NUTRITIONAL MEDICINE REVIEWS

Coenzyme Q10: A Review of Clinical Use and Efficacy

Karin Elgar

ABSTRACT

Coenzyme Q10 (CoQ10) plays an essential role in energy production as part of the mitochondrial electron transfer chain. It also has antioxidant functions and is important for gene regulation, especially of genes involved in cell signalling, metabolism, inflammation, transport and transcription control. Whilst we can obtain small amounts from our diet, most CoQ10 is synthesised in our bodies, which is why it is not considered to be a vitamin. Production declines with age and may also be impaired through illness and/or certain medications, making supplementation an interesting intervention. Although clinical research has been mixed in some indications, CoQ10 supplementation has been found to be a safe and effective intervention in a variety of conditions, including cardiometabolic disorders, fibromyalgia syndrome, migraine and male infertility.

Cite as (AMA): Elgar K. (2021) Coenzyme Q10: A Review of Clinical Use and Efficacy. *Nutr Med Rev*., 1 (1), xxx.
Affiliation: K. Elgar is with the Nutritional Medicine Institute, London, UK.
Article history: Received 10 March 2021. Peer-reviewed and received in revised form 13 May 2021. Accepted 17 May 2021. Available online xxx.
Published by: The Nutritional Medicine Institute **www.nmi.health**

INTRODUCTION

Coenzyme Q10 (CoQ10), also called ubiquinone, is a fat-soluble, vitamin-like substance which, as the name suggests, is ubiquitous to all cellular membranes in our bodies. It plays an essential role in mitochondrial function as part of the electron transfer chain, which produces adenosine triphosphate (ATP), the energy currency of our cells. CoQ10 also has important antioxidant functions, preventing oxidation of lipids, proteins and DNA by recycling other antioxidants, including vitamins C and E, increasing production of antioxidant enzymes, such as superoxide dismutase, and preserving nitric oxide (NO).[1] CoQ10 also plays a role in regulating gene expression, in particular of genes involved in cell signalling, metabolism, inflammation, transport and transcription control.[2]

We can obtain CoQ10, although generally in small amounts only, through our diet, in particular from organ meats like heart and liver, which contain in the range of 22–282 mg/kg.[3] CoQ10 is also synthesised in our bodies via the mevalonate pathway, which is also involved in the synthesis of cholesterol,[1] and is therefore not considered to be a vitamin. Dietary supplements provide CoQ10 in either the oxidised form (ubiquinone) or the reduced form (ubiquinol); where publications have specified which form was used, this is mentioned in the section: 'Clinical uses'. As CoQ10 switches rapidly between these two forms, the choice of supplement appears to be less important than the lipid carrier or other excipients that affect absorption and/or bioavailability.[4] There also appears to be significant variation in terms of absorption and bioavailability between individuals.[4] Being fat-soluble, CoQ10 is best taken with a meal, which increases absorption threefold.[2]

Endogenous CoQ10 levels depend on rates of both production and consumption. Levels of CoQ10 decline as we age, but can also decrease through illness or use of certain medications, for example, statins. Severe deficiency can be due to genetic defects as, for example, seen in cerebellar ataxia, Leigh syndrome and infantile encephalopathy.[2]

CoQ10 can be measured in serum and plasma, although it is unclear how well this correlates with tissue concentrations.[5] Establishing CoQ10 levels may help identify those who would benefit most from supplementation, and regular testing may also be useful to monitor the efficacy of supplementation in view of both inter-individual variability of absorption and variable bioavailability of different formulations.[5]

In view of its important role in energy production, gene regulation and as an antioxidant, CoQ10 supplements have become popular for a large range of clinical uses. The aim of this paper is to review the evidence from human clinical trials.

CLINICAL USES

Athletic performance

Due to its important role in energy metabolism and as an antioxidant, CoQ10 has received much attention in sports nutrition, both in untrained and trained individuals, to boost performance and reduce oxidative stress and muscle damage.

In 2003, a review of 11 clinical trials investigating CoQ10 for athletic performance found mixed results, with six studies showing benefits and five showing no benefits.[6] The authors noted that those articles reporting nil effects were more likely to be published in peer-reviewed journals than those reporting positive results, more of which were published as conference proceedings only. The authors of the review also pointed out that all studies only included small numbers of participants (maximum 28) and were of different designs, making conclusions difficult. Since then, more randomised-controlled trials (RCTs) have been published but, again, most of them were small in size.

In elite athletes, the results from mostly small double-blind, placebo-controlled trials are largely positive, with CoQ10 supplementation having positive effects on oxidative stress, inflammatory markers and performance.[7,8,9,10] In relation to muscle damage, two studies showed inconsistent results – with one showing benefits[11] and one not.[12] Most studies used 300 mg per day for 2–4 weeks.

In non-elite, trained and untrained people, the evidence is mixed, with some studies reporting benefits in terms of inflammation,[13] bone formation,[14] oxidative stress/antioxidant

status,[15,16,17,18] performance[19,20] and muscle damage,[21] whilst others found no benefit for performance,[15,22,23,24,25,26] muscle damage[15,22,27,28] and oxidative stress.[22,23,24,27,28] One small study even found increased muscle damage and poorer performance with CoQ10 supplementation.[29,30] Dosages used ranged from 90 to 300 mg per day, and duration of supplementation ranged from 8 days to 12 weeks. Nil results have been observed with low as well as with higher dosages.

It should be noted that most of the trials were small and results may therefore have failed to reach statistical significance. Specific outcomes studied in the trials varied widely, as did study designs, making it difficult to compare trials and explain the contradictory findings. Both ubiquinone and ubiquinol have been used in these trials, and results were inconsistent for both compounds.

Based on the above studies, a dosage recommendation would be 300 mg per day for at least 4 weeks.

Bipolar disorder

Bipolar disorder (BPD) is a chronic and recurrent mental health disorder characterised by extreme changes in mood with episodes of mania and major depression.[31] Mitochondrial dysfunction, oxidative stress and inflammation are thought to play important roles in the development of the condition.[32] As CoQ10 can affect all three, a couple of RCTs have investigated its potential benefits alongside usual treatment regimes.

One open-label study in 32 older patients with BPD used 400 mg per day for 2 weeks, and then the dose was titrated up to 800 mg per day for another 2 weeks. Significant improvements were seen within 2 weeks. After 4 weeks, the MADRS score (Montgomery Asberg Depression Rating Scale, a scale of 0–60) had improved by 8 points.[33] A similar size effect on MADRS score was seen in a double-blind, placebo-controlled trial of 69 patients, using 200 mg CoQ10 per day for 8 weeks, with a gradual improvement.[32] The latter study also observed a decrease in oxidative stress and inflammatory markers, suggesting that the antioxidant and anti-inflammatory properties of CoQ10 may explain the mechanism of its benefits in BPD.[34]

Although evidence is limited, it appears that CoQ10 is of benefit alongside the usual treatment in BPD, and a dose of 200 mg per day for 8 weeks has been used successfully in clinical trials.

Cardiovascular disease and risk factors

Cardiovascular disease (CVD) is a general term for diseases that affect the heart and blood vessels, and is collectively one of the main causes of death in Western countries. CVD usually develops over many years, and risk factors include hypertension (high blood pressure), abnormal blood lipids, smoking and poor diet.

Few clinical trials on dietary supplements, like CoQ10, run for long enough to ascertain their potential benefits in reducing mortality and morbidity from CVD. Most studies therefore investigate risk factors as an outcome, and the ones relevant to CoQ10 are discussed below.

Two longer-term, double-blind clinical trials that reported on cardiac deaths and cardiovascular events have shown significant benefits of CoQ10, the largest and longest one being the Q-SYMBIO trial. Both are discussed below.[35,36]

Because CoQ10 has also been shown to improve a range of risk factors (even in the face of some mixed/contradictory evidence, see below), supplementation of 120–300 mg for at least a year could be beneficial for people with or at elevated risk of CVD.

Dyslipidaemia

Dyslipidaemia, abnormal levels of blood lipids including triglycerides and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, is considered to be an important risk factor for CVD.

A meta-analysis of 21 RCTs, involving 1039 participants with metabolic disorders, found that CoQ10 supplementation led to a significant decrease in triglycerides, but did not affect total, LDL or HDL cholesterol levels, with higher dosages (200 mg) appearing to be more beneficial than lower dosages.[37] Another meta-analysis,[38] including eight RCTs with a total of 526 patients with coronary artery disease (CAD), found that in this patient population, CoQ10 significantly lowered total cholesterol

and increased HDL cholesterol but had no effect on triglycerides, whilst improvements in LDL cholesterol and lipoprotein(a) failed to reach statistical significance. Dosages in the trials included in the meta-analyses ranged from 100 to 300 mg per day for 4–12 weeks in most studies, with two studies lasting 24 and 48 weeks, respectively.

