
NovaQ10©

# Coenzyme Q10

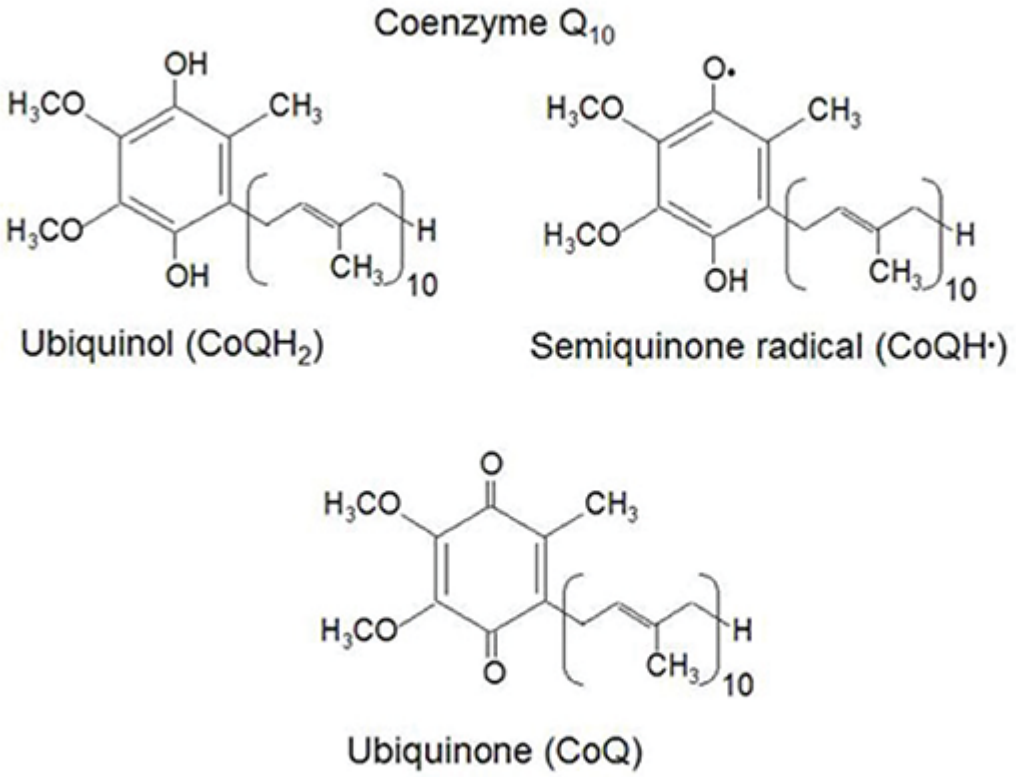
## Summary


- Coenzyme $Q_{10}$ is a fat-soluble compound primarily synthesized by the body and also consumed in the diet.
- Coenzyme $Q_{10}$ 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 $Q_{10}$ to prevent deficiency in healthy people, although tissue levels of coenzyme $Q_{10}$ decline with age. *(More information)*
- Oral supplementation of coenzyme $Q_{10}$ increases plasma, lipoprotein, and blood vessel levels, but it is unclear whether tissue coenzyme $Q_{10}$ levels are increased, especially in healthy individuals. *(More information)*
- Coenzyme $Q_{10}$ supplementation has resulted in clinical and metabolic improvement in some patients with hereditary mitochondrial disorders. *(More information)*
- Although coenzyme $Q_{10}$ supplementation may be a useful adjunct to conventional medical therapy for congestive heart failure, additional research is needed. *(More information)*
- Roles for coenzyme $Q_{10}$ supplementation in cardiovascular disease, neurodegenerative diseases, cancer, and diabetes require further research. *(More information)*
- Coenzyme $Q_{10}$ supplementation does not appear to improve athletic performance. *(More information)*
- Although coenzyme $Q_{10}$ 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 $Q_{10}$, it is unclear whether coenzyme $Q_{10}$ supplementation provides any health benefit to patients taking these drugs. *(More information)*


## Introduction

Coenzyme $Q_{10}$ is a member of the ubiquinone family of compounds. All animals, including humans, can synthesize ubiquinones, hence, coenzyme $Q_{10}$ 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, ubidecaquinone or coenzyme $Q_{10}$, has a "tail" of 10 isoprene units (a total of 50 carbon atoms) attached to its benzoquinone "head" (**Figure 1**) (2).

