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The Role of Oxidative Stress and Mitochondrial Dysfunction in the Pathogenesis of Fibromyalgia

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1. Introduction

Fibromyalgia (FM) is a common pain syndrome accompanied by other symptoms such as tender spots, decreased pain threshold, fatigue, headache, sleep disturbances, and depression. It is a chronic condition characterized by a pattern of vague symptoms that are difficult to diagnose and treat. FM is diagnosed according to the classification criteria established by the American College of Rheumatology (ACR) (Wolfe et al., 1990) and routine laboratory investigations usually yield normal results (Yunus et al., 1981). The prevalence of FM in industrialized countries ranges from 0.4% to 4% (it affects at least 5 million individuals in the United States and 800,000 in Spain) in the population being 11 times more frequent in women than in men (Lawrence et al., 2008). Its high prevalence makes fibromyalgia a major problem in developed countries in the recent years. FM causes work absenteeism and has been associated with high medical services utilization cost and considerable disability. Furthermore, the use of medications and medical necessities increased markedly across many measures once diagnosis was made. It has been estimated that annual health service cost of FM patients was twice that of patients with chronic widespread pain and pain-free controls. The fact that its diagnostic criteria are only clinical, and that its etiopathogenesis has not yet been clarified makes very difficult the study and therapeutical approach of the disease. Although the etiology of FM remains unclear, evidence suggests that biologic, genetic, and environmental factors are involved. It is considered that the changes in the neuronal activity in the central nervous system, abnormal metabolism of biogenic amines, immunological disorders and oxidative stress may among others factors contribute to the development of the disease. For all these reasons is urgent to do more research in the diagnosis, pathophysiology and therapy of FM.

Fibromyalgia syndrome has been related to disturbances of hypothalamic–pituitary axis together with neurotransmission imbalance, involving excitatory amino acids,
catecholamines, substance P and serotonin (5-HT) (Russell et al, 1994; Crofford et al, 1996; Neeck, 2002). Patient's symptoms may derive from poor stressor modulation, sensitization of specific nociceptor neurons and pain threshold diminution in response to multiple environmental factors, such as mechanical or emotional trauma, chronic stress or even infections. In recent years, new information to our understanding of FM pathophysiology has emerged. Some genetic polymorphisms and antibodies have been associated with FM, as the serotonergic system genotype of 5-HTT (Bazzichi et al., 2006a; Tander et al., 2008), catechol-O-methyltransferase gene polymorphism (Gursoy et al., 2004), D4 dopamine receptor exon II repeat polymorphism (Buskila et al., 2004), and antibodies against serotonin (Klein et al., 1992; Werle et al., 2001). It has also been postulated alterations in the metabolism, transport and reuptake of serotonin (Alnigenis & Barland, 2001; Schwarz et al., 2002) and substance P (Staud & Spaeth, 2008). Moreover, cytokines homeostasis has been considered to play a role in the pathogenesis of FM (Wallace, 2001; Wallace et al., 2006). Conversely, several studies have shown mitochondrial dysfunction and high levels of oxidative stress markers in FM patients, suggesting that this process may contribute to the pathophysiology of this disease. However, whether oxidative stress is the cause or the effect in FM is controversial (Ozgocmen et al, 2006).

2. Mitochondrial dysfunction in disease and FM

2.1 About mitochondria
Mitochondria are dynamic organelles that play a central role in many cellular functions including the generation of chemical energy (adenosine triphosphate, ATP), heat, and intracellular calcium homeostasis. They are also responsible for the formation of reactive oxygen species (ROS) and for triggering the programmed cell death or apoptosis (Turrens, 2003). The primary metabolic function of mitochondria is oxidative phosphorylation, an energy-generating process that couples oxidation of respiratory substrates to the synthesis of ATP (Pieczenik & Neustadt, 2007). The mitochondrial respiratory chain (MRC) is composed of five multisubunit enzyme complexes. Both the mitochondrial DNA (mtDNA) and the nuclear DNA (nDNA) encode for polypeptide components of these complexes. Electron transport between MRC complexes I–IV is coupled to the extrusion of protons across the inner mitochondrial membrane by proton pump components of the respiratory chain. This movement of protons creates an electrochemical gradient ($\Delta\psi_m$) across the inner mitochondrial membrane. Protons return to the mitochondrial matrix by flowing through ATP synthase (complex V), which utilizes the energy thus produced to synthesize ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi). Both the mtDNA and the nDNA encode for polypeptide components of these complexes. As a consequence, mutations in either genome can cause MRC dysfunction that impairs transport of electrons and/or protons and decreases ATP synthesis. Primary or secondary genetic diseases affecting MRC or secondary mitochondrial dysfunctions usually affect brain and skeletal muscle because of their energy requirements. Besides MRC enzyme complexes, two electron carriers, coenzyme Q$_{10}$ (CoQ) and cytochrome c, are essential for mitochondrial synthesis of ATP. CoQ transports electrons from complexes I and II to complex III and is essential for the stability of complex III. CoQ is a lipid-soluble component of virtually all cell membranes. It is composed of a benzoquinone ring with a polyisoprenyl side-chain. The number of isoprene units is species specific, e.g. 10 in humans (CoQ$_{10}$). CoQ also functions as an antioxidant that
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Protects cells both by direct ROS scavenging and by regenerating other antioxidants such as vitamins C and E (Turunen et al., 2004). CoQ deficiency impairs oxidative phosphorylation and causes clinically heterogeneous mitochondrial diseases named CoQ deficiency syndrome. An increasing number of patients with primary inherited CoQ deficiencies are being identified (Littarru & Tiano, 2010). These forms are transmitted as autosomal recessive traits and respond to CoQ supplementation, making accurate diagnosis of great practical importance. CoQ deficiency can be also 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 levels could be a useful biological marker of mitochondrial function (Haas et al., 2008). CoQ deficiency induces decreased mitochondrial respiratory enzymes activity, reduced expression of mitochondrial proteins involved in oxidative phosphorylation, decreased mitochondrial membrane potential, increased production of ROS, mitochondrial permeabilization, mitophagy of dysfunctional mitochondria, reduced growth rates and cell death (Quinzii et al., 2008; Rodriguez-Hernandez et al., 2009, Cotan et al, 2011).

