

## Clinical applications of coenzyme Q10

Juan Garrido-Maraver<sup>1</sup>, Mario D. Cordero<sup>2</sup>, Manuel Oropesa-Avila<sup>1</sup>, Alejandro Fernandez Vega<sup>1</sup>, Mario de la Mata<sup>1</sup>, Ana Delgado Pavon<sup>1</sup>, Elisabet Alcocer-Gomez<sup>1</sup>, Carmen Perez Calero<sup>1</sup>, Marina Villanueva Paz<sup>1</sup>, Macarena Alanis<sup>1</sup>, Isabel de Laverá<sup>1</sup>, David Cotan<sup>1</sup>, Jose A. Sanchez-Alcazar<sup>1</sup>

<sup>1</sup>Centro Andaluz de Biología del Desarrollo (CABD), and Centro de Investigación Biomedica en Red, Enfermedades Raras, Instituto de Salud Carlos III, Universidad Pablo de Olavide-Consejo Superior de Investigaciones Científicas, Sevilla 41013, Spain. <sup>2</sup>Facultad de Odontología, Universidad de Sevilla, Sevilla 41009, Spain

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### 1. ABSTRACT

Coenzyme Q10 (CoQ10) or ubiquinone was known for its key role in mitochondrial bioenergetics as electron and proton carrier; later studies demonstrated its presence in other cellular membranes and in blood plasma, and extensively investigated its antioxidant role. These two functions constitute the basis for supporting the clinical indication of CoQ10. Furthermore, recent data indicate that CoQ10 affects expression of genes involved in human cell signalling, 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, ageing-related

oxidative stress and carcinogenesis processes, and also a secondary effect of statin treatment. Many neurodegenerative disorders, diabetes, cancer, fibromyalgia, muscular and cardiovascular diseases have been associated with low CoQ10 levels. CoQ10 treatment does not cause serious adverse effects in humans and new formulations have been developed that increase CoQ10 absorption and tissue distribution. Oral CoQ10 treatment is a frequent mitochondrial energizer and antioxidant strategy in many diseases that may provide a significant symptomatic benefit.

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**Table 1.** Most frequent physiologic and clinical applications of coenzyme Q<sub>10</sub>

Physiologic and clinical applications	References
Human coenzyme Q <sub>10</sub> deficiencies	(34)
Mitochondrial diseases	(40)
Fibromyalgia	(51, 52)
Cardiac failure	(139)
Ischemic heart disease	(140)
Interaction with statins	(141)
Hypertension	(73)
Diabetes	(102)
Endothelial function	(142)
Pre-eclampsia	(117)
<b>Neurodegenerative diseases</b>	
Parkinson's disease	(143)
Huntington's disease	(86)
Alzheimer's disease	(88)
Friedreich's ataxia	(144)
Cancer	(99)
Aging	(120)
<b>Other pathological conditions</b>	
Migraine	(145)
Down's syndrome	(119)
Periodontal Disease	(112)
Asthenozoospermia	(108)

## 2. INTRODUCTION

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) 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 CoQ<sub>10</sub> is also known as ubiquinone. It is found in cell membranes and is particularly well known for its role in the electron transport chain in mitochondrial membranes during aerobic cellular respiration. Adequate amounts of CoQ<sub>10</sub> are necessary for cellular respiration and ATP production. CoQ<sub>10</sub> 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 (1). CoQ<sub>10</sub> was also recognized to have an effect on gene expression that might account for its effects on overall tissue metabolism (2, 3).

Although the chemical structure of CoQ<sub>10</sub> is similar to that of vitamin K, CoQ<sub>10</sub> is not considered a vitamin because it is the only lipid-soluble antioxidant that animal cells synthesize *de novo* in the body (4). Cells generally rely on biosynthesis for their supply of CoQ<sub>10</sub>. Endogenous levels are subject to regulation by physiological factors that are related to the oxidative activity of the organism (5, 6). Para-hydroxybenzoic acid from the amino acid tyrosine is the first aromatic precursor in the biosynthetic pathway of CoQ<sub>10</sub> in humans and constitutes the quinoid ring structure of the CoQ<sub>10</sub> molecule. The tail, consisting of 10 isoprenoid units, is derived from the mevalonate pathway (7). Endogenous CoQ<sub>10</sub> levels are determined by both the rate of production and the rate of consumption in the body. These levels can be altered in a number of disease states, among which cardiovascular disease and degenerative muscle disorders have been well documented in humans (8).

