Targeted treatment of age-related fibromyalgia with supplemental coenzyme Q10

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Introduction

Fibromyalgia is a chronic disabling disorder, affecting up to 5% of the UK population. In addition to the cardinal symptoms of muscle pain and fatigue, fibromyalgia patients also suffer from a wide range of co-morbidities, including headache, anxiety/depression, sleep deprivation, memory and concentration disturbances as well as digestive dysfunction (Guymer and Littlejohn, 2013). The reason people develop fibromyalgia is not fully understood, and conventional prescribed drug treatments may be of limited effectiveness. Treatment has progressed from inappropriate use of nonsteroidal anti-inflammatory drugs (NSAID) and opioid type pain relieving drugs, through the use of anticonvulsants such as pregablin and gabapentin, and antidepressants such as amitriptyline, to non-pharmacological treatments such as cognitive behavioural therapy or specific exercise regimes (Guymer and Littlejohn, 2013). However, the symptomatic relief conferred by these various treatments can be very variable, and there is a need for additional therapeutic strategies, including those based on nutritional supplementation. Therefore, the aim of this chapter will be to provide information on nutritional treatment strategies targeted to pain relief in fibromyalgia, focussing upon coenzyme Q10 (CoQ10) and the evidence supporting its therapeutic utility in the treatment of this disorder.

Pathogenesis of fibromyalgia

The pathological mechanisms underlying fibromyalgia are thought to involve mitochondrial dysfunction, oxidative stress and dysregulation of the inflammatory response (Romano et al, 2015). However, there is a growing consensus that the oxidative stress and inflammation associated with fibromyalgia originate from mitochondrial dysfunction (Cordero et al., 2010A; Cordero et al., 2014B). Evidence of oxidative stress in fibromyalgia has been indicated by increased levels of the lipid peroxidation production, malondialdehyde in blood mononuclear cells(BMC) and plasma of patients with this condition in conjunction with decreased activity of the antioxidant enzyme, catalyse (Cordero et al., 2012). Furthermore, an increase in mitochondrial reactive oxygen species (ROS) generation was reported in the BMC of patients with fibromyalgia in a study conducted by Cordero el al in 2013. Indices of the dysregulation of inflammation in fibromyalgia have been denoted by increased serum/plasma levels of the pro-inflammatory cytokines, TNF-alpha (Cordero et

al., 2013A), (interleukin-IL) IL-8 and IL-1Ra (Wallace et al., 2001) and IL-1B and IL-18 (Cordero et al., 2014B). Decreased levels of ATP (Cordero et al., 2012; Castro-marrevo et al., 2013; Cordero et al., 2013A), a decreased mitochondrial DNA content relative to that of nuclear DNA (Cordero et al., 2012; Castro-Marrevo et al., 2013) together with a diminution in the status of the mitochondrial respiratory chain(MRC) carrier, CoQ10 (Cordero et al., 2010A;Cordero et a., 2012; Cordero et al., 2013A) and a decreased mitochondrial membrane potential have all been reported in the BMC of patients with fibromyalgia strongly supporting evidence of mitochondrial dysfunction in this disorder.

Within the confines of this chapter, it would not be possible to outline all the mechanisms that have been proposed to account for the oxidative stress, inflammatory response and mitochondrial dysfunction reported in fibromyalgia. However, a paradigm will be offered based on the results of studies from the current literature to account for these pathological anomalies in fibromyalgia.
Mitochondrial dysfunction appears to be one of the primary events initiating both ROS generation and inflammation in fibromyalgia (Cordero et al., 2011; Cordero et al., 2013A). The cause of the MRC impairment with deficiencies in the activities of the MRC enzymes, complex I,II, III and IV [Figure 1] together a reduced expression in the protein levels of complexes I and III as well as a diminution in the expression of the electron carrier cytochrome c (Cordero et al., 2014B). It has been suggested that the MRC impairment may be related to the down regulation of genes encoding for the regulatory proteins, PGC-1α, TFAM and NRF1 that has been reported in fibromyalgia and which would be expected to impair mitochondrial biogenesis (Cordero et al., 2014B). An impairment in mitochondrial biogenesis in this disorder may account for the decrease in both mitochondrial DNA copy number and the activity of the mitochondrial marker enzyme, citrate synthase in BMC isolated from patients with fibromyalgia (Cordero et al., 2012; Castro-Marrevo et al., 2013). However, the deficit in CoQ10 status which has been widely reported in fibromyalgia may also be an important causative factor for the mitochondrial dysfunction determined in this order. A deficit in cellular CoQ10 status has been associated with multiple MRC enzyme deficiencies, decreased mitochondrial membrane potential and a concomitant reduction in ATP levels(Duberley et al., 2013) which have all been documented in fibromyalgia (Cordero et al., 2010B).
In addition to its role as an electron carrier in the MRC, CoQ10 also serves as a potent lipid soluble antioxidant (Hargreaves, 2003), and accordingly a deficiency in cellular CoQ10 status has been associated with an increase in mitochondrial ROS generation which has also been reported in the BMC of fibromyalgia patients (Duberley et a., 2013 Cordero et al., 2014B). This increase in ROS generation together with the accumulation of the products of mitochondrial DNA oxidation have been reported to be potent activators of the NLRP3 inflammasome, a cytosolic oligomeric protein complex present in the cells of the immune system and which regulates the innate immune response (Zhen and Zhang, 2019).

