

Coenzyme Q₁₀: Is There a Clinical Role and a Case for Measurement?

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Abstract

Coenzyme Q₁₀ (CoQ₁₀) is an essential cofactor in the mitochondrial electron transport pathway, and is also a lipid-soluble antioxidant. It is endogenously synthesised via the mevalonate pathway, and some is obtained from the diet. CoQ₁₀ supplements are available over the counter from health food shops and pharmacies. CoQ₁₀ deficiency has been implicated in several clinical disorders, including but not confined to heart failure, hypertension, Parkinson's disease and malignancy. Statin, 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor therapy inhibits conversion of HMG-CoA to mevalonate and lowers plasma CoQ₁₀ concentrations. The case for measurement of plasma CoQ₁₀ is based on the relationship between levels and outcomes, as in chronic heart failure, where it may identify individuals most likely to benefit from supplementation therapy. During CoQ₁₀ supplementation plasma CoQ₁₀ levels should be monitored to ensure efficacy, given that there is variable bioavailability between commercial formulations, and known inter-individual variation in CoQ₁₀ absorption. Knowledge of biological variation and reference change values is important to determine whether a significant change in plasma CoQ₁₀ has occurred, whether a reduction for example following statin therapy or an increase following supplementation. Emerging evidence will determine whether CoQ₁₀ does indeed have an important clinical role and in particular, whether there is a case for measurement.

Introduction

CoQ₁₀, a 1,4-benzoquinone with a 50-carbon isoprenoid side chain, was first isolated from beef heart mitochondria by Frederick Crane of Wisconsin, USA, in 1957.¹ Various CoQ homologues, containing different numbers of isoprenoid units in the sidechain, exist and both CoQ₉ and CoQ₁₀ are present in human plasma. The latter is the dominant homologue.² CoQ₁₀ is present in the body in both the reduced (ubiquinol, CoQ₁₀H₂) and oxidised (ubiquinone, CoQ₁₀) forms. Oxidised CoQ₁₀ is reduced to CoQ₁₀H₂ in the mitochondria by flavoenzymes including mitochondrial succinate dehydrogenase and NADH dehydrogenase.³ CoQ₁₀ is lipophilic and transported in lipoprotein particles in the circulation. It is not surprising therefore that plasma CoQ₁₀ correlates positively with plasma total cholesterol and LDL-cholesterol.⁴⁻¹¹ CoQ is synthesised in the body, and is also obtained from the diet, with meat products being the largest source in the normal diet.¹²

CoQ₁₀ is an essential cofactor in mitochondrial oxidative phosphorylation, and is necessary for ATP production (Figure 1). In this role, CoQ₁₀ acts as a mobile electron carrier, transferring electrons from complex I (NADH coenzyme Q

reductase) to complex III (cytochrome bc₁ complex) or from complex II (succinate dehydrogenase) to complex III. The reduced form of CoQ₁₀ is also an antioxidant, and is the only endogenously synthesised lipophilic antioxidant. It can act as an antioxidant directly, protecting biological membranes against oxidation,¹³ as well as inhibiting the peroxidation of lipoprotein lipids present in the circulation.¹⁴ Indeed, supplementation with exogenous CoQ₁₀ has been shown to lead to an increase in the CoQ₁₀H₂ content of LDL, and a decrease of their peroxidisability.¹⁵ As an antioxidant, CoQ₁₀H₂ may also have a role recycling α -tocopherol, as reviewed by Sohal.¹⁶

Measurement of CoQ₁₀

Methodological Aspects

CoQ₁₀ is almost always measured by high performance liquid chromatography (HPLC) after extraction from plasma or tissue. Because of the highly hydrophobic nature of CoQ₁₀, it is usually separated on a highly hydrophobic reverse-phase column such as a C18-column with a high carbon load, with a mobile phase based on lower alcohols, sometimes with hexane or heptane included.