Dietary supplementation affecting CoQ<sub>10</sub> 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 signalling, intermediary metabolism, transport and transcription control and inflammation, among others, indicating an important role for CoQ<sub>10</sub> as a potent gene regulator (2, 9). However, the molecular mechanisms whereby CoQ<sub>10</sub> is inducing these pleiotropic effects has yet to be completely understood (3).

Numerous disease processes, associated with CoQ<sub>10</sub> deficiency, can benefit from CoQ<sub>10</sub> supplementation including primary and secondary CoQ<sub>10</sub> deficiencies, mitochondrial diseases, fibromyalgia, cardiovascular disease, neurodegenerative diseases, cancer, diabetes mellitus, male infertility and periodontal disease (Table 1).

Tissue deficiencies or subnormal serum levels of CoQ<sub>10</sub> have been reported in a wide range of medical conditions, including primary CoQ<sub>10</sub> deficiencies (10) and secondary CoQ<sub>10</sub> deficiencies such as, mitochondrial diseases (11). CoQ<sub>10</sub> levels decline with advancing age, and this decline might contribute in part to some of the manifestations of aging (12). CoQ<sub>10</sub> deficiency could result from: (1) impaired CoQ<sub>10</sub> synthesis due to nutritional deficiencies (such as vitamin B6 deficiency, a cofactor essential for CoQ<sub>10</sub> biosynthesis), (2) a genetic or acquired defect in CoQ<sub>10</sub> synthesis or utilization, or (3) increased tissue needs resulting from a particular disease. Clinical presentations of severe CoQ<sub>10</sub> deficiency include encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh syndrome with growth retardation and isolated myopathy. Since oral administration of CoQ<sub>10</sub> can increase tissue levels of the nutrient, it is possible to correct CoQ<sub>10</sub> deficiency and is particularly essential in the life-threatening infantile encephalopathy (13).

## 3. ABSORPTION, TISSUE UPTAKE AND PHARMACOKINETICS

Plasma CoQ<sub>10</sub> concentrations are usually used for the estimation of CoQ<sub>10</sub> status in humans primarily because of the ease of sample collection. Reported plasma CoQ<sub>10</sub> ranged from 0.40 to 1.91 µmol/l (0.34-1.65 µg/ml) (4).

**Table 2.** Functions of coenzyme Q<sub>10</sub>

Function	References
Electron and proton carrier in the mitochondrial respiratory chain	(146)
Participation in extra-mitochondrial electron transport (plasma membranes, lysosomes)	(147, 148)
Endogenously synthesized, lipid-soluble antioxidant	(5, 149)
Regulation of mitochondrial permeability transition pores	(150)
Required for activation of mitochondrial uncoupling proteins	(151)
CoQ <sub>10</sub> exerts multiple anti-inflammatory effects by influencing the expression of NFκ-B <sup>1</sup> -dependent genes	(152)
Regulation of the physicochemical properties of membranes	(8)
By protecting LDL <sup>2</sup> from oxidation, this lipid also has anti-atherosclerotic properties	(153)
Modulation of the amount of h2-integrins on the surface of blood monocytes which counteracts monocyte-endothelial cell interactions	(154)
Improvement of endothelial dysfunction (probably by increasing nitric oxide)	(155)
It is required for the biosynthesis of pyrimidine nucleotides because it is an essential co-factor for dihydro-orotate dehydrogenase	(156)
Mitophagy modulator	(45)
Inflammasome modulator	(157)

Abbreviations: Nuclear Transcription Factor-kappa B<sup>1</sup>; Low Density Lipoprotein<sup>2</sup>.

However, these measurements reflect dietary intake rather than tissue status. Moreover, the relationship between plasma and tissue CoQ<sub>10</sub> levels is not yet clear, and plasma levels should only be regarded as a surrogate for tissue (14), and in particular mitochondrial levels, where any therapeutic effect of CoQ<sub>10</sub> may be expected to be most important. The primary problem with measuring tissue levels is access to tissue samples. Skin fibroblasts, muscle biopsies, and blood mononuclear cells (BMCs) may reflect better actual tissue CoQ<sub>10</sub> levels. Blood cells have been used for estimates of CoQ<sub>10</sub> in tissues (15). CoQ<sub>10</sub> content of BMCs was shown to correlate with skeletal muscle CoQ<sub>10</sub> in un-supplemented subjects whereas the plasma concentrations did not (16). There would appear to be no clinical value in measuring erythrocyte CoQ<sub>10</sub>, but there may be a possible case for considering its measurement in platelets or other mitochondria-containing blood cells such as BMCs, though pertinent reference ranges would need to be established (17).