2.1.1 Reactive Oxygen Species (ROS)

In addition to energy, mitochondrial oxidative phosphorylation also generates ROS. When the MRC becomes highly reduced, the excess electrons from complex I or complex III can be passed directly to O₂ to generate superoxide anion (O₂⁻). Superoxide is transformed to hydrogen peroxide (H₂O₂) by the detoxification enzymes manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/Zn SOD), and then to water by catalase, glutathione peroxidase (GPX) or peroxidredoxin III (PRX III). However, when these enzymes cannot convert ROS such as the superoxide radical to water fast enough, oxidative damage occurs and accumulates in the mitochondria. If H₂O₂ encounters a reduced transition metal or is mixed with O₂⁻ the H₂O₂ can be further reduced to hydroxyl radical (OH•), the most potent oxidizing agent among ROS. Additionally, nitric oxide (NO) is produced within the mitochondria by mitochondrial nitric oxide synthase (mtNOS) and also freely diffuses into the mitochondria from the cytosol. NO reacts with O₂⁻ to produce peroxynitrite (ONOO⁻). Together, these two radicals as well as others can do great damage to mitochondria and other cellular components (Turrens, 2003).

Under normal physiological conditions, ROS production is highly regulated. However, if the respiratory chain is inhibited, or key mitochondrial components, such as CoQ, are deficient, then, electrons accumulate on the MRC carriers, greatly increasing the rate of a single electron being transferred to O₂ to generate O₂⁻. An excessive mitochondrial ROS production can exceed the cellular antioxidant defense and the cumulative damage can ultimately destroy the cell by necrosis or apoptosis.

2.1.2 Selective degradation of mitochondria: Mitophagy

Degradation of excess or dysfunctional organelles is one of the major problems that eukaryotes face to maintain cell integrity and to adapt cellular activities to environmental changes. To solve this fundamental issue, cells utilize autophagy, which is a self-eating system that generates double-membrane vesicles called autophagosomes, sequesters cytoplasmic components as cargoes, and transports them to lysosomes for degradation (Klionsky, 2005). In the past decade, more than 30 autophagy-related genes (ATG) required for selective and/or nonselective autophagic functions have been identified. Selective autophagy contributes to the
control of both quality and quantity of organelles. It is conceivable that mitochondria are the primary targets of selective autophagy, because they accumulate oxidative damage due to their own by-products, ROS (Bhatia-Kiššová I & Camougrand, 2010). Consistent with this idea, autophagy-dependent clearance of dysfunctional mitochondria is important for organelle quality control. The term mitophagy refers to the selective removal of mitochondria by autophagy. It has been proposed that ROS damage can induce mitochondria permeabilization by the opening of permeability transition pores in the mitochondrial inner membrane (Kim, 2007). This, in turn, leads to a simultaneous collapse of mitochondrial membrane potential and the elimination of dysfunctional mitochondria. Consistent with this idea, autophagy-dependent clearance of dysfunctional mitochondria by mitophagy is important for organelle quality control and can play a pivotal role in mitochondria related diseases (Gottlieb et al, 2010).

