Coenzyme Q10 and non-alcoholic fatty liver disease: an overview

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in the UK, for which little effective conventional treatment is available. Mitochondrial dysfunction, oxidative stress and inflammation have been implicated in the pathogenesis of NAFLD. This article is focussed on the role of the vitamin-like substance coenzyme Q10 (CoQ10) in NAFLD, since CoQ10 has a key role in mitochondrial function, as well as having antioxidant and anti-inflammatory action. CoQ10 levels are depleted in NAFLD, and studies in animal models and human subjects have indicated supplementation with CoQ10 can significantly reduce oxidative stress and inflammation characteristic of NAFLD. In addition, NAFLD patients are at increased risk of developing heart failure, and supplementary CoQ10 may help to reduce this risk. Supplementary CoQ10 is generally well tolerated, with no significant adverse effects reported in long term use.

Key words

coenzyme Q10; non-alcoholic fatty liver disease; mitochondrial dysfunction; oxidative stress; inflammation.

Introduction

The liver is a complex organ which performs a wide range of essential functions to maintain normal health- examples include digestion, immune function and detoxification. There are more than one hundred types of liver disease, ranging from common disorders such as non-alcoholic fatty liver disease (NAFLD) and alcohol related liver disease (ARLD), to less common inherited disorders such as haemochromatosis and primary biliary cholangitis. The liver has a high functional reserve, and usually liver disorders do not cause any obvious symptoms until the liver has suffered a substantial amount of tissue damage; typical symptoms include loss of appetite, weight loss and jaundice (Fan, 2010). The liver has a high capacity to regenerate damaged tissue, but is eventually compromised by permanent scarring (cirrhosis), which represents a common final stage of the different types of liver disease (Fan, 2010). Cirrhosis is typically preceded by the deposition of fat within liver tissue, which can occur in both alcohol consuming and non-consuming individuals. There is currently little effective treatment for NAFLD. This article is focussed on the role of CoQ10 deficiency and supplementation in NAFLD.

Non-alcoholic fatty liver disease

NAFLD is defined as the accumulation of fat, principally as triglyceride, in hepatic cells, exceeding 5-10% of liver weight (Chalasani et al, 2012). NAFLD is the most common liver disorder worldwide; its prevalence in the general population is estimated at 20-30%, but this rises to 60-70% in obese individuals, and 70-90% in those with diabetes (Browning et al, 2004). NAFLD occurs in every age group but especially in people in their 40s and 50s. The condition is closely linked to metabolic syndrome, which is a cluster of abnormalities including increased abdominal fat, poor ability to use the hormone insulin, high blood pressure and high blood levels of triglycerides. NAFLD develops in 4 main stages, namely simple steatosis characterised by initial fat deposition, non-alcoholic steatohepatitis (NASH) associated with liver inflammation, fibrotic scar tissue formation, and cirrhotic liver scarring/liver failure (Benedict & Zhang,

2017).Typically 10-20% of patients progress to NASH, with 10-20% of these developing fibrosis and ultimately cirrhosis (Pappachan et al, 2017). Liver biopsy remains the gold standard for diagnosis of NAFLD.

Coenzyme Q10 and liver function

Coenzyme Q10 (CoQ10) is a vitamin-like substance with a number of important cellular functions of relevance to liver metabolism and liver disorders. Firstly, CoQ10 plays a key role in the biochemical process supplying all cells with the energy they require for normal functioning; specifically CoQ10 is an intermediate in the electron transport system that generates energy in the chemical form of ATP, shuttling electrons from complexes I and II to complex III of the mitochondrial respiratory chain (Hargreaves, 2003). An adequate supply of CoQ10 is of particular importance in tissues with a high energy requirement, such as the liver and heart. Although CoQ10 is synthesised throughout the body, because of its size and high metabolic capacity, the liver is the major site of CoQ10 synthesis. In patients with liver disease where metabolic capacity has been compromised, in addition to its direct effect on liver function, reduction in CoQ10 production is also likely to have a deleterious effect on heart function.

Secondly, CoQ10 is a major lipid soluble antioxidant, protecting cell membranes, particularly those within mitochondria, from free radical induced oxidative damage (Hargreaves, 2003). Such oxidative stress has been implicated in the pathogenesis of a number of liver disorders, particularly NAFLD. CoQ10 is the only endogenously synthesised liposoluble antioxidant.

