Abtsract
Amongst the potential causes of chronic kidney disease (CKD), mitochondrial respiratory chain (MRC) dysfunction, oxidative stress and inflammation have beenimplicated as contributor factors to the pathogenesis of this broad ranging disorder. In view of the reported ability of coenzyme Q10 (CoQ10) to restore electron flow in the MRC, as well as to increase cellular antioxidant capacity and mediate inflammation, CoQ10 supplementation may offer some therapeutic potential in the treatment of patients with CKD, in which evidence of oxidative stress/inflammation and/or MRC dysfunction have been identified. The following review will outline our current knowledge on the use of CoQ10 in the treatment of CKD, as well as discussing the involvement MRC dysfunction, oxidative stress and inflammation in this disorder.

Introduction

CKD isdefined as a permanent loss of kidney function, characterised by a reduced ability of the kidneys to excrete waste products of metabolism, resulting in the build-up of uremic toxins in the blood (Barret et al., 2014). CKD is classified into five stages, depending on the glomerular filtration rate (GFR); this is the rate of filtration across the glomerular filtration barrier, measured in units of ml/min/1.73m^2, with normal values typically in the range 90-120. Patients with severe CKD (stage 5) are typically treated by dialysis to remove uremic toxins, correct electrolyte and acid base imbalance and, in patients with reduce urine output, regulate body water (Dhondup and Qian, 2011). It is estimated that the prevalence of CKD in the general UK population is approximately 10% (Public Health England, 2014). There are a number of causes of CKD, with hypertension and diabetes being amongst the most prominent (Romagnani et al., 2017).

CoQ10 is a lipophilic molecule consisting of a benzoquinone nucleus and an isoprenoid side chain [Figure 1] that plays a key role in cellular energy generation within the mitochondrial respiratory chain (MRC) [Figure 2], as well as having an important antioxidant and anti-inflammatory action (Fan et al. 2017). CoQ10 occurs within the body in two very closely related chemical forms, an oxidised form (ubiquinone) [Figure 1a] and a reduced form (ubiquinol) [Figure 1b]. The chemical structure of CoQ10 is relatively complex, and ubiquinol differs from ubiquinone only by the addition of an extra two hydrogen atoms. The antioxidant activity of CoQ10 is provided by ubiquinol (Hargreaves, 2015). The reductive regeneration of ubiquinol is vital to maintain its antioxidant function. The MRC ensures that the inner mitochondrial membrane CoQ10 pool is kept in its fully reduced ubiquinol state (Aberg et al. 1992). The enzyme, electron transfer flavoprotein-ubiquinone oxidoreductase (ETFDH) also contributes to the reduction of the CoQ10 pool within the inner mitochondrial membrane (Gempel et al. 2007). CoQ10 is reduced to ubiquinol on the outer surface of the inner mitochondrial membrane by the enzyme, dihydroorotate dehydrogenase during pyrimidine synthesis (Turunen et al. 2004). In the plasma and endomembranes (membranes of the

different organelles within the cytoplasm of the cell) there are at least four enzymes that are known to maintain CoQ10 in its ubiquinol form. These enzymes are NADH cytochrome b5 reductase, NADH/NADPH oxidoreductase, NADPH coenzyme Q reductase (NQO1) and dihydro-orotate dehydrogenase (NQO1;Villalba & Navas 2000; Takahashi et al. 1996).

In addition to their antioxidant potential however, the therapeutic efficacy of CoQ10 and its synthetic analogues such idebenone in the treatment of MRC disorders is also thought to rely on their ability to enhance electron flow in the MRC (Hargreaves, 2014; Neergheen et al., 2017).

Mitochondrial dysfunction in CKD

The waste products of metabolism, uremic toxins are normally excreted in the urine, but can accumulate as a result of CKD and have been reported to cause impairment of MRC function (Mutsaers et al., 2013; Granata et al., 2015) [Figure 2]. This can result from inhibition of MRC complex II (succinate: ubiquinol reductase) and/or complex IV (cytochrome c oxidase) activities (Granata et al., 2009; Granata et al., 2015). Furthermore, in vitro studies have indicated that the CKD reported in patients with primary hyperaldosteronism may result from aldosterone induced mitochondrial dysfunction in the podocytes. The mitochondrial dysfunction appears to result from an aldosterone induced decrease in mitochondrial DNA (mtDNA) copy number as a consequence of increased mitochondrial reactive oxygen species (ROS) generation (Su et al., 2013).

Interestingly, a decrease in mtDNA has also been reported in Finnish type congenital nephrotic syndrome (Solin et al. 2000). Once impaired, the MRC becomes a major source of ROS which can result in oxidative stress, once cellular antioxidant defences have been overwhelmed (Stepien et al., 2017), and has been reported in animal models of CKD (Owada et al., 2010). The major sites of ROS generation within the MRC are at complex I and III (Quinlan et al. 2013). Oxidative stress can also result in inflammation which can mediate a host of chronic diseases (Stepien et al., 2017; refs: DelaCruz & Kang, 2018; Grazioli & Pugia, 2018; Meyer et al, 2018). In addition, the levels of a number of pro-inflammatory cytokines considered to be uremic toxins increase in CKD, contributing to the pathophysiology of this condition (Castillo-Rodriguez et al., 2017).The release of mitochondria-derived damage-associated molecular patterns (DAMPs) as the result of mitochondrial dysfunction. may also contribute to the inflammatory response by interacting with receptors similar to those involved in the pathogen-associated immune response (Picca et al., 2017). Furthermore, an study in a mouse model of Parkinson`s disease has indicated that mitochondrial dysfunction is able to multiply the inflammasome signalling pathway-driven proinflammatory cascade in microglia (Sarkar et al., 2017). Moreover, inflammation has also been associated with the inhibition of MRC enzyme activity as illustrated in the autoimmune inflammatory disorder, multiple sclerosis (Hargreaves et al. 2018) as well as the systemic inflammatory response syndrome, Sepsis (Stepien et al., 2017). MRC dysfunction, oxidative stress and inflammation can interact in a mutually reinforcing manner, with deleterious effects on the functioning of all tissues, but particularly those with high energy demands such as the heart and

kidneys.

