

Coenzyme Q₁₀ Therapy

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Key Words

Clinical indications · Coenzyme Q₁₀ · Coenzyme Q₁₀-related compounds · Pharmacokinetics

Abstract

For a number of years, coenzyme Q₁₀ (CoQ₁₀) was known for its key role in mitochondrial bioenergetics; later studies demonstrated its presence in other subcellular fractions and in blood plasma, and extensively investigated its antioxidant role. These 2 functions constitute the basis for supporting the clinical use of CoQ₁₀. Also, at the inner mitochondrial membrane level, CoQ₁₀ is recognized as an obligatory cofactor for the function of uncoupling proteins and a modulator of the mitochondrial transition pore. Furthermore, recent data indicate that CoQ₁₀ affects the expression of genes involved in human cell signaling, metabolism and transport, and some of the effects of CoQ₁₀ supplementation may be due to this property. CoQ₁₀ deficiencies are due to autosomal recessive mutations, mitochondrial diseases, aging-related oxidative stress and carcinogenesis processes, and also statin treatment. Many neurodegenerative disorders, diabetes, cancer, and muscular and cardiovascular diseases have been associated with low CoQ₁₀ levels as well as different ataxias and encephalomyopathies. CoQ₁₀ treatment does not cause serious adverse effects in humans and new formu-

lations have been developed that increase CoQ₁₀ absorption and tissue distribution. Oral administration of CoQ₁₀ is a frequent antioxidant strategy in many diseases that may provide a significant symptomatic benefit.

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Coenzyme Q₁₀ (CoQ₁₀) is an essential compound found naturally in virtually every cell in the human body. Because of its ubiquitous presence in nature and its quinone structure, CoQ₁₀ is also known as ubiquinone. CoQ₁₀ is a lipid-soluble substance whose primary role is as an essential intermediate of the electron transport system in the mitochondria. Adequate amounts of CoQ₁₀ are necessary for cellular respiration and ATP production. CoQ₁₀ also functions as an intercellular antioxidant, and its presence was then demonstrated in all cell membranes and in blood, both in high- and in low-density lipoproteins, where it is endowed with antioxidant properties [Crane, 2001]. CoQ₁₀ was also recognized to have an effect on gene expression [Groneberg et al., 2005; Schmelzer et al., 2008]. Dietary supplementation affecting CoQ₁₀ levels has been shown in a number of organisms to cause multiple phenotypic effects, which can be explained on the basis of its significant impact on the expression of many genes mainly involved in cell signaling, intermedi-

Table 1. The most frequent physiological and clinical indications of CoQ₁₀

	References
<i>Clinical indications</i>	
Human CoQ ₁₀ deficiencies	Quinzii and Hirano, 2011
Mitochondrial diseases	Kerr, 2010
Fibromyalgia	Cordero et al., 2011, 2012
Cardiac failure	Adarsh et al., 2008
Ischemic heart disease	Celik and Iyisoy, 2009
Interaction with statins	Caso et al., 2007
Hypertension	Rosenfeldt et al., 2007
Endothelial function	Belardinelli et al., 2006
Diabetes	Golbidi et al., 2011
Cancer	Roffe et al., 2004
<i>Neurodegenerative diseases</i>	
Parkinson's disease	Henchcliffe and Beal, 2008
Huntington's disease	Stack et al., 2008
Alzheimer's disease	Lee et al., 2009
Friedreich's ataxia	Cooper et al., 2008
<i>Other conditions</i>	
Asthenozoospermia	Mancini and Balercia, 2011
Periodontal disease	Prakash et al., 2010
Migraine	Sándor et al., 2005
Pre-eclampsia	Teran et al., 2009
Down's syndrome	Tiano and Busciglio, 2011
Aging	López-Lluch et al., 2010

ary metabolism, transport and transcription control, and inflammation, among others, indicating an important role for CoQ₁₀ as a potent gene regulator [Groneberg et al., 2005; Santos-González et al., 2007]. However, the molecular mechanisms whereby CoQ₁₀ induces these pleiotropic effects has yet to be completely understood [Schmelzer et al., 2008].

Numerous disease processes associated with CoQ₁₀ deficiency can benefit from CoQ₁₀ supplementation, including primary and secondary CoQ₁₀ deficiencies, mitochondrial diseases, fibromyalgia, cardiovascular disease, neurodegenerative diseases, cancer, diabetes mellitus, male infertility, and periodontal disease (table 1).

CoQ₁₀ Deficiency States

Tissue deficiencies or subnormal serum levels of CoQ₁₀ have been reported in a wide range of medical conditions, including primary CoQ₁₀ deficiencies [Emmanuele et al., 2012] and secondary CoQ₁₀ deficiencies such as mitochondrial diseases [Sacconi et al., 2010]. CoQ₁₀ levels decline with advancing age, and this decline may contribute in part to some of the manifestations of aging [Sohal and

Forster, 2007]. CoQ₁₀ deficiency could result from: (1) impaired CoQ₁₀ synthesis due to nutritional deficiencies (such as vitamin B₆ deficiency, a cofactor essential for CoQ₁₀ biosynthesis), (2) a genetic or acquired defect in CoQ₁₀ synthesis or utilization, or (3) increased tissue needs resulting from a particular disease. Clinical presentations of severe CoQ₁₀ deficiency include encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh syndrome with growth retardation, and isolated myopathy. Since oral administration of CoQ₁₀ can increase tissue levels of the nutrient, it is possible to correct CoQ₁₀ deficiency and is particularly essential in the life-threatening infantile encephalopathy [Quinzii et al., 2007].

Absorption, Tissue Uptake and Pharmacokinetics

Plasma CoQ₁₀ concentrations are usually used for the estimation of the CoQ₁₀ status in humans primarily because of easy sample collection. Reported plasma CoQ₁₀ ranged from 0.40 to 1.91 μmol/l (0.34–1.65 μg/ml) [Bhagavan and Chopra, 2006]. CoQ₁₀ is also naturally found in dietary sources, with large amounts present in heart, chicken leg, herring, and trout. The daily intake from food was estimated to be 3–5 mg CoQ₁₀ a day. However, in tissues with unimpaired synthetic capacity, it appears that CoQ₁₀ reaches a saturation level, and nutritional supplement of CoQ₁₀ in the diet does not increase tissue levels above normal [Beal, 1999; Weber et al., 1997].

Intestinal absorption is 3-fold faster if CoQ₁₀ is administered with food intake [Ochiai et al., 2007]. Following absorption, CoQ₁₀ appears in plasma lipoproteins and in liver, but usually not in heart or kidney [Zhang et al., 1995]. However, with higher supplementations (150 mg/kg/day), heart and the skeletal muscle showed a significant increase in total CoQ₁₀, suggesting that higher plasma CoQ₁₀ concentrations are necessary to facilitate uptake by peripheral tissues [Kwong et al., 2002]. Biochemical characteristics of CoQ₁₀ are important for our understanding of uptake and distribution following oral ingestion. CoQ₁₀ is absorbed slowly from the small intestine, possibly because it has a high molecular weight and is not very water soluble, passes into the lymphatics, and finally to the blood and tissues. Research on exogenous CoQ₁₀ absorption and bioavailability varies greatly depending on the type of CoQ₁₀ preparation studied. CoQ₁₀ absorption is probably a complex process and dependent upon active and passive transport mechanisms [Palamkula et al., 2005]. A study on intestinal absorption of 30 mg CoQ₁₀ administered in a meal or as powder in cap-

sules to healthy subjects found no significant difference in absorption for these 2 routes of administration [Weber et al., 1997]. Although not all research is in agreement, the general consensus is that slightly better absorption is achieved with oil-based forms of CoQ₁₀ [Weis et al., 1994; Lyon et al., 2001]. Further studies are needed to elucidate whether age, gender, lipoprotein status, diet, dosage formulation, or other factors may affect the bioavailability of CoQ₁₀ with chronic dosing [Miles, 2007].