In vitro and *in vivo* studies using BMC isolated from fibromyalgia patients have reported increased gene expression of the NLRP3 protein, a component of the inflammasome as well as the caspase-1, an inflammatory response initiator

together with increased serum and cell culture levels of the inflammatory cytokines, IL-1β and IL-18 in association with a deficit in cellular CoQ10 status (Cordero et al., 2014B). Pharmacologically induced CoQ10 deficiency in BMC from healthy volunteers has also been reported to cause an increase in the synthesis of the pro-inflammatory cytokine, TNF-alpha which also accompanied an increase in mitochondrial ROS production (Cordero et al., 2013A). As well as promoting the inflammatory response by generating ROS and oxidized mitochondrial DNA products, a CoQ10 deficiency may also remove the inhibitory effect of this molecule on inflammasome activation(Cordero et al., 2013A). A high positive correlation has been reported between serum IL-1β and IL-18 levels and the pain scores in fibromyalgia patients indicating the importance of inflammation in the pathophysiology of this disorder (Cordero et al., 2014B). Furthermore, inflammatory cytokines have been reported to induce fatigue, fever, sleep and myalgia which are symptoms reported in fibromyalgia (Wallace et al., 2001).

The putative mechanisms that have been implicated in the generation of oxidative stress and inflammation in fibromyalgia are outlined in Figure 2. Although there is some evidence to indicate that a deficiency in cellular CoQ10 status may be an important triggering event in the mitochondrial dysfunction, oxidative stress and inflammation associated with fibromyalgia, the actual factors responsible for this deficiency have yet to be elucidated.

Overall, Fibromyalgia is thought to result from a self-reinforcing, increasingly destructive process of impaired energy production, free radical damage and inflammation.

Fibromyalgia and ageing

Fibromyalgia is a disorder that can occur at any age in both men and women; however fibromyalgia tends be considered by some medical practitioners as a condition primarily affecting middle aged women. Thus fibromyalgia in older patients has tended to be understudied, and because of the likelihood of other age related problems, diagnosis of fibromyalgia in the elderly may be overlooked. Only six clinical studies relating specifically to fibromyalgia in the elderly have been published in the medical literature over the past 30 years. In 1988 Yunus et al first reported that fibromyalgia in the elderly was often unrecognised, and treated with inappropriate medications such as steroids. The most recent study by Jacobsen et al (2015) found that more than 80% of older (55 to 95 years) patients with fibromyalgia were subject to pain, lack of mobility and sleep disruption resulting from under-treatment; in addition many of these patients were using ineffective and potentially harmful opioid or steroid type medications.

Two non-pharmacological interventions known to benefit fibromyalgia are exercise and nutrition (Busch et al, 2011; Bjorklund et al, 2018). Exercise is an important part of the treatment in fibromyalgia, and it also helps keep weight down, which reduces the stresses on the joints; however older individuals may

find taking part in such exercise regimes challenging. With regard to nutrition, supplementation may benefit the primary symptoms or co-morbidities associated with fibromyalgia. Fibromyalgia patients are at increased risk of disorders such as diabetes, thyroid dysfunction, cardiovascular disease, and osteoporosis. In view of its MRC electron carrier and antioxidant functions, CoQ10, supplementation with CoQ10 may benefit the cardinal symptoms of muscle pain and fatigue, as well as headache and migraine which have been associated with cellular energy failure and oxidative stress (Hargreaves, 2003; Corder et al., 2012). In addition, nutritional supplementation may benefit co-morbidities such as gastrointestinal dysfunction (probiotics), osteoporosis (calcium, vitamin D3, vitamin K2), sleep problems (melatonin), and thyroid dysfunction (selenium) (Mohabbat et al., 2019).