CoQ<sub>10</sub> is 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 CoQ<sub>10</sub> a day. However, in tissues with unimpaired synthetic capacity, it appears that CoQ<sub>10</sub> reaches a saturation level, and nutritional supplement of CoQ<sub>10</sub> in the diet does not increase tissue levels above normal (18, 19). Intestinal absorption is threefold faster if CoQ<sub>10</sub> is administered with food intake (20). Following absorption, CoQ<sub>10</sub> appears in plasma lipoproteins and in liver, but usually not in heart or kidney (21). However, with higher supplementations (150 mg/kg/d), heart and the skeletal muscle showed a significant increase in total CoQ<sub>10</sub> suggesting that higher plasma CoQ<sub>10</sub> concentrations are necessary to facilitate uptake by peripheral tissues (22). Biochemical characteristics of CoQ<sub>10</sub> are important for our understanding of uptake and distribution following oral ingestion. CoQ<sub>10</sub> 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 CoQ<sub>10</sub> absorption and bioavailability varies greatly depending on the type of CoQ<sub>10</sub> preparation studied. CoQ<sub>10</sub> absorption is probably a complex process and dependent upon active and passive transport mechanisms (23). A

study on intestinal absorption of 30 mg CoQ<sub>10</sub> administered in a meal or as powder in capsules to healthy subjects found no significant difference in absorption for these two routes of administration (24). Although not all research is in agreement, the general consensus is that slightly better absorption is achieved with oil-based forms of CoQ<sub>10</sub> (25, 26). Further studies are needed to elucidate whether age, gender, lipoprotein status, diet, dosage formulation, or other factors may affect the bioavailability of CoQ<sub>10</sub> with chronic dosing (27).

CoQ<sub>10</sub> dosage guidelines, which appeared to be safe and well tolerated, were suggested for adults (up to 1,200 mg/day) (28) and for children (up to 10 mg/kg/day) (29), although higher doses are recommended in particular pathological conditions. Monitoring trough CoQ<sub>10</sub> plasma concentrations may be considered after 3-4 weeks of constant dosing, when steady-state conditions exist (30). Steady-state plasma concentrations at these dosage levels generally ranged from 5 to 10 µg/mL (27).

#### 4. MECHANISM OF ACTION

Due to its involvement in ATP synthesis, CoQ<sub>10</sub> 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. CoQ<sub>10</sub> is our only lipid-soluble antioxidant synthesized endogenously and efficiently prevents oxidation of proteins, lipids and DNA. The fundamental role of CoQ<sub>10</sub> 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 (31). Today, several other important functions are also associated with CoQ<sub>10</sub> (Table 2).

#### 5. CLINICAL INDICATIONS

##### 5.1. Treatment of coenzyme Q<sub>10</sub> deficiencies

CoQ<sub>10</sub> deficiency is a treatable condition and therefore its diagnosis is essential, especially for pediatricians and infantile neurologists. The diagnosis can be made by direct measurement of CoQ<sub>10</sub> in muscle, and reinforced by the presence of reduced biochemical activities of respiratory chain complexes, in particular,

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complexes I+III and II+III. Molecular genetic testing has revealed causative mutations in a small proportion of patients indicating that screening for DNA mutations is not yet effective for diagnosing CoQ<sub>10</sub> deficiency (10). An early treatment with high-dose CoQ<sub>10</sub> might radically change the natural history of this group of diseases (32). Patients with all forms of CoQ<sub>10</sub> deficiency have shown clinical improvement with oral CoQ<sub>10</sub> supplementation, but cerebral symptoms are only partially ameliorated, probably because of irreversible structural brain damage before treatment and because of poor penetration of CoQ<sub>10</sub> across the blood-brain barrier (33).

CoQ<sub>10</sub> deficiency is involved in cardiomyopathies and degenerative muscle and neuronal diseases. The major phenotypes provoked by CoQ<sub>10</sub> deficiencies are encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh syndrome with growth retardation, ataxia, nephrotic syndrome and isolated myopathy (34).

