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COENZYME Q10 AND ITS ROLE IN HUMAN HEALTH

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}), known as ubiquinone or ubidecarenone, is a fat-soluble, vitamin-like substance found throughout the body which is involved in various types of essential cellular process. Coenzyme Q is well defined as a crucial component of the oxidative phosphorylation process in mitochondria which converts the energy in carbohydrates and fatty acids into ATP to drive cellular machinery and synthesis. New roles for coenzyme Q in other cellular functions are only becoming recognized. The new aspects have developed from the recognition that coenzyme Q can undergo oxidation/reduction reactions in other cell membranes such as lysosomes, Golgi or plasma membranes. In mitochondria and lysosomes, coenzyme Q undergoes reduction/oxidation cycles during which it transfers protons across the membrane to form a proton gradient. The presence of high concentrations of quinol in all membranes provides a basis for antioxidant action either by direct reaction with radicals or by regeneration of tocopherol and ascorbate. Evidence for a function in redox control of cell signaling and gene expression is developing from studies on coenzyme Q stimulation of cell growth, inhibition of apoptosis, control of thiol groups, formation of hydrogen peroxide and control of membrane channels. Deficiency of coenzyme Q has been described based on failure of biosynthesis caused by gene mutation, inhibition of biosynthesis by HMG coA reductase inhibitors (statins) or for unknown reasons in ageing and cancer. Correction of deficiency requires supplementation with higher levels of coenzyme Q than are available in the diet.

KEYWORDS: Redox component, polyisoprenoid side-chain, Antioxidant radical, mitochondrial encephalomyopathy, Energy starvation, glycaemic control.

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone or ubidecarenone, is a fat-soluble, vitamin-like substance found throughout the body but especially in heart, liver, kidney, and brain [1,2,3,4]. CoQ_{10} is involved in a variety of essential cellular processes such as acting as a redox component of transmembrane electron transport systems in the respiratory chain of mitochondria and as a stabilizing agent in cellular membranes [5]. CoQ_{10} is an essential component for production of cellular energy in the form of adenosine triphosphate (ATP) [5]. CoQ10 can give up electrons easily thus acting as a powerful antioxidant against free radical [6]. Ninety five per cent of energy of the human body is generated this way [7, 8]. It is used as a nutritional supplement and also in the treatment of cardiovascular disorders such as angina pectoris, hypertension, and congestive heart failure [9]. Also, many studies have reported the immunostimulating action of CoQ_{10} [10]. It is thought that the incomplete and slow absorption of CoQ_{10} from the gastrointestinal tract is attributed to its poor water solubility and high molecular weight [11, 12]. Absorption follows the same process as that of lipids and the uptake mechanism appears to be similar to that of vitamin E, another lipid-soluble nutrient. This process in the human body involves the secretion into the small intestines of pancreatic enzymes and bile that facilitate emulsification and micelle formation that is required for the absorption of lipophilic substances [13]. Food intake (and the presence of lipids) stimulates bodily biliary excretion of bile acids and greatly enhances the absorption of CoQ_{10}. Exogenous CoQ_{10} is absorbed from the small intestinal tract and is best absorbed if it is taken with a meal. Serum concentration of CoQ_{10} in fed condition is higher than in fasting conditions [14, 15]. Data on the metabolism of CoQ_{10} in animals and humans are limited [16]. A study with ^{14}C-labeled CoQ_{10} in rats showed most of the radioactivity in the liver 2 hours after oral administration when the peak plasma radioactivity was observed, but it should be noted that CoQ_9 is the predominant form of coenzyme Q in rats [17]. It appears that CoQ_{10} is metabolised in all tissues, while a major route for its elimination is biliary and fecal excretion. After the withdrawal of CoQ_{10} supplementation, the levels return to normal within a few days, irrespective of the type of formulation used [18].

History

CoQ10 was first isolated from beef heart mitochondria by Dr. Frederick Crane of Wisconsin, U.S.A., in 1957 [19]. The same year, Professor Morton of England defined a compound obtained from vitamin A deficient rat liver to be the same as CoQ10 [20]. Professor Morton

introduced the name ubiquinone, meaning the ubiquitous quinone. In 1958, Professor Karl Folkers and coworkers at Merck, Inc., determined the precise chemical structure of CoQ10: 2, 3 dimethoxy-5 methyl-6 decaprenyl benzoquinone synthesized it, and were the first to produce it by fermentation. In the mid-1960's, Professor Yamamura of Japan became the first in the world to use coenzyme Q7 (a related compound) in the treatment of human disease: congestive heart failure. In 1966, Mellors and Tappel showed that reduced CoQ6 was an effective antioxidant [21, 22]. In 1972 Gian Paolo Littarru of Italy along with Professor Karl Folkers documented a deficiency of CoQ10 in human heart disease [23]. By the mid-1970's, the Japanese perfected the industrial technology to produce pure CoQ10 in quantities sufficient for larger clinical trials. Peter Mitchell received the Nobel Prize in 1978 for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory, which includes the vital protonmotive role of CoQ10 in energy transfer systems [24, 25, 26, 27]. In the early 1980's, there was a considerable acceleration in the number and size of clinical trials. These resulted in part from the availability of pure CoQ10 in large quantities from pharmaceutical companies in Japan and from the capacity to directly measure CoQ10 in blood and tissue by high performance liquid chromatography. Lars Ernster of Sweden enlarged upon CoQ10's importance as an antioxidant and free radical scavenger [28]. Professor Karl Folkers went on to receive the Priestly Medal from the American Chemical Society in 1986 and the National Medal of Science from President Bush in 1990 for his work with CoQ10 and other vitamins.