Only one of the studies in the above meta-analyses had more than 65 study subjects: a double-blind study comparing CoQ10, 120 mg per day, versus B vitamins for 48 weeks in 144 patients after myocardial infarction.[35] This study showed that CoQ10 increased HDL cholesterol, and total to HDL cholesterol ratio decreased more than the control (B vitamins). Patients in the CoQ10 group also had significantly less cardiac events and cardiac deaths than the control group. A more recent double-blind, placebo-controlled study of 101 patients with dyslipidaemia showed that CoQ10, 120 mg per day for 24 weeks, significantly reduced triglycerides and LDL cholesterol.[39]

Whilst results are contradictory, the overall evidence suggests that CoQ10 may be beneficial in terms of improving blood lipids. The two biggest RCTs saw beneficial effects at a dosage of 120 mg per day for 24–48 weeks, suggesting that (to see significant benefits) supplementation should last at least 6 months.

Possible mechanisms include the beneficial effect of CoQ10 on glucose/insulin metabolism (see below), and its ability to reduce oxidative stress and regulate expression of genes involved in lipid metabolism.[37,38]

Endothelial dysfunction

The endothelium is the inner layer of blood vessels, and it controls vascular relaxation and contraction. In endothelial dysfunction there is an imbalance between vasodilating substances (which widen the blood vessels) and vasoconstricting substances (which narrow the blood vessels). NO plays an important role in mediating this vasodilation and constriction. Endothelial dysfunction is involved in the development of atherosclerosis and, as such, is a risk factor for CVD. High blood pressure, smoking and diabetes are thought to contribute to endothelial dysfunction.[40]

A 2012 meta-analysis of five studies, totalling 194 participants with endothelial dysfunction, found that CoQ10 was significantly better than placebo in improving endothelial function, determined as flow-mediated dilation.[41] Dosages used in the trials ranged from 150 to 300 mg per day, and study durations from 4 to 12 weeks. Since then, four double-blind, placebo-controlled trials have confirmed the benefits of CoQ10 in endothelial dysfunction,[42,43,44,45] of which three reported to have used ubiquinol.[42,44,45]

Dosages between 150 mg and 400 mg for at least 4 weeks have shown benefits, although longer duration has led to greater improvements.

The mechanisms involved are thought to be increased NO bioavailability, anti-inflammatory activity and enhanced LDL antioxidant protection.[41,42]

Heart failure

Heart failure, also called congestive heart failure, occurs when the heart muscle does not pump blood as efficiently as it should because it is too weak or stiff, resulting in symptoms such as shortness of breath, fatigue, and swollen ankles and legs. Common causes include high blood pressure and narrowed arteries supplying the heart muscle itself (CAD).

Heart failure can be divided into heart failure with reduced (less than 40%) ejection fraction (the percentage of the blood in the left ventricle that is pumped out with each heartbeat) and with preserved ejection fraction, where ejection fraction is normal or at least above 40%, and it is the relaxation, rather than the contraction, of the left ventricle that is affected.[46]

A 2017 meta-analysis of 14 RCTs with 2149 patients found that CoQ10 significantly reduced mortality and increased exercise capacity compared with placebo, whilst improvements in left heart ejection fraction and New York Heart Association (NYHA) cardiac function classification failed to reach statistical significance.[47] A number of reviews on the topic have also come to the conclusion that CoQ10 is effective in reducing mortality and morbidity in patients with heart failure.[48,49,50,51]

By far the largest double-blind, placebo-controlled trial of CoQ10 in heart failure is the Q-SYMBIO trial,[36] where 420 patients with moderate to severe heart failure received either CoQ10, 100 mg three times per day, or placebo for 2 years. Whilst there were no significant differences in short-term outcomes, only 15% of patients on CoQ10 had major cardiovascular events (the primary end-point of the study) compared with 26% of patients who received placebo. Both cardiac and all-cause mortality were significantly lower in the CoQ10 group, who also experienced a significant improvement of NYHA class compared with placebo. In this trial, the placebo group had more adverse events than the CoQ10 group.

CoQ10 has also shown benefits in children with dilated cardiomyopathy.[52,53,54] Dosages ranged from 3 to 10 mg per kg of body weight (mg/kg) per day, and duration of supplementation ranged from 24 weeks to 9 months. One of the studies reported the use of ubiquinol (10 mg/kg for 24 weeks).[53]

Overall, it appears that higher dosages, for example, 300 mg per day, and longer duration of supplementation may be needed to get the full benefits in terms of heart function.

The mechanisms by which CoQ10 exerts its benefits in heart failure are probably multiple, including an increased energy production in the failing heart, reduced oxidative stress (which tends to be high in these patients) and improved endothelial function (see also above).[36]

Hypertension

Hypertension is the largest known risk factor for heart disease and, globally, hypertension is the second biggest risk factor for overall mortality and morbidity, after poor diet.[55] In 2015, one in four men and one in five women worldwide had high blood pressure.[56]

A couple of early open-label studies showed significant blood-pressure-lowering effects of CoQ10 in patients with essential hypertension: one showed a reduction from 164.5 to 146.7 mmHg for systolic and from 98.1 to 86.1 mmHg for diastolic blood pressure;[57] whilst in the other, more than half of patients receiving CoQ10 were able to stop their anti-hypertensive drugs, whilst only 3% had to add another drug after 1–6 months of supplementation.[58]

A Cochrane review of three double-blind, placebo-controlled trials in 2016 concluded that the evidence suggests that CoQ10 does not lower blood pressure; however, the meta-analysis only included two of these studies with a total of 50 participants, the third study was excluded due to high risk of bias.[59] Both studies used 100 mg per day for 10 or 12 weeks.

In 2018, a review and meta-analysis of 17 RCTs, totalling 684 patients with hypertension and metabolic disease, found that overall there was a statistically significant reduction in systolic blood pressure, whilst reduction in diastolic blood pressure did not reach statistical significance.[60] Whilst seven of the individual trials found benefits of CoQ10 on blood pressure, the other 10 did not find any effect. Studies using dosages between 100 and 150 mg per day found better results than those using more than 150 mg per day. One study using 900 mg per day found no effect, although this was of shorter duration (4 weeks) than most other studies (8–24 weeks). The authors do not discuss a possible explanation for this finding, other than that a limitation of many studies is that dietary intakes and/or baseline CoQ10 levels are not always established.[60]

Since then, another double-blind, placebo-controlled trial with 101 dylipidaemic patients not taking any hypoglycaemic or hypolipidaemic drugs found that CoQ10, 120 mg per day for 24 weeks, reduced systolic and diastolic blood pressure from 134 mmHg to 125 mmHg, and from 85 mmHg to 78 mmHg, respectively, compared with a reduction from 129 mmHg to 127 mmHg and from 82 mmHg to 80 mmHg, respectively, with placebo. Beneficial effects were seen at 12 weeks.[39]

CoQ10 has also been studied alongside and/or against omega-3 fatty acids with conflicting results. Two studies showed that CoQ10 (150 mg or 200 mg per day) significantly reduced blood pressure alongside either omega-3 fatty acids and/or hypolipidaemic drugs in patients with hypertriglyceridaemia,[61,62] whilst another study found no effects of CoQ10 either alone or with omega-3 fatty acids on blood pressure in patients with chronic kidney disease.[63] Dosages of polyunsaturated fatty acids (PUFAs) were 3000 mg PUFAs (not further described),[61] 2520 mg omega-3 PUFAs [dose of eicosapentaenoic

acid (EPA) and docosahexaenoic acid (DHA) not reported],[62] and 1840 mg EPA and 1520 mg DHA per day,[63] respectively.

The reasons for the contradictory results are unclear. Overall, there appears to be a beneficial effect of CoQ10 in hypertension, with dosages of 100–150 mg being effective.

Some authors have hypothesised that the benefits may be due to improvements in myocardial bioenergetics through CoQ10, which would suggest that longer periods (more than 1 month) of supplementation may be required to see effects.[58] Other authors suggest that the benefits are mediated by the antioxidant effects of CoQ10, which may improve endothelial function via the NO cycle.[60]

Diabetes and dysglycaemia

People with type 2 diabetes mellitus (T2DM) have lower CoQ10 levels than healthy people, and supplementation has been shown to increase levels.[64]

Three meta-analyses evaluated the potential of CoQ10 on glycaemic control, and found significant benefits in patients with diabetes,[65,66] and patients with diabetes and/or other cardiometabolic conditions.[67] CoQ10 has also been shown to improve other risk factors in people with T2DM, such as biomarkers for endothelial function, inflammation, antioxidant status and lipid profiles, although not all studies found improvements in all markers.[39,45,68,69,70] Both the ubiquinone[70] and the ubiquinol[45,68] forms have shown benefits.

