Oral coenzyme Q10 supplementation improves clinical symptoms and recovers pathological alterations in BMCs in a fibromyalgia patient

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Effect of coenzyme Q_{10} evaluated by 1990 and 2010 ACR Diagnostic Criteria for Fibromyalgia and SCL-90-R: Four case reports and literature review

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ABSTRACT

Recently, Coenzyme Q_{10} (CoQ_{10}) deficiency has been implicated in the pathophysiology of fibromyalgia (FM). It is our objective to present the findings of the FM evaluation before and after oral CoQ_{10} treatment using the American College of Rheumatology (ACR) Diagnostic Criteria of 1990 and 2010, and Symptom Checklist-Revised (Scl-90-R). Four patients with FM were examined using the trigger points, the Fibromyalgia Impact Questionnaire, visual analog scale (pain, fatigue, and sleep), Widespread Pain Index, symptom severity scale, and Scl-90-R. Previously, CoQ_{10} contents from patients were analyzed by high-performance liquid chromatography. All patients showed CoQ_{10} deficiency. All patients meet the ACR 1990 and 2010 criteria. After treatment, all patients showed an important improvement in clinical symptoms in all evaluation methods. According to our results, and evaluated by three methods, patients with FM are candidates for treatment with CoQ_{10}. However, more controlled clinical trials and investigations are needed to clarify the precise mechanism(s) by which CoQ_{10} may contribute in pathological and therapeutic processes of FM and to provide data on its effectiveness in FM.

Introduction

Coenzyme Q_{10} (CoQ_{10}) plays a crucial role in cellular metabolism acting as the electron carrier between complexes I and II and the complex III of the mitochondrial respiratory chain; and also is an antioxidant [1]. CoQ_{10} often is reduced in patients with myopathy, either as a primary or secondary event, and patients with all forms of CoQ_{10} deficiency have shown clinical improvements after initiating oral CoQ_{10} supplementation [2].

Fibromyalgia (FM) is a common chronic pain syndrome accompanied by other symptoms such as fatigue, headache, sleep disturbances, and depression. It is diagnosed according to the classification criteria established by the 1990 American College of Rheumatology Diagnostic Criteria (ACR 1990) [3] and in the 2010 Diagnostic Criteria (ACR 2010) [4]. Pathophysiological mechanisms of FM are difficult to identify and current drug therapies demonstrate limited effectiveness, only focused on the management of single symptoms. Recently, we have demonstrated CoQ_{10} deficiency and oxidative stress [5]. Moreover, CoQ_{10} supplementation of cultured blood cells derived from patients with FM was able to restore the mitochondrial alterations found in these cells. According to these results, we postulated that CoQ_{10} could be used as an alternative therapeutic approach for FM. In this respect, a 2002 study reported beneficial effects of oral CoQ_{10} supplementation in FM patients [6], and our group also found a significant improvement of clinical symptoms of patients with FM after oral CoQ_{10} supplementation [7–9].

In this study, we evaluated the effect of oral CoQ_{10} treatment in four patients with FM and CoQ_{10} deficiency using three methods: the 1990 ACR, 2010 ACR diagnostic criteria, and the Symptom Checklist-Revised (SCL-90-R).

Methods

Patients

In brief, four women ages 49, 43, 65, and 66 y, were enrolled into the study. This study was performed with the informed consent of participants and the approval of the local ethical committee. The diagnosis of FM was established according to ACR criteria [3,4]. All patients met 1990 ACR and 2010 ACR diagnostic criteria. The patients had not taken any drug during a 15 d period before the collection of the samples. Routine laboratory tests yield normal results (data not shown). Statistical analysis was done using mean and SDs, and *t* test was done on an intention to assay the treatment effect. SPSS 19 was used. All patients presented high score of visual analog scale (VAS) of pain, fatigue, problems

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Table 1
Clinical changes in FM patients pre- and post-treatment with Coenzyme Q_{10}

	Patient 1	Patient 2	Patient 3	Patient 4
	Pre/Post	Pre/Post	Pre/Post	Pre/Post
Tender points	17/8	12/5	11/7	14/6
FIQ total score, range 0–80	65/33	60/23	69/38	56/21
VAS pain total score, range 0–10	8/3	7/3	6/2	9/4
VAS fatigue total score, range 0–10	9/4	7/2	7/3	8/3
VAS sleep total score, range 0–10	8/3	7.3	6/4	9/4
WPI, range 3–6, > or =7	8/6	7/2	6/3	8/4
SS, range > or = 9, > or =5	9/6	7/4	8/3	7/5

FIQ, Fibromyalgia Impact Questionnaire; Pre/post, pretreatment and post-treatment with CoQ_{10}; SS, symptom severity scale; VAS, visual analog scale; WPI, Widespread pain index

sleeping, and the Fibromyalgia Impact Questionnaire (FIQ) (Table 1). The patients were evaluated including a Widespread Pain Index (WPI) and symptom severity (SS) scale recommended by ACR [4], and SCL-90-R pre- and post-treatment. After informed consent and the approval of the local ethical committee were obtained, the patients were treated orally with 300 mg/d CoQ_{10} divided in three doses. After 9 mo of treatment, the patients were evaluated.

