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Coenzyme Q_{10} in the Treatment of Mitochondrial Disease

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Abstract

Currently, there is a paucity of available treatment strategies for oxidative phosphorylation disorders. Coenzyme Q_{10} (CoQ_{10}) and related synthetic quinones are the only agents to date that have proven to be beneficial in the treatment of these heterogeneous disorders. The therapeutic efficacy of CoQ_{10} is not restricted to patients with an underlying CoQ_{10} deficiency and is thought to result from its ability to restore electron flow in the mitochondrial respiratory chain (MRC) as well as to increase the cellular antioxidant capacity. At present, however, there is no consensus on the appropriate dosage or therapeutic plasma level of CoQ_{10}, and this information will be required before CoQ_{10} can be utilized effectively in the treatment of mitochondrial disease. The following review will outline our current knowledge on the use of CoQ_{10} in the treatment of MRC disorders and primary CoQ_{10} deficiencies.

Keywords

coenzyme Q_{10}, mitochondrial respiratory chain (MRC), oxidative stress, antioxidant

Introduction

The mitochondrial respiratory chain (MRC; Figure 1) is located in the inner mitochondrial membrane and consists of 4 enzyme complexes: complex I (NADH: ubiquinone reductase; EC 1.6.5.3), complex II (succinate: ubiquinone reductase; EC 1.3.5.1), complex III (ubiquinol: cytochrome c reductase; EC 1.10.2.2), and complex IV (cytochrome c oxidase; EC 1.9.3.1;).[1,2] The MRC together with complex V (adenosine triphosphate [ATP] synthase; EC 3.6.3.14) synthesizes ATP, the energy currency of the cell by the process of oxidative phosphorylation.[1,2] In addition to existing as discrete entities, recent studies have indicated that the MRC enzymes can also exist as supercomplexes within the inner mitochondrial membrane consisting of aggregates of complexes I, III, and IV; complexes I and III; and complexes III and IV.[3]

The MRC disorders are a heterogeneous group of multisystemic diseases that develop as the result of mutations in either nuclear or mitochondrial DNA.[2] Once believed to be rare, inherited disorders of the MRC are now thought to represent one of the more commoner groups of inborn errors of metabolism with a birth prevalence of 1 in 5000.[4] The treatment of MRC disorders is extremely difficult and in general woefully inadequate with no overall consensus on appropriate therapeutic strategies.[5] To date, coenzyme Q_{10} (CoQ_{10}) and its analogues are among a small group of agents that have been reported to offer some therapeutic potential in the treatment of MRC disorders.

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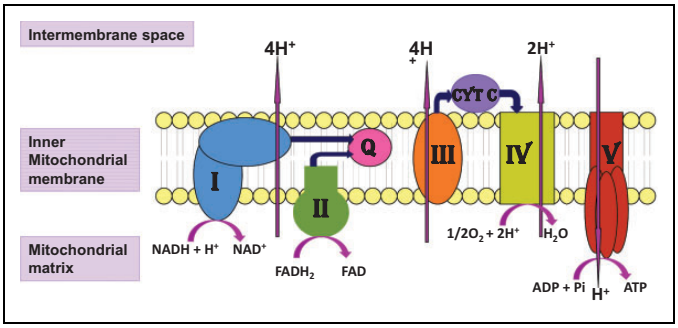

Figure 1. Mitochondrial respiratory chain (MRC).

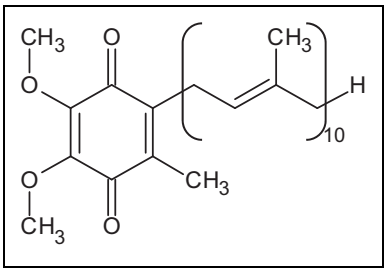

Figure 2. Structure of coenzyme Q_{10} (CoQ_{10}).

Coenzyme Q_{10}

Coenzyme Q_{10} is a small lipophilic molecule consisting of a benzoquinone nucleus and an isoprenoid side chain (Figure 2), which is synthesized by all cells apart from red blood cells, and shares a common biosynthetic pathway with cholesterol.[6] Coenzyme Q_{10} serves as an essential electron carrier within the MRC, transferring electrons derived from complexes I and II to complex III and therefore allowing a continuous passage of electrons within the chain, which is essential for the process of oxidative phosphorylation. In addition to its role as an electron carrier, CoQ_{10} functions as a lipid-soluble antioxidant, protecting cellular membranes and plasma lipoproteins against free radical–induced oxidation.[7] The antioxidant function of CoQ_{10} is attributed to its fully reduced ubiquinol form.[7] Other functions of CoQ_{10} include membrane stabilization and modulation of gene expression.[8,9] In view of all these functions, a deficiency in CoQ_{10} status could conceivably contribute to disease pathophysiology by causing a failure in mitochondrial energy metabolism, compromising cellular antioxidant capacity as well as adversely affecting membrane stability and gene expression. A deficiency in CoQ_{10} status can result from either a genetic defect in the CoQ_{10} biosynthetic pathway, known as a primary deficiency, or as the result of a mutation in a gene not directly involved in CoQ_{10} biosynthesis, known as a secondary deficiency.[10]

