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Review article

Clinical aspects of coenzyme Q_{10}: An update

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Abstract The fundamental role of coenzyme Q_{10} (CoQ_{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_{10} in improving endothelial function. The possible relation between CoQ_{10} deficiency and statin side effects is highly debated, particularly the key issue of whether CoQ_{10} supplementation counteracts statin myalgias. Furthermore, in cardiac patients, plasma CoQ_{10} was found to be an independent predictor of mortality. Studies on CoQ_{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_{10} deficiencies have been identified, involving different genes of the CoQ_{10} biosynthetic pathway; some of these conditions were found to be highly responsive to CoQ_{10} administration. The initial observations of CoQ_{10} effects in Parkinson's and Huntington's diseases have been extended to Friedreich's ataxia, where CoQ_{10} and other quinones have been tested. CoQ_{10} is presently being used in a large phase III trial in Parkinson's disease. CoQ_{10} has been found to improve sperm count and motility on asthenozoospermia. Moreover, for the first time CoQ_{10} was found to decrease the incidence of preeclampsia in pregnancy. The ability of CoQ_{10} to mitigate headache symptoms in adults was also verified in pediatric and adolescent populations.

Keywords: Coenzyme Q_{10}; Cardiovascular disease; Mitochondrial myopathies; Reproductive medicine

Introduction

Coenzyme Q (CoQ_{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_{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_{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_{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_{10} at doses of 100 mg three times daily. CoQ_{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_{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

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Table 1
Recognized biochemical functions of coenzyme Q_{10}

Recognized biochemical functions	Reference
Mitochondrial bioenergetics	
General aspects	48
Super complexes	49
Permeability transition pore	48
Uncoupling proteins	48
Antioxidant	48
Gene induction	1

randomized, controlled clinical trials, one crossover study, and eight open-label observational studies. When trial results were pooled, CoQ_{10} produced decreases of up to 17 mmHg in systolic and 10 mmHg in diastolic blood pressures. The CoQ_{10} effect on blood pressure is likely related to the improvement in endothelial function mentioned earlier.

The effect of CoQ_{10} therapy in hypertrophic cardiomyopathy has also recently been reported [6]. At a dose of 200 mg/d, together with conventional therapy, CoQ_{10} significantly improved diastolic dysfunction, New York Heart Association class, quality of life, and the 6-min walk test. Post-treatment echocardiogram showed significant reduction in left ventricular outflow tract gradient in obstructive cases (12 of 46) in the treatment group. There were also decreases in mean interventricular septal thickness and posterior wall thickness.

Another field where CoQ_{10} confirmed previous positive results [7] is coronary artery bypass graft surgery. In the most recent trial in this field [8], a group of patients undergoing coronary artery bypass graft surgery were treated with CoQ_{10}, starting 7–10 d preoperatively (150–180 mg/d) until the morning of surgery. The CoQ_{10}-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 CoQ_{10} in the perioperative period in cardiac surgery lies in its ability to antagonize ischemia reperfusion damage (Table 2).

Predictive value of plasma CoQ_{10} levels in cardiac patients

In the past, plasma CoQ_{10} levels were found to be lower in ethnic groups more prone to cardiovascular disease [9]; more specifically, lower CoQ_{10} and CoQ_{10}/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, CoQ_{10} 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 CoQ_{10} and survival in patients with chronic heart failure. Plasma CoQ_{10} 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.

Table 2
Physiologic and clinical applications of coenzyme Q_{10}

Physiologic and clinical applications	References
Exercise performance	23
Antifatigue effects	24
Reducing exercise-induced muscular injury	25,27
Hypertension	5
Cardiac failure	3,6
Ischemic heart disease	7,8
Interaction with statins	11–18
Endothelial function	3
Interaction with extracellular superoxide dismutase	4
Predictive values of plasma levels	9,10
Sperm motility	19,20
Pre-eclampsia	21,22
Neurodegenerative diseases	
Parkinson's disease	38,39
Friedreich's ataxia	36,37
Skin protection	41
Human coenzyme Q_{10} deficiencies	30–35
Migraine	46,47

Lower CoQ_{10} and CoQ_{10}/lipid ratios predicted poorer survival, according to the receiver operating characteristics curve. CoQ_{10} was an independent predictor of survival, and the strength of association between CoQ_{10} and mortality was greater than that observed for N-terminus pro–brain natriuretic peptide. The investigators concluded that it is therefore plausible that CoQ_{10} deficiency might be an important pathogenic mechanism associated with worse outcomes in chronic heart failure.

