Coenzyme Q10: A Review of Essential Functions

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Abstract

This article represents a review of Coenzyme Q10 (CoQ10),a compound found naturally in the energy-producing center of the cell known as the mitochondria.

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}) is a compound found naturally in the energy-producing center of the cell known as the mitochondria. It was first isolated from the mitochondria of bovine hearts in 1957 at the University of Wisconsin.(1) Identification of the chemical structure and synthesis was completed by 1958.(2) Research conducted in the 1960s and 1970s demonstrated that CoQ_{10} acts as an antioxidant and plays a central role in mitochondrial oxidative phosphorylation. CoQ_{10} is involved in the making of an important molecule known as ATP. ATP serves as the cell's major energy source and drives a number of biological processes including muscle contraction and the production of protein. CoQ_{10} also works as an antioxidant.(1)

Antioxidants are substances that scavenge free radicals, damaging compounds in the body that alter cell membranes, tamper with DNA, and even cause cell death. Free radicals occur naturally in the body, but environmental toxins (including ultraviolet light, radiation, cigarette smoking, and air pollution) can also increase the number of these damaging particles. Free radicals are believed to contribute to the aging process as well as the development of a number of health problems including heart disease and cancer. Antioxidants such as CoQ_{10} can neutralize free radicals and may reduce or even help prevent some of the damage they cause.(3)

PHARMACOLOGY

CoQ_{10} (2,3-dimethoxy-5-methylbenzoquinone) is chemically classified as a fat-soluble quinone ring attached to 10 isoprene side units, structurally similar to vitamin K. (Fig. 1) In humans, CoQ_{10} is found in relatively higher concentrations in cells with high energy requirements such as heart, liver, muscle, and pancreas. Normal blood levels range from 0.7–1.0 µg/mL. Human cells synthesize CoQ_{10} from the amino acid tyrosine, in an eight-step aromatic pathway, requiring adequate levels of vitamins such as folic acid, niacin, riboflavin, and pyridoxine (Fig.2). A deficiency in any of these nutrients would result in a deficiency in CoQ_{10}.(4)

Figure 1

Figure 1: Structure of Coenzyme Q 10

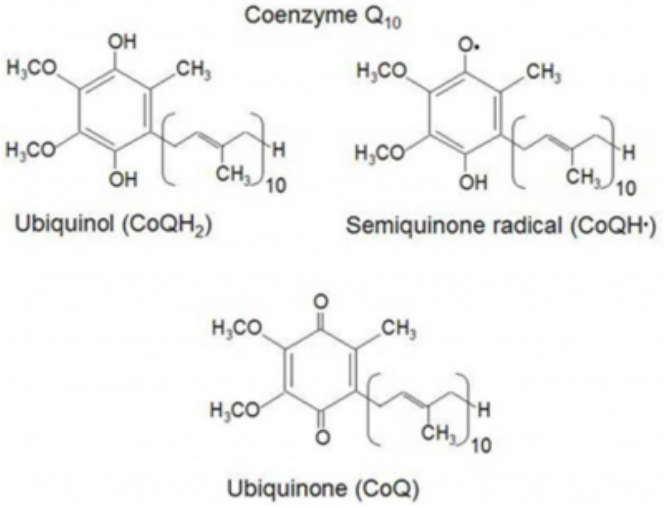
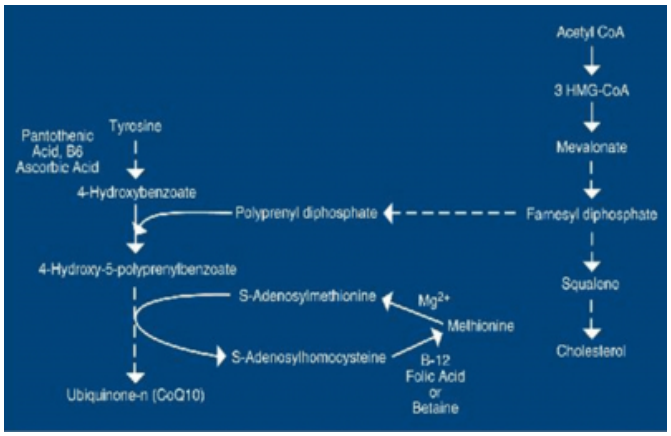