Primary CoQ_{10} Deficiencies

The first reported cases of CoQ_{10} deficiency in the literature described 2 sisters born to unrelated parents who presented with recurrent rhabdomyolysis, seizures, and mental retardation.[11] On assessment, the muscle CoQ_{10} status of these patients was found to be approximately 3.7% of mean control values indicating the evidence of a primary defect in CoQ_{10} biosynthesis, as yet however, the genetic cause of this defect has yet to be elucidated. Since this time, well over 150 patients have been reported with CoQ_{10} deficiency, although there are no precise epidemiological data for the overall incidence of this condition.[12] Coenzyme Q_{10} deficiency appears to have a particularly heterogeneous clinical presentation, although it can be divided into 5 distinct clinical phenotypes: encephalomyopathy, severe infantile multisystemic disease, nephropathy, cerebellar ataxia, and isolated myopathy.[12] In most cases, the family history indicates an autosomal recessive mode of inheritance; and to date, mutations in 9 genes involved in the human CoQ_{10} biosynthetic pathway have been reported (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ7*, *ADCK3*, *ADCK4*, and *COQ9*).[13,14]

Secondary CoQ_{10} Deficiencies

Overall, the incidence of secondary CoQ_{10} deficiencies appears to be more common than that of primary CoQ_{10} deficiencies,[10] being a common feature among diseases, such as MRC disorders.[10,12,15,16] Furthermore, it has been suggested that a deficit in CoQ_{10} status may be a good predictor of an MRC deficiency.[17] Indeed, a CoQ_{10} deficiency has been reported in patients with a range of MRC disorders originating from mutations either in mitochondrial DNA such as Kearns Sayre Syndrome or nuclear DNA such as mitochondrial DNA depletion syndrome.[16,18,19,20] A CoQ_{10} deficiency has been detected in plasma/serum[18,19,21] as well as in muscle[15,17] in these patient groups. The cause of the CoQ_{10} deficiency in MRC disorders has yet to be fully elucidated, but it may result from the oxidative degradation of CoQ_{10} as a consequence of the increase in oxidative stress that is associated with MRC dysfunction[22] or just be a reflection of generalized mitochondrial impairment.[16] The decrease of plasma/serum CoQ_{10} levels in patients may also reflect an increased utilization or requirement by the MRC defective tissue(s)/organ(s) as well as liver impairment, as this is the major site of synthesis for circulatory CoQ_{10}.[23] Furthermore, since the enzymes involved in CoQ_{10} synthesis are thought to exist in a superenzyme complex closely associated with the MRC in the inner mitochondrial membrane, an incomplete or abnormal MRC may adversely impact on the structural formation of the CoQ_{10} superenzyme complex resulting in impaired CoQ_{10} biosynthesis.[24]

Treatment of Primary CoQ_{10} Deficiency

A primary CoQ_{10} deficiency is unique among MRC disorders in that it is potentially treatable if oral supplementation is commenced with high-dose CoQ_{10} during the early stages of the disease with clinical improvement being reported in all forms of this condition.[25] However, treatment protocols for CoQ_{10}-deficient patients have not yet been standardized, and results have varied between studies.[25] Although muscle

symptoms associated with CoQ_{10} deficiency appear to improve in most cases upon CoQ_{10} supplementation, cerebral symptoms are generally less responsive to treatment.[12] This is illustrated in patients with the ataxic presentation of CoQ_{10} deficiency who show a variable response to CoQ_{10} supplementation. Four patients with mutations in the *ADCK3* gene have been reported to show improvement following CoQ_{10} supplementation with stabilization of the cerebellar ataxic features, reduction in myoclonus, improvement in speech, and ataxic symptoms.[12,26] In contrast, no improvement in symptoms have been reported in 7 patients carrying mutations in the same gene.[27,28] Furthermore, 11 patients with cerebellar ataxia and CoQ_{10} deficiency of undefined molecular cause also failed to show any sign of clinical improvement following CoQ_{10} supplementation.[29,30] In addition, despite almost complete amelioration of muscle symptoms, cerebral symptoms in patients with the encephalomyopathic phenotype again showed a variable response to CoQ_{10} treatment.[11,31,32] The reasons for the refractory nature of the neurological sequelae associated with a CoQ_{10} deficiency are as yet unknown and may be a consequence of irreversible damage prior to supplementation, the retention of CoQ_{10} in the blood-brain barrier (BBB) itself or simply reflect poor transport across the BBB. Animal studies have indicated that CoQ_{10} can be transported across the BBB following high-dose supplementation.[33,34] However, it is uncertain whether the degree of CoQ_{10} uptake demonstrated in these animal studies would be sufficient to replenish the cerebral levels of this quinone in a deficiency state.

Patients who develop renal dysfunction as the result of a CoQ_{10} deficiency appear to respond well to high-dose CoQ_{10} supplementation if treatment is initiated early in the course of diseases, with progressive recovery of renal function and decreased proteinuria being reported.[35,36] In contrast, CoQ_{10} supplementation was reported to be unsuccessful in inducing the recovery of renal function once chronic renal failure had developed.[37] In order to exploit the "window of opportunity" whereby organ dysfunction may be amenable to CoQ_{10} treatment, supplementation at birth has been suggested for siblings of CoQ_{10}-deficient patients.[38]