CoQ₁₀ dosage guidelines, which appeared to be safe and well tolerated, were suggested for adults (up to 1,200 mg/day) [Hathcock and Shao, 2006] and for children (up to 10 mg/kg/day) [Miles et al., 2006]. Monitoring CoQ₁₀ plasma concentrations may be considered after 3–4 weeks of constant dosing, when steady-state conditions exist [Hosoe et al., 2007]. Steady-state plasma concentrations at these dosage levels generally ranged from 5 to 10 µg/ml [Miles, 2007].

Mechanism of Action

Due to its involvement in ATP synthesis, CoQ₁₀ affects the function of all cells in the body, especially those with high-energy demand, making it essential for the health of all tissues and organs. CoQ₁₀ is our only lipid-soluble antioxidant synthesized endogenously and efficiently prevents oxidation of proteins, lipids and DNA. The fundamental role of CoQ₁₀ in mitochondrial bioenergetics and its well-acknowledged antioxidant properties constitute the basis for its clinical applications, although some of its effects may be related to a gene induction mechanism [Littarru and Tiano, 2010]. Today, several other important functions are also associated with this lipid [Bentinger et al., 2010].

Clinical Indications

Treatment of CoQ₁₀ Deficiencies

CoQ₁₀ deficiency is a treatable condition; therefore, its diagnosis is essential, especially for pediatricians and child neurologists. An early treatment with high-dose CoQ₁₀ may radically change the natural history of this group of diseases [DiMauro et al., 2007]. Patients with all forms of CoQ₁₀ deficiency have shown clinical improvement with oral CoQ₁₀ supplementation, but cerebral symptoms are only partially ameliorated (probably because of irreversible structural brain damage before treatment and because of poor penetration of CoQ₁₀ across the blood-brain barrier) [Rötig et al., 2007].

CoQ₁₀ deficiency is involved in cardiomyopathies and degenerative muscle and neuronal diseases. The major phenotypes provoked by CoQ₁₀ deficiencies are encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh syndrome with growth retardation, ataxia, nephrotic syndrome, and isolated myopathy [Quinzii and Hirano, 2011].

The cerebellum may have the narrowest safety margin and, therefore, would be the first tissue to suffer from a pathological shortage of CoQ₁₀ [Naini et al., 2003]. The most severe human CoQ₁₀ deficiencies are due to autosomal recessive mutations and can be classified as primary deficiencies when mutations affect CoQ₁₀ biosynthetic genes or secondary if the cause is related to other genetic defects [Quinzii and Hirano, 2011].

The first CoQ₁₀-deficient patients reported by Ogasahara et al. [1989] were 2 sisters (12 and 14 years old), and symptoms were alleviated after 3 months of receiving 50 mg of CoQ₁₀ 3 times daily [Ogasahara et al., 1989]. Patients with encephalomyopathy and renal failure were treated with oral CoQ₁₀ at doses from 5 mg/kg/day [Rötig et al., 2000] or 30 mg/kg/day [Salviati et al., 2005]; a patient with myopathic phenotype of CoQ₁₀ deficiency received 500 mg/day of CoQ₁₀ [Gempel et al., 2007], and a patient with cerebellar ataxia was treated with oral CoQ₁₀ supplementation with an initial dose of 2,500 mg/day. The doses were decreased every 3 months [Artuch et al., 2006]. These cases showed a good to very good response to CoQ₁₀ supplementation, with the main symptoms related to cerebellar dysfunction disappearing and the international cooperative ataxia rating scale (ICARS) scores decreasing after 16 months of supplementation.

However, a daily oral therapy that included 50 mg CoQ₁₀ beginning at age 3 months did not lead to clinical improvement in an infant with Leigh syndrome and nephropathy; the child died after 5 months [Quinzii et al., 2006]. The lack of clinical improvement may have been due to low dosage, poor penetration of CoQ₁₀ formulation, the severity of brain damage prior to oral supplementation, or a combination of these factors.

Patients with secondary deficiency in CoQ₁₀ and cerebellar ataxias also improved with CoQ₁₀ supplementation [Quinzii et al., 2005; Gempel et al., 2007] or even resulted in full recovery [Gempel et al., 2007]. Furthermore, myopathic CoQ₁₀ deficiency also responded dramatically to CoQ₁₀ supplementation, and after 8 months of treatment, excessive lipid storage resolved, CoQ₁₀ level normalized, mitochondrial enzymes increased, and the proportion of apoptotic fibers decreased from 30 to 10% in 2 brothers with myopathic CoQ₁₀ deficiency [Di

Giovanni et al., 2001]. Mancuso et al. [2010] reported another case of the myopathic form of CoQ₁₀ deficiency with excellent response to therapy.

Mitochondrial Disorders

CoQ₁₀ is frequently reduced in muscle tissue of patients with mitochondrial myopathy [Sacconi et al., 2010], and CoQ₁₀ is very widely used for primary mitochondrial disorders treatment [Kerr, 2010]. Numerous case reports and small, open-label studies describe mitochondrial diseases of varying severity that have responded to CoQ₁₀ supplementation, typically in dosages from 30 to 300 mg/day [Gold et al., 1996; Berbel-Garcia et al., 2004]. A 3-month trial included 8 patients with mitochondrial encephalomyopathies supplemented with 160 mg CoQ₁₀/day. Although the researchers reported a trend towards improved muscle endurance, less fatigue during daily duties, and decreased serum lactate and pyruvate levels, only the muscle endurance results reached statistical significance. The study authors hypothesized the dosage was too low to provide significant benefit [Chen et al., 1997]. In a 6-month double-blind clinical trial, 44 patients with mitochondrial myopathies from multiple centers were treated with 2 mg/kg CoQ₁₀ daily. Sixteen of 24 patients experienced at least a 25% decrease in post-exercise lactate levels and were selected as 'responders' to continue the study. After a further 3 months at the same dose, no significant differences were observed between the responder and placebo groups. The lack of long-term therapeutic effects in the responders may be attributed to the relatively low dose and short duration of the study [Bresolin et al., 1990]. Overall, it appears that larger CoQ₁₀ dosages are indicated for mitochondrial disorders. Recently, our group has demonstrated the benefits of CoQ₁₀ supplementation in several cellular models of mitochondrial diseases [Rodríguez-Hernández et al., 2009; Cotán et al., 2011; De la Mata et al., 2012; Garrido-Maraver et al., 2012]. However, the clinical evidence supporting a benefit of CoQ₁₀ treatment in primary mitochondrial disease is limited. Reasons for this include the relative rarity and heterogeneity of mitochondrial diseases [Haas, 2007].

Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome with unknown etiology and a wide spectrum of symptoms such as allodynia, debilitating fatigue, joint stiffness, and migraine. Recent studies have shown some evidences demonstrating that oxidative stress is associated to clinical symptoms in FM. Recent findings of our group have shown reduced levels of CoQ₁₀, a decreased mitochon-

drial membrane potential, increased levels of mitochondrial superoxide, and increased levels of lipid peroxidation in blood mononuclear cells from FM patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria by mitophagy [Cordero et al., 2010]. In another study, FM patients were clinically evaluated using the Visual Analogical Scale of pain (VAS), and the Fibromyalgia Impact Questionnaire (FIQ). FM patients with CoQ₁₀ deficiency showed a significant reduction on symptoms after CoQ₁₀ treatment [Cordero et al., 2011, 2012]. Determination of CoQ₁₀ deficiency and subsequent supplementation in FM may result in significant clinical improvement.

