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REVIEW

Potential role of coenzyme Q_{10} in health and disease conditions

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Abstract: Coenzyme Q_{10} (CoQ_{10}), an endogenously produced compound, is found in all human cells. Within the mitochondria, it plays a substantial role in energy production by acting as a mobile electron carrier in the electron transport chain. Outside the mitochondria, it acts as an excellent antioxidant by sequestering free radicals and working synergistically with other antioxidants, including vitamin E. Dietary contribution is limited, making endogenous production the primary source for optimal function. Now widely available as an over-the-counter supplement, CoQ_{10} has gained attention for its possible therapeutic use in minimizing the outcomes of certain metabolic diseases, notably cardiovascular disease, diabetes, neurodegenerative disease, and cancer. Research has shown positive results in subjects supplemented with CoQ_{10}, especially in relation to upregulating antioxidant capability. Emerging research suggests beneficial effects of CoQ_{10} supplementation in individuals on statin medications. CoQ_{10} supplementation in individuals participating in strenuous exercise seems to exert some beneficial effects, although the data are conflicting with other types of physical activity. This broad review of current CoQ_{10} literature, while outlining its physiological/functional significance in health and disease conditions, also offers a dietitian's perspective on its potential use as a supplement in the promotion of health and management of disease conditions.

Keywords: coenzyme Q, antioxidant, oxidative stress, dietary supplement, statin

Introduction

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone or ubidecarenone, is a vitamin-like nutrient and lipid-soluble compound. As its name implies, it is ubiquitous and present in all human cells. It is primarily located in the mitochondria and also found in cell membranes and lipoproteins. The primary function of CoQ_{10} is its role in cellular energy production, where, along the inner mitochondrial membrane, the electron transport chain (ETC) uses CoQ_{10} as a component in oxidative phosphorylation converting products of metabolism (carbohydrates, fats, and proteins) into energy as ATP.[1] Ubiquinol ($CoQH_2$), the fully reduced form of CoQ_{10}, has the unique ability to act as a potent fat-soluble antioxidant free radical scavenger by affecting the initiation and propagation of reactive oxygen species (ROS), which cause oxidative stress leading to detrimental effects in damaging lipids, proteins, DNA, and the overall functional status of the mitochondria.[2–4] CoQ_{10} levels decrease with aging, and this loss of antioxidant power coupled with increased ROS production can result in an age-related oxidative stress that can influence the development of other metabolic conditions.[3] It has been speculated that CoQ_{10} supplementation may be effective as an antioxidant in treating

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certain pathological conditions.[5] The purpose of this review was to provide an understanding of CoQ_{10}'s biological functions in relation to its potential use as a supplement for health and in the management of chronic diseases.

Historical significance

CoQ_{10} was first isolated and characterized in 1955 by a research group headed by Professor RA Morton at Liverpool University, Liverpool, UK.[6] This same group later went on to fully elucidate the chemical structure of CoQ_{10}.[7] In 1958, Karl Folkers (Merck Sharp & Dohme Inc., Kenilworth, NJ, USA) and Otto Isler (Hoffman-La Roche Inc., Little Falls, NJ, USA) developed the first process for synthesizing CoQ_{10}.[8] Two years later, Crane et al raised the possibility that CoQ_{10} may function within the mitochondrial electron transport chain (ETC).[9] In the following years, CoQ_{10} research gained much attention when it was found to be deficient in patients suffering from cardiovascular conditions.[10] In 1975, Dr Peter Mitchell developed the theory that ATP synthesis was driven by an electrochemical gradient across the inner mitochondrial membrane. This characterization of biological energy transfer, in which CoQ_{10} was necessary, won him the Nobel Prize in 1978.[11]

Structure, synthesis, and absorption

CoQ_{10} is a naturally occurring benzoquinone with a 10-unit isoprenyl tail. Although structurally similar to vitamin K, CoQ_{10} cannot be labeled a vitamin due to the body's ability to synthesize it de novo.[12] It has a molecular weight of 865 g/mol and a melting point of 49°C and exhibits limited solubility in fats and oils. Upon exposure to light and temperature (>55°C), CoQ_{10} becomes progressively unstable, and its yellow gold color darkens to a deep gold hue. A solidified state is more stable, especially in terms of photo degradation, than a liquefied state. Furthermore, the addition of other antioxidants, such as vitamins E and C, will enhance the stability of CoQ_{10}. Kommuru et al showed that combinations of ascorbic acid and EDTA, both powerful antioxidants, with CoQ_{10} resulted in a more stable formulation when exposed to light and heat.[13]

CoQ_{10} exists in both the oxidized (ubiquinone) and reduced (ubiquinol) forms. The semiquinone intermediate radical, CoQH·, plays a role in antioxidant activity (Figure 1). Both ubiquinone and ubiquinol are lipid soluble due to the presence of the 10-unit isoprene tail. They act as a redox pair where the conversion of one form to the other can be readily achieved depending on when and where their functions are needed in the body. For example, tissues that involve high aerobic activity contain more of the oxidized form (ubiquinone) than the reduced form.[12] In blood circulation, ~95% of CoQ_{10} is present in the ubiquinol form. The ratio between ubiquinone and ubiquinol in the blood has shown to be a measure of oxidative stress. Factors such as aging and certain disease conditions have shown to minimize ubiquinol levels in the body, possibly due to increased oxidative and nitrosative stress and also because the body loses the ability to reduce ubiquinone, thus resulting in a lower amount of total CoQ_{10}.[11]

