpha-tocopherol (alpha-TOH, biologically the most active form of vitamin E) are suppressed while CoQ10H₂ is present (4). In isolated mitochondria, coenzyme Q10 can protect membrane proteins and DNA from the oxidative damage that accompanies lipid peroxidation (1). In addition to neutralizing free radicals directly, CoQ10H₂ is capable of regenerating alpha-TOH from its one-electron oxidation product, alpha-tocopheroxyl radical (alpha-TO \cdot).

Nutrient Interactions

Vitamin E

Alpha-tocopherol (vitamin E) and coenzyme Q10 are the principal fat-soluble antioxidants in membranes and lipoproteins. When alpha-TOH neutralizes a free radical, such as a lipid peroxy radical (LOO \cdot), it becomes oxidized itself, forming alpha-TO \cdot , which can promote the oxidation of lipoprotein lipids under certain conditions in the test tube. When the reduced form of coenzyme Q10 (CoQ10H₂) reacts with alpha-TO \cdot , alpha-TOH is regenerated and the semiquinone radical (CoQ10H \cdot) is formed. It is possible for CoQ10H \cdot to react with oxygen (O₂) to produce superoxide anion radical (O₂ \cdot^-), which is a much less oxidizing radical than LOO \cdot . However, CoQ10H \cdot can also reduce alpha-TO \cdot back to alpha-TOH, resulting in the formation of fully oxidized coenzyme Q10 (CoQ10), which does not react with O₂ to form O₂ \cdot^- (See Reaction Scheme) (4, 5).

Deficiency

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 (6). 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 (7). The extent to which dietary consumption contributes to tissue coenzyme Q10 levels is not clear.

Primary coenzyme Q10 deficiency is a rare, autosomal recessive disorder caused by genetic defects in coenzyme Q10 biosynthesis. The resultant low tissue levels of coenzyme Q10 severely compromise neuronal and muscular function. Oral coenzyme Q10 supplementation has been shown to improve neurological and muscular symptoms in some patients with primary coenzyme Q10 deficiency (8). Coenzyme Q10 levels have been found to decline gradually with age in a number of different tissues (1, 9), but it is unclear whether this age-associated decline constitutes a deficiency (see Disease Prevention). Decreased plasma levels of coenzyme Q10 have been observed in individuals with diabetes, cancer, and congestive heart failure (see Disease Treatment). 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 (see HMG-CoA reductase inhibitors (statins) under Drug Interactions), although it remains unclear whether this has clinical or symptomatic implications.

Disease Prevention

Aging

According to the free radical and mitochondrial theories of aging, oxidative damage of cell structures by reactive oxygen species (ROS) plays an important role in the functional declines that accompany aging (10). ROS are generated by mitochondria as a byproduct of ATP production. If not neutralized by antioxidants, ROS may damage mitochondria over time, causing them to function less efficiently and to generate more damaging ROS in a self-perpetuating cycle. Coenzyme Q10 plays an important role in mitochondrial ATP synthesis and functions as an antioxidant in mitochondrial membranes. Moreover, tissue levels of coenzyme Q10 have been reported to decline with age (9). One of the hallmarks of aging is a decline in energy metabolism in many tissues, especially liver, heart, and skeletal muscle. 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 lifespans of rats or mice (12, 13); however, one study showed that coenzyme Q10 supplementation attenuates the age-related increase in DNA damage (14). Presently, there is no scientific evidence that coenzyme Q10 supplementation prolongs life or prevents age-related functional declines in humans.

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 (CoQ10H₂) inhibits the oxidation of LDL in the test tube (in vitro) and works together with α -TOH to inhibit LDL oxidation by reducing the α -TO \cdot back to α -TOH. In the absence of a co-antioxidant, such as CoQ10H₂ (or vitamin C), α -TOH can, under certain conditions, promote the oxidation of LDL in vitro (4). Supplementation with coenzyme Q10 increases the concentration of CoQ10H₂ in human LDL (15). 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 (16). Interestingly, co-supplementation of these mice with α -TOH and coenzyme Q10 was more effective in inhibiting atherosclerosis than supplementation with either α -TOH or coenzyme Q10 alone (17). Another important step in the development of atherosclerosis is the recruitment of immune cells known as monocytes into the blood vessel walls. This recruitment is dependent in part on monocyte expression of cell adhesion molecules (integrins). Supplementation of ten healthy men and women with 200 mg/day of coenzyme Q10 for ten weeks resulted in significant decreases in monocyte expression of integrins, suggesting another potential mechanism for the inhibition of atherosclerosis by coenzyme Q10 (18). Although coenzyme Q10 supplementation shows promise as an inhibitor of LDL oxidation and atherosclerosis, more research is needed to determine whether coenzyme Q10 supplementation can inhibit the development or progression of atherosclerosis in humans.