Cardiovascular Disease

Oxidative stress plays a central role in the pathogenesis of cardiovascular diseases including heart failure and hypertension. Heart failure is often characterized by a loss of contractile function due to an energy depletion status in the mitochondria that has been associated with low endogenous CoQ₁₀ levels. Myocardial deficiency of CoQ₁₀ has been demonstrated in endomyocardial biopsy samples from patients with cardiomyopathy, and deficiency of CoQ₁₀ correlated with the severity of disease, suggesting that therapy with CoQ₁₀ can result in improving the quality of life of cardiac patients by enhancing myocardial contractility [Folkers et al., 1985b]. Numerous studies have investigated the benefit of CoQ₁₀ supplementation for improving cardiovascular function via enhanced energy production, improved contractility of cardiac muscles, and its potent antioxidant activity, particularly the prevention of low-density lipoproteins oxidation. Langsjoen et al. [1994a] published a study summarizing 8 years of research on the benefits of CoQ₁₀ in clinical cardiology. Since this study, numerous other studies have demonstrated the usefulness of CoQ₁₀ supplementation for various cardiovascular conditions. Research has shown CoQ₁₀ levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure [Folkers et al., 1970, 1985a]. Two important meta-analyses reported significant benefits of CoQ₁₀ on heart failure of various causes [Mortensen, 2003; Sander et al., 2006]. Dilated cardiomyopathy is a form of cardiac muscle disease characterized by ventricular dilation, contractile dysfunction and eventual congestive heart failure. In patients with stable moderate congestive heart failure, oral CoQ₁₀ supplementation was shown to ameliorate cardiac contractility and endothelial dysfunction [Littarru and Tiano, 2007].

Atherosclerosis

CoQ₁₀ in its reduced form, ubiquinol (CoQ₁₀H₂), inhibits protein and DNA oxidation, but it is the effect on lipid peroxidation that has been most deeply studied. Ubiquinol inhibits the peroxidation of cell membrane lipids and lipoprotein lipids present in circulation. Dietary supplementation with CoQ₁₀ results in increased resistance of low-density lipoproteins to the initiation of lipid peroxidation [Mohr et al., 1992]. Moreover, CoQ₁₀ has a direct anti-atherogenic effect, which has also been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet [Witting et al., 2000]. CoQ₁₀ supplement at a dose of 150 mg/day can decrease oxidative stress, increase antioxidant enzyme activity and decrease the inflammatory marker IL-6 in patients with atherosclerosis [Lee et al. 2012a, b].

Dyslipidemia and Statin Drugs

Elevated cholesterol and the associated dyslipidemia are commonly treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibiting drugs (statins). Because both cholesterol and CoQ₁₀ synthesis depend on HMG-CoA reductase, both can be blocked. Different mechanisms have been proposed to explain statin-induced myopathy, including reduction of mevalonate pathway products, induction of apoptosis, mitochondrial dysfunction, and genetic predisposition [Mas and Mori, 2010]. Depletion in CoQ₁₀ may account for the statin-induced myopathies observed in some patients, the most serious of which is rhabdomyolysis. From 1990 to 2004, 13 controlled trials demonstrated significant CoQ₁₀ depletion secondary to statin therapy [Hargreaves et al., 2005]. Consequently, supplementing with CoQ₁₀ is highly recommended to prevent the myopathic side effects associated with the statin drugs. Recently, it has also been reported statin has side effects on energy and exertional fatigue [Golomb et al., 2012]. However, clinical evidence supporting CoQ₁₀'s use in the treatment of statin-induced myopathy is limited and controversial [Wyman et al., 2010].

Hypertension

Depending on the class, various antihypertensive drugs can have adverse effects, such as depression, cough, and cardiac and renal dysfunction [Hadj et al., 2007; Pepe et al., 2007]. Furthermore, many patients need to take more than one drug to control their blood pressure, increasing their risk of side effects. Some researchers believe CoQ₁₀ supplementation may reduce the need to take multiple antihypertensive drugs [Langsjoen et al., 1994b].

CoQ₁₀ appears to lower blood pressure. The exact mechanism is not known, but one theory is that it reduces peripheral resistance by preserving nitric oxide [Pepe et al., 2007]. Nitric oxide relaxes peripheral arteries, lowering blood pressure. In some forms of hypertension, superoxide radicals that inactivate nitric oxide are overproduced; CoQ₁₀, with its antioxidant effects, may prevent the inactivation of nitric oxide by these free radicals. Alternatively, CoQ₁₀ may boost the production of the prostaglandin prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, or it may enhance the sensitivity of arterial smooth muscles to prostaglandin prostacyclin, or both [Lönnrot et al., 1998]. A recent meta-analysis of clinical trials investigating the use of CoQ₁₀ for hypertension assessed overall efficacy. Blood pressure reduction was noted in all 12 trials, regardless of whether CoQ₁₀ was given alone or as an adjunct to standard antihypertensive medication, without significant side effects [Rosenfeldt et al., 2007]. In some cases, it seems reasonable to recommend this product as an adjunct to conventional antihypertensive therapy. However, larger, well-designed clinical trials of CoQ₁₀'s antihypertensive effects on specific clinical outcomes, such as the risk of stroke or myocardial infarction, are needed to define its true therapeutic value [Wyman et al., 2010].

Diabetes

Diabetes is a chronic metabolic disorder that continues to present as a major health problem worldwide. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action and is associated with chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism. Many studies suggest a central role for oxidative stress in the pathogenesis of this multifaceted metabolic disorder. This has prompted investigations in the use of antioxidants as a complementary therapeutic approach [Golbidi et al., 2011]. Serum CoQ₁₀ levels in type 2 diabetic patients are often decreased and may be associated with subclinical diabetic cardiomyopathy, reversible by CoQ₁₀ supplementation [Miyake et al., 1999]. In 3 separate randomized, double-blind clinical trials, a total of 194 dyslipidemic type 2 diabetic patients received 200 mg CoQ₁₀ or a placebo daily for 12 weeks. One study also compared CoQ₁₀ stand-alone treatment to a CoQ₁₀-fenofibrate combination and to fenofibrate (a lipid-lowering medication) alone. Primary outcomes were endothelial function of the brachial artery [Watts et al., 2002], blood pressure [Hodgson et al., 2002], glycemic control [Hodgson et al., 2002], and forearm microcirculatory function [Playford et al., 2003]. CoQ₁₀

supplementation in this population raised plasma CoQ₁₀ levels, improved endothelial function in the brachial artery, significantly decreased both systolic and diastolic blood pressure, decreased glycosylated hemoglobin (HbA1C), and, in combination with fenofibrate, markedly improved both endothelial and non-endothelial forearm vasodilation.

Furthermore, it has been demonstrated that a 12-week treatment with ubiquinone improves clinical outcomes and nerve conduction parameters of diabetic polyneuropathy; furthermore, it reduces oxidative stress without significant adverse events [Hernández-Ojeda et al., 2012].

Cancer

Decreased levels of CoQ₁₀ have been found in plasma of women with breast cancer and in cancerous breast tissue, and low levels correlated with a worse prognosis [Jolliet et al., 1998]. Case reports demonstrated 390 mg CoQ₁₀ daily resulted in tumor regression and disappearance of previously diagnosed metastasis. Approximately 1–3 years later, depending on the case, metastases had not reappeared [Lockwood et al., 1994; Rusciani et al., 2006].