**Figure 1. Chemical Structure of Coenzyme $Q_{10}$**




Coenzyme Q can exist in three oxidation states: the fully reduced ubiquinol form ($CoQH_2$), the radical semiquinone intermediate (CoQH·), and the fully oxidized ubiquinone form (CoQ).

## Biological Activities

Coenzyme $Q_{10}$ 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 $Q_{10}$ to accept and donate electrons is a critical feature in its biochemical functions. Coenzyme $Q_{10}$ can exist in three oxidation states (see **Figure 1** above): (1) the fully reduced ubiquinol form ($CoQ_{10}H_2$), (2) the radical semiquinone intermediate ($CoQ_{10}H\cdot$), and (3) the fully oxidized ubiquinone form ($CoQ_{10}$).

### 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 $Q_{10}$. Research suggests that coenzyme $Q_{10}$ plays an important role in the transport of protons across lysosomal membranes to maintain the optimal pH (2, 3).

## Antioxidant functions

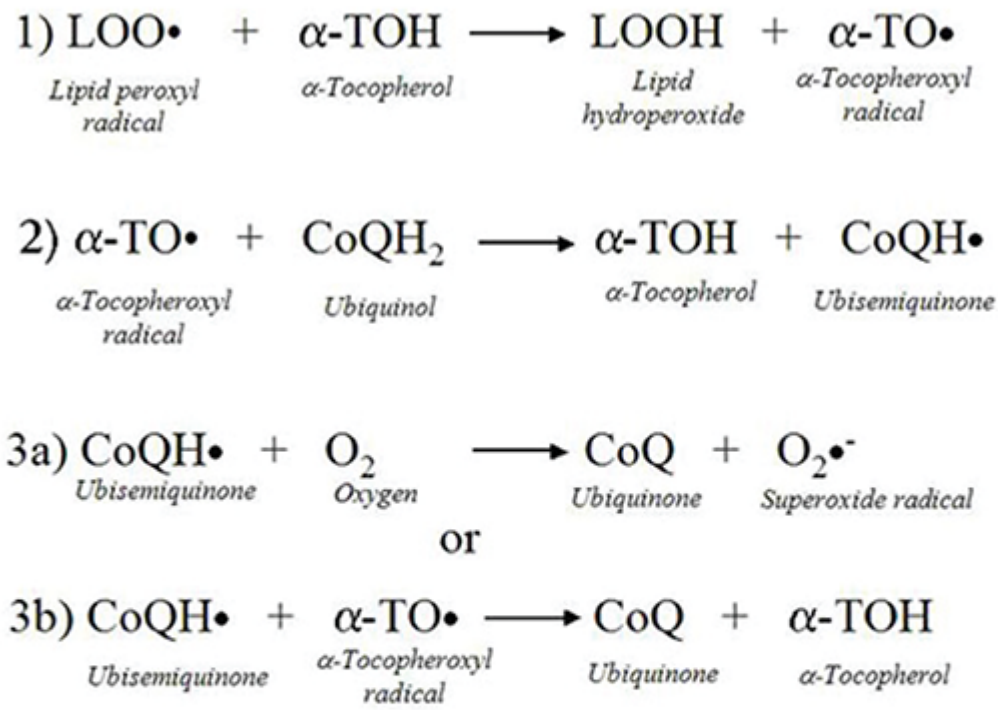
In its reduced form, $CoQ_{10}H_2$ is an effective fat-soluble antioxidant. The presence of a significant amount of $CoQ_{10}H_2$ in cell membranes, along with enzymes that are capable of reducing oxidized $CoQ_{10}$ back to $CoQ_{10}H_2$, supports the idea that $CoQ_{10}H_2$ is an important cellular antioxidant (2). $CoQ_{10}H_2$ 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*, $CoQ_{10}H_2$ is the first antioxidant consumed. Moreover, the formation of oxidized lipids and the consumption of α-tocopherol (α-TOH, biologically the most active form of vitamin E) are suppressed while $CoQ_{10}H_2$ is present (4). In isolated mitochondria, coenzyme $Q_{10}$ can protect membrane proteins and DNA from the oxidative damage that accompanies lipid peroxidation (1). In addition to neutralizing free radicals directly, $CoQ_{10}H_2$ is capable of regenerating α-TOH from its one-electron oxidation product, α-tocopheroxyl radical (α-TO·).

