

22 Coenzyme Q₁₀

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 10 isoprene units (a total of 50 carbon atoms) attached to its benzoquinone “head” (Fig. 22.1).²

Function

Coenzyme Q₁₀ is soluble in lipids (fats) and is found in virtually all cell membranes, as well as lipoprotein.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 (Fig. 22.1): (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 Q₁₀ in the inner mitochondrial membrane. As part of the mitochondrial electron transport chain, coenzyme Q₁₀ accepts electrons from reducing equivalents generated during fatty acid and glucose metabolism and then transfers them to electron acceptors. At the same time, coenzyme Q₁₀ 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 acidic 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 α -tocopherol (α -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 α -TOH from its one-electron oxidation product, α -tocopheroxyl radical (α -TO·).

Nutrient Interactions

Vitamin E

α -Tocopherol (vitamin E) and coenzyme Q₁₀ are the principal fat-soluble antioxidants in membranes and lipoproteins. When α -TOH neutraliz-

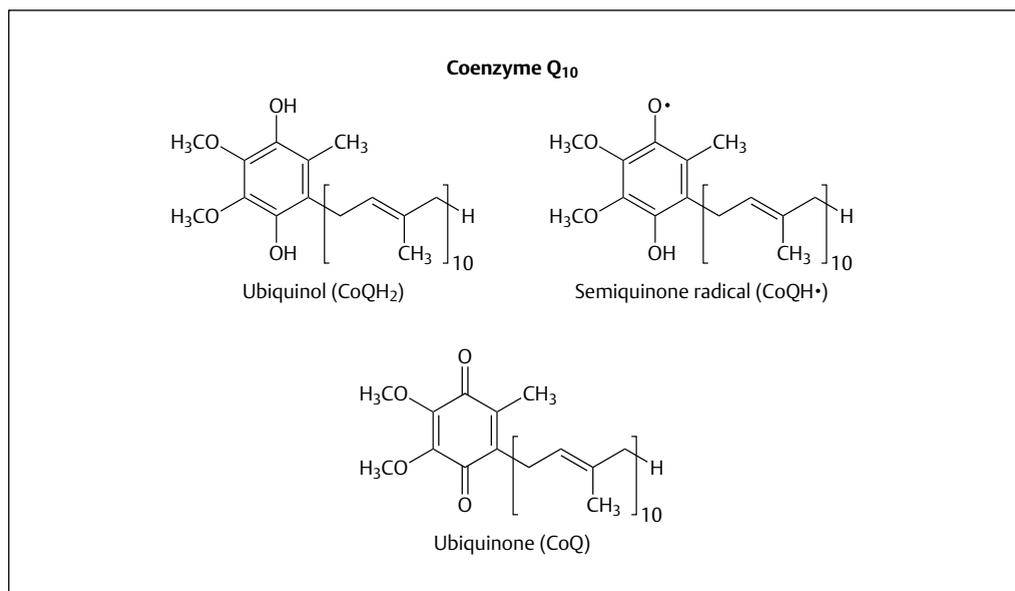


Fig. 22.1 Chemical structure of coenzyme Q₁₀. Coenzyme Q₁₀ can exist in three oxidation states: the fully reduced ubiquinol form (CoQH₂), the radical semiquinone intermediate (CoQH•), and the fully oxidized ubiquinone form (CoQ).

es 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 Q₁₀ (Co-Q₁₀H₂) reacts with α-TO•, α-TOH is regenerated and the semiquinone radical (CoQ₁₀H•) is formed. It is possible for CoQ₁₀H• to react with oxygen (O₂) to produce superoxide anion radical (O₂^{-•}), which is a much less oxidizing radical than LOO•. However, CoQ₁₀H• can also reduce α-TO• back to α-TOH, resulting in the formation of fully oxidized coenzyme Q₁₀ (CoQ₁₀), which does not react with O₂ to form O₂^{-•} (Fig. 22.2).^{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 provide sufficient coenzyme Q₁₀ for healthy individuals.⁶ It has been estimated that dietary consumption contributes approximately 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 several different tissues,^{1,9} but it is unclear whether this age-associated decline constitutes a deficiency (see the Disease Prevention section below). Decreased plasma levels of coenzyme Q₁₀ have been observed in individuals with diabetes, cancer, and congestive heart failure (see the Disease Treatment section below). Lipid-lowering medications that inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a critical enzyme in both cholesterol and coenzyme Q₁₀ biosynthesis, decrease plasma coenzyme Q₁₀ levels (see the section on Drug Interactions below), although it remains unclear whether this has clinical or symptomatic implications.