Figure 2

Figure 2: Coenzyme Q Synthesis



MECHANISM OF ACTION

Electron Transport Chain to Produce ATP: CoQ_{10}, found in the inner mitochondrial membrane, is the cofactor for at least three mitochondrial enzymes (complexes I, II and III) that play a vital role in oxidative phosphorylation. It functions as the only non-protein component of the electron transport chain (ETC) in addition to not being attached to a protein itself. This unique characteristic enables CoQ_{10} to move and transfer electrons between flavoproteins and cytochromes. Each pair of electrons processed by the ETC must first interact with CoQ_{10}, which is considered the central rate-limiting constituent of the mitochondrial respiratory chain. Therefore, CoQ_{10} plays an essential role in adenosine triphosphate (ATP), or biological energy, production. ([5,6,7,8])

Membrane Stabilization and Fluidity: The membrane stabilizing property of CoQ_{10} has been postulated to involve the phospholipid-protein interaction that increases prostaglandin (especially prostacyclin) metabolism. It is thought that CoQ_{10} stabilizes myocardial calcium-dependent ion channels and prevents the depletion of metabolites essential for ATP synthesis. CoQ_{10} also decreases blood viscosity, and improves blood flow to cardiac muscle in patients with ischemic heart disease.([9])

COENZYME Q DEFICIENCY

Normal blood and tissue levels of CoQ_{10} have been well established by numerous investigators around the world. Significantly decreased levels of CoQ_{10} have been noted in a wide variety of diseases in both animal and human studies. Insufficient dietary CoQ_{10}, impairment in CoQ_{10} biosynthesis, excessive utilization of CoQ_{10} by the body, or any combination of the three, may cause CoQ_{10} deficiency. Decreased dietary intake is presumed in chronic malnutrition and cachexia.([20])

The relative contribution of CoQ_{10} biosynthesis versus dietary CoQ_{10} is under investigation. Karl Folkers takes the position that the dominant source of CoQ_{10} in man is biosynthesis. This complex, 17-step process, requiring at least seven vitamins (vitamin B2 - riboflavin, vitamin B3 - niacinamide, vitamin B6, folic acid, vitamin B12, vitamin C, and pantothenic acid) and several trace elements, is, by its nature, highly vulnerable. Karl Folkers argues that suboptimal nutrient intake in man is almost universal and that there is subsequent secondary impairment in CoQ_{10} biosynthesis. This would mean that average or "normal" levels of CoQ_{10} are really suboptimal and the very low levels observed in advanced disease states represent only the tip of a deficiency "ice berg".

HMG-CoA reductase inhibitors used to treat elevated blood cholesterol levels by blocking cholesterol biosynthesis also block CoQ_{10} biosynthesis.([21]) The resulting lowering of blood CoQ_{10} level is due to the partially shared biosynthetic pathway of CoQ_{10} and cholesterol. In patients with heart failure this is more than a laboratory observation. It has a significant harmful effect, which can be negated by oral CoQ_{10} supplementation.([22])

Increased body consumption of CoQ_{10} is the presumed cause of low blood CoQ_{10} levels seen in excessive exertion, hypermetabolism, and acute shock states. It is likely that all three mechanisms (insufficient dietary CoQ_{10}, impaired CoQ_{10} biosynthesis, and excessive utilization of CoQ_{10}) are operable to varying degrees in most cases of observed CoQ_{10} deficiency.

WHAT ARE THE PRINCIPAL USES OF COQ?

CoQ_{10} supplementation is used primarily in the treatment of cardiovascular diseases such as elevated cholesterol levels, high blood pressure, congestive heart failure, cardiomyopathy, mitral valve prolapse, coronary artery bypass surgery, and angina. Considerable scientific studies have validated these uses.([10,11,12]) CoQ_{10} has also been shown to be helpful in diabetes; periodontal disease; immune deficiency; cancer; as a weight-loss aid; and muscular dystrophy. Since the response of CoQ_{10} can take time, a noticeable improvement might not occur until 8 or more weeks after therapy is begun.

Several clinical trials and case series have provided evidence, supporting the use of CoQ_{10} in the prevention and treatment of various disorders related to oxidative stress.

(Table 1) It has been shown that CoQ_{10}'s antioxidant properties and central role in mitochondrial oxidative phosphorylation make it useful as adjunct therapy for cardiovascular diseases such as CHF, hypertension, stable angina, drug-induced cardiotoxicity, and ventricular arrhythmia, and non-cardiac conditions including cancer, periodontal disease, compromised immune systems, COPD, and muscular dystrophy. Therefore, healthcare professionals are advocating its use as a supplement.