In vitro studies have indicated that the use of modified precursors of the quinone ring of CoQ_{10} to bypass the enzymatic defect may be effective in treating specific mutations of the *COQ6* and *COQ7* genes.[39] Studies in yeast harboring the mutant *COQ6* gene revealed that treatment with vanillic acid as well as 3-4-hydroxybenzoic acid could restore respiratory growth.[13,14] These compounds may therefore prove efficacious in the treatment of patients with *COQ6* mutations and are now being evaluated in mammalian cells.[40] The CoQ_{10} analogue, 2,4-dihydroxybenzoic acid, also demonstrated some therapeutic potential by its ability to restore CoQ_{10} biosynthesis in *COQ7* mutant human fibroblasts.[42]

Treatment of MRC Disorders

At present, there are no standardized therapeutic protocols for the treatment of patients with oxidative phosphorylation disorders, and treatment can vary between specialist centers. An extensive review about the current status of small molecule treatments and clinical trials in mitochondrial patients has recently been published.[41] However, once diagnosed, patients generally receive a "mitochondrial cocktail" containing antioxidants and cofactors for the various constituents of the MRC. The "cocktail" can consist of antioxidants such as vitamin E and C, the flavoprotein precursor riboflavin, and creatine monohydrate to assist in ATP generation.[43,44] Coenzyme Q_{10} is often a constituent of this "cocktail" because in addition to serving as an antioxidant it can serve to restore electron flow in the MRC.[45] Unfortunately, it has been suggested that patients with complex V deficiencies such as those with the clinical syndrome Neuropathy, ataxia, and retinitis pigmentosa (NARP), which has been associated with increased oxidative stress, may not benefit from CoQ_{10} therapy.[46] This is because the general blockage of electron flow in the MRC as the result of a complex V deficiency may impede the redox recycling of ubiquinol from CoQ_{10}, which is facilitated by redox exchange with the MRC. A number of small studies have assessed the therapeutic potential of CoQ_{10} in the treatment of MRC disorders with variable outcomes,[15,18,19,47,48] although evidence of clinical improvement has been documented in a number of these studies with reports of increased strength,[49] accelerated postexercise recovery,[50] and improvement in oxygen consumption.[51] Coenzyme Q_{10} therapy was also reported to correct pancreatic β-cell dysfunction in patients with mitochondrial encephalomyopathy and lactic acidosis and diabetes mellitus.[52] However, the most consistent finding appears to be at the biochemical level with a decrease in plasma/serum lactate and pyruvate levels being widely reported following exercise[48,51,53,54,55,56,57,58]. In contrast, some studies have shown no evidence of clinical or biochemical improvement in patients following CoQ_{10} supplementation[59,60]. The failure to elicit a therapeutic effect in these studies may in part be attributable to the dosage or duration of the CoQ_{10} supplementation employed. However, it has been suggested that patients who show some form of biochemical or clinical improvement (responders) following CoQ_{10} supplementation may be those patients who harbor an underlying CoQ_{10} deficiency[19,61]. This is demonstrated in the study by Sacconi et al[15] who reported the evidence of clinical improvement in 7 out of 8 patients with MRC disorder having an underlying CoQ_{10} deficiency following CoQ_{10} supplementation, as opposed to clinical benefit being reported in only 1 out of 15 patients with MRC disorder having no evidence of a muscle CoQ_{10} deficiency. This illustrates the importance of determining CoQ_{10} status prior to commencing CoQ_{10} supplementation in order to identify this subgroup of patients who may respond to treatment. An in vitro study by Chan and colleagues[62] reported that CoQ_{10} supplementation of hepatocytes with a pharmacologically induced MRC complex I deficiency was able to restore both mitochondrial membrane potential (MMP) and cellular antioxidant status. This indicated the potential of CoQ_{10} to be reduced by cytosolic DT-diaphorase (NQO1 or NAD(P)H: quinone oxidoreductase) and then bypass the deficiency at complex I, feeding electrons directly into

complex III of the MRC to restore MMP. The short-chain synthetic quinone analogue of CoQ_{10}, idebenone, is also thought to display a similar mechanism of action in the treatment of the mitochondrial disorder, Lebers hereditary optic neuropathy, which in general results from an MRC complex I deficiency.[45] However, in vitro studies have demonstrated the potential of idebenone to inhibit complex I activity and therefore, the therapeutic efficacy of this quinone in vivo may be attributable to a metabolite of this drug formed following the administration.[45] Another synthetic quinone, EPI-743, which is also reduced by NQO1 activity has shown some beneficial effects in the treatment of patients with MRC disorders.[63] Although its precise mechanism of cellular action has yet to be fully elucidated, EPI-743 treatment has been shown to replenish the level of the antioxidant, reduced glutathione (GSH), possibly resulting from its ability to facilitate the transfer of electrons between NOQ1 and GSH reductase.[64] In addition to its ability to restore cellular GSH status, the beneficial effects of EPI-743 in the treatment of mitochondrial disease may result from its possible interaction with the transcription factor, nuclear factor E2-related factor 2 (Nrf2), which regulates both the expression of antioxidant proteins and cellular energy metabolism.[63,65]