In 117 melanoma patients without metastasis, plasma CoQ₁₀ levels were significantly lower than in control subjects and were associated with primary tumor thickness, with the highest CoQ₁₀ levels associated with thinner tumors. In addition, patients who developed metastases had lower CoQ₁₀ levels than those who did not, and subjects with lower baseline CoQ₁₀ levels had shorter disease-free intervals [Rusciani et al., 2006]. Low plasma levels of CoQ₁₀ have been demonstrated in cervical intraepithelial neoplasia and cervical cancer [Palan et al., 2003].

Mechanisms for CoQ₁₀'s benefit for cancer may include immune system enhancement and antioxidant activity. CoQ₁₀ can be depleted by the use of the chemotherapeutic drug doxorubicin (Adriamycin®), resulting in cardiotoxicity if a high enough cumulative dose is achieved. Supplemental CoQ₁₀ (100–200 mg/day) can prevent cardiac damage, as well as diarrhea and stomatitis that are caused by this agent, without decreasing its chemotherapeutic effectiveness [Domae et al., 1981]. A systematic review of controlled trials in cancer patients revealed CoQ₁₀ provides protection against cardiotoxicity and liver toxicity in patients receiving anthracycline chemotherapy drugs, such as doxorubicin [Roffe et al., 2004]. Recently, it has been reported that chemotherapeutic drugs such as camptothecin, etoposide, doxorubicin and methotrexate induced an increase in CoQ₁₀ levels in cancer cell lines by upregulation of *COQ7*, *COQ4* and *COQ8* gene expression, as part of an antioxidant response against

free radical production [Brea-Calvo et al., 2006]. On the other hand, compositions containing reduced CoQ₁₀ (in foods and beverages) have been proposed for preventing cancer and for mitigating the adverse reactions of anti-cancer agents [Villalba et al., 2010].

Neurological Conditions

Parkinson's Disease

A number of preclinical studies in both in vitro and in vivo models of Parkinson's disease (PD) have demonstrated that CoQ₁₀ can protect the nigrostriatal dopaminergic system. Some clinical trials have looked at the neuroprotective effects of CoQ₁₀ in patients in early and mid-stage PD [Liu et al., 2011]. Research suggests CoQ₁₀ may play a role in the cellular dysfunction found in PD, providing a protective agent for Parkinsonian patients [Shults et al., 1999]. Significantly reduced levels of CoQ₁₀ have been observed in blood and platelet mitochondria [Shults et al., 1997] and plasma [Sohmiya et al., 2004] of PD patients. Since 1998, at least 4 clinical trials on the efficacy of CoQ₁₀ in PD have been conducted [Shults et al., 1998, 2004; Horstink and van Engelen, 2003; Müller et al., 2003].

Results seem to indicate a positive effect, warranting larger double-blind, placebo-controlled trials. Recently, it has been demonstrated that cellular pathophysiological alterations associated with mitochondrial dysfunction in induced pluripotent stem cell-derived neural cells from familial PD patients and at-risk individuals could be rescued with CoQ₁₀ [Cooper et al., 2012].

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative genetic disorder caused by an expansion of CAG repeats in the HD gene encoding for huntingtin (Htt), resulting in progressive death of striatal neurons, with clinical symptoms of chorea, dementia and dramatic weight loss. Metabolic and mitochondrial dysfunction caused by the expanded polyglutamine sequence have been described along with other mechanisms of neurodegeneration previously described in human tissues and animal models of HD [Naia et al., 2011]. Strong evidence exists for early oxidative stress in HD, coupled with mitochondrial dysfunction, each exacerbating the other and leading to an energy deficit [Stack et al., 2008]. If oxidative damage plays a role in HD, then therapeutic strategies that reduce reactive oxygen species may ameliorate the neurodegenerative process. One such strategy using CoQ₁₀ has been proposed. High-dose CoQ₁₀ is safe and tolerable in HD

patients. In addition, there are parallels in reducing markers of oxidative stress in both HD mice and HD patients after CoQ₁₀ treatment [Stack et al., 2008].

Alzheimer's Disease

Increasing evidence suggests that Alzheimer's disease is associated with oxidative damage that is caused in part by mitochondrial dysfunction [Wadsworth et al., 2008]. Studies have shown CoQ₁₀ to be neuroprotective in Alzheimer's disease through protection of oxidative damage and attenuation of mitochondrial dysfunction [Lee et al., 2009].

However, in a recent double-blind, placebo-controlled clinical trial (Trial Registration clinicaltrials.gov Identifier: NCT00117403), antioxidant treatment, including CoQ₁₀, did not influence cerebrospinal fluid biomarkers related to amyloid or tau pathology [Galasko et al., 2012].

Friedreich's Ataxia

There is extensive evidence that mitochondrial respiratory chain dysfunction, oxidative damage and iron accumulation play significant roles in the disease mechanism. Therapeutic avenues for patients with Friedreich's ataxia (FRDA) are beginning to be explored in particular targeting antioxidant protection, enhancement of mitochondrial oxidative phosphorylation, iron chelation, and more recently increasing FRDA transcription. The use of quinone therapy has been the most extensively studied to date with clear benefits demonstrated using evaluations of both disease biomarkers and clinical symptoms [Cooper and Schapira, 2007].

An open-label pilot trial explored the use of 400 mg CoQ₁₀ plus 2,100 IU of vitamin E daily in 10 patients with FRDA for 47 months. A sustained improvement in mitochondrial energy synthesis was observed that was associated with a decrease of disease progression and improved cardiac function [Hart et al., 2005]. However, results are less satisfactory in shorter studies. Idebenone, a synthetic analog of CoQ₁₀, did not significantly alter neurological function in FRDA during the 6-month study. Larger studies of longer duration may be needed to assess the therapeutic potential of drug candidates on neurological function in FRDA [Lynch et al., 2010].

Other Conditions

Male Infertility

Both the bioenergetic and the antioxidant role of CoQ₁₀ suggest a possible involvement in sperm biochemistry and

male infertility [Mancini and Balercia, 2011]. CoQ₁₀ can be quantified in seminal fluid, where its concentration correlates with sperm count and motility [Mancini et al., 1994]. It was found that distribution of CoQ₁₀ between sperm cells and seminal plasma was altered in varicocele patients, who also presented a higher level of oxidative stress and lower total antioxidant capacity. The redox status of CoQ₁₀ in seminal fluid was also determined: an inverse correlation was found between ubiquinol/ubiquinone ratio and hydroperoxide levels and between this ratio and the percentage of abnormal sperm forms. Subsequently, CoQ₁₀ was administered to a group of idiopathic asthenozoospermic infertile patients. Treatment led to a significant increase in the concentration of CoQ₁₀, both in seminal plasma and sperm cells, and improvement in sperm motility [Mancini et al., 2005]. In a recent study, it has been demonstrated that CoQ₁₀ improves semen quality and pregnancy rate [Safarinejad, 2012].

Periodontal Disease

Periodontal disease is an inflammatory disease process resulting from the interaction of a bacterial attack and host inflammatory response. Arrays of molecules are considered to mediate the inflammatory response at one time or another, among these are free radicals and reactive oxygen species (ROS). Periodontal pathogens can induce ROS overproduction and, thus, may cause collagen and periodontal cell breakdown. When ROS are scavenged by antioxidants, there can be a reduction of collagen degradation. Ubiquinol (reduced form of CoQ₁₀) serves as an endogenous antioxidant which increases the concentration of CoQ₁₀ in the diseased gingiva and effectively suppresses advanced periodontal inflammation [Prakash et al., 2010].

