Oxidative Stress Correlates with Headache Symptoms in Fibromyalgia: Coenzyme Q₁₀ Effect on Clinical Improvement

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Abstract

Background: Fibromyalgia (FM) is a chronic pain syndrome with unknown etiology and a wide spectrum of symptoms such as allodynia, debilitating fatigue, joint stiffness and migraine. Recent studies have shown some evidences demonstrating that oxidative stress is associated to clinical symptoms in FM of fibromyalgia. We examined oxidative stress and bioenergetic status in blood mononuclear cells (BMCs) and its association to headache symptoms in FM patients. The effects of oral coenzyme Q₁₀ (CoQ₁₀) supplementation on biochemical markers and clinical improvement were also evaluated.

Methods: We studied 20 FM patients and 15 healthy controls. Clinical parameters were evaluated using the Fibromyalgia Impact Questionnaire (FIQ), visual analogues scales (VAS), and the Headache Impact Test (HIT-6). Oxidative stress was determined by measuring CoQ₁₀, catalase and lipid peroxidation (LPO) levels in BMCs. Bioenergetic status was assessed by measuring ATP levels in BMCs.

Results: We found decreased CoQ₁₀, catalase and ATP levels in BMCs from FM patients as compared to normal control (P<0.05 and P<0.001, respectively). We also found increased level of LPO in BMCs from FM patients as compared to normal control (P<0.001). Significant negative correlations between CoQ₁₀ or catalase levels in BMCs and headache parameters were observed (r = −0.59, P<0.05; r = −0.68, P<0.05, respectively). Furthermore, LPO levels showed a significant positive correlation with HIT-6 (r = 0.33, P<0.05). Oral CoQ₁₀ supplementation restored biochemical parameters and induced a significant improvement in clinical and headache symptoms (P<0.001).

Discussion: The results of this study suggest a role for mitochondrial dysfunction and oxidative stress in the headache symptoms associated with FM. CoQ₁₀ supplementation should be examined in a larger placebo controlled trial as a possible treatment in FM.

Introduction

Fibromyalgia (FM) is a common chronic pain syndrome with an unknown etiology, which has been associated with a wide spectrum of symptoms such as allodynia, debilitating fatigue, joint stiffness and depression. FM is diagnosed according to the classification criteria established by the American College of Rheumatology (ACR) [1]. Despite being a common disorder that affects at least 5 million individuals in the United States [2], its pathogenic mechanism remains elusive. In addition to the described symptoms, a high prevalence of FM has been found among patients with transformed migraine and headaches [3,4]. Common genetic basis, synergistically working with other factors (emotional, personality features, stressful events and medication overuse) should cause a chronic antinociceptive system alteration and therefore a progressive increase (hyperalgesia) and diffusion (panalgesia) of pain. It has been hypothesized that episodic migraine, chronic daily headaches and FM may actually be a continuum of the same disorder [5].

Recently, oxidative stress has been proposed as a relevant event in the pathogenesis of FM and headaches [6,7]. Previously, our group has detected decreased coenzyme Q₁₀ (CoQ₁₀) levels and increased mitochondrial reactive oxygen species (ROS) production in blood mononuclear cells (BMCs) from FM patients [8]. Furthermore, oxidative stress showed a significant correlation with clinical symptoms in FM [6].
CoQ_{10} levels and mitochondrial dysfunction have also been implicated in the pathophysiology of migraine, and it has been reported that oral CoQ_{10} supplementation improved clinical symptoms [9].

The aim of this paper was first to establish a possible correlation between oxidative stress parameters and severity of headaches in FM, and secondly to study the effects of oral CoQ_{10} supplementation on the improvement in headache symptoms.

**Patients and Methods**

**Ethics Statement**

Written informed consent and the approval of the ethical committee of University Pablo de Olavide and Universitary Hospital Virgen Macarena from Seville were obtained, according to the principles of the Declaration of Helsinki.