Nutritional supplementation and ageing

Nutritional supplementation may be of particular importance in the elderly. The body requires a range of nutrients to maintain normal functioning; some of these, such as CoQ10 and glucosamine, are manufactured wholly or mainly within the body, whilst many (such as vitamins) must be derived from the normal diet. As people age, their bodies become less efficient at manufacturing nutrients such as CoQ10, or absorbing dietary nutrients from the digestive tract. As an example, optimum production of CoQ10 occurs around twenty five years of age, production then gradually declines with increasing age, such that production at age sixty five is approximately half that at twenty five. Thus supplementation with CoQ10 in older individuals with fibromyalgia addresses two issues, a deficiency known to occur in fibromyalgia, and a deficiency known to result from the normal ageing process (Kalen et al., 1989).

Similarly, the elderly are at risk of the potential deficiency in a wide range of other essential nutrients, and a study by Borg et al (2015) identified deficiencies of vitamin D3, vitamins B1, B2 and B12, calcium, magnesium and selenium as being of particular public health concern. Selenium is a trace element essential for the activity of 25 selenoproteins involved in the regulation of the inflammatory response and cellular antioxidant capacity, and therefore a deficiency in this trace element may lead to a weakening of the immune system and a compromised antioxidant capacity which are both integral to the pathophysiology of fibromyalgia (Hargreaves and Mantle, 2019). As noted above, many of these nutrients have been found to be depleted in fibromyalgia, with a corresponding benefit on symptoms following supplementation. Therefore, again supplementation addresses two issues, deficiency due to fibromyalgia and deficiency due to ageing (Eisinger et al., 1994; Mohabbat et al., 2019).

Coenzyme Q10

CoQ10 is a lipid soluble molecule consisting of a benzoquinone nucleus derived from tyrosine and an isoprenoid side chain which is synthesised in all the cells of the body apart from red blood cells as the presence of mitochondria are

required for its synthesis (Hargreaves, 2003). As previously mentioned, the major function of CoQ10 is that of an electron carrier in the MRC where is transports electrons derived from complex I and complex III to complex III enabling a continuous passage of electrons within the MRC a prerequisite for oxidative phosphorylation and cellular ATP generation (Figure 1; Hargreaves, 2003). CoQ10 also serves as an important lipid soluble antioxidant protecting cellular membranes and circulatory lipoproteins against free radical induced oxidative damage (Hargreaves, 2003; Mantle, 2015). The antioxidant function of CoQ10 is attributed to its fully reduced ubiquinol form addition to acting as an antioxidant in its own right is also involved in the regeneration of other antioxidants such as a-tocopherol (the active antioxidant form of vitamin E) and vitamin C (Crane, 2001). One of the principle enzymes involved in reducing CoQ10 into its ubiquinol form is the selenium-containing enzyme thioredoxin reductase, and therefore, a deficit in selenium status may compromise cellular antioxidant capacity (Xia et al, 2003). Furthermore, selenium is also serves as a prosphetic group for the antioxidant enzyme glutathione peroxidase (Hargreaves and Mantle, 2019). In addition to its role as an electron carrier and antioxidant, CoQ10 has also been shown to directly affect the expression of a number of genes, including some of those involved in inflammation (Mantle, 2015). It has been suggested that CoQ10 is able to elicit an anti-inflammatory response by both its antioxidant function as well as by controlling the gene expression of the transcription factor, fNFkappaB1 which has a key role in regulating the immune response to infection (Schmelzer et al., 2008).

An adequate supply of CoQ10 is essential for normal functioning of mitochondria. Although some CoQ10 is obtained from the normal diet (approximately 5mg/day), most of the daily CoQ10 requirement (estimated at 500mg) is synthesised within the body (Mantle, 2015). As noted above, 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 ageing process, CoQ10 levels have also been shown to be depleted in a variety of disorders, including fibromyalgia, as well as by statin-type drugs. Dietary supplementation with CoQ10 therefore provides a mechanism to maintain adequate levels within the body (Hargreaves, 2003; Mantle, 2015).