## Nutrient interactions

### *Vitamin E*

α-Tocopherol (vitamin E) and coenzyme $Q_{10}$ are the principal fat-soluble antioxidants in membranes and lipoproteins. When α-TOH neutralizes a free radical, such as a lipid peroxyl radical (LOO·), it becomes oxidized itself, forming α-TO·, which can promote the oxidation of lipoprotein lipids under certain conditions in the test tube. When the reduced form of coenzyme $Q_{10}$ ($CoQ_{10}H_2$) reacts with α-TO·, α-TOH is regenerated and the semiquinone radical ($CoQ_{10}H$·) is formed. It is possible for $CoQ_{10}H$· to react with oxygen ($O_2$) to produce superoxide anion radical ($O_2$·-), which is a much less oxidizing radical than LOO·. However, $CoQ_{10}H$· can also reduce α-TO· back to α-TOH, resulting in the formation of fully oxidized coenzyme $Q_{10}$ ($CoQ_{10}$), which does not react with $O_2$ to form $O_2$·- (**Figure 2**) (4, 5).

**Figure 2. Potential Interactions Between Coenzyme Q and α-Tocopherol**




When α-tocopherol (α-TOH) neutralizes a free radical, such as a lipid peroxyl radical (LOO·), it becomes oxidized itself, forming the α-tocopheroxyl radical (α-TO·), which can promote the oxidation of lipoprotein lipids under certain conditions in the test tube (Reaction 1). When the reduced form of coenzyme Q ($CoQH_2$) reacts with α-TO·, α-TOH is regenerated and the semiquinone radical (CoQH·) is formed (Reaction 2). It is possible for CoQH· to react with oxygen ($O_2$) to produce superoxide ($O_2^{\cdot-}$), which is a much less oxidizing radical than LOO· (Reaction 3a). Alternatively, CoQH· can also reduce α-TO· back to α-TOH, resulting in the formation of fully oxidized coenzyme Q (CoQ), which does not react with $O_2$ to form $O_2^{\cdot-}$ (Reaction 3b).

## Deficiency

Symptoms of coenzyme $Q_{10}$ deficiency have not been reported in the general population, so it is generally assumed that normal biosynthesis and a varied diet provides sufficient coenzyme $Q_{10}$ for healthy individuals (6). It has been estimated that dietary consumption contributes about 25% of plasma coenzyme $Q_{10}$, but there are currently no specific dietary intake recommendations for coenzyme $Q_{10}$ from the Institute of Medicine or other agencies (7). The extent to which dietary consumption contributes to tissue coenzyme $Q_{10}$ levels is not clear.