2.2 Mitochondrial dysfunction and disease

Since the first mitochondrial dysfunction was described in 1962 (Luft et al, 1962), biomedicine research has advanced in the understanding of the role that mitochondria play in health, disease, and aging. Besides the inherited mitochondrial diseases, a wide range of seemingly unrelated disorders, such as schizophrenia, bipolar disease, dementia, Alzheimer’s disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson’s disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, retinitis pigmentosa, diabetes, hepatitis C, primary biliary cirrhosis, and fibromyalgia (FM), have the common pathophysiological mechanisms of production of mitochondrial ROS resulting in mitochondrial dysfunction (Pieczenik & Neustadt, 2007). As a consequence of these findings, antioxidant therapies hold promise of improving mitochondrial performance in these diseases. Although the underlying characteristic of all of them is lack of adequate energy to meet cellular needs, they vary considerably from disease to disease and from case to case in their effects on different organ systems, age at onset, and rate of progression, even within families whose members have identical genetic mutations. No symptom is pathognomonic, and no single organ system is universally affected. Although a few syndromes are well-described, any combination of organ dysfunctions may occur. However, these diseases most often affect the central and peripheral nervous systems, but can affect any organs or tissues, including the muscles, liver, kidneys, heart, ears, eyes, and endocrine system (Cohen & Gold, 2001) (Table 1).

Damage to mitochondria is caused primarily by ROS generated by the mitochondria themselves. Within the mitochondria, components that are particularly vulnerable to free radicals include lipids, proteins, oxidative phosphorylation enzymes, and mtDNA (Shigenaga et al., 1994; Tanaka et al., 1996). Direct damage to mitochondrial proteins decreases their affinity for substrates or coenzymes and, thereby, decreases their function (Liu et al., 2002). Compounding the problem, once a mitochondrion is damaged, mitochondrial function can be further compromised by increasing the cellular requirements for energy repair processes (Aw & Jones, 1989). Mitochondrial dysfunction can also result in a feed forward process, whereby mitochondrial damage causes additional damage. Generated ROS can be released into cytosol and trigger “ROS-induced ROS-release” (RIRR) in neighboring mitochondria. This mitochondrion-to-mitochondrion ROS-signaling constitutes a positive feedback mechanism for enhanced ROS production potentially leading to significant mitochondrial injury (Zorov et al, 2006).
Furthermore, ROS have an established role in inflammation. Increased levels of inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukins, have been associated with mitochondrial dysfunction and increased ROS generation (Naik & Dixit, 2011), and it has been hypothesized that abnormal production of cytokines may play a role in the pathogenesis of FM (Wallace et al., 2001). IL-1, IL-6 and IL-8 are dysregulated in the syndrome and therapies directed against these cytokines may be of potential importance in the management of fibromyalgia (Wallace, 2006). However, different studies with conflicting results (Uçeyler et al., 2006; Bazzichi et al., 2007) make necessary more studies to better understand the role of cytokines in FM.

### 2.3 Mitochondrial dysfunction in FM

Because the main symptoms in FM (pain, stiffness and fatigue) are located in the muscles, muscle biopsies, mostly from the trapezius, have been studied. In most cases, mitochondrial morphologic alterations have been found in muscle biopsies from FM patients. Histochemical analysis demonstrated type II fiber atrophy and the “moth-eaten” appearance of type I fibers. Electron microscopic findings were most impressive, and included, subsarcolemmal mitochondrial accumulation (Kalyan-Raman et al., 1984), myofibrillarlysis with deposition of glycogen and abnormal mitochondria (Yunus et al., 1986), low number of mitochondria (Sprott et al., 2004), electrons-dense inclusions and lack of inner membrane (Hénriksson et al., 1982), ragged red fibres (Bengtsson et al., 1988), and single fiber defects of cytochrome-c-oxidase, the complex IV of oxidative phosphorylation (Drewes et al., 1993, Pöngratz & Späth, 1998). The presence of moth-eaten and ragged-red fibres indicates uneven distribution and proliferation of mitochondria. Accumulation of mitochondria is seen in Gomori trichrome staining, and this gives the ragged appearance.

Table 1. Signs and symptoms associated with mitochondrial dysfunction (Cohen & Gold, 2001).

| Organs | Sign and Symptoms |
|--------|------------------|
| Brain  | Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events |
| Ears   | Sensorineural hearing loss, aminoglycoside sensitivity |
| Eyes   | Optic neuropathy and retinitis pigmentosa |
| Heart  | Cardiac conduction defects (heart blocks), cardiomyopathy |
| Kidneys | Proximal renal tubular dysfunction (Fanconi syndrome); possible loss of protein (amino acids), magnesium, phosphorus, calcium, and other electrolytes |
| Liver  | Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure |
| Muscles| Hypotonia, weakness, cramping, muscle pain, ptosis, ophthalmoplegia |
| Nerves | Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent deep tendon reflexes, neuropathic gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudoobstruction), fainting, absent or excessive sweating, aberrant temperature regulation |
| Pancreas| Diabetes and exocrine pancreatic failure |
| Systemic| Failure to gain weight, short stature, fatigue, and respiratory problems including intermittent air hunger |
Mitochondrial proliferation may be a compensatory phenomenon in disorders or pathophysiological states affecting oxidative metabolism (Bengtsson, 2002). It is interesting to mention that ragged red fibres, subsarcolemmal mitochondrial accumulation and alteration in ultrastructure, number and size of mitochondrial are typical defects and markers found in genuine mitochondrial diseases (MELAS, MERRF, Kearns-Sayre syndrome, Pearson syndrome, Leigh syndrome, etc) (Haas et al., 2008). However, red ragged fibers appear to be also related to insufficient blood supply (Heffner & Barron, 1978), and abnormal capillary microcirculation in tender points was found in FM patients (Lund et al, 1986). Microcirculation in the muscle is controlled by the sympathetic nervous system and others local and humoral factors. Therefore, the contribution of the vasoconstrictor activity of the sympathetic nervous system that produces local hypoxia in muscle and fiber damage should be considered in the pathogenesis of red ragged fibers in FM.

