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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 time more frequent in women than in men (Lawrence et el., 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 serotoninergic system genotype of 5–HTT (Bazzichi et al., 2006a; Tander et al., 2008), catechol-O-methytransferase 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 polyprenyl side-chain. The number of isoprene units is specie specific, e.g. 10 in humans ($CoQ_{10}$). CoQ also functions as an antioxidant that

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 $O_2$ to generate superoxide anion ($O_2^{-}$). Superoxide is transformed to hydrogen peroxide ($H_2O_2$) 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 $H_2O_2$ encounters a reduced transition metal or is mixed with $O_2^{-}$, the $H_2O_2$ can be further reduced to hydroxyl radical ($OH^{\bullet}$), 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 $O_2^{-}$ 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 $O_2$ to generate $O_2^{-}$. 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).

| 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, opthalmoplegia |
| 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 |

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

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 trapezious, 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 phosphorilation (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.

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 sulfhydryl groups |
| Bagis et al., 2005 | 85/80 | Serum | LP/Superoxide Dismutase (SOD) |
| Cordero et al., 2009 | 40/25 | Plasma/BMCs | LP/ROS/Protein carbonyls/$CoQ_{10}$ |
| Cordero et al., 2010 | 20/10 | Plasma/BMCs | LP/Superoxide Anion/$CoQ_{10}$ |
| Cordero et al., 2010 | 2/2 | Skin biosies | LP/$CoQ_{10}$ |
| 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 |
| Nazıroğlu 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-acetilcysteine), 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).

**Control Patient**

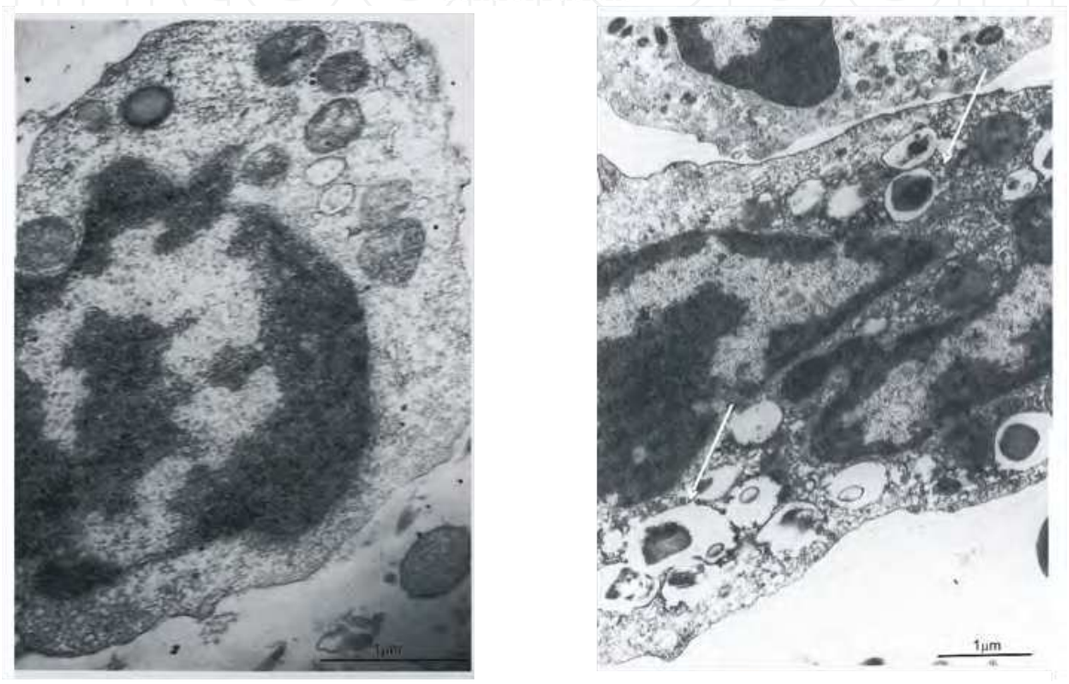



Fig. 1. Ultrastructure of BMCs from FM patients. Control BMCs is showing mitochondria with a typical ultrastructure. Autophagosome with mitochondria (arrows) were present in BMCs from a representative FM patient; Bar =1 µm. (Cordero et al., 2010a).

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 for 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 o serum. On this point, it has recently been reported increased levels of hydrogen peroxide in neutrophils from FM patients (Kaufmann et al., 2008). Interesting, 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).