Although a number of small studies and case reports have illustrated the potential benefits of CoQ_{10} in the treatment of patients with MRC disorder,[25] few controlled clinical trials have been conducted to evaluate its effectiveness. The trials that have been undertaken to date generally included patients with MRC disorder having variable genotypes and clinical phenotypes making it difficult to draw any firm conclusions to the responsiveness of particular groups of patients to CoQ_{10} therapy[21,48,66,67]. Although 2 trials demonstrated no benefit in any of the outcomes,[61] evidence of improvement in muscle strength[21] and a decrease in plasma lactate levels following exercise[48] was reported. It has been suggested that both the dose of CoQ_{10} administered and the duration of the study are factors that may compromise the therapeutic efficacy of CoQ_{10} in clinical trials[21,58]. The paucity of controlled clinical trials that have evaluated CoQ_{10} in the treatment of mitochondrial disease can be attributed to the difficulties encountered in recruiting sufficient patients and the relatively large expense of conducting such trials. However, phase 3 of a large-scale, double-blind, randomized clinical trial evaluating CoQ_{10} in the treatment of children with primary MRC disease has been completed, although the results are yet to be published.[42]

Absorption and Bioavailability of CoQ_{10} Formulations

Although all cells of the body apart from red blood cells are capable of synthesizing CoQ_{10}, the body also receives CoQ_{10} from dietary sources such as meat, fish, and some vegetables, with an estimated intake of 3 to 5 mg per day.[68] In view of its similar physicochemical properties to that of vitamin E, CoQ_{10} appears to follow an analogous pattern of digestive uptake. Gastric digestion releases dietary CoQ_{10} from the food matrix, secretions from the pancreas, and bile and then facilitates micelle formation leading to absorption of the solubilized lipid in the small intestine. Coenzyme Q_{10} is then incorporated into chylomicrons and transported via the lymphatic system into the circulation.[69] Following absorption from the gastrointestinal (GI) tract, CoQ_{10} is reduced into its ubiquinol form which is thought to occur in the enterocytes of intestine prior to its entry into the lymphatic system.[70] After release into the circulation, chylomicron remnants are readily taken up by the liver, where ubiquinol is repackaged into lipoproteins, primarily, low-density lipoproteins, and then rereleased into the circulation.[71] In general, tissues with a high-metabolic turnover or energy demand, such as the heart, kidney, liver, and muscle, contain relatively high concentrations of CoQ_{10}, and it is thought that most of this CoQ_{10} pool is synthesized in such tissues. Approximately 95% of plasma and 61% to 95% of tissue CoQ_{10} are present in the reduced, ubiquinol form.[71,72] The brain and lungs are exceptions with $\leq$25% of total CoQ_{10} being found as ubiquinol.[72] This may reflect the higher degree of oxidative stress in these 2 tissues.

In cases of primary and secondary CoQ_{10} deficiency, acquisition of CoQ_{10} from the diet may be insufficient to meet cellular requirements as intestinal absorption of CoQ_{10} is very limited[71] and supplementation may be a consideration. An important factor to consider which may influence the clinical response to CoQ_{10} supplementation is the type of CoQ_{10} formulation employed, as this will have an important bearing on absorption and bioavailability.[40,73]

In view of their superior absorption, the use of gel and oil-based formulations of CoQ_{10} has been recommended in preference to tablets[74] in the treatment of patients with mitochondrial disorders. Recently, a study by Martinefski et al[75] reported that liquid emulsion improved the bioavailability of CoQ_{10} with respect to solid formulations. Following administration, CoQ_{10} takes approximately 6 hours to reach its maximal plasma concentration. Subsequently, a second plasma CoQ_{10} peak is often observed at about 24 hours, which has been attributed to enterohepatic recycling as well as redistribution to the circulation.[76,77] Once administered, the circulatory half-life of CoQ_{10} has been reported to be approximately 36 hours requiring a 2-week period of cessation of treatment before it returns to its baseline level following 4 weeks of supplementation.[78] There is a lot of debate at present as to whether formulations of ubiquinol have a better absorption from the GI tract than those of CoQ_{10}. It has been estimated that the GI absorption of ubiquinol is 3 to 4 times greater than that of CoQ_{10}.[74,79] However, since upon absorption from the GI tract, CoQ_{10} undergoes reduction to ubiquinol, the purported superior bioavailability of ubiquinol formulations to that of CoQ_{10} may in part be attributable to the matrix in which the quinol is encapsulated. Furthermore, there is limited data available from patient studies and no clear indications of dosage compatibility.[40] Interestingly, ubiquinol treatment, in contrast to an equivalent dosage of CoQ_{10}, was reported to increase the CoQ_{10} status of mitochondria from the cerebrum of a mouse model of CoQ_{10} deficiency due to a *COQ9* mutation.[79] The results of this study may therefore

have important implications for the treatment of the cerebral presentations of CoQ_{10} deficiency.

The efficiency of absorption of CoQ_{10} formulations has been reported to decrease as the dosage increases with a suggested block of GI absorption above 2400 mg,[74] and split doses have been recommended in preference to a single dose.[80] Dietary fat together with grapefruit juice consumption have been reported to improve the absorption of CoQ_{10}.[74,81] In contrast, ingestion of high-dose vitamin E together with CoQ_{10} may impede the absorption of CoQ_{10} resulting in lower plasma levels of the quinone,[82] possibly as a result of competition during the GI absorption process.