Dosages used were generally in the range of 100–300 mg per day, and studies lasted for 4–24 weeks.

The mechanism involved is thought to be reductions in oxidative stress, leading to better mitochondrial function, which may in turn improve glycaemic control in patients with T2DM.[65]

Fatigue

Due to its importance in energy production as part of the mitochondrial electron transfer chain, it is intuitive to consider CoQ10 to alleviate fatigue or enhance energy in both healthy people and those with conditions associated with fatigue. However, the benefit of CoQ10 for fatigue appears to differ across patient populations, and thus its use may benefit from personalisation.

Fatigue in healthy adults

Two studies looked at the effect of CoQ10 on fatigue in response to cognitive or physical tasks in healthy volunteers with or without mild fatigue, and found significant reductions in fatigue.[20,71] Smaller effects were seen with 100 mg per day, and larger effects with 150 mg or 300 mg per day, suggesting that higher dosages are more effective. Improvements with 300 mg were seen after only 8 days of supplementation, whilst the other study used 100 mg versus 150 mg for 12 weeks. Improvements were mirrored by increases in serum CoQ10 levels.

A study using 200 mg CoQ10 for 12 weeks in healthy but obese adults found an improvement in fatigue, although this failed to reach statistical significance when compared with placebo.[72]

Two more studies that looked at the effect of CoQ10 on exercise performance found benefits in terms of exercise performance but not fatigue.[10,19] Dosages used were 300 mg for 1 month and 100 mg for 8 weeks, respectively.

Only two articles specified whether the reduced or oxidised form of CoQ10 was used: one study using ubiquinol, 100 mg or 150 mg per day, found significant improvements;[71] whilst in one study using ubiquinone, 200 mg per day, improvements were not statistically significant.[72]

Overall, the evidence for the use of CoQ10 to reduce fatigue in generally healthy people is contradictory. Dosages of 150–300 mg per day may be needed to see an effect. Although benefits of 300 mg per day for 8 days have been seen, a longer duration may be necessary to obtain significant results.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a complex, poorly understood disorder, with extreme fatigue being the most common symptom. Mitochondrial dysfunction is thought to play an important role in CFS, and CoQ10 is therefore a likely candidate for supplemental support.

However, only two clinical trials have assessed the effectiveness of CoQ10 on its own in CFS. One open-label study found no benefits in terms of clinical outcomes (including fatigue) or oxidative stress with CoQ10 (as ubiquinol), 150 mg per day for 8 weeks.[73] A double-blind, placebo-controlled trial by the same investigators, using the same dosing regimen but for 12 weeks, found small but statistically significant improvements in arithmetic tasks, awakening at night and autonomic nervous function, but not fatigue or depression.[73] In both studies, patients had low plasma levels of CoQ10 before the start of supplementation, and CoQ10 supplementation increased blood levels.

Two further studies looked at CoQ10 alongside nicotinamide adenine dinucleotide (NADH, another important nutrient for cellular energy production). One study, using 50 mg CoQ10 and 5 mg NADH per day for 8 weeks, found no significant improvements in terms of fatigue,[74] whilst the other, using 200 mg CoQ10 and 20 mg NADH per day for 8 weeks, found significant improvements in both fatigue and biochemical markers.[75]

The dosages used in all these trials are low compared with those used in other studies, for example, for fibromyalgia syndrome (FMS; see below), which may be the reason for the lack of efficacy in some of these trials. It is also important to bear in mind that, being a complex disorder, it would be unlikely for one nutrient alone to lead to significant improvements in CFS. The fact that a combination of CoQ10 and NADH, with CoQ10 at 200 mg per day, offered some benefit despite the fairly low dose is encouraging.

A dose of at least 200 mg CoQ10 for at least 8 weeks and ideally in combination with other relevant nutrients to support mitochondrial function could be suggested in CFS.

Fibromyalgia syndrome

FMS has a lot of overlap with CFS, with fatigue being a prominent symptom alongside widespread pain. As for CFS, the exact causes are unknown, but mitochondrial dysfunction and oxidative stress are thought to play important roles.[76]

A number of clinical trials have shown evidence for a significant benefit of CoQ10 (as ubiquinone) in this patient population. The earliest evidence comes from an open-label study of CoQ10, 200 mg per day, alongside Ginkgo biloba, which showed a significant gradual improvement in quality of life over the 12-week study period.[77]

Following a case series where impressive results with CoQ10 supplementation in four patients with FMS were found,[78] Cordero et al. in Spain conducted a number of controlled studies that showed a significant benefit of CoQ10, 100 mg three times per day, in patients with FMS, with a halving of pain scores and significant reductions in depression, headaches, tender points and fatigue.[79,80] A small double-blind, placebo-controlled trial by these investigators evaluated a host of biochemical and other disease markers to elucidate possible mechanisms. They found that, compared with healthy controls, FMS sufferers had lower levels of CoQ10 and ATP, increased oxidative stress, inflammation and mitochondrial dysfunction, which were to some extent explained by changes in gene expression.[81,82,83] In these studies, supplementation with CoQ10, 100 mg three times per day, improved inflammation, oxidative stress and mitochondrial function, leading to improvements in fatigue by 50%. Serotonin levels were also increased, with a reduction in depression.[83]

A more recent double-blind, placebo-controlled study also found beneficial effects of CoQ10, 300 mg per day for 40 days, alongside pregabalin (an anti-convulsant and anti-anxiolytic drug that is also used for neuropathic pain, FMS and other indications) in patients with FMS, with greater reductions in pain, anxiety and brain activity, mitochondrial oxidative stress and inflammation than pregabalin alone.[84]

A Japanese study in children aged 8–18 years with juvenile FMS found that patients had significantly lower plasma levels of ubiquinol-10, and an increased ratio of ubiquinone-10 to total CoQ10 (%CoQ10), compared with healthy controls, suggesting that FMS is associated with CoQ10 deficiency and increased oxidative stress.[85] Supplementation with CoQ10 (as ubiquinol), 100 mg per day, led to significant improvements in biochemical markers as well as fatigue, but not pain or quality of life. Beneficial effects were seen as early as within 2 weeks. The authors suggested that higher dosages

might give better benefits in this paediatric patient population.

Overall, the evidence for the use of CoQ10 in FMS is good, with a dose of 300 mg per day for at least 3 months suggested. Based on the evidence above, as with CFS, combining CoQ10 with other nutrients or botanicals may give even better results, although relevant studies are lacking.

There appear to be a number of mechanisms involved in the beneficial effects of CoQ10, including improved mitochondrial function, reduced inflammation and oxidative stress, and increased serotonin levels, which may be due, at least in part, to modulation of gene expression.[81,82,83]

Fertility and pregnancy

Male subfertility

Sperm cells, in particular their membranes, are susceptible to oxidative damage, and such damage is thought to be responsible for 30–80% of cases of male subfertility.[86] The antioxidant properties of CoQ10 could therefore be expected to be beneficial to sperm health, and therefore male fertility.

A 2020 meta-analysis of three double-blind, placebo-controlled trials, totalling 296 patients with reduced sperm motility only or reduced sperm motility and count, found that CoQ10, at dosages of 200–300 mg per day for 12–26 weeks, significantly increased sperm counts, motility and forward motility.[87] Only one of the trials reported pregnancy rates, which was 6/28 in the CoQ10 group and 3/27 in the placebo group.[88]

Several studies, RCTs and uncontrolled studies not included in the above meta-analysis have also consistently shown improvements in sperm counts and motility, and some, but not all, have found improvements in sperm morphology where it had also been abnormal.[89,90,91,92,93,94,95] Only one of these trials, an open-label, prospective study, reported pregnancy as an outcome and found a 34.1% pregnancy rate within a mean of 8.4 months.[96]

The evidence is overwhelmingly in favour of CoQ10 in male subfertility and the most commonly used dose was 200 mg per day, although one study compared a daily dose of 200 mg with 400 mg and found better results with the higher dose.[91] As it takes 3 months for sperm cells to mature, duration of supplementation should be a minimum of 3 months. Study durations ranged from 3 to 12 months, with benefits seen after 3 months. All studies that specified the form of CoQ10 had used the ubiquinol form.[89,91,92,93,95]

The mechanism of action is thought to be the ability of CoQ10 to increase antioxidant capacity, which has indeed been observed in some of the above studies.[89,90,91,94]

Female subfertility

A number of studies have also investigated female subfertility, most of them focussing on CoQ10 supplementation prior to assisted fertilisation, with promising results in terms of fertilisation rates, retrieved egg cells and reduction in number of abnormal chromosome counts, although improved pregnancy rates on the whole failed to reach statistical significance.[97,98,99] Dosages in these studies were 600 mg per day for at least 1 month.

The use of CoQ10 for women whose subfertility is due to polycystic ovarian syndrome (PCOS) is discussed below.