Results

A statistically significant decrement of VAS pain ($t = 15.59$; $P < 0.01$), VAS fatigue ($t = 19$; $P < 0.01$), and VAS sleep ($t = 5.66$; $P < 0.01$), FIQ ($t = 24.51$; $P < 0.01$), and tender points ($t = 6.48$; $P < 0.01$) were observed (Table 2). All patients reported an improvement in pain, fatigue, and sleep. Interestingly, WPI ($t = 5.17$; $P < 0.01$) and SS ($t = 6.48$; $P < 0.01$) also were statistically significant reduced after CoQ_{10} treatment.

For SCL-90-R, a clinically significant improvement was observed in all items, being statistically significant for the reduction in somatization ($t = 4.08$; $P < 0.05$) and anxiety ($t = 6.24$; $P < 0.01$) items.

Literature review

CoQ_{10} deficiency impairs oxidative phosphorylation and causes clinically heterogeneous mitochondrial diseases named the CoQ_{10} deficiency syndrome. An increasing number of patients with primary inherited CoQ_{10} deficiencies are being identified [10]. These forms are transmitted as autosomal recessive traits and respond to CoQ_{10} supplementation, making accurate diagnosis of great practical importance. CoQ_{10} deficiency also can be a secondary consequence of different diseases or by treatment with drugs such as statins. Given the critical role of CoQ in mitochondria function, it has been suggested that CoQ_{10} levels could be a useful biological marker of mitochondrial function [11]. CoQ_{10} deficiency induces decreased mitochondrial respiratory enzyme activity, reduced expression of mitochondrial proteins involved in oxidative phosphorylation, decreased mitochondrial membrane potential, increased production of reactive oxygen species (ROS), mitochondrial permeabilization, mitophagy of dysfunctional mitochondria, reduced growth rates, and cell death [12,13]. An earlier study reported [14] that CoQ_{10}-deficient patients benefit from oral CoQ_{10} supplementation.

Table 2
Symptom Checklist-Revised changes in FM patients pre- and post-treatment with CoQ_{10}

	Patient 1	Patient 2	Patient 3	Patient 4
	Pre/Post	Pre/Post	Pre/Post	Pre/Post
Somatization	2.75/2.58	1/0.75	1.25/0.83	2.33/1.67
Obsessive-compulsive	3.33/2.5	0.4/0.4	1.17/1.6	1.4/1.2
Interpersonal sensitivity	2.33/2.89	0.11/0.11	0/0	0.89/0.22
Depression	2.08/2	0.08/0.08	0.54/1.08	1.46/0.69
Anxiety	2.5/1.8	0.2/0	0.4/0	1.7/1.1
Hostility	2.5/1.5	0.83/0.67	0.17/0	0.33/0.17
Phobic anxiety	0.14/1.43	0/0	0/0	0.57/0
Paranoid ideation	1/1.5	0.17/0.33	0/0	0.1/0
Psychoticism	1.2/1.7	0.1/0.1	0/0.1	0.3/0.1

Statin myopathy and CoQ_{10}

Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors that decrease the synthesis of mevalonate, a key metabolic step in the cholesterol synthesis pathway. These drugs can produce a variety of muscle-related complaints or myopathies. Because the mevalonate pathway also leads to the biosynthesis of the isoprenoid side chain of CoQ_{10}, different studies have addressed the possibility of CoQ_{10} being an etiologic factor in statin myopathy. It was highlighted that, besides decreasing plasma CoQ_{10} levels, statin treatment leads to lower lymphocyte levels of CoQ_{10}. There are no univocal results about the effect of statin treatments on CoQ_{10} levels in skeletal muscle [15,16], yet more recently, it was reported that high-dose statins did decrease muscle CoQ_{10} and mitochondrial respiratory chain activities, possibly related to the decrease in the number or volume of muscle mitochondria [17]. Regarding the effect of CoQ_{10} supplementation, this was found not to improve statin tolerance or myalgia in one study [18], whereas another study [19] reported a positive effect of CoQ_{10} on pain severity and pain interference in daily activities in a group of statin-treated patients showing myopathic symptoms.