Therefore, in view of the association between CKD, MRC dysfunction, oxidative stress and inflammation, it is the purpose of this article to discuss evidence for the potential role of CoQ10 in the treatment of patients with CKD.

CoQ10

CoQ10 plays a key role in the biochemical process that supplies all cells with the energy required for their normal functioning. Specifically, CoQ10 serves an electron carrier in the MRC transferring electrons derived from complex I (NADH:ubiquinone reductase) and complex II to complex III allowing a continuous passage of electrons within the chain which is required for the process of oxidative phosphorylation and consequent ATP production (Hargreaves, 2003) [Figure 2]. In its reduced ubiquinol form, CoQ10 also functions as a potent lipid soluble antioxidant which is considered more efficient than vitamin E (Frei et al. 1990). It has been suggested that ubiquinol acts earlier in the prevention of lipid peroxidation than vitamin E (Ernster & Forsmark-Andree 1993) and is also able to regenerate the active α-tocopherol form of the vitamin from the α-tocopheroxyl radical. Ubiquinol is able to inhibit lipid peroxidation (Ernster et al. 1992; Ernster & Dallner 1995) and is present in the membranes of all other subcellular organelles, such as microsomes, lysosomes and the Golgi apparatus (Crane, 2001;Turunen et al., 2004; Littarru et al. 2007). In the plasma membrane, ubiquinol can prevent lipid peroxidation by itself or by reducing the antioxidants, α-tocopherol and vitamin C (Navas et al. 2007). Ubiquinol also plays an important role as an antioxidant protecting circulatory lipoproteins from free radical induced oxidative damage (Romagnoli et al. 1994; Alleva et al. 1995). It is important to stress that ROS can serve as a r signalling molecule regulating important biological and physiological functions within the cell (Finkel, 2011).However, excessive production of ROS will overwhelm the intracellular antioxidant defenses causing oxidative damage to lipids, proteins and DNA (Cross et al., 1987; Matsuzaki et al, 2009). In addition, gene expression profiling has shown that CoQ10 influences the expression of several hundred genes (Guttierez-Mariscal et al, 2018). In particular, studies in cell culture, animal models and human subjects have shown that CoQ10 can directly regulate gene expression relevant to inflammation and fat metabolism (Schmelzer et al 2008). At least 13 genes are involved in the biosynthesis of CoQ10 itself, and mutations 10 of these genes have been reported to result in primary CoQ10 deficiency (Awad et al. 2018;Yubero et al. 2018).

An adequate supply of CoQ10 is essential for the normal functioning of mitochondria. Most of the daily CoQ10 requirement is synthesized within the body, with a small amount being obtained from dietary sources (Weber et al., 1997). CoQ10 biosynthesis is a multistage process with the benzoquinone nucleus being derived from tyrosine and the isoprenoid side chain being derived from acetyl-CoA via the mevalonate pathway (Turunen et al. 2004). Following the condensation of the side chain and benzoquinone nucleus, the final modification of the benzoquinone nucleus to form CoQ10 occurs within the mitochondria (Turunen et al. 2004; Navas et al. 2007). CoQ10 is present within all cellular membranes including the plasma membrane, however it

found in the highest amounts within the outer and inner membranes of the mitochondria, lysosomes and Golgi body where it serves as a respiratory chain redox carrier, proton transporter and antioxidant. (Turunen et al. 2004). As people age, the body becomes less efficient at producing its own supply of CoQ10 (Navas et al. 2007); with levels in cardiac tissue at age 65 being less than 50% of those at age 25, this is why people may choose to take supplemental CoQ10 to correct this potential deficit (Kalen et al., 1989). An important factor to consider which may influence the efficacy of CoQ10 supplementation is the type of CoQ10 formulation employed, as this will influence the bioavailability of CoQ10 absorbed from the digestive tract into the bloodstream. When supplemental CoQ10 is first produced (via a yeast fermentation process), it is obtained in the form of crystals which cannot be absorbed from the digestive tract (Mantle, 2015). It is essential that these crystals are dispersed into single CoQ10 molecules (and remain dispersed during the product shelf-life) for optimum bioavailability, but manufacturers vary greatly in their ability to achieve this goal. In view of their superior absorption, the use of gel and oil based formulations of CoQ10 have been recommended in preference to tablets in the treatment of patients with mitochondrial disease (Weis et al., 1994) . Recently, a study by Martinefski et al (2017) reported that soft gel formulations improved the bioavailability of CoQ10 with respect to solid formulations.