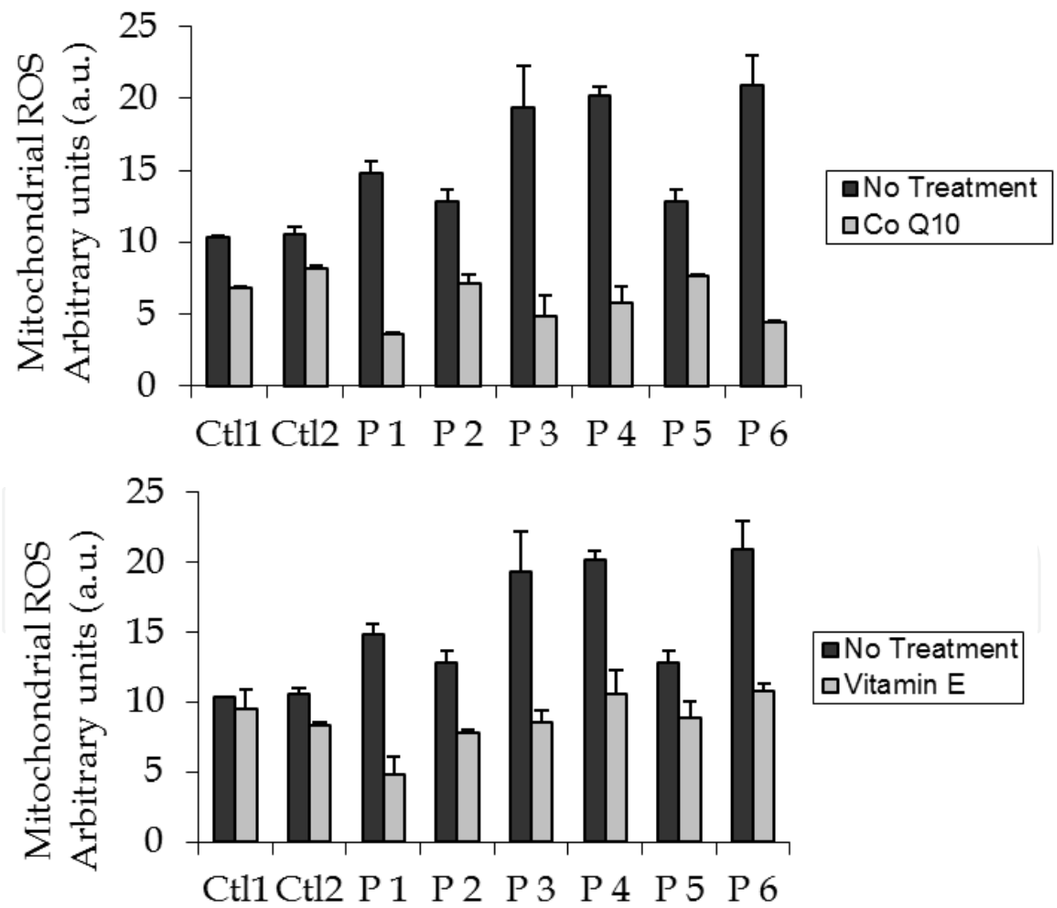



Fig. 2. Effect of $CoQ_{10}$ (up) and Vitamin E (down) about mitochondrial ROS production in BMCs from FM patients compared to healthy patients.

| | 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 |
| Stiffnes | 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 3. Characteristic findings of the FM patients and control group. Values are means ±SD. *P<0.001. (Unpublished data).

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**).

| | LP in cells<br>r | LP in plasma<br>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** |

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

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 (Nazıroğlu 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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## 7. References

Acuna-Castroviejo, D.; Escames, G. &Reiter RJ. (2006). Melatonin therapy in fibromyalgia. *J Pineal Res,* 40,1, (Jan) (98–99), ISSN 0742-3098.

Acuña-Castroviejo, D.; López, L.C.; Escames, G.; López, A.; García, J.A. & Reiter, R.J. (2011). Melatonin-mitochondria interplay in health and disease. *Curr Top Med Chem*. 11, 2, (Jan) (221-40), ISSN 0742-3098.

Adhihetty, P.J.; Taivassalo, T.; Haller, R.G.; Walkinshaw, D.R. & Hood, D.A. (2007). The effect of training on the expression of mitochondrial biogenesis- and apoptosis-related proteins in skeletal muscle of patients with mtDNA defects. *Am J Physiol Endocrinol Metab*. 93, 3, (Sep) (E672-80), ISSN 0193-1849.