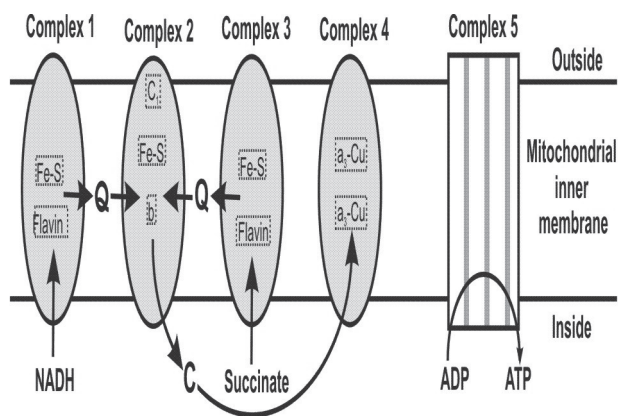


Figure 1. The mitochondrial electron transport chain. NADH = nicotinamide adenine dinucleotide, **Q** = CoQ₁₀, **C** = cytochrome C, Fe-S = iron-sulfur clusters, C₁ = cytochrome C₁, b = cytochrome b, a₁-Cu = copper associated with cytochrome a₁, ADP = adenosine diphosphate, ATP = adenosine triphosphate. Arrows indicate the flow of electrons through the pathway.

Extraction

Although some older methods use two-phase extraction systems, with combinations of hexane and lower alcohols, protein precipitation and extraction with 1-propanol is simple, more direct, and is now the method of choice. To obtain quantitative extraction the ratio of the volume of propanol to plasma or tissue should be greater than 5.⁷

Detection

Electrochemical detection is the most sensitive and selective detection method,¹⁷ and allows measurement of both ubiquinone and ubiquinol in the same plasma sample. Electrochemical detection is also sensitive enough to detect CoQ₉ in human plasma simultaneously with CoQ₁₀.² Tandem mass spectrometric detection has been used,¹⁸ but since the ubiquinones and ubiquinols of both CoQ₉ and CoQ₁₀ give the same fragmentation ions there is no obvious advantage compared with electrochemical detection.

Internal Standards

When simple liquid-liquid extraction of CoQ₁₀ from plasma is achieved using 1-propanol, recovery is approximately 100% and it is questionable whether an internal standard is necessary. The most commonly used internal standard for measurement of CoQ₁₀ is CoQ₉, however since CoQ₉ is found endogenously in human plasma, it is not an ideal internal standard.²

Percentage of Reduced CoQ of total CoQ₁₀

CoQ₁₀H₂ is rapidly oxidised to CoQ₁₀ by oxygen, hence measuring it in plasma specimens is demanding. The percentage CoQ₁₀H₂ of total CoQ₁₀ in plasma has been reported variously from 51 to 96%,^{7,8,19-27} and it is presumed that this discrepancy is due to a variable conversion of CoQ₁₀H₂ to

CoQ₁₀ before analysis. To maintain the endogenous CoQ₁₀H₂ it is necessary to employ meticulous pre-analytical sample handling, processing blood samples rapidly and freezing plasma to -80 °C. Therefore it is not practicable to offer the routine analysis of the percentage of CoQ₁₀H₂ in the total CoQ₁₀ as a clinical diagnostic test.

Plasma and Tissue CoQ₁₀

Measurement of both plasma^{20,28} and tissue CoQ₁₀ has been reported.²⁹ However, the relationship between plasma and tissue CoQ₁₀ levels is not yet clear, and plasma levels should only be regarded as a surrogate for tissue,³⁰ and in particular mitochondrial levels, where any therapeutic effect of CoQ₁₀ may be expected to be most important. The primary problem with measuring tissue levels is access to tissue samples. Blood cells have been used for estimates of CoQ₁₀ in tissues.³¹ CoQ₁₀ content of blood mononuclear cells was shown to correlate with skeletal muscle CoQ in unsupplemented subjects whereas the plasma concentrations did not.³² There would appear to be no clinical value in measuring erythrocyte CoQ₁₀, but there may be a possible case for considering its measurement in platelets or other mitochondria-containing blood cells, though pertinent reference ranges would need to be established.

Reference Interval

It has been well established that the adult reference interval for plasma or serum CoQ₁₀ is approximately 0.5 – 1.7 μmol/L.^{4,26,33,34} Because plasma CoQ₁₀ and lipid concentrations correlate strongly, it has been proposed that lipids should be considered when measuring plasma CoQ₁₀,^{5,9} and the ratio of CoQ₁₀ to total- or LDL-cholesterol reported.