At present, there is considerable debate on whether formulations of ubiquinol, CoQ10 in its fully reduced form (Hargreaves, 2003), have a better absorption from the GI tract than those of CoQ10. It is reported that the absorption of ubiquinol by the gastrointestinal tract is 3-4 times greater than that of CoQ10[2] Bhagavan and Chopra, 2007; Garcia-Corzo et al., 2014). However, upon absorption from the GI tract, CoQ10 undergoes reduction to ubiquinol, therefore, the reported superior bioavailability of ubiquinol formulations to that of CoQ10 may be attributable to the matrix in which the ubiquinol is encapsulated. Furthermore, at present there is limited data available from clinical studies, and there are no indications of dosage compatibility Desbats et al., 2015).

CoQ10 and kidney function in CKD

Plasma CoQ10 levels have been reported to be significantly lower in CKD patients (with or without haemodialysis), compared to normal controls (Triolo et al., 1994; Macunluoglu et al., 2014; Yeung et al., 2015). The cause of this deficit in serum CoQ10 levels is as yet uncertain, however, it may be associated with the increased oxidative stress reported in CKD (Oberg.et al., 2004). The oxidative stress in CKD as a result of either MRC dysfunction or from other sources (Galli et al., 2001) may cause an increased degradation of CoQ10 (Miranda et al., 1999). Furthermore, it has been suggested that the enzymes involved in CoQ10 biosynthesis may exist in a super enzyme complex which is located in mitochondria in close proximity to MRC in the inner mitochondrial membrane (Marbois et al. 2005; Ashraf et al.2013) A deficiency in MRC enzyme activity may therefore impact upon the structural formation or function of the CoQ10 super enzyme complex possibly as the result of increased ROS generation which has been associated with MRC enzyme dysfunction (Quinlan et al. 2013) causing oxidative stress induced impairment

of CoQ10 biosynthetic enzymes, which may therefore compromise CoQ10 biosynthesis (Yubero et al., 2016).

There is some evidence that CoQ10 supplementation may improve renal function and reduce the need for dialysis in patients with CKD. In a randomised controlled study (Singh et al., 2000) 97 CKD patients were given supplementary CoQ10 (3 x 100mg daily for 3 months) or placebo. There was a significant improvement in markers of renal function (e.g. serum creatinine) in CoQ10 supplemented patients compared to placebo, in both dialysed and non-dialysed patients. In particular, the number of patients requiring dialysis in the CoQ10 treated group decreased from 21 to 12, whilst remaining unchanged at 24 in the placebo group. In an animal model of CKD, the reduced form of CoQ10, ubiquinol, was found to decrease kidney superoxide levels as well ameliorating renal dysfunction (Ishikawa et al., 2015).

Decreased CoQ10 levels may be a particular issue in CKD patients prescribed the cholesterol-lowering drugs `statins,` since some studies have reported a deficit in CoQ10 status in association with this pharmacotherapy in a subset of patients. It has been suggested that these patients may have some form of underlying mitochondrial disease and therefore may be more susceptible to the adverse effects of statin therapy (Hargreaves et al., 2016). Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, the rate limiting enzyme in cholesterol biosynthesis. Statins can also inhibit the body's production of coenzyme Q10 (CoQ10), which is synthesised via the same biochemical pathway as cholesterol. The statin induced reduction in CoQ10 levels has been well documented in both animal model and clinical studies. Adverse effects in some patients (particularly muscle pain) resulting from statin use has been rationalised in terms of CoQ10 depletion; supplementation with CoQ10 is effective in ameliorating statin-induced muscle pain (Skarlovnik et al. 2014; Littlefield et al, 2014. Qu et al. 2018)

CoQ10, oxidative stress and haemodialysis

Although haemodialysis is essential for removing uremic toxins, it is a consequence of the procedure that individuals are subject to additional oxidative stress (a result of neutrophil exposure to the synthetic material comprising the dialyser membrane), in addition to the oxidative stress associated with CKD. A number of clinical studies have reported that supplementation with CoQ10 significantly improves outcome in haemodialysis patients by reducing markers of oxidative stress and inflammation. In a randomised controlled trial, Zahed et al (Zahed et al., 2016) reported that CoQ10 supplementation (100mg/day for 3 months) in end stage CKD patients undergoing haemodialysis significantly reduced serum levels of the inflammatory marker C-reactive protein. An open label dose escalation study by Yeung et al (2015) showed supplementation with CoQ10 over the range 300-1800mg/day for 14 days to be safe and well tolerated, significantly reducing plasma levels of the oxidative stress marker isofuran. It was suggested by Yeung et al (2015) that the decrease in oxidative stress observed in patients following CoQ10 treatment may have resulted from the ability of this molecule to improve mitochondrial function rather than as a consequence

of any systemic antioxidant effect.

CoQ10 and cardiovascular disease in CKD patients

Patients with CKD are at high risk of developing cardiovascular disease, with a 10-20 fold increased risk of cardiovascular mortality compared to non-CKD individuals. In particular, there is a high prevalence of atrial fibrillation in CKD patients (Huang et al., 2016). Overall, approximately 50% of deaths in CKD patients result from cardiovascular disease, rather than as a direct consequence of kidney failure. Conversely, cardiovascular disease can cause CKD leading to a vicious circle in which each disorder exacerbates the other. Thus, treatment of CKD can reduce the incidence of cardiovascular disease, and treatment of cardiovascular disease can reduce further deterioration in renal function. In this regard, a randomised controlled clinical trial (Q-SYMBIO) of patients with chronic heart failure (in whom CoQ10 levels are depleted), supplementation with CoQ10 (Bio-Quinone Q10 Gold 200mg/day for 2 years) reduced the risk of cardiovascular related mortality by 43% (Mortensen et al., 2014). Similarly, the KISEL-10 study was a randomised controlled clinical trial, involving long term (5 year) supplementation of a normal elderly population with coenzyme Q10 (Bio-Quinone 100mg/day) and selenium (SelenoPrecise, 200mcg/day). Cardiovascular mortality was significantly reduced in supplemented individuals by 53%; in addition, biochemical markers of systemic oxidative stress and inflammation were significantly reduced, and heart function, hospitalisation frequency and quality of life significantly improved (Alehagen et al. 2013; Alehagen et al. Alehagen et al. 2015a; Alehagen et al. 2015b; Johansson et al. 2015).