The cerebellum may have the narrowest safety margin and, therefore, would be the first tissue to suffer from a pathological shortage of CoQ<sub>10</sub> (35). The most severe human CoQ<sub>10</sub> deficiencies are due to autosomal recessive mutations and can be classified as primary deficiencies when mutations affect CoQ<sub>10</sub> biosynthetic genes (COQ genes) or secondary if the cause is related to other genetic defects (34). In 1989, Ogasahara and colleagues reported the first case of primary CoQ<sub>10</sub> deficiency in skeletal muscle (36). Currently, more than 100 patients with CoQ<sub>10</sub> deficiency have been reported. Most patients with the infantile-onset multisystemic variant have genetically confirmed primary CoQ<sub>10</sub> deficiency (10). Mutations have been described in COQ2, PDSS2, COQ9, PDSS1, and COQ6. Patients with COQ2 mutations have presented with either infantile multisystemic syndrome or isolated nephropathy. A subgroup of patients with juvenile-onset cerebellar ataxia has primary CoQ<sub>10</sub> deficiency due to mutations in the ADCK3 gene. Secondary deficiencies include diseases caused by mutations in genes unrelated to ubiquinone biosynthesis, for example aprataxin (APTX) gene, causing ataxia and oculomotor apraxia (37), electron-transferring-flavoprotein dehydrogenase gene (ETFDH), causing isolated myopathy (38), and BRAF gene, causing cardiofaciocutaneous syndrome (39). However, the majority of patients with cerebellar ataxia and CoQ<sub>10</sub> deficiency still lack molecular diagnosis. Patients with CoQ<sub>10</sub> deficiency showed variable responses to CoQ<sub>10</sub> treatment. The recommend oral supplementation doses are up to 2,400 mg daily in adult patients and up to 30 mg/kg daily in pediatric patients, divided into three doses per day (10). Clinical improvement after CoQ<sub>10</sub> supplementation was reported in many patients, but treatment protocols have not been standardized, and results have not been uniform in all the patients.

### 5.2. Mitochondrial disorders

CoQ<sub>10</sub> is frequently reduced in muscle of patients with mitochondrial myopathy (11) and CoQ<sub>10</sub> is very widely used for primary mitochondrial disorders treatment (40). Numerous case reports and small, open-label studies describe mitochondrial diseases of varying severity that

have responded to CoQ<sub>10</sub> supplementation, typically in dosages from 30-300 mg/day (41, 42). A three-month trial included eight patients with mitochondrial encephalomyopathies supplemented with 160 mg CoQ<sub>10</sub>/day. Although the researchers reported a trend toward 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 (43). In a six months double-blind clinical trial, 44 patients with mitochondrial myopathies from multiple centers were treated with 2 mg/kg CoQ<sub>10</sub> daily. Sixteen of 24 patients experienced at least a 25 percent decrease in post-exercise lactate levels and were selected as “responders” to continue the study. After a further three months at the same dose, no significant differences were observed between the responder and placebo groups. The lack of long-term therapeutic effect in the responders may be attributed to the relatively low dose and short duration of the study (44). Overall, it appears that larger CoQ<sub>10</sub> dosages are indicated for mitochondrial disorders. Recently, our group has demonstrated the benefits of CoQ<sub>10</sub> supplementation in several cellular models of mitochondrial diseases (45-48). However, the clinical evidence supporting a treatment benefit for CoQ<sub>10</sub> in primary mitochondrial disease whilst positive is limited. Reasons for this include the relative rarity and the heterogeneity of mitochondrial diseases included in clinical trials (49).

### 5.3. 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 of fibromyalgia. Recent findings of our group has shown reduced levels of CoQ<sub>10</sub>, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide and increased levels of lipid peroxidation in blood mononuclear cells (BMCs) from FM patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria by mitophagy (50). In other work, FM patients were evaluated clinically with Visual Analogical Scale of pain (VAS), and Fibromyalgia Impact Questionnaire (FIQ). FM patients with CoQ<sub>10</sub> deficiency showed a significant reduction on symptoms after CoQ<sub>10</sub> treatment (51, 52).

Recently, a randomized, double-blind, placebo-controlled trial was carried out to evaluate the effects of forty days of CoQ<sub>10</sub> supplementation (300 mg/day) on clinical and gene expression in 20 FM patients (53). An important clinical improvement was evident after CoQ<sub>10</sub> versus placebo treatment showing a reduction in pain, tender points, fatigue, and morning tiredness. Furthermore, CoQ<sub>10</sub> supplementation induced a recovery of inflammation, antioxidant enzymes, mitochondrial biogenesis and AMPK (5' adenosine monophosphate-activated protein kinase) gene expression levels. These results lead to the hypothesis that CoQ<sub>10</sub> have a potential

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therapeutic effect in FM, and indicate new potential molecular targets for the therapy of this disease. Therefore, determination of CoQ<sub>10</sub> deficiency and subsequent supplementation in FM may result in significant clinical improvement.