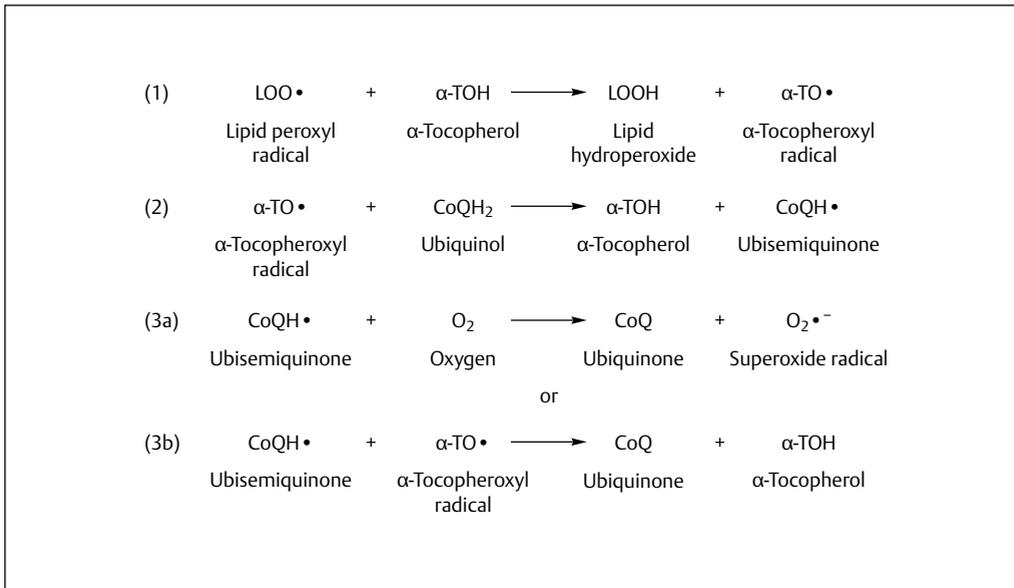


Fig. 22.2 Potential interactions between coenzyme Q_{10} and α -tocopherol. When α -tocopherol ($\alpha\text{-TOH}$) neutralizes a free radical, such as a lipid hydroperoxyl radical ($\text{LOO}\cdot$), it becomes oxidized itself, forming the α -tocopheroxyl radical ($\alpha\text{-TO}\cdot$), which can promote the oxidation of lipoproteins under certain conditions in the test tube (Reaction 1). When the reduced form of coenzyme Q_{10} (CoQH_2) reacts with $\alpha\text{-TO}\cdot$, $\alpha\text{-TOH}$ is regenerat-

ed and the semiquinone radical ($\text{CoQH}\cdot$) is formed (Reaction 2). It is possible for $\text{CoQH}\cdot$ to react with oxygen (O_2) to produce superoxide ($\text{O}_2\cdot^-$), which is a much less-oxidizing radical than $\text{LOO}\cdot$ (Reaction 3a). However, $\text{CoQH}\cdot$ can also reduce $\alpha\text{-TO}\cdot$ back to $\alpha\text{-TOH}$, resulting in the formation of fully oxidized coenzyme Q_{10} (CoQ), which does not react with O_2 to form $\text{O}_2\cdot^-$ (Reaction 3b).

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 by-product 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 decline in humans.