Akkuş, S.; Naziroğlu, M.; Eriş, S.; Yalman, K.; Yilmaz, N. & Yener, M. (2009). Levels of lipid peroxidation, nitric oxide, and antioxidant vitamins in plasma of patients with fibromyalgia.*Cell Biochem Funct*. 27, 4, (Jun) (181-5), ISSN 0263-6484.

Ali, A.; Njike, V.Y.; Northrup, V.; Sabina, A.B.; Williams, A.L.; Liberti, L.S.; et al. (2009). Intravenous micronutrient therapy (Myers' Cocktail) for fibromyalgia: a placebo-controlled pilot study. *J Altern Complement Med*. 15, 3, (Mar) (247-57), ISSN 1075-5535.

Alnigenis, M.N.Y. & Barland, P.(2001). Fibromyalgia syndrome and serotonin. *Clin Exp Rheumatol* 19, 2, (Mar-Apr) (205–210), ISSN 0392-856X.

Altindag, O. & Celik, H. (2006). Total antioxidant capacity and the severity of the pain in patients with fibromyalgia. *Redox Rep*. 11, 3, (Jun) (131-5), ISSN 1351-0002.

Altindag, O.; Gur, A.; Calgan, N.; Soran, N.; Celik, H. & Selek, S. (2007). Paraoxonase and arylesterase activities in fibromyalgia. *Redox Rep*. 12, 3, (Jun) (134-8), ISSN 1351-0002.

Armstrong, D.J.; Meenagh, G.K.; Bickle, I.; Lee, A.S.; Curran, E.S. & Finch, M.B. (2007). Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol*. 26, 4, (Jul) (551-4), ISSN 0770-3198.

Badsha, H.; Daher, M. & Kong, K.O. (2009). Myalgias or non-specific muscle pain in Arab or Indo-Pakistani patients may indicate vitamin D deficiency. *Clin Rheumatol*. 28, 8, (Aug) (971–973), ISSN 0770-3198.

Bagis, S.; Tamer, L.; Sahin, G.; Bilgin, R.; Guler, H.; Ercan, B. & Erdogan, C. (2005). Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder?. *Rheumatol Int*. 25, 3, (Apr) (188-90), ISSN 0172-8172.

Bhatia-Kiššová, I. & Camougrand, N. (2010). Mitophagy in yeast: actors and physiological roles. *FEMS Yeast Res*. 10, 8, (Dec) (1023–1034), ISSN 1567-1356.

Bazzichi, L.; Giannaccini, G.; Betti, L.; Italiani, P.; Fabbrini, L.; Defeo, F.; et al. (2006). Peripheral benzodiazepine receptors on platelets of fibromyalgic patients. *Clinical Biochem.* 39, 9, (Sep) (867–72), ISSN 0009-9120.

Bazzichi, L.; Giannaccini, G.; Betti, L.; Mascia, G.; Fabbrini, L.; Italiani, P.; et al. (2006b). Alteration of serotonin transporter density and activity in fibromyalgia. *Arthritis Res Ther* 8, 4, Jun) (R99), ISSN 1478-6354.

Bazzichi, L.; Rossi, A.; Massimetti, G.; et al. (2007). Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. Clin. Exp. Rheumatol. 25, 2, (Mar-Apr) (225–230), ISSN 0392-856X.

Bazzichi, L.; Giannaccini, G.; Betti, L.; Fabbrini, L.; Schmid, L.; Palego, L.; et al. (2008). ATP, calcium and magnesium levels in platelets of patients with primaryfibromyalgia. *Clin Biochem*. 41, 13, (Sep), (1084-90), ISSN 0009-9120.

Bengtsson, A. (2002). The muscle in fibromyalgia. *Rheumatology (Oxford)*. 41, 7, (Jul) (721-4), ISSN 1462-0324.

Bengtsson, A.; Henriksson, K.G. & Larsson, J. (1986). Muscle biopsy in primary fibromyalgia. Light-microscopical and histochemical findings. *Scand J Rheumatol*. 15, 1, (Jan) (1-6), ISSN 0300-9742.

Bilici, M.; Efe, H.; Koroglu, M.A.; Uydu, H.A.; Bekaroglu, M. & Deger, O. (2001). Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *Journal of affective disorders.* 64, 1, (Apr) (43-51), ISSN 0165-0327.

Buskila, D.; Cohen, H.; Neumann, L. & Ebstein, R.P. (2004). An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. *Mol Psychiatry.* 9, 8, (Aug) (730–731), ISSN 1359-4184.

Cachofeiro, V.; Goicochea, M.; de Vinuesa, S.G.; Oubiña, P.; Lahera, V. & Luño, J. (2008). Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. *Kidney Int.* 111, Suppl, (Dec) (S4-9), ISSN 0098-6577.