$^{31}$P Magnetic Resonance Spectroscopy (MRS) analysis in muscle has provided objective evidence for metabolic abnormalities consistent with clinical symptoms of weakness and fatigue in patients with FM (Park et al., 1998). The MRS examinations showed phosphocreatine (PCr) and ATP concentrations in muscles of FM patients to be 15% below normal values during rest and exercise. The reduced levels of PCr and ATP in the patients’ muscles correlate with clinical observations regarding weakness and pain during exercise. In this study, pain was inversely correlated with ATP and PCr levels. Reduction in ATP levels also has been observed in the erythrocytes of FM patients, suggesting that this may be a more systemic phenomenon than was previously assumed (Russell et al, 1993). Recently, it has also been noted a decrease of ATP levels in platelets from FM patients (Bazzichi et al., 2008). Blood platelets represent an easily available and simple peripheral model to study bioenergetics alterations in FM. Platelets possess mitochondria, the entire pool of enzymes or proteins involved in oxidative energy production and, consequently, they are active in ATP turnover (Niu et al, 1996). Moreover, platelets present on their plasma membrane either pain/inflammation or neurochemical sites, such as adenosine/monoamine receptors and transporters (Marazziti et al, 1999; Martini et al, 2004), enabling the study of either neurochemistry or ATP energy metabolism in FM. Some recent have shown a significant increase of the platelet peripheral benzodiazepine receptor (PBR) (now named traslocator protein, TSPO, (Papadopoulos et al, 2006) together with high plasma levels of the pro-inflammatory chemokine interleukine 8 (IL-8), low serum cortisol (Bazzichi et al, 2006a) as well as a reduced density and functionality of the platelet serotonin transporter (SERT) (Bazzichi et al, 2006b) in FM patients.

3. Mitochondrial dysfunction, oxidative stress in FM

In general, oxidative stress could be defined as an imbalance between the presence of high levels of ROS and reactive nitrogen species (RNS), and the antioxidative defense mechanisms. These toxic molecules are formed via oxidation-reduction reactions and are highly reactive since they have an odd number of electrons. ROS generated under physiological conditions are essential for life, as they are involved in bactericidal activity of phagocytes, and in signal transduction pathways, regulating cell growth and reduction–oxidation (redox) status (Davies, 1995). ROS includes free radicals, such as hydroxyl and superoxide radicals, and non-radicals, including hydrogen peroxide and singlet oxygen. Oxidative stress and generation of free radicals, as primary or secondary event, have been related in a great number of diseases. It has been suggested that oxidative stress is linked to
both the initiation and the progression of Parkinson’s disease (Zhou et al., 2008), and strong evidence exists for early oxidative stress in Huntington’s disease (Stack et al., 2008). Moreover, numerous studies demonstrate that different biomarkers of oxidative-stress-mediated events are elevated in the Alzheimer disease (Praticò, 2008) and renal disease (even in early chronic kidney disease) (Cachofeiro et al., 2008). Moreover, oxidative stress is believed to aggravate the symptoms of many diseases, including hemolytic anemias (Fibach & Rachmilewitz, 2008), amyotrophic lateral sclerosis (Orrell et al., 2008), and metabolic syndrome (Whaley-Connell et al., 2011).

It is known that ROS overproduction induces lipid peroxidation (LP) leading to oxidative destruction of polyunsaturated fatty acids, the main structural component of cellular membranes, and the production of toxic and reactive aldehyde metabolites such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) (Draper et al., 2000; Esterbauer et al., 1991). These highly cytotoxic metabolites, produced in relatively large amounts, can diffuse from their site of origin to attack distant targets and form covalent bonds with various molecules. Therefore, recognition of LP is of interest, as the deleterious effects of this process might be prevented by administration of scavenging systems or antioxidants.