Sources of Q10

Besides endogenous synthesis, CoQ10 is also supplied to the organism by various foods.

Dietary Sources: CoQ10 levels in selected food are as under [29].

Table 1: Different CQ10 Sources.

Types of food	Different sources	CQ_{10} con-centration [mg/kg]	Types of food	Different sources	CoQ_{10} con-centration [mg/kg]	Types of food	Different sources	CoQ_{10} con-centration [mg/kg]
Beef	Heart	113	**oils**	Sun flower	4 - 15	**Vegetables**	Parsley	8 - 26
	Liver	39-50		olive	4 - 160		Broccoli	6 - 9
	Muscle	26-40		soyabean	54 - 280		Cauliflower	2 - 7
Pork	Heart	118 – 128	**Nuts**	Peanuts	27		Chinese Cabbage	2 - 5
	Muscle	13.8 – 45		Sea same seeds	18-23	**Fruits**	Avocado	10
Chicken	116.2 – 132.2			Hazelnuts	17		Black currant	3
				Almonds	5 – 14		Orange	1 – 2

Chemistry and Bioavailability of Cq10

CoQ10 belongs to the group of quinones. It is composed of a p-benzoquinone ring system and a polyisoprenoid side-chain. The length of the side-chain is responsible for the lipophilicity of the molecule. The side-chain in CoQ10 consists of ten isoprene units. This makes the molecule highly lipophilic [30]. Therefore CoQ10 can freely move within the cellular membranes. Unfortunately, the bioavailability of CoQ10 is very low in the intestines after oral application [31]. Several attempts have been made in the last few years to improve the intestinal absorption of CoQ10. Researchers either tried to modify the molecular structure or change the compositions of the CoQ10 preparations to improve the bioavailability. As a matter of fact, the investigation of both structure modifications and delivery systems revealed that bioavailability of CoQ10 after oral application can be significantly enhanced choosing a proper formulation. [32, 33]

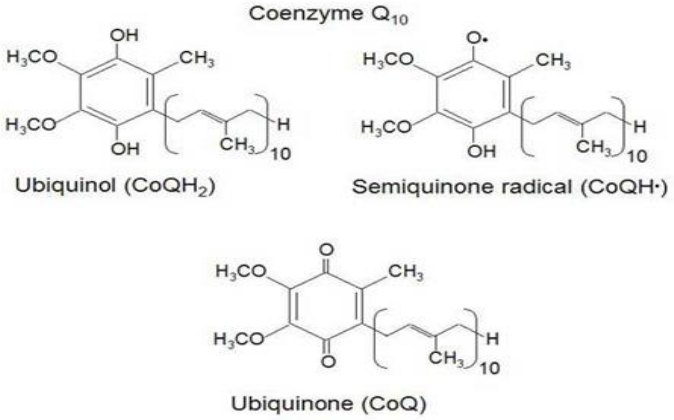

Figure 1: Chemistry of CQ10.

Biosynthesis

The endogenous biosynthesis is quite a complex process which involves at least ten genes. Most of the proteins of these genes have not been yet purified and, although the regulation of this biosynthesis pathway is largely unknown [34][35], it is up-regulated under oxidative stress in rats [36]. Starting from acetyl-CoA, a multi step process of mevalonate pathway produces farnesyl-PP (FPP), the precursor for cholesterol, CoQ10 and isoprenylated protein. The pathway involves HMG Co-A reductase the long isoprenoid side-chain of CoQ10 is synthesised by condensing FPP by enzymes [37]. The next step involves condensation of this polyisoprenoid side-chain with 4 hydroxybenzoate, catalysed by polyprenyl-4-hydroxybenzoate transferase. Hydroxybenzoate is synthesized from tyrosine or phenylalanine. In addition to mitochondria, these initial reactions also occur in the endoplasmic reticulum and peroxisomes indicating multiple sites of synthesis [38].