Clinical studies on CoQ10 supplementation in fibromyalgia

Fibromyalgia patients have been shown to have depleted tissue levels (up to 40-50% of normal) of CoQ10, together with increased levels of mitochondrial dysfunction, oxidative stress and inflammation, both in adult (Cordero et al, 2013A; Castro-Marrero et al, 2013) and juvenile (Miyamae et al, 2013) patients. A recent Norwegian clinical study has highlighted the link between fibromyalgia and inflammation. The study (Groven et al, 2019) comprised 150 women aged 18 to 60, divided equally into three groups: fibromyalgia patients, chronic fatigue syndrome patients and healthy controls. Blood samples from the study were taken from all participants and analysed for levels of high-sensitivity C-reactive protein (hsCRP), a sensitive biochemical marker of inflammation.
Both the fibromyalgia (1.3 mg/L) and chronic fatigue syndrome patients (0.94

mg/L) had significantly increased mean levels of hsCRP, compared to healthy controls (0.60 mg/L). The results from this study are noteworthy, since inflammation is a well known cause of pain and fatigue (Sluka & Clauw, 2016).

A number of clinical studies have been undertaken to investigate the effect of CoQ10 supplementation on fibromyalgia symptoms. The rationale for using CoQ10 in the treatment of fibromyalgia is multifaceted: To replenish the underlying CoQ10 deficiency associated with this disorder; to increase electron flow in the MRC; to enhance cellular antioxidant capacity and to module the inflammatory response.

Thus Cordero et al (2012) correlated headache symptoms with reduced CoQ10 levels and increased oxidative stress. Following CoQ10 supplementation (300 mg/day for 3 months) there was a significant decrease in oxidative stress as indicated by an increase in the activity of antioxidant enzyme, catalase and a significant decrease in level of the lipid oxidation production, malondialdehyde in the BMC of fibromyalgia patients which was accompanied by significant improvement in headache symptoms in the fibromyalgia patients. Similarly, a randomised, double-blind, placebo-controlled clinical study in 20 fibromyalgia patients found supplementation with CoQ10 (Pharma Nord Bio-Quinone, 300mg/day for 40 days) significantly reduced (by more than 50%) pain and fatigue; there was a corresponding improvement in mitochondrial energy generation as indicated by BMC ATP levels, and reduced oxidative stress and inflammation, as assessed by the circulatory levels of the inflammatory cytokines, IL-1b and IL-18 (Cordero et al, 2014B). In the latter study, psychopathological symptoms symptoms (including depression) were significantly improved following CoQ10 supplementation compared to placebo; this improvement was linked to the effect of CoQ10 supplementation in reducing oxidative stress and inflammation, and increasing levels of the neurotransmitter, serotonin (Alcocer-Gomez et al, 2014; Alcocer-Gomez et al, 2017).

Several studies have reported abnormal blood lipid profiles in patients with fibromyalgia. For example, Gurer et al (2006) in a study of 80 women with fibromyalgia, reported increased blood levels of total and LDL-cholesterol compared to normal control subjects. In a study carried out in Spain at Seville University, Cordero et al (2014A) evaluated the blood lipid profiles of 180 patients with fibromyalgia. Approximately two thirds of these patients had increased levels of total cholesterol and LDL-cholesterol, which correlated with the severity of their fibromyalgia symptoms assessed using tenderpoint, Fibromyalgia Impact Questionaire (FIQ) and Visual Analogue Scales (VAS) of pain. These increases in cholesterol may result in part from genetic factors, as well as from lack of exercise and increased body mass index (BMI). The lack of physical activity and increased total/ LDL-cholesterol blood levels may explain the increased risk of cardiovascular disease in fibromyalgia patients noted by Acosta-Manzano et al (2017).

Various studies have demonstrated that coenzyme Q10 can help to control cholesterol levels in the blood. Firstly, CoQ10 can reduce cholesterol levels by directly inhibiting the genes responsible for the biosynthesis of low density

lipoprotein (LDL) cholesterol. Secondly, CoQ10 is circulated in the blood using LDL cholesterol as a carrier; at the same time the antioxidant action of CoQ10 helps to prevent the LDL cholesterol from being oxidatively damaged by free radicals, thereby reducing the risk of atherosclerosis. Thirdly, in addition to inhibiting cholesterol synthesis, statin drugs also inhibit the body's production of CoQ10, which is produced via the same biochemical pathway (Hargreaves et al., 2005; Mantle, 2015). Supplementation with CoQ10 can reduce statin associated adverse effects, such as muscle pain or the increased risk of diabetes. Randomised controlled clinical trials have shown supplemental CoQ10, alone or in combination with other supplements, can significantly reduce total blood or LDL cholesterol levels in hypercholesterolaemic subjects. Thus, studies by Schmelzer et al in 2011 using 150mg CoQ10/day for 2 weeks) and Monteri et al in 2014 using 200mg CoQ10 for 12 weeks reported significant reductions of approximately 15% in LDL cholesterol levels following CoQ10 supplementation. A study by Miyamae et al in 2013 also reported that ubiquinol treatment (100 mg/day for 12 weeks) of patients with juvenile fibromyalgia resulted in decreased circulatory level of free cholesterol and cholesterol esters indicating that ubiquinol supplementation improved cholesterol metabolism as well as improving chronic fatigue scores as measured by the Chalder Fatigue Scale.

