Coenzyme Q10 Regulates Serotonin Levels and Depressive Symptoms in Fibromyalgia Patients: Results of a Small Clinical Trial.

ARTICLE in JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY · FEBRUARY 2014
Impact Factor: 3.24 · DOI: 10.1097/JCP.0000000000000097 · Source: PubMed

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Coenzyme Q<sub>10</sub> Regulates Serotonin Levels and Depressive Symptoms in Fibromyalgia Patients

Results of a Small Clinical Trial

To the Editors:

Despite discrepancies about the role of the serotonergic system in the pathophysiology of fibromyalgia (FM), the presence of disturbances of serotonin function in this disease is evident. Serotonin is an important modulator of pain perception, sleep, fatigue, cognition, and mood in normal subjects, supporting the conclusion that disturbances in these functions (hallmark symptoms of patients with FM) can be the result of abnormalities in serotonin content, metabolism, or transmission. Furthermore, serotonin function alterations have provided the basis for several therapeutic options in FM, being serotonin reuptake inhibitors widely used for its treatment. Coenzyme Q (CoQ<sub>10</sub>) deficiency is also another pathological alteration observed in patients with FM and it has been reported that CoQ<sub>10</sub> supplementation significantly improves the clinical symptoms associated with the disease. CoQ<sub>10</sub> possesses antidepressant properties and it has a major role in the pathophysiology of several diseases associated with depressive symptoms such as major depression, myalgic encephalomyelitis, and FM. Following up our earlier work on the mechanisms of therapeutic effects of CoQ<sub>10</sub> in FM in a clinical trial (ISRCTN 21164124), here we show the effect of 40 days of CoQ<sub>10</sub> versus placebo supplementation on serotonin levels in platelets from FM patients and depressive symptoms improvement.

The study protocol was reviewed and approved by the Ethical Committee of the University of Sevilla. All the participants of the study gave their written informed consent before initiating the study. This study was carried out in compliance with the Declaration of Helsinki, and all the International Conferences on Harmonisation and Good Clinical Practice Guidelines. Twenty patients diagnosed with FM were distributed in a clinical trial as described in Cordero et al. The patients were diagnosed with FM by exclusion of other diseases and syndromes, and in accordance with the American College of Rheumatology criteria. Subjects were randomized in a double-blind fashion, according to a 1:1 ratio, to CoQ<sub>10</sub> or placebo. Ten subjects received CoQ<sub>10</sub> (Pharma Nord, Vejle, Denmark) in soft gel capsules for 40 days (300 mg of CoQ<sub>10</sub> divided into 3 daily doses), whereas another group of 10 subjects received a matching placebo.

Early morning samples of blood were collected under fasting conditions and platelets were isolated. CoQ<sub>10</sub> levels were determined by HPLC and serotonin levels by ELISA (GenWay, San Diego, CA). CoQ<sub>10</sub> deficiency was induced in healthy platelets by 1 mM P-aminobenzoate (PABA; Sigma Chemical Co, St Louis, MO) treatment. Depression was evaluated by the Beck Depression Inventory (BDI) scale.

DISCUSSION

As expected, FM patients had markedly higher levels of depression [BDI, 22.3 (1.1)] (P < 0.001). CoQ<sub>10</sub> and serotonin levels in platelets from FM patients were significantly reduced in respect to controls (Fig. 1A). Interestingly, CoQ<sub>10</sub> and serotonin content in platelets from non-treated patients showed a strong positive correlation (Fig. 1C). Several studies have suggested that platelets are good models of neuronal serotonergic cells. Both types of cells are major storage sites for serotonin, and interestingly serotonin levels in cerebrospinal fluid are strongly correlated with serotonin levels in platelets. Therefore, our results may reflect the critical role of CoQ<sub>10</sub> deficiency in the functional alterations of the serotonergic system.

The evidence base for the clinical effectiveness of treatment with CoQ<sub>10</sub> may be explained via its ability to ameliorate oxidative stress and protect mitochondria. However, there is no information about the effect of CoQ<sub>10</sub> treatment in serotonin levels. In our study, CoQ<sub>10</sub> and serotonin levels in platelets from FM patients were restored in the COQ<sub>10</sub>-treated group compared to placebo group (Fig. 1A) and B). Interestingly, a notable improvement in depressive symptoms evaluated with the BDI scale was also observed in the CoQ<sub>10</sub>-treated group compared to the placebo group (placebo group, 24.1 (3.5); CoQ<sub>10</sub> group, 6.2 (1.9)) (P < 0.001).

To verify the role of CoQ<sub>10</sub> in the serotonergic alterations observed in FM patients, we induced CoQ<sub>10</sub> deficiency in platelets from healthy controls by inhibiting the endogenous biosynthesis of CoQ<sub>10</sub> with PABA treatment, a competitive inhibitor of polyphenyl-4-hydroxybenzoate transferase (Coq2p). Platelets were cultured for 24 hours in the presence of 1 mM PABA, or alternatively PABA + 10 μM CoQ<sub>10</sub>, and PABA + 10 mM N-acetylcysteine (N-Acet) (Sigma Chemical Co). Serotonin levels in platelets were significantly reduced by PABA treatment (Fig. 1D). Reduced serotonin levels in platelets were restored in the presence of 2 antioxidants, CoQ<sub>10</sub>, or N-Acet, being more significant in platelets treated with CoQ<sub>10</sub>. Taken together, these results suggest that CoQ<sub>10</sub> supplementation may play an essential role in the regulation of bioenergetics status in platelets and in other cells such as neurons of the central nervous system. CoQ<sub>10</sub> is an important component of the mitochondrial respiratory chain enabling the generation of adenosine triphosphate by oxidative phosphorylation. Because adenosine triphosphate levels have been observed to be reduced in platelets from FM patients and FM has been related with alterations of the hypothalamic-pituitary-adrenal (HPA) axis, and hormone and neurotransmitter secretion, a possible explanation for our results is that CoQ<sub>10</sub> may play a role in the regulation of bioenergetics status in platelets and other cells such as neurons of the central nervous system and, therefore, may affect serotonin content, transmission, and function. These results may also contribute to explain the antidepressant effect of CoQ<sub>10</sub> treatment. Our findings also support the hypothesis that CoQ<sub>10</sub> supplementation can be used as an alternative therapy for controlling depression.

Further analyses involving more patients in double-blind placebo-controlled clinical trials are required to confirm these observations. Indeed, our research group is currently working in this direction, based on the conclusions of the exploratory work discussed in this article.

AUTHOR DISCLOSURE INFORMATION
The authors declare no conflicts of interest.

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FIGURE 1. A, CoQ10 levels were reduced in platelets from FM patients. CoQ10 levels were restored after oral CoQ10 supplementation versus placebo. B, Serotonin levels were reduced in platelets from FM patients compared with platelets from healthy controls. After supplementation, CoQ10 induced a significant increase of serotonin levels. *P < 0.01 between before and after CoQ10 supplementation FM patients. *P < 0.01 between FM patients and healthy controls. C, Correlation between CoQ10 and serotonin levels in platelets. The strength of the association was established by calculating Pearson correlation coefficient (r). D, Induced CoQ10 deficiency in vitro leads to serotonin deficiency in platelets. Reduced levels of serotonin were restored by antioxidants but more significantly with CoQ10 treatment. Data represent the mean (SD) of 3 separate experiments. *P < 0.001 between control, PABA, and PABA with CoQ10. **P < 0.01 between PABA and PABA with N-Acet.