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 (19). Neuromuscular and widespread tissue coenzyme Q10 deficiencies have been found in a very small subpopulation of individuals with mitochondrial encephalomyopathies (20, 21). In those rare individuals with genetic defects in coenzyme Q10 biosynthesis, coenzyme Q10 supplementation has resulted in substantial improvement (22, 23). 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 (23).

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. In coronary artery disease, accumulation of atherosclerotic plaque in the coronary arteries may prevent parts of the heart muscle from getting adequate blood supply, ultimately resulting in cardiac damage and impaired

pumping ability. Myocardial infarction (MI) may also damage the heart muscle, leading to heart failure. Because physical exercise increases the demand on the weakened heart, measures of exercise tolerance are frequently used to monitor the severity of heart failure. Echocardiography is also used to determine the left ventricular ejection fraction, an objective measure of the heart's pumping ability (25). The finding that myocardial coenzyme Q10 levels were lower in patients with more severe versus milder heart failure led to several clinical trials of coenzyme Q10 supplementation in heart failure patients (26). 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 (27-29). However, other researchers have found that supplementing the diet with 100-200 mg/day of coenzyme Q10, along with conventional medical therapy, did not significantly improve left ventricular ejection fraction or exercise performance in heart failure patients (30, 31). A 2006 meta-analysis of ten randomized controlled trials found that coenzyme Q10 supplementation (99-200 mg/day for one to six months) in heart failure patients resulted in a significant, 3.7% improvement in left ventricular ejection fraction; the effect was stronger in patients not taking angiotensin-converting enzyme inhibitors (32). A slight increase in cardiac output (0.28 L/min) was also found with coenzyme Q10 supplementation, but this analysis only included two trials (60 mg/day for one month or 200 mg/day for three months) (32). A recent study in 236 heart failure patients found that lower plasma coenzyme Q10 levels were associated with a heightened risk of mortality (33); however, a larger study of 1,191 heart failure patients 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 (34). Although there is some evidence that coenzyme Q10 supplementation may be of benefit, large well-designed intervention trials are needed to determine whether coenzyme Q10 supplementation has value as an adjunct to conventional medical therapy in the treatment of congestive heart failure. One such large trial is presently being conducted.

Myocardial infarction and cardiac surgery

The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction (MI) or during cardiac surgery. Increased generation of ROS when the heart muscle's oxygen supply is restored (reperfusion) is thought to be an important contributor to myocardial damage occurring during ischemia-reperfusion. Pretreatment of animals with coenzyme Q10 has been found to decrease myocardial damage due to ischemia-reperfusion (35). Another potential source of ischemia-reperfusion injury is aortic clamping during some types of cardiac surgery, such as coronary artery bypass graft (CABG) surgery. 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 (36, 37). 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 (38), suggesting that preoperative coenzyme Q10 treatment may need to commence at least one week prior to CABG surgery in order to realize any benefit. Although the results are promising, these trials have included relatively few people and have only examined outcomes shortly after CABG surgery.

Angina pectoris

Myocardial ischemia may also lead to chest pain known as angina pectoris. People with angina pectoris often experience symptoms 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 (28). In most of the studies, coenzyme Q10 supplementation improved exercise tolerance and reduced or delayed electrocardiographic changes associated with myocardial ischemia compared to placebo. However, only two of the studies found significant decreases in symptom frequency and nitroglycerin consumption with coenzyme Q10 supplementation. Presently, there is only limited evidence suggesting that coenzyme Q10 supplementation would be a useful adjunct to conventional angina therapy.

Hypertension

The results of several small, uncontrolled studies in humans suggest that coenzyme Q10 supplementation could be beneficial in the treatment of hypertension (37). More recently, two short-term placebo-controlled trials found that coenzyme Q10 supplementation resulted in moderate blood pressure decreases in hypertensive individuals. 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 an average of 6 mm Hg, in comparison to a placebo containing B-complex vitamins (39). 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 (40). 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 (41). The four randomized controlled trials included in this meta-analysis used doses of 100-120 mg/day of coenzyme Q10.