Factors Affecting Plasma CoQ₁₀ Concentration

Whether there is a gender difference in CoQ₁₀ levels is controversial, with both a significant difference^{4,6,35} and no difference^{19,33,36} being reported. Although there was a significant gender difference in both total CoQ₁₀ and the CoQ₁₀ to total cholesterol ratio, we found no basis for stratification of the total CoQ₁₀ reference interval for gender according to the Harris and Boyd criteria.^{4,37}

The effect of ageing on CoQ₁₀ is unclear, with reports that CoQ₁₀ correlates positively with age, an association which disappears when total cholesterol is included in multivariate analysis,^{4,10} or conversely that there is no association between CoQ₁₀ and age.^{35,38} Clinically healthy infants (1-12 months) and preschoolers (1-6 years) have been shown to have significantly higher total CoQ₁₀ than school aged children (6-15 years) (median CoQ₁₀ 0.98, 1.0 and 0.81, respectively).³⁹ The ratio of CoQ₁₀ to total cholesterol was significantly higher in the infants compared to the elder subgroups.³⁹ Furthermore, Menke et al. reported that infants in the first to fourth month

of age have significantly lower total CoQ₁₀ than subgroups of infants aged five to eight, or nine to twelve months.³⁹ CoQ₁₀ has been shown to correlate positively with BMI.^{4,6,10,35,40}

There is substantial evidence that plasma CoQ₁₀ is reduced by the cholesterol lowering medication HMG-CoA reductase inhibitors (statins). This is not surprising, since both CoQ₁₀ and cholesterol are synthesised by the mevalonate pathway (Figure 2). Numerous studies have demonstrated reductions of up to 54% in plasma/serum CoQ₁₀ concentrations following statin therapy.^{41,42} The magnitude of the statin-induced depletion of CoQ₁₀ levels has been shown to be dose related,⁴³ and is reversible on cessation of statin therapy.⁴⁴ It is possible the reduction in circulating CoQ₁₀ may reflect decreased LDL-cholesterol concentrations. However, several studies have reported a lower CoQ₁₀ to LDL-cholesterol ratio after statin treatment,^{43,45,46} suggesting CoQ₁₀ depletion may not only be due to a reduction in LDL-cholesterol carriers, although this has not been consistently shown in all trials.^{44,47,48}

Circulating concentrations of CoQ₁₀ do not necessarily reflect tissue CoQ₁₀ concentrations, and clinical studies evaluating the effect of statin treatment on skeletal muscle CoQ levels are contradictory. In an early trial, four weeks of simvastatin (20 mg/day) produced a 47% increase in muscle CoQ₁₀ concentrations,⁴⁸ and six months of treatment with 20 mg/day of simvastatin gave a similar result.⁴⁷ One trial comparing the effect of eight weeks of simvastatin 80 mg/day, atorvastatin 40 mg/day, or placebo on muscle CoQ₁₀ levels, reported a 34% reduction in those treated with simvastatin.⁴⁹ However, in a recent study there was no significant difference in the mean intramuscular CoQ₁₀ concentration in patients with statin-related myopathy compared to controls.⁵⁰

Several studies have shown that supplementation with oral CoQ₁₀ can restore plasma CoQ₁₀ levels in patients receiving statin therapy.⁵¹⁻⁵³ The long-term effect of statin-induced plasma CoQ₁₀ decreases, especially considering the increasingly popular intensive lipid lowering via statins, is not yet clear, and should be monitored.

CoQ₁₀ Supplementation

There are many different brands of CoQ₁₀ supplement available, and their formulations can differ widely in respect to whether they contain reduced or oxidised CoQ₁₀, whether they are dry powder capsules or CoQ₁₀ dispersed in oil, and whether they contain surfactants and emulsifiers, such as lecithin and polysorbate 80 to improve absorption. There is a significant difference in bioavailability of the various brands and formulations of CoQ₁₀ supplement.⁵⁴ The majority of bioavailability studies have focussed on plasma CoQ₁₀