Statins and CoQ_{10}

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 Q_{10}, different studies have addressed the possibility of CoQ_{10} 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 CoQ_{10} levels, statin treatment leads to lower lymphocyte levels of CoQ_{10}. There are no univocal results about the effect of statin treatments on CoQ_{10} levels in skeletal muscle [13,14], yet more recently [15] it was reported that high-dose statins did decrease muscle CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} [16]. Regarding the effect of CoQ_{10}

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 CoQ_{10} 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 CoQ_{10} treatment in improving semen quality in men with idiopathic infertility [19]. Oxidized and reduced CoQ_{10} concentration significantly increased in seminal plasma and sperm cells, together with sperm motility, after 6 mo of therapy with 200 mg/d of CoQ_{10}. Increased concentrations of CoQ_{10} and QH_2 (reduced CoQ_{10}) in seminal plasma and sperm cells, the improvement of semen kinetic features and treatment, and the evidence of a direct correlation between CoQ_{10} 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 of CoQ_{10}/d or placebo for 26 wk. Statistically significant improvement was found in the CoQ_{10} group regarding sperm count and motility values, with a positive correlation between treatment duration of CoQ_{10} and sperm count and mean sperm motility. The CoQ_{10} 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 CoQ_{10} group. None of the patients' wives reported pregnancy during the study period.

In 2009 Teran et al. [21] reported the results of CoQ_{10} supplementation in reducing the risk of pre-eclampsia. Pregnant women at increased risk of pre-eclampsia received 200 mg of CoQ_{10} 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 CoQ_{10}-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 CoQ_{10} in improving endothelial function [4] could have particular importance in pre-eclampsia in which endothelial dysfunction is known to play a pathogenetic role [22].

CoQ_{10} and physical exercise

In the past some studies had shown an improvement, by giving CoQ_{10}, 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 CoQ_{10} plasma levels significantly correlated with muscle CoQ_{10} levels, maximal oxygen consumption, and treadmill time to exhaustion. A trend for increased time to exhaustion was observed after 2 wk of CoQ_{10} supplementation ($P = 0.06$) [23]. In another trial, oral administration of CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} was found to prevent plasma oxidative damage induced by playing soccer [27].

For the first time a study examined the acute effects of CoQ_{10} and placebo on autonomic nervous activity and energy metabolism at rest and during exercise [28]. Fat oxidation significantly increased during exercise in the CoQ_{10} group; results suggested that CoQ_{10} 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 CoQ_{10}/d. Muscle strength, muscle endurance and quality of life increased statistically significantly in all 14 patients but there was no significant difference between the CoQ_{10} and placebo groups [29].

Human CoQ_{10} deficiencies

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

Neurodegenerative diseases

During the past few years CoQ_{10} 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 CoQ_{10} 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 CoQ_{10}/vitamin E groups, demonstrated improvement in clinical symptoms in 49% of patients. This respondent group had significantly lower baseline serum CoQ_{10} levels [37]. The therapeutic implications of CoQ_{10} in Parkinson's disease were also recently discussed in a review by Henchcliffe and Beal [38]. CoQ_{10} had already been shown to slow progression of the disease when given at high dosages [39]. A large phase III trail comparing placebo and 1200 and 2400 mg of CoQ_{10} daily is currently underway.

A recent magnetic resonance spectroscopic study was also conducted in patients with progressive supranuclear palsy treated with CoQ_{10}; 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 Q_{10} is also being used in the treatment of other different clinical conditions. Inui et al. [41] recently discussed the mechanisms by which CoQ_{10} inhibits ultraviolet B–induced wrinkle formation in vitro and in vivo. Results indicated that CoQ_{10} inhibits the production of interleukin-6 and metalloproteinases. Collagenase, an enzyme that degrades collagen fibers, is one of these metalloproteinases and its inhibition by CoQ_{10} likely contributed to protect dermal fiber composition from degradation, leading to rejuvenation of wrinkled skin.

Coenzyme Q_{10} 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 CoQ_{10} 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 CoQ_{10} [45].

Another field where the beneficial effects of CoQ_{10} 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 CoQ_{10}. In 2005 Sándor et al. [46] reported the first positive effect of CoQ_{10} in migraine prophylaxis. Subsequently, Hershey et al. [47] assessed plasma CoQ_{10} levels in a large group of pediatric patients attending a tertiary care center for frequent headaches. Patients with low CoQ_{10} were treated with CoQ_{10} 1–3 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}. For those patients taking CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} in improving cellular bioenergetics.

References

[1] Groneberg DA, Kindermann B, Althammer M, Klapper M, Vormann J, Littarru GP, Döring F. Coenzyme Q_{10} affects expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. Int J Biochem Cell Biol 2005;37:1208–18.

[2] Littarru GP, Tiano L. Clinical aspects of coenzyme Q_{10}: an update. Curr Opin Clin Nutr Metab Care 2005;8:641–6.