**Patients**

All samples were obtained after informed consent from patients and the approval of the local ethical committee was obtained according to the principles of the Declaration of Helsinki. The study consisted of 20 women diagnosed with FM and 15 healthy women. The inclusion criteria was fibromyalgia that had been diagnosed for the previous 2 to 3 years, based on the current ACR diagnostic criteria. Exclusion criteria were acute infectious diseases in the previous 3 weeks; past or present neurological, psychiatric, metabolic, autoimmune, allergy-related, or chronic inflammatory disease; undesired habits (e.g., smoking, alcohol, etc.); oral diseases (e.g., periodontitis); medical conditions that required glucocorticoid treatment, use of analgesics, statin or antidepressant drugs; past or current substance abuse or dependence and pregnancy or current breastfeeding. Healthy volunteers were all males and had been taking no drugs or vitamin/nutritional supplement during the 3 week period prior to the collection of the blood samples. Before the study, the patients reported using paracetamol on demand. Clinical data was obtained from physical examination, and evaluated using the Fibromyalgia Impact Questionnaire (FIQ) including visual analogues scales about general and diffuse pain typical of FM (VAS), and Headache Impact Test (HIT-6).

**Blood mononuclear cells**

Heparinized blood samples were collected after 12-hours fasting from patients and healthy control subjects. BMCs were purified from heparinized blood by isopycnic centrifugation using Histopaque-1119 and Histopaque-1077 (Sigma Chemical Co., St. Louis, MO, USA).

**Measurement of CoQ10 levels**

CoQ_{10} content in BMCs were analyzed by HPLC (Beckman Coulter, Brea, CA, USA; 166-126 HPLC) with ultraviolet detection (275 nm), according to the method described above [8].

**Lipid peroxidation**

Lipid peroxidation in cells was determined by analyzing the accumulation of lipoperoxides using a commercial kit from Cayman Chemical (Ann Arbor, Michigan, USA). TBARS are expressed in terms of malondialdehyde (MDA) levels. In these assays, an MDA standard is used to construct a standard curve against which unknown samples can be plotted.

**Catalase determination**

A spectrophotometric method described by Beer and Sizer (1952) [10] was used for measuring the breakdown of hydrogen peroxide by catalase. Briefly, activity was determined by using 35 μg of cell lysate, prepared in a lysis buffer composed of 0.9% NaCl, 20 mM Tris.ClH, pH = 7.6, 0.1% triton X-100, 1 mM phenylmethylsulfonylfuoride and 0.01% leupeptine with gentle shaking, in a kinetic spectrophotometric assay that measures a decrease in the absorbance of hydrogen peroxide.

**ATP levels**

ATP levels were determined by a bioluminescence assay using an ATP determination kit from Invitrogen-Molecular Probes (Eugene, OR, USA) according to the instructions of the manufacturer.

**Oral CoQ_{10} supplementation**

Ten volunteer patients were supplemented with CoQ_{10} (Pharma Nord, Vejle, Denmark) with soft gel capsules for 3 months (300 mg/day CoQ_{10} divided in three doses). After 3 months of treatment, heparinized blood samples were collected after 12-hours fasting and 24 hours after the last dose, and clinical symptoms were evaluated. The CoQ_{10} formulation consisted of soft gelatin capsules containing 100 mg of ubiquinone emulsified with diglyceryl monoooleate, beeswax, soy lecithin and canola oil.

**Statistical Analysis**

All results are expressed as mean ± SD unless stated otherwise. The unpaired Student’s t test was used to evaluate the significance of differences between groups. Statistical analyses included Pearson’s correlations between CoQ_{10}, catalase, and MDA levels in compared with Hit-6 score. P values less than 0.05 were considered significant. Data were analysed using the SPSS/PC statistical software package (SPSS for Windows, 19, 2010, SPSS Inc. Chicago, IL, USA).

**Results**

**Oxidative stress in FM**

The mean age of patients was 46.6±5 years for the FM group and 44.9±4 years for the control group. The mean duration of symptoms in the FM group was 10.1±2.2 years. The mean tender point score in the FM group was 14.8±1.7 points. According to the International Headache Society (IHS) criteria, the headache was tension-type headache. The mean of frequency of headache was 3.7±1 per week. The duration of headache episodes was 10±2 hours. The patients did not describe any symptoms such as nausea, photophobia, or aura.

The most prominent features of these FM patients were pain and stiffness. They were sedentary people and routine laboratory tests yielded normal results for glucose, urea, uric acid, total protein, creatinine, aspartate aminotransferase, alanine aminotransferase, cholesterol and triglycerides (data not shown). The number and subgroup distribution of BMCs (monocytes and lymphocytes) in FM patients were in the normal range (data not shown).

