Coenzyme Q\textsubscript{10} supplementation – In ageing and disease

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\begin{abstract}
Coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) is an essential component of the mitochondrial electron transport chain. It is also an antioxidant in cellular membranes and lipoproteins. All cells produce CoQ\textsubscript{10} by a specialized cytoplasmatic-mitochondrial pathway. CoQ\textsubscript{10} deficiency can result from genetic failure or ageing. Some drugs including statins, widely used by elderly, may inhibit endogenous CoQ\textsubscript{10} synthesis. There are also chronic diseases with lower levels of CoQ\textsubscript{10} in tissues and organs. High doses of CoQ\textsubscript{10} may increase both circulating and intracellular levels, but there are conflicting results regarding bioavailability. Here, we review the current knowledge of CoQ\textsubscript{10} biosynthesis and primary and acquired CoQ\textsubscript{10} deficiency, and results from clinical trials based on CoQ\textsubscript{10} supplementation. There are indications that supplementation positively affects mitochondrial deficiency syndrome and some of the symptoms of ageing. Cardiovascular disease and inflammation appear to be alleviated by the antioxidant effect of CoQ\textsubscript{10}. There is a need for further studies and well-designed clinical trials, with CoQ\textsubscript{10} in a formulation of proven bioavailability, involving a greater number of participants undergoing longer treatments in order to assess the benefits of CoQ\textsubscript{10} treatment in neurodegenerative disorders, as well as in metabolic syndrome and its complications.
\end{abstract}

1. Introduction

Coenzyme Q (CoQ) is a lipid-soluble antioxidant that is produced de novo in animal cells (Laredj et al., 2014) (Fig. 1). CoQ is also called ubiquinone since the molecule contains a quinone ring, in addition to its apparently ubiquitous presence in all animal cells (Garrido-Maraver et al., 2014). The quinone core, which is a benzoquinone ring, has a polyisoprenoid tail containing 10 subunits in humans, and from 6 to 10 subunits in various animal species (Fig. 2). Here we will use the name CoQ\textsubscript{10}. Besides being a crucial component in the mitochondrial electron transport chain, in its reduced form, ubiquinol, it also plays an important role as antioxidant in lipid structures, such as cellular membranes and lipoproteins, protecting these from damaging oxidative processes (López-Lluch et al., 2010).

According to the mitochondrial free radical theory of ageing, originally proposed by Harman (1972), injury to mitochondria is an important factor in cellular ageing. Later, Eirin et al. (2016) suggested that generation of reactive oxygen species (ROS) from the mitochondrial respiratory chain increases with age, with mitochondrial DNA presumably being a major target for mitochondrial-derived ROS. Injury to mitochondrial DNA impairs the function of the respiratory chain resulting in additional ROS formation and DNA lesions and acceleration of cellular ageing (Poulose and Raju, 2014), whereas maintenance of adequate CoQ10H2-levels appears to induce reparations of oxidative damage through direct interaction with DNA repair enzymes (Schniertshauer et al., 2020).

In addition to inborn errors in CoQ\textsubscript{10} synthesis (Fig. 1), the level of CoQ\textsubscript{10} declines with age, and food supplements are marketed with claims to restore the levels and improve health (Mantle and Dybbing, 2020). The aim of this this paper is to review the role of CoQ\textsubscript{10} for human health with a specific focus on ageing and diseases related to ageing and possible clinical benefits of supplementation.

2. Physiology of CoQ\textsubscript{10}

CoQ\textsubscript{10} is both located in the mitochondria and in extramitochondrial structures. It can exist in three different oxidation states, the fully oxidized state (ubiquinone), the partially reduced state (ubisemiquinone), and the fully reduced state (ubiquinol) (Fig. 2). In the mitochondria it is found in the inner membrane where it transports electrons...
Mechanisms of Ageing and Development 197 (2021) 111521