In recent years, several studies have shown increased level of oxidative stress markers in FM suggesting that this process may have a role in the pathophysiology of this disease (Table 2). High levels of LP and protein carbonyls are two of the most documented oxidative damage markers to be associated with FM.

| Author(s) | N(FM/Ctl) | Sample(s) | Parameter |
|-----------|-----------|------------|-----------|
| Akkus et al., 2009 | 30/30 | Plasma | Lipid peroxidation (LP)/Vitamins A,C,E/Beta-Carotene |
| Altindag et al., 2006 | 20/20 | Plasma | Total Antioxidant Status (TAS) |
| Altindag et al., 2007 | 42/53 | Serum | lipid hydroperoxide (LOOH)/TAS/ free sulphydryl groups |
| Bagis et al., 2005 | 85/80 | Serum | LP/Superoxide Dismutase (SOD) |
| Cordero et al., 2009 | 40/25 | Plasma/BMCs | LP/ROS/Protein carbonyls/CoQ10 |
| Cordero et al., 2010 | 20/10 | Plasma/BMCs | LP/Superoxide Anion/CoQ10 |
| Cordero et al., 2010 | 2/2 | Skin biopsies | LP/CoQ10 |
| Chung et al., 2009 | 48/96 | Urine | F2 isoprostanes |
| Hein et al., 2002 | 41/46 | Serum | Pentosidine |
| Kaufmann et al., 2008 | 22/22 | Neutrophils | Hydrogen peroxide |
| Naziroğlu et al., 2010 | 32/30 | Plasma/ Erythrocytes | LP/Glutathione peroxidase/Vitamins A and E |
| Ozgocmen et al., 2006 | 30/16 | Serum | LP/ SOD/Xanthine oxidase |
| Sendur et al., 2009 | 37/37 | Serum | Catalase/Glutathione |

Table 2. References about oxidative stress in Fibromyalgia.
Thus, high levels of MDA, a final product of LP, and increased level of protein carbonyls, as result of protein oxidation have been reported in plasma from FM patients. Furthermore, it has been observed that total antioxidant capacity and superoxide dismutase (SOD), catalase and glutathione levels are reduced in FM patients.

Furthermore, increased LP has been described in patients suffering from depression and fatigue, two typical symptoms found in FM patients (Bilici et al., 2001; Vecchiet et al., 2003). Studies on depression have signaled a possible link between depression and LP (Evans, 2003), and the peroxidation-reducing effect of different selective serotonin reuptake inhibitors in major depression has been demonstrated (Bilici et al., 2001). It has been suggested that alterations in phospholipids which are structural components of cell membrane in the brain, may induce changes in membrane microviscosity and, consequently, in various neurotransmitter systems, which are thought be related to the pathology of depression, e.g., serotonin (5-HT), and noradrenaline (Maes et al., 1996; Tsutsumi et al., 1988). LP of cell membranes can modify receptor accessibility, dynamics, ligand binding and action, and therefore altering neurotransmitter functions (Lenaz, 1987). Oxidative stress may also affect the expression of membrane functional proteins and receptors, by interfering with intracellular signalling and receptors turnover, including serotonergic receptors (Maes et al., 2007).

The role of oxidative stress in peripheral neuropathic pain, one of the most prominent symptoms in FM, was recently also tested by assessing the effects of antioxidants (acetyl-L-carnitine, alpha-lipoic acid, and vitamin C) on pain behaviour in a rat model of neuropathic pain induced by the antineoplastic agent oxaliplatin (Joseph et al., 2008). Each agent, administered locally at the site of mechanical nociceptive testing in the skin, markedly inhibited the oxaliplatin-induced hyperalgesia. Finally, ROS also appear to contribute to hyperalgesia induced by PKCε (Joseph et al., 2010), potentially linking this mitochondrial pathway to the hyperalgesic priming model of chronic peripheral pain. Furthermore, ROS are known to be implicated in the etiology of pain by inducing peripheral and central hyperalgesia (Wang et al., 2004). Superoxide plays a major role in the development of pain through direct peripheral sensitization, the release of various cytokines (for example, TNF-α, IL-1β, and IL-6), the formation of peroxynitrite (ONOO-), and PARP activation (Wang et al., 2004). Although, the mechanisms by which increased oxidative stress can affect specifically muscle sensitivity remain to be established, it may be that oxidative damage in muscles results in lowering the threshold of nociceptors locally, thus producing and altered nociception (Fulle et al., 2000).