A randomised controlled trial in haemodialysis patients reported that supplementation with CoQ10 (1200mg/day for 4 months) resulted in a significant decrease in the level of plasma F2-isoprostanes, a bio-marker of oxidative stress (Rivara et al, 2017). To date no randomised controlled trials have been carried out to determine clinical outcome for reducing cardiovascular risk in CKD patients.

The ratio of plasma CoQ10 vs LDL cholesterol+ VLDL cholesterol, considered to be more important in athersclerosis prevention than the ratio of HDL:LDL cholesterol (Tomasetti et al.,1999)was significantly lower in CKD patients (with or without dialysis) compared to controls.

Epicardial fat thickness, a new risk factor for cardiovascular disease, was found to be significantly greater in CKD patients undergoing haemodialysis compared to controls and correlated with reduced plasma CoQ10 levels (Lippa et al., 2000). Similarly, coronary flow reserve, an indicator of atherosclerosis, was reported to be significantly lower in haemodialysis patients, correlating inversely with serum CoQ10 levels (Macunluoglu et al., 2013).

CKD and MRC disorders

CKD can also be a clinical presentation of primary MRC disorders which can result in either tubular defects and/or glomerulopathies, the latter being the

more common clinical presentation (Emma et al., 2016). In view of the high metabolic demand of renal tubular cells they are very susceptible to deficits in mitochondrial energy metabolism and, consequently, renal tubular defects are frequently reported in patients with MRC disorders (Emma and Salviati, 2017). Amongst the tubular disorders, Fanconi Syndrome, which is a disorder of inadequate reabsorption in the proximal renal tubules of the kidney has often been reported as one of the clinical presentations from a variety of mitochondrial diseases (Emma and Salviati, 2017).

In addition to renal tubular disorders, glomerulopathies have also been reported amongst the clinical sequelae of patients presenting with the mitochondrial disease. Although renal involvement is rare in patients with MELAS (mitochondrial encephalopathy lactic acidosis and stroke like episodes), patients harbouring the 3243 A>G mtDNA point mutation have been reported to present with renal disease as the result of glomerular dysfunction (Hall et al., 2015). Although no assessment of the CoQ10 status of MELAS patients was undertaken in the study by Hall et al (2015), previous studies have reported evidence of a deficit in CoQ10 status in patients with various mtDNA disorders (Hargreaves et al., 2014). Prompt diagnosis of a deficit in CoQ10 status is imperative, since a dramatic improvement in the clinical status of such patients has been reported following CoQ10 supplementation (Montini et al., 2015).

Inherited defects in CoQ10 biosynthesis have also been associated with glomerular disease with the urinary space occupied by swollen podocytes with extensive foot process fusion and containing high numbers of dysmorphic mitochondria (Emma and Salviati. 2017). Defects in CoQ10 metabolism appear to specifically impair podocyte function and should be considered amongst the other causes of a podocytopathy (Singh et al. 2015). At present it is uncertain why podocyte function is so sensitive to a deficit in CoQ10 status. However, in view of their dependence on oxidative phosphorylation for energy generation together with high mitochondrial enrichment, a deficit in CoQ10 status would be effected to impair MRC function as well as compromising cellular antioxidant status (Hargreaves, 2003).

In humans, at least 13 genes are thought to be involved in the biosynthesis of CoQ10, and mutations in 10 of these genes have been identified to date (Doimo et al. 2014; Awad et al. 2018; Yubero et al. 2018). Renal dysfunction in association with CoQ10 deficiency was first reported by Rotig et al (2000) in three siblings with severe encephalomyopathy and steroid resistant nephrotic syndrome. A further two siblings with steroid resistant nephrotic syndrome and CoQ10 deficiency were reported (Salviati et sl., 2005). Subsequent investigations identified mutations in the *COQ2* gene (which encodes 4-hydroxybenzoate polyprenyl transferase) of these two siblings making them the first patients with a primary CoQ10 deficiency to achieve a genetic diagnosis (Quinzii et al.,2006).

, mutations in *PDSSI, PDSS2, CoQ6* and *ADCK 44* genes have been associated with steroid resistant nephrotic syndrome and CoQ10 deficiency (Emma and Salviati, 2017). However, in contrast to the other mutations which present with both neurological and renal dysfunction, steroid resistant nephrotic syndrome

appears to be the sole clinical presentation of patients with mutations in *ADCK 44* gene. The *ADCK 44* gene encodes for a putative kinase which is thought to have a regulatory function within the CoQ10 biosynthetic pathway, possibly by interaction with the enzymes of the CoQ10 super-complex (Ashraf et al., 2013).