Migraine

Evidence indicates that impaired energy metabolism may be present in brains of migraine sufferers. Rozen et al. [2002] supplemented migraine patients with 150 mg CoQ₁₀ daily for 3 months and demonstrated a 50% reduction in the frequency of migraine headaches, regardless of whether patients experienced aura or not. Deficiency of CoQ₁₀ may be common in pediatric and adolescent migraine. Determination of deficiency and consequent supplementation may result in clinical improvement [Hershey et al., 2007].

Pregnancy

Plasma CoQ₁₀ levels rise with each trimester of pregnancy and fetal wasting with subsequent spontaneous abortion has been correlated with low levels of CoQ₁₀

[Noia et al., 1996]. Supplementation with CoQ₁₀ reduces the risk of developing pre-eclampsia (gestational hypertension in association with significant amounts of protein in the urine) in women at risk for the condition [Teran et al., 2009].

Down's Syndrome

Down's syndrome (DS) is a chromosomal abnormality (trisomy 21) associated with a complex phenotype. Oxidative stress is known to play a major role in this pathology both due to genetic and epigenetic factors, suggesting that oxidative imbalance contributes to the clinical manifestation of DS [Tiano et al., 2011]. Structural changes and abnormal function of mitochondria have been documented in DS cells, patients and animal models. DS cells in culture exhibit a wide array of functional mitochondrial abnormalities. Two studies have investigated the effect of CoQ₁₀ treatment on DNA damage in DS patients. Results suggest that the effect of CoQ₁₀ treatment in DS not only reflects antioxidant efficacy, but likely modulates DNA repair mechanisms [Tiano and Busciglio, 2011].

Aging

The decrease of CoQ₁₀ levels during aging could be one of the main factors in the development of chronic diseases in old people. Furthermore, since CoQ₁₀ is not only an antioxidant, but also is involved in a plethora of cellular processes, appropriate uptake of CoQ₁₀ into cells is crucial for the improvement of cell activity during aging. Maintenance of CoQ₁₀ functional levels at cell membranes either by dietary supplementation or by improving endogenous synthesis can be a key strategy to enhance health during aging [López-Lluch et al., 2010].

Drug-Nutrient Interactions

Cholesterol-lowering drugs such as lovastatin and pravastatin inhibit the enzyme HMG-CoA reductase, required for synthesis of cholesterol as well as CoQ₁₀, resulting in a decreased serum CoQ₁₀ [Mortensen et al., 1997]. Beta blockers propranolol and metoprolol [Kishi et al., 1977], and phenothiazines and tricyclic antidepressants have been shown to inhibit CoQ₁₀-dependent enzymes [Moreno-Fernández et al., 2012]. CoQ₁₀'s effects on platelet function may increase the risk of bleeding in patients taking antiplatelet drugs such as aspirin [Serebruany et al., 1997]. On the other hand, since it acts like vitamin K, it may counteract the anticoagulant effects of

warfarin [Singh et al., 2007]. CoQ₁₀ may have an additive antihypertensive effect when given with antihypertensive drugs [Bonakdar and Guarneri, 2005]. CoQ₁₀ may improve beta-cell function and enhance insulin sensitivity, which may reduce insulin requirements for diabetic patients [Hodgson et al., 2002].

Toxicity

CoQ₁₀ treatment is safe, even at the highest doses cited in the literature. Most clinical trials have not reported significant adverse effects that necessitated stopping therapy [Hidaka et al., 2008]. However, gastrointestinal effects such as abdominal discomfort, nausea, vomiting, diarrhea, and anorexia have occurred [Hidaka et al., 2008]. Allergic rash and headache have also been reported [Hidaka et al., 2008]. In addition, CoQ₁₀'s antiplatelet effect may increase the risk of bleeding [Greenberg and Frishman, 1990]. It undergoes biotransformation in the liver and is eliminated primarily via the biliary tract [Greenberg and Frishman, 1990], so it can accumulate in patients with hepatic impairment or biliary obstruction.

CoQ₁₀-Related Compounds

Intestinal absorption of dietary CoQ₁₀ is very limited and only chronic ingestion of relatively large doses of CoQ₁₀ increase CoQ₁₀ concentrations, especially in heart and brain mitochondria in rodent models [Bhagavan and Chopra, 2006]. For this reason, less hydrophobic structural derivatives of CoQ₁₀, and therefore, with better pharmacokinetic profiles, are emerging as promising drugs for treating diseases with mitochondrial dysfunction. Idebenone and MitoQ have already been evaluated in clinical trials for safety, toxicity and their effect for treating different diseases [Villalba et al., 2010].