Pre-eclampsia

Pre-eclampsia is a pregnancy-related condition, characterised by hypertension, proteinuria (protein in urine) and oedema, which is potentially life-threatening to both mother and baby. Mitochondrial dysfunction, leading to lack of cellular energy and increased free radicals/ oxidative stress, has been considered to be an underlying mechanism, and abnormal CoQ10 levels have been observed in pre-eclampsia, suggesting CoQ10 supplementation may be beneficial for prevention.[100]

Only one double-blind, placebo-controlled trial has investigated supplementation with CoQ10, 200 mg per day from week 20 of pregnancy until delivery, in 197 women at increased risk of pre-eclampsia:[101] 25.6% of women in the placebo group and 14.4% of women in the CoQ10 group developed pre-eclampsia, a statistically significant result.

Migraine

Whilst the causes of migraines are not completely understood, vascular and neuronal

dysfunction are thought to play important roles, and may be due to impaired oxygen metabolism, oxidative stress and inflammation.[102] Being able to positively affect all three, CoQ10 has been considered as a prime candidate for prevention of migraines. Positive influences of CoQ10 on inflammatory markers in patients with migraines have been observed in parallel with symptomatic improvements.[103]

Two double-blind, placebo-controlled and three open-label studies have evaluated the efficacy of CoQ10 in the prevention of migraines in adults, and all found significant benefits in terms of reducing the number of attacks per month.[103,104,105,106,107] The severity and duration of attacks also significantly decreased, although this did not reach statistical significance in all studies. Up to 80% of study participants had improvements of more than 50% in frequency or days with migraines.

Improvements have been seen at dosages as low as 100 mg per day,[105] although dosages of up to 600 mg per day have been used, and benefits have been seen within 4 weeks with further improvements over the following 2–3 months of supplementation.

CoQ10 has also been studied in combination with other nutrients, namely curcumin,[108] L-carnitine,[109] feverfew and magnesium,[110] and beneficial effects of these combinations were reported.

Two clinical trials evaluated the benefits of CoQ10 in children and adolescents with migraines. In a double-blind, placebo-controlled crossover study, participants in both the active CoQ10 (100 mg per day) as well as the placebo group experienced very significant improvements in frequency, duration and severity of migraines. Within the first 4 weeks, frequency of migraines reduced from 19 to 11 in the CoQ10 group, and from 21 to 14.5 in the placebo group. Further improvements were seen over the following 3 months, but differences between groups were only statistically significant for frequency at 4 weeks.[111]

An open-label study assessed 1556 consecutive 3–22 year olds with migraines for their serum CoQ10 level, and found that almost a third were below the reference range. Two-hundred and fifty-two patients with low CoQ10 levels started to supplement at a dose of 1–3 mg/kg per day. After an average follow-up of just over 3 months, CoQ10 levels had significantly increased in these patients, migraine frequency reduced from 19.2 to 12.5, and 46.3% of patients reported a reduction in migraines of more than 50%.[112] Due to lack of blinding and placebo control, it is difficult to conclude whether these improvements were due to supplementation or not, as a very significant placebo effect has been demonstrated in this population.[111]

The evidence supports the use of CoQ10 for migraines in adults, with dosages of at least 100 mg per day for at least 4 weeks. For children and adolescents, it is unclear whether benefits observed are due to a placebo effect or the active compound.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is caused by a build-up of fat within liver cells, and risk factors include obesity/overweight, metabolic syndrome and T2DM.[113]

Two double-blind, placebo-controlled trials investigated the use of CoQ10, 100 mg per day, in patients with NAFLD. One trial, which lasted 12 weeks, found improvements in liver aminotransferases (a marker of liver function), inflammatory markers and NAFLD grade.[114] The other trial also found improvements in one aminotransferase and a marker for oxidative stress, but other biochemical markers failed to reach statistical significance, possibly due to the short, 4-week duration of the trial.[115]

Although evidence is limited, CoQ10, at a dose of at least 100 mg per day for at least 12 weeks, appears to be a valuable option for people with NAFLD, especially due to the fact that these patients also commonly have other co-morbidities and biochemical abnormalities for which CoQ10 has also been shown to be beneficial.

The mechanisms for the benefit of CoQ10 in NAFLD are most likely its anti-inflammatory and antioxidant effects.[114]

Neurodegenerative diseases

Alzheimer's disease

Oxidative stress and mitochondrial dysfunction are thought to play a role in the development of Alzheimer's disease, and preclinical studies have shown CoQ10 to have neuroprotective effects.[2] However, there is only one small double-blind, placebo-controlled trial in humans that looked at the effects of CoQ10, 400 mg three times per day for 16 weeks, on biomarkers in the cerebrospinal fluid, which found CoQ10 to be of no benefit with regards to biomarkers or cognitive function.[116]

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system, and oxidative stress is thought to play an important role in the development of MS lesions, making CoQ10 a likely candidate for intervention.

One double-blind, placebo-controlled trial of 45 patients with relapsing–remitting MS found significant improvements in fatigue and depression with 500 mg CoQ10 per day for 12 weeks.[117] This study also found a significant decrease in oxidative stress, an increase in antioxidant capacity and a reduction in inflammatory, but no change in anti-inflammatory, markers.[118,119]

An open-label study using CoQ10, 200 mg per day for 12 weeks, found similar results, reduced oxidative damage and a shift towards a more anti-inflammatory milieu in the peripheral blood, and small but significant clinical improvements in depression, pain, disability score and fatigue.[120]

These are promising results, although unfortunately no data on longer-term supplementation are available. A dose of 200–500 mg CoQ10 per day for at least 3 months could be suggested.

Parkinson's disease

Mitochondrial dysfunction and oxidative stress are thought to play a role in the development of Parkinson's disease (PD).[121] Patients with PD have been shown to have higher rates of CoQ10 deficiency in peripheral blood mononuclear cells (a marker of general CoQ10 deficiency)[122] and, more specifically, in cells of the cortex region of the brain.[123] It therefore seems logical that improving CoQ10 status through supplementation may be of benefit in patients with PD.

Indeed, a number of RCTs have been conducted into the potential use of CoQ10 in PD. In 2011, a Cochrane review and meta-analysis[124] found some benefits of high-dose CoQ10 in patients with PD; however, this review was later withdrawn due to a number of methodological shortcomings.[125]

Since then, two more meta-analyses have not found any benefit of CoQ10 on motor function or progression of disease.[121,126] A small double-blind, placebo-controlled pilot study found some benefit of CoQ10 (as ubiquinol) in patients experiencing 'wearing off' (where levodopa treatment stops controlling symptoms satisfactorily), but not in early PD patients not yet treated with levodopa.[127]

An RCT combining CoQ10 (300 mg per day, as ubiquinone) and carnitine (10 g per day) found the combination to significantly slow cognitive decline but not any other PD symptoms over placebo.[128]

Overall, to date, the evidence to support the use of CoQ10 to improve PD symptoms or progression is weak.

Periodontal disease

Periodontal, or gum, disease is thought to be caused by bacterial pathogens causing an inflammatory response with increased production of reactive oxygen species, aggressive molecules that cause tissue damage, leading to inflammation, receding gums and potentially tooth loss. Antioxidants like CoQ10 are thought to reduce this damage.[2] Decreased levels of CoQ10 have been observed in gingival (gum) tissues in people with periodontal disease compared with healthy controls.[129] CoQ10 supplementation is therefore commonly suggested for periodontal disease.

Most research in this area has focussed on topical, gingival, application of CoQ10. Only four small clinical studies with between eight and 22 patients have been conducted with oral CoQ10, all but one were open-label, uncontrolled trials.[130,131,132] All studies found significant improvements in some parameters (periodontal

score, gingival index, pocket depth, inflammation and bacterial composition of the pocket fluid), but not plaque size/score. Where reported, dosages were 90–100 mg per day for 1–6 months.

Whilst the evidence is not as strong as one would hope, it is promising and, due to the fact that CoQ10 is safe and has many other benefits, supplementation with at least 100 mg per day would be worth considering for this indication.

Polycystic ovarian syndrome

Whilst generally considered a gynaecological condition, an important underlying cause of PCOS is thought to be insulin resistance. Women with PCOS have a higher risk of developing T2DM than women without PCOS, and they may also be at increased risk of CVD.[133]

A double-blind, placebo-controlled trial of 60 women with PCOS found that 100 mg CoQ10, alongside standard treatment with metformin, improved glycaemic control and total and LDL cholesterol, but not other blood lipids.[134] In another double-blind, placebo-controlled trial, CoQ10, 200 mg per day for 8 weeks, was also shown to significantly improve biomarkers for inflammation and endothelial function in women with PCOS.[43]

Another double-blind, placebo-controlled study found that CoQ10, 200 mg per day for 8 weeks, improved glycaemic control and testosterone levels.[135] The same study showed more improvements when CoQ10 was combined with vitamin E, 400 IU per day, in terms of glycaemic control, hormone levels and lipid profiles.[135,136]

Infertility is a common issue in PCOS, and CoQ10, 180 mg per day, has been shown to be effective in improving fertility alongside the fertility drug clomiphene in women with PCOS who did not respond to clomiphene alone.[137]

Based on the above studies, CoQ10 at a dose of 200 mg per day for at least 8 weeks appears to be promising in supporting women with PCOS.