Patients who develop steroid resistant nephrotic syndrome as a result of a CoQ10 deficiency appear to respond well to high dose CoQ10 supplementation if treatment is initiated early in the diseases course with progressive recovery of renal function and decreased proteinuria being reported Diomedi-Cammassei et al., 2007; Heeringa et al., 2011; Cao et al., 2017). Unfortunately, CoQ10 supplementation was reported to be unsuccessful in inducing recovery of renal function once chronic renal failure had developed (Montini et al., 2008) Supplementation with CoQ10 at doses of 30-50 mg/kg/day have been recommended (Emma and Salviati, 2017). However, at present there is no consensus on the appropriate dosage that should be used to treat these disorders. In order to exploit the `window of opportunity` whereby organ dysfunction may be amenable to CoQ10 treatment, supplementation at birth has been recommended for siblings of patients with confirmed CoQ10 deficiencies (Desbats et al., 2015).

Clinical monitoring of CoQ10 status

Clinical monitoring of CoQ10 status is generally based on plasma determinations, however the level of circulatory CoQ10 is influenced by both diet and circulatory lipoprotein status (Yubero et al., 2014). There is uncertainty if plasma CoQ10 status reflects that of other tissues and is an appropriate surrogate for use in this assessment (Yubero et al., 2014). Skeletal muscle is the tissue of choice for this determination, however in view of the possibility that there may be tissue specific isoenzymes in the CoQ10 biosynthetic pathway or that a CoQ10 deficiency may be localised to a single organ, other surrogates may be more appropriate to assess renal CoQ10 status (Yubero et al., 2014). At present, there are no studies that have assessed the CoQ10 status of normal human renal tissue due to the invasive nature of a kidney biopsy. However urinary tract CoQ10 analysis could be an appropriate approach for assessing kidney CoQ10 status, and may help fulfill the critical need for less invasive procedures to determine tissue CoQ10 status. Recently, a new methodology for the measurement of CoQ10 in urine has been standardized, including the establishment of reference values for a paediatric control population (Yubero et al., 2015). This new evaluation of urinary tract CoQ10 is a non-invasive procedure that might be useful for estimating CoQ10 kidney status for diagnosis and especially for CoQ10 treatment monitoring.

Conclusion

In conclusion, we have reviewed published literature providing a rationale for the role of CoQ10 in the pathogenesis of CKD. Several clinical studies (both randomised controlled and open) have been identified that indicated oral supplementation with CoQ10 in CKD patients could improve kidney function in both non-dialysed and dialysed patients. Similarly, clinical studies have

demonstrated that oral supplementation with CoQ10 is effective, when administered sufficiently early, in preventing renal dysfunction manifesting in patients with genetically related primary CoQ10 deficiency. In addition to its role in renal function, it has been suggested that supplementation with COQ10 may be effective in reducing the risk of developing cardiovascular disease in CKD patients. However, to date, no randomised controlled trials have been carried out to investigate the efficacy of CoQ10 supplementation on clinical outcome for cardiovascular disease in CKD patients, and this is a promising area for future research.

Summary: key points

1. Mitochondrial dysfunction, oxidative stress and inflammation have been implicated in the pathogenesis of CKD.

2. Depletion of CoQ10 levels, which has an important role in mitochondrial cellular energy generation and as an antioxidant/anti-inflammatory, has been demonstrated in CKD patients.

3. Depletion of CoQ10 in CKD can result primarily from genetic defects in the CoQ10 biosynthesis pathway, or secondarily from oxidative stress linked to the CKD disease process (e.g. uremic toxin accumulation) and/or haemodialysis.

4. Randomised controlled clinical trials have shown oral supplementation with CoQ10 can improve renal function and reduce the need for dialysis in CKD patients, or improve the clinical status in patients undergoing dialysis.

5. Supplementation of CoQ10 at an early stage is of particular importance in kidney disease linked to genetic mutations in the biosynthetic pathway, since patients may show a dramatic clinical improvement if CoQ10 deficiency is corrected as soon as practicable.

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References

Alehagan U, Johansson P, Björnstedt M, Rosén A, Dahlström U. Cardiovascular mortality and N-terminal proBNP reduced after combined selenium and CoQ10 supplementation: a 5 year prospective randomised double blind placebo controlled trial among elderly Swedish citizens. Int J Cardiol; 167:1860-1866, 2013

Alehagan U, Lindahl TL, Aaseth J, Svensson E, Johansson P. Levels of sP-selectin and hs-CRP decrease with dietary intervention with selenium and CoQ10. PLOS ONE; 10:e0137680, 2015a.

Alehagan U, Aaseth J, Johansson P. Less increase of copeptin and MR-proADM due to intervention with selenium and CoQ10 for 4 years- follow up results of a randomised controlled trial in elderly citizens. Biofactors; 41: 443-452, 2015b.

Alleva, R., Tomasetti, M., Battino, M, et al. The roles of coenzyme Q10 and vitamin E on the peroxidation of human low density lipoprotein subfractions. Proceedings of the National Academy of Sciences of the United States of America. 1995; 92(20):9388–91.

Ashraf S, Gee HY, Woerner S, Xie LX, Warner V, Lovric S et al. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. *J Clin Invest* 2013;**123**: 5179-5189.

Awad AM, Bradley MC, Fernández-Del-Río L, Nag A, Tsui HS, Clarke CF. CoQ10 deficiencies: pathways in yeast and humans. Essays Biochem; 62: 361-376, 2018.

Barreto FC, Stinghen AE, Oliveira RB, et al. The quest for a better understanding of CKD complications: an update on uremic toxins. *J Bras Nefrol* 2014; **36**: 221-235.

Bentinger M, Brismar K, Dallner G. The antioxidant role of CoQ10. *Mitochondrion* 2007; **7**:41-50.