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References

- Adarsh K, Kaur H, Mohan V: Coenzyme Q₁₀ (CoQ₁₀) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). *Biofactors* 32:145–149 (2008).
- Artuch R, Brea-Calvo G, Briones P, Aracil A, Galván M, et al: Cerebellar ataxia with coenzyme Q₁₀ deficiency: diagnosis and follow-up after coenzyme Q₁₀ supplementation. *J Neurol Sci* 246:153–158 (2006).
- Beal MF: Coenzyme Q₁₀ administration and its potential for treatment of neurodegenerative diseases. *Biofactors* 9:261–266 (1999).
- Belardinelli R, Mućaj A, Lacalaprice F, Solenghi M, Seddaiu G, et al: Coenzyme Q₁₀ and exercise training in chronic heart failure. *Eur Heart J* 27:2675–2681 (2006).
- Bentinger M, Tekle M, Dallner G: Coenzyme Q –biosynthesis and functions. *Biochem Biophys Res Commun* 396:74–79 (2010).
- Berbel-García A, Barbera-Farre JR, Etessam JP, Salio AM, Cabello A, et al: Coenzyme Q₁₀ improves lactic acidosis, stroke-like episodes, and epilepsy in a patient with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). *Clin Neuropharmacol* 27:187–191 (2004).
- Bhagavan HN, Chopra RK: Coenzyme Q₁₀: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res* 40:445–453 (2006).
- Bonafdar RA, Guarneri E: Coenzyme Q₁₀. *Am Fam Physician* 72:1065–1070 (2005).
- Brea-Calvo G, Rodríguez-Hernández A, Fernández-Ayala DJ, Navas P, Sánchez-Alcázar JA: Chemotherapy induces an increase in coenzyme Q₁₀ levels in cancer cell lines. *Free Radic Biol Med* 40:1293–1302 (2006).
- Bresolin N, Doriguzzi C, Ponzetto C, Angelini C, Moroni I, et al: Ubidecarenone in the treatment of mitochondrial myopathies: a multicenter double-blind trial. *J Neurol Sci* 100:70–78 (1990).
- Caso G, Kelly P, McNurlan MA, Lawson WE: Effect of coenzyme Q₁₀ on myopathic symptoms in patients treated with statins. *Am J Cardiol* 99:1409–1412 (2007).
- Celik T, Iyisoy A: Coenzyme Q₁₀ and coronary artery bypass surgery: what we have learned from clinical trials. *J Cardiothorac Vasc Anesth* 23:935–936 (2009).
- Cooper JM, Schapira AH: Friedreich's ataxia: coenzyme Q₁₀ and vitamin E therapy. *Mitochondrion* 7 Suppl:S127–135 (2007).
- Cooper JM, Korlipara LV, Hart PE, Bradley JL, Schapira AH: Coenzyme Q₁₀ and vitamin E deficiency in Friedreich's ataxia: predictor of efficacy of vitamin E and coenzyme Q₁₀ therapy. *Eur J Neurol* 15:1371–1379 (2008).
- Cooper O, Seo H, Andrabi S, Guardia-Laguarta C, Graziotto J, et al: Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson's disease. *Sci Transl Med* 4:141ra190 (2012).
- Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, et al: Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther* 12:R17 (2010).
- Cordero MD, Alcocer-Gómez E, de Miguel M, Cano-García FJ, Luque CM, et al: Coenzyme Q₁₀: a novel therapeutic approach for Fibromyalgia? Case series with 5 patients. *Mitochondrion* 11:623–625 (2011).
- Cordero MD, Cano-García FJ, Alcocer-Gómez E, De Miguel M, Sánchez-Alcázar JA: Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q₁₀ effect on clinical improvement. *PLoS One* 7:e35677 (2012).
- Cotán D, Cordero MD, Garrido-Maraver J, Oropesa-Ávila M, Rodríguez-Hernández A, et al: Secondary coenzyme Q₁₀ deficiency triggers mitochondria degradation by mitophagy in MELAS fibroblasts. *FASEB J* 25:2669–2687 (2011).
- Crane FL: Biochemical functions of coenzyme Q₁₀. *J Am Coll Nutr* 20:591–598 (2001).
- Chen RS, Huang CC, Chu NS: Coenzyme Q₁₀ treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. *Eur Neurol* 37:212–218 (1997).
- De la Mata M, Garrido-Maraver J, Cotán D, Cordero MD, Oropesa-Avila M, et al: Recovery of MERRF fibroblasts and cybrids pathophysiology by Coenzyme Q₁₀. *Neurotherapeutics* 9:446–463 (2012).
- Di Giovanni S, Mirabella M, Spinazzola A, Crociani P, Silvestri G, et al: Coenzyme Q₁₀ reverses pathological phenotype and reduces apoptosis in familial CoQ₁₀ deficiency. *Neurology* 57:515–518 (2001).
- DiMauro S, Quinzii CM, Hirano M: Mutations in coenzyme Q₁₀ biosynthetic genes. *J Clin Invest* 117:587–589 (2007).
- Domae N, Sawada H, Matsuyama E, Konishi T, Uchino H: Cardiomyopathy and other chronic toxic effects induced in rabbits by doxorubicin and possible prevention by coenzyme Q₁₀. *Cancer Treat Rep* 65:79–91 (1981).
- Emmanuele V, López LC, Berardo A, Naini A, Tadesse S, et al: Heterogeneity of coenzyme Q₁₀ deficiency: patient study and literature review. *Arch Neurol* 69:978–983 (2012).
- Folkers K, Littarru GP, Ho L, Runge TM, Havenonnda S, Cooley D: Evidence for a deficiency of coenzyme Q₁₀ in human heart disease. *Int Z Vitaminforsch* 40:380–390 (1970).
- Folkers K, Vadhanavikrit S, Mortensen SA: Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q₁₀. *Proc Natl Acad Sci USA* 82:901–904 (1985a).
- Folkers K, Wolaniuk J, Simonsen R, Morishita M, Vadhanavikrit S: Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q₁₀. *Proc Natl Acad Sci USA* 82:4513–4516 (1985b).
- Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, et al: Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch Neurol* 69:836–841 (2012).
- Garrido-Maraver J, Cordero MD, Moñino ID, Pereira-Arenas S, Lechuga-Vieco AV, et al: Screening of effective pharmacological treatments for MELAS syndrome using yeasts, fibroblasts and cybrids models of the disease. *Br J Pharmacol* 167:1311–1328 (2012).
- Gempel K, Topaloglu H, Talim B, Schneiderat P, Schoser BG, et al: The myopathic form of coenzyme Q₁₀ deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (*ETFDH*) gene. *Brain* 130:2037–2044 (2007).
- Golbidi S, Ebadi SA, Laher I: Antioxidants in the treatment of diabetes. *Curr Diabetes Rev* 7:106–125 (2011).
- Gold R, Seibel P, Reinelt G, Schindler R, Landwehr P, et al: Phosphorus magnetic resonance spectroscopy in the evaluation of mitochondrial myopathies: results of a 6-month therapy study with coenzyme Q. *Eur Neurol* 36:191–196 (1996).
- Golomb BA, Evans MA, Dimsdale JE, White HL: Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. *Arch Intern Med* 172:1180–1182 (2012).
- Greenberg S, Frishman WH: Co-enzyme Q₁₀: a new drug for cardiovascular disease. *J Clin Pharmacol* 30:596–608 (1990).
- Gronenberg DA, Kindermann B, Althammer M, Klapper M, Vormann J, et al: Coenzyme Q₁₀ affects expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. *Int J Biochem Cell Biol* 37:1208–1218 (2005).
- Haas RH: The evidence basis for coenzyme Q therapy in oxidative phosphorylation disease. *Mitochondrion* 7(suppl):S136–S145 (2007).
- Hadj A, Pepe S, Rosenfeldt F: The clinical application of metabolic therapy for cardiovascular disease. *Heart Lung Circ* 16(suppl 3):S56–S64 (2007).
- Hargreaves IP, Duncan AJ, Heales SJ, Land JM: The effect of HMG-CoA reductase inhibitors on coenzyme Q₁₀: possible biochemical/clinical implications. *Drug Saf* 28:659–676 (2005).
- Hart PE, Lodi R, Rajagopalan B, Bradley JL, Crilley JG, et al: Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. *Arch Neurol* 62:621–626 (2005).
- Hathcock JN, Shao A: Risk assessment for coenzyme Q₁₀ (Ubiquinone). *Regul Toxicol Pharmacol* 45:282–288 (2006).
- Henchcliffe C, Beal MF: Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol* 4:600–609 (2008).