In recent works, we have examined mitochondrial bioenergetics and antioxidant defenses in Blood mononuclears cells (BMCs) from FM patients. As CoQ deficiency had been suggested to be useful as a mitochondrial dysfunction marker, we addressed mitochondrial dysfunction in BMCs from FM patients and examined whether mitochondrial disturbance could be involved in the pathophysiology of oxidative stress in FM. We analyzed CoQ levels in BMCs and plasma from FM patients. We observed an altered distribution of CoQ levels between plasma and cells (high levels in plasma and low levels in cells) (Cordero et al., 2009). We found that CoQ-deficient BMCs in FM patients showed high level of mitochondrial ROS production and increased levels of LP. To confirm oxidative stress in FM, BMCs of one representative patient were treated with three antioxidants (CoQ, vitamin E, and N-acetylcyysteine), and mitochondrial ROS production was examined. Both CoQ and vitamin E, two well known lipophilic antioxidants, induced a significantly reduction of ROS.
(Figure 2). These results suggest that ROS were produced in the lipophilic environment of mitochondrial membranes, and that CoQ deficiency may be involved in the oxidative stress observed in FM. In addition, biochemical analysis of citrate synthase indicated a depletion of mitochondrial mass, suggesting selective mitochondrial degradation in BMCs from FM patients. These results were confirmed by electron microscopy that clearly showed autophagosomes where mitochondria are being degraded (Figure 1). Mitophagy can be beneficial for the cells by eliminating dysfunctional mitochondria, but excessive mitophagy can promote cell injury and may contribute to the pathophysiology of FM (Cordero et al., 2010a).

In general, there is poor correlation between plasma and tissues levels of CoQ, and even patients with genetically proven CoQ deficiency may have plasma CoQ levels at a normal range. However, there is a positive correlation between the content of CoQ in skeletal muscle, dermal fibroblasts and BMCs (Land et al., 2007; Duncan et al., 2005). Furthermore, mitochondrial dysfunction and oxidative stress has also been observed in skin biopsies from FM patients. The biopsies showed CoQ deficiency, increased level of LP, and a decrease in complex II + III and complex IV (Cordero et al., 2010b). Interestingly, it is known that CoQ deficiency induces decreased activities of complex II + III, complex III and complex IV (Quinzii et al., 2008). Furthermore, fibroblasts from skin of some patients with CoQ deficiency syndrome show a higher production of ROS in mitochondria (Quinzii et al., 2008). Therefore, skin fibroblasts and BMCs can be helpful for biochemical diagnosis of mitochondrial defects in FM patients. As is shown in Table 2, most of the studies about oxidative stress markers (MDA levels) in FM have used plasma or serum as experimental
sample. However, it has to be taken into account that plasma or serum MDA levels depend on the balance between MDA formation and its detoxification and can be affected by many factors, such as the dilutional effect of plasma, and the renal and/or tissue clearance. Therefore, it would be desirable to measure oxidative stress markers in blood cells rather than in plasma or serum. On this point, it has recently been reported increased levels of hydrogen peroxide in neutrophils from FM patients (Kaufmann et al., 2008). Interestingly, there are some discrepancies about the correlation between symptoms and LP and oxidative stress in FM. Significant correlation has been observed between antioxidants levels in plasma and serum, visual analogue scale (VAS) of pain, and morning stiffness (Altindag & Celik, 2007; Sendur et al., 2009). However, Bagis et al. found no correlation between VAS of pain and LP or SOD in serum (Bagis et al., 2005). On the other hand, Ozgocmen et al. found a significant correlation between depression and LP in serum but not between the biochemical parameters and clinical measures of pain and fatigue (Ozgocmen et al., 2006). This controversy could be ascribed to a methodological problem because LP levels may show higher levels and reflect better the degree of oxidative stress if LP measurement is performed in cells rather than in plasma or serum. In fact, we have selected 65 FM patients and evaluated the association between LP and clinical symptoms (Table 3).

Fig. 2. Effect of CoQ10 (up) and Vitamin E (down) about mitochondrial ROS production in BMCs from FM patients compared to healthy patients.
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Table 3. Characteristic findings of the FM patients and control group. Values are means ±SD. *P<0.001. (Unpublished data).

|                        | Patients       | Control       |
|------------------------|----------------|---------------|
| Age (years)            | 45.8±11        | 44.3±12       |
| Tender points          | 15.4±2.8       | ?             |
| Duration of disease (years) | 10.4±6.4     | ?             |
| Sex (males/female)     | 5/60           | 5/40          |
| BMI kg/m²              | 27.4±4.2       | 23.31±09      |
| VAS Total score        | 5.9±1.8*       | 0.5±0.8       |
| FIQ Total score, range 0 - 80 | 54.5±16*   | 3±1.6         |
| Pain                   | 7.3±2.2*       | 0.7±0.3       |
| Fatigue                | 7.6±1.9*       | 1.2±0.9       |
| Morning tiredness      | 6.7±2.2*       | 1.1±1.0       |
| Stiffness              | 5.9±2.3*       | 0.6±0.1       |
| Anxiety                | 5.8±2.7*       | 1±0.9         |
| Depression             | 5.2±2.7*       | 1.2±0.8       |
| Beck Depression Inventory | 18.5±8.6*  | 4±1.9         |

Table 4. Correlation between LP and clinical findings in FM patients. *P<0.05; **P<0.01. r, Pearson's Correlation Coefficient (Unpublished data).