CoQ_{10} is ubiquitous in human tissues with the highest levels in the heart, liver, and kidney, participating in aerobic cellular respiration generating ATP. The synthesis of endogenous CoQ_{10} is highly complex, involving multiple compounds including B-vitamins and vitamin C. The quinone structure is derived from tyrosine, the methyl groups are supplied by methionine via S-adenosylmethonine, and the isoprenoid side chain originates from the mevalonate pathway (Figure 2). This pathway links CoQ_{10} production to the development of cholesterol. Thus, the deficiency of any of these compounds can affect the endogenous production of CoQ_{10}.[12]

Multiple ways to commercially produce CoQ_{10} are available. There are two isomeric forms of CoQ_{10}, which determine whether a supplement is a natural or synthetic version of the compound (Figure 3). Natural CoQ_{10} is an all-*trans* isomer, while the synthetic compound is a mixture of both the *trans*- and *cis*-isomers.[14] Yeast or bacterial fermentation

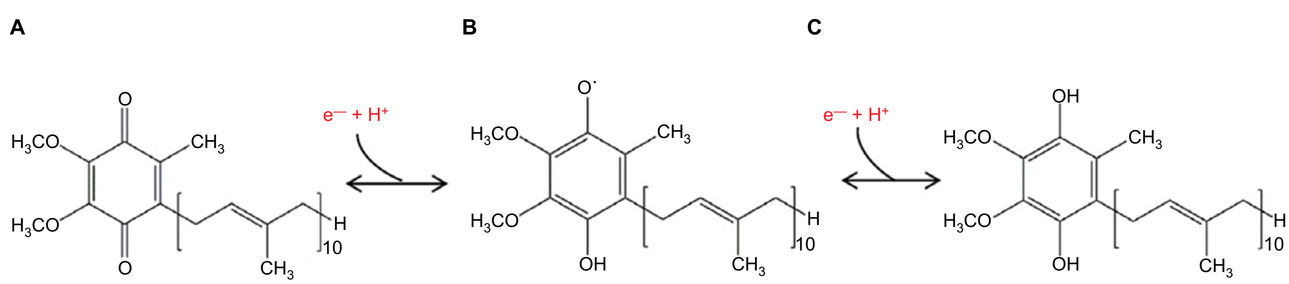

Figure 1 Structure of CoQ_{10}. (**A**) Ubiquinone, CoQ (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone); (**B**) semiquinone radical form, CoQH·; and (**C**) ubiquinol, $CoQH_2$ (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzohydroquinone).
Abbreviation: CoQ_{10}, coenzyme Q_{10}.

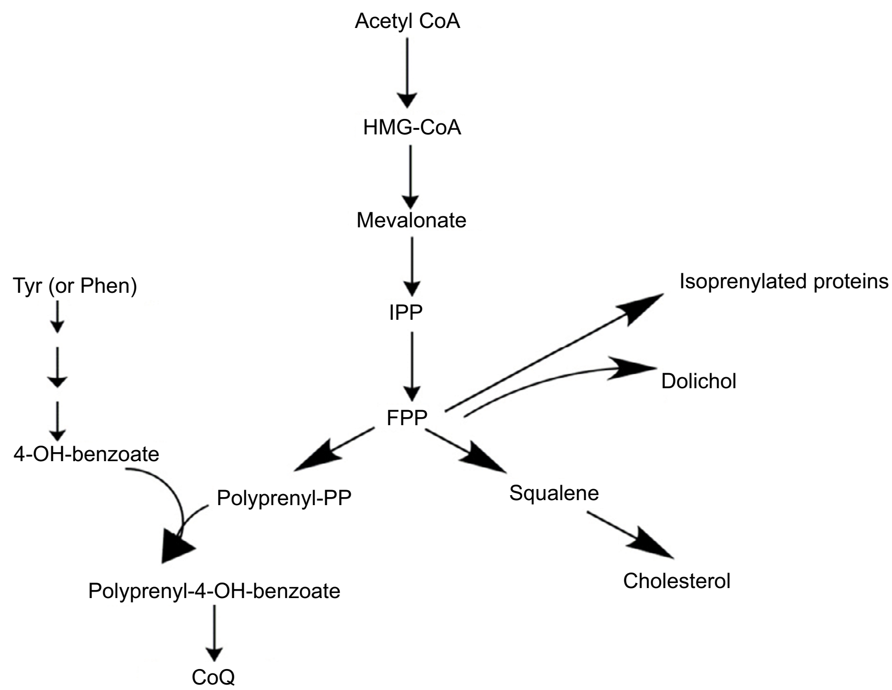

Figure 2 The mevalonate pathway. It comprises the reactions beginning with acetyl CoA to the production of IPP and FPP, which are substrates for the production of cholesterol, dolichol, isoprenylated proteins, and CoQ.
Abbreviations: CoA, coenzyme A reductase; CoQ, coenzyme Q; FPP, farnesyl pyrophosphate; HMG, 3-hydroxy-3-methylglutaryl; IPP, isoprenyl-pyrophosphate.

