Clinical aspects of coenzyme Q\textsubscript{10}: An update

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Abstract

The fundamental role of coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) 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. Cardiovascular disease is still the main field of study and the latest findings confirm a role of CoQ\textsubscript{10} in improving endothelial function. The possible relation between CoQ\textsubscript{10} deficiency and statin side effects is highly debated, particularly the key issue of whether CoQ\textsubscript{10} supplementation counteracts statin myalgias. Furthermore, in cardiac patients, plasma CoQ\textsubscript{10} was found to be an independent predictor of mortality. Studies on CoQ\textsubscript{10} and physical exercise have confirmed its effect in improving subjective fatigue sensation and physical performance and in opposing exercise-related damage. In the field of mitochondrial myopathies, primary CoQ\textsubscript{10} deficiencies have been identified, involving different genes of the CoQ\textsubscript{10} biosynthetic pathway; some of these conditions were found to be highly responsive to CoQ\textsubscript{10} administration. The initial observations of CoQ\textsubscript{10} effects in Parkinson’s and Huntington’s diseases have been extended to Friedreich’s ataxia, where CoQ\textsubscript{10} and other quinones have been tested. CoQ\textsubscript{10} is presently being used in a large phase III trial in Parkinson’s disease. CoQ\textsubscript{10} has been found to improve sperm count on asthenozoospermia. Moreover, for the first time CoQ\textsubscript{10} was found to decrease the incidence of preeclampsia in pregnancy. The ability of CoQ\textsubscript{10} to mitigate headache symptoms in adults was also verified in pediatric and adolescent populations. © 2010 Elsevier Inc. All rights reserved.

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Introduction

Coenzyme Q (CoQ\textsubscript{10} in humans) is a key component of the mitochondrial respiratory chain and, for a number of years, it was mainly known for its role in oxidative phosphorylation; its presence was then demonstrated in other subcellular fractions and in plasma lipoproteins, where it is endowed with antioxidant properties. CoQ\textsubscript{10} was also recognized to have an effect on gene expression [1]. These three functions underlie the rationale for its use in clinical practice and as a food supplement. This report constitutes an overview of new clinical findings in these past 4 y and is basically a further update of our previous report published in 2005 [2] (Table 1).

Cardiovascular disease

Cardiovascular effects of CoQ\textsubscript{10} can be ascribed to its bioenergetic role, to its capability of antagonizing oxidation of plasma low-density lipoprotein, and to its effect in ameliorating endothelial function [3]. Among the recent data produced by our laboratory, CoQ\textsubscript{10} was found to improve endothelium-bound extracellular superoxide dismutase (ecSOD) [4] in patients affected by coronary artery disease. Patients with coronary artery disease have decreased levels of ecSOD, an enzyme that is thought to protect blood vessels against oxidant-induced damage. This was a double-blind, randomized, controlled study of 35 patients with ischemic heart disease; the patients in the intervention group were treated with CoQ\textsubscript{10} at doses of 100 mg three times daily. CoQ\textsubscript{10} treatment determined a significant improvement in ecSOD activity, more pronounced in patients who had initial low values of ecSOD and therefore likely exposed to greater oxidative stress. This effect was accompanied by an increase of maximal oxygen uptake and of flow-mediated dilation, a recognized index of endothelial function.

Since 1975 many studies have been conducted on the effect of CoQ\textsubscript{10} on hypertension. This issue was reviewed in 2007 by Rosenfeldt et al. [5] who carried out a meta-analysis of the clinical trials. The studies included three...
CoQ10, starting 7–10 d preoperatively (150–180 mg/d) until morning of surgery. The CoQ10-treated group of patients had significantly fewer reperfusion arrhythmias, lower total inotropic requirement, mediastinal drainage, blood requirement, and shorter hospitalization compared with the control group. The biochemical rationale for using CoQ10 in the perioperative period in cardiac surgery lies in its ability to antagonize ischemia reperfusion damage (Table 2).

### Predictive value of plasma CoQ10 levels in cardiac patients

In the past, plasma CoQ10 levels were found to be lower in ethnic groups more prone to cardiovascular disease [9]; more specifically, lower CoQ10 and CoQ10/cholesterol ratio were found in plasma from people in an Indian community living in Singapore compared with the corresponding levels in the Chinese inhabitants. However, CoQ10 levels have not been previously related to outcomes of heart failure in observational studies. A recent study by Molyneux et al. [10] investigated the relation between plasma CoQ10 and survival in patients with chronic heart failure. Plasma CoQ10 was found to be an independent predictor of mortality in a cohort of 236 selected patients, for whom the median follow-up time was 2.7 y (0.1–5.8 y). A total of 76 events (deaths) occurred. Lower CoQ10 and CoQ10/lipid ratios predicted poorer survival, according to the receiver operating characteristics curve. CoQ10 was an independent predictor of survival, and the strength of association between CoQ10 and mortality was greater than that observed for N-terminus pro–brain natriuretic peptide. The investigators concluded that it is therefore plausible that CoQ10 deficiency might be an important pathogenic mechanism associated with worse outcomes in chronic heart failure.