Bhagavan HN, Chopra RK. Plasma CoQ10 response to oral ingestion of CoQ10 formulations. *Mitochondrion* 2007;**7**: 78-88, 2007.

Cao Q, Li GM, Xu H, et al. CoQ10 treatment for one child with CoQ6 gene mutation induced nephrotic syndrome. *Zhonghua Er Ke Za Zhi* 2017; **55**: 135-138, 2017.

Castillo-Rodriguez E, Prado R, Cleary C, Sanchez MS, Nino ND, Sanz AB et al. Kidney injury marker 1 and neutrophil gelatinase associated lipocalin in CKD. *Nephron 2017;* **136**: 263-267.

Crane FL. Biochemical functions of CoQ10. J Am Coll Nutr. 2000; 20: 591-598.

Cross CE, Halliwell B, Borish ET, et al. Oxygen radicals and human disease. Annals of internal medicine. 1987;107:526–545.

Delacruz CS, Kang MJ. Mitochondrial dysfunction and damage associated molecular patterns in chronic inflammatory diseases. Mitochondrion; 41: 37-44.

Desbats MA, Lunardi G, Doimo M, Trevoisson E, Salviati L. Genetic bases and clinical manifestations of Coq10 deficiency. *J Inherit Metab Dis* 2015; **38**: 145-156.

Dhondup T, Qian Q. Electrolyte and acid-base disorders in CKD and end-stage kidney failure. *Blood Purif* 2017; **43**: 179-188.
Diomedi-Cammassei F, Santorelli FM, Caridi G, et al. CoQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. *J Am Soc Nephrol 2007*; **18**: 2773-2780.

Doimo M, Desbats MA, Cerqua C, Cassina M, Trevisson E, Salviati L. Genetics of CoQ10 deficiency. *Mol Syndromol* 2014; **5**: 156-162.

Emma F, Montini G, Parikh SM, Salviati L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. *Nat Rev Nephrol* 2016; **12(5)**:267-280.

Emma F, Salviati L. Mitochondrial cytopathies and the kidney. *Nephrol Ther*; **13 Suppl 1**:S23-S28, 2017

Ernster, L. & Dallner, G.. Biochemical, physiological and medical aspects

of ubiquinone function. Biochimica et biophysica acta. 1995; 1271(1):

195–204.

Ernster, L. & Forsmark-Andree, P. Ubiquinol: an endogenous antioxidant in aerobic organisms. *The Journal of clinical investigation*. 1993; 71: 60–65.

Ernster, L., Forsmark, P. & Nordenbrand, K., 1992. The mode of action of lipid-

soluble antioxidants in biological membranes. Relationship between the effects

of ubiquinol and vitamin E as inhibitors of lipid peroxidation in

submitochondrial particles. Journal of Nutritional Science and Vitaminology.

1992; S-19-4: 548–551.

Fan L, Feng Y, Chen GC, et al. Effects of CoQ10 supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2017*;* **119**: 128-136.

Finkel T. Signal transduction by reactive oxygen species. J Cell Biol. 2011;194:7–15

Frei, B., Kim, M.C. & Ames, B.N. Ubiquinol-10 is an effective lipid-soluble

antioxidant at physiological concentrations. Proceedings of the National

Academy of Sciences of the United States of America.1990; 87(12):.4879–83.

Galli F, Varga Z, Balla J, et al. Vitamin E, lipid profile and peroxidation in hemodialysis patients. *Kidney Int* 2001; **78**: 148-154.

Garcia-Corzo L, Luna-Sanchez M, Doerrier C, Ortiz F, Escames G, Lopez LC. Ubiquinol-10 ameliorates mitochondrial encephalopathy associated with CoQ10 deficiency. *Biochim Biophys Acta* 2014; **1842**: 893-901.

Granata S, Gassa A, Tomei P, Lupo A, Zaza G. Mitochondria: a new therapeutic target in CKD. *Nutr Metab* 2015*;***49**: doi: 10.1186/s12986-015-0044.

Gempel K, Topaloglu H, Talim B, et al. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. Brain. 2007;130(Pt 8):2037-44.

Granata S, Zaza G, Simone S, et al. Mitochondrial dysregulation and oxidative stress in patients with CKD. *BMC Genomics* 2009; **10**: doi: 10.1186/1471-2164-10-388.

Grazioli S, Pugia J. Mitochondrial damage associated molecular patterns: from inflammatory signalling to human diseases. Front Immunol; 9:832; 2018.

Gutierrez-Mariscal FM, Yubero-Serano EM, Villalba JM, Lopez-Miranda J. Coenzyme Q10: from bench to clinic in aging diseases, a translational review. Crit Rev Food Sci Nutr; 16: 1-18, 2018.

Hall AM, Vilasi A, Perez I, Lapsley M, Alston CL, Pitcealthy RD et al. The urinary proteome and metabonome differ from normal in adults with mitochondrial disease. *Kidney Int* 2015*;* **87**: 610-622.

Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. *Int J Biochem Cell Biol 2014*; **49**: 105-111.

Hargreaves IP, Al Sharhrani M, Wainright L, Heales SJ. (2016) Drug induced mitochondrial toxicity. *Drug Saf* 2016*;* **39**: 661-674.

Hargreaves IP, Mody N, Land J, et al. Blood Mononuclear Cell Mitochondrial Respiratory Chain Complex IV Activity Is Decreased in Multiple Sclerosis Patients: Effects of β-Interferon Treatment. J Clin Med. 2018; 7(2: pii: E36.