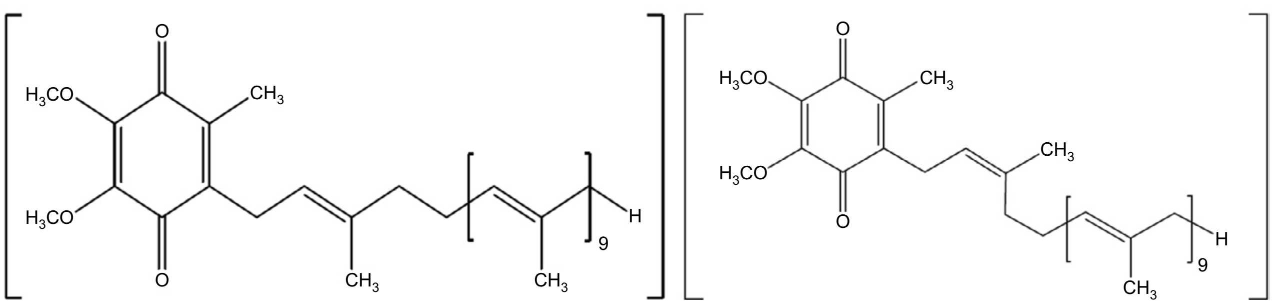

Figure 3 Isomeric forms of CoQ_{10}. (**A**) Natural all-*trans* form, (**B**) synthetic (-*cis* and -*trans*) form.
Abbreviation: CoQ_{10}, coenzyme Q_{10}.

remains the most widely used production method due to its specificity toward the natural all-*trans* isomer. The advantage of an all-*trans* isomeric form is that it is structurally identical to CoQ_{10} that is endogenously made in the human body, making it biologically active.[15] Alternatively, there is a lower-cost semichemical synthesis that uses a tobacco by-product, solanesol, which contributes tyrosine to the ring structure and the phytyl side chain. This production method contains *cis*- and *trans*-isomers that give the isoprenoid tail a bent shape rather than a straight shape. Because the cis-form is not produced in the body and has a different structure, the efficacy and safety of supplementing this form of CoQ_{10} are yet to be fully understood compared with the all *trans*-isomeric supplements.

As a lipophilic substance, CoQ_{10} absorption is enhanced by the presence of lipids, similar to vitamin E.[12] Secretions from the pancreas and bile initiate the emulsification process and micelle formation that enhances CoQ_{10} absorption. Due to its molecular weight and hydrophobic nature, CoQ_{10} must be dissolved to single molecules in order to be facilitated by lipid carriers in a passive diffusion process along the small intestine.[16] There is no specific location within the small intestine where absorption takes place. Increased consumption leads to a lower absorption rate of CoQ_{10}, as roughly 60% of oral dosage forms are excreted in the feces.[12] Plasma CoQ_{10} concentrations increase with increasing doses of CoQ_{10} and plateau at 2,400 mg, with a decreased efficiency of absorption at higher dosages.[17] Either during absorption or after absorption, CoQ_{10} is reduced to ubiquinol and incorporated into chylomicrons and transported to the liver.[16] Eventually, these are packaged into lipoprotein particles and released into circulation.[12] Plasma CoQ_{10} is mainly packaged into very low-density lipoprotein (LDL)/LDL particles, with a small amount incorporated into high-density lipoprotein (HDL) particles. Among its many functions, it is this transport mechanism of CoQ_{10}, along with α-tocopherol, that protects lipoproteins from lipid peroxidation.[16]

Food sources, supplement, and assessment of status

Widely distributed in nature, CoQ_{10} is found in both plants and animals. However, animal products tend to have the greatest amount of CoQ_{10} compared with other sources. Tissues with the highest energy demands typically contain high amounts of CoQ_{10}, including the heart, liver, and kidney.[18,19] Nonanimal products also contain fair amounts of CoQ_{10}, the most being in broccoli, spinach, soybean/canola/palm oils, nuts, and legumes (Table 1).[20] Contribution from dietary sources is limited, and in the absence of a supplement, endogenous production is left as the major source of CoQ_{10} in the body for regulation and maintenance. Levels obtained from the diet are estimated to be only 3–5 mg per day (~1%), while the total body pool is 0.5–1.5 g with a half-life varying from 35 to 100 hours, depending on the activity in a given body tissue.[2] CoQ_{10} supplements were initially based on ubiquinone powder in the form of tablets, capsules, and oil-based softgels. The bioavailability of these supplements tended to be poor due to their hygroscopic nature.[21] However, newer, ubiquinol-based formulations with increased stability and high bioavailability, including Q-Gel, Q-Nol, and Kaneka QH, are available commercially.[21,22] Supplemental dosages in different strengths generally range from 15 to 100 mg. Larger doses for patients are well recognized under pathological conditions such as heart disease, neurodegenerative disorders, cancer, and diabetes.[16] CoQ_{10} supplementation appears to be safe, found in both human and animal studies, with minimal adverse effects. The most common symptoms range from abdominal discomfort to slight nausea. Dosages in the 600–1,200 mg range, seen in Parkinson's disease (PD) and Huntingdon's disease trials, have shown no adverse effects. In a pilot study conducted by Shults et al, doses at 3,000 mg were tolerated in PD patients, and any adverse events were labeled unrelated to CoQ_{10} supplementation.[23]

Table 1 Comparison of dietary food sources with contributive values for CoQ_{10} per single serving[17,18]

Food source	Serving size	CoQ_{10} (mg)
Pork heart, fried	3 ounces	17
Sardines	2 ounces	3.4
Soybean oil	2 tablespoons	2.6
Herring, steamed	3 ounces	1.9
Chicken, fried	3 ounces	1.8
Pork chop, fried	3 ounces	1.7
Peanuts	2 ounces	1.3
Spinach, raw	1/2 cup	1
Broccoli, steamed	1/2 cup	0.7
Egg, boiled	1 each	0.1
Potato, boiled	1 medium	0.06
Cucumber	1/2 cup	0.01

Abbreviation: CoQ_{10}, coenzyme Q_{10}.