### 5.4. 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 CoQ<sub>10</sub> levels. Myocardial deficiency of CoQ<sub>10</sub> has been demonstrated in endomyocardial biopsy samples from patients with cardiomyopathy, and deficiency of CoQ<sub>10</sub> correlated with the severity of disease, suggesting that therapy with CoQ<sub>10</sub> can result in improving quality of life of cardiac patients by enhancing myocardial contractility (14). Numerous studies have investigated the benefit of CoQ<sub>10</sub> supplementation for improving cardiovascular function via enhanced energy production, improved contractility of cardiac muscle, and its potent antioxidant activity, particularly prevention of low-density lipoproteins (LDL) oxidation. In 1994, Langsjoen *et al* published a study summarizing eight years of research on the benefits of CoQ<sub>10</sub> in clinical cardiology (54). Since this study, numerous other studies have demonstrated the usefulness of CoQ<sub>10</sub> supplementation for various cardiovascular conditions. Research has shown CoQ<sub>10</sub> levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure (55, 56). Two important meta-analyses reported significant benefit of CoQ<sub>10</sub> on heart failure from various causes (57, 58). 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 CoQ<sub>10</sub> supplementation was shown to ameliorate cardiac contractility and endothelial dysfunction (59).

#### 5.4.1. Atherosclerosis

CoQ<sub>10</sub> in its reduced form, ubiquinol (CoQ<sub>10</sub>H<sub>2</sub>), 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 the circulation. Dietary supplementation with CoQ<sub>10</sub> results in increased resistance of LDL to the initiation of lipid peroxidation (60). Moreover, CoQ<sub>10</sub> has a direct anti-atherogenic effect, which has also been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet (61). CoQ<sub>10</sub> 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 (62, 63).

#### 5.4.2. 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 CoQ<sub>10</sub> 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 (64). Depletion in CoQ<sub>10</sub> may account for the statin-induced myopathies observed in some patients, the most serious of which is rhabdomyolysis. It is therefore important that clinicians understand the mechanism of action of these drugs as well as their overall effect at a biochemical level. From 1990-2004, 13 controlled trials have demonstrated significant CoQ<sub>10</sub> depletion secondary to statin therapy (65). Consequently, supplementing with CoQ<sub>10</sub> is highly recommended to prevent the myopathic side effects associated with the statin drugs. Recently, it has also been reported statin side effects on energy and exertional fatigue (66). However, clinical evidence supporting CoQ<sub>10</sub>'s use in the treatment of statin-induced myopathy is limited and controversial (67).

In a study by Oh *et al.* (68), 133 patients from a 291-subject sample were found to be intolerant to statin monotherapy. The investigators showed that genetic variations in the COQ2 gene, which is involved in CoQ<sub>10</sub> biosynthesis, were significantly associated with an increased prevalence of statin intolerance. These preliminary pharmacogenetic results support the hypothesis that statin intolerance is associated with genetic variation in the COQ2 gene. It is therefore possible that an unidentified relationship exists between statin intolerance and CoQ<sub>10</sub> deficiency. One way to address this problem is through a genomic analysis of susceptibility genes, which would reveal the likelihood of a pharmacogenetic link to statin intolerance. This approach may help in the prevention of muscle-related symptoms through the supplementation of both statins and CoQ<sub>10</sub>.

#### 5.4.3. Hypertension

Depending on the class, various antihypertensive drugs can have adverse effects such as depression, cough, and cardiac and renal dysfunction (69, 70). Furthermore, many patients need to take more than one drug to control their blood pressure, increasing their risk of side effects. Some researchers believe CoQ<sub>10</sub> supplementation may reduce the need to take multiple antihypertensive drugs (71).

CoQ<sub>10</sub> appears to lower blood pressure. The exact mechanism is not known, but one theory is that it reduces peripheral resistance by preserving nitric oxide (70). Nitric oxide relaxes peripheral arteries, lowering blood pressure. In some forms of hypertension, superoxide radicals that inactivate nitric oxide are overproduced; CoQ<sub>10</sub>, with its antioxidant effects, may prevent the inactivation of nitric oxide by these free radicals. Alternatively, CoQ<sub>10</sub> may boost the production of the prostaglandin prostacyclin (PGI<sub>2</sub>) a potent vasodilator and inhibitor of platelet aggregation, or it may enhance the sensitivity of arterial smooth muscle to PGI<sub>2</sub>, or both (72). A meta-analysis of clinical trials investigating the use of CoQ<sub>10</sub> for hypertension assessed overall efficacy. Blood pressure reduction was noted in all 12 trials, regardless of whether CoQ<sub>10</sub> was given alone or as an adjunct to standard antihypertensive medication, without significant side

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effects (73). In a recent randomized, double-blind, placebo-controlled 12-week crossover trial, the authors conclude that it is possible that CoQ<sub>10</sub> may improve blood pressure control under some circumstances, but any effects are likely to be smaller than reported in previous meta-analyses (74). In some cases, it seems reasonable to recommend this product as an adjunct to conventional antihypertensive therapy. However, larger, well-designed clinical trials of CoQ<sub>10</sub>'s antihypertensive effects on specific clinical outcomes such as the risk of stroke or myocardial infarction are needed to define its true therapeutic value (67).