Thirdly, CoQ10 has been shown to modulate directly the expression of a number of genes, including those involved in inflammation and cholesterol synthesis respectively. Thus CoQ10 modulates expression of the protein complex nuclear factor kappa beta (NFkß), the so-called “master switch” of inflammation (Pala et al, 2016). Similarly randomised controlled clinical trials have shown supplemental CoQ10, alone or in combination with other supplements, can significantly reduce total blood or LDL cholesterol levels. Thus, studies by Schmelzer et al (2011; 150mg CoQ10/day for 2 weeks) and Monteri et al (2014; 200mg CoQ10 for 12 weeks) reported significant reductions of approximately 15% in LDL cholesterol levels following CoQ10 supplementation. In addition, Mazza et al (2018) showed that treatment with a combination of CoQ10 (30mg/day for 2 months) and red yeast rice reduced total and LDL cholesterol levels by approximately 20%.

The three functions of CoQ10 outlined above are of particular relevance to NAFLD; increased oxidative stress and inflammation have both been implicated in the pathogenesis of NAFLD (Spahis et al, 2017), whilst heart failure has been reported as one of the major causes of death in NAFLD patients (Francque et al, 2016). NAFLD is associated with heart failure, arrhythmias, valve dysfunction and atherosclerosis (Sirbu et al, 2016). Alcohol-related liver disease is similarly associated with an increased risk of cardiovascular disorders; these include alcoholic cardiomyopathy, arterial hypertension and atrial fibrillation (Milic et al, 2016).

CoQ10 deficiency

The body's daily requirement for CoQ10 has not been accurately quantified, but has been estimated as 500mg/day; this is based on a total CoQ10 body pool of 2gm and average tissue turnover time of 4 days. Most of this daily requirement must be manufactured within the body, since a relatively small proportion, estimated at 5mg/day (Weber et al, 1997), is derived from the normal diet. As people age, the

capacity of the body to synthesise its own CoQ10 decreases; optimal production occurs around the mid-twenties, with a continual decline in tissue levels thereafter (Kalen et al, 1989). In addition to the normal aging process, CoQ10 levels have also been shown to be depleted in a variety of disorders, as well as statin type drugs. Reduced CoQ10 levels may be a particular problem in patients with fatty liver disease prescribed statins, since in addition to inhibiting cholesterol synthesis, statins also inhibit the production of CoQ10. Dietary supplementation with CoQ10 therefore provides a mechanism to maintain adequate levels within the body, and a rationale for the dosages of CoQ10 used in clinical trials, typically 200-400mg/day.

Preclinical studies on CoQ10 supplementation

A number of studies in animal models have demonstrated the ability of CoQ10 to reduce or prevent the development of liver cirrhosis following a variety of toxic insults; these include exposure to medicinal drugs (Fouad & Jresat, 2012), toxic chemicals (Choi et al, 2009), and parasitic microorganisms (Othman et al, 2008). For example, in the study by Fouad & Jresat (2012), the ability of CoQ10 to protect liver tissue against free radical induced oxidative damage was demonstrated; when acute liver injury was induced in rats via administration of acetaminophen-more commonly known as paracetamol, subsequent administration of CoQ10 reduced cirrhotic tissue damage via its antioxidant and anti-inflammatory action. In rats prone to developing NAFLD, dietary supplementation with CoQ10 prevented further progression to cirrhosis, via down regulation of markers of free radical induced oxidative stress and inflammation (Tarry-Adkins et al, 2016). Similarly, in rats fed a high fat diet, supplementation with CoQ10 reduced lipid synthesis and increased fatty acid oxidation, resulting in reduced serum triglyceride levels, reduced total and LDL cholesterol levels, and reductions in weight gain (Chen et al, 2019).