Caso, G.; Kelly, P.; McNurlan, M.A. & Lawson, W.E. (2007). Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol.* 99, 10, (May) (1409-12), ISSN 0002-9149.

Citera, G.; Arias, A.; Maldonado-Cocco, J.A.; Lázaro, M.A.; Rosemffet, M.G.; Brusco, L.I.; et al. (2000). The effect of melatonin in patients with fibromyalgia: a pilot study. *Clin Rheumatol*. 19, 1, (Jan) (9–13), ISSN 0770-3198.

Clark, I.A.; Alleva, L.M. & Vissel, B. (2010). The roles of TNF in brain dysfunction and disease. *Pharmacol Ther.* 128, 3, (Dec) (519-48), ISSN 0163-7258.

Cohen, B.H. & Gold, D.R.. (2001). Mitochondrial cytopathy in adults: what we know so far. *Cleve Clin J Med*. 68, 7, (Jul) (625–626, 629–642) ISSN 0891-1150.

Cordero, M.D.; Moreno-Fernández, A.M.; deMiguel, M.; Bonal, P.; Campa, F.; Jiménez-Jiménez, L.M.; et al. (2009). Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. *Clin Biochem*. 42, 7-8, (May) (732-5), ISSN 0009-9120.

Cordero, M.D.; Moreno-Fernández, A.M.; Gomez-Skarmeta, J.L.; de Miguel, M.; Garrido-Maraver, J.; Oropesa-Avila, M.; et al. (2009). Coenzyme Q10 and alpha-tocopherol protect against amitriptyline toxicity. *Toxicol Appl Pharmacol*. 235, 3, (Jan) (329-37) ISSN 0041-008X.

Cordero, M.D.; De Miguel, M.; Moreno Fernández, A.M.; Carmona López, I.M.; Garrido Maraver, J.; Cotán, D.; et al. (2010a). Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther*. 12, 1, (Jan) (R17), ISSN 1478-6354.

Cordero, M.D.; Moreno-Fernández, A.M.; Carmona-López, M.I.; Sánchez-Alcázar, J.A.; Rodríguez, A.F.; Navas, P. & de Miguel, M. (2010b). Mitochondrial dysfunction in skin biopsies and blood mononuclear cells from two cases of fibromyalgia patients. *Clin Biochem*. 43, 13-14, (Sep) (1174-6), ISSN 0009-9120.

Cordero, M.D.; Alcocer-Gómez, E.; Cano-García, F.J.; de Miguel, M.; Campa, F.; Bona, P. & Moreno Fernández, A.M. (2011a). The effect of Coenzyme Q10 on symptoms of mother and son with Fibromyalgia Syndrome. *J Muscoskel Pain*. 19, 2, (Apr) (118-9), ISSN 1058-2452.

Cordero, M.D.; Alcocer-Gómez, E.; de Miguel, M.; Cano-García, F.J.; Luque, C.M.; Fernández-Riejo, P.; et al. (2011b). Coenzyme Q(10): A novel therapeutic approach for Fibromyalgia? Case series with 5 patients. *Mitochondrion*. 11, 4, (Jul) (623-5), ISSN 1567-7249.

Cotán, D.; Cordero, M.D.; Garrido-Maraver, J.; Oropesa-Ávila, M.; Rodríguez-Hernández, A.; Gómez Izquierdo, L.; et al.(2011). Secondary coenzyme Q10 deficiency triggers mitochondria degradation by mitophagy in MELAS fibroblasts. *FASEB J*. (May), pp, ISSN 0892-6638.

Crofford, L.J.; Engleberg, N.C. & Demitrack, M.A. (1996). Neurohormonal perturbations in fibromyalgia. *Baillieres Clin Rheumatol*. 10, 2, (May) (365–78), ISSN 0950-3579.

Dadabhoy, D.; Crofford, L.J.; Spaeth, M.; Russell, I.J. & Clauw, D.J. (2008). Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. *Arthritis Res Ther*. 10, 4, (211), ISSN 1478-6354.

Davies, K.J. (1995). Oxidative stress: the paradox of aerobic life. *Biochem Soc Symp*.61, (1–31), ISSN 0067-8694.

Draper, H.H.; Csallany, A.S. & Hadley, M. (2000). Urinary aldehydes as indicators of lipid peroxidation in vivo. *Free Radic Biol Med*. 29, 11, (Dec) (1071-7), ISSN 0891-5849.