### 5.5. Neurological conditions

#### 5.5.1. Parkinson's disease

A number of preclinical studies in both *in vitro* and *in vivo* models of Parkinson's disease (PD) have demonstrated that CoQ<sub>10</sub> can protect the nigrostriatal dopaminergic system and some clinical trials have looked at the neuroprotective effects of CoQ<sub>10</sub> in patients with early and mid-stage PD (75). Research suggests CoQ<sub>10</sub> may play a role in the cellular dysfunction found in PD, providing a protective agent for Parkinsonian patients (76). Significantly reduced levels of CoQ<sub>10</sub> have been observed in blood and platelet mitochondria (77), and plasma (78) of PD patients. Therefore, deficiency of CoQ<sub>10</sub> should be explored as a potential peripheral biomarker of antioxidant status in PD (79).

Since 1998, at least four clinical trials on the efficacy of CoQ<sub>10</sub> in PD have been conducted (80-83). 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 CoQ<sub>10</sub> (84).

#### 5.5.2. 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 (85). Strong evidence exists for early oxidative stress in HD, coupled with mitochondrial dysfunction, each exacerbating the other and leading to an energy deficit (86). 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 CoQ<sub>10</sub> has been proposed. High-dose CoQ<sub>10</sub> 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 CoQ<sub>10</sub> treatment (86).

#### 5.5.3. Alzheimer's disease

Increasing evidence suggests that Alzheimer's disease (AD) is associated with oxidative damage that is

caused in part by mitochondrial dysfunction (87). Studies have shown CoQ<sub>10</sub> to be neuroprotective in AD through protection of oxidative damage and attenuation of mitochondrial dysfunction (88).

However, in a recent double-blind, placebo-controlled clinical trial (Trial Registration [clinicaltrials.gov](https://clinicaltrials.gov) Identifier: NCT00117403) antioxidant treatment, including CoQ<sub>10</sub>, did not influence cerebrospinal fluid biomarkers related to amyloid or tau pathology (89).

#### 5.5.4. 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 frataxin 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 (90).

An open-label, pilot trial explored the use of 400 mg CoQ<sub>10</sub> plus 2,100 IU 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 slowing of disease progression and improved cardiac function (91). However, results are less satisfactory in shorter studies. Idebenone, a structural analog of CoQ<sub>10</sub> with a benzoquinone nucleus and a hydroxydecyl side chain 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 (92). In a recent review, Parkinson *et al.* (93) conclude that although much time and expense has been expended on clinical trials of antioxidant therapies in FRDA, definitive answers as to efficacy remain elusive. Prescribing patterns consequently remain inconsistent and many patients currently incur significant costs in procuring antioxidant supplements privately, without robust clinical evidence.

#### 5.6. Cancer

Decreased levels of CoQ<sub>10</sub> have been found in plasma of women with breast cancer and in cancerous breast tissue, and low levels correlated with a worse prognosis (94). Case reports demonstrated 390 mg CoQ<sub>10</sub> daily resulted in tumor regression and disappearance of previously diagnosed metastasis. One to three years later, depending on the case, metastases had not reappeared (95, 96). In 117 melanoma patients without metastasis, plasma CoQ<sub>10</sub> levels were significantly lower than in control subjects and were associated with primary tumor thickness, with the highest CoQ<sub>10</sub> levels associated with thinner tumors. In addition, patients who developed metastases had lower CoQ<sub>10</sub> levels than those who did not, and subjects with lower baseline CoQ<sub>10</sub> levels had shorter disease-free intervals (96). Low plasma levels of CoQ<sub>10</sub> have been demonstrated in cervical intraepithelial neoplasia and cervical cancer (97).