from the complexes I and II to complex III, thus providing energy for proton translocation to the intermembrane space. CoQ\textsubscript{10} transfers two electrons to cytochrome c in complex III in the electron chain; what happens is that ubiquinol donates the first electron to the Rieske iron-sulfur protein and the unstable ubisemiquinone then donates an electron to the low-potential heme of cytochrome b (Wang and Hekimi, 2016). In this way the reduced form of CoQ\textsubscript{10} (ubiquinol) is oxidized to ubiquinone. The reduced form (ubiquinol) can then be restored by accepting electrons either from complex I or II in the electron transport chain or from some other source, such as from acyl-CoA dehydrogenase. The electron chain transfer flavoprotein (ETF) and the electron transfer flavoprotein ubiquinone oxidoreductase (ETF:QO) are central elements in the donation of electrons from a series of dehydrogenases to ubiquinone in the respiratory chain (Henriques et al., 2021). The redox cycling of ubiquinol to ubiquinone and back to ubiquinol and thereby being an electron carrier supporting the proton pump is known as the Q-cycle (Wang and Hekimi, 2016). Despite a regeneration of CoQ\textsubscript{10} in the respiratory chain, deficiency may occur in the heart muscle during heart failure (Mortensen et al., 1984) and supply by CoQ\textsubscript{10} synthesis is of vital importance.

Coenzyme Q10 may also play a pro-oxidant role as the unstable ubisemiquinone may react with molecular oxygen and form superoxide radicals (Fig. 2). In the mitochondria these are released into the intermembrane space but cannot cross membranes. Superoxide dismutase enzymes convert superoxide radicals into hydrogen peroxide, which can pass membranes and diffuse into inner mitochondrial space and the cytosol. The regulated formation of the reactive oxygen substances (ROS) may not only be deleterious but also serve as signaling messengers (Linnane et al., 2007; Wang and Hekimi, 2016).

Functional adequacy of CoQ\textsubscript{10} is also important for the expression of several genes related to cell signaling pathways interfering with inflammation and metabolism (Schmelzer et al., 2008; Abdi et al., 2020).

In addition to its functional roles, CoQ\textsubscript{10} is also a structural component, inter alia in complexes I and III in the mitochondrial electron chain.
Regarding its entry into skeletal muscle (Paredes-Fuentes et al., 2020). J. Aaseth et al.
solubility it first enters the lymph system and thereafter passes into selenoenzyme thioredoxin reductase 1 (TNXRD1) in the cytosol (Fig. 2) in its reduced form, ubiquinol, is upon oxidation reduced either by the central station in the electron chain (Morgenstern et al., 2017).

Core attachment as well as the formation of the complex multiprotein syntheatic step, the tail-to-core attachment, is catalyzed by the UbiA prenyltransferase domain-containing protein-1 (UBIAD1), which exhibits multi-subcellular localization, i.e. in mitochondria, endoplasmic reticulum and Golgi apparatus. UBIAD1 is also known to participate in the vitamin K2 synthesis (Nakagawa et al., 2014). UBIAD1 appears to protect cardiovascular tissues from eNOS-dependent oxidative stress via synthesis of CoQ10 (Mugoni et al., 2013). In the mitochondria the tail-to-core attachment as well as the formation of the complex multiprotein known as the “synthome” take place, the latter multiprotein constituting a central station in the electron chain (Morgenstern et al., 2017).

Non-mitochondrial CoQ10 that works as a lipid-soluble anti-oxidant in its reduced form, ubiquinol, is upon oxidation reduced either by the selenoenzyme thioredoxin reductase 1 (TNXRD1) in the cytosol (Fig. 2) or by the NADPH-dependent coenzyme Q reductase (Xia et al., 2003; Nordman et al., 2003; Takahashi et al., 2008).

Given the central role of CoQ10 in the cell, genetic or acquired deficiency states can lead to several disorders associated with symptoms from cardiovascular, immunological and neurological systems. Its deficiency has also been discussed in relation to the pathogenesis of metabolic syndrome and type 2 diabetes (Garrido-Maraver et al., 2014). Nowadays, CoQ10 is used as ubiquinone in food supplements, but its conversion from the oxidized form to reduced form (CoQ10H2, ubiquinol) is essential for its functions (Zhang et al., 2018).