Coenzyme Q_{10} Monitoring and Dosage

In view of its relative accessibility, clinical monitoring of CoQ_{10} status is generally based on plasma determinations with an established reference interval ranging from 0.5 to 1.7 μM. However, this will vary between centers.[83] Although the level of plasma CoQ_{10} is influenced by both diet and circulatory lipoprotein status, it may have utility in identifying both evidence of cellular CoQ_{10} deficiency[19] and increased tissue utilization and demand.[18] However, in view of the questionable reliability of plasma CoQ_{10} status to reflect that of cells, blood mononuclear cells[84] and urine epithelial cells[85] may be more appropriate surrogates to determine endogenous CoQ_{10} status. However, the "gold standard" for the assessment of tissue CoQ_{10} status is skeletal muscle, and this is commonly used to identify evidence of an underlying CoQ_{10} deficiency.[86]

Currently, there is no consensus on the dosage of CoQ_{10} or the plasma level required that may prove efficacious in the treatment of patients with a primary CoQ_{10} deficiency and/or MRC disorders. Coenzyme Q_{10} supplementation is safe and well tolerated, exhibiting an excellent safety profile with doses as high as 2400 mg/d being used in the treatment of Parkinson disease.[87] Typically, doses in the range 5 to 30 mg/kg/d have been administered to patients with documented low levels of tissue CoQ_{10} as well as those with a primary CoQ_{10} deficiency.[25,88,89] In the absence of a demonstrable CoQ_{10} deficiency, doses of 5 to 30 mg/kg/d may also be used in the treatment of cases of known and suspected mitochondrial disease.[25,78] In Parkinson disease, a plasma CoQ_{10} level of 4.6 μmol/L was reported to be the most effective in slowing functional decline in patients.[90] An in vitro study using CoQ_{10}-deficient human fibroblasts has shown evidence of an improvement in bioenergetics status/normalization of cellular antioxidant status following 7 days of treatment with 5 μM CoQ_{10}.[91] Furthermore, a recent study by Duberley et al[92] indicated that supplementation with >10 μM CoQ_{10} may be required to restore MRC enzyme activities to control levels in CoQ_{10}-deficient human neuroblastoma cells. To date, the highest plasma CoQ_{10} concentration reported is 10.7 μmol/L, using a solubilized ubiquinol formulation[74,83] that may have the potential to show some therapeutic efficacy in the treatment of the neurological presentation of CoQ_{10} deficiency. These latter in vitro studies indicate that the dosage/plasma level of CoQ_{10} required to elicit biochemical or clinical improvement may be dependent on the organ of disease presentation.

Discussion/Conclusion

The ability of CoQ_{10} to demonstrate some beneficial effect in the treatment of mitochondrial disease is thought to rely mainly on its ability to restore electron flow in the MRC and replenish cellular antioxidant capacity. As would be expected, patients with an underlying deficit in CoQ_{10} status may be more responsive to such therapy. However, factors such as the time of diagnosis, the dosage, and duration of CoQ_{10} therapy may influence the efficacy of this treatment. Although a number of case reports and small studies have indicated some therapeutic potential of CoQ_{10} in the treatment of patients with MRC disorders and primary CoQ_{10} deficiencies, there is as yet no consensus of the dosage or plasma level of CoQ_{10} required to achieve some clinical benefit and whether this is influenced by the organ of disease presentation. Determination of CoQ_{10} status in other biological specimens beyond plasma/serum may also be advisable. In this sense, CoQ_{10} monitoring in blood mononuclear cells[84] or in urine samples[85] may better reflect the cellular uptake of exogenous CoQ_{10}. Furthermore, in view of the purported impermeability of the BBB to CoQ_{10}, monitoring of cerebral spinal fluid CoQ_{10} levels in preference to those of plasma may be more appropriate in patients with cerebral disease presentations.[93] The possibility arises that the underlying cause of a particular oxidative phosphorylation disorder may dictate the appropriate quinone therapy to implement, whether utilizing CoQ_{10}, a synthetic quinone, or a combination of the 2 in the treatment regime. At present however, this information is not available, and studies aimed at establishing these treatment protocols may improve the therapeutic efficacy of quinone supplementation.

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References

1. Land JM, Morgan-Hughes JA, Hargreaves I, Heales SJ. Mitochondrial disease: a historical, biochemical, and London perspective. *Neurochem Res*. 2004;29(3):488-491.
2. Rahman S, Hanna MG. Mitochondrial disorders: diagnosis and new treatments in mitochondrial disease. *J Neurol Neurosurg Psychiatry*. 2009;80(9):943-953.