Clinical studies on CoQ10 supplementation in NAFLD

With regard to clinical studies, Yessilova et al (2005) found that blood CoQ10 levels were depleted in NAFLD patients, with the decrease in CoQ10 correlating with increased liver inflammation and cirrhosis. Farhangi et al (2014) reported the first randomised controlled trial supplementing CoQ10 in NAFLD patients. The study comprised 41 NAFLD patients, 31 male and 10 female aged 20-65 years, diagnosed via ultrasonography. Patients supplemented with 100 mg/day CoQ10 for 4 weeks showed significant reductions($p<0.05$) in the levels of biochemical markers of inflammation and oxidative stress (serum aspartate aminotransferase, total antioxidant capacity), as well as waist circumference. The most recent randomised controlled trial (Farsi et al, 2016) comprised 41 NAFLD patients (28 male, 13 female), aged 19-54 years with BMI in the range 25-35 Kg/m2. NAFLD status was established by absence of alcohol consumption, elevated liver enzymes, and ultrasonography. The grade of hepatic steatosis, defined as the % of hepatocytes containing fat droplets, was categorised via a 4 point grading system of normal, mild, moderate and severe. Individuals given 100mg CoQ10 per day for 3 months showed significant reductions ($p<0.05$) compared to placebo in the levels of blood markers for liver inflammation and damage; aspartate aminotransferase ($p=0.012$), gamma-glutamyl peptidase, ($p=0.039$), high sensitivity C-reactive protein ($p=0.02$), TNF-alpha ($p=0.049$), and a lower percentage of liver cells with fat droplet inclusions (reduction in NAFLD grade $p=0.046$). CoQ10 was well tolerated, with no significasnt adverse effects reported,

Other clinical studies on CoQ10 of relevance to NAFLD

As noted above, the risk of developing cardiovascular disease is substantially increased in NAFLD patients, with heart failure being a major cause of death. To date there have been no randomised controlled trials to investigate the effect of CoQ10 supplementation specifically on heart failure in NAFLD. However, two randomised controlled clinical studies are relevant to this issue, namely Q-SYMBIO and KISEL-10.

The Q-SYMBIO study was carried out in 420 patients with chronic heart failure, New York Heart Association (NYHA) class III and V. The effect of CoQ10 supplementation, at a prescribed dose of ~~3~~ x 100mg/day for 2 years, on symptoms and biomarker status ~~-~~hence the trial acronym Q-SYMBIO~~-~~were assessed, as an adjuvant to conventional medication of ACE inhibitors and beta blockers. Assessment included clinical examination, echocardiography and pro-BNP status. The primary long-term endpoint was time to first major adverse cardiovascular event (MACE), which included unplanned hospitalisation due to worsening heart failure and cardiovascular death. Supplementation with CoQ10 significantly reduced the relative risk of MACE by 42%, with a reduction in both cardiac related deaths (43%) and all cause mortality (42%). The authors concluded that these beneficial effects of CoQ10 resulted from improved cellular energy provision within heart tissue (Mortensen, 2014).

The KISEL-10 study was carried out on normal elderly individuals (70-88yrs) from the Kinda region of Stockholm (Alehagen et al, 2013); 440 participants were supplemented with 200mg/day coenzyme Q10 (CoQ10; Bio-Quinone 100mg) and 200mcg/day selenium (SelenoPrecise), or placebo, over a 5 year period, hence the trial acronym KISEL-10. Clinical examination, echocardiography and biomarker measurements were carried out at 6-month intervals. Quality of life was quantified using the Short Form-36 (SF-36), Cardiac Health Profile (CHP) and Overall Quality of Life (overall-QOL) questionnaires. Supplementation with CoQ10 and selenium resulted in a significant reduction in the number of days in hospital, and significantly slowed the deterioration in health related quality of life. Echocardiography showed significantly better cardiac function in supplemented participants, whose risk of cardiovascular mortality was significantly reduced by 53%. Further analysis of data from the original study have subsequently been reported; there were significant reductions in the blood levels of C-reactive protein and sP-selectin as markers of inflammation, and copeptin and adrenomedullin as markers of oxidative stress, in addition to levels of pro-BNP. The authors of the KISEL-10 study concluded that the reduction in cardiovascular mortality risk in elderly subjects was in part the result of a reduction in the fibrosis of cardiac tissue (Alehagen et al, 2018).

The Q-SYMBIO and KISEL-10 studies thus provide a rationale that supplementation with CoQ10 may reduce the risk of heart failure in patients with NAFLD, or prevent cardiovascular disease developing in NAFLD patients where this is not already present. In addition, these studies provide further evidence for the systemic antioxidant, anti-inflammatory and anti-fibrotic activity of CoQ10 of relevance to NAFLD.