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 (42). Atherosclerosis is associated with impairment of vascular endothelial function, thereby compromising the ability of blood vessels to relax and permit normal blood flow. Endothelium-dependent blood vessel relaxation (vasodilation) is impaired in individuals with elevated serum cholesterol levels as well as in patients with coronary artery disease or diabetes. 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 (43). Another placebo-controlled study in 23 type 2 diabetics taking statins (HMG-CoA reductase inhibitors) found that 200 mg/day of coenzyme Q10 for 12 weeks improved flow-mediated dilatation, but not nitrate-mediated dilatation, of the brachial artery (44). However, a placebo-controlled trial in 80 type 2 diabetics found that this supplementation protocol did not improve endothelial function (45).

In a study of 12 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 (46). 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 (47). Yet, it is important to mention that this study was not placebo-controlled and, importantly, the authors reported that the subjects' mean baseline for flow-mediated vasodilation was below zero. A randomized, double-blind, placebo-controlled trial in 22 patients with coronary artery disease found that 300 mg/day of coenzyme Q10 for one month improved endothelium-dependent vasodilation (48). 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 (49). 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 (50). Large-scale studies are needed to further elucidate the therapeutic role of coenzyme Q10 in endothelial dysfunction.

Diabetes mellitus

Diabetes mellitus is a condition of increased oxidative stress and impaired energy metabolism. Plasma levels of reduced coenzyme Q10 (CoQ10H₂) have been found to be lower in diabetic patients than healthy controls when normalized to plasma cholesterol levels (51, 52). However, supplementation with 100 mg/day of coenzyme Q10 for three months neither improved glycemic (blood glucose) control nor decreased insulin requirements in type 1 (insulin-dependent) diabetics compared to placebo (53). 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 (non-insulin dependent) diabetics (45, 54). Because coenzyme Q10 supplementation did not influence glycemic control in either study, the authors of both studies concluded that coenzyme Q10 supplements could be used safely in diabetic patients as adjunct therapy for cardiovascular diseases.

Maternally inherited diabetes mellitus and deafness (MIDD) is the result of a mutation in mitochondrial DNA, which is inherited exclusively from one's mother. Although mitochondrial diabetes accounts for less than 1% of all diabetes, there is some evidence that long-term coenzyme Q10 supplementation (150 mg/day) may improve insulin secretion and prevent progressive hearing loss in these patients (55, 56).

Neurodegenerative diseases

Parkinson's disease

Parkinson's disease is a degenerative neurological disorder characterized by tremors, muscular rigidity, and slow movements. It is estimated to affect approximately 1% of Americans over the age of 65. Although the causes of Parkinson's disease are not all known, 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 are thought to play a role. 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 (57, 58). 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 (59). 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, substantia nigra, and cerebellum (60). 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 (61). 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. However, the difference was statistically significant only in the group taking 1,200 mg/day. A smaller placebo-controlled trial showed that oral administration of 360 mg/day of coenzyme Q10 for four weeks moderately benefited Parkinson's disease patients (62). More recently, a randomized, double-blind, placebo-controlled trial in 106 patients with midstage Parkinson's disease reported that 300 mg/day of nanoparticulate coenzyme Q10 for three months had no therapeutic benefit (63). Another trial found that 2,400 mg/day of coenzyme Q10 for 12 months was not effective in early Parkinson's disease (64). 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 (65).

Huntington's disease

Huntington's disease is an inherited neurodegenerative disorder characterized by selective degeneration of nerve cells known as striatal spiny neurons. Symptoms, such as movement disorders and impaired cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. Animal models indicate that impaired mitochondrial function and glutamate-mediated neurotoxicity may play roles in the pathology of Huntington's disease. 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 (66, 67). Feeding a combination of coenzyme Q10 (0.2% of diet) and remacemide (0.007% of diet) to transgenic mice that express the Huntington's disease protein (HD-N171-82Q mice) resulted in improved motor performance and/or survival (68, 69). Remacemide is an antagonist of the neuronal receptor that is activated by glutamate.