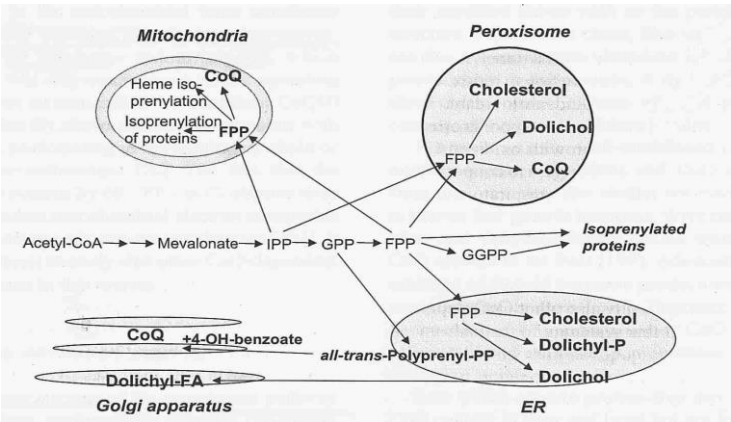

Figure 2: Biosynthetic pathway.

BIOCHEMICAL ASPECTS

Role in Mitochondrial Electron Transport

CoQ_{10} is fat-soluble and is therefore mobile in cellular membranes; it plays a unique role in the electron transport chain (ETC). In the inner mitochondrial membrane, electrons from NADH and succinate pass through the ETC to oxygen, which is reduced to water. The transfer of electrons through ETC results in the pumping of H+ across the membrane creating a proton gradient across the membrane, which is used by ATP synthase (located on the membrane) to generate ATP. CoQ_{10} functions as an electron carrier from enzyme complex I and enzyme complex II to complex III in this process. This is crucial in the process, since no other molecule can perform this function. Recent research now establishes that Vitamin K_2 co-performs this role with CoQ10 [39]. Thus, CoQ_{10} functions in every cell of the body to synthesize energy.

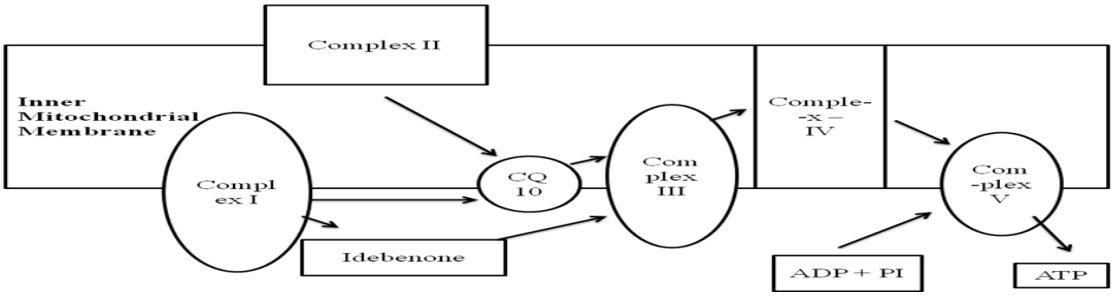

Figure 3: CoQ10 in the mitochondrial electron transport chain. Coenzyme Q10 is a component of the electron transport chain located within the inner mitochondrial membrane, required for oxidative phosphorylation leading to ATP generation. It accepts electrons from complexes I (NADH-ubiquinone oxidoreductase) and II (succinate dehydrogenase) for transfer to complex III (ubiquinol-cytochrome c reductase). Idebenone is similarly involved in transfer of electrons from complex I to complex III.

Antioxidant Activity

Coenzyme Q is well located in membranes in close proximity to the unsaturated lipid chains to act as a primary scavenger of free radicals. The amount of CoQ in many membranes is from three to 30 times the tocopherol content [40]. Since much of the coenzyme Q in cell membranes is in the quinol form [41], it can be a very effective antioxidant [42]. Even more important is the presence of enzymes in all membranes which can reduce any coenzyme Q quinone radical generated by reaction with lipid or oxygen radicals. At least three enzymes are known which can keep the coenzyme Q reduced in plasma and endomembranes [43]. These enzymes are (1) NADH cytochrome b5 reductase [44], (2) NADH/NADPH oxidoreductase (DT diaphorase [44]), (3) NADPH coenzyme Q reductase[45]. In mitochondria the NADH and succinate dehydrogenases can keep coenzyme Q partly reduced. Reductases 1 and 3 in endomembranes can be especially important by one electron transfer to rereduce any semiquinone generated by reaction of quinol with a radical. The DT diaphorase is unique since it can directly reduce, by 2 electron transfer, any quinine formed without intermediate formation of the semiquinone.

Under conditions of oxidative stress induced by nutritional lack of selenium and tocopherol, the coenzyme Q in membranes is greatly increased. The amount of DT diaphorase attached to membranes where it can reduce coenzyme Q is also remarkably increased [46]. Similar decrease in tocopherol induced by peroxisomal proliferator is accompanied by a large increase in coenzyme Q [40]. A direct demonstration of the effectiveness of coenzyme Q as an antioxidant can be shown with coenzyme Q deficient yeast. A yeast mutant deficient in coenzyme Q synthesis shows more lipid peroxide formation than normal yeast [47]. Another direct demonstration of elimination of free radicals is shown by coenzyme Q treatment of skin in older persons. Luminescence from free radicals is eliminated when a skin cream containing coenzyme Q is applied [48]. In addition to direct antioxidant radical scavenging, the quinol can rescue tocopheryl radicals produced by reaction with lipid or oxygen radicals by direct reduction back to tocopherol without coenzyme Q in a membrane, regeneration of tocopherol is very slow [49]. The regeneration of tocopherol can also be observed in low density lipoprotein where a small amount of coenzyme Q protects a larger amount of tocopherol. This function is presumably favored by the high percent of quinol present in blood [50, 51]. There is some evidence that the coenzyme Q dependent electron transport across the plasma membrane can be used to regenerate ascorbate outside the cell from ascorbate radical (monodehydroascorbate [52]). Ascorbate inside the cell can be regenerated by a

glutathione based system. Regeneration outside requires electron transfer through the plasma membrane, some of which depends on the presence of coenzyme Q in the membrane.