### Statins and CoQ10

Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors that decrease te synthesis of mevalonate, a key metabolic step in the cholesterol synthesis pathway. These efficient drugs can produce a variety of muscle-related complaints or myopathies. Because the mevalonate pathway also leads to the biosynthesis of the isoprenoid side chain of coenzyme Q10, different studies have addressed the possibility of CoQ10 being an etiologic factor in statin myopathy. This issue has been extensively investigated and it is worthwhile to mention two reviews [11,12]. It was highlighted that, besides decreasing plasma CoQ10 levels, statin treatment leads to lower lymphocyte levels of CoQ10. There are no univocal results about the effect of statin treatments on CoQ10 levels in skeletal muscle [13,14], yet more recently [15] it was reported that high-dose statins did decrease muscle CoQ10 and mitochondrial respiratory chain activities, possibly related to the decrease in the number or volume of muscle mitochondria. In a 2008 study an inverse correlation between atorvastatin-induced changes in CoQ10 and pro–brain natriuretic peptide was found. It was concluded that long-term treatment with atorvastatin might increase plasma levels of pro–brain natriuretic peptide in patients with coronary heart disease when accompanied by a greater reduction in plasma CoQ10 [16]. Regarding the effect of CoQ10
supplementation, this was found not to improve statin tolerance or myalgia in one study [17], whereas Caso et al. [18] reported a positive effect of CoQ10 on pain severity and pain interference in daily activities in a group of statin-treated patients showing myopathic symptoms.

Reproductive medicine

A recent publication from our group confirmed, in a placebo-controlled, double-blind, randomized trial, the efficacy of CoQ10 treatment in improving semen quality in men with idiopathic infertility [19]. Oxidized and reduced CoQ10 concentration significantly increased in seminal plasma and sperm cells, together with sperm motility, after 6 mo of therapy with 200 mg/d of CoQ10. Increased concentrations of CoQ10 and QH2 (reduced CoQ10) in seminal plasma and sperm cells, the improvement of semen kinetic features and treatment, and the evidence of a direct correlation between CoQ10 concentrations and sperm motility strongly support a cause–effect relation. Similar results were found by Safarinejad [20]. In this study 212 infertile men with idiopathic oligoasthenoteratospermia were treated with 300 mg/d of CoQ10 or placebo for 26 wk. Statistically significant improvement was found in the CoQ10 group regarding sperm count and motility values, with a positive correlation between treatment duration of CoQ10 and sperm count and mean sperm motility. The CoQ10 group had a significant decrease in serum follicle-stimulating hormone and luteinizing hormone at the 26-wk treatment phase. The investigators highlight that a lower serum follicle-stimulating hormone implies better spermatogenesis. Moreover, inhibin B, which reflects Sertoli’s cell function, increased in the CoQ10 group. None of the patients’ wives reported pregnancy during the study period.

In 2009 Teran et al. [21] reported the results of CoQ10 supplementation in reducing the risk of pre-eclampsia. Pregnant women at increased risk of pre-eclampsia received 200 mg of CoQ10 or placebo daily from 20 wk of pregnancy until delivery. The overall rate of pre-eclampsia was 20% and there was a significant difference in the placebo group (25.6%) compared with the CoQ10-treated one (14.4%). Pre-eclampsia is a common disorder of human pregnancy in which the normal hemodynamic response to pregnancy is compromised. It remains a leading cause of maternal morbidity and mortality and is associated with a significant increase in perinatal mortality. The newly recognized role of CoQ10 in improving endothelial function [4] could have particular importance in pre-eclampsia in which endothelial dysfunction is known to play a pathogenetic role [22].

CoQ10 and physical exercise

In the past some studies had shown an improvement, by giving CoQ10, of aerobic capacity, anaerobic threshold, and physical performance. Other studies did not find an ergogenic effect. These issues have recently been addressed in three studies published in 2008 [23–25]. One of these studies showed that after a single administration of CoQ10 plasma levels significantly correlated with muscle CoQ10 levels, maximal oxygen consumption, and treadmill time to exhaustion. A trend for increased time to exhaustion was observed after 2 wk of CoQ10 supplementation ($P = 0.06$) [23]. In another trial, oral administration of CoQ10 improved subjective fatigue sensation and physical performance [24]. The third study was a double-blind study where a group of kendo athletes showed lower levels of creatine kinase, myoglobin, and lipid peroxides compared with the corresponding values in the placebo group [25].

In a study where CoQ10 had been taken in combination with vitamins C and E, administration of this antioxidant cocktail further increased endothelial nitric oxide synthase and uncoupling protein-3 mRNA content after exercise [26]. Moreover, supplementation with a combination of antioxidants including CoQ10 was found to prevent plasma oxidative damage induced by playing soccer [27].