It was recently shown that the R6/2 mouse model of Huntington's disease exhibits a progressive decline in behavioral and neurological symptoms similar to that of the human condition (70). Thus, R6/2 mice may be an ideal model to investigate potential therapies for Huntington's disease. Some, but not all, studies employing these mice have shown that dietary supplementation with coenzyme Q10 (0.2% of diet) improves motor performance and overall survival and helps to prevent body weight loss; coenzyme Q10 supplementation has also been associated with reductions in the various hallmarks of Huntington's disease, i.e., brain atrophy, ventricular enlargement, and striatal neuronal atrophy (68, 71). Interestingly, co-administration of coenzyme Q10 with remacemide, the antibiotic minocycline, or creatine has been shown to result in even greater improvements in most measured parameters (68, 71, 72).

To date, only one clinical trial has examined whether coenzyme Q10 might be efficacious in human patients with Huntington's disease. 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 nonsignificant 13% decrease in the decline (73). A recent 20-week pilot trial examined the safety and tolerability of increasing dosages of coenzyme Q10 (1,200 mg/day, 2,400 mg/day, and 3,600 mg/day) in eight healthy subjects and in 20 patients with Huntington's disease; 22 of the subjects completed the study (74). All dosages were generally well tolerated, with gastrointestinal symptoms being the most frequently reported adverse effect. Blood levels of coenzyme Q10 at the end of the study were not higher than the levels resulting from the intermediate dose, suggesting that the 2,400 mg/day effectively maximizes blood coenzyme Q10

levels and potentially avoid any side effects with higher dosages (74). A phase III clinical trial administering 2,400 mg/day of coenzyme Q10 or placebo for five years is currently recruiting participants with Huntington's disease (75). At present, there is insufficient evidence to recommend coenzyme Q10 supplements to Huntington's disease patients.

Friedreich's ataxia

Friedreich's ataxia (FRDA) is an inherited, autosomal recessive neurodegenerative disease caused by mutations in the gene that encodes frataxin, a protein of unknown function that is primarily located in the mitochondria. Decreased expression of frataxin is associated with accumulation of iron within the mitochondria, thereby resulting in increased oxidative stress; imbalances in iron-sulfur containing proteins, including mitochondrial aconitase; and reduced activities of the mitochondrial respiratory chain (76). Clinically, FRDA is a progressive disease characterized by limb ataxia and CNS abnormalities that result from sensory nerve degeneration (77, 78). In addition, FRDA patients experience symptoms of hypertrophic cardiomyopathy and diabetes (79). A pilot study administering coenzyme Q10 (200 mg/day) and vitamin E (2,100 IU/day) to ten FRDA patients found that energy metabolism of cardiac and skeletal muscle was improved after only three months of therapy (80). Follow-up assessments at 47 months indicated that cardiac and skeletal muscle improvements were maintained and that FRDA patients showed significant increases in fractional shortening, a measure of cardiac function. Moreover, the therapy was effective at preventing the progressive decline of neurological function (81). A recent study reported that both coenzyme Q10 and vitamin E deficiencies are quite common among FRDA patients and that cosupplementation with both compounds, at doses as low as 30mg/day of coenzyme Q10 and 4 IU/day of vitamin E, may improve disease symptoms (82). Large-scale randomized clinical trials are necessary to determine whether coenzyme Q10, in conjunction with vitamin E, has therapeutic benefit in FRDA.

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 (83). Although a few case reports and an uncontrolled trial suggest that coenzyme Q10 supplementation may be beneficial as an adjunct to conventional therapy for breast cancer (84), the lack of controlled clinical trials makes it impossible to determine the effects, if any, of coenzyme Q10 supplementation in cancer patients.

Performance

Athletic performance

Although coenzyme Q10 supplementation has improved exercise tolerance in some individuals with mitochondrial encephalomyopathies (see Deficiency) (19), there is little evidence that it improves athletic performance in healthy individuals. 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 (VO₂ max) and exercise time to exhaustion (85-89). 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 (90). Two studies actually found significantly greater improvement in measures of anaerobic (86) and aerobic (85) exercise performance after supplementation with a placebo compared to coenzyme Q10. Studies on the effect of supplementation on physical performance in women are lacking, but there is little reason to suspect a gender difference in the response to coenzyme Q10 supplementation.

Sources

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).