Table-2. Coenzyme Q in Cell Membranes and Relation to Tocopherol {Data based on [53, 40].}

Rat Liver Membranes	CoQ/_toc mol/mol	CoQ g/mg protein
Mitochondria (cristae)	35	1.9
Plasma membrane	21	0.7
Peroxisomes	3	0.3
Lysosomes	3	1.9
Golgi membranes	1	2.6
Endoplasmic reticulum	1	0.2

Clinical Aspects of Coq10

Primary CoQ10 Deficiency

Ogashara et al. described the first patients (two sisters) with primary CoQ10 deficiency in 1989. The patients, aged 12 and 14, had progressive muscle weakness, abnormal fatigue, and central nervous system dysfunction from early childhood. The CoQ10 concentration in their muscles was markedly decreased, being about 5% of normal, but was normal in serum and cultured fibroblasts [54]. It was concluded that the primary defect in these sisters probably involved a tissue-specific isozyme in the CoQ10 synthetic pathway of muscle and brain, and both patients improved remarkably with oral CoQ10[54]. In 2000, Rötig reported a much more dramatic variant of CoQ10 deficiency, which presented as infantile mitochondrial encephalomyopathy (a CoQ10 biosynthetic defect) with widespread CoQ10 deficiency and nephritic syndrome [55]. In 2007, Mollet and colleagues documented molecular defects in three of the nine genes required for CoQ10 biosynthesis, all of which are associated with early and severe clinical presentations [56]. CoQ10 deficiency can be classified into four major clinical categories as below, probably representing a mixture of primary and secondary CoQ10 deficiency.

1. Myopathy with recurrent myoglobinuria and CNS involvement.
2. Cerebellar ataxia with variable CNS involvement.
3. Isolated myopathy.
4. Infantile mitochondrial encephalomyopathy.

The most severe and earliest presenting variant of CoQ10 deficiency is infantile mitochondrial encephalomyopathy, which occurs due to defects in CoQ10 biosynthesis. More

recently, genetic defects in steps of CoQ10 biosynthesis have been characterised (CoQ2, PDSS1, PDSS2) with the likelihood that other steps will also be shown to be implicated in clinical disorders and with the corollary that CoQ10 supplementation may confer clinical benefit [57]. Exogenous CoQ10 supplementation has been shown to lead to improvements in the status of patients with CoQ10 deficiency [54, 55, 58, 59, 60].

Coq10 and Its Implication in Disease States

Statin Myopathy

The underlying pathophysiology of statin-induced myopathy is unknown, but one postulated mechanism is mitochondrial dysfunction through depletion of CoQ10 [61], since CoQ10 is an essential cofactor in the mitochondrial electron transport chain [62] and mitochondria are essential for normal muscle function. Post-marketing studies have indicated up to 13.6% of statin treated patients experience some degree of myopathy [63], and as targets for cholesterol reduction become progressively lower, necessitating higher statin doses, the risk of side effects, particularly myopathies, has increased [64,65]. A small number of studies have provided some evidence of impaired mitochondrial function in statin-induced myopathy. De Pinieux et al. observed significant elevations in the lactate to pyruvate ratio, an indirect marker of mitochondrial dysfunction, in statin-treated hypercholesterolaemic patients compared to untreated patients ($p<0.02$) and controls ($p<0.001$) [66], Additionally, four case reports of statin induced myopathy, despite normal creatine kinase levels, demonstrated increased intramuscular lipid, diminished cytochrome oxidase staining and ragged red muscle fibres in muscle biopsy samples, findings consistent with mitochondrial dysfunction [67]. These abnormalities resolved following discontinuation of statin therapy in the three patients who had repeat biopsies. In contrast, a study by Lamperti et al. revealed that only 2 of 18 muscle biopsies taken from patients with statin-induced myopathy showed evidence of mitochondrial dysfunction, along with mildly decreased intramuscular CoQ10 levels [68]. To date, only two randomised trials have investigated the effect of CoQ10 administration on statin-induced myalgia, with contrasting results [69, 70]. In the first study, Caso et al. Reported a 40% reduction in myopathic pain ($p<0.001$) after 30 days of 100 mg/day of CoQ10 supplementation compared with no change following 400 IU/day of vitamin E in patients with statin-related myopathy on concurrent statin treatment [69]. This trial lacked a placebo-control design and patients were not on a standardised dose or type of statin. In the second study, we randomised 44 patients with prior statin-induced myalgia to treatment with 200 mg/day of CoQ10 or placebo for 12 weeks in combination with upward dose titration of