CoQ_{10} status is assayed by high-performance liquid chromatography–ultraviolet detection, postextraction from the tissue or plasma.[24] Electrochemical detection, which measures both ubiquinone and ubiquinol in the same sample, can also be used.[1] However, pathologically deficient levels of CoQ_{10} present in specific tissues, such as the heart and muscle, may not be detected in the plasma at a given time. A skeletal muscle biopsy is the preferred tissue to determine the endogenous CoQ_{10} status of patients.[25]

Role in health

Due to its location in the mitochondria, the predominant function of CoQ_{10} is in energy production. CoQ_{10} is positioned between the flavoprotein complexes I, II, and III, where it acts as a mobile electron carrier.[26] Using its redox capabilities, CoQ_{10} shuttles electrons from Complex I (reduced nicotinamide adenine dinucleotide [NADH]–ubiquinone reductase) and Complex II (succinate –ubiquinone reductase) to Complex III (ubiquinol cytochrome c reductase) (Figure 4). Because human life cannot be sustained without this process, the need for ubiquinone is high. Subsequently, ubiquinol is rapidly converted into oxidized ubiquinone, creating a cycle for the generation of ATP.[1]

In the mid-1970s, Peter Mitchell developed a theory that the redox ability of CoQ_{10} may play an additional role than electron transport. He found that protonation inside the mitochondria during reduction and deprotonation outside the membrane during oxidation built an electrical gradient between the membranes. Ultimately, this results in a driving force for adenosine diphosphate to be converted to ATP.[11] Furthermore, uncoupling proteins (UCPs) are situated along the inner mitochondrial membrane that pulls protons from the outside to the inside of the membrane. Mitchell's theory predicted that any proton leak not "coupled" with ATP synthesis would provoke uncoupling of respiration and thermogenesis.[2,27] As the production of ROS in mitochondria is caused by respiratory activity and, in some instances,

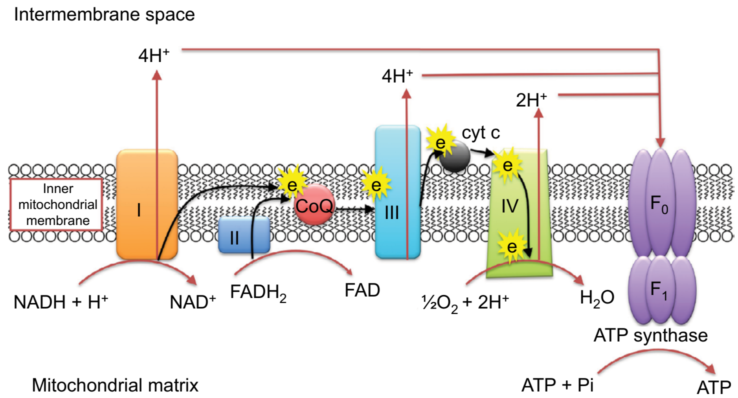

Figure 4 Role of CoQ_{10} in the mitochondrial electron transport chain.
Abbreviations: ADP, adenosine diphosphate; CoQ_{10}, coenzyme Q_{10}; FAD, flavin adenine dinucleotide; FADH, reduced flavin adenine dinucleotide.

semi-ubiquinone, a decrease in the mitochondrial proton gradient caused by UCP activity could lower this potential. In the presence of oxidized CoQ_{10}, Echtay et al found that fatty acids could deliver protons to UCP in the inner membrane more efficiently, which then get translocated into the mitochondrial matrix.[28]

In the reduced form as ubiquinol, CoQ_{10} has the ability to act as a potent fat-soluble antioxidant outside the mitochondrial membrane. Not only can it recycle and regenerate other antioxidants such as vitamins E and C, but it can also uniquely affect the initiation and propagation of ROS.[2] Mitochondria are major producers of O_2^- and H_2O_2 as oxygen consumption is heavily involved in the production of ATP. Depending on the state of respiration, the leakage of electrons coupled with free radical formation can induce oxidative stress in DNA, lipids, and proteins.[2] Lipid peroxidation, as the most studied and reviewed, involves the loss of hydrogen from a polyunsaturated fatty acid, resulting in a peroxyl radical. Reduced $CoQH_2$ (ubiquinol) loosely holds electrons and acts to eliminate lipid peroxyl radicals by either directly producing semiquinone radical ($CoQH^{\cdot}$) or scavenging other peroxyl radicals (Figure 5). As vitamin E also plays a role in free radical attainment, $CoQH_2$ has the ability to regenerate vitamin E from subsequent α-tocopherol radical formation. In animal models, depleted levels of α-tocopherol followed by the subsequent oxidation of ubiquinol suggest that α-tocopherol and ubiquinol act in concert to quench free radicals.[12]

Another notable function of CoQ_{10} would be the ability to interact with dihydrolipoic acid, a powerful radical scavenger, by transferring a pair of electrons. This helps to keep CoQ_{10} in the reduced state, thereby maximizing antioxidant capacity in other extra-mitochondrial membranes.[27] CoQ_{10} has also been linked to improving superoxide dismutase