Statin-induced myopathy

Statins are cholesterol-lowering drugs, and have become a cornerstone of CVD prevention. Statin-associated muscle disorders are a common side-effect, affecting 7–29% of patients on statins, and often necessitate drug discontinuation.[138] Statins reduce CoQ10 levels[139] as they block the mevalonate pathway through which we produce CoQ10.[140] As such, CoQ10 supplementation appears logical, especially knowing its importance to the heart muscle.

Interestingly, therefore, the most recent meta-analysis of seven double-blind studies of CoQ10 in statin-induced muscle pain found no benefit.[138] Another meta-analysis of 12 RCTs on the other hand found a significant benefit of CoQ10 for muscle pain, weakness, tiredness and cramps, although not plasma creatine kinase (a marker of heart and/or skeletal muscle damage).[141] Dosages used in the studies included in the above meta-analyses ranged from 100 to 600 mg per day for 1–3 months. Overall, conclusions drawn from reviews are contradictory, with some suggesting a benefit[142] whilst others do not.[140]

An earlier small open-label, uncontrolled trial of 28 patients with statin-induced myopathy found that CoQ10, 60 mg per day, significantly reduced muscle pain (by 54%) and weakness (by 44%) after 6 months of supplementation, although no statistically significant improvement was seen at 3 months,[143] raising the question as to the length of treatment necessary to see results.

It should be stressed that research has focussed on the treatment, rather than prevention, of statin-induced myopathies and that there is no evidence from adequate clinical trials whether CoQ10 may be beneficial for prevention, as theoretical considerations would suggest it is.

Due to the fact that patients on statins are considered to be at risk of CVD and often also have other cardiovascular risk factors and co-morbidities for which CoQ10 has been shown to be of benefit, supplementing CoQ10 alongside statins appears to be prudent at a dose dependent on individual risks and co-morbidities.

SAFETY

Oral CoQ10 supplements are generally well tolerated and no serious adverse effects have been reported in clinical trials. Gastrointestinal side-effects, such as appetite suppression, diarrhoea, epigastric discomfort, heartburn, nausea and vomiting, have been reported in less than 1% of patients.[144]

Dosages of up to 1200 mg per day in adults and up to 10 mg/kg per day in children appear to be safe, and higher dosages have been used for some conditions.[2]

DRUG INTERACTIONS/CAUTIONS

No information on drug interactions has been published. The following potential concerns are of a theoretical nature.

Alkylating agents (types of cancer chemotherapy)

These work by inducing oxidative stress; theoretically, the antioxidant effect of CoQ10 could be counterproductive.[145] Although the clinical relevance of this is unclear, due to lack of research in this area, supplementation during cancer chemotherapy may be best avoided.[1]

Blood-pressure-lowering drugs

As CoQ10 appears to reduce blood pressure (see above), theoretically there could be additive effects with anti-hypertensive drugs, leading to blood pressure dropping too low, although in many of the above studies CoQ10 has been used alongside anti-hypertensive drugs.

Warfarin (anticoagulant drug)

CoQ10 is chemically similar to vitamin K, which has a pro-coagulant effect, and may theoretically reduce the effect of warfarin. Cases where CoQ10 has reduced the effectiveness of warfarin have been reported in the literature,[146,147] although a double-blind, placebo-controlled crossover trial of 21 patients on long-term stable warfarin treatment did not show any effects of CoQ10, 100 mg per day for 4 weeks.[148] As a precautionary measure, patients on warfarin should have their warfarin dose monitored more closely if they choose to supplement with CoQ10.

Pregnancy

There is insufficient clinical research to establish the safety of CoQ10 during pregnancy.

One study used CoQ10 100 mg twice per day from week 20 of pregnancy with no apparent safety concerns.[101] However, until further research confirms the safety of CoQ10 during pregnancy, it should only be used on the advice of a suitably qualified practitioner.

Breastfeeding

CoQ10 is a normal constituent of human breastmilk with concentrations varying by country, possibly due to dietary or genetic factors or differences in measurement techniques; ranges reported have varied from 0.27 µg/l to 1.6 mg/l, and one study found no correlation between maternal plasma levels and levels in breastmilk.

No further information is available on the potential effects of supplemental CoQ10 on breastfed babies, or on lactation and breastmilk.

Age limits/minimum age

CoQ10 has been used safely and successfully in children and adolescents from 3 years old in a variety of conditions, including migraines, dilated cardiomyopathy and juvenile fibromyalgia, as discussed above. Dosages used have been in the range of 1–10 mg/kg with durations of up to 9 months.[144]

CONCLUSION

Although there are some contradictory findings, overall CoQ10 has been shown to be of benefit in a wide range of disorders, with dosages of 100–300 mg, depending on clinical use. As most publications do not specify whether the ubiquinone or ubiquinol form was used, at present there are insufficient data to conclude whether one is superior to the other.

ACKNOWLEDGEMENTS

Author contributions: K. Elgar carried out the literature review and formulated the manuscript.

Peer-reviewers and editors: the Nutritional Medicine Institute thanks the peer-reviewers and editors for their important contributions.

Funding: Open Access publication was made possible by funding from Pure Encapsulations, Sudbury, MA, USA. No other funding or sponsorship has been received for this work.

Declaration of interest: K. Elgar has received consultancy fees from Pure Encapsulations, Sudbury, MA, USA.

BIBLIOGRAPHY

[1] Sood, B. & Keenaghan, M. (2020) Coenzyme Q10. In: StatPearls (online).

[2] Garrido-Maraver, J. et al. (2014) Clinical applications of coenzyme Q10. Front. Biosci. (Landmark Ed.), 19, 619–633.

[3] Pravst, I., Zmitek, K. & Zmitek, J. (2010) Coenzyme Q10 contents in foods and fortification strategies. Crit. Rev. Food Sci. Nutr., 50, 269–280.

[4] López-Lluch, G., Del Pozo-Cruz, J., Sánchez-Cuesta, A., Cortés-Rodríguez, A. B. & Navas, P. (2019) Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization. Nutrition, 57, 133–140.

[5] Molyneux, S. L., Young, J. M., Florkowski, C. M., Lever, M. & George, P. M. (2008) Coenzyme Q10: is there a clinical role and a case for measurement? Clin. Biochem. Rev., 29, 71–82.

[6] Rosenfeldt, F., Hilton, D., Pepe, S. & Krum, H. (2003) Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. Biofactors, 18, 91–100.

[7] Emami, A., Tofighi, A., Asri-Rezaei, S. & Bazargani-Gilani, B. (2018) The effect of short-term coenzyme Q10 supplementation and pre-cooling strategy on cardiac damage markers in elite swimmers. Br. J. Nutr., 119, 381–390.

[8] Armanfar, M., Jafari, A., Dehghan, G. R. & Abdizadeh, L. (2015) Effect of coenzyme Q10 supplementation on exercise-induced response of inflammatory indicators and blood lactate in male runners. Med. J. Islam. Repub. Iran, 29, 202.

[9] Shimizu, K. et al. (2015) Coenzyme Q10 supplementation downregulates the increase of monocytes expressing toll-like receptor 4 in response to 6-day intensive training in kendo athletes. Appl. Physiol. Nutr. Metab., 40, 575–581.

[10] Gharahdaghi, N., Shabkhiz, F., Azarboo, E. & Keyhanian, A. (2013) The effects of daily coenzyme Q10 supplementation on VO2 max, vVO2 max and intermittent exercise performance in soccer players. Life Sci. J., 10, 22–28.

[11] Kon, M. et al. (2008) Reducing exercise-induced muscular injury in kendo athletes with supplementation of coenzyme Q10. Br. J. Nutr., 100, 903–909.

[12] Kizaki, K. et al. (2015) Effect of reduced coenzyme Q10 (ubiquinol) supplementation on blood pressure and muscle damage during kendo training camp: a double-blind, randomized controlled study. J. Sports Med. Phys. Fitness, 55, 797–804.

[13] Diaz-Castro, J. et al. (2020) Beneficial effect of ubiquinol on hematological and inflammatory signaling during exercise. Nutrients, 12, 424.

[14] Diaz-Castro, J. et al. (2020) Ubiquinol supplementation modulates energy metabolism and bone turnover during high intensity exercise. Food Funct., 11, 7523–7531.