simvastatin at 10 mg/day, doubling every 4 weeks if tolerated to a maximum of 40 mg/day [70]. Plasma CoQ10 increased with supplementation, but there were no significant differences in the myalgia score change (median 6.0 vs 2.3, p = 0.63), in the number of patients who tolerated 40 mg/day simvastatin (CoQ10 16/22 (73%) vs 13/22 (59%), p = 0.34); or in the number remaining on any simvastatin dose (16/22 (73%) vs 18/22 (82%), p=0.47), between statin and CoQ10 therapy and statin alone. Adequately powered randomised controlled trials are now required to establish if there is a role for CoQ10 supplementation in reducing or eliminating statin myopathy. Considerations for such trials should include clearly defined myopathy by statin withdraw and rechallenge, initiation of CoQ prior to statin therapy, a more objective myopathic pain score and muscle biopsy studies. An important factor contributing to statin related myopathy may be genetic susceptibility to muscle disorders and underlying metabolic myopathies. Oh et al. reported a 2.33–2.58 fold increase in the relative risk of statin intolerance associated with polymorphisms in the *CoQ2* gene [71]. Furthermore, Vladutiu et al. observed a four-fold increase in mutant alleles of common mutations for three metabolic myopathies: carnitine palmitoyltransferase II deficiency, McArdle's disease and myoadenylate deaminase deficiency, in individuals with primarily statin-induced myopathies [72]. Individuals with mutations for underlying metabolic myopathies may therefore represent a subgroup of the statin-treated population for whom CoQ10 may be more likely to confer a clinical benefit. More recently the CYP2D6*4 polymorphism, which reduces statin metabolism, has been linked to statin-induced muscle effects [73]. Improved identification and detection of relevant susceptibility genotypes may allow CoQ10 to be more appropriately targeted in patients with statin-myalgia, leading to a further enhanced safety profile for statins.

Heart Failure

Given the importance of CoQ10 in mitochondrial electron transport and ATP synthesis, its depletion has been postulated to compromise myocardial energy generation and lead to "Energy starvation" of the myocardium, considered to be a pathogenic mechanism of chronic heart failure (CHF) [74]. Recent evidence suggests a role for CoQ10 as a predictor of outcomes and also as an adjunctive clinical therapy and supplementation is routine in some countries, such as Japan [74]. Myocardial depletion of CoQ10 has been demonstrated in heart failure and the severity of the deficiency has been found to correlate with the severity of symptoms, with patients in NYHA class IV having significantly lower CoQ10 in endomyocardial biopsy samples than those in NYHA class I [75]. This myocardial CoQ10

deficiency in patients with cardiomyopathy was also reversed by CoQ10 therapy [75]. An interesting observation is that total cholesterol is related to survival in CHF [76, 77]. In the study of Rauchhaus et al. serum total cholesterol was independently associated with total mortality in a CHF cohort, with increasing total serum cholesterol predicting survival (hazard ratio 0.64, 95% CI 0.48 to 0.86), independent of the aetiology of CHF, age, left ventricular ejection fraction and exercise capacity [76]. Postulated mechanisms for this association were that cholesterol may be limiting lipo-polysaccharide-induced production of cytokines and that high cholesterol may provide "greater metabolic reserve" to deal with the CHF syndrome. The authors did not, however, make reference to CoQ10, which is known to correlate with plasma total and LDL-cholesterol concentration [78], and which could be postulated to explain the worse outcomes seen in patients with low cholesterol in CHF patients. Cardiac cachexia (lean tissue wasting associated with heart failure) was not thought to be an important mechanism, given that lipid levels were no different between patients with and without cachexia and that survival was independent of the presence of cachexia [76].

In a recent observational study, we showed that CoQ10 levels, but not statin therapy (known to lower CoQ10 in heart failure [79]) were an independent predictor of total mortality in an observational study of 236 subjects with heart failure [80]. We were unable to confirm that cholesterol was associated with survival in this cohort [80], although our patients were older and followed for longer than the cohort of Rauchhaus et al.[76], Meta-analyses of CoQ10 supplementation in CHF have been undertaken [81,82], Soja and Mortensen [81] reviewed eight doubleblind placebo-controlled studies and reported a significant improvement in stroke volume, ejection fraction, cardiac output, cardiac index and end diastolic volume index, as a consequence of CoQ10 supplementation [83-90]. In a more recent meta-analysis, Sander et al. reviewed eleven studies [82], ten that evaluated ejection fraction [83,85-87,90-95] and two that evaluated cardiac output [89,91] with CoQ10 doses ranging from 60-200 mg/ day and treatment periods ranging from 1-6 months. Overall, a 3.7% (95%CI 1.59-5.77) net improvement in the ejection fraction was found, and cardiac output was increased on average of 0.28 L/minute (95%CI 0.03-0.53) [82]. An international, randomised, double-blind multi-centre intervention study, "Q-SYMBIO" has been initiated with CoQ10 supplementation in CHF patients and focus on symptoms, biomarker status (BNP) and long-term outcomes [74]. This study is expected to report in 2009. Coupled with the findings of the meta-analyses [81,82] a positive result to Q-SYMBIO may be expected to increase the acceptance of CoQ10 as an adjunctive therapy in addition to the current medical strategies.