Figure 3

Table 1: Potential Clinical Uses for CoQPotential

Cardiovascular Disease	Arteriosclerosis/Ischemic Heart Disease Chronic Heart Failure Toxin-Induced Cardiomyopathy Hypertension Arrhythmias
Neurodegenerative Disease	Neurogenic Atrophic Disease Muscular Dystrophy
Cancer	Breast Lung Prostate Pancreatic
Periodontal Disease	Inflamed gingiva
Immune Deficiency Disease	AIDS

HEART DISEASE ()

Researchers believe that the beneficial effect of CoQ_{10} in the prevention and treatment of heart disease is due to its ability to improve energy production in cells, inhibit blood clot formation, and act as an antioxidant. One important study, for example, found that people who received daily CoQ_{10} supplements within 3 days of a heart attack were significantly less likely to experience subsequent heart attacks and chest pain. In addition, these same patients were less likely to die of heart disease than those who did not receive the supplements.

CONGESTIVE HEART FAILURE (CHF)()

Levels of CoQ_{10} are low in people with CHF, a debilitating disease that occurs when the heart is not able to pump blood effectively. This can cause blood to pool in parts of the body such as the lungs and legs. Information from many research studies suggests that CoQ_{10} supplements help reduce swelling in the legs, enhance breathing by reducing fluid in the lungs, and increase exercise capacity in people with CHF. Not all studies agree, however. As a result, some experts conclude that CoQ_{10} supplements do not contribute any benefit to the usual conventional treatment for CHF. More conclusive research will help resolve the debate.

HIGH BLOOD PRESSURE ()

Several studies involving small numbers of people suggest that CoQ_{10} may lower blood pressure. However, it may take 4 to 12 weeks before any beneficial effect is observed. More research with greater numbers of people is needed to assess the value of CoQ_{10} in the treatment of high blood pressure.

HIGH CHOLESTEROL ()

Levels of CoQ_{10} tend to be lower in people with high cholesterol compared to healthy individuals of the same age. In addition, certain cholesterol-lowering drugs called statins (such as atorvastatin, cerivastatin, lovastatin, pravastatin, simvastatin) appear to deplete natural levels of CoQ_{10} in the body. Taking CoQ_{10} supplements can correct the deficiency caused by statin medications without affecting the medication's positive effects on cholesterol levels.

DIABETES ()

CoQ_{10} supplements may improve heart health and blood sugar and help manage high cholesterol and high blood pressure in individuals with diabetes. (High blood pressure, high cholesterol, and heart disease are all common problems associated with diabetes). Despite some concern that CoQ_{10} may cause a sudden and dramatic drop in blood sugar (called hypoglycemia), two recent studies of people with diabetes given CoQ_{10} two times per day showed no hypoglycemic response. The safest bet if you have diabetes is to talk to your doctor or registered dietitian about the possible use of CoQ_{10}.

HEART SURGERY ()

Research indicates that introducing CoQ_{10} prior to heart surgery, including bypass surgery and heart transplantation, can reduce damage caused by free radicals, strengthen heart function, and lower the incidence of irregular heart beat (arrhythmias) during the recovery phase.

BREAST CANCER ()

Studies of women with breast cancer suggest that CoQ_{10} supplements (in addition to conventional treatment and a

nutritional regimen including other antioxidants and essential fatty acids) may shrink tumors, reduce pain associated with the condition, and cause partial remission in some individuals. It is important to recognize that the beneficial effects these women experienced cannot be attributed to CoQ_{10} alone. Additional antioxidants used in these studies include vitamins C, E, and selenium.

OTHER ()

Preliminary studies also suggest that CoQ_{10} may:

- Improve immune function in individuals with immune deficiencies (such as AIDS) and chronic infections (such as yeast and other viral infections)
- Increase sperm motility leading to enhanced fertility
- Be used as part of the treatment for Alzheimer's disease
- Reduce damage from stroke
- Boost athletic performance
- Enhance physical activity in people with fatigue syndromes
- Improve exercise tolerance in individuals with muscular dystrophy