2.1. Intestinal absorption and distribution

The blood plasma concentration of ubiquinone is generally in the range of 0.40–2.0 μmol/L (0.35–1.7 mg/L) (Bhagavan and Chopra, 2006). CoQ10 is absorbed from the intestine, but due to its low water solubility it first enters the lymph system and thereafter passes into systemic circulation (Palamakula et al., 2005). The CoQ10 absorption may be retarded by coadministration of vitamin E (Constantinescu et al., 2007), and its bioavailability also depends on carrier lipids in the supplement used (López-Lluch et al., 2019). The bioavailability and entry into tissues and mitochondria of supplemental CoQ10 have been a matter of discussion as some studies in rats only showed a very low intestinal absorption and transport into tissues except for liver, spleen, and white blood cells, with low levels in hepatic mitochondria (Zhang et al., 1996; Bentinger et al., 2003). On the other hand, in a study in mice receiving daily 148 or 654 mg CoQ10 per kg body weight for eleven weeks both CoQ9 and CoQ10 were increased in homogenates and in mitochondria of liver, skeletal muscle and heart, in addition to mitochondria of the brain (Kamzalov et al., 2003). In rats, doses of 150 mg/kg/day or higher can lead to raised levels of total CoQ10 in the heart and muscles, indicating that peripheral tissues may accumulate CoQ10 when present in high concentrations in the plasma (Kwong et al., 2002). Conflicting results has also been reported in humans receiving supplemental CoQ10 regarding its entry into skeletal muscle (Paredes-Fuentes et al., 2020).

Differences in bioavailability of CoQ10 can be ascribed to differences in chemical and physical form and vehicle given, e.g. carrier lipids and solubilization (López-Lluch et al., 2019). Thus, use of different pharmaceutical formulations may explain observed differences in results of clinical trials.

3. Genetic deficiencies of CoQ10

In patients suffering from the very rare inherited diseases of genetic CoQ10 deficiency with impaired ATP generation the diagnosis is usually based on decreased CoQ10 levels measured in skeletal muscle (Gorman et al., 2016; Rodríguez-Aguilera et al., 2017). Primary CoQ10 deficiencies are caused by mutations in genes that encode enzymes in the biosynthesis of the coenzyme. In addition, there also exist some few secondary CoQ10 deficiencies caused by defects in other mitochondrial functions that are only indirectly related to the CoQ10 biosynthesis.

Here, we will only briefly discuss the primary CoQ10 deficiencies. CoQ10 is involved in crucial biochemical reactions among which the production of ATP in the mitochondrial respiratory chain is of particular importance. The CoQ10 biosynthesis requires at least 13 genes, and mutations in these genes cause primary CoQ10 deficiency. Mutations known to cause primary CoQ10 deficiency can occur in the following genes: PDSS1, PDSS2, COQ2, COQ4, COQ6, ADCK3, ADCK4, and COQ9 (Doimo et al., 2014). The resulting disorders are dependent on the location and extent of the genetic defect characterized by highly heterogeneous clinical signs, with varying severity (Rüttig et al., 2007). The age of disease onset can be from birth to old age. Clinical manifestations that might indicate primary CoQ10 deficiency are: (a) nephrotic syndrome associated with deafness, retinopathy, and other neurological defects; or (b) encephalopathy including strokes, cerebellar ataxia, neuropathy, and intellectual disability. In these deficiencies pathogenic mutations have occurred in genes directly involved in the CoQ10 biosynthesis (Desbats et al., 2016).

Reduced CoQ10 levels resulting from pathologies caused by mutations in genes encoding other components of the electronic chain without primarily involving the CoQ10 biosynthesis have been discussed by Yubero et al. (2016). As for the primary CoQ10 deficiencies, the European Medicine Agency has recently approved ubiquinol as an orphan therapeutic drug (Hernández-Camacho et al., 2018). In addition to primary deficiencies in the synthesis of CoQ10, secondary deficiencies such as impaired function of the ubiquinone electron donor system ETF and ETF:QO has been reported, which may result in a deficient function of Q-cycle (Henriques et al., 2021; Navas et al., 2021).

4. CoQ10 deficiency in older age groups and effects of statins and bisphosphonates

The endogenous production of CoQ10 decreases after the age of 20, and the myocardial concentration of CoQ10 is reduced to about half at the age of 80 (Fig. 3) (Kalén et al., 1989; Gutierrez-Mariscal et al., 2019). In a group of elderly individuals given a combination of selenium and ubiquinone over a 4-year period, an improved physical performance was reported (Johansson et al., 2015), and CoQ10 supplementation appears to confer health benefits in elderly people by preventing oxidative stress associated with cardiovascular and other diseases (González-Guardia et al., 2010). By its presence in practically all cellular membranes, CoQ10 offers antioxidant protection against liperoxidation (Fig. 2). It also forms a component of low-and high-density lipoproteins in the blood and thereby protects these against lipid peroxidation and may reduce risk of arteriosclerosis (Pacanowski et al., 2008).
et al., 2015).