For the first time a study examined the acute effects of CoQ10 and placebo on autonomic nervous activity and energy metabolism at rest and during exercise [28]. Fat oxidation significantly increased during exercise in the CoQ10 group; results suggested that CoQ10 increases autonomic nervous activity during low-intensity exercise.

In a double-blind pilot study patients with post-polio syndrome were treated with 200 mg of CoQ10/d. Muscle strength, muscle endurance and quality of life increased statistically significantly in all 14 patients but there was no significant difference between the CoQ10 and placebo groups [29].

Human CoQ10 deficiencies

Coenzyme $Q_{10}$ treatment had previously been shown to be effective in several cases of mitochondrial myopathies, which were sometimes associated with low CoQ10 muscle levels. Primary CoQ10 deficiencies, due to mutations in ubiquinone biosynthetic genes, have now been identified and they have been associated with four major clinical phenotypes [30] and in some cases there have been excellent responses to oral CoQ10 treatment. Defects have been identified concerning genes involved in different steps of CoQ10 biosynthesis [31]. It has been ascertained that respiratory chain dysfunction and oxidative stress correlate with the severity of primary CoQ10 deficiency [32]. Some of these conditions, in which nephropathy plays an important role, are highly responsive to CoQ10 administration [33,34]. Very recently a new genetic defect in the COQ9 gene was identified, leading to a primary CoQ10 deficiency potentially treatable with CoQ10 supplementation [35].

Neurodegenerative diseases

During the past few years CoQ10 has been used in different neurodegenerative diseases where a common
biochemical feature is the evidence of oxidative stress and damage and mitochondrial respiratory chain dysfunction. Friedreich’s ataxia is one of these conditions; treatment with CoQ10 and vitamin E caused a prolonged improvement in cardiac and skeletal muscle bioenergetics and clinical scores [36]. Another study, where patients were randomly divided into high- or low-dose CoQ10/vitamin E groups, demonstrated improvement in clinical symptoms in 49% of patients. This respondent group had significantly lower baseline serum CoQ10 levels [37]. The therapeutic implications of CoQ10 in Parkinson’s disease were also recently discussed in a review by Henchcliffe and Beal [38]. CoQ10 had already been shown to slow progression of the disease when given at high dosages [39]. A large phase III trial comparing placebo and 1200 and 2400 mg of CoQ10 daily is currently underway.

A recent magnetic resonance spectroscopic study was also conducted in patients with progressive supranuclear palsy treated with CoQ10; a significant increase of the ratio of high-energy to low-energy phosphates was indicative of improved oxidative phosphorylation of the occipital cortex [40].

Other clinical aspects

Coenzyme Q10 is also being used in the treatment of other different clinical conditions. Inui et al. [41] recently discussed the mechanisms by which CoQ10 inhibits ultraviolet B–induced wrinkle formation in vitro and in vivo. Results indicated that CoQ10 inhibits the production of interleukin-6 and metalloproteinases. Collagenase, an enzyme that degrades collagen fibers, is one of these metalloproteinases and its inhibition by CoQ10 likely contributed to protect dermal fiber composition from degradation, leading to rejuvenation of wrinkled skin.

Coenzyme Q10 has also been administered to children affected by Down’s syndrome, in an attempt to counteract the oxidative imbalance present in this condition [42,43], with promising results.

Different studies have highlighted an antiangiogenic and hypolipidemic activity of CoQ10 supplementation in patients with breast cancer undergoing tamoxifen therapy [44].

Maternally inherited diabetes and deafness is a subtype of diabetes where a known mutation affects insulin secretion. A 2008 study described the case of a patient with maternally inherited diabetes and deafness who developed chronic intestinal pseudo-obstruction and favorably responded to CoQ10 [45].

Another field where the beneficial effects of CoQ10 may be related to its mitochondrial function and antioxidant properties is migraine, a condition where some inflammatory components may produce reactive oxygen species, leading to overconsumption of CoQ10. In 2005 Sándor et al. [46] reported the first positive effect of CoQ10 in migraine prophylaxis. Subsequently, Hershey et al. [47] assessed plasma CoQ10 levels in a large group of pediatric patients attending a tertiary care center for frequent headaches. Patients with low CoQ10 were treated with CoQ10 1–3 mg · kg·d−1. For those patients taking CoQ10 the headache frequency decreased from 19.2 ± 9.8 to 12.5 ± 10.8 d/mo (P < 0.001), with a 50% reduction in headache frequency in 46.3%. The PedMIDAS score decreased from 47.4 ± 50.6 to 22.8 ± 30.6 (P < 0.001), with a grade decrease from 2.6 ± 1.2 to 1.9 ± 1.0 (P < 0.001).

The effects of CoQ10 highlighted in this variegated group of clinical conditions are likely related to its antioxidant properties, although we cannot exclude, also in these cases, a possible involvement of CoQ10 in improving cellular bioenergetics.

References