[15] Orlando, P. et al. (2018) Effect of ubiquinol supplementation on biochemical and oxidative stress indexes after intense exercise in young athletes. Redox Rep., 23, 136–145.

[16] Cooke, M. et al. (2008) Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. J. Int. Soc. Sports Nutr., 5, 8.

[17] Sarmiento, A. et al. (2016) Short-term ubiquinol supplementation reduces oxidative stress associated with strenuous exercise in healthy adults: A randomized trial. Biofactors, 42, 612–622.

[18] Gül, I. et al. (2011) Oxidative stress and antioxidant defense in plasma after repeated bouts of supramaximal exercise: the effect of coenzyme Q10. J. Sports Med. Phys. Fitness, 51, 305–312.

[19] Gökbel, H., Gül, I., Belviranl, M. & Okudan, N. (2010) The effects of coenzyme Q10 supplementation on performance during repeated bouts of supramaximal exercise in sedentary men. J. Strength Cond. Res., 24, 97–102.

[20] Mizuno, K. et al. (2008) Antifatigue effects of coenzyme Q10 during physical fatigue. Nutrition, 24, 293–299.

[21] Suzuki, Y., Nagato, S., Sakuraba, K., Morio, K. & Sawaki, K. (2020) Short-term Ubiquinol-10 supplementation alleviates tissue damage in muscle and fatigue caused by strenuous exercise in male distance runners. Int. J. Vitam. Nutr. Res., 1–10, doi:10.1024/0300-9831/a000627.

[22] Ostman, B., Sjödin, A., Michaëlsson, K. & Byberg, L. (2012) Coenzyme Q10 supplementation and exercise-induced oxidative stress in humans. Nutrition, 28, 403–417.

[23] Bloomer, R. J., Canale, R. E., McCarthy, C. G. & Farney, T. M. (2012) Impact of oral ubiquinol on blood oxidative stress and exercise performance. Oxid. Med. Cell. Longev., 2012, 465 020.

[24] Gokbel, H. et al. (2016) Effects of coenzyme Q10 supplementation on exercise performance and markers of oxidative stress in hemodialysis patients: a double-blind placebo-controlled crossover trial. Am. J. Ther., 23, e1736–e1743.

[25] Porter, D. A. et al. (1995) The effect of oral coenzyme Q10 on the exercise tolerance of middle-aged, untrained men. Int. J. Sports Med., 16, 421–427.

[26] Laaksonen, R., Fogelholm, M., Himberg, J. J., Laakso, J. & Salorinne, Y. (1995) Ubiquinone supplementation and exercise capacity in trained young and older men. Eur. J. Appl. Physiol. Occup. Physiol., 72, 95–100.

[27] Okudan, N., Belviranli, M. & Torlak, S. (2018) Coenzyme Q10 does not prevent exercise-induced muscle damage and oxidative stress in sedentary men. J. Sports Med. Phys. Fitness, 58, 889–894.

[28] Kaikkonen, J. et al. (1998) Effect of combined coenzyme Q10 and d-alpha-tocopheryl acetate supplementation on exercise-induced lipid peroxidation and muscular damage: a placebo-controlled double-blind study in marathon runners. Free Radic. Res., 29, 85–92.

[29] Malm, C., Svensson, M., Sjöberg, B., Ekblom, B. & Sjödin, B. (1996) Supplementation with ubiquinone-10 causes cellular damage during intense exercise. Acta Physiol. Scand., 157, 511–512.

[30] Malm, C., Svensson, M., Ekblom, B. & Sjödin, B. (1997) Effects of ubiquinone-10 supplementation and high intensity training on physical performance in humans. Acta Physiol. Scand., 161, 379–384.

[31] NHS (2019) Bipolar disorder. https://www.nhs.uk/mental-health/conditions/bipolar-disorder/.

[32] Mehrpooya, M., Yasrebifar, F., Haghighi, M., Mohammadi, Y. & Jahangard, L. (2018) Evaluating the effect of coenzyme Q10 augmentation on treatment of bipolar depression: a double-blind controlled clinical trial. J. Clin. Psychopharmacol., 38, 460–466.

[33] Forester, B. P. et al. (2015) Antidepressant effects of open label treatment with coenzyme Q10 in geriatric bipolar depression. J. Clin. Psychopharmacol., 35, 338–340.

[34] Jahangard, L., Yasrebifar, F., Haghighi, M., Ranjbar, A. & Mehrpooya, M. (2019) Influence of adjuvant Coenzyme Q10 on inflammatory and oxidative stress biomarkers in patients with bipolar disorders during the depressive episode. Mol. Biol. Rep., 46, 5333–5343.

[35] Singh, R. B. et al. (2003) Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. Mol. Cell. Biochem., 246, 75–82.

[36] Mortensen, S. A. et al. (2014) The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC. Heart Fail., 2, 641–649.

[37] Sharifi, N. et al. (2018) The effects of coenzyme Q10 supplementation on lipid profiles among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. Curr. Pharm. Des., 24, 2729–2742.

[38] Jorat, M. V. et al. (2018) The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis., 17, 230.

[39] Zhang, P. et al. (2018) Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals. J. Clin. Lipidol., 12, 417–427. e5.

[40] (2019) Endothelial dysfunction. diabetes.co.uk https://www.diabetes.co.uk/diabetes-complications/endothelial-dysfunction.html.

[41] Gao, L. et al. (2012) Effects of coenzyme Q10 on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. Atherosclerosis, 221, 311–316.

[42] Sabbatinelli, J. et al. (2020) Ubiquinol ameliorates endothelial dysfunction in subjects with mild-to-moderate dyslipidemia: a randomized clinical trial. Nutrients, 12, 1098.

[43] Taghizadeh, S., Izadi, A., Shirazi, S., Parizad, M. & Pourghassem Gargari, B. (2020) The effect of coenzyme Q10 supplementation on inflammatory and endothelial dysfunction markers in overweight/obese polycystic ovary syndrome patients. Gynecol. Endocrinol., 1–5, doi:10.1080/09513590.2020.1779689.

[44] Kawashima, C. et al. (2020) Ubiquinol improves endothelial function in patients with heart failure with reduced ejection fraction: a single-center, randomized double-blind placebo-controlled crossover pilot study. Am. J. Cardiovasc. Drugs, 20, 363–372.

[45] Al-Kuraishy, H. M., Al-Gareeb, A. I., Shams, H. A. & Al-Mamorri, F. (2019) Endothelial dysfunction and inflammatory biomarkers as a response factor of concurrent coenzyme Q10 add-on metformin in patients with type 2 diabetes mellitus. J. Lab. Physicians, 11, 317–322.

[46] Harding, M. (2018) Heart Failure Diagnosis and Investigation. patient.info https://patient.info/doctor/heart-failure-diagnosis-and-investigation#.

[47] Lei, L. & Liu, Y. (2017) Efficacy of coenzyme Q10 in patients with cardiac failure: a meta-analysis of clinical trials. BMC Cardiovasc. Disord., 17, 196.

[48] Jafari, M., Mousavi, S. M., Asgharzadeh, A. & Yazdani, N. (2018) Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J., 70 Suppl 1, S111–S117.

[49] Jankowski, J., Korzeniowska, K., Cieślewicz, A. & Jabłecka, A. (2016) Coenzyme Q10 – a new player in the treatment of heart failure? Pharmacol. Rep., 68, 1015–1019.

[50] Oleck, S. & Ventura, H. O. (2016) Coenzyme Q10 and utility in heart failure: just another supplement? Curr. Heart Fail. Rep., 13, 190–195.

[51] DiNicolantonio, J. J., Bhutani, J., McCarty, M. F. & O'Keefe, J. H. (2015) Coenzyme Q10 for the treatment of heart failure: a review of the literature. Open Heart, 2, e000326.

[52] Kocharian, A., Shabanian, R., Rafiei-Khorgami, M., Kiani, A. & Heidari-Bateni, G. (2009) Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. Cardiol. Young, 19, 501–506.

[53] Chen, F.-L., Chang, P.-S., Lin, Y.-C. & Lin, P.-T. (2018) A pilot clinical study of liquid ubiquinol supplementation on cardiac function in pediatric dilated cardiomyopathy. Nutrients, 10, 1697.

[54] Soongswang, J. et al. (2005) The effect of coenzyme Q10 on idiopathic chronic dilated cardiomyopathy in children. Pediatr. Cardiol., 26, 361–366.

[55] Forouzanfar, M. H. et al. (2015) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 386, 2287–2323.

[56] World Health Organization (2019) Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension.

[57] Digiesi, V. et al. (1994) Coenzyme Q10 in essential hypertension. Mol. Aspects Med., 15 Suppl, s257–s263.

[58] Langsjoen, P., Langsjoen, P., Willis, R. & Folkers, K. (1994) Treatment of essential hypertension with coenzyme Q10. Mol. Aspects Med., 15 Suppl, S265–S272.