3. Lapuente-Brun E, Moreno-Loshuertos R, Acin-Perez R, et al. Super-complex assembly determines electron flux in the mitochondrial electron transport chain. *Science*. 2013;340(6140): 1567-1570.
4. Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007; 120(6):1326-1333.
5. Dimauro S, Mancuso M, Naini A. Mitochondrial encephalomyopathies: therapeutic approach. *Ann N Y Acad Sci*. 2004;1011:232-245.
6. Hargreaves IP. Ubiquinone: cholesterol's reclusive cousin. *Ann Clin Biochem*. 2003;40(pt 3):207-218.
7. Bentinger M, Brismar K, Dallner G. The antioxidant role of coenzyme Q. *Mitochondrion*. 2007;7(suppl);S41-S51.
8. Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. *Biochem Biophys Acta*. 2004;1660(1-2):171-199.
9. Groneberg DA, Kindermann B, Althammer M, 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*. 2005;37(6):1208-1218.
10. Yubero D, Montero R, Martin MA, et al. Secondary coenzyme Q10 deficiencies in oxidative phosphorylation (OXPHOS) and non –OXPHOS disorders. *Mitochondrion*. 2016;30:51-58.
11. Ogasahara S, Engel AG, Frens D, Mack D. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. *Proc Natl Acad Sci USA*. 1989;86(7):2379-2382.
12. Emmanuele V, Lopez LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. *Arch Neurol*. 2012;69(8):979-983.
13. Doimo M, Desbats MA, Cerqua C, Cassina M, Trevisson E, Salviati L. Genetics of coenzyme Q10 deficiencies. *Mol Syndromol*. 2014;5(3-4):156-162.
14. Doimo M, Trevisson E, Airik R, et al. Effect of vanillic acid on CoQ6 mutants identified in patients with coenzyme Q10 deficiency. *Biochim Biophys Acta*. 2014;1842(1):1-6.
15. Sacconi S, Trevisson E, Salviati L, et al. Coenzyme Q10 is frequently reduced in muscle of patients with mitochondrial myopathy. *Neuromuscul Disord*. 2010;20(1):44-48.
16. Montero R, Grazina M, Lopez-Gallardo E, et al. Coenzyme Q10 deficiency in mitochondrial DNA depletion syndromes. *Mitochondrion*. 2013;13(4):337-341.
17. Miles MV, Miles L, Tang LM, et al. Systemic evaluation of muscle coenzyme Q10 content in children with mitochondrial respiratory chain enzyme deficiencies. *Mitochondrion*. 2008; 8(2):170-180.
18. Bresolin N, Bet L, Binda A, et al. Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. *Neurology*. 1988;38(6):892-899.
19. Zierz S, Jahns G, Jerusalem F. Coenzyme Q in serum and muscle of 5 patients with Kearns-Sayre syndrome and 12 patients with ophthalmoplegia plus. *J Neurol*. 1989;236(2):97-101.
20. Matsuoka M, Nagawa F, Okazaki K, et al. Detection of somatic DNA recombination in transgenic mouse brain. *Science*. 1991; 254(5028):81-86.
21. Chen RS, Huang CC, Chu NS. Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. *Eur Neurol*. 1997;37(4):212-218.
22. Miranda S, Foncea R, Guerrero J, Leighton F. Oxidative stress and upregulation of mitochondrial biogenesis genes in mitochondrial DNA-depleted HeLa cells. *Biochem Biophys Res Commun*. 1999;258(1):44-49.
23. Hargreaves IP, Duncan AJ, Heales SJR, Land JM. The effect of HMG-CoA reductase inhibitors on coenzyme Q10: possible biochemical/clinical implications. *Drug Saf*. 2005;28(8):659-676.
24. He CH, Xie LX, Allan CM, Tran UC, Clarke CF. Coenzyme Q supplementation or over-expression of the yeast Coq8 putative kinase stabilizes multi-subunit coq polypeptide complexes in yeast coq null mutants. *Biochim Biophys Acta*. 2014;1841(4):630-644.
25. Marin SE, Haas RH. Coenzyme Q10 and the treatment of mitochondrial disease. In: Hargreaves IP, Hargreaves AK, eds. *Coenzyme Q_{10}: From fact to fiction*. New York: Nova Science Publishers, Inc. 2015;85–107.
26. Liu YT, Hersheson J, Plagnol V, et al. Autosomal-recessive cerebellar ataxia caused by a novel ADCK3 mutation that elongates the protein: clinical, genetic and biochemical characterisation. *J Neurol Neurosurg Psychiatry*. 2014;85(5):493-498.
27. Mollet J, Delahodde A, Serre V, et al. CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures. *Am J Hum Genet*. 2008;82(3):623-630.
28. Horvath R, Czermin B, Gulati S, et al. Adult-onset cerebellar ataxia due to mutations in CABC1/ADCK3. *J Neurol Neurosurg Psychiatry*. 2012;83(2):174-178.
29. Lamperti C, Naini A, Hirano M, et al. Cerebellar ataxia and coenzyme Q10 deficiency. *Neurology*. 2003;60(7):1206-1208.
30. Terracciano A, Renaldo F, Zanni G, et al. The use of muscle biopsy in the diagnosis of undefined ataxia with cerebellar atrophy in children. *Eur J Paediatr Neurol*. 2012;16(3):248-256.
31. Sobreira C, Hirano M, Shanske S, et al. Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. *Neurology*. 1997; 48(5):1238-1243.
32. Di Giovanni S, Mirabella M, Spinazzola A, et al. Coenzyme Q10 reverses pathological phenotype and reduces apoptosis in familial CoQ10 deficiency. *Neurology*. 2001;57(3):515-518.
33. Smith KM, Matson S, Matson WR, et al. Dose ranging and efficacy study of high dose coenzyme Q10 formulations in Huntington's disease. *Biochim Biophys Acta*. 2006;1762(6):616-626.
34. Mathews RT, Yang L, Browne S, Baik M, Beal F. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci USA*. 1998; 95(15):8892-8897.
35. Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, et al. COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. *J Am Soc Nephrol*. 2007; 18(10):2773-2780.
36. Heeringa SF, Chernin G, Chaki M, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. *J Clin Invest*. 2011;121(5):2013-2024.
37. Montini G, Malaventura C, Salviat L. Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. *N Eng J Med*. 2008;358(26):2849-2850.
38. Desbats MA, Vetro A, Limongeli I, et al. Primary coenzyme Q10 deficiency presenting as fatal neonatal multiorgan failure. *Eur J Hum Genet*. 2015b;23(9):1254-1258.