Drewes, A.M.; Andreasen, A.; Schrøder, H.D.; Høgsaa, B. & Jennum, P. (1993). Pathology of skeletal muscle in fibromyalgia: a histo-immuno-chemical and ultrastructural study. *Br J Rheumatol*. 32, 6, (Jun) (479-83) ISSN 0263-7103.

Duncan, A. J.; Heales, S. J.; Mills, K.; Eaton, S.; Land, J. M. & Hargreaves, I. P.(2005). Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. *Clin Chem*. 51, 12, (Dec) (2380-2) ISSN 0009-9147.

Esterbauer, H.; Schaur, R.J. & Zollner, H. (1991). Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic Biol Med*. 11, 1, (Dec) (81-128), ISSN 0891-5849.

Evans, P.H. (1993). Free radicals in brain metabolism and pathology. *Br Med Bull*. 49, 3, (Jul) (577-87), ISSN 0007-1420.

Fibach, E. & Rachmilewitz, E. (2008). The role of oxidative stress in hemolytic anemia. *Curr Mol Med*. 8, 7, (Nov) (609-19), ISSN 1566-5240.

Fulle, S.; Mecocci, P.; Fano, G.; Vecchiet, I.; Vecchini, A.; Racciotti, D.; et al. (2000). Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome. *Free Radic Biol Med.* 29, 12, (Dec) (1252-9) ISSN 0891-5849.

Gottlieb, R.A. & Carreira, R.S. (2010). Autophagy in health and disease. 5. Mitophagy as a way of life. *Am J Physiol Cell Physiol*. 299, 2, (Aug) (C203-10) ISSN 0363-6143.

Gursoy, S.; Erdal, E.; Herken, H.; Madenci, E.; Alasehirli, B. & Erdal, N. (2003). Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int*. 23, 3, (May) (104–107), ISSN 0172-8172.

Haas, R.H.; Parikh, S.; Falk, M.J.; Saneto, R.P.; Wolf, N.I.; Darin, N.; et al. (2008). The in-depth evaluation of suspected mitochondrial disease. *Mol Genet Metab.* 94, 1, (May) (16-37), ISSN 1096-7193.

Heffner, R.R. & Barron, S.A. (1978). The early effects of ischemia upon skeletal muscle mitochondria. J Neurol Sci. 38, 3, (Oct) (295-315), ISSN 0022-510X.

Hein, G. & Franke, S. (2002). Are advanced glycation end-product-modified proteins of pathogenetic importance in fibromyalgia? *Rheumatology (Oxford)*. 41, 10, (Oct) (1163-7), ISSN 1462-0324.

Hénriksson, K.G.; Bengtsson, A.; Larsson, J.; Lindström, F. & Thornell, L.E. (1982). Muscle biopsy findings of possible diagnostic importance in primary fibromyalgia (fibrositis,myofascial syndrome). *Lancet*. 2, 8312, (Dec) (1395), ISSN 0140-6736.

Hussain, S.A.; Al-Khalifa, I.I.; Jasim, N.A. & Gorial, F.I. (2011). Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res*. 50, 3, (Apr) (267-71) ISSN 0742-3098.

Joseph, E.K.; Chen, X.; Bogen, O. & Levine, J.D. (2008). Oxaliplatin acts on IB4-positive nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy. *J Pain*. 9, 5, (May) (463–472) ISSN 1526-5900.

Joseph, E.K. & Levine, J.D. (2010). Multiple PKCepsilon-dependent mechanisms mediating mechanical hyperalgesia. *Pain*. 150, 1, (Jul) (17–21) ISSN 0304-3959.

Jung, H.J.; Park, E.H. & Lim, C.J. (2009). Evaluation of anti-angiogenic, anti-inflammatory and antinociceptive activity of coenzyme Q(10) in experimental animals. *J Pharm Pharmacol*. 61, 10, (Oct) (1391-5), ISSN 0022-3573.

Kalyan-Raman, U.P.; Kalyan-Raman, K.; Yunus, M.B. & Masi, A.T. (1984). Muscle pathology in primary fibromyalgia syndrome: a light microscopic, histochemical and ultrastructural study. *J Rheumatol.* 11, 6, (Dec) (808-13) ISSN 0315-162X.

Kaufmann, I.; Schelling, G.; Eisner, C.; Richter, H.P.; Krauseneck, T.; Vogeser, M.;et al. (2008). Anandamide and neutrophil function in patients with fibromyalgia. *Psychoneuroendocrinology*. 33, 5, (Jun) (676-85), ISSN 0306-4530.