A

$$CoQH_2 + LOO\bullet \rightarrow CoQH\bullet + H^+ + LOOH$$

$$CoQH\bullet + H^+ + LOO\bullet \rightarrow CoQ + LOOH$$

B

$$\alpha\text{-TOH} + LOO\bullet \rightarrow LOOH + \alpha\text{-TOH}\bullet$$

$$\alpha\text{-TOH}\bullet + CoQH_2 \rightarrow \alpha\text{-TOH} + CoQH\bullet$$

$$CoQH\bullet + \alpha\text{-TOH}\bullet \rightarrow CoQ + \alpha\text{-TOH}$$

Figure 5 (**A**) Action of CoQ alone or with (**B**) vitamin E on lipid peroxidation.
Abbreviations: α-TOH, α-tocopherol; CoQ, ubiquinone; $CoQH^{\cdot}$, semi-ubiquinone; $CoQH_2$, ubiquinol; Cyt c, cytochrome c; LOO, lipid peroxyl radical.

(SOD) function. Endothelial nitrous oxide, an important factor in vascular homeostasis, works to inhibit platelet aggregation and inflammation. ROS produced via oxidative stress in heart failure and diabetic patients could increase NO^- production by forming peroxynitrite, a potent oxidizing species, which can exacerbate the oxidative stress. CoQ_{10}, as an antioxidant, protects NO^- from forming a pro-oxidant species to preserve endothelial activity. This, in turn, could enhance SOD activity.[29]

CoQ_{10} status in disease states

Cardiovascular disease (CVD)

CVD accounts for the death of >2150 Americans each day, averaging one death every 40 seconds. This includes hypertension, heart failure, and coronary artery (heart) disease (CAD/CHD), which alone caused one of six deaths in 2010.[30] Patients with CVD have been shown to be deficient in CoQ_{10}. Those with CAD have been reported to have lower amounts of ubiquinol compared with healthy subjects, suggesting that a decreased ratio of reduced to oxidized CoQ_{10} instigates more oxidative stress.[31]

Extracellular SOD (ecSOD) serves to lower oxidative damage by catalyzing the dismutation of superoxide to oxygen and hydrogen peroxide.[29] Littarru and Tiano found that patients with CAD had lowered amounts of ecSOD.[32] Supplementation with 100 mg of CoQ_{10} three times a day in a controlled, randomized study resulted in a significant increase in ecSOD activity in those patients who were deficient in ecSOD.[33] As previously mentioned, a possible scenario could be that CoQ_{10} salvages NO^- by scavenging free radicals. In addition, NO^- can interact with cellular targets, can participate in intracellular signaling, and can increase the expression of ecSOD.[29,34] A higher ecSOD activity could further protect NO^- from becoming inactivated by O_2^-.[33] The mechanism in lowering blood pressure for hypertensive patients can also be attributed to this preservation of the endothelium. Rosenfeldt et al reviewed eight different trials, four placebo-controlled and four non-placebo-controlled trials, in which patients were given 100–200 mg of CoQ_{10} for 8–12 weeks. The results of all studies combined averaged a decrease of 16 mm Hg systolic and 10 mm Hg diastolic blood pressure.[35] Similar results were found even at higher dosages. Littarru et al reported 50% of patients being able to quit using other antihypertensive medications after an administration of 225 mg CoQ_{10} in the trial group.[29] In 1993, Morisco et al performed one of the largest controlled trials (n=641) on cardiomyopathy/heart failure. Patients received either 2 mg CoQ_{10} per kg/day or placebo for 1 year. Improvement in arrhythmias and episodes of pulmonary edema/asthma were documented in the supplemented group.[36]

CoQ_{10} may be effective in cosupplementation with other compounds for CAD patients. A case–control study in Taiwan studied the effects on coadministering CoQ_{10} with vitamin B6, a precursor for the biosynthesis of CoQ_{10} from tyrosine.[37] They found a positive correlation with CoQ_{10} and vitamin B6 levels and a reduced risk in CAD. Vitamin B6 was suggested not only to promote the synthesis of CoQ_{10} but also to minimize homocysteine levels.[37] In conjunction with this finding, Lee et al also investigated the effect of CoQ_{10} supplementation on inflammatory markers in patients with CAD.[38] Forty subjects supplemented with higher levels of CoQ_{10} (150 mg/day) had higher ecSOD levels with lower inflammatory markers (IL-6 and C-reactive protein) and malondialdehyde.[38] Although homocysteine levels were not affected by CoQ_{10} supplementation in this case, the results suggest CoQ_{10} and vitamin B6 supplementation could possibly work synergistically in maximizing antioxidant potential and minimizing inflammatory response.

In its role in decreasing oxidative stress, CoQ_{10} supplementation has had successful results in shorter hospital stays for patients undergoing surgical procedures pertaining to cardio blood vessels. Under ischemic conditions, returning blood flow through a vessel can cause inflammatory rather than restorative responses, known as ischemic reperfusion (IR) injury.[30] Patients given 150–180 mg of CoQ_{10} a day for 1 week prior to coronary artery bypass surgery in a trial were shown to have fewer reperfusion arrhythmias, blood requirements, and mediastinal drainage in comparison with control subjects.[32] The ability of CoQ_{10} to inhibit subsequent IR damage during the surgical time frame may suggest benefits for cardiac patients in whom medication may not be enough to treat their condition.