[3] Belardinelli R, Muçaj A, Lacalaprice F, Solenghi M, Seddaiu G, Principi F, et al. Coenzyme Q_{10} and exercise training in chronic heart failure. Eur Heart J 2006;27:2675–81.

[4] Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP. Effect of coenzyme Q_{10} administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study. Eur Heart J 2007;28:2249–55.

[5] Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, Watts GF. Coenzyme Q_{10} in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum Hypertens 2007;21:297–306.

[6] Adarsh K, Kaur H, Mohan V. Coenzyme Q_{10} (CoQ_{10}) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). Biofactors 2008;32:145–9.

[7] Celik T, Iyisoy A. Coenzyme Q_{10} and coronary artery bypass surgery: what we have learned from clinical trials. J Cardiothorac Vasc Anesth 2009, Epub ahead of print.

[8] Makhija N, Sendasgupta C, Kiran U, Lakshmy R, Hote MP, Choudhary SK, et al. The role of oral coenzyme Q_{10} in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2008;22:832–9.

[9] Hughes K, Lee BL, Feng X, Lee J, Ong CN. Coenzyme Q_{10} and differences in coronary heart disease risk in Asian Indians and Chinese. Free Radic Biol Med 2002;32:132–8.

[10] Molyneux SL, Florkowski CM, George PM, Pilbrow AP, Frampton CM, Lever M, Richards AM. Coenzyme Q_{10}: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008;52:1435–41.

[11] Littarru GP, Langsjoen P. Coenzyme Q_{10} and statins: biochemical and clinical implications. Mitochondrion 2007;7(suppl):S168–74.

[12] Marcoff L, Thompson PD. The role of coenzyme Q_{10} in statin-associated myopathy: a systematic review. J Am Coll Cardiol 2007;49:2231–7.

[13] Lamperti C, Naini AB, Lucchini V, Prelle A, Bresolin N, Moggio M, et al. Muscle coenzyme Q_{10} level in statin-related myopathy. Arch Neurol 2005;62:1709–12.

[14] Laaksonen R, Jokelainen K, Sahi T, Tikkanen MJ, Himberg JJ. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther 1995;57:62–6.

[15] Paiva H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. Clin Pharmacol Ther 2005;78:60–8.

[16] Suzuki T, Nozawa T, Sobajima M, Igarashi N, Matsuki A, Fujii N, Inoue H. Atorvastatin-induced changes in plasma coenzyme Q_{10} and brain natriuretic peptide in patients with coronary artery disease. Int Heart J 2008;49:423–33.

[17] Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM, Scott RS. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. Am J Cardiol 2007;100:1400–3.

[18] Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme Q_{10} on myopathic symptoms in patients treated with statins. Am J Cardiol 2007;99:1409–12.

[19] Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S, et al. Coenzyme Q_{10} treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertil Steril 2009;91:1785–92.

[20] Safarinejad MR. Efficacy of coenzyme Q_{10} on semen parameters, sperm function and reproductive hormones in infertile men. J Urol 2009;182:237–48.

[21] Teran E, Hernandez I, Nieto B, Tavara R, Ocampo JE, Calle A. Coenzyme Q_{10} supplementation during pregnancy reduces the risk of preeclampsia. Int J Gynaecol Obstet 2009;105:43–5.

[22] Teran E, Escudero C, Vivero S, Molina G, Calle A. NO in early pregnancy and development of preeclampsia. Hypertension 2006;47:e17.

[23] Cooke M, Iosia M, Buford T, Shelmadine B, Hudson G, Kerksick C, et al. Effects of acute and 14-day coenzyme Q_{10} supplementation on exercise performance in both trained and untrained individuals. J Int Soc Sports Nutr 2008;5:8.

[24] Mizuno K, Tanaka M, Nozaki S, Mizuma H, Ataka S, Tahara T, et al. Antifatigue effects of coenzyme Q_{10} during physical fatigue. Nutrition 2008;24:293–9.

[25] Kon M, Tanabe K, Akimoto T, Kimura F, Tanimura Y, Shimizu K, et al. Reducing exercise-induced muscular injury in kendo athletes with supplementation of coenzyme Q_{10}. Br J Nutr 2008;100:903–9.

[26] Hellsten Y, Nielsen JJ, Lykkesfeldt J, Bruhn M, Silveira L, Pilegaard H, Bangsbo J. Antioxidant supplementation enhances the exercise-induced increase in mitochondrial uncoupling protein 3 and endothelial nitric oxide synthase mRNA content in human skeletal muscle. Free Radic Biol Med 2007;43:353–61.