Interest has recently focussed on whether statins may confer benefit or not in patients with CHF, given the likely underlying ischemic aetiology in many patients [96]. However, the Controlled Rosuvastatin Multinational Trial in heart Failure (CORONA) investigators failed to show a reduction in major vascular events in older patients with systolic heart failure [97]. One explanation for this may be the reduction in CoQ10, as we have shown to occur in patients with non-ischaemic heart failure [79].We showed that 40 mg atorvastatin led to a 33% reduction in CoQ10 levels in non-ischaemic heart failure subjects, though this did not compromise improvements in endothelial function [79]. A significant association ($r = -0.585$, $p = 0.011$), between CoQ10 reductions and improvement in endothelial function as measured in the resistance arteries with forearm plethysmography suggested that the improvement in endothelial function with atorvastatin therapy is mediated by "non-lipid pleiotropic" pathways.

This study indicates a role of CoQ10 as a potential surrogate marker for improvement in endothelial function in resistance vessels. Given these observations and the complex interplay of cholesterol, statin therapy and clinical outcomes in heart failure, future trials incorporating a CoQ10 supplementation arm together with statin may be expected to confer improved clinical outcomes that CORONA did not show [97]. We have shown that CoQ10 predicts mortality in heart failure, and in all of the intervention trials undertaken to date, those achieving higher plasma CoQ10 levels showed better clinical outcomes [74]. Hence there may be a case for measurement of plasma CoQ10 levels, in order to identify those subjects at increased risk of mortality and who might benefit from CoQ10 intervention [80].

Myocardial `Protection in Cardiac Surgery

CoQ10 supplementation in pre-operative cardiac patients improved right and left ventricular myocardial ultrastructure, which was measured by light microscopy both pre and postoperative [98]. Researches even revealed that pretreatment with CoQ10 is effective in preserving heart function following coronary artery bypass surgery (CABG) and valvular surgery [99]. Naylar worked with rabbit heart model of coronary insufficiency and reperfusion, presented with CoQ10 role in preserving an oxygen deficient myocardium [100].

Hypertension

There are not very many studies on the role of CoQ10 in hypertension [101-103]. In earlier studies, Yamagami *et al.* used CoQ10 in 29 patients with hypertension with some success. In a randomized double blind trial on 59 patients receiving antihypertensive drugs, the effects of

oral treatment with CoQ10 (60mg twice daily) were compared for 8 weeks in 30 intervention group and 29 control group patients known to have hypertension and presenting with acute CAD [103]. After 8 weeks of follow-up, the following indices were reduced in the CoQ10 group: systolic and diastolic blood pressure, fasting and 2-h plasma insulin, glucose, triglycerides, lipid peroxides, malondialdehyde and diene conjugates. The following indices were increased; HDL cholesterol, vitamins A, C, E and beta-carotene ($P<0.05$).

These findings indicate that treatment with CoQ10 decreases blood pressure possibly by decreasing oxidative stress and insulin response in patients with known hypertension receiving conventional antihypertensive drugs. In a recent study by Langsjoen *et al.* [103] in 109 patients with known essential hypertension, CoQ10 (225 mg/day average) was administered to achieve serum level of 2 ug/ml, in conjunction with anti-hypertensive drugs. There was a need to withdraw one to three drugs in 51 % of patients. The decrease in systolic blood pressure was from 159 to 147 mmHg, mean and in diastolic blood pressure from 94 to 85 mmHg. In a meta-analysis of the clinical trials CoQ10 has shown the potential in hypertensive patients to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg without significant side effects [104]. A further study [105], showed that CoQ10 causes a significant decrease in serum catecholamines and possibly reduces peripheral vascular resistance.

The available data indicate that a double blind randomized study should be conducted with higher doses (100-200 mg/day) of CoQ10 with a long-term follow up. to CoQ10.HDL cholesterol showed a significant increase in the intervention group. CoQ10 treatment was also associated with significant reductions in thiobarbituric acid reactive substances, malondialdehyde and diene conjugates indicating an overall decrease in oxidative stress. The effects of the administration of CoQ10 (5mg/kg/day) (group A, n=10) and placebo (group B, n=10) were compared over 24 weeks in a randomized, single blind controlled trial [106]. There were two groups of rabbits receiving a Tran's fatty acid rich diet (5-8g/day) for 36 weeks. Oxidized rabbits chow with vitamin C plus ferric chloride was administered for 4 weeks in all rabbits. Intervention with CoQ10 after feeding of TFA rich diet was associated with a significant decline in thiobarbituric acid reactive substances (TBARS), diene conjugates and malondialdehyde, as well as an increase in plasma levels of vitamin E in the CoQ10 group compared to placebo group. The aortic and coronary artery plaque quality also showed beneficial effects which would be discussed later [107]. The antihypertensive effect of CoQ10