[59] Ho, M. J., Li, E. C. K. & Wright, J. M. (2016) Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst. Rev., 3, CD007435.

[60] Tabrizi, R. et al. (2018) The effects of coenzyme Q10 supplementation on blood pressures among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. High Blood Press. Cardiovasc. Prev., 25, 41–50.

[61] Cicero, A. F. G. et al. (2005) Possible role of ubiquinone in the treatment of massive hypertriglyceridemia resistant to PUFA and fibrates. Biomed. Pharmacother., 59, 312–317.

[62] Tóth, Š. et al. (2017) Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. J. Basic Clin. Physiol. Pharmacol., 28, 327–336.

[63] Mori, T. A. et al. (2009) The effects of [omega]3 fatty acids and coenzyme Q10 on blood pressure and heart rate in chronic kidney disease: a randomized controlled trial. J. Hypertens., 27, 1863–1872.

[64] Shen, Q. & Pierce, J. D. (2015) Supplementation of coenzyme Q10 among patients with type 2 diabetes mellitus. Healthcare (Basel, Switzerland), 3, 296–309.

[65] Zhang, S.-Y., Yang, K.-L., Zeng, L.-T., Wu, X.-H. & Huang, H.-Y. (2018) Effectiveness of coenzyme Q10 supplementation for type 2 diabetes mellitus: a systematic review and meta-analysis. Int. J. Endocrinol., 2018, 6484839.

[66] Moradi, M., Haghighatdoost, F., Feizi, A., Larijani, B. & Azadbakht, L. (2016) Effect of coenzyme Q10 supplementation on diabetes biomarkers: a systematic review and meta-analysis of randomized controlled clinical trials. Arch. Iran. Med., 19, 588–596.

[67] Stojanović, M. & Radenković, M. (2017) A meta-analysis of randomized and placebo-controlled clinical trials suggests that coenzyme Q10 at low dose improves glucose and HbA1c levels. Nutr. Res., 38, 1–12.

[68] Yen, C.-H., Chu, Y.-J., Lee, B.-J., Lin, Y.-C. & Lin, P.-T. (2018) Effect of liquid ubiquinol supplementation on glucose, lipids and antioxidant capacity in type 2 diabetes patients: a double-blind, randomised, placebo-controlled trial. Br. J. Nutr., 120, 57–63.

[69] Mirhashemi, S. M., Najafi, V., Raygan, F. & Asemi, Z. (2016) The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction: A randomized, double-blind, placebo-controlled trial. ARYA Atheroscler., 12, 158–165.

[70] Montano, S. J. et al. (2015) Glutaredoxin mediated redox effects of coenzyme Q10 treatment in type 1 and type 2 diabetes patients. BBA Clin., 4, 14–20.

[71] Mizuno, K., Sasaki, A. T., Watanabe, K. & Watanabe, Y. (2020) Ubiquinol-10 intake is effective in relieving mild fatigue in healthy individuals. Nutrients, 12, 1640.

[72] Lee, Y.-J., Cho, W.-J., Kim, J.-K. & Lee, D.-C. (2011) Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: a double-blind randomized controlled study. J. Med. Food, 14, 386–390.

[73] Fukuda, S. et al. (2016) Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. Biofactors, 42, 431–440.

[74] Castro-Marrero, J. et al. (2016) Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome – a randomized, controlled, double-blind trial. Clin. Nutr., 35, 826–834.

[75] Castro-Marrero, J. et al. (2015) Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? Antioxid. Redox Signal., 22, 679–685.

[76] Morris, G., Anderson, G., Berk, M. & Maes, M. (2013) Coenzyme Q10 depletion in medical and neuropsychiatric disorders: potential repercussions and therapeutic implications. Mol. Neurobiol., 48, 883–903.

[77] Lister, R. E. (2002) An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with Ginkgo biloba extract in fibromyalgia syndrome. J. Int. Med. Res., 30, 195–199.

[78] Alcocer-Gómez, E., Cano-García, F. J. & Cordero, M. D. (2013) Effect of coenzyme Q10 evaluated by 1990 and 2010 ACR Diagnostic Criteria for Fibromyalgia and SCL-90-R: four case reports and literature review. Nutrition, 29, 1422–1425.

[79] Cordero, M. D. et al. (2012) Coenzyme Q10 in salivary cells correlate with blood cells in Fibromyalgia: improvement in clinical and biochemical parameter after oral treatment. Clin. Biochem., 45, 509–511.

[80] Cordero, M. D., Cano-García, F. J., Alcocer-Gómez, E., De Miguel, M. & Sánchez-Alcázar, J. A. (2012) Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q_{10} effect on clinical improvement. PLoS One, 7, e35677.

[81] Cordero, M. D. et al. (2013) Can coenzyme q10 improve clinical and molecular parameters in fibromyalgia? Antioxid. Redox Signal., 19, 1356–1361.

[82] Cordero, M. D. et al. (2014) NLRP3 inflammasome is activated in fibromyalgia: the effect of coenzyme Q10. Antioxid. Redox Signal., 20, 1169–1180.

[83] Alcocer-Gómez, E., Sánchez-Alcázar, J. A. & Cordero, M. D. (2014) Coenzyme q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial. J. Clin. Psychopharmacol., 34, 277–278.

[84] Sawaddiruk, P. et al. (2019) Coenzyme Q10 supplementation alleviates pain in pregabalin-treated fibromyalgia patients via reducing brain activity and mitochondrial dysfunction. Free Radic. Res., 53, 901–909.

[85] Miyamae, T. et al. (2013) Increased oxidative stress and coenzyme Q10 deficiency in juvenile fibromyalgia: amelioration of hypercholesterolemia and fatigue by ubiquinol-10 supplementation. Redox Rep., 18, 12–19.

[86] Lafuente, R. et al. (2013) Coenzyme Q10 and male infertility: a meta-analysis. J. Assist. Reprod. Genet., 30, 1147–1156.

[87] Vishvkarma, R., Alahmar, A. T., Gupta, G. & Rajender, S. (2020) Coenzyme Q10 effect on semen parameters: Profound or meagre? Andrologia, 52, e13570.

[88] Balercia, G. et al. (2009) Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertil. Steril., 91, 1785–1792.

[89] Alahmar, A. T. & Sengupta, P. (2020) Impact of coenzyme Q10 and selenium on seminal fluid parameters and antioxidant status in men with idiopathic infertility. Biol. Trace Elem. Res., doi:10.1007/s12011-020-02251-3.

[90] Alahmar, A. T., Calogero, A. E., Sengupta, P. & Dutta, S. (2020) Coenzyme Q10 improves sperm parameters, oxidative stress markers and sperm DNA fragmentation in infertile patients with idiopathic oligoasthenozoospermia. World J. Mens Health, doi:10.5534/wjmh.190145.

[91] Alahmar, A. T. (2019) The impact of two doses of coenzyme Q10 on semen parameters and antioxidant status in men with idiopathic oligoasthenoteratozoospermia. Clin. Exp. Reprod. Med., 46, 112–118.

[92] Thakur, A. S. et al. (2015) Effect of ubiquinol therapy on sperm parameters and serum testosterone levels in oligoasthenozoospermic infertile men. J. Clin. Diagn. Res., 9, BC01-3.

[93] Cakiroglu, B., Eyyupoglu, S. E., Gozukucuk, R. & Uyanik, B. S. (2014) Ubiquinol effect on sperm parameters in subfertile men who have astheno-teratozoospermia with normal sperm concentration. Nephrourol. Mon., 6, e16870.

[94] Nadjarzadeh, A. et al. (2014) Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial. Andrologia, 46, 177–183.

[95] Safarinejad, M. R., Safarinejad, S., Shafiei, N. & Safarinejad, S. (2012) Effects of the reduced form of coenzyme Q10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. J. Urol., 188, 526–531.

[96] Safarinejad, M. R. (2012) The effect of coenzyme Q_{10} supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. Int. Urol. Nephrol., 44, 689–700.

[97] Xu, Y. et al. (2018) Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod. Biol. Endocrinol., 16, 29.

[98] Gat, I. et al. (2016) The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve. Gynecol. Endocrinol., 32, 534–537.

[99] Bentov, Y., Hannam, T., Jurisicova, A., Esfandiari, N. & Casper, R. F. (2014) Coenzyme Q10 supplementation and oocyte aneuploidy in women undergoing IVF-ICSI treatment. Clin. Med. Insights Reprod. Heal., 8, 31–36.

[100] Teran, E. et al. (2018) Mitochondria and coenzyme Q10 in the pathogenesis of preeclampsia. Front. Physiol., 9, 1561.

[101] Teran, E. et al. (2009) Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. Int. J. Gynaecol. Obstet., 105, 43–45.

