This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier’s archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/authorsrights
Introduction

Coenzyme Q10 (CoQ10) 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]. CoQ10 often is reduced in patients with myopathy, either as a primary or secondary event, and patients with all forms of CoQ10 deficiency have shown clinical improvements after initiating oral CoQ10 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 (ACR) 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 CoQ10 deficiency and oxidative stress [5]. Moreover, CoQ10 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 CoQ10 could be used as an alternative therapeutic approach for FM. In this respect, a 2002 study reported beneficial effects of oral CoQ10 supplementation in FM patients [6], and our group also found a significant improvement of clinical symptoms of patients with FM after oral CoQ10 supplementation [7-9].

In this study, we evaluated the effect of oral CoQ10 treatment in four patients with FM and CoQ10 deficiency using three methods: the 1990 ACR, 2010 ACR diagnostic criteria, and the Symptom Checklist-Revised (SCL-90-R).
CoQ10 deficiency impairs oxidative phosphorylation and causes clinically heterogeneous mitochondrial diseases named the CoQ10 deficiency syndrome. An increasing number of patients with primary inherited CoQ10 deficiencies are being identified [10]. These forms are transmitted as autosomal recessive traits and respond to CoQ10 supplementation, making accurate diagnosis of great practical importance. CoQ10 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 CoQ10 levels could be a useful biological marker of mitochondrial function [11]. CoQ10 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, morphologic dysfunction, reduced growth rates, and cell death [12,13]. An earlier study reported [14] that CoQ10-deficient patients benefit from oral CoQ10 supplementation.

Statin myopathy and CoQ10

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 CoQ10, different studies have addressed the possibility of CoQ10 being an etiologic factor in statin myopathy. It was highlighted that, besides decreasing plasma CoQ10 levels, statin treatment leads to lower lymphocyte levels of CoQ10. There are no univocal results about the effect of statin treatments on CoQ10 levels in skeletal muscle [15,16], yet more recently, it was reported that high-dose statins did decrease muscle CoQ10 and mitochondrial respiratory chain activities, possibly related to the decrease in the number or volume of muscle mitochondria [17]. Regarding the effect of CoQ10 supplementation, this was found not to improve statin tolerance or myalgia in one study [18], whereas another study [19] reported a positive effect of CoQ10 on pain severity and pain interference in daily activities in a group of statin-treated patients showing myopathic symptoms.

Neurodegenerative diseases and CoQ10

During the past few years, CoQ10 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 CoQ10 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 CoQ10/vitamin E groups, demonstrated improvement in clinical symptoms in 49% of patients. This responder group had significantly lower baseline serum CoQ10 levels [21]. The therapeutic implications of CoQ10 in Parkinson’s disease also were recently discussed in a review [22]. CoQ10 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 CoQ10 daily is currently under way. A recent magnetic resonance spectroscopic study also was conducted in patients with progressive supranuclear palsy treated with CoQ10; 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 CoQ10

Another field where the beneficial effects of CoQ10 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 CoQ10. A 2005 study [25] reported the first positive effect of CoQ10 in migraine.
Fatigue and CoQ10

Fatigue is another typical symptom found in FM patients. Low levels of CoQ10 in plasma in patients with chronic fatigue syndrome have been reported [30], and it has been suggested that this syndrome would benefit from CoQ10 supplementation in order to normalize the low CoQ10 levels [30]. Furthermore, fatigue or lack of energy has been frequently reported in patients taking statins [31]. Finally, studies on CoQ10 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 CoQ10-deficient patients benefit from oral CoQ10 supplementation. CoQ10 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, CoQ10 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 CoQ10 induces AMP-activated protein kinase (AMPK) activation. CoQ10 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 CoQ10 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 CoQ10 may contribute in pathological and therapeutic processes of FM and provide data on effectiveness in FM.

References