Cardiovascular Disease

Oxidative modification of LDL in arterial walls is thought to represent an early event leading to the development of atherosclerosis. Reduced coenzyme Q_{10} ($\text{CoQ}_{10}\text{H}_2$) inhibits the oxidation of LDL in the test tube (in vitro) and works together with $\alpha\text{-TOH}$ to inhibit LDL oxidation by reducing the $\alpha\text{-TO}\cdot$ back to $\alpha\text{-TOH}$. In the absence of a co-antioxidant, such as $\text{CoQ}_{10}\text{H}_2$ (or vitamin C), $\alpha\text{-TOH}$ can, under certain conditions, promote the oxi-

dation of LDL in vitro.⁴ Supplementation with coenzyme Q₁₀ increases the concentration of Co-Q₁₀H₂ in human LDL.¹⁵ Studies in apolipoprotein-E-deficient mice, an animal model of atherosclerosis, found that coenzyme Q₁₀ supplementation with suprapharmacological 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). Giving supplements of 200 mg/day of coenzyme Q₁₀ to 10 healthy men and women for 10 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.²⁴

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 patients with heart failure.²⁶ Several small intervention trials that administered supplemental coenzyme Q₁₀ (100–300 mg/day of coenzyme Q₁₀ for 1–3 months) to patients with congestive heart failure, 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 patients with heart failure.^{30,31} A 2006 meta-analysis of 10 randomized controlled trials found that coenzyme Q₁₀ supplementation (99–200 mg/day for 1–6 months) in patients with heart failure 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 1 month or 200 mg/day for 3 months).³² A recent study in 236 patients with heart failure found that lower plasma coenzyme Q₁₀ levels were associated with a heightened risk

of mortality;³³ however, a larger study of 1191 patients with heart failure found that plasma coenzyme Q₁₀ level was a biomarker of advanced heart disease and not an independent predictor of clinical outcomes in patients with heart failure.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 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 1 week prior to CABG surgery 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, for example, 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 with 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 decreases in blood pressure in hypertensive individuals. The addition of 120 mg/day of coenzyme Q₁₀ to conventional medical therapy for 8 weeks in patients with hypertension and coronary artery disease decreased systolic blood pressure by an average of 12 mmHg and diastolic blood pressure by an average of 6 mmHg, 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 mmHg in systolic blood pressure compared with 300 IU/day of vitamin E 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 mmHg and diastolic blood pressure by 8–10 mmHg.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 patients with diabetes and abnormal serum lipid profiles, although it did not restore vasodilation to levels seen in individuals who did not have diabetes.⁴³ Another placebo-controlled study in 23 individuals with type 2 diabetes 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 individuals with type 2 diabetes 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 crossover 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 1 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 8 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 4–12 weeks) resulted in a clinically significant, 1.7% increase in flow-dependent endothelial-mediated dilatation.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 patients with diabetes than in healthy controls, when normalized to plasma cholesterol levels.^{51,52} However, supplementation with 100 mg/day of coenzyme Q₁₀ for 3 months neither improved glycemic (blood glucose) control nor decreased insulin requirements in patients with type 1 (insulin-dependent) diabetes compared with placebo.⁵³ Similarly, 200 mg/day of coenzyme Q₁₀ supplementation for 12 weeks or 6 months did not improve glycemic control or serum lipid profiles in individuals with type 2 (noninsulin-dependent) diabetes.^{44,54} 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 patients with diabetes as adjunct therapy for cardiovascular diseases.

Maternally inherited diabetes mellitus and deafness 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 supplementation with coenzyme Q₁₀ (150 mg/day) may improve insulin secretion and prevent progressive hearing loss in these patients.^{55,56}

Neurodegenerative Diseases

Parkinson Disease

Parkinson 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 years. Although the causes of Parkinson 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 disease.^{57,58} One study also found higher concentrations of oxidized coenzyme Q₁₀ in the cerebrospinal fluid of patients

with untreated Parkinson disease compared with healthy controls.⁵⁹ Additionally, a study of coenzyme Q₁₀ levels in postmortem Parkinson disease patients found lower levels of total coenzyme Q₁₀ in the cortex region of the brain compared with 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 1200 mg/day of coenzyme Q₁₀ in 80 people with early Parkinson disease.⁶¹ Coenzyme Q₁₀ supplementation was well tolerated at all doses and was associated with slower deterioration of function in patients with Parkinson disease compared with placebo. However, the difference was statistically significant only in the group taking 1200 mg/day. A smaller placebo-controlled trial showed that oral administration of 360 mg/day of coenzyme Q₁₀ for 4 weeks moderately benefited patients with Parkinson disease.⁶² More recently, a randomized, double-blind, placebo-controlled trial in 106 patients with midstage Parkinson disease reported that 300 mg/day of nanoparticulate coenzyme Q₁₀ for 3 months had no therapeutic benefit.⁶³ Another trial found that 2400 mg/day of coenzyme Q₁₀ for 12 months was not effective in early Parkinson disease.⁶⁴ A phase III clinical trial of coenzyme Q₁₀ (1200–2400 mg/day) and vitamin E (1200 IU/day) supplementation in patients with Parkinson disease was recently terminated because it was unlikely that such a treatment was effective in treating Parkinson disease.⁶⁵