The first step in benzoquinone biosynthesis (the conversion of tyrosine to 4-hydroxyphenylpyruvic acid) requires vitamin B6 in the form of pyridoxal 5'-phosphate. Thus, adequate vitamin B6 nutrition is essential for coenzyme Q10 biosynthesis. 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 status (91). However, further research is required to determine the clinical significance of this association.

Food 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. Rich sources of dietary coenzyme Q10 include mainly meat, poultry, and fish. Other relatively rich sources include soybean and canola oils, and nuts. Fruits, vegetables, eggs, and dairy products are moderate sources of coenzyme Q10. Approximately 14%-32% of coenzyme Q10 was lost during frying of vegetables and eggs, but the coenzyme Q10 content of these foods did not change when they were boiled. Some relatively rich dietary sources and their coenzyme Q10 content in milligrams (mg) (92-94).

Supplements

Coenzyme Q10 is available without a prescription as a dietary supplement in the U.S. Supplemental doses for adults range from 30-100 mg/day, which is considerably 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 (95). Absorption of coenzyme Q10 decreases with increasing supplemental dose; total intestinal absorption is likely less than 10% in humans. Coenzyme Q10 is fat-soluble and is best absorbed with fat in a meal. Doses higher than 100 mg/day are generally divided into two or three doses throughout the day (7, 96).

Does oral coenzyme Q10 supplementation increase tissue levels?

Oral supplementation with coenzyme Q10 is known to increase blood and lipoprotein concentrations of coenzyme Q10 in humans (2, 12, 15). However, it is not clear whether oral supplementation increases coenzyme Q10 concentrations in other tissues of individuals with normal endogenous coenzyme Q10 biosynthesis. Oral coenzyme Q10 supplementation of young healthy animals has not generally resulted in increased tissue concentrations, other than in the liver, spleen, and blood vessels (97, 98). Supplementation of healthy men with 120 mg/day for three weeks did not increase skeletal muscle concentrations of coenzyme Q10 (99). However, supplementation may increase coenzyme Q10 levels in tissues that are deficient. For example, oral supplementation of aged rats increased brain coenzyme Q10 concentrations (100), and a study of 24 older adults supplemented with 300 mg/day of coenzyme Q10 or placebo for at least seven days prior to cardiac surgery found that the coenzyme Q10 content of atrial tissue was significantly increased in those taking coenzyme Q10, especially in those over 70 years of age (36). Additionally, in a study of patients with left ventricular dysfunction, supplementation with 150 mg/day of coenzyme Q10 for four weeks before cardiac surgery increased coenzyme Q10 levels in the heart but not in skeletal muscle (101). Clearly, this is an area of research that requires further investigation.

Safety

Toxicity

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 (61) and 600 mg/day for up to 30 months (73). In fact, 1,200 mg/day has recently been proposed as the observed safe level (OSL) for coenzyme Q10 (102). Some people have experienced gastrointestinal symptoms, such as nausea, diarrhea, appetite suppression, heartburn, and abdominal discomfort. These adverse effects may be minimized if daily doses higher than 100 mg are divided 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 breast-feeding women should be avoided (96, 103).

Drug Interactions

Warfarin

Concomitant use of warfarin (Coumadin) and coenzyme Q10 supplements has been reported to decrease the anticoagulant effect of warfarin in at least four cases (104). An individual on warfarin should not begin taking coenzyme Q10 supplements without consulting the health care provider who is managing his or her anticoagulant therapy. If warfarin and coenzyme Q10 are to be used concomitantly, blood tests to assess clotting time (prothrombin time; PT/INR) should be monitored frequently, especially in the first two weeks.

HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase is an enzyme that plays a critical role in the regulation of cholesterol synthesis as well as coenzyme Q10 synthesis, although it is now recognized that there are additional rate-limiting steps in the biosynthesis of cholesterol and coenzyme Q10. 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, including simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor, Altacor, Altoprev), rosuvastatin (Crestor), and atorvastatin (Lipitor), has been shown to decrease blood plasma or serum levels of coenzyme Q10 (105-114). 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 (115, 116). 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. Also, very few studies have examined coenzyme Q10 content in target organs; thus, it is not clear whether statin therapy affects coenzyme Q10 concentrations in the body's tissues (111, 113, 117). At present, more research is needed to determine whether coenzyme Q10 supplementation might be beneficial for those taking HMG-CoA reductase inhibitors.

References

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