The beneficial effects of CoQ10 as an adjunct therapy to the commonly used anticonvulsant, pregabalin which is commonly used to reduce the pain sensation in fibromyalgia was recently demonstrated in a study by Sawaddiruk et al (2019). In this study, randomised placebo-controlled clinical study 11 fibromylagia patients were randomly allocated to pregabalin alone or with pregabalin with CoQ10. The results of the study indicated that although pregbalin treatment alone reduced pain and anxiety in the patients, pregbalin together with CoQ10 treatment reduced pain, anxiety as well as reducing mitochondrial oxidative stress in BMC and inflammation in the fibromyalgia patients compared to baseline.

Safety and bioavailability of CoQ10

CoQ10 is generally well tolerated, with no serious adverse effects reported in long term use (Hiaka et al, 2008). Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed. The safety of CoQ10 has been confirmed in more than 200 randomised controlled trials, on a wide range of disorders. Several case studies have suggested that CoQ10 may interfere with the action of warfarin; however a randomised controlled clinical trial showed CoQ10 supplementation at 100mg/day had no effect on the clinical action of warfarin (Engelsen et al, 2003).

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). 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 undoubtedly result from inadequate bioavailability, and insufficient dosage or treatment duration.

Conclusion

In view of the ability of CoQ10 supplementation to restore an underlying CoQ10 deficiency in fibromyalgia patients together with its ability to improve MRC activity, restore cellular antioxidant capacity and ameliorate inflammation all of which are factors associated with the pathophysiology of fibromyalgia, CoQ10 therapy should be considered an appropriate adjunct treatment for this chronic pain disorder as shown in Figure 3. However, larger controlled clinical trials are still required to provide further data of the effective of CoQ10 in the treatment of fibromyalgia.

References

Acosta-Manzano P et al (2017) Do women with fibromyalgia present higher cardiovascular risk profile than healthy women? Clin Exp Rheumatol; 105: 61-67.

Alcocer-Gomez et al (2014) CoQ10 regulates serotonin levels and depressive symptoms in fibromyalgia symptoms. J Clin Psychopharmacol; 34: 277-278.

Alcozer-Gomez et al (2017) Effect of CoQ10 on psychopathological symptoms in fibromyalgia patients. CNS Neurosci Ther; 23: 188-189.

Bjorklund G et al (2018) Fibromyaslgia and nutrition: therapeutic possibilities? Biomed Pharmacotherapy; 103: 531-538.

Borg S et al (2015) Micronutient intakes and potential inadequacies of community dwelling older adults: a ststematic review. Br J Nutr; 113: 1195-1206.

Busch AJ et al (2011) Exercise therapy for fibromyalgia. Curr Pain Headache Rep; 15: 358-367.

Castro-Marrero J et al (2013) Could mitochondrial dysfunction be a differentiating marker between CFS and fibromyalgia? Antioxid Redox Signal; 19: 1855-1860.

Cordero et al (2010A). Oxidative stress and mitochondrial dysfunction in

fibromyalgia.. Neuro Endocrinol Lett. 2010;31(2):169-73.

Cordero et al (2010B). Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. Arthritis Research & Therapy; 12: R17.

Cordero et al (2011). Clinical symptoms in fibromyalgia are better associated to lipid peroxidation levels in blood mononuclear cells rather than in plasma. PLoS One; 6: 226915.

Cordero MD et al (2012) Oxidative stress correlates with headache symptoms in fibromyalgia: CoQ10 effect on clinical improvement. PLOS One; 7: e35677.

Cordero MD et al (2013A) Is inflammation a mitochondrial dysfunction dependent event in fibromyalgia? Antioxid Redox Signal; 18: 800-807.

Cordero MD et al (2013B) Can CoQ10 improve clinical and molecular parameters in fibromyalgia? Antioxd Redox Signal; 19: 1356-1361.