To evaluate the antioxidant system in FM patients, CoQ_{10} and catalase levels in BMCs were examined and compared to control subjects. Both, CoQ_{10} and catalase levels were significantly reduced in FM patients, 64.3% and 40% respectively (Figure 1A and 1B). We also determined LPO levels in BMCs from FM patients as a marker of oxidative stress-induced membrane damage by ROS. FM patients showed higher LPO levels in BMCs, 610% with respect to control subjects (Figure 1C).
To determine whether the observed CoQ10 deficiency had an effect on cellular bioenergetics, we measured intracellular ATP levels in BMCs from control and FM patients. ATP levels were reduced to 70% of the control value in BMCs from FM patients (Figure 1D).

Headache correlates with oxidative stress in FM patients

All FM patients showed high HIT-6 scores compared with control subjects (Table 1). To examine whether headache symptoms were associated with increased oxidative stress, Pearson’s correlation coefficients (r) were performed between CoQ10, catalase or LPO levels and HIT-6 scores. Figure 2 shows a significant negative correlation between CoQ10 and catalase levels and HIT-6 (r = 0.59, P < 0.05; r = 0.68, P < 0.05, respectively). Furthermore, LPO levels showed a significant positive correlation with HIT-6 (r = 0.33, P < 0.05). No correlation of ATP levels and HIT-6 scores was found (data not shown).

Influence of oral Coenzyme Q10 supplementation

Table 2 shows levels of biochemical markers in control subjects and before and after treatment with CoQ10. In FM patients treated with CoQ10, all levels of oxidative stress markers were similar to those measured in control subjects. CoQ10 supplementation significantly increased levels of CoQ10, ATP and catalase but all levels were lower than those seen in controls. In contrast, MDA in BMCs declined and fell to levels similar to those seen in controls. These biochemical marker changes were associated with improvement of clinical measured by tender points, FIQ VAS and HIT-6 scores.

We observed a significant increase of CoQ10 levels after treatment (135.6 ± 6.3 pretreatment and 221.6 ± 11.3 posttreatment, P < 0.001) (respect to control, 224.1 ± 12.5; P < 0.001), ATP levels (61.3 ± 4.9 pretreatment and 191.1 ± 6.7 posttreatment, P < 0.001) (respect to control, 202.8 ± 22.1; P < 0.001) and catalase levels (35.6 ± 10.1 pretreatment and 85.2 ± 15.3 posttreatment, P < 0.001) (respect to control, 96.5 ± 14.8; P < 0.001) in BMCs, a reduction of LPO levels (30.3 ± 5.9 pretreatment and 5.1 ± 1.6 posttreatment, P < 0.001) (respect to control, 6 ± 1; P < 0.001) and a marked improvement of clinical symptoms (FIQ: P < 0.01; VAS: P < 0.01; HIT-6: P < 0.05) (Table 2). No biochemical alterations were detected after CoQ10 treatment: glucose 82.3 ± 10.16 mg/dL (normal range: 76–110), urea 29.7 ± 5.31 mg/dL (normal range: 10–45), uric acid 5.1 ± 1.41 mg/dL (normal range: 2.5–7.5), total protein 7.2 ± 1.01 g/dL (normal range: 6.6–8.7), creatinine 0.9 ± 0.13 mg/dL (normal range: 0.5–1.1), aspartate aminotransferase 24.3 ± 5.17 mU/mL (normal range: 10–40), alanine ami-
transferase 21.2 ± 8.1 mU/mL (normal range: 10–40), total cholesterol 205 ± 9.01 mg/dL (normal range: < 220), and triglycerides 168 ± 31.13 mg/dL (normal range: 150–200).

Discussion

In the present study we have confirmed a significant increase of oxidative stress in FM patients, showing a marked decrease of CoQ10, ATP and catalase levels and a significant increase of LPO levels in BMCs compared to control subjects.