Of interest in this context is that the endogenous synthesis of CoQ10 is inhibited by certain classes of drugs such as statins and bisphosphonates, often used by elderly people (Littarru and Langsjoen, 2007). Statins are inhibitors of the synthesis of mevalonate, an intermediate molecule acting as a precursor for both cholesterol and CoQ10. In an in vitro skin model, statin addition resulted in CoQ10 deprivation and signs of ageing, but upon addition of CoQ10 to the medium, the tissue levels could be restored, and markers of ageing were reduced (Marcheggiani et al., 2021). The reduced form, CoQ10H2, appeared more bioavailable and even improved oxidative status of mitochondria. Statins are extensively used in the treatment of several abnormalities associated with the age-related diseases in the cardiovascular system, such as hypercholesterolemia, particularly after heart infarction and stroke, and such treatment may reduce the plasma levels of circulating CoQ10 (Nawar et al., 2003). In some patients, statins may cause side effects, such as myalgia and general discomfort, which have been attributed inter alia to the inhibition of coenzyme CoQ10 synthesis (Mollazadeh et al., 2021). It is well-established that depletion of coenzyme Q10 has an association with myopathies due to abnormal function of mitochondria in the cell. Although a part of the statin-induced lowering of CoQ10 could be explained by a decrease in the circulating levels of LDL-cholesterol, it is relevant here that statins also reduce the levels of CoQ10 in blood platelets. Furthermore, it has been observed that the combination therapy of the statin simvastatin and an inhibitor of intestinal cholesterol absorption, ezetimibe, reduced the levels of CoQ10 while treatment with ezetimibe alone did not reduce these levels (Berthold et al., 2006).

Another class of CoQ10 inhibitors is bisphosphonates, which are used in the treatment of osteoporosis with symptoms of increased bone fragility (Kalyan et al., 2014). Like statins, the use of some of these agents may cause side effects like muscle pain, general discomfort, and even osteonecrosis in some few cases. These side effects might be precipitated by the ability of high-dosed bisphosphonates to reduce the levels of CoQ10 by inhibiting farnesyl pyrophosphate synthase, an enzyme that catalyzes a crucial step in the synthesis of CoQ10 (Tricarico et al., 2015). For patients undergoing treatment with statins or bisphosphonates, proper supplementation of CoQ10 is thought to act beneficial in preventing some of the side effects.

5. Clinical supplementation with CoQ10 (ubiquinone)

5.1. Form of supplementation in various conditions

Whereas the reduced form of CoQ10, (CoQ10H2, ubiquinol) has been approved for the treatment of genetic CoQ10 deficiencies (Hernandez-Camacho et al., 2018), dietary supplementation in other conditions has mostly made use of the oxidized form of CoQ10, often in combination with an antioxidant such as selenium or vitamin C. Such combinations are presumed to reduce oxidative stress and thereby act as a potential therapeutic strategy to alleviate or retard the development of some age-related disorders (Sharogorsky et al., 2010). However, there are also commercially available dietary supplements with the reduced form of CoQ10. The use of nano-lipid particles and other modifications in the vehicle and formulation increases, the bioavailability in comparison with conventional Q10 products (Lopez-Lluch et al., 2019; Wei et al., 2019).

5.2. Combining CoQ10 with selenium

When combining selenium supplementation with oxidized CoQ10, the coenzyme is presumed to be reduced to CoQ10H2 by the action of the selenoenzyme TNXRD (Xia et al., 2003). Combined CoQ10 (200 mg/day) and selenium (200 μg/day) supplementation for four years in an elderly Swedish population low in selenium appeared to protect against cardiovascular disease with plaque formation (Alehagen et al., 2018a). In many cases atherosclerosis represents a complication to type 2 diabetes (T2DM), a disease characterized by disruption of carbohydrate and lipid metabolism. Today, insulin resistance, obesity and T2DM with its serious complications are unprecedented global health concerns (Khan et al., 2020).

It has been observed that patients with T2DM have low levels of CoQ10 in their plasma, and supplementation with CoQ10 and selenium in the same study as referred to above also appeared to reduce formation of advanced glycated products (Alehagen et al., 2020a). Furthermore, supplementation with CoQ10 alleviated endothelial dysfunction associated with diabetic complications (Hamilton et al., 2009; Watts et al., 2002). Hence, in the population given coenzyme Q10, combined with selenium, Alehagen et al. observed a significant decrease in the plasma concentrations of von Willebrand factor and PAI-1 (plasminogen activator inhibitor-1), which was interpreted as a normalization of endothelial function in the supplemented subjects as compared with those given placebo (Alehagen et al., 2020b).