Mitochondrial diseases

Mitochondrial respiratory chain (MRC) disorders develop as a result of mutations in either nuclear or mitochondrial DNA. CoQ_{10} has been shown to offer potential benefits in the treatment of these heterogeneous disorders. Both in patients with a defect in CoQ_{10} biosynthesis and in those with MRC disorders, not associated with CoQ_{10} deficiency, CoQ_{10} and its synthetic analogs demonstrate some therapeutic benefits, potentially working to improve electron flow through the MRC and increase antioxidant capacity.[39]

Diabetes

Attributing to ROS formation, hyperglycemia can play a major role in causing complications pertaining to vascular health. CoQ_{10} status in individuals with diabetes has led to conflicting results due to the nature of the disease. A diabetic may be deficient or adequate in plasma CoQ_{10} in comparison with nondiabetic individuals. Individuals with type 2 diabetes (T2D) showed lower levels of total CoQ_{10} and a decreased ratio of ubiquinol to total CoQ_{10}.[4] Hasegawa et al observed changes in antioxidant status in T2D patients who displayed higher amounts of ubiquinone compared with ubiquinol.[40] However, plasma CoQ_{10} levels in individuals with type 1 diabetes were increased, suggesting that severity and type could influence CoQ_{10} status.[41]

Individuals with T2D may benefit from the antioxidant action of CoQ_{10} supplementation, as levels are reduced in these patients. Few clinical studies have shown an improvement in glycemic profile with supplementation of ubiquinone. This may be due to the impaired conversion of ubiquinone to ubiquinol.[41] With the increasing availability of ubiquinol supplements in recent years, T2D patients have responded positively in terms of increased status. Mezawa et al supplemented nine patients, who continued to take their hypoglycemic medications, with 200 mg of ubiquinol for 12 weeks.[42] Results showed significant improvements in hemoglobin A1c

(HbA1c) and prevention of the formation of advanced glycation end products, but with no effect on lipid profiles or blood pressure. Hodgson et al, in addition to improved HbA1c, found that blood pressure was improved in a randomized double-blind placebo-controlled study with uncomplicated T2D patients.[43] One case study reported that diabetics with congestive heart failure displayed an improvement in systolic and left ventricular function upon supplementation.[44] In combination with anti-hyperglycemic drugs, CoQ_{10} may benefit T2D patients without adverse effects.

Neurodegenerative disease

In a similar manner where ROS attacks lipids and proteins, nucleic acids also succumb to the effects of oxidative stress. Mitochondrial DNA, as a consequence of being located in proximity to ROS formation, is more prone to subsequent damage. Any dysfunction to the mitochondria could result in irreversible mutations of genes that synthesize ATP. Thus, oxidative damage has the ability to cause permanent changes in how our body produces energy, which could lead to cell apoptosis.[45] CoQ_{10} concentrations have been shown to be decreased in Alzheimer's disease (AD) and PD patients. In an antioxidant assessment, Mischley et al proposed that CoQ_{10} becomes conditionally essential in PD patients and that supplementation may be clinically beneficial.[46] Because of its involvement in the ETC, an elevation in CoQ_{10} becomes relevant because of its potential in restoring function to damaged mitochondria.[25] Wadsworth et al thus concluded that it may be attributed to CoQ_{10} antioxidant and/or activation of UCP molecules, which lower membrane potential and stress in the mitochondria.[47] Although CoQ_{10} levels in the brain and mitochondria were unchanged in this study, further research in vivo may be necessary to determine the mechanism specific to CoQ_{10} neuroprotective effects.

Cancer

In the 1970s, Karl Folkers postulated that CoQ_{10} was needed for normal cell respiration and that any loss or decrease in its bioavailability could alter cell function.[48,49] This change in function, leading to the increase in lipid peroxidation, inflammation, and oxidative damage, could lead to the possible development of cancer. An observational study reported that individuals with lung, pancreas, or especially breast cancer were more likely to have low plasma CoQ_{10} levels compared with healthy controls.[49] A study by Bliznakov illustrated that injected doses of CoQ_{10} (150–750 μg) in mice significantly delayed the onset of 3,4,9,10-dibenzpyrene-induced tumor formation, decreased tumor size, and reduced mortality rates compared with mice that were not given a supplemental injection.[50] A more recent trial showed similar results in male Sprague–Dawley rats, where CoQ_{10} supplementation (0.4 mg/kg/day) demonstrated therapeutic potential against trichloroacetic acid–induced hepatocellular carcinoma, mediated by the suppression of lipid peroxidation, the prevention of reduced glutathione depletion, and decreased elevations of tumor necrosis factor-α and nitric oxide in liver tissue.[51] CoQ_{10} use with chemotherapy was shown to be effective in patients suffering from breast cancer. Tamoxifen, an estrogen-specific receptor antagonist, is used for therapy in all stages of breast carcinomas, which may result in possible side effects leading to oxidative stress. Supplementing CoQ_{10}, riboflavin, and niacin (100, 10, and 50 mg/day doses, respectively) was shown to counteract derangements in blood profiles in combination with Tamoxifen, including hyperlipidemia.[52] The antioxidant and anti-inflammatory properties of CoQ_{10} are suggested to be responsible for the anticancer effect found in such studies.