Neurodegenerative diseases and CoQ_{10}

During the past few years, CoQ_{10} has been used in different neurodegenerative diseases where a common biochemical feature is the evidence of mitochondrial respiratory chain dysfunction and oxidative stress damage. Friedreich's ataxia is one of these conditions; treatment with CoQ_{10} and vitamin E caused a prolonged improvement in cardiac and skeletal muscle bioenergetics and clinical scores [20]. Another study, in which patients with Friedreich's ataxia were randomly divided into high- or low-dose CoQ_{10}/vitamin E groups, demonstrated improvement in clinical symptoms in 49% of patients. This respondent group had significantly lower baseline serum CoQ_{10} levels [21]. The therapeutic implications of CoQ_{10} in Parkinson's disease also were recently discussed in a review [22]. CoQ_{10} already has been shown to slow progression of the disease when given at high dosages [23]. A large Phase III trial comparing placebo and 1200 mg and 2400 mg of CoQ_{10} daily is currently under way. A recent magnetic resonance spectroscopic study also was conducted in patients with progressive supranuclear palsy treated with CoQ_{10}; a significant increase of the ratio of high-energy to low-energy phosphates was indicative of improved oxidative phosphorylation of the occipital cortex [24].

Migraine and CoQ_{10}

Another field where the beneficial effects of CoQ_{10} may be related to its mitochondrial function and antioxidant properties is migraine, a condition where some inflammatory components may produce ROS, leading to overconsumption of CoQ_{10}. A 2005 study [25] reported the first positive effect of CoQ_{10} in migraine

prophylaxis. A subsequent study [26] assessed plasma CoQ_{10} levels in a large group of pediatric patients attending a tertiary care center for frequent headaches. Patients with low CoQ_{10} were treated with CoQ_{10}. For those patients taking CoQ_{10}, both headache frequency and migraine evaluation questionnaire scores decreased significantly. Interestingly, migraine is frequently associated with FM, which may have a common pathophysiological basis [27].

Depression and CoQ_{10}

There is now evidence that major depression is accompanied by an induction of inflammatory and oxidative and nitrosative stress pathways and by a lowered antioxidant status. Studies on depression, a typical symptom found in FM patients [28], have elucidated a possible link between depression and CoQ_{10}. One study showed that plasma CoQ_{10} was significantly lower in depressed patients than in normal controls and suggested that depressed patients may benefit from CoQ_{10} supplementation [29].

Fatigue and CoQ_{10}

Fatigue is another typical symptom found in FM patients. Low levels of CoQ_{10} in plasma in patients with chronic fatigue syndrome have been reported [30], and it has been suggested that patients with this syndrome would benefit from CoQ_{10} supplementation in order to normalize the low CoQ_{10} levels [30]. Furthermore, fatigue or lack of energy has been frequently reported in patients taking statins [31]. Finally, studies on CoQ_{10} and physical exercise have confirmed its effect in improving subjective fatigue sensation and physical performance and in opposing exercise-related damage [32].

Discussion

It has been known since early on [14] that CoQ_{10}-deficient patients benefit from oral CoQ_{10} supplementation. CoQ_{10} could be a potential drug candidate in the treatment of FM for at least two main reasons. First, it is a mitochondrial cofactor with the potential to improve mitochondrial function. Second, CoQ_{10} is a powerful free radical scavenger that can mitigate lipid peroxidation and DNA damage caused by oxidative stress [33]. Recently, oxidative stress has been proposed to be involved on symptoms of FM [34], therefore, it is plausible that the benefits demonstrated in this study may be due, in part, to its antioxidant activity. However, recently we have shown by means of one clinical trial that CoQ_{10} induces AMP-activated protein kinase (AMPK) activation. CoQ_{10} induced a recovery of inflammation, antioxidant enzymes, mitochondrial biogenesis, and AMPK gene expression levels, associated with phosphorylation of AMPK activity [35]. AMPK is a master regulator of cell energy levels that has been reported to play a master regulatory role in these processes as described in several other diseases [36]. AMPK could be the principal mechanism by which CoQ_{10} would improve the health of patients with FM.

According to our data, oral CoQ10 treatment, evaluated with three different methods, could be a new therapeutic approach in FM. However, more controlled clinical trials and investigations are required to clarify the precise mechanism(s) by which CoQ_{10} may contribute in pathological and therapeutic processes of FM and provide data on effectiveness in FM.

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