|                      | LP in cells r | LP in plasma r |
|----------------------|---------------|----------------|
| VAS                  | 0.584**       | 0.452**        |
| FIQ total score      | 0.823**       | 0.578**        |
| Pain                 | 0.564**       | 0.410**        |
| Fatigue              | 0.617**       | 0.311**        |
| Morning tiredness    | 0.574**       | 0.397**        |
| Stiffness            | 0.669**       | 0.402**        |
| Anxiety              | 0.591**       | 0.433**        |
| Depression           | 0.632**       | 0.561**        |
| Beck Depression Inventory | 0.875**   | 0.579**        |

We have observed significant correlation between LP levels BMCs or plasma and clinical parameters. However, LP levels in BMCs are better associated than LP levels in plasma to clinical symptoms in FM (Table 4), (Unpublished data).

Alternatively, as mentioned above, it has been observed low levels of SOD in plasma of FM patients (Bagis et al., 2005, Ozgocmen et al., 2006). SOD is an enzyme presents in all cells that catalyzes the conversion of superoxide free radicals to oxygen and hydrogen peroxide. It is the most powerful antioxidant produced by the body and has been used as a marker of antioxidant defense (Marklund SL (1990). Therefore, SOD deficiency in FM may account for a low protection of cells against ROS damage and support the hypothesis of FM as an oxidative disorder. Besides mitochondrial dysfunction many others objective and measurable biomarkers has been proposed that may facilitate diagnosis and monitor the activity of FM (Dadabhoy et al, 2008).
4. Therapeutic implication of mitochondrial dysfunction in fibromyalgia

An important problem in FM is the moderate effectiveness of pharmacological therapies. In general, about half of all treated patients seem to experience a 30% reduction of symptoms, suggesting that many patients with fibromyalgia will require additional therapies (Staud, 2010). But, in most cases, high incidence of secondary effects is induced by pharmacological therapy, and many drugs may induce mitochondrial damage (Neustadt & Pieczenik, 2008). Mitochondria can be damaged both directly and indirectly by medications. Medications can directly inhibit mtDNA transcription of MRC complexes, damage through other mechanisms MRC components, and inhibit enzymes required for any of the steps of glycolysis and β-oxidation. Indirectly, medications may damage mitochondrial via the production of free radicals, by decreasing endogenous antioxidants such as glutathione and by depleting the body of nutrients required for the creation or proper function of mitochondrial enzymes or MRC complexes. Damage to mitochondria may explain the side effects of many medications. Therefore, treatment with these drugs in patients with mitochondrial dysfunction could be counterproductive. In this respect, amitriptyline is a tricyclic antidepressant frequently recommended in FM treatment. There are evidences to support the short-term efficacy of amitriptyline 25mg/day in FM (Nishishinya et al, 2008). However, there is no evidence to support the efficacy of amitriptyline at higher doses or for periods longer than 8 weeks. Furthermore, amitriptyline causes a dose-related cytotoxic effect in neurons beginning at clinically relevant concentrations by a mechanism dependent on mitochondrial depolarization (Lirk et al, 2006). Recently, our group has reported that amitriptyline at high doses induced CoQ deficiency and mitochondrial dysfunction in an in vitro cellular assay (Cordero et al., 2009). Moreover, CoQ and alpha-tocopherol supplementation prevented the cellular damage induced by amitriptyline. This data suggests that high dose or long-period of amitriptyline treatment should be done with caution monitoring mitochondrial function and, in case of CoQ deficiency, supplementing with CoQ could prevent its adverse effects.

However, since oxidative stress may arise as a consequence of mitochondrial dysfunction or interfere with mitochondrial function, reducing oxidative stress emerges as a form of mitochondrial medicine that could be beneficial in FM patients. Thus, CoQ frequently used in mitochondrial disease treatment to boost mitochondria function and prevent ROS damage (Tiano et al., 2011; Stack et al., 2008; Zhou et al., 2008; Quinzii & Hirano, 2010), might be an alternative treatment in FM.

Beneficial effects of CoQ administration in FM patients have been observed in a previous pilot study (Lister, 2002). In this study, Lister et al reported beneficial effects of oral CoQ and Gingko Biloba supplementation in FM patients. They observed an important improvement in quality-of-life scores that justified the need for a larger scale clinical trial and further investigations into the possible mechanism of action of CoQ. In our studies, oral CoQ treatment significantly improved clinical symptoms and decrease oxidative stress in several cases of FM (Cordero et al., 2011a; Cordero e al., 2011b). Nevertheless, more controlled clinical trials are needed to provide data on effectiveness of CoQ in FM.