OVERVIEW CLINICAL USES

Congestive Heart Failure (CHF): Several open and controlled studies have examined the efficacy of CoQ_{10} as adjunctive therapy for treating CHF. The presence of increasing symptoms associated with CHF has been correlated to the severity of CoQ_{10} deficiency. In one study, the mean myocardial tissue level (µg/dry weight) of CoQ_{10} from endomyocardial biopsies obtained during catheterization in control subjects, New York Heart Association (NYHA) Class I with normal hemodynamic findings and normal biopsy morphology, were compared to that of NYHA Functional Class III or IV patients; these levels were reported as 0.42 and 0.28, respectively.([23,24]) The authors concluded that CoQ_{10} myocardial tissue levels in CHF patients are on average 33% lower than in control patients. The degree of CoQ_{10} deficiency correlated with the severity of symptoms and presence of dilated cardiomyopathy in NYHA Class III and IV patients. Study by Jameson et al.([25]) analyzed serum CoQ_{10}, alpha-tocopherol, and free cholesterol levels in 94 consecutive hospitalized patients over 50 years of age. Patients exhibiting a significantly lower serum free cholesterol-related CoQ_{10} value (CoQ_{10} levels expressed per milligram of free cholesterol) had an increased risk of CHF, severe myalgia, concomitant use of cytostatic and lipid-lowering drug therapy, and/or death within a six-month follow-up.

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. 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 4 placebo-controlled trials found that coenzyme Q_{10} pretreatment (60-300 mg/d 7-14 days prior to surgery) provided some benefit in short-term outcome measures after CABG surgery. 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} twelve hours prior to surgery, 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. ([23])

Hypertension: The results of several small, uncontrolled studies in humans suggest that coenzyme Q_{10} supplementation could be beneficial in the treatment of hypertension. 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/d of coenzyme Q_{10} to conventional medical therapy for 8 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 compared to a placebo containing B-complex vitamins. In patients with isolated systolic hypertension, supplementation with 120 mg/d of coenzyme Q_{10} and 300 IU/day of vitamin E for 12 weeks resulted in an average decrease of 17 mm Hg in systolic blood pressure compared with 300 IU/day of

vitamin E alone.[24] Further research is needed to determine whether coenzyme Q_{10} supplementation can provide significant long-term benefit in the treatment of hypertension.

Diabetes mellitus : Diabetes mellitus is a condition of increased oxidative stress and impaired energy metabolism. Plasma levels of reduced coenzyme Q_{10} ($CoQH_2$) have been found to be lower in diabetic patients than healthy controls when normalized to plasma cholesterol levels. However, supplementation with 100 mg/d of coenzyme Q_{10} for 3 months neither improved glycemic (blood glucose) control nor decreased insulin requirements in Type 1 (insulin-dependent) diabetics compared to placebo. Similarly, 200 mg/d of coenzyme Q_{10} supplementation for 6 months did not improve glycemic control or serum lipid profiles in Type 2 (non-insulin dependent) diabetics. Since coenzyme Q_{10} supplementation did not interfere with 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 diseases.

Cancer: Numerous studies have noted the incidence of CoQ_{10} deficiency in a variety of cancers including breast, lung, prostate, pancreatic and colon cancer.[26,27,28] In an open-label study of 32 breast cancer patients with metastases to axillary lymph nodes, 90 mg/day of CoQ_{10} plus high-dose antioxidant therapy with vitamin C, vitamin E, beta carotene, selenium, and omega-3 and omega-6 fatty acids were given in addition to conventional surgery and chemotherapy. During the 18-month study period, none of the patients showed signs of further metastases and six of the 32 patients had partial tumor regression.[29,30]

Immune Modulation: Studies have demonstrated that the degree of CoQ_{10} deficiency is correlated with the severity of immune compromised diseases. Patients with acquired immune deficiency syndrome (AIDS) showed statistically significant lower CoQ_{10} serum concentrations than AIDS-related complex (ARC) patients, who in turn had lower levels than healthy subjects.[31] A clinical case series of eight adult patients treated with 60 mg/day of CoQ_{10} reported significant increases in serum IgG levels over 1–4 months.[32]

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. [33,34] A 16-month randomized placebo-controlled trial evaluated the safety and efficacy of 300, 600, or 1200 mg/d of coenzyme Q_{10} in 80 people with early Parkinson's disease. Coenzyme Q_{10} supplementation was well tolerated at all doses and 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 1200 mg/d. Although these preliminary findings are promising, they need to be confirmed in larger clinical trials before recommending the use of coenzyme Q_{10} in early Parkinson's disease.

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.[35,36] However, feeding transgenic mice that express the Huntington's disease protein a combination of coenzyme Q_{10} and remacemide resulted in only transiently improved motor performance and did not prolong survival.[37] Remacemide is an antagonist of the neuronal receptor that is activated by glutamate. A 30-month randomized placebo-controlled trial of coenzyme Q_{10} (600 mg/d), 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.[38] Currently, there is insufficient evidence to support a recommendation for coenzyme Q_{10} supplementation in early Huntington's disease.