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Mechanisms for CoQ<sub>10</sub>'s benefit for cancer may include immune system enhancement and antioxidant activity. CoQ<sub>10</sub> can be depleted by the use of the chemotherapeutic drug doxorubicin (Adriamycin®), resulting in cardiotoxicity if a high enough cumulative dose is achieved. Supplemental CoQ<sub>10</sub> (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 (98). A systematic review of controlled trials in cancer patients revealed that CoQ<sub>10</sub> provides protection against cardiotoxicity and liver toxicity in patients receiving anthracycline chemotherapy drugs, such as doxorubicin (99). Moreover, it has been reported that chemotherapeutic drugs such as camptothecin, etoposide, doxorubicin and methotrexate induced an increase in CoQ<sub>10</sub> levels in cancer cell lines by upregulation of COQ7, COQ4 and COQ8 gene expression, as part of an antioxidant response against free radical production (100). On the other hand, compositions containing reduced CoQ<sub>10</sub> (in foods and beverages) have been proposed for preventing cancer and for mitigating the adverse reactions of anticancer agents (101).

### 5.7. 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 (102). Serum CoQ<sub>10</sub> levels in type 2 diabetic patients are often decreased and may be associated with subclinical diabetic cardiomyopathy, reversible by CoQ<sub>10</sub> supplementation (103). In three separate randomized, double-blind clinical trials, a total of 194 dyslipidemic type 2 diabetic patients received 200 mg CoQ<sub>10</sub> or placebo daily for 12 weeks. One study also compared CoQ<sub>10</sub> stand-alone treatment to a CoQ<sub>10</sub>-fenofibrate combination and to fenofibrate (a lipid lowering medication) alone. Primary outcomes were endothelial function of the brachial artery (104), blood pressure (105), glycemic control, (105) and forearm microcirculatory function (106). CoQ<sub>10</sub> supplementation in this population raised plasma CoQ<sub>10</sub> 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 twelve weeks treatment with ubiquinone improves clinical outcomes and nerve conduction parameters of diabetic polyneuropathy; furthermore, it reduces oxidative stress without significant adverse events (107). These data identify CoQ<sub>10</sub> as a potential candidate for future treatment of peripheral neuropathy in type 2 diabetes.

### 5.8. Male infertility

Both the bioenergetic and the antioxidant role of CoQ<sub>10</sub> suggest a possible involvement in sperm

biochemistry and male infertility (108). CoQ<sub>10</sub> can be quantified in seminal fluid, where its concentration correlates with sperm count and motility (109). It was found that distribution of CoQ<sub>10</sub> 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 CoQ<sub>10</sub> 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, CoQ<sub>10</sub> was administered to a group of idiopathic asthenozoospermic infertile patients. Treatment led to a significant increase in the concentration of CoQ<sub>10</sub>, both in seminal plasma and sperm cells, and improvement in sperm motility (110). In a recent study, it has been demonstrated that CoQ<sub>10</sub> improves semen quality and pregnancy rate (111).

### 5.9. 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 serves as an endogenous antioxidant which increases the concentration of CoQ<sub>10</sub> in the diseased gingiva and effectively suppresses advanced periodontal inflammation (112).

### 5.10. Migraine

There are strong similarities between migraine and encephalomyopathies due to mitochondrial disorders, in which patients suffer genetic abnormalities in mitochondrial energy production to produce lactic acidosis, stroke, and migraine headaches. The theory of migraine as a mitochondrial disorder seems to have abundant evidence (113). Arising from these extensive neurophysiological studies, treatment of metabolic encephalomyopathies with pharmacological doses of riboflavin and CoQ<sub>10</sub> has shown positive benefits. The same treatment has now been applied to migraine, adding clinical support to the theory that migraine is a mitochondrial disorder. Currently, riboflavin and CoQ<sub>10</sub> supplementation has been recommended widely as safe and effective prophylactic therapy for migraine. Evidence indicates impaired energy metabolism may be present in brains of migraine sufferers. Rozen *et al* supplemented migraine patients with 150 mg CoQ<sub>10</sub> daily for three months and demonstrated a 50-percent reduction in number of days with migraine headache, regardless of whether patients experienced aura or not (114). Deficiency of CoQ<sub>10</sub> may be common in pediatric and adolescent migraine. Determination of deficiency and consequent supplementation may result in clinical improvement (115).

### 5.11. Pregnancy

Plasma CoQ<sub>10</sub> levels rise with each trimester of pregnancy and fetal wasting with subsequent spontaneous abortion has been correlated with low levels of CoQ<sub>10</sub>

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(116). Supplementation with CoQ<sub>10</sub> 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 (117).