Smoking and CoQ_{10} status

As a biomarker of oxidative stress, antioxidants have been shown to be decreased in smokers, particularly in patients at a risk of CVD and/or chronic heart failure or with altered cholesterol metabolism.[53] However, CoQ_{10} research on smokers with unremarkable medical history is lacking. Al-Bazi et al[53] studied 55 young healthy adult smokers (30 males and 25 females) and 51 nonsmokers (26 males and 25 females) by measuring CoQ_{10} plasma concentrations and lipid levels. They found that smokers had significantly lower CoQ_{10} concentrations than those who did not smoke. Furthermore, female smokers had lower total cholesterol, HDL, LDL, and CoQ_{10}/LDL ratio than male smokers. On the contrary, Zita et al found that baseline CoQ_{10} status was increased in healthy men who smoked 1–10 cigarettes a day versus nonsmoking men.[54] Ninety percent of the men in this study showed an increase in CoQ_{10} status regardless of smoking frequency upon CoQ_{10} supplementation with 30 and 100 mg doses daily for 2 months. Large-scale studies on smokers with no previous medical condition may aid in clarifying whether smoking is an independent risk factor for low CoQ_{10} status.

Exercise and CoQ_{10} Supplementation

Regular exercise is known to exert exceptional benefits in lowering the risk for the development of chronic disease and overall mortality pertaining to these diseases.[55] Conversely, increased intensity and duration can result in episodes of fatigue and muscle injury due to ROS produced during an exercise session. As a scavenging antioxidant, it has been theorized that CoQ_{10} supplementation before exercise could protect muscle cells and subsequently improve the aspects of physical performance. Östman et al tested this theory in a 8-week, double-blind controlled trial in 23 healthy men who followed a moderate-exercise regimen, half of whom (n=12) were given a daily dose of 90 mg CoQ_{10}.[56] No significant effects were demonstrated in terms of decreased oxidative stress or increased physical capacity. However, studies on the influence on CoQ_{10} supplementation in high-intensity exercise are scarce, yet promising. Strenuous exercises, such as marathon running, cycling, and intense aerobic training, have become increasingly prominent in the society. The concern is that damage to muscle cells in this type of workout can act as a catalyst for progressive oxidative stress and inflammation in the muscle. Díaz-Castro et al[55] compared two groups composed of high-effort runners to distinguish any possible changes in inflammatory and oxidative stress markers after CoQ_{10} administration. The CoQ group (CG) received five capsules of 30 mg CoQ_{10} tablets beginning 2 days before the trial, with one capsule taken at every meal leading up to the trial day. After a 50-km mountainous run, the placebo group witnessed a significant increase in pro-inflammatory cytokines as well as in isoprostanes and hydroperoxides, which characterize free radical damage. However, the supplemented CG did not demonstrate increases in oxidative stress markers and witnessed a spike in catalase activity, an indication of antioxidant enhancement.[55] These results provide a rationale for further insight into the mechanism by which CoQ_{10} ameliorates ROS damage.

Drug interactions

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMG-CoA), a rate-limiting step that converts HMG-CoA to mevalonate in the production of cholesterol.[57] Considered a gold standard for the treatment of hypercholesterolemia, statins have been linked to the development of certain myopathies ranging from myalgia to rhabdomyolysis.[12] While the incidence of myopathy is usually low, myopathy and rhabdomyolysis are more frequent when statins are combined with other drugs that inhibit cytochrome P450-dependent metabolism of statins in the liver (eg, itraconazole and erythromycin), thereby potentially increasing statin bioavailability. Research speculates that myopathy may be the result of HMG-CoA inhibition, which shuts off the production of mevalonate constituents, such as CoQ_{10}.[32] Approximately 60% of CoQ_{10} is carried by LDL cholesterol, which could explain why levels are decreased in the absence of a transport carrier.[3] High-dose statin use has been shown to reduce plasma CoQ_{10} levels in hypercholesterolemia patients in comparison with healthy controls and has also resulted in an increase in lactate/pyruvate ratios.[58] It has also been reported that high-statin use decreased muscle CoQ_{10} levels and MRC activity, possibly related to a lowered mitochondria volume.[32,59] Mitochondrial dysfunction, in response to low CoQ_{10} and subsequent inefficiency of the respiratory chain, could thus be the end result for patients on long-term statin therapy.[4] The mechanism on how statins cause a decrease in CoQ_{10} levels independent of lowering lipid levels still remains unclear.

The consequence of statin use may be counteracted by the supplementation of CoQ_{10}. However, this issue to this day remains controversial and debated in terms of efficacy.[31] Molyneux et al[1] supplemented patients with prior statin-induced myalgia (n=44) with 200 mg/day of CoQ_{10} or placebo for 12 weeks in combination with a statin at 10 mg/day. Although plasma levels of CoQ_{10} were increased, supplementation had no significant effects in patients who tolerated the statin (73% vs 59%) or in their myalgia score change between statin and statin/CoQ_{10} administration (6.0 vs 2.3, respectively).[1] On the contrary, Caso et al found that muscle pain was diminished by 40%, and daily activities were increased by 38% in myalgia patients receiving statins after 100 mg CoQ_{10} per day for 30 days.[60] As future study is needed to form a definitive resolution with statin and CoQ_{10} therapy, the repercussions of CoQ_{10} deficiency should be known to clinicians for at-risk patients. Monitoring CoQ_{10} levels in patients who are currently on a statin can help control its potential adverse effects. It may also be beneficial to prescribe the lowest dosage needed to minimize cholesterol levels as to avoid a decrease in CoQ_{10} and induce myopathy.[4] The excellent safety record of CoQ_{10} also makes it reasonable for patients to supplement this compound as a safeguard against any negative effects, if any, of statin therapy.