Studies have indicated that the use of some other antioxidants than selenium, specifically the water-soluble agent vitamin C in a combination of lipid soluble CoQ10, displayed synergistic antioxidant effects. A recent study in an animal model showed that combination of CoQ10 and vitamin C significantly reduced the cerebral level of oxidative stress induced by a lipopolysaccharide infusion, as reflected by a reduction in the levels of malondialdehyde, and amyloid-beta (Aβ) proteins (El-Laithy et al., 2018).

5.3. Safety of CoQ10 supplementation

Clinical trials, systematic reviews, and meta-analyses have examined the safety and efficacy of CoQ10 in the treatment of human diseases. With regards to safety, the highest dose for long-term CoQ10 supplementation is 1200 mg daily, although doses as high as 3000 mg/day have been used in short-term clinical trials (Hatchcock and Shao, 2006). Several factors including a relatively small number of well-controlled clinical trials, differences in designs, plus a limited number of patients enrolled, in addition to rather short follow-up periods contribute to inconsistencies in the published data. Although taking these limitations into account, CoQ10 can be considered an adjuvant in the treatment of different diseases, especially in some conditions affecting the elderly, which are briefly discussed in the paragraphs below.

5.4. Cardiovascular diseases

Persistent heart failure that is accompanied by increased formation of reactive oxygen species (ROS) can be attenuated with endogenous or exogenous antioxidants. A systematic review has examined the efficacy of CoQ10 supplementation in the prevention of cardiovascular disease without lifestyle intervention (Flowers et al., 2014). The authors interpreted the results to indicate a significant reduction in systolic blood pressure without improvements in other risk factors such as for instance total cholesterol. Another meta-analysis that examined the impact of CoQ10 on the prevention of complications in patients undergoing cardiac surgery concluded that CoQ10 therapy reduces the appearance of ventricular arrhythmias after surgery (de Frutos et al., 2015). A 2-year treatment with CoQ10 (300 mg/day) as adjuvant therapy in a randomized, controlled multicenter trial on 420 patients suffering from heart failure demonstrated a reduction in major cardiovascular events (Mortensen et al., 2014). A recent study from Japan consecutively enrolled 242 patients admitted to the coronary unit with cardiovascular disease. During a follow-up of 3.2 years it was observed that the mean serum CoQ10 levels were significantly lower in the non-survivors than in the survivors, and a multivariate Cox regression analysis demonstrated that a low CoQ10 level was associated with poor prognosis (Shimizu et al., 2021).

In the study mentioned above on the effects of long-term treatment with CoQ10 (200 mg/day) plus selenium (200 μg as selenized yeast) in a
Swedish healthy elderly population, we revealed a significant reduction in cardiovascular mortality during the 4-year treatment period, as well as during an extended observation period of 12 years, compared with those taking a placebo during the intervention period (Alehagen and Aaseth, 2015; Alehagen et al., 2018b). Here, it is relevant that CoQ10 combined with selenium also reduced the levels of glycosylated plasma proteins and D-dimer, which represent risk factors for cardiovascular mortality (Alehagen et al., 2020a).

5.5. Inflammation

Chronic inflammation and oxidative stress occur in many age-related diseases, including cardiovascular diseases, diabetes and chronic kidney disease. A recent meta-analysis explored the efficacy of CoQ10 on the plasma concentrations of C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) in patients with various diseases with significant inflammation as a common factor and concluded that CoQ10 in doses ranging from 60 to 500 mg/day for periods from one week to four months significantly decreased production of inflammatory cytokines (Fan et al., 2017). In another analysis, diseases characterized by chronic, low grade inflammation responded well to CoQ10 supplementation with significant decrease in circulating TNF-α without having significant effect on CRP (Zhai et al., 2017). Of note, a deficient CoQ10 status also might be involved in the pathogenesis of fibromyalgia, a clinical condition with chronic muscle pain often accompanied by stiff joints, pain, and fatigue. It was observed that patients with this disease had increased levels of mitochondrial oxidative stress, which was ascribed to low level of CoQ10, as administration of CoQ10 improved the clinical symptoms of a small group of patients (Cordero et al., 2011). Alleviation of symptoms of chronic fatigue syndrome or myalgic encephalopathy has also been reported after supplementation with CoQ10 combined with a niacin derivative (Campagnolo et al., 2017).