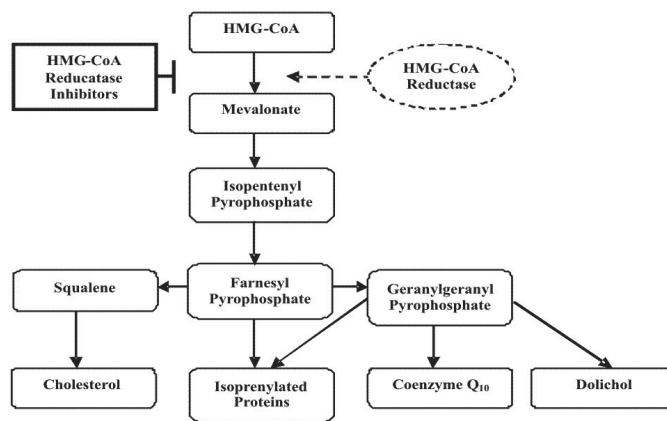


Figure 2. The mevalonate pathway. Inhibition by HMG-CoA reductase by statins leads to depletion in products of the pathway including cholesterol and possibly CoQ₁₀.

levels rather than the mitochondrion, however new analogues have been developed with a view to enhanced mitochondrial uptake, including mitoquinone-Q (Mito-Q)⁵⁵. These drugs are currently under investigation. Moreover, there is also a significant difference in absorption of CoQ₁₀ from supplements between individuals.^{36,40,54,56-58} These two points highlight the need for measurement of plasma CoQ₁₀ concentrations during supplementation, to monitor efficacy.

Biological Variation, Reference Change Value, and Index of Individuality

Biological variation quantifies changes in the concentration of an analyte over time. For CoQ₁₀, the CoQ₁₀ to LDL-cholesterol ratio, and the CoQ₁₀ to total cholesterol ratio in healthy young males, the intra-individual variation is 12, 15 and 14%, respectively, and the inter-individual variation is 29, 26, and 18%, respectively.⁴ From this biological variation data the reference change value (RCV), an estimate of the percentage change required in the concentration of an analyte for the change to be (at a specified probability) likely to be due to something other than normal biological variation, can be calculated. The RCV for a 95% significant change in CoQ₁₀ is 35%, and for a 99% significant change is 46%.⁴ An index of individuality (II) (intra-individual variation/inter-individual variation), which numerically determines whether reference intervals are of use when determining whether a change in the concentration of an analyte is significant or not, can also be calculated. When the II is high (>1.4) reference intervals are helpful, but when the II is low (<0.6) a clinically significant change in the concentration of the analyte can occur, while the concentration still remains within the reference interval. The II for CoQ₁₀ is 0.42, which is low. Thus many individuals can experience a significant reduction in plasma CoQ₁₀, and others a significant increase, while their values remain within the reference interval.⁴

Clinical Aspects of CoQ₁₀

Primary CoQ₁₀ Deficiency

Ogashara et al. described the first patients (two sisters) with primary CoQ₁₀ deficiency in 1989.⁵⁹ 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.⁵⁹ 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 CoQ₁₀.⁵⁹

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.⁶⁰ 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.⁶¹

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.⁶² Exogenous CoQ₁₀ supplementation has been shown to lead to improvements in the status of patients with CoQ₁₀ deficiency.^{59,60,63-65}

CoQ₁₀ and Statin Myopathy

The underlying pathophysiology of statin-induced myopathy is unknown, but one postulated mechanism is mitochondrial dysfunction through depletion of CoQ₁₀,⁶⁶ since CoQ₁₀ is an essential cofactor in the mitochondrial electron transport chain⁶⁷ (Figure 1) 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,⁶⁸ and as targets for cholesterol reduction become

progressively lower, necessitating higher statin doses, the risk of side effects, particularly myopathies, has increased.^{69,70}

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 ($p < 0.001$).⁴⁵ 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.⁷¹ 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.⁵⁰

To date, only two randomised trials have investigated the effect of CoQ₁₀ administration on statin-induced myalgia, with contrasting results.^{72,73} 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.⁷² 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.⁷³ 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 re-challenge, 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.⁷⁴ 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.⁷⁵ 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.⁷⁶ 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.