occurs gradually over several months, and the CoQ10 dose required for effectiveness varies between patients [108]. The mechanism for the hypotensive action of CoQ10 may be through CoQ10H2 acting as an antioxidant, decreasing the oxidative stress known to occur in hypertension [109]. In this role, CoQ10H2 may counteract vasoconstriction resulting from impaired ability of the endothelium to induce nitric oxide mediated relaxation of underlying smooth muscle [109] Further studies on the role of CoQ10 as an antihypertensive agent are required, with double-blind, randomised, placebo control, and adequate supplementation for efficacy which will require analysis of plasma CoQ10 levels.

Type 2 Diabetes and Insulin Resistance

A growing body of evidence indicates that oxidative stress plays a critical role in the pathogenesis of type 2 diabetes mellitus and its complications [110]. CoQ10 deficiency in type 2 diabetes results from impaired mitochondrial substrate metabolism [111] and increased oxidative stress [110]. In diabetes, CoQ10 deficiency is thought to contribute to endothelial dysfunction, and may also be linked to impaired beta-cell function and the development of insulin resistance [112]. Low plasma CoQ10 concentrations have been negatively correlated with poor glycaemic control and diabetic complications [113] Since CoQ10 plays an important role in the mitochondrial electron transport chain, and as a potent antioxidant, oral supplementation may be an attractive therapy in type 2 diabetes.

Accordingly, a number of clinical trials have shown that CoQ10 can improve glycaemic control, [114, 115] and lower plasma insulin; 104 although these findings are inconsistent with other studies. In addition, several trials have demonstrated a significant blood pressure lowering effect of CoQ10 in patients with type 2 diabetes.[114, 115] Furthermore, Watts et al. reported an improvement in endothelial function of conduit arteries (i.e. flow mediated dilation of the brachial artery) following 12 weeks of oral CoQ10 therapy in dyslipidemic patients with type 2 diabetes [116]. Conversely, two further trials in type 2 diabetic patients failed to show any improvement in microcirculatory function with CoQ10 monotherapy, suggesting that the effect of CoQ10 may be specific to the vascular bed [117, 118]. Playford et al. did however, observe a significant increase in endotheliumdependent microcirculatory perfusion in type 2 diabetes, with combined CoQ10 and fenofibrate therapy, suggesting that CoQ10 may have the potential to augment the benefits of PPAR-α agonists on vascular function [117]. CoQ10 supplementation may also enhance the ability of other anti-atherogenic

agents such as statins [112]. Further studies, including clinical outcome trials are required to confirm whether there is a role for CoQ10 in treatment of diabetes and its complications.

Malignancy

CoQ10 may have a role as adjunctive therapy in cancer. In the 1990s there were reports describing regression of metastases in breast cancer patients [119], and suggested CoQ10 deficiency in cancer patients [120], More recently, patients with melanoma were found to have significantly lower plasma CoQ10 levels than controls, and patients who developed metastases had significantly lower plasma CoQ10 compared to those in the metastasis-free subgroup, such that plasma CoQ10 concentrations were a significant predictor of metastasis [121]. Co-supplementation of CoQ10 (100 mg/day), riboflavin (10 mg/day) and niacin (50 mg/day) in postmenopausal breast cancer patients treated with Tamoxifen (10 mg twice daily) counteracted Tamoxifen-induced hyperlipidaemia to normal levels [122]. It has also been suggested that CoQ10 may protect the heart from anthracycline-induced cardiotoxicity [123], and additionally that it may stimulate the immune system [124]. However, there are some concerns regarding CoQ10 supplementation in cancer patients receiving some other anti-cancer treatments, for example, Brea-Calvo et al. found an increased concentration of CoQ10 (due to increased biosynthesis) in cancer cell lines after chemotherapy treatment with camptothecin, etoposide, doxorubicin and methotrexate [125]. Inhibition of CoQ10 biosynthesis enhanced camptothecin cytotoxicity, suggesting that CoQ10 increase is implicated in the cellular defence under chemotherapy treatment, and may contribute to cell survival [125]. Further research into the use of CoQ10 as an adjuvant treatment in cancer is therefore required.