Coenzyme Q10 (CoQ10) is present in every membrane of all cells in the body. CoQ10 transfers electrons from complexes I and II to complex III in the mitochondrial respiratory chain and fulfills a critical role in mitochondrial ATP production, playing a crucial role in cellular metabolism; regulating mitochondrial uncoupling proteins, the mitochondrial permeability transition pore, β-oxidation of fatty acids, nucleotide metabolism and production of reactive oxygen species (ROS) [11,12]. It has been widely demonstrated that CoQ10 is essential for respiratory chain efficacy, and as antioxidant [13,14,15]. CoQ10 deficiency has been associated with several diseases with the typical symptoms found in FM patients [16,17]. Interestingly, CoQ10 deficiency has been detected in depression and chronic fatigue [18,19], two typical symptoms found in FM patients. Furthermore, both symptoms were markedly improved after CoQ10 supplementation. Our results are in agreement with those of previous reports which have shown that CoQ10 deficiency is associated with decreased ATP levels and increased oxidative stress [20,21]. Oxidative stress and, in particular, LPO levels have been implicated in the severity of the clinical symptoms in FM and it has been suggested that antioxidant therapy could be beneficial in FM [6]. On the other hand, the oxidant-antioxidant balance disorders underlie a number of acute and chronic diseases of the central nervous system (CNS) [22]. Clinical conditions affecting the nervous system range from mild cognitive perturbations such as headache or migraine, to life-threatening acute courses such as meningitis, and to chronic neurodegenerative diseases such as multiple sclerosis. One common feature in clinical dysfunctions within the nervous system is redox regulation, with an imbalance in oxidative stress versus antioxidants being characteristic of pathological conditions. It is believed that oxidative stress and LPO play a role in the pathogenesis of migraine by regulating cerebral blood flow and energy metabolism and may constitute a trigger threshold for migraine attacks [23,24]. Moreover, emerging data suggest that LPO may underlie the neuronal alterations and neurotoxicity observed in numerous neuropathological conditions. Direct application of LPO, either in vivo or in vitro, has been shown to be cytotoxic and to mimic neuronal alterations observed in neuropathological conditions. In addition, prevention of LPO has been demonstrated to be neuroprotective in a variety of neuropathological paradigms [25]. It is known that LPO, as a consequence of oxidative stress, indirectly reflects intracellular ROS generation, and ROS are known to be implicated in the etiology of pain, one of the most prominent symptoms in FM, by inducing peripheral and central hyperalgesia [26].

Our results show an important significant correlation between LPO levels and headache symptoms in FM patients. Antioxidants (CoQ10 and catalase) levels also showed a significant negative correlation with headache symptoms. CoQ10 has two important functions in cells: first, CoQ10 is a mitochondrial cofactor with the potential to boost mitochondrial function, and second, CoQ10 is a powerful free radical scavenger that can mitigate lipid peroxidation and DNA damage caused by oxidative stress [27]. In our study, we have observed a marked improvement in headache

Table 1. Characteristic finding of FM patients and control groups.

|                   | Patients (n = 20) | Control (n = 15) |
|-------------------|------------------|-----------------|
| Age (yr)          | 46.6 ± 5         | 44.9 ± 4        |
| Tender points     | 14.8 ± 1.7       | ---             |
| Duration of disease (years) | 10.1 ± 4.2 | ---             |
| FIQ Total score, range 0–100/100 | 6.9 ± 5.6* | 7.1 ± 1.4 |
| VAS, range 0–10   | 61.8 ± 1.3*      | 36.1 ± 1.1      |
| HIT-6, range 36–78 | 61.8 ± 1.3* | 36.1 ± 1.1      |

VAS: Visual Analogue Scale; FIQ: Fibromyalgia Impact Questionnaire; HIT-6: Headache Impact Test. Values are means ± SD, *P<0.001.

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Figure 2. Correlation of CoQ10, catalase or lipid peroxidation levels in BMCs from FM patients and HIT-6 levels.

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symptoms and a significant recovery in oxidative stress markers after CoQ10 supplementation, suggesting that CoQ10 may be involved in the pathophysiology of headache symptoms in FM.

Mitochondria have long been postulated to be involved in the etiology of migraine, although a direct link has not been identified [28]. In addition, the inflammatory component of migraines may produce oxygen free radicals, consuming CoQ10 and inducing CoQ10 deficiency [29].