Heeringa SF, Chenin G, Chaki M,et al. CoQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. *J Clin Invest* 2011*;* **121**: 2013-2024.

Huang SY, Chen YA, Chen SA, Chen YJ, Lin YK: Uremic toxins- novel arrhythmogenic factors in CKD related atrial fibrillation. *Acta Cardiol Sin 2016*; **32**: 259-264.

Ishikawa A, Kawarazaki H, Ando K, et al. Renal preservation efect of ubiquinol, the reduced form of CoQ10. *Clin Exp Nephrol 2011*; **15**: 30-33.

Johansson P, Dahlström Ö, Dahlström U, Alehagen U. Improved health related quality of life and more days out of hospital with supplementation with selenium and CoQ10 combined. J Nutr Health Aging; 19: 870-877, 2015.

Kalen A, Appelkvist E, Dallner G. Age related changes in lipid composition of rat and human tissues. *Lipids* 1989; **24**: 579-584.

Lippa S, Colacicco L, Bondanini F, et al. Plasma levels of CoQ10, vitamin E and lipids in uremic patients on conservative therapy and hemodialysis treatment: some biochemical and clinical implications. *Clin Chim Acta* 2000; **292**: 81-91.

Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: Recent developments. Molecular Biotechnology. 2007; 37(1): 31-37.

Littlefield N, Beckstrand RL, Luthy KE. Statins effect on plasma levels of CoQ10 and improvement in myopathy with supplementation. J Am Assoc Nurse Pract; 26: 85-90, 2014

Macunluoglu B, Atakan A, Ari E, et al. Epicardial fat tissue thickness is correlated with diminished levels of CoQ10, a major antioxidant in hemodialysis patients. *Clin Biochem* 2014; **47**: 1231-1234.

Marbois, B., et al., Coq3 and Coq4 define a polypeptide complex in yeast mitochondria for the biosynthesis of coenzyme Q. J Biol Chem. 2005; 280(21): 20231-8.

Martinefski M, Samassa P, Buontempo F, Hocht C, Tripodi V. Relative

bioavailability of CoQ10 formulation for paediatric individualised therapy. *J Pharm Pharmaco*l 2017; **69**: 567-573.

Mantle D. Coenzyme Q10 and cardiovascular disease: an overview. *Brit J Cardiol* 2015; **22(4)**: 1-7.

Matsuzaki S, Szweda PA, Szweda LI, Humphries KM. Regulated production of free radicals by the mitochondrial electron transport chain: Cardiac ischemic preconditioning. Adv Drug Deliv Rev; 61: 1324-1331, 2009.

Meyer A, Laverny G, Bernardi L, Charles AL, Alsaleh G, Pottecher J et al. Mitochondria: an organelle of bacterial origin controlling inflammation. Front Immunol; 9:536, 2018.

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**: 44-49.

Montini G, Malaventura C, Salviati L. Early CoQ10 supplementation in primary CoQ10 deficiency. *N Enl J Med* 2008; **358**: 2849-2850.

Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of CoQ10 on morbidity and mortality in chronic heart failure: the Q-SYMBIO randomized double blind trial. *JACC Heart Failure* 2014: **2**: 641-649.

Mutsaers HA, Wilmer MJ, Jawnsen J et al. Uremic toxins inhibit renal metabolic capacity through interference with glucuronidation and mitochondrial respiration. *Biochim Biophys Acta* 2013; **1832**: 142-150.

Navas P, Villalba JM, de Cabo R. The importance of plasma membrane coenzyme Q in aging and stress responses. Mitochondrion.2007; 7S: S34-S40.

Neergheen V, Chalasani A, Wainwright L, et al. Coenzyme Q_{10} in the treatment of mitochondrial disease. J Inborn Errors of Metab Screenin.2017;5: 1-8.

Oberg BP, McMenamin E, Lucas FL, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe CKD. *Kidney Int* 2004; **65**: 1009-1016

Owada S, Maeba T, Sugano Y, et al. Spherical carbon adsorbent protects deterioration of renal function in CKD rats through inhibition of ROS production from mitochondria and reduction of serum lipid peroxidation. *Nephron Exp Nephro*l 2010; **115**: doi 10.1159/000313491.

Picca A, Lezza AMS, Leeuwenburgh C, et al. Fueling Inflamm-Aging through Mitochondrial Dysfunction: Mechanisms and Molecular Targets. Int J Mol Sci. 2017; 18(5):933.

Public Health England. CKD prevalence model: UK renal registry, 2014:Pp 1-16.

Qu H, Guo M, Chai H, Wang W, Gao Z, Shi D. Effects of CoQ10 on statin induced myopathy:an updated meta-analysis of randomised controlled trials. J Am Heart Assoc; 7: e009835, 2018.

Quinlan CL, Perevoshchikova IV, Hey-Mojensen M, et al. Sites of reactive oxygen species generation by mitochondria oxidizing different substrates. Redox Biology. 2013; 1(1): 304-312.

Quinzii C, Naini A, Salviati L, et al. A mutation in para-hydroxybenzoate-polyprenyl transferase causes primary CoQ10 deficiency. *Am J Hum Genet 2006;* **78**: 345-349.

Rivara MB, Yeung CK, Cohen C, Phillips BR, Ruzinski J, Rock D et al. Effect of CoQ10 on biomarkers of oxidative stress and cardiac function in hemodioalysis patients: the CoQ10 biomarker trial. Am J Kidney Dis; 69:389-399, 2017.