Klein, R.; Beansch, M. & Berg, P.A. (1992). Clinical relevance of antibodies against serotonin and gangliosides in patients with primary fibromyalgia syndrome. *Psychoneuroendocrinology*. 17, 5, (Jun) (593–598) ISSN 0306-4530.

Klionsky, D.J. (2005). Autophagy.*Curr Biol*. 15. 8, (Apr) (R282-3) ISSN 0960-9822.

Kim, I.; Rodriguez-Enriquez, S. & Lemasters, J.J. (2007). Selective degradation of mitochondria by mitophagy. *Arch Biochem Biophys*. 462, 2, (Jun) (245-53), ISSN 0003-9861.

Land, J.M., Heales, S.J., Duncan, A.J., Hargreaves, I.P., 2007. Some observations upon biochemical causes of ataxia and a new disease entity ubiquinone, CoQ10 deficiency. *Neurochem Res*. 32, 4-5, (Apr-May) (837-43), ISSN 0364-3190.

Lawrence, R.C.; Felson, D.T.; Helmick, C.G.; Arnold, L.M.; Choi, H.; Deyo, R.A.; et al. (2008). National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 58, 1, (Jun) (26-35), ISSN 0004-3591.

Lenaz, G. (1987).Lipid fluidity and membrane protein dynamics. *Bioscience reports*. 7, 11, (Nov) (823-37) ISSN 0144-8463.

Lenaz, G.; Fato, R.; Formiggini, G. & Genova, M.L. (2007). The role of Coenzyme Q in mitochondrial electron transport. *Mitochondrion*. 7, Suppl, (Jun) (S8–33) ISSN 1567-7249.

Lirk, P.; Haller, I.; Hausott, B.; Ingorokva, S.; Deibl, M.; Gerner, P. & Klimaschewski, L. (2006). The neurotoxic effects of amitriptyline are mediated by apoptosis and are effectively blocked by inhibition of caspase activity. *Anesth Analg*. 102, 6, (Jun) (1728-33), ISSN 0003-2999.

Lister, R.E. (2002). An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with Ginkgo biloba extract in fibromyalgia syndrome. *J Int Med Res*. 30, 2, (Mar-Apr) (195-9), ISSN 0300-0605.

Littarru, G.P. & Tiano, L. (2010). Clinical aspects of coenzyme Q10: an update. *Nutrition*. 26, 3, (Mar) (250-4), ISSN 0899-9007.

Luft, R.; Ikkos, D.; Palmieri, G.; Ernster, L. & Afzelius, B. (1962). A case of severe hypermetabolism of nonthyroid origin with a defect in the maintenance of mitochondrial respiratory control: a correlated clinical, biochemical, and morphological study. *J Clin Invest*.41, (Sep) (1776-804), ISSN 0021-9738.

Lund, N.; Bengtsson, A. & Thorborg, P. (1986). Muscle tissue oxygen pressure in primary fibromyalgia. *Scand J Rheumatol*. 15, 2, (165-73), ISSN 0300-9742.

Maes, M.; Smith, R.; Christophe, A.; Cosyns, P.; Desnyder, R. & Meltzer, H. (1996). Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *Journal of affective disorders*. 38, 1, (Apr) (35-46), ISSN 0165-0327.

Maes, M.; Mihaylova, I. & Leunis, J.C. (2007). Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression. *Neuro endocrinology letters*. 28, 6, (Dec) (861-7), ISSN 0172-780X.

Menzies, V. & Lyon, D.E.. (2010). Integrated review of the association of cytokines with fibromyalgia and fibromyalgia core symptoms. *Biol Res Nurs*. 11, 4, (Apr) (387-94), ISSN 1099-8004.

Marazziti, D.; Dell'Osso, L.; Presta, S.; Pfanner, C.; Rossi, A.; Masala, I.; et al. (1999). Platelet [3H]paroxetine binding in patients with OCD-related disorders. *Psychiatry Res*. 89, 3, (Dec) (223–8), ISSN 0165-1781.

Martini, C.; Trincavelli, M.L.; Tuscano, D.; Carmassi, C.; Ciapparellim, A.; Lucacchini, A.; et al (2004). Serotonin-mediated phosphorylation of extracellular regulated kinases in platelets of patients with panic disorder versus controls. *Neurochem Int*. 44, 8, (Jun) (627–39), ISSN 0197-0186.

Marklund, S.L. (1990). Expression of extracellular superoxide dismutase by human cell lines. *Biochem J*. 266, 1, (Feb) (213-9), ISSN 0264-6021.

Naik, E. & Dixit, V.M. (2011). Mitochondrial reactive oxygen species drive proinflammatory cytokine production. *J Exp Med*. 208, 3, (Mar) (417-20), ISSN 0022-1007.