Clinical studies have generated evidence that FM is associated with immune dysregulation of circulatory levels of pro-inflammatory cytokines, affecting neural function of pain-related neurotransmitters [30]. Cytokines, depending on their concentration, induce symptoms, such as fatigue, fever, sleep, pain, and myalgia [31], all of which develop in FM patients. Alterations in pro-inflammatory cytokine levels have been observed in the serum and skin biopsies of FM patients [32,33]. Interestingly, several studies have also suggested that inflammatory processes are involved in the physiopathology of migraine [34,35]. The inflammatory and pain component of FM and migraine is based on the rationale of using nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of both symptoms. However, while the use of NSAIDs in fibromyalgia is a fairly common practice, little objective evidence is available upon which to assess the efficacy of these agents [36]. There are multiple mechanisms of action upon which the NSAIDs act. There have been conflicting reports as to whether NSAIDs such as acetylsalicylic acid are effective in protecting neurons against neurotoxicity. Acetaminophen has been shown to rescue neuronal cells from mitochondrial redox impairment, liperoxidative products and MDA generation [37]. Furthermore, acetaminophen also reduced the cytoplasmic accumulation of peroxides. Acetylsalicylic acid and acetaminophen inhibit lipid peroxidation and cell damage, in vivo, in the rat hippocampus [30]. The results obtained when NSAIDs are combined with benzodiazepines have also been inconsistent [39]. However, NSAIDs can be helpful in reducing pain flares induced by excessive physical activity, tendinitis or bursitis, although they should only be used on an as needed basis in order to avoid side effects [40].

In addition to pro-inflammatory cytokines, CoQ10 deficiency is also involved in inflammation. A significant negative correlation has been observed between CoQ10 and pro-inflammatory markers in septic shock patients [41], and expression profiling revealed that CoQ10 influences the expression of inflammatory genes suggested that CoQ10 exerts anti-inflammatory properties. In another study, administration of CoQ10 significantly attenuated the increase of oxidative and nitrative stress markers and inflammatory markers in an animal model of metabolic syndrome [42].

In summary, headache symptoms in FM could be a consequence of oxidative stress and both may share common pathophysiologic basis. Furthermore, CoQ10 treatment showed a remarkable improvement in clinical symptoms and headache in FM. Detection of CoQ10 deficiency and subsequent CoQ10 supplementation may result in clinical improvement in FM. Further analysis involving double-blind placebo-controlled clinical trials will be required to confirm this observation.

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Author Contributions

Conceived and designed the experiments: MDC JASA. Performed the experiments: MDC FJCG EAG FJCG MDM. Contributed reagents/materials/analysis tools: MDC MDM JASA. Wrote the paper: MDC JASA.



Table 2. Clinical symptoms and biochemical markers after CoQ10 treatment.

|                      | Pre-treatment (n = 10) | Post-treatment (n = 10) | Control levels (n = 15) |
|----------------------|-----------------------|------------------------|------------------------|
| Tender points        | 13.9 ± 1.2            | 9 ± 0.5*               | —                      |
| FIQ total score, range 0–100 | 59.2 ± 4.2†           | 30.1 ± 2*              | 7.1 ± 1.4              |
| VAS, range 0–10      | 7.1 ± 1.2†            | 3.5 ± 0.8*             | 0.8 ± 0.3              |
| HIT-6, range 36–78   | 60.8 ± 1.4†           | 36.9 ± 1.7*            | 36.1 ± 1.1             |
| CoQ10 (pmol/mg protein) | 135.6 ± 6.3†          | 221.6 ± 11.3*          | 224.4 ± 12.3           |
| ATP (nmol/mg protein)   | 61.3 ± 4.9†          | 191.1 ± 6.7*            | 202.8 ± 22.1           |
| Catalase (U/mg protein) | 35.6 ± 10.1†          | 85.2 ± 15.3*            | 96.5 ± 14.8            |
| MDA in BMCs (nmol/million cells) | 30.3 ± 5.9†          | 5.1 ± 1.6*                | 6 ± 1                  |

VAS: Visual Analogue Scale; FIQ: Fibromyalgia Impact Questionnaire; HIT-6: Headache Impact Test; MDA: Malondialdehyde; BMCs: Blood mononuclear cells. Values are means ± SD.

*P < 0.001 between pre and post treatment;
†P < 0.001 between pretreatment and control.

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