- Hernández-Ojeda J, Cardona-Muñoz EG, Román-Pintos LM, Troyo-Sanromán R, Ortiz-Lazareno PC, et al: The effect of ubiquinone in diabetic polyneuropathy: a randomized double-blind placebo-controlled study. *J Diabetes Complications* 26:352–358 (2012).
- Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, et al: Coenzyme Q₁₀ deficiency and response to supplementation in pediatric and adolescent migraine. *Headache* 47:73–80 (2007).
- Hidaka T, Fujii K, Funahashi I, Fukutomi N, Hosoe K: Safety assessment of coenzyme Q₁₀ (CoQ₁₀). *Biofactors* 32:199–208 (2008).
- Hodgson JM, Watts GF, Playford DA, Burke V, Croft KD: Coenzyme Q₁₀ improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr* 56:1137–1142 (2002).
- Horstink MW, van Engelen BG: The effect of coenzyme Q₁₀ therapy in Parkinson disease could be symptomatic. *Arch Neurol* 60:1170–1172 (2003).
- Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M: Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. *Regul Toxicol Pharmacol* 47:19–28 (2007).
- Joliet P, Simon N, Barré J, Pons JY, Boukef M, et al: Plasma coenzyme Q₁₀ concentrations in breast cancer: prognosis and therapeutic consequences. *Int J Clin Pharmacol Ther* 36:506–509 (1998).
- Kerr DS: Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. *Mol Genet Metab* 99:246–255 (2010).
- Kishi T, Watanabe T, Folkers K: Bioenergetics in clinical medicine XV. Inhibition of coenzyme Q₁₀-enzymes by clinically used adrenergic blockers of beta-receptors. *Res Commun Chem Pathol Pharmacol* 17:157–164 (1977).
- Kwong LK, Kamzalov S, Rebrin I, Bayne AC, Jana CK, et al: Effects of coenzyme Q₁₀ administration on its tissue concentrations, mitochondrial oxidant generation, and oxidative stress in the rat. *Free Radic Biol Med* 33:627–638 (2002).
- Langsjoen H, Langsjoen P, Willis R, Folkers K: Usefulness of coenzyme Q₁₀ in clinical cardiology: a long-term study. *Mol Aspects Med* 15(suppl):S165–S175 (1994a).
- Langsjoen P, Willis R, Folkers K: Treatment of essential hypertension with coenzyme Q₁₀. *Mol Aspects Med* 15 Suppl:S265–272 (1994b).
- Lee BJ, Huang YC, Chen SJ, Lin PT: Coenzyme Q₁₀ supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. *Nutrition* 28:250–255 (2012a).
- Lee BJ, Huang YC, Chen SJ, Lin PT: Effects of coenzyme Q₁₀ supplementation on inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, and homocysteine) in patients with coronary artery disease. *Nutrition* 28:767–772 (2012b).
- Lee J, Boo JH, Ryu H: The failure of mitochondria leads to neurodegeneration: do mitochondria need a jump start? *Adv Drug Deliv Rev* 61:1316–1323 (2009).
- Littarru GP, Tiano L: Bioenergetic and antioxidant properties of coenzyme Q₁₀: recent developments. *Mol Biotechnol* 37:31–37 (2007).
- Littarru GP, Tiano L: Clinical aspects of coenzyme Q₁₀: an update. *Nutrition* 26:250–254 (2010).
- Liu J, Wang L, Zhan SY, Xia Y: Coenzyme Q₁₀ for Parkinson's disease. *Cochrane Database Syst Rev* CD008150 (2011).
- Lockwood K, Moesgaard S, Hanioka T, Folkers K: Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q₁₀. *Mol Aspects Med* 15(suppl):S231–S240 (1994).
- Lönnrot K, Pörsti I, Alho H, Wu X, Hervonen A, Tolvanen JP: Control of arterial tone after long-term coenzyme Q₁₀ supplementation in senescent rats. *Br J Pharmacol* 124:1500–1506 (1998).
- López-Lluch G, Rodríguez-Aguilera JC, Santos-Ocaña C, Navas P: Is coenzyme Q a key factor in aging? *Mech Ageing Dev* 131:225–235 (2010).
- Lynch DR, Perlman SL, Meier T: A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. *Arch Neurol* 67:941–947 (2010).
- Lyon W, Van den Brink O, Pepe S, Wolk M, Marasco S, Rosenfeldt FL: Similar therapeutic serum levels attained with emulsified and oil-based preparations of coenzyme Q₁₀. *Asia Pac J Clin Nutr* 10:212–215 (2001).
- Mancini A, Balercia G: Coenzyme Q₁₀ in male infertility: physiopathology and therapy. *Biofactors* 37:374–380 (2011).
- Mancini A, De Marinis L, Oradei A, Hallgass ME, Conte G, et al: Coenzyme Q₁₀ concentrations in normal and pathological human seminal fluid. *J Androl* 15:591–594 (1994).
- Mancini A, De Marinis L, Littarru GP, Balercia G: An update of Coenzyme Q₁₀ implications in male infertility: biochemical and therapeutic aspects. *Biofactors* 25:165–174 (2005).
- Mancuso M, Orsucci D, Volpi L, Calsolaro V, Siciliano G: Coenzyme Q₁₀ in neuromuscular and neurodegenerative disorders. *Curr Drug Targets* 11:111–121 (2010).
- Mas E, Mori TA: Coenzyme Q₁₀ and statin myalgia: what is the evidence? *Curr Atheroscler Rep* 12:407–413 (2010).
- Miles MV: The uptake and distribution of coenzyme Q₁₀. *Mitochondrion* 7(suppl):S72–S77 (2007).
- Miles MV, Patterson BJ, Schapiro MB, Hickey FJ, Chalfonte-Evans M, et al: Coenzyme Q₁₀ absorption and tolerance in children with Down syndrome: a dose-ranging trial. *Pediatr Neurol* 35:30–37 (2006).
- Miyake Y, Shouzu A, Nishikawa M, Yonemoto T, Shimizu H, et al: Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q₁₀ in diabetic patients. *Arzneimittelforschung* 49:324–329 (1999).
- Mohr D, Bowry VW, Stocker R: Dietary supplementation with coenzyme Q₁₀ results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoprotein to the initiation of lipid peroxidation. *Biochim Biophys Acta* 1126:247–254 (1992).
- Moreno-Fernández AM, Cordero MD, Garrido-Maraver J, Alcocer-Gómez E, Casas-Barquero N, et al: Oral treatment with amitriptyline induces coenzyme Q deficiency and oxidative stress in psychiatric patients. *J Psychiatr Res* 46:341–345 (2012).
- Mortensen SA: Overview on coenzyme Q₁₀ as adjunctive therapy in chronic heart failure. Rationale, design and end-points of 'Q-symbio' – a multinational trial. *Biofactors* 18:79–89 (2003).
- Mortensen SA, Leth A, Agner E, Rohde M: Dose-related decrease of serum coenzyme Q₁₀ during treatment with HMG-CoA reductase inhibitors. *Mol Aspects Med* 18(suppl):S137–S144 (1997).
- Müller T, Büttne T, Gholipour AF, Kuhn W: Coenzyme Q₁₀ supplementation provides mild symptomatic benefit in patients with Parkinson's disease. *Neurosci Lett* 341:201–204 (2003).
- Naia L, Ribeiro MJ, Rego AC: Mitochondrial and metabolic-based protective strategies in Huntington's disease: the case of creatine and coenzyme Q. *Rev Neurosci* 23:13–28 (2011).
- Naini A, Lewis VJ, Hirano M, DiMauro S: Primary coenzyme Q₁₀ deficiency and the brain. *Biofactors* 18:145–152 (2003).
- Noia G, Littarru GP, De Santis M, Oradei A, Mac-tromarino C, et al: Coenzyme Q₁₀ in pregnancy. *Fetal Diagn Ther* 11:264–270 (1996).
- Ochiai A, Itagaki S, Kurokawa T, Kobayashi M, Hirano T, Iseki K: Improvement in intestinal coenzyme Q₁₀ absorption by food intake. *Yakugaku Zasshi* 127:1251–1254 (2007).
- Ogasahara S, Engel AG, Frens D, Mack D: Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. *Proc Natl Acad Sci USA* 86:2379–2382 (1989).
- Palamakula A, Soliman M, Khan MM: Regional permeability of coenzyme Q₁₀ in isolated rat gastrointestinal tracts. *Pharmazie* 60:212–214 (2005).
- Palan PR, Mikhail MS, Shaban DW, Romney SL: Plasma concentrations of coenzyme Q₁₀ and tocopherols in cervical intraepithelial neoplasia and cervical cancer. *Eur J Cancer Prev* 12:321–326 (2003).
- Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL: Coenzyme Q₁₀ in cardiovascular disease. *Mitochondrion* 7(suppl):S154–S167 (2007).
- Playford DA, Watts GF, Croft KD, Burke V: Combined effect of coenzyme Q₁₀ and fenofibrate on forearm microcirculatory function in type 2 diabetes. *Atherosclerosis* 168:169–179 (2003).