Romagnoli, A., Oradei, A., Destito, C. Protective role in vivo of coenzyme Q10

during reperfusion of ischemic limbs. Molecular aspects of medicine. 1994; 15

Suppl:177–85.

Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. *Nat Rev Dis Primers* 2017; 3:doi: 10.1038/nrdp.2017.88.

Rotig A, Geromel V, Chretien D, Kadhom N, Edery P, Lebideau M et al. Quinone responsive multiple respiratory chain dysfunction due to widespread CoQ10 deficiency. *Lancet 2000;* **356**: 391-395.

Salviati L, Sacconi S, Murer L, et al: Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10 responsive condition. *Neurology 2005*; **65**: 606-608.

Sarkar S, Malovic E, Harishchandra DS, et al. Mitochondrial impairment in microglia amplifies NLRP3 inflammasome proinflammatory signaling in cell culture and animal models of Parkinson's disease. NPJ Parkinsons Dis. 2017;3:30: doi: 10.1038/s41531-017-0032-2. eCollection 2017.

Schmelzer C, Lindner I, Rimbach G, Menke T, Doring F. Function of coenzyme Q10 in inflammation and gene expression. *Biofactors* 2008; **32**(1-3):179-183.

Singh RB, Kumar A, Niaz MA, Singh RG, Gujrati S, Singh VP et al. Randomised double blind placebo controlled trial of CoQ10 in chronic renal failure. *J Nutr Environ Med* 2000*;* **10**: 281-288.

Singh L, Singh G, Dinda AK. Understanding podocytopathy and its relevance to clinical nephrology. *Indian J Nephrol* 2015;**25**: 1-7.

Skarlovnik A, Janic M, Lunder M, Turk M, Sabovic M. CoQ10 supplementation decreases statin related mild to moderate muscle symptoms: a randomised controlled study. Med Sci Monit; 20: 2183-2188, 2014.

Solin ML, Pitkanen S, Taanman JW, Holthofer H. Mitochondrial dysfunction in congenital nephrotic syndrome. *Lab Invest 2000;* **80**: 1227-1232.

Stepien KM, Heaton R, Rankin S, et al. Evidence of oxidative stress and secondary mitochondrial dysfunction in metabolic and non-metabolic disorders. *J Clin Med* 2017; **6**: doi: 10.3390/jcm6070071.

Su M, Yuan Y, Huang S, et al. Mitochondrial dysfunction is an early event in aldosterone induced podocyte injury. *Am J Physiol Renal Physiol* 2013; **305**: 520-531.

Takahashi, T., Okamoto, T. & Kishi, T. Characterization of NADPH

dependent ubiquinone reductase activity in rat liver cytosol: effect of various

factors on ubiquinone-reducing activity and discrimination from other quinone reductases. Journal of biochemistry, 1996;119(2): pp.256–63.

Tomasetti M, Alleva R, Solenghi M, Littarru GP. Distribution of antioxidants among blood components and lipoproteins: significance of lipids/CoQ10 ratio as a possible marker of incresed risk for atherosclerosis. *Biofactors* 1999; **9**: 231-240.

Triolo L, Lippa S, De Sole P, Mori R. Serum CoQ10 in uremic patients on chronic hemodialysis. *Nephron* 1994; **66**: 153-156.

Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. Biochimica et Biophysica Acta (BBA) Biomembranes. 2004; 1660(1–2): 171-199.

Villalba, J.M. & Navas, P. Plasma Membrane Redox System in the Control of

Apoptosis. Antioxidants and redox signalling.2000; 2(2):213–230.

Weber C et al.The CoQ10 content of the average Danish diet. Int J Vitam Nutr Res 1997; **67**: 123-129.

Weis M, Mortensen SA, Rassing MR, Poulsen G, Rasmussen SN. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. *Mol Aspects Med* 1994*;* **15(S)**: 273-280.

Yeung CK et al. CoQ10 dose escalation study in hemodialysis patients: safety, tolerability and effect on oxidative stress. *BMC Nephrology* 2015; **16**: 183-191.

Yubero D, Montero R, Artuch R, et al. Biochemical diagnosis of CoQ10 deficiency. *Mol Syndromol* ***2014***; 5: 147-155.

Yubero D, Montero R, Martin MA, et al. Secondary CoQ10 deficiencies in oxidative phosphorylation (OXPHOS) and non-OXPHOS disorders. *Mitochondrion* 2016; **30**: 51-58.

Yubero D, Montero R, Ramos M, Navas P, Hargreaves IP. Determination of urinary CoQ10 by HPLC with electrochemical detection: reference values for a paediatric population. *Biofactors* 2015; **41**: 424-430.

Yubero D, Montero R, Santos-Ocana C, Salviati L, Navas P,Artuch R. Molecular diagnosis of Coq10 deficiency: an update. Expert Rev Mol Diagn; 18:491-498, 2018.

Zahed NS, Ghassami M, Nikbahkt H. Effects of CoQ10 supplementation on C-reactive protein and homocysteine as inflammatory markers in hemodialysis patients: a randomised controlled trial. *J Nephropathol 2016*; **5**: 38-43.

Figure Legends

Figure 1. Diagram of the mitochondrial respiratory chain (MRC) and complex V illustrating proton (H+) movement during oxidative phosphorylation. Q: Coenzyme Q_1 and Cyt C: Cytochrome c

Figure 2: Figure 1: Structures of Coenzyme Q_{10} ($CoQ_{10;}$ A) and ubiquinol (B).