5.6. Neurodegenerative diseases

Early studies in animal models noted that CoQ10 could preserve mitochondrial function and reduce the loss of dopaminergic neurons characterizing Parkinson’s disease (Schulz and Beal, 1995). Further, a screening for oxidative stress markers in patients with Parkinson’s disease reported lower levels of CoQ10 and higher levels of lipoprotein oxidation in the plasma, cerebrospinal fluid, and the cortex region of the brain compared with non-affected individuals (Buhmann et al., 2004; Hargreaves et al., 2008). Moreover, deficiency in circulating CoQ10 was observed at a higher frequency in Parkinson’s disease patients than in controls (Mischley et al., 2012). Clinical trials in patients suffering from this disease indicated that CoQ10 supplementation could delay the functional decline (Shults, 2003). Four randomized, double-blind, placebo-controlled studies comparing CoQ10 treatment in 452 patients at early or mid-stage Parkinson’s disease reported improvements in daily activities (Liu et al., 2011).

Based on observations in this disease, it has been suggested that CoQ10 supplementation could also benefit patients suffering from other neurodegenerative diseases. However, a review including recent clinical trials testing CoQ10 supplementation reported lack of improvement in motor functions in patients with unspecified neurodegenerative diseases (Negida et al., 2016). Specifically, there is no evidence to indicate that CoQ10 supplementation can delay the progression of Huntington’s disease (McGarry et al., 2017) or of Alzheimer’s disease (Galasko et al., 2012). A poor transport of CoQ10 across the blood-brain barrier may explain the latter results (Wainwright, 2018; Wainwright et al., 2020).

In another rather heterogeneous neuropsychiatric disease, autistic spectrum disorders (ASDs), a role of CoQ10 has been proposed (Crane et al., 2014). Treatment with a combination of CoQ10 and B-vitamins appears to be associated with some improvements in ASD patients (Rossignol and Frye, 2012). Treatment with CoQ10 has also been found to confer protection against progression of oxidative damage and mitochondrial dysfunction in Down syndrome patients (Tiano and Busciglio, 2011).

6. Concluding remarks

Mitochondrial CoQ10 is an important cofactor present in the inner mitochondrial membrane and crucial for ATP synthesis in addition to forming an essential component in the cellular antioxidant defense mechanism. Non-mitochondrial CoQ10 has important functions in cellular membrane and lipoproteins by preventing lipoperoxidation and regulating eNOS activity. Various observations have confirmed that reduced biosynthesis, genetically or acquired, of coenzyme Q adversely affects crucial vascular and cerebral functions of the human body. The natural protection against disorders with oxidative stress and inflammation is considered a major contributing factor. For example, many patients with diabetes type 2, cardiovascular disorders, atherosclerosis, and neurodegenerative disorders have lowered levels of CoQ10 in their plasma. The use of certain drugs for the management of cholesterol metabolism disorders, such as statins, can significantly compromise CoQ10 levels in the body due to their inhibitory effects on its synthesis. A combined supplementation of CoQ10 (ubiquinone) with selenium, particularly in populations low in selenium, or vitamin C (ascorbic acid), an important water-soluble antioxidant, appears to optimize its antioxidant and anti-inflammatory effects, presumably by converting the coenzyme into its active reduced state, ubiquinol (CoQ9H2).

Early supplementation with CoQ9H2 in various primary deficiencies can improve mitochondrial functions. Supplementation with CoQ10 may also confer antioxidant protection to organs and tissues affected by various pathophysiological conditions. The ability of CoQ10 to protect against the release of proinflammatory markers provides an attractive anti-inflammatory therapeutic for the treatment of some human diseases in ageing. The absorption of CoQ10 is slow and limited due to its hydrophobicity, and studies using high doses of CoQ10 or CoQ9H2 in a formulation with proven bioavailability are needed. More studies performed on humans in focused and well-designed trials are requested in order to understand the clinical effects of CoQ10.

Author contributions

J.Aas, JA, and UA have written the paper draft. J.Aas, JA and UA have a final responsibility for the content. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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