Codero MD et al (2014A) Clinical symptoms in fibromyalgia are associated to overweight and lipid profile. Rheumatol Int; 34: 19-22.

Cordero MD et al (2014B) NLRP3 inflammasome is activated in fibromyalgia: the effect of CoQ10. Antioxd Redox Signal; 20: 1169-1180.

Duberley KE et al (2013). Human neuronal coenzyme Q10 deficiency results in global loss of mitochondrial respiratory chain activity, increased mitochondrial oxidative stress and reversal of ATP synthase activity: implications for pathogenesis and treatment.J Inherit Metab Dis;36(1):63-73.

Crane, F.L. (2001). Biochemical functions of coenzyme Q10. Journal of the American College of Nutrition 20: 591-598.

Eisinger J et al (1994). Selenium and magnesium status in fibromyalgia. Magnes Res.;7(3-4):285-8.

Engelsen J et al (2003). Effect of CoQ10 and Ginkgo biloba on warfarin dosage in patients on long term warfarin treatment. A double blind placebo controlled cross-over trial. Ugeaskr Laeger; 165: 1868-1871.

Groven N et al (2019) Patients with fibromyalgia and chronic fatigue syndrome show increased hsCRP compared to healthy controls. Brain Behav Immun; Epub ahead of print.

Gurer G et al (2006) Serum lipid profile in fibromyalgia women. Clin Rheumatol; 25: 300-303.

Guymer E, Littlejohn G (2013). Fibromyalgia. Aust Fam Physician.;42(10):690-4.

Hargreaves IP (2003). Ubiquinone: cholesterol's reclusive cousin. Ann Clin Biochem;40(Pt 3):207-18.

Hargreaves IP et al (2005). The effect of HMG-CoA reductase inhibitors on coenzyme Q10: possible biochemical/clinical implications. Drug Saf ;28(8):659-76.

Hargreaves IP, Mantle D (2019). Supplementation with selenium and coenzyme Q10 in critically ill patients. Brit J Hosp Med; 80(10): 589-593.

Hidaka T et al (2008). Safety assessment of CoQ10. Biofactors; 32(1-4): 199-208.

Jacobson SA et al (2015) Characterization of Fibromyalgia Symptoms in Patients 55 to 95 Years Old: a Longitudinal Study Showing Symptom Persistence with Suboptimal Treatment. Aging Clin Exp Res; 27: 75-82.

Kalén A, et al |(1989). Age-related changes in the lipid compositions of rat and human tissues. Lipids.;24:579–584.

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

Miyamae T et al (2013) Increased oxidative stress and CoQ10 deficiency in juvenile fibromyalgia: amelioration of hypercholesterolemia and fatigue by ubiquinol-10 supplementation. Redox Rep; 18: 12-19.

Mohabbat AB et al (2019). Use of Complementary and Integrative Therapies by Fibromyalgia Patients: A 14-Year Follow-up Study. Mayo Clin Proc Innov Qual Outcomes.;3(4):418-428.

Romano GF et al (2015) Fibromyalgia and chronic fatigue: the underlying biology and related theoretical issues. Adv Psychosom Med: 34: 61-77.

Sawaddiruk et al (2019). Coenzyme Q10 supplementation alleviates pain in pregabalin-treated fibromyalgia patients via reducing brain activity and mitochondrial dysfunction. Free Radic Res. 2019 Aug;53(8):901-909

Sluka, KA, Clauw DJ (2016). Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience; 338: 114–129.

Schmelzer C, et al (2008). Functions of coenzyme Q10 in inflammation and gene expression. Biofactors;32(1-4):179-83.

Schmelzer C et al (2011) Ubiquinol-Induced Gene Expression Signatures are Translated into Altered Parameters of Erythropoiesis and Reduced Low Density Lipoprotein Cholesterol Levels in Humans. Life, 63: 42–48.

Wallace DJ et al (2001). Cytokines play an aetiopathogenetic role in fibromyalgia:a hyphothesis and pilot study. Rheumatology,40: 743-749.

Xia L, et al (2003) The mammalian selenoenzyme thioredoxin reductase reduces ubiquinone. A novel mechanism for defence against oxidative stress. J Biol Chem; 278: 2141-2146.

Yunus MB et al (1988) Fibromyalgia syndrome among the elderly. Comparison with younger patients. J Am Geriatric Soc;36 (11):987–995

Zhen YU, Zhang HU (2019). NLRP3 Inflammasome and Inflammatory Bowel Disease. Front Immunol; 10: 276.