Safety of CoQ10

The safety of CoQ10 has been assessed by Hidaka et al (2008) and Hosoe et al (2007). CoQ10 is generally well tolerated, with no serious adverse effects reported in long term use. Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed. CoQ10 is well tolerated in healthy adults at an intake of 900 mg/day, and in rats at a dose of up to 1200 mg/Kg/day. In addition, Yamaguchi et al (2009) reported that

CoQ10 had no genotoxic activity. CoQ10 is not recommended for pregnant or lactating women, in whom the effects of CoQ10 have not been extensively studied. The safety of CoQ10 has been confirmed in more than 200 randomised controlled trials, on a wide range of disorders.

Bioavailability of CoQ10

Bioavailability is defined as the proportion of an ingested substance that reaches the blood circulation. Because of its relatively large molecular size and lipid solubility, the bioavailability of CoQ10 is intrinsically low. CoQ10 is absorbed from the intestinal tract via the same mechanism as other lipid soluble nutrients, via a lipid carrier through mucosal cells initially into the lymph, and thence into the bloodstream; thus absorption is optimised when CoQ10 is dissolved in a carrier oil, preferably soya or palm oil. The delayed peak concentration of CoQ10 in blood is a consequence of this initial absorption into the lymphatic system. However, incorporation of supplemental CoQ10 in liposomal, micellular or nanoparticle form cannot increase the absorption of CoQ10 through intestinal cells into the lymph. CoQ10 cannot be made more water soluble, as any alteration to the molecular structure means that the molecule is no longer CoQ10. When supplemental CoQ10 is first produced, via a yeast fermentation process, it is obtained in the form of crystals which cannot be absorbed from the digestive tract. It is essential that these crystals are dispersed into single CoQ10 molecules, and remain dispersed during the product shelf-life, to enable optimum bioavailability; adding CoQ10 crystals to a carrier oil without such dispersal, a cost saving technique used by some manufacturers, is inadequate. Disparity in the findings of clinical trials supplementing CoQ10 in diabetes undoubtedly results from the use of supplements with inadequate bioavailability and/or insufficient dosage or treatment duration. These issues have been addressed in the recent clinical study of CoQ10 bioavailability by Lopez-Lluch et al (2019). The bioavailability of seven different supplement formulations containing 100 mg of CoQ_{10} was evaluated in 14 young healthy individuals. Bioavailability was measured as area under the curve of plasma CoQ_{10} levels over 48 h after ingestion of a single dose. Measurements were repeated in the same group of 14 volunteers in a double-blind crossover design with a minimum of 4 wk washout between intakes. Bioavailability of the formulations showed large differences that were statistically significant. The best absorbable formulation was a soft-gel capsule containing ubiquinone (Bio-Quinone Q10). The matrix used to dissolve CoQ_{10} and the proportion and addition of preservatives such as vitamin C affected the bioavailability of CoQ_{10}.

Summary

There is considerable evidence from pre-clinical studies in a number of animal model systems for the capacity of supplemental CoQ10 to reduce or prevent liver tissue damage by a variety of toxic agents, and these data provide a plausible rationale for the supplementation of CoQ10 in patients with liver disease. Although only two randomised controlled clinical studies, comprising some 82 patients, supplementing CoQ10 in NAFLD have been carried out to date, the results of significantly reduced biomarkers of liver tissue injury have been sufficiently encouraging to consider such a novel therapeutic approach in the future management of NAFLD patients.

Key points

1. NAFLD is the most common liver disorder in the UK, for which little effective conventional treatment is available.
2. Mitochondrial dysfunction, oxidative stress and inflammation have been implicated in the pathogenesis of NAFLD.
3. Levels of the vitamin like substance coenzyme Q10 (CoQ10), which has a key role in normal mitochondrial function, antioxidant and anti-ctivity, are depleted in NAFLD.
4. Oral supplemention with CoQ10 can significantly reduce oxidative stress and inflammation characteristic of NAFLD.
5. Supplementary CoQ10 is generally well tolerated, with no significant adverse effects reported in long term use.

Reflective questions

1. Reflect on the role of coenzyme Q10 (CoQ10) in normal liver function.
2. Consider how you would use the information in this article to benefit patients with NAFLD.
3. Reflect on how you would use the information in this article to inform fellow healthcare professionals, who may be unfamiliar with the background to NAFLD or CoQ10.
4. Are there other liver disorders which could potentially benefit from supplementation with CoQ10?

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