### 5.12. Down's syndrome

Down 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 (118). 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 CoQ<sub>10</sub> treatment on DNA damage in DS patients. Results suggest that the effect of CoQ<sub>10</sub> treatment in DS not only reflects antioxidant efficacy, but likely modulates DNA repair mechanisms (119).

### 5.13. Aging

Decrease of CoQ<sub>10</sub> levels during aging could be one of the main factors in the development of chronic diseases in old people. Furthermore, since CoQ<sub>10</sub> is not only an antioxidant but also is involved in a plethora of cellular processes appropriate uptake of CoQ<sub>10</sub> into cellular is crucial for improvement of cell activity during aging. Maintenance of CoQ<sub>10</sub> functional levels at cell membranes either by dietary supplementation or by improving endogenous synthesis can be a key strategy to enhance health during aging (120).

## 6. COSMETICS

Topical antioxidants have been used to treat photoaged and chronologically aged skin (121). Free radicals are known to promote oxidation of nucleic acids, proteins, and lipids and can damage intracellular structures including DNA (122). Free radicals also up-regulate transcription factors such as activator protein 1 (AP-1) and nuclear transcription factor-kappa B (NF-κB) (123). AP-1 is responsible for production of metalloproteinases that break down existing collagen, contributing to skin wrinkling (124). NF-κ B up-regulates transcription of proinflammatory mediators such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (125). Acting through cell-surface receptors, these proinflammatory mediators further activate AP-1 and NF-κB, resulting in more damage. It is the sum of these events that are responsible for skin aging (126).

In the skin CoQ<sub>10</sub> acts as an antioxidant with 10-fold higher levels in the epidermis than in the dermis (127). The reduction in the efficiency of antioxidant systems has been proposed as a factor of skin ageing. Therefore, in the cosmetic industry the antioxidant CoQ<sub>10</sub> is widely used in anti-ageing products (128). Lipid nanoparticles, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), are innovative carrier systems for CoQ<sub>10</sub> that are derived from oil/water emulsions (129).

## 7. 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 CoQ<sub>10</sub>, resulting in decreased serum CoQ<sub>10</sub> (130). Beta blockers, propranolol and metoprolol, (131) phenothiazines and tricyclic antidepressants have been shown to inhibit CoQ<sub>10</sub>-dependent enzymes (132). CoQ<sub>10</sub>'s effects on platelet function may increase the risk of bleeding in patients taking antiplatelet drugs such as aspirin (133). On the other hand, since it acts like vitamin K, it may counteract the anticoagulant effects of warfarin (134). CoQ<sub>10</sub> may have an additive antihypertensive effect when given with antihypertensive drugs (135). CoQ<sub>10</sub> may improve beta-cell function and enhance insulin sensitivity, which may reduce insulin requirements for diabetic patients (105).

## 8. TOXICITY

CoQ<sub>10</sub> 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 (136). However, gastrointestinal effects such as abdominal discomfort, nausea, vomiting, diarrhea, and anorexia have occurred (136). Allergic rash and headache have also been reported (136). In addition, CoQ<sub>10</sub>'s antiplatelet effect may increase the risk of bleeding (137). It undergoes biotransformation in the liver and is eliminated primarily via the biliary tract (137), therefore it can accumulate in patients with hepatic impairment or biliary obstruction.

## 9. COENZYME Q<sub>10</sub>-RELATED COMPOUNDS

Intestinal absorption of dietary CoQ<sub>10</sub> is very limited and only chronic ingestion of relatively large doses of CoQ<sub>10</sub> increase CoQ<sub>10</sub> concentrations especially in heart and brain mitochondria in rodent models (4). For this reason, the development of less hydrophobic structural derivatives of CoQ<sub>10</sub>, and therefore with better pharmacokinetics profiles, are emerging as promising drugs for treating diseases with mitochondrial dysfunction. Idebenone and MitoQ have been evaluated in clinical trials for safety, toxicity and their effect for treating different diseases (101).

Several advancements have been made to enhance the bioavailability of CoQ<sub>10</sub> using various new formulations and approaches like size reduction, solubility enhancement (by solid dispersion, prodrug, complexation, ionization) and use of novel drug carriers such as liposomes, microspheres, nanoparticles, nanoemulsions and self-emulsifying system (138).

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**Send correspondence to:** Jose A. Sánchez Alcázar. Centro Andaluz de Biología del Desarrollo (CABD). Universidad Pablo de Olavide-Consejo Superior de Investigaciones Científicas, Carretera de Utrera Km 1, Sevilla 41013, Spain, Tel: 34 954978071, Fax: 34 954349376, E-mail: jasanalc@upo.es