[102] Parohan, M., Sarraf, P., Javanbakht, M. H., Ranji-Burachaloo, S. & Djalali, M. (2020) Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose-response meta-analysis of randomized controlled trials. Nutr. Neurosci., 23, 868–875.

[103] Dahri, M., Tarighat-Esfanjani, A., Asghari-Jafarabadi, M. & Hashemilar, M. (2019) Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. Nutr. Neurosci., 22, 607–615.

[104] Sándor, P. S. et al. (2005) Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology, 64, 713–715.

[105] Shoeibi, A. et al. (2017) Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurol. Belg., 117, 103–109.

[106] Dalla Volta, G., Carli, D., Zavarise, P., Ngonga, G. & Vollaro, S. (2015) Pilot study on the use of coenzyme Q10 in a group of patients with episodic migraine without aura. J. Headache Pain, 16, A186.

[107] Rozen, T. D. et al. (2002) Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia, 22, 137–141.

[108] Parohan, M. et al. (2019) The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial. Nutr. Neurosci., 1–10, doi:10.1080/1028415X.2019.1627770.

[109] Hajihashemi, P., Askari, G., Khorvash, F., Reza Maracy, M. & Nourian, M. (2019) The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial. Cephalalgia, 39, 648–654.

[110] Guilbot, A., Bangratz, M., Ait Abdellah, S. & Lucas, C. (2017) A combination of coenzyme Q10, feverfew and magnesium for migraine prophylaxis: a prospective observational study. BMC Complement. Altern. Med., 17, 433.

[111] Slater, S. K. et al. (2011) A randomized, double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of pediatric and adolescent migraine. Cephalalgia, 31, 897–905.

[112] Hershey, A. D. et al. (2007) Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache, 47, 73–80.

[113] NHS (2018) Non-alcoholic fatty liver disease (NAFLD). https://www.nhs.uk/conditions/non-alcoholic-fatty-liver-disease/.

[114] Farsi, F. et al. (2016) Functions of coenzyme Q10 supplementation on liver enzymes, markers of systemic inflammation, and adipokines in patients affected by nonalcoholic fatty liver disease: a double-blind, placebo-controlled, randomized clinical trial. J. Am. Coll. Nutr., 35, 346–353.

[115] Farhangi, M. A., Alipour, B., Jafarvand, E. & Khoshbaten, M. (2014) Oral coenzyme Q10 supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. Arch. Med. Res., 45, 589–595.

[116] Galasko, D. R. et al. (2012) Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Arch. Neurol., 69, 836–841.

[117] Sanoobar, M., Dehghan, P., Khalili, M., Azimi, A. & Seifar, F. (2016) Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: A double blind randomized clinical trial. Nutr. Neurosci., 19, 138–143.

[118] Sanoobar, M. et al. (2013) Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis. Int. J. Neurosci., 123, 776–782.

[119] Sanoobar, M. et al. (2015) Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr. Neurosci., 18, 169–176.

[120] Moccia, M. et al. (2019) Coenzyme Q10 supplementation reduces peripheral oxidative stress and inflammation in interferon-β1a-treated multiple sclerosis. Ther. Adv. Neurol. Disord., 12, 1756286418819074.

[121] Zhu, Z.-G. et al. (2017) The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials. Neurol. Sci., 38, 215–224.

[122] Mischley, L. K., Allen, J. & Bradley, R. (2012) Coenzyme Q10 deficiency in patients with Parkinson's disease. J. Neurol. Sci., 318, 72–75.

[123] Hargreaves, I. P., Lane, A. & Sleiman, P. M. A. (2008) The coenzyme Q10 status of the brain regions of Parkinson's disease patients. Neurosci. Lett., 447, 17–19.

[124] Liu, J., Wang, L., Zhan, S.-Y. & Xia, Y. (2011) Coenzyme Q10 for Parkinson's disease. Cochrane Database Syst. Rev., CD008150,doi:10.1002/14651858.CD008150.pub2.

[125] Liu, J., Wang, L.-N., Zhan, S.-Y. & Xia, Y. (2012) WITHDRAWN: Coenzyme Q10 for Parkinson's disease. Cochrane Database Syst. Rev., CD008150, doi:10.1002/14651858.CD008150.pub3.

[126] Negida, A. et al. (2016) Coenzyme Q10 for patients with Parkinson's disease: a systematic review and meta-analysis. CNS Neurol. Disord. Drug Targets, 15, 45–53.

[127] Yoritaka, A. et al. (2015) Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease. Parkinsonism Relat. Disord., 21, 911–916.

[128] Li, Z. et al. (2015) The effect of creatine and coenzyme q10 combination therapy on mild cognitive impairment in Parkinson's disease. Eur. Neurol., 73, 205–211.

[129] Prakash, S., Sunitha, J. & Hans, M. (2010) Role of coenzyme Q(10) as an antioxidant and bioenergizer in periodontal diseases. Indian J. Pharmacol., 42, 334–337.

[130] Wilkinson, E. G., Arnold, R. M., Folkers, K., Hansen, I. & Kishi, H. (1975) Bioenergetics in clinical medicine. II. Adjunctive treatment with coenzyme Q in periodontal therapy. Res. Commun. Chem. Pathol. Pharmacol., 12, 111–123.

[131] McRee, J. T. J., Hanioka, T., Shizukuishi, S. & Folkers, K. (1993) Therapy with Coenzyme Q10 for patients with periodontal disease. 1. Effect of Coenzyme Q10 on subgingival micro-organisms. J. Dent. Heal., 43, 659–666.

[132] Denny, N., Chapple, I. & Matthews, J. (1999) Antioxidant and anti-inflammatory effects of coenzyme Q10: A preliminary study. J. Dent. Res., 78, 543.

[133] Harding, M. (2016) Polycystic Ovary Syndrome. patient.info https://patient.info/doctor/polycystic-ovary-syndrome-pro.

[134] Samimi, M. et al. (2017) The effects of coenzyme Q10 supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin. Endocrinol. (Oxf)., 86, 560–566.

[135] Izadi, A. et al. (2019) Hormonal and metabolic effects of coenzyme Q10 and/or vitamin E in patients with polycystic ovary syndrome. J. Clin. Endocrinol. Metab., 104, 319–327.

[136] Izadi, A., Shirazi, S., Taghizadeh, S. & Gargari, B. P. (2019) Independent and additive effects of coenzyme Q10 and vitamin E on cardiometabolic outcomes and visceral adiposity in women with polycystic ovary syndrome. Arch. Med. Res., 50, 1–10.

[137] El Refaeey, A., Selem, A. & Badawy, A. (2014) Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. Reprod. Biomed. Online, 29, 119–124.

[138] Kennedy, C., Köller, Y. & Surkova, E. (2020) Effect of Coenzyme Q10 on statin-associated myalgia and adherence to statin therapy: A systematic review and meta-analysis. Atherosclerosis, 299, 1–8.

[139] Qu, H. et al. (2018) The effect of statin treatment on circulating coenzyme Q10 concentrations: an updated meta-analysis of randomized controlled trials. Eur. J. Med. Res., 23, 57.

[140] Zaleski, A. L., Taylor, B. A. & Thompson, P. D. (2018) Coenzyme Q10 as treatment for statin-associated muscle symptoms-a good idea, but.... Adv. Nutr., 9, 519S–523S.

[141] Qu, H. et al. (2018) Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. J. Am. Heart Assoc., 7, e009835.

[142] Littlefield, N., Beckstrand, R. L. & Luthy, K. E. (2014) Statins' effect on plasma levels of Coenzyme Q10 and improvement in myopathy with supplementation. J. Am. Assoc. Nurse Pract., 26, 85–90.

[143] Zlatohlavek, L., Vrablik, M., Grauova, B., Motykova, E. & Ceska, R. (2012) The effect of coenzyme Q10 in statin myopathy. Neuro Endocrinol. Lett., 33 Suppl 2, 98–101.

[144] Coenzyme Q10 (2020) naturalmedicines. therapeuticresearch.com https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=938#dosing.

[145] Portakal, O. et al. (2000) Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients. Clin. Biochem., 33, 279–284.

[146] Spigset, O. (1994) Reduced effect of warfarin caused by ubidecarenone. Lancet (London, England), 344, 1372–1373.

[147] Landbo, C. & Almdal, T. P. (1998) [Interaction between warfarin and coenzyme Q10]. Ugeskr. Laeger, 160, 3226–3227.

[148] Engelsen, J., Nielsen, J. D. & Hansen, K. F. W. (2003) [Effect of Coenzyme Q10 and Ginkgo biloba on warfarin dosage in patients on long-term warfarin treatment. A randomized, double-blind, placebo-controlled cross-over trial]. Ugeskr. Laeger, 165, 1868–1871.

[149] Coenzyme Q10 (2006).