Huntington Disease

Huntington 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 disease. Coenzyme Q₁₀ supplementation has been found to decrease brain lesion size in animal models of Huntington disease and to decrease brain lactate levels in patients with Huntington disease.^{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 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 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 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 prevent loss of body weight; coenzyme Q₁₀ supplementation has also been associated with reductions in the various hallmarks of Huntington 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 disease. A 30-month, randomized, placebo-controlled trial of coenzyme Q₁₀ (600 mg/day), remacemide, or both in 347 patients with early Huntington 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 (1200 mg/day, 2400 mg/day, and 3600 mg/day) in eight healthy subjects and in 20 patients with Huntington 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 2400 mg/day dose effectively maximizes blood coenzyme Q₁₀ levels and potentially avoids any side effects with higher dosages.⁷⁴ A phase III clinical trial administering 2400 mg/day of coenzyme Q₁₀ or placebo for 5 years is currently recruiting participants with Huntington

disease.⁷⁵ At present, there is insufficient evidence to recommend coenzyme Q₁₀ supplements to patients with Huntington disease.

Friedreich Ataxia

Friedreich 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 proteins, including mitochondrial aconitase; and reduced activities of the mitochondrial respiratory chain.⁷⁶ Clinically, FRDA is a progressive disease characterized by limb ataxia and abnormalities of the central nervous system 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 (2100 IU/day) to 10 FRDA patients found that energy metabolism of cardiac and skeletal muscle was improved after only 3 months of therapy.⁸⁰ Follow-up assessments at 47 months indicated that cardiac and skeletal muscle improvements were maintained and that patients with FRDA 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 deficiencies of both coenzyme Q₁₀ and vitamin E are quite common among FRDA patients and that co-supplementation with both compounds, at doses as low as 30 mg/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 patients with cancer.

Performance

Athletic Performance

Although coenzyme Q₁₀ supplementation has improved exercise tolerance in some individuals with mitochondrial encephalomyopathies (see the Deficiency section above),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 3–8 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 and exercise time to exhaustion.^{85–89} One study found the maximal cycling workload to be slightly (4%) increased after 8 weeks of coenzyme Q₁₀ supplementation compared with placebo, although measures of aerobic power were not increased.⁹⁰ Two studies actually found significantly greater improvement in measures of anaerobic⁸⁶ and aerobic⁸⁵ exercise performance after supplementation with a placebo compared with coenzyme Q₁₀. Studies on the effect of supplementation on physical performance in women are lacking, but there is little reason to suspect a sex 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 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 are listed in Table 22.1.^{92–94}

Supplements

Coenzyme Q₁₀ is available without a prescription as a dietary supplement in the United States. 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 3000 mg/day have been used to treat early Parkinson 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 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}

Table 22.1 Coenzyme Q₁₀ content of selected foods^{92–94}

Food	Serving	Coenzyme Q ₁₀ (mg)
Beef, fried	3 oz ^a	2.6
Herring, marinated	3 oz	2.3
Chicken, fried	3 oz	1.4
Soybean oil	1 tbsp	1.3
Canola oil	1 tbsp	1.0
Rainbow trout, steamed	3 oz	0.9
Peanuts, roasted	1 oz	0.8
Sesame seeds, roasted	1 oz	0.7
Pistachio nuts, roasted	1 oz	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 A 3-oz serving of meat or fish is about the size of a deck of cards.

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} Giving supplements of 120 mg/day for 3 weeks to healthy men 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 given supplements of 300 mg/day of coenzyme Q₁₀ or placebo for at least 7 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 aged over 70 years.³⁶ Ad-