Primary coenzyme $Q_{10}$ deficiency is a rare, autosomal recessive disorder caused by genetic defects in coenzyme $Q_{10}$ biosynthesis. The resultant low tissue levels of coenzyme $Q_{10}$ severely compromise neuronal and muscular function. Oral coenzyme $Q_{10}$ supplementation has been shown to improve neurological and muscular symptoms in some patients with primary coenzyme $Q_{10}$ deficiency (8). Coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ biosynthesis, decrease plasma coenzyme $Q_{10}$ 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 $Q_{10}$ plays an important role in mitochondrial ATP synthesis and functions as an antioxidant in mitochondrial membranes. Moreover, tissue levels of coenzyme $Q_{10}$ 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 $Q_{10}$ levels may play a role in this decline (11). In recent studies, lifelong dietary supplementation with coenzyme $Q_{10}$ increased tissue concentrations of coenzyme $Q_{10}$ but did not increase the lifespans of rats or mice (12, 13); however, one study showed that coenzyme $Q_{10}$ supplementation attenuates the age-related increase in DNA damage (14). Presently, there is no scientific evidence that coenzyme $Q_{10}$ 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 $Q_{10}$ ($CoQ_{10}H_2$) 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· back to α-TOH. In the absence of a co-antioxidant, such as $CoQ_{10}H_2$ (or vitamin C), α-TOH can, under certain conditions, promote the oxidation of LDL *in vitro* (4). Supplementation with coenzyme $Q_{10}$ increases the concentration of $CoQ_{10}H_2$ in human LDL (15). Studies in apolipoprotein E-deficient mice, an animal model of atherosclerosis, found that coenzyme $Q_{10}$ supplementation with supra-pharmacological amounts of coenzyme $Q_{10}$ significantly inhibited the formation of atherosclerotic lesions (16). Interestingly, co-supplementation of these mice with α-TOH and coenzyme $Q_{10}$ was more effective in inhibiting atherosclerosis than supplementation with either α-TOH or coenzyme $Q_{10}$ 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 10 healthy men and women with 200 mg/day of coenzyme $Q_{10}$ for 10 weeks resulted in significant decreases in monocyte expression of integrins, suggesting another potential mechanism for the inhibition of atherosclerosis by coenzyme $Q_{10}$ (18). Although coenzyme $Q_{10}$ supplementation shows promise as an inhibitor of LDL oxidation and atherosclerosis, more research is needed to determine whether coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation has resulted in clinical and metabolic improvement in some patients with various types of mitochondrial encephalomyopathies (19). Neuromuscular and widespread tissue coenzyme $Q_{10}$ 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 $Q_{10}$ biosynthesis, coenzyme $Q_{10}$ supplementation has resulted in substantial improvement (22, 23). It is not clear whether coenzyme $Q_{10}$ 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 disease

***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 $Q_{10}$ levels were lower in patients with more severe versus milder heart failure led to several clinical trials of coenzyme $Q_{10}$ supplementation in heart failure patients (26). A number of small intervention trials that administered supplemental coenzyme $Q_{10}$ (100-300 mg/day of coenzyme $Q_{10}$ 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 $Q_{10}$, 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 10 randomized controlled trials found that coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ levels were associated with a heightened risk of mortality (33); however, a larger study of 1,191 heart failure patients found that plasma coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation may be of benefit, large well-designed intervention trials are needed to determine whether coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ supplementation to be of benefit, patients were treated with 600 mg of coenzyme $Q_{10}$ 12 hours prior to surgery (38), suggesting that preoperative coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation (60-600 mg/day) in addition to conventional medical therapy in patients with chronic stable angina (28). In most of the studies, coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation. Presently, there is only limited evidence suggesting that coenzyme $Q_{10}$ supplementation would be a useful adjunct to conventional angina therapy.

#### *Hypertension*

The results of several small, uncontrolled studies in humans suggest that coenzyme $Q_{10}$ supplementation could be beneficial in the treatment of hypertension (37). More recently, two short-term placebo-controlled trials found that coenzyme $Q_{10}$ supplementation resulted in moderate blood pressure decreases in hypertensive individuals. The addition of 120 mg/day of coenzyme $Q_{10}$ 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 $Q_{10}$ (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 $Q_{10}$ 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 $Q_{10}$.

#### *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 disease (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 $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ did not affect endothelium-dependent vasodilation (46). A prospective, randomized cross-over study of 25 men with endothelial dysfunction found that coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ (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 $Q_{10}$ in endothelial dysfunction.

### Diabetes mellitus

Diabetes mellitus is a condition of increased oxidative stress and impaired energy metabolism. Plasma levels of reduced coenzyme $Q_{10}$ ($CoQ_{10}H_2$) 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 $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ supplementation did not influence glycemic control in either study, the authors of both studies concluded that coenzyme $Q_{10}$ supplements could be used safely in diabetic patients as adjunct therapy for cardiovascular disease.