Parkinson's Disease

Parkinson's disease (PD) is a degenerative neurological disorder characterised by tremor, rigidity and slowness of movement, believed to result from a progressive loss of dopaminergic neurons in the substantia nigra [126]. Although the pathological cause of PD is not well understood, mitochondrial dysfunction and oxidative stress are key features of this disorder. Initial evidence implicating mitochondrial respiratory chain dysfunction in PD came from findings that the mitochondrial complex I inhibitor MPTP induces a parkinsonian syndrome [127]. Subsequent investigations have demonstrated reduced activity of complex I in platelet mitochondria of PD patients [128], and also in the substantia nigra, but not other areas of the brain in individuals with PD [129], CoQ10 concentrations in platelet mitochondria have

been shown to be significantly lower in PD patients compared to matched controls and to correlate with complex I and II/III activity, suggesting that CoQ10 depletion may contribute to cellular dysfunction in PD [130]. Furthermore, the CoQ10 ratio of the oxidised to the reduced form is elevated in parkinsonian patients, suggesting increased oxidative stress in PD [131]. Taken together, these findings and the dual function of CoQ10 as both an electron acceptor for complexes I and II and a potent antioxidant [62], provide support for the idea that CoQ10 may be a therapeutic strategy in PD. Oral CoQ10 administration in PD patients has been shown to increase plasma CoQ10 levels [132], and has been reported to be safe and well tolerated [133-137] at doses as high as 2400 mg [135]. Shults et al. investigated the effects of CoQ10 in early PD and found that 1,200 mg/day of CoQ10 slows the progressive deterioration of functions in PD as indicated by the total Unified Parkinson Disease Rating Scale (UPDRS), although it did not affect the UPDRS motor score or postpone the onset of symptomatic therapy [134]. In addition, CoQ10 at a dose of 1,200 mg/day was associated with improved complex I activity in this trial [134]. Another trial demonstrated improved motor function in patients with early PD following six months of treatment with up to 1,500 mg/day of CoQ10 [138], however this study was not placebo controlled. In contrast, other trials have failed to demonstrate significant beneficial effects of CoQ10 in either early PD patients or in those receiving symptomatic therapy [135-137]. Large phase III trials are needed to confirm the positive findings of the study by Shults et al [134] and planning is currently underway for one such trial in patients with early PD. [139]. It is anticipated that 600 patients will be randomised to 1,200, or 2,400 mg CoQ10/day or placebo for a 16 month follow-up period, with a primary outcome of the change in total UPDRS or to the need for symptomatic therapy. The findings from this trial may help establish whether CoQ10 is an appropriate neuroprotective agent for PD.

Huntington's Disease (HD)

As in PD, there have been considerable efforts to determine whether CoQ10 could provide a neuroprotective effect. Ten subjects with HD were studied in a six-month open-label trial of tolerability and efficacy of CoQ10. Doses ranged from 600 to 1,200 mg per day, with no significant effect on clinical scores at three or six months [140]. In addition to clinical endpoints, proton magnetic resonance spectroscopy (1H-MRS) has been used in HD as a marker of CoQ10 effects. Increased lactate concentrations in the cerebral cortex and basal ganglia, as measured by 1H-MRS, have been shown to decrease with CoQ10 administration, and subsequently elevate upon withdrawal of treatment [141]. This finding supports the

predicted metabolic effect of oral CoQ10 in cerebral tissue, and is suggestive of an effect upon mitochondrial metabolism. In 2001 the Huntington Study Group published the CARE-HD trial, a randomized, placebo-controlled, multicenter, double-blind trial of CoQ10 300 mg twice daily in 174 subjects with early HD [142]. This therapy was compared with remacemide 600 mg daily, combination therapy, or placebo. Patients were followed every four to five months for 30 months, at which point no significant reduction in functional decline was observed with any therapy. However, CoQ10 treatment resulted in a trend toward fewer declines in total functional capacity of the Unified HD Rating Scale (UHDRS), the primary endpoint of the trial. This benefit was observed only after a year of treatment, thus a symptomatic effect of CoQ10 is unlikely to explain it. Interestingly, secondary analyses of functional and cognitive decline showed significant slowing with CoQ10 treatment. While this study was powered to detect 35%–40% reduction in decline, detection of smaller benefits and even confirmation of the effects seen in this study would require a prohibitively large sample size.12,46,85 Pre-2CARE was a small, pilot, open-label, dose-ranging study in 20 HD and six healthy subjects [143]. CoQ10 was administered at doses of 1,200 mg daily for one month, 2,400 mg daily for the next month, and then 3,600 mg daily continued for 12 weeks. An ongoing large phase III clinical trial of high dose CoQ10 in HD (2CARE – NCT00608881) is now testing these potential effects. This trial has an estimated enrollment of 608 patients, and will compare the effects of CoQ10 2400 mg/day with placebo for five years on change in total functional capacity.

CONCLUSIONS

CoQ10 deficiency has been implicated in several clinical disorders and in some areas there is a rationale for supplementation therapy. The case for measurement of CoQ10 is related to the relationship between levels and outcomes, as in CHF, where it may identify individuals most likely to benefit from supplementation therapy. Where supplementation is occurring plasma CoQ10 levels should be monitored to ensure efficacy, especially given the variable bioavailability between commercial formulations and known inter-individual variation in CoQ10 absorption [144] Furthermore, an understanding of biological variation, the reference change and least significant change values are important to determine whether a significant change has occurred, whether a reduction, for example as a result of statin therapy or an increase, with supplementation. Emerging evidence will determine whether CoQ10 does indeed have an important clinical role and in particular, whether there is a case for measurement. There is an urgent need to identify agents that will provide neuroprotection and

slow disease progression in several diseases that have an enormous collective impact on our society.

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