- Prakash S, Sunitha J, Hans M: Role of coenzyme Q₁₀ as an antioxidant and bioenergizer in periodontal diseases. *Indian J Pharmacol* 42: 334–337 (2010).
- Quinzii CM, Hirano M: Primary and secondary CoQ₁₀ deficiencies in humans. *Biofactors* 37: 361–365 (2011).
- Quinzii CM, Kattah AG, Naini A, Akman HO, Mootha VK, et al: Coenzyme Q deficiency and cerebellar ataxia associated with an aprataxin mutation. *Neurology* 64:539–541 (2005).
- Quinzii C, Naini A, Salviati L, Trevisson E, Navas P, et al: A mutation in para-hydroxybenzoate-polyprenyl transferase (COQ2) causes primary coenzyme Q₁₀ deficiency. *Am J Hum Genet* 78:345–349 (2006).
- Quinzii CM, DiMauro S, Hirano M: Human coenzyme Q₁₀ deficiency. *Neurochem Res* 32: 723–727 (2007).
- Rodríguez-Hernández A, Cordero MD, Salviati L, Artuch R, Pineda M, et al: Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. *Autophagy* 5:19–32 (2009).
- Roffe L, Schmidt K, Ernst E: Efficacy of coenzyme Q₁₀ for improved tolerability of cancer treatments: a systematic review. *J Clin Oncol* 22: 4418–4424 (2004).
- Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, et al: Coenzyme Q₁₀ in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens* 21:297–306 (2007).
- Rötig A, Appelkvist EL, Geromel V, Chretien D, Kadhom N, et al: Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q₁₀ deficiency. *Lancet* 356:391–395 (2000).
- Rötig A, Mollet J, Rio M, Munnich A: Infantile and pediatric quinone deficiency diseases. *Mitochondrion* 7(suppl):S112–S121 (2007).
- Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, et al: Open label trial of coenzyme Q₁₀ as a migraine preventive. *Cephalalgia* 22:137–141 (2002).
- Rusciani L, Proietti I, Rusciani A, Paradisi A, Sbordoni G, et al: Low plasma coenzyme Q₁₀ levels as an independent prognostic factor for melanoma progression. *J Am Acad Dermatol* 54:234–241 (2006).
- Sacconi S, Trevisson E, Salviati L, Aymé S, Rigal O, et al: Coenzyme Q₁₀ is frequently reduced in muscle of patients with mitochondrial myopathy. *Neuromuscul Disord* 20:44–48 (2010).
- Safarinejad MR: The effect of coenzyme Q₁₀ supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. *Int Urol Nephrol* 44:689–700 (2012).
- Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, et al: Infantile encephalomyopathy and nephropathy with CoQ₁₀ deficiency: a CoQ₁₀-responsive condition. *Neurology* 65: 606–608 (2005).
- Sander S, Coleman CI, Patel AA, Kluger J, White CM: The impact of coenzyme Q₁₀ on systolic function in patients with chronic heart failure. *J Card Fail* 12:464–472 (2006).
- Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, et al: Efficacy of coenzyme Q₁₀ in migraine prophylaxis: a randomized controlled trial. *Neurology* 64:713–715 (2005).
- Santos-González M, Gómez Díaz C, Navas P, Villalba JM: Modifications of plasma proteome in long-lived rats fed on a coenzyme Q₁₀-supplemented diet. *Exp Gerontol* 42: 798–806 (2007).
- Schmelzer C, Lindner I, Rimbach G, Niklowitz P, Menke T, Döring F: Functions of coenzyme Q₁₀ in inflammation and gene expression. *Biofactors* 32:179–183 (2008).
- Serebruany VL, Ordóñez JV, Herzog WR, Rohde M, Mortensen SA, et al: Dietary coenzyme Q₁₀ supplementation alters platelet size and inhibits human vitronectin (CD51/CD61) receptor expression. *J Cardiovasc Pharmacol* 29:16–22 (1997).
- Shults CW, Haas RH, Passov D, Beal MF: Coenzyme Q₁₀ levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. *Ann Neurol* 42:261–264 (1997).
- Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH: Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q₁₀ in parkinsonian patients. *Neurology* 50:793–795 (1998).
- Shults CW, Haas RH, Beal MF: A possible role of coenzyme Q₁₀ in the etiology and treatment of Parkinson's disease. *Biofactors* 9:267–272 (1999).
- Shults CW, Flint Beal M, Song D, Fontaine D: Pilot trial of high dosages of coenzyme Q₁₀ in patients with Parkinson's disease. *Exp Neurol* 188:491–494 (2004).
- Singh U, Devaraj S, Jialal I: Coenzyme Q₁₀ supplementation and heart failure. *Nutr Rev* 65: 286–293 (2007).
- Sohal RS, Forster MJ: Coenzyme Q, oxidative stress and aging. *Mitochondrion* 7(suppl): S103–S111 (2007).
- Sohmiya M, Tanaka M, Tak NW, Yanagisawa M, Tanino Y, et al: Redox status of plasma coenzyme Q₁₀ indicates elevated systemic oxidative stress in Parkinson's disease. *J Neurosci* 223:161–166 (2004).
- Stack EC, Matson WR, Ferrante RJ: Evidence of oxidant damage in Huntington's disease: translational strategies using antioxidants. *Ann N Y Acad Sci* 1147:79–92 (2008).
- Teran E, Hernandez I, Nieto B, Távora R, Ocampo JE, Calle A: Coenzyme Q₁₀ supplementation during pregnancy reduces the risk of pre-eclampsia. *Int J Gynaecol Obstet* 105:43–45 (2009).
- Tiano L, Busciglio J: Mitochondrial dysfunction and Down's syndrome: is there a role for coenzyme Q₁₀? *Biofactors* 37:386–392 (2011).
- Tiano L, Carnevali P, Padella L, Santoro L, Principi F, et al: Effect of Coenzyme Q₁₀ in mitigating oxidative DNA damage in Down syndrome patients, a double blind randomized controlled trial. *Neurobiol Aging* 32:2103–2105 (2011).
- Villalba JM, Parrado C, Santos-González M, Alcázar FJ: Therapeutic use of coenzyme Q₁₀ and coenzyme Q₁₀-related compounds and formulations. *Expert Opin Investig Drugs* 19: 535–554 (2010).
- Wadsworth TL, Bishop JA, Pappu AS, Woltjer RL, Quinn JF: Evaluation of coenzyme Q as an antioxidant strategy for Alzheimer's disease. *J Alzheimers Dis* 14:225–234 (2008).
- Watts GF, Playford DA, Croft KD, Ward NC, Mori TA, Burke V: Coenzyme Q₁₀ improves endothelial dysfunction of the brachial artery in type II diabetes mellitus. *Diabetologia* 45: 420–426 (2002).
- Weber C, Bysted A, Holmer G: Intestinal absorption of coenzyme Q₁₀ administered in a meal or as capsules to healthy subjects. *Nutr Res* 17: 941–945 (1997).
- Weis M, Mortensen SA, Rassing MR, Møller-Søndergaard J, Poulsen G, Rasmussen SN: Bioavailability of four oral coenzyme Q₁₀ formulations in healthy volunteers. *Mol Aspects Med* 15(suppl):S273–S280 (1994).
- Witting PK, Pettersson K, Letters J, Stocker R: Anti-atherogenic effect of coenzyme Q₁₀ in apolipoprotein E gene knockout mice. *Free Radic Biol Med* 29:295–305 (2000).
- Wyman M, Leonard M, Morledge T: Coenzyme Q₁₀: a therapy for hypertension and statin-induced myalgia? *Cleve Clin J Med* 77:435–442 (2010).
- Zhang Y, Aberg F, Appelkvist EL, Dallner G, Ernster L: Uptake of dietary coenzyme Q supplement is limited in rats. *J Nutr* 125:446–453 (1995).