Nazıroğlu, M.; Akkuş, S.; Soyupek, F.; Yalman, K.; Çelik, Ö.; Eriş, S. & Uslusoy, G.A. (2010). Vitamins C and E treatment combined with exercise modulates oxidative stress markers in blood of patients with fibromyalgia: a controlled clinical pilot study. *Stress*. 13, 6, (Nov) (498-505), ISSN 1025-3890.

Neeck, G. (2002). Pathogenic mechanisms of fibromyalgia. *Ageing Res Rev*. 1, 2, (Apr) (243–55), ISSN 1568-1637.

Neustadt, J. & Pieczenik, S.R. (2008). Medication-induced mitochondrial damage and disease. *Mol Nutr Food Res*. 52, 7, (Jul) (780-8) ISSN 1613-4125.

Nishishinya, B.; Urrútia, G.; Walitt, B.; Rodriguez, A.; Bonfill, X.; Alegre, C. & Darko, G. (2008). Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. *Rheumatology (Oxford)*. 47, 12, (Dec) (1741–1746), ISSN 1462-0324.

Niu, X.; Arthur, P.; Abas, L.; Whisson, M. & Guppy, M. (1996). Carboydrate metabolism in human platelets in a low glucose medium under aerobic conditions. *Biochim Biophys Acta*. 1291, 2, (Oct) (97–106), ISSN 0006-3002.

Norman, A.W.; Nemere, I.; Zhou, L.X.; Bishop, J.E.; Lowe, K.E.; Maiyar, A.C.; et al. (1992). 1,25(OH)2-vitamin D3, a steroid hormone that produces biologic effects via both genomic and nongenomic pathways. *J Steroid Biochem Mol Biol*. 41,3-8, (Mar) (231-40), ISSN 0960-0760.

Orrell, R.W.; Lane, R.J. & Ross, M. (2008). A systematic review of antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. *Amyotroph Lateral Scler*. 9, 4, (Aug) (195-211), ISSN 1748-2968.

Ortega, E.; Bote, M.E.; Giraldo, E. & García, J.J. (2010). Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. *Scand J Med Sci Sports*. doi: 10.1111/j.1600-0838.2010.01132.x, (Jun), ISSN 0905-7188.

Ozgocmen, S.; Ozyurt, H.; Sogut, S.; Akyol, O.; Ardicoglu, O. & Yildizhan, H. (2006). Antioxidant status, lipid peroxidation and nitric oxide in fibromyalgia: etiologic and therapeutic concerns. *Rheumatol Int*. 26, 7, (May) (598-603), ISSN 0172-8172.

Park, J.H.; Phothimat, P.; Oates, C.T.; Hernanz-Schulman, M. & Olsen, N.J. (1998). Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. *Arthritis Rheum*. 41, 3, (Mar) (406-13), ISSN 0004-3591.

Papadopoulos, V.; Baraldi, M.; Guilarte, T.R.; Knudsen, T.B.; Lacapère, J.J.; Lindemann, P.; et al. (2006). Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. *Trends Pharmacol Sci*. 27, 8, (Aug) (402–9), ISSN 0165-6147.

Pieczenik, S.R. & Neustadt, J. (2007). Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol*. 83, 1, (Aug) (84-92), ISSN 0014-4800.

Pongratz, D.E. & Späth, M. (1998). Morphologic aspects of fibromyalgia. *Z Rheumatol*. 57, 2, (47-51), ISSN 0340-1855.

Praticò, D. (2008). Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci*. 29, 12, (Dec) (609-15), ISSN 0165-6147.

Quinzii, C.M.; Lopez, L.C.; Von-Moltke, J.; Naini, A.; Krishna, S.; Schuelke, M.; et al (2008). Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. *Faseb J.* 22, 6, (Jun) (1874-85), ISSN 0892-6638.

Quinzii, C.M. & Hirano, M. (2010). Coenzyme Q and mitochondrial disease. *Dev Disabil Res Rev*. 16, 2, (Jun) (183-8), ISSN 1940-5510.

Rizza, T.; Vazquez-Memije, M.E.; Meschini, M.C.; Bianchi, M.; Tozzi, G.; Nesti, C.;et al. (2009). Assaying ATP synthesis in cultured cells: a valuable tool for the diagnosis of patients with mitochondrial disorders. *Biochem Biophys Res Commun*. 383, 1, (May) (58-62), ISSN 0006-291X.