39. Ozeir M, Muhlenhoff U, Webert R, et al. Coenzyme Q biosynthesis: CoQ6 deficiency. *Chem Biol*. 2011;18(9):1134-1142.
40. Desbats MA, Lunardi G, Doimo M, Trevisson E, Salviati L. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ10) deficiency. *J Inherit Metab Dis*. 2015;38(1):145-56.
41. Freyer C, Stranneheim H, Naess K, et al. Rescue of primary ubiquinone deficiency due to a novel COQ7 defect using 2,4-dihydroxybensoic acid. *J Med Genet*. 2015;52(11):779-783.
42. Koopman WJH, Beyrath J, Fung CW, et al. Mitochondrial disorders in children: toward development of small-molecule treatment strategies. *EMBO Mol Med*. 2016;8(4):311-327.
43. Chinnery P, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondria disorders. *Cochrane Database Syst Rev*. 2006; 25(1):CD004426.
44. Kerr DS. Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. *Mol Genet Metab*. 2010;99(3):246-255.
45. Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. *Int J Biochem Cell Biol*. 2014;49:105-111.
46. Geromel V, Darin N, Chretien D, et al. Coenzyme Q10 and idebenone in the therapy of respiratory chain diseases: rational and comparative benefits. *Mol Genet Metab*. 2002;77(1-2):21-30.
47. Nishikawa Y, Takahashi M, Yorifuji S, et al. Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome c oxidase deficiency: a 31P NMR study. *Neurology*. 1989;39(3):399-403.
48. Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. A randomized trial of coenzyme Q10 in mitochondrial disorders. *Muscle Nerve* 2010;42(5):739-748.
49. Ogasahara S, Yorifuji S, Nishikawa Y, et al. Improvement of abnormal pyruvate metabolism and cardiac conduction defect with coenzyme Q10 in Kearns-Sayre syndrome. *Neurology*. 1985;35(3):372-377.
50. Ihara Y, Namba R, Kuroda S, Sato T, Shirabe T. Mitochondrial encephalopmyopathy (MELAS): pathological study and successful therapy with coenzyme Q10 and idebenone. *J Neurol Sci*. 1989;90(3):263-271.
51. Abe K, Matsuo Y, Kadekawa J, Inoue S, Yanagihara T. Effect of coenzyme Q10 in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): evaluation by noninvasive tissue oximetry. *J Neurol Sci*. 1999; 162(1):65-68.
52. Liou CW, Huang CC, Lin TK, Tsai JL, Wei YH. Correction of pancreatic beta-cell dysfunction with coenzyme Q(10) in a patient with mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes syndrome and diabetes mellitus. *Eur Neurol*. 2000;43(1):54-55.
53. Ogasahara S, Nishikawa Y, Yorifuli S, et al. Treatment of Kearns-Sayre syndrome with coenzyme Q10. *Neurology*. 1986;36(1): 45-53.
54. Goda S, Hamada T, Ishimoto S, Kobayashi T, Goto I, Kuroiwa Y. Clinical improvement after administration of coenzyme Q10 in a patient with mitochondrial encephalomyopathy. *J Neurol*. 1987; 234(1):62-63.
55. Bendahan D, Desnuelle C, Vanuxem D, , et al. 31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. *Neurology*. 1992;42(6):1203-1208.
56. Fadic R, Johns DR. Clinical spectrum of mitochondrial diseases. *Semin Neurol*. 1996;16(1):11-20.
57. Chan A, Reichmann H, Kogel A, et al. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. *J Neurol*. 1998;245(10):681-685.
58. Bresolin N, Doriguzzi C, Ponzetto C, et al. Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. *J Neurol Sci*. 1990;100(1-2):70-78.
59. Matthews PM, Ford B, Dandurand RJ, et al. Coenzyme Q10 with multiple vitamins is generally ineffective in treatment of mitochondrial disease. *Neurology*. 1993;43(5):884-890.
60. Zierz S, von Wersebe O, Bleistein J, Jerusalem F. Exogenous Coenzyme Q (Coq) Fails to Increase Coq in Skeletal Muscle of Two Patients With Mitochondrial Myopathies. *J Neurol Sci*. 1990;95(3):283-290.
61. Chan A, Reichmann H, Kögel A, Beck A, Gold R. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. *J Neurol*. 1989;245(10):681-685.
62. Chan T, Teng S, Wilson J, Galati G, Khan S, O'Brien PJ. Coenzyme Q cytoprotective mechanisms for mitochondrial complex I cytopathies involves NAD(P)H Quinone oxidoreductase 1 (NQO1). *J Free Radic Res*. 2002;36(4):421-427
63. Enns GM, Kinsma SL, Perlman SL, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. *Mol Genet Metab*. 2012;105(1):91-102.
64. Martinelli D, Catteruccia M, Piemonte F, et al. EPI-743 reverses the progression of the pediatric mitochondrial disease. *Mol Genet Metab*. 2012;107(3):383-388.
65. Homstrom KH, Baird L, Zhang Y, et al. NrF2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. *Biol Open*. 2013;2(8):761-770.
66. Muller W, Reimers CD, Berninger T, et al. Coenzyme Q10 in ophthalmoplegia plus—a double blind, cross over therapeutic trial. *J Neurol Sci*. 1990;98(suppl):442.
67. Rodriguez MC, MacDonald JR, Mahoney DJ, Parise G, Beal MF, Tarnopolsky MA. Beneficial effects of creatine, CoQ10 and lipoic acid in mitochondrial disorders. *Muscle Nerve*. 2007;35(2): 235-242.
68. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, et al. Clinical applications of coenzyme Q10. *Front Biosci*. 2014; 19:619-633.
69. Katayama K, Fujita T. Studies on lymphatic absorption of 1', 2'-(3 H)-coenzyme Q10 in rats. *Chem Pharm Bull*. 1972;20(12): 2585-2592.
70. Bhagavan HN, Chopra RK, Craft NE, Chitchumroonchokchai C, Failla ML. Assessment of coenzyme Q10 absorption using an in vitro digestion-Caco-2 cell model. *Int J Pharm*. 2007;333(1-2): 112-117.
71. Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res*. 2006;40(5):445-453.
72. Aberg F, Appelkvist EL, Dallner G, Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch Biochem Biophys*. 1992;295(2):230-234.