Other medications

Some other commonly prescribed drugs taken with CoQ_{10} have been reported to be influenced by the supplement's activity. Along the same lines of statin use, β-blockers are culprits in lowering endogenous production and depletion of CoQ_{10}. These compounds, especially propranolol, are used to treat hypertension. In some patients, the drug adversely affected myocardial function by hindering important CoQ_{10} enzymes.[61] Concurrent therapy with CoQ_{10} may be beneficial to compensate for the inhibitory effect.

There have been speculations on CoQ_{10} and its effect on patients taking blood-thinning medications, such as warfarin, by negating their anticoagulant activity. However, clinical evidence is still lacking. In fact, one controlled study showed that supplementation of 100 mg CoQ_{10} in 24 warfarin patients had no long-term effects on prothrombin time over a 4-month period.[62] A recent study has shown that amitriptyline, anti-depressant drug, downregulated CoQ_{10} biosynthesis and that CoQ_{10} supplementation offered protection against amitriptyline toxicity.[63,64] Hypoglycemic drugs have also been shown to deplete CoQ_{10} status in vivo, and supplementing diabetic patients with ubiquinol has been linked to an improved glycemic profile. It is thus recommended that clinicians adjust the dosage of common diabetic medications, such as sulfonylureas and biguanides, to get the most out of both compounds.[16]

A dietitian's perspective

From a patient care perspective, the registered dietitian/nutritionist (RDN) is interested in the effect of supplementation of CoQ_{10} for patients diagnosed with CVD, diabetes, cancer, and other conditions affected by the loss of CoQ_{10} due to lower production levels in the body, in prescribed drug use for the treatment of various disorders, such as use of statin drugs to reduce cholesterol, or in conditions where increased need for antioxidants may prove beneficial to health.

Since the availability of CoQ_{10} from dietary sources is limited, and dependent on additional nutrient intake, including vitamin B6, vitamin C, other B vitamins, and amino acids, a priority of the RDN is the assessment of current diet intake and subsequent recommendation of modifications in food consumption to meet recommended dietary reference intakes and needs. Adequate intakes of B vitamins and vitamins C and E as well as other antioxidants, fiber, and nutrients can also be an important step in the modification of symptoms in many disease conditions.

Supplementation of CoQ_{10} has been suggested as a means to increase body levels when production of CoQ_{10} is decreased and/or if an increased level of CoQ_{10} is needed in certain disease states. Evidence that the supplement use of CoQ_{10} modifies symptoms of disease has varying levels of effectiveness. In the USA, supplement use of CoQ_{10} has been rated "possibly effective" for conditions such as congestive heart failure, age-related macular degeneration, diabetic neuropathy, high blood pressure, migraine headache, and muscular dystrophy.[65] According to the Evidence Analysis Library of the Academy of Nutrition and Dietetics, its effectiveness when used to treat muscle pain associated with the use of statin drugs to treat high blood cholesterol is not yet conclusive.[66] The use of CoQ_{10} as a supplement should be evaluated for clients/patients on an individual basis along with an assessment of current dietary intake, drug prescriptions, and other medicines and supplements used.

Conclusion

CoQ_{10} is a vitamin-like compound synthesized in every cell in the body. Mitochondria contain the highest concentration of CoQ_{10} and play a significant role in the production of ATP. Thus, tissues such as the heart and muscle are in need of substantial amounts due to their high energy requirement. Outside the respiratory chain, CoQ_{10} also acts as a lipophilic antioxidant to reduce the damaging effects of ROS in the body. Because CoQ_{10} is made de novo within the body, contribution through the diet is not necessary under normal circumstances. However, factors such as increased age and oxidative stress via metabolic discrepancies can make this nutrient conditionally essential. It has been shown that age-related changes are most evident in the mitochondria and that decreases in CoQ_{10} content may be specific to certain tissues rather than ubiquitous.[67] Age and disease have also shown to influence increased oxidized CoQ_{10} compared with the reduced form, which may result in decreased levels of total CoQ_{10}.[2] In such cases, resupply through diet alone may not be a conclusive answer. Absorption of CoQ_{10} from dietary contribution is slow and inefficient because of its weight and hydrophobic nature. With the increasing availability of the over-the-counter forms, CoQ_{10} supplementation may be the best therapeutic source when endogenous CoQ_{10} synthesis is impaired. Ultimately, CoQ_{10} may aid in preventing and/or minimizing metabolic conditions that may lead to CVD, diabetes, neurodegenerative disorders, and cancer. Clinical studies encompassing these disease states where improvements in mitochondrial and antioxidant function are shown provide implications for therapeutic CoQ_{10} supplementation. The safety record of CoQ_{10} also makes it an excellent compound for human trials. Limitations in CoQ_{10} supplementation include its high cost and absorption efficiency, as both ubiquinone and ubiquinol are now available for purchase in products with varied solubility formulations. In addition, most of the clinical studies on CoQ_{10} supplementation reviewed had a relatively small number of participants and short-term duration. Future long-term studies on its use with larger amounts of subjects suffering from conditions caused by oxidative stress would lead to a more defined understanding of CoQ_{10} action in alleviating the resulting symptoms of deficiency.

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Disclosure

The authors report no conflicts of interest in this work.

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