Rodriguez-Hernandez, A.; Cordero, M.D.; Salviati, L.; Artuch, R.; Pineda, M.; Briones, P.; et al. (2009). Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. *Autophagy*. 5, 1, (Jan) (19-32) ISSN 1554-8627.

Russell, I.J.; Vipraio, G.A. & Abraham, G.E. (1993). Red cell nucleotide abnormalities in fibromyalgia syndrome (abstr). *Arthritis Rheum*. 36,(S223), ISSN 0004-3591.

Russell, I.J.; Orr, M.D.; Littman, B.;Vipraio, G.A.; Alboukrek, D.; Michalek, J.E.; et al. (1994). Elevated cerebrospinal fluid levels of substance P in patients with thefibromyalgia syndrome. *Arthritis Rheum*. 37, 11, (Nov) (1593–601), ISSN 0004-3591.

Safdar, A.; Bourgeois, J.M.; Ogborn, D.I.; Little, J.P.; Hettinga, B.P.; Akhtar, M.; et al. (2011a). Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice. *Proc Natl Acad Sci U S A*. 108, 10, (Mar) (4135-40), ISSN 0027-8424.

Safdar, A.; Little, J.P.; Stokl, A.J.; Hettinga, B.P.; Akhtar, M.; Tarnopolsky, M.A. (2011b). Exercise increases mitochondrial PGC-1alpha content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis. *J Biol Chem*. 286, 12, (Mar) (10605-17), ISSN 0021-9258.

Sandor, P.S.; Di Clemente, L.; Coppola, G.; Saenger, U.; Fumal, A.; Magis, D.; et al. (2005). Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*. 64, 4, (Feb) (713–5), ISSN 0028-3878.

Sañudo, B.; Galiano, D.; Carrasco, L.; de Hoyo, M.; McVeigh, J.G. (2011). Effects of a prolonged exercise program on key health outcomes in women with fibromyalgia: a randomized controlled trial. *J Rehabil Med.* 43, 6, (May) (521-6), ISSN 1650-1977.

Schmelzer, C.; Lindner, I.; Rimbach, G.; Niklowitz, P.; Menke, T. & Döring, F. (2008). Functions of coenzyme Q10 in inflammation and gene expression. *Biofactors*. 32, 1-4, (Dec) (179-83), ISSN 0951-6433.

Schwarz, M.J.; Offenbaecher, M.; Neumeister, A.; Ewert, T.; Willeit, M.; Praschak-Rieder, N.; et al. (2002). Evidence for an altered tryptophan metabolism in fibromyalgia. *Neurobiol Dis*. 11, 3, (Dec) (434-42), ISSN 0969-9961.

Sendur, O.F.; Turan, Y.; Tastaban, E.; Yenisey, C. & Serter, M. (2009). Serum antioxidants and nitric oxide levels in fibromyalgia: a controlled study. *Rheumatol Int*. 29, 6, (Apr) (629-33), ISSN 0172-8172.

Sprott, H.; Salemi, S.; Gay, R.E.; Bradley, L.A.; Alarcón, G.S.; Oh, S.J.; et al. (2004). Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres. *Ann Rheum Dis*. 63, 3, (Mar) (245-51), ISSN 0003-4967.

Stack, E.C.; Matson, W.R. & Ferrante, R.J. (2008). Evidence of oxidant damage in Huntington's disease: translational strategies using antioxidants. *Ann N Y Acad Sci*. 1147, (Dec) (79-92), ISSN 0077-8923.

Staud, R. & Spaeth, M. (2008). Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia. *CNS Spectr*. 13, 3 Suppl 5, (Mar) (12-7), ISSN 1092-8529.

Staud, R. (2010). Pharmacological treatment of fibromyalgia syndrome: new developments. *Drugs*. 70, 1, (Jan) (1-14), ISSN 0012-6667.

Stephens, S.; Feldman, B.M.; Bradley, N.; Schneiderman, J.; Wright, V.; Singh-Grewal, D.; et al. (2008). Feasibility and effectiveness of an aerobic exercise program in children with fibromyalgia: results of a randomized controlled pilot trial. *Arthritis Rheum*. 59, 10, (Oct) (1399-406), ISSN 0004-3591.

Straube, S.; Andrew Moore, R.;Derry, S. & McQuay, H.J. (2009). Vitamin D and chronic pain. *PAIN*. 141, 1-2, (Jan) (10–13), ISSN 0304-3959.

Tander, B.; Gunes, S.; Boke, O.; Alayli, G.; Kara, N.; Bagci, H. & Canturk, F. (2008). Polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase genes: a study on fibromyalgia susceptibility. *