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 $Q_{10}$ 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 $Q_{10}$ is the electron acceptor for complex I as well as an antioxidant, and decreased ratios of reduced to oxidized coenzyme $Q_{10}$ have been found in platelets of individuals with Parkinson's disease (57, 58). One study also found higher concentrations of oxidized coenzyme $Q_{10}$ in the cerebrospinal fluid of patients with untreated Parkinson's disease compared to healthy controls (59). Additionally, a study of coenzyme $Q_{10}$ levels in postmortem Parkinson's disease patients found lower levels of total coenzyme $Q_{10}$ 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 $Q_{10}$ in 80 people with early Parkinson's disease (61). Coenzyme $Q_{10}$ 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 $Q_{10}$ 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 nanoparticular coenzyme $Q_{10}$ for three months had no therapeutic benefit (63). Another trial found that 2,400 mg/day of coenzyme $Q_{10}$ for 12 months was not effective in early Parkinson's disease (64). A phase III clinical trial of coenzyme $Q_{10}$ (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 $Q_{10}$ 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 $Q_{10}$ (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 $Q_{10}$ (0.2% of diet) improves motor performance and

overall survival and helps to prevent body weight loss; coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ might be efficacious in human patients with Huntington's disease. A 30-month, randomized, placebo-controlled trial of coenzyme $Q_{10}$ (600 mg/day), remacemide, or both in 347 patients with early Huntington's disease found that neither coenzyme $Q_{10}$ nor remacemide significantly altered the decline in total functional capacity, although coenzyme $Q_{10}$ 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 $Q_{10}$ (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 $Q_{10}$ 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 $Q_{10}$ levels and potentially avoid any side effects with higher dosages (74). A phase III clinical trial administering 2,400 mg/day of coenzyme $Q_{10}$ or placebo for five years is currently recruiting participants with Huntington's disease (75). At present, there is insufficient evidence to recommend coenzyme $Q_{10}$ 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 $Q_{10}$ (200 mg/day) and vitamin E (2,100 IU/day) to 10 FDRA 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 $Q_{10}$ 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 $Q_{10}$ and 4 IU/day of vitamin E, may improve disease symptoms (82). Large-scale randomized clinical trials are necessary to determine whether coenzyme $Q_{10}$, in conjunction with vitamin E, has therapeutic benefit in FRDA.

### Cancer

Interest in coenzyme $Q_{10}$ 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 $Q_{10}$ levels than healthy controls (83). Although a few case reports and an uncontrolled trial suggest that coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation in cancer patients.

## Performance

### Athletic performance

Although coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation for three to eight weeks on physical performance in trained and untrained men. Most found no significant differences between groups taking coenzyme $Q_{10}$ and groups taking placebos with respect to measures of aerobic exercise performance, such as maximal oxygen consumption ($VO_2$ 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 $Q_{10}$ 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 $Q_{10}$. 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 $Q_{10}$ supplementation.

## Sources

### Biosynthesis

Coenzyme $Q_{10}$ is synthesized in most human tissues. The biosynthesis of coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $B_6$ in the form of pyridoxal 5'-phosphate. Thus, adequate vitamin $B_6$ nutrition is essential for coenzyme $Q_{10}$ biosynthesis. A pilot study in 29 patients and healthy volunteers found significant positive correlations between blood levels of coenzyme $Q_{10}$ and measures of vitamin $B_6$ 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 $Q_{10}$ 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 $Q_{10}$. Rich sources of dietary coenzyme $Q_{10}$ include mainly meat, poultry, and fish. Other relatively rich sources include soybean and canola oils, and nuts. Fruit, vegetables, eggs, and dairy products are moderate sources of coenzyme $Q_{10}$. Approximately 14%-32% of coenzyme $Q_{10}$ was lost during frying of vegetables and eggs, but the coenzyme $Q_{10}$ content of these foods did not change when they were boiled. Some relatively rich dietary sources and their coenzyme $Q_{10}$ content in milligrams (mg) are listed in **Table 1** (92-94).