[27] Tauler P, Ferrer MD, Sureda A, Pujol P, Drobnic F, Tur JA, Pons A. Supplementation with an antioxidant cocktail containing coenzyme Q prevents plasma oxidative damage induced by soccer. Eur J Appl Physiol 2008;104:777–85.

[28] Zheng A, Moritani T. Influence of CoQ_{10} on autonomic nervous activity and energy metabolism during exercise in healthy subjects. J Nutr Sci Vitaminol (Tokyo) 2008;54:286–90.

[29] Skough K, Krossén C, Heiwe S, Theorell H, Borg K. Effects of resistance training in combination with coenzyme Q_{10} supplementation in patients with post-polio: a pilot study. J Rehabil Med 2008;40:773–5.

[30] Quinzii CM, López LC, Naini A, DiMauro S, Hirano M. Human CoQ_{10} deficiencies. Biofactors 2008;32:113–8.

[31] Mollet J, Giurgea I, Schlemmer D, Dallner G, Chretien D, Delahodde A, et al. Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders. J Clin Invest 2007;117:765–72.

[32] Quinzii CM, López LC, Von-Moltke J, Naini A, Krishna S, Schuelke M, et al. Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ_{10} deficiency. FASEB J 2008; 22:1874–85.

[33] Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, Laverda AM, et al. Infantile encephalomyopathy and nephropathy with CoQ_{10} deficiency: a CoQ_{10}-responsive condition. Neurology 2005;65:606–8.

[34] Montini G, Malaventura C, Salviati L. Early coenzyme Q_{10} supplementation in primary coenzyme Q_{10} deficiency. N Engl J Med 2008; 358:2849–50.

[35] Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, López LC, et al. A nonsense mutation in COQ9 causes autosomal-recessive neonatal-onset primary coenzyme Q_{10} deficiency: a potentially treatable form of mitochondrial disease. Am J Hum Genet 2009;84:558–66.

[36] Cooper JM, Schapira AH. Friedreich's ataxia: coenzyme Q_{10} and vitamin E therapy. Mitochondrion 2007;7(suppl):S127–35.

[37] Cooper JM, Korlipara LV, Hart PE, Bradley JL, Schapira AH. Coenzyme Q_{10} and vitamin E deficiency in Friedreich's ataxia: predictor of efficacy of vitamin E and coenzyme Q_{10} therapy. Eur J Neurol 2008;15:1371–9.

[38] Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 2008;4:600–9.

[39] Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, et al., Parkinson Study Group. Effects of coenzyme Q_{10} in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002;59:1541–50.

[40] Stamelou M, Reuss A, Pilatus U, Magerkurth J, Niklowitz P, Eggert KM, et al. Short-term effects of coenzyme Q_{10} in progressive supranuclear palsy: a randomized, placebo-controlled trial. Mov Disord 2008;23:942–9.

[41] Inui M, Ooe M, Fujii K, Matsunaka H, Yoshida M, Ichihashi M. Mechanisms of inhibitory effects of CoQ_{10} on UVB-induced wrinkle formation in vitro and in vivo. Biofactors 2008;32:237–43.

[42] Tiano L, Padella L, Carnevali P, Gabrielli O, Bruge F, Principi F, Littarru GP. Coenzyme Q_{10} and oxidative imbalance in Down syndrome: biochemical and clinical aspects. Biofactors 2008;32:161–7.

[43] Miles MV, Patterson BJ, Chalfonte-Evans ML, Horn PS, Hickey FJ, Schapiro MB, et al. Coenzyme Q_{10} (ubiquinol-10) supplementation improves oxidative imbalance in children with trisomy 21. Pediatr Neurol 2007;37:398–403.

[44] Sachdanandam P. Antiangiogenic and hypolipidemic activity of coenzyme Q_{10} supplementation to breast cancer patients undergoing Tamoxifen therapy. Biofactors 2008;32:151–9.

[45] Bergamin CS, Rolim LC, Dib SA, Moisés RS. Unusual occurrence of intestinal pseudo obstruction in a patient with maternally inherited diabetes and deafness (MIDD) and favorable outcome with coenzyme Q_{10}. Arq Bras Endocrinol Metabol 2008;52:1345–9.

[46] Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q_{10} in migraine prophylaxis: a randomized controlled trial. Neurology 2005;64:713–5.

[47] Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, et al. Coenzyme Q_{10} deficiency and response to supplementation in pediatric and adolescent migraine. Headache 2007;47:73–80.

[48] Dallner G, Stocker R, Coenzyme Q. In: Paul Coates, editor. Encyclopedia of dietary supplements. New York: Marcel Dekker; 2005, p. 121–31.

[49] Genova ML, Bianchi C, Lenaz G. Supercomplex organization of the mitochondrial respiratory chain and the role of the coenzyme Q pool: pathophysiological implications. BioFactors 2005;25:5–20.