73. Trevisson E, Dimauro S, Nava P, et al. Coenzyme Q10 deficiency in muscle. *Curr Opin Neurol*. 2011;24(5):449-456.
74. Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme 10 formulations. *Mitochondrion*. 2007;7(suppl):S78-S88.
75. Martinefski M, Samassa P, Buontempo F, Höcht C, Lucangioli S, Tripodi V. Relative bioavailability of coenzyme Q10 formulation for paediatric individualized therapy. *J Pharm Pharmacol*. 2017; 69(5):567-573. doi:10.1111/jphp.12613.
76. Miles MV, Horn P, Miles L. Bioequivalence of coenzyme Q10 from over-the counter supplements. *Nutr Res*. 2002;22(8): 919-929.
77. Weis M, Mortensen SA, Rassing MR, Møller-Sonnergaard J, Poulsen G, Rasmussen SN. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. *Mol Aspects Med*. 1994; 15(suppl): s273-s280.
78. Parikh S, Saneto R, Falk MJ, et al. A modern approach to the treatment of mitochondrial disease. *Curr Treat Options Neurol*. 2009;11(6):414-430.
79. Garcia-Corzo L, Luna-Sanchez M, Doerrier C, et al. Ubiquinol-10 ameliorates mitochondrial encephalopathy associated with CoQ10 deficiency. *Biochim Biophys Acta*. 2014;1842(7): 893-901.
80. Miles MV, Patterson BJ, Schapiro MB, et al. Coenzyme Q10 absorption and tolerance in children with Down syndrome: a dose ranging trial. *Pediatr Neurol*. 2006;35(1):30-37.
81. Itagaki S, Ochiai A, Kobayash M, Sugawara M, Hirano T, Iseki K. Grapefruit juice enhance the uptake of coenzyme Q10 in the human intestinal cell-line Caco-2. *Food Chem*. 2010;120(2): 552-555.
82. Kaikkonen J, Nyyssonen K, Tomasi A, et al. Antioxidative efficacy of parallel and combined supplementation with coenzyme Q10 d-alpha-tocopherol in mildly hypercholesterolemic subjects: a randomized placebo-controlled clinical study. *Free Radic Res*. 2000;33(3):329-340.
83. Molyneux SL, Young JM, Florkowski CM, et al. Coenzyme Q10: is there a clinical role and a case for measurement? *Clin Biochem Rev*. 2008;29(2):71-81.
84. Duncan AJ, Heales SJ, Mills K, Eaton S, Land JM, Hargreaves IP. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle and plasma by HPLC with a di-propoxy-coenzyme Q10 as an internal standard. *Clin Chem*. 2005;51(12): 2380-2382.
85. Yubero D, Montero R, Ramos M, et al. Determination of urinary coenzyme Q10 by HPLC with electrochemical detection: reference values for a paediatric population. *Biofactors*. 2015;41(6): 424-430.
86. Yubero D, Montero R, Artuch R, Land JM, Heales SJ, Hargreaves IP. Biochemical diagnosis of coenzyme Q10 deficiency. *Mol Syndromol*. 2014;5(3-4):147-155.
87. Shults CW, Beal F, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp Neurol*. 2004;188(2):491-494.
88. Rotig A, Appelkvist EL, Geromel V, et al. Quinone-responsive multiple respiratory chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet*. 2000;356(9227):391-395.
89. Pineda M, Montero R, Aracil A, et al. Coenzyme Q(10)-responsive ataxia: 2-year-treatment follow-up. *Mov Disord*. 2010;25(9): 1262-1268.
90. Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol*. 2002;59(10):1541-1550.
91. Lopez LC, Quinzii CM, Area E, et al. Treatment of CoQ10 deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. *PloS One*. 2010;5(7): e11897.
92. Duberley KE, Heales SJ, Abramov AY, et al. Effect of Coenzyme Q10 supplementation on mitochondrial electron transport chain activity and mitochondrial oxidative stress in Coenzyme Q10 deficient human neuronal cells. *Int J Biochem Cell Biol*. 2014; 50:60-63.
93. Duberley KE, Hargreaves IP, Chaiwatanasirikul KA, et al. Coenzyme Q10 quantification in muscle, fibroblasts and cerebrospinal fluid by liquid chromatography/tandem mass spectrometry using a novel deuterated internal standard. *Rapid Commun Mass Spectrom*. 2013;27(9):924-930.