FORMULATIONS AND DOSAGE

Exogenous supplies of CoQ_{10} are found in foods such as fish and fish oils, organ meats and germ of whole grains. However, in some cases dietary intake may be inadequate to meet the body's needs. The average diet is estimated to provide approximately 10 mg/day of CoQ_{10}. Commercially available CoQ_{10} is produced by the fermentation of beets and sugar cane, using special strains of yeast. Dosage forms currently available include powder-filled capsules, powder-based tablets, softgel capsules, fully solubilized softgel capsules, chewable wafers, intravenous solution, and intra-oral spray. Assessment of the bioavailability of various dosage formulations demonstrated that the fully solubilized softgel capsule (Q-gel) achieved the highest serum CoQ_{10} concentration.(39)

Doses of 30–60 mg/day (approximately 1 mg/kg of body weight) are generally recommended to prevent CoQ_{10} deficiency and to maintain normal serum concentrations of 0.7–1.0 µg/mL. However, therapeutic doses of 100–200 mg/day are advocated for the treatment of chronic heart disease. These higher doses may achieve serum concentrations of 2.0–3.0 µg/mL, reported by some investigators to have a positive impact on cardiovascular health. Doses used in the treatment of breast cancer range from 90–390 mg/day (Table 2). Divided doses are recommended to minimize adverse effects when doses exceed 100 mg/day. Maximum absorption of CoQ_{10} can be achieved if taken with meals that contain fat.(40)

Figure 4

Table 2: CoQ Recommended Intake

Disease	Usual Doses
Cardiovascular	
Chronic Heart Failure	100–200 mg
Stable Angina	150–200 mg
Hypertension	100–200 mg
Cardiotoxicity	50 mg
Cardiac Surgery/Arrhythmia	100–200 mg
Miscellaneous	
Breast Cancer	90–390 mg
Periodontal Disease	50 mg
Immunocompromised	100 mg

ADVERSE EFFECTS

Documented adverse effects associated with the use of CoQ_{10} in humans have been minor and include epigastric discomfort (0.39%), appetite suppression (0.23%), nausea (0.16%) and diarrhea (0.12%).(4) These complaints are dose-related and minimized with dose reduction and/or dose division. Higher than usual doses exceeding 300 mg/day have been associated with elevated serum LDH and SGOT levels, however no hepatic toxicity has been observed. Late night administration has also been reported to cause insomnia.(40)

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 4 cases.(41) An individual on warfarin should not begin taking coenzyme Q_{10} supplements without consulting the health care provider that 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}. A number of studies have observed decreases in plasma or serum coenzyme Q_{10} levels in people on HMG-CoA reductase inhibitor therapy, especially those taking simvastatin (Zocor).(42,43,44) In contrast to most earlier studies, a randomized cross-over trial in healthy individuals found no significant changes in serum coenzyme Q_{10} levels after 4 weeks of pravastatin (Pravachol) and atorvastatin (Lipitor) therapy despite significant decreases in total and LDL-cholesterol levels on both medications. In rats, high doses of lovastatin for 4 weeks decreased blood, liver, and heart concentrations of coenzyme Q.(45) However, it is not clear whether HMG-CoA reductase inhibitor therapy decreases tissue coenzyme Q_{10} concentrations in humans. Although simvastatin treatment for 6 months lowered serum coenzyme Q_{10} levels in patients with high serum cholesterol, skeletal muscle concentrations of coenzyme Q_{10} were not decreased compared to baseline or healthy controls.(46) At present, more controlled research is needed to determine whether coenzyme Q_{10} supplementation is beneficial for those taking HMG-CoA reductase inhibitors.

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.
- Endogenous synthesis and dietary intake appear to provide sufficient coenzyme Q10 to prevent deficiency in healthy people.
- 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.
- Coenzyme Q10 supplementation has resulted in clinical and metabolic improvement in some patients with hereditary mitochondrial disorders.
- Although coenzyme Q10 supplementation may be a useful adjunct to conventional medical therapy for congestive heart failure, additional research is needed.
- Roles for coenzyme Q10 supplementation in other cardiovascular diseases, neurodegenerative diseases, cancer, and diabetes require further research.
- Coenzyme Q10 supplementation does not appear to improve athletic performance.
- Although coenzyme Q10 supplements are relatively safe, they may decrease the anticoagulant efficacy of warfarin (Coumadin).
- Presently, it is unclear whether individuals taking cholesterol-lowering medications, known as HMG-CoA reductase inhibitors (statins), would benefit from coenzyme Q10

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