CoQ₁₀ and 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).⁷⁷ 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.⁷⁷

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.³⁰ This myocardial CoQ₁₀ deficiency in patients with cardiomyopathy was also reversed by CoQ₁₀ therapy.³⁰

An interesting observation is that total cholesterol is related to survival in CHF.^{78,79} 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.⁷⁸ 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,⁴ 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.⁷⁸

In a recent observational study, we showed that CoQ₁₀ levels, but not statin therapy (known to lower CoQ₁₀ in heart failure⁴¹) 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.⁷⁸

Meta-analyses of CoQ₁₀ supplementation in CHF have been undertaken.^{81,82} Soja and Mortensen⁸¹ reviewed eight double-blind 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.⁷⁷ 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.⁴¹ 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.⁴¹ 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.⁷⁷ 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

CoQ₁₀ and Hypertension

A recent meta-analysis of CoQ₁₀ in the treatment of hypertension (12 clinical trials, 362 patients) concluded that, in hypertensive patients, CoQ₁₀ has the potential to lower systolic and diastolic blood pressure, without significant side effects.⁹⁸ A blood pressure lowering effect of CoQ₁₀ was found across three types of studies including randomised controlled, crossover, and open label. Decreases in systolic blood pressure ranged from 11 to 17 mmHg and in diastolic blood pressure from 8 to 10 mmHg.⁹⁸ In three of the 12 studies CoQ₁₀ was given in addition to existing anti-hypertensive medication, and in one of these more than 50% of the patients were able to cease taking at least one anti-hypertensive medication during the trial.⁹⁸ The antihypertensive effect of CoQ₁₀ occurs gradually over several months, and the CoQ₁₀ dose required for effectiveness varies between patients.⁹⁹

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.⁹⁸ In this role, CoQ₁₀H₂ may counteract vasoconstriction resulting from impaired ability of the endothelium to induce nitric oxide mediated relaxation of underlying smooth muscle.⁹⁸

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.

CoQ₁₀ and 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.¹⁰⁰ CoQ₁₀ deficiency in type

2 diabetes results from impaired mitochondrial substrate metabolism,¹⁰¹ and increased oxidative stress.¹⁰⁰ 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.¹⁰² Low plasma CoQ₁₀ concentrations have been negatively correlated with poor glycaemic control and diabetic complications.¹⁰³ 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,^{104,105} 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.^{104,105} 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.¹⁰⁶ 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.^{107,108} Playford et al. did however, observe a significant increase in endothelium-dependent 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.¹⁰⁷ CoQ₁₀ supplementation may also enhance the ability of other anti-atherogenic agents such as statins.¹⁰² Further studies, including clinical outcome trials are required to confirm whether there is a role for CoQ₁₀ in treatment of diabetes and its complications.

CoQ₁₀ and 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,¹⁰⁹ and suggested CoQ₁₀ deficiency in cancer patients.¹¹⁰ 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.¹¹¹ 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.¹¹² It has also been suggested that CoQ₁₀ may protect the heart from anthracycline-induced cardiotoxicity,¹¹³ and additionally that it may stimulate the immune system.¹¹⁴ 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.¹¹⁵ 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.¹¹⁵ Further research into the use of CoQ₁₀ as an adjuvant treatment in cancer is therefore required.

CoQ₁₀ and 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.¹¹⁶ 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.¹¹⁷ Subsequent investigations have demonstrated reduced activity of complex I in platelet mitochondria of PD patients,¹¹⁸ and also in the substantia nigra, but not other areas of the brain in individuals with PD.¹¹⁹ 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.¹²⁰ Furthermore, the CoQ₁₀ ratio of the oxidised to the reduced form is elevated in parkinsonian patients, suggesting increased oxidative stress in PD.¹²¹ Taken together, these findings and the dual function of CoQ₁₀ as both an electron acceptor for complexes I and II and a potent antioxidant,⁶⁷ 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,¹²² and has been reported to be safe and well tolerated,¹²²⁻¹²⁶ at doses as high as 2400 mg.¹²⁴ 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.¹²³ In addition, CoQ₁₀ at a dose of 1,200 mg/day was associated with improved complex I activity in this trial.¹²³ Another trial demonstrated improved motor function in patients with early PD following six months of treatment with up to 1,500 mg/day of CoQ₁₀,¹²⁷ 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.¹²⁴⁻¹²⁶

Large phase III trials are needed to confirm the positive findings of the study by Shults et al.¹²³ and planning is currently underway for one such trial in patients with early PD.¹²⁸ 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.

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.⁵⁴ Furthermore, an understanding of biological variation, the reference range 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.

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