Table 1. Some Food Sources of Coenzyme $Q_{10}$

| Food | Serving | Coenzyme $Q_{10}$ (mg) |
|---|---|---|
| Beef, fried | 3 ounces* | 2.6 |
| Herring, marinated | 3 ounces | 2.3 |
| Chicken, fried | 3 ounces | 1.4 |
| Soybean oil | 1 tablespoon | 1.3 |
| Canola oil | 1 tablespoon | 1.0 |
| Rainbow trout, steamed | 3 ounces | 0.9 |
| Peanuts, roasted | 1 ounce | 0.8 |
| Sesame seeds, roasted | 1 ounce | 0.7 |

| | | |
|---|---|---|
| Pistachio nuts, roasted | 1 ounce | 0.6 |
| Broccoli, boiled | ½ cup, chopped | 0.5 |
| Cauliflower, boiled | ½ cup, chopped | 0.4 |
| Orange | 1 medium | 0.3 |
| Strawberries | ½ cup | 0.1 |
| Egg, boiled | 1 medium | 0.1 |
| *A 3-ounce serving of meat or fish is about the size of a deck of cards. | | |

### Supplements

Coenzyme $Q_{10}$ is available without a prescription as a dietary supplement in the US Supplemental doses for adults range from 30-100 mg/day, which is considerably higher than normal dietary coenzyme $Q_{10}$ 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 $Q_{10}$ decreases with increasing supplemental dose; total intestinal absorption is likely less than 10% in humans. Coenzyme $Q_{10}$ 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 $Q_{10}$ supplementation increase tissue levels?

Oral supplementation with coenzyme $Q_{10}$ is known to increase blood and lipoprotein concentrations of coenzyme $Q_{10}$ in humans (2, 12, 15). However, it is not clear whether oral supplementation increases coenzyme $Q_{10}$ concentrations in other tissues of individuals with normal endogenous coenzyme $Q_{10}$ biosynthesis. Oral coenzyme $Q_{10}$ 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 $Q_{10}$ (99). However, supplementation may increase coenzyme $Q_{10}$ levels in tissues that are deficient. For example, oral supplementation of aged rats increased brain coenzyme $Q_{10}$ concentrations (100), and a study of 24 older adults supplemented with 300 mg/day of coenzyme $Q_{10}$ or placebo for at least seven days prior to cardiac surgery found that the coenzyme $Q_{10}$ content of atrial tissue was significantly increased in those taking coenzyme $Q_{10}$, 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 $Q_{10}$ for four weeks before cardiac surgery increased coenzyme $Q_{10}$ 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 $Q_{10}$ 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 $Q_{10}$ (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 $Q_{10}$ supplements by pregnant or breast-feeding women should be avoided (96, 103).

### Drug interactions

#### *Warfarin*

Concomitant use of warfarin (Coumadin) and coenzyme $Q_{10}$ 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 $Q_{10}$ supplements without consulting the health care provider who is managing his or her anticoagulant therapy. If warfarin and coenzyme $Q_{10}$ 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 $Q_{10}$ synthesis, although it is now recognized that there are additional rate-limiting steps in the biosynthesis of cholesterol and coenzyme $Q_{10}$. HMG-CoA reductase inhibitors, also known as statins, are widely used cholesterol-lowering medications that may also decrease the endogenous synthesis of coenzyme $Q_{10}$. Therapeutic use of statins, including simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor, Altocor, Altoprev), rosuvastatin (Crestor), and atorvastatin (Lipitor), has been shown to decrease blood plasma or serum levels of coenzyme $Q_{10}$ (105-114). However, it has been suggested that blood coenzyme $Q_{10}$ concentrations should be reported only after normalizing to total lipid or cholesterol levels because coenzyme $Q_{10}$ circulates with lipoproteins and levels of coenzyme $Q_{10}$ 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 $Q_{10}$ levels independent of a reduction in circulating lipids. Also, very few studies have examined coenzyme $Q_{10}$ content in target organs; thus, it is not clear whether statin therapy affects coenzyme $Q_{10}$ concentrations in the body's tissues (111, 113, 117). At present, more research is needed to determine whether coenzyme $Q_{10}$ supplementation might be beneficial for those taking HMG-CoA reductase inhibitors.

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