CoQ is a potential drug candidate in the treatment of FM for at least two main reasons. First, CoQ is a mitochondrial cofactor with the potential to improve mitochondrial function. Second, CoQ is a powerful free radical scavenger that can mitigate LP and DNA damage caused by oxidative stress (Lenaz G et al, 2007). Thus, CoQ supplementation has been proven to be beneficial in patient with muscle pain associated with statin treatment (Caso et
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(al., 2007), and migraine prophylaxis (Sandor et al., 2005). Furthermore, CoQ has shown anti-inflammatory and anti-nociceptive activity (Jung et al., 2009), regulating inflammatory gene expression as proinflammatory cytokine TNF-alpha (Schmelzer et al., 2008) which has been demonstrated to have a role in FM (Menzies et al., 2010).

Other antioxidants treatment has been assayed in FM. Melatonin, the pineal hormone with pleiotropic activity is a known powerful antioxidant and anti-inflammatory and increasing experimental and clinical evidence shows its beneficial effects against oxidative/nitrosative stress status, including that involving mitochondrial dysfunction (Acuña Castroviejo et al., 2011). Treatment of FM patients with 3 mg melatonin daily for 30 days significantly improved the tender point count, severity of pain, global physical assessments, and sleep (Citera et al., 2000). Moreover, in a limited number of cases, administration of 6 mg/day melatonin to patients with FMS resulted in normal sleep/wake cycles, normal diurnal activity, lack of pain, and fatigue and claims significant improvement of the behavioral symptoms including lack of depression (Acuna-Castroviejo et al., 2006). Recently, in a double-blind, placebo-controlled clinical study was demonstrated that administration of melatonin, alone or in a combination with fluoxetine, was effective in the treatment of patients with FM (Hussain et al., 2011). The "Myers' cocktail", an intravenous vitamin-and-mineral formula (IVMT) for the treatment of a wide range of clinical conditions, which has vitamin c as antioxidant, has been assayed also, and most subjects experienced relief as compared to baseline, but no statistically significant differences were seen between IVMT and placebo (Ali et al., 2009).

Vitamin D which controls calcium and phosphorus metabolism (Norman et al, 1992), is also a membrane antioxidant (Wiseman H, 1993) whose deficiency has been linked to chronic pain, muscle weakness (Straube et al, 2009; Zhang et al, 2010) and fibromyalgia (Armstrong et al 2007). Subsequently, studies evaluating the effects of high-dose vitamin D treatment have been demonstrated to improve clinical symptoms in FM (Badsha et al 2009).

One of the most investigated non-pharmacological therapies in the treatment of FM is moderate aerobic exercise, which has found some improvement in patients (Stephens et al., 2008). A long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia (Sañudo et al., 2011). Aquatic exercise program also has showed an improvement on symptoms an anti-inflammatory effect in FM (Ortega et al., 2010). Interestingly, exercise therapies have been shown to provide significant benefits in patients with mitochondrial diseases because they induce an increase in mitochondrial biogenesis and an increase of the same size, which is proposed as an alternative therapeutic strategy in these conditions (Adhihetty et al., 2007; Safdar et al., 2011a). PGC-1α, an important regulator of mitochondrial biogenesis via regulating transcription of nuclear-encoded mitochondrial genes, is increased by exercise (Safdar et al., 2011b). This may explain to some extent the improvement seen in patients with FM. Antioxidant treatment combined with exercise has also been shown to modulate oxidative stress markers in FM patients (Naziroğlu et al, 2010)

5. Conclusion

Mitochondria and oxidative stress may play an essential role in the pathophysiology of FM. Since oxidative stress may either arise as a consequence of mitochondrial dysfunction or else interfere with mitochondrial function, reducing oxidative stress emerges as a form of mitochondrial medicine that could be beneficial in FM patients.
Our study supports the hypothesis that CoQ deficiency and mitochondrial dysfunction can contribute to cell bioenergetics imbalance, compromising cell functionality in BMCs of FM patients. Abnormal BMCs performance can promote oxidative stress and may contribute to altered nociception in FM. CoQ deficiency in FM patients, or in a subgroup of them, could also be important to initiate CoQ supplementation. Nevertheless, more research is needed to establish a primary causation between mitochondrial dysfunction and FM.

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Given the potential problems that can obscure any scientific enterprise, inconsistent results across studies are bound to occur. How are we to decide what is true? Let’s turn to philosophy for a reasonable answer. The mathematician-philosopher Bertrand Russell approached a similar problem in his monograph The Problems of Philosophy (Russell B, 1912). He addressed the following question: How do we know that anything is "real"? Is the only reality subjective and simply in our minds, as Bishop Berkeley challenged, or can we mostly believe the objective reality? His pragmatic answer: All possibilities may be true, but when the preponderance of evidence indicates that objective reality and knowledge are the most probable case, go with it. If the preponderance of all evidence about the clinical description of fibromyalgia and it’s pathogenic mechanisms and treatment strategies indicate a highly probable interrelated hypothesis, go with it. The direction of the literature on the whole trumps the less likely tangents. At the same time, remember Bertrand Russell and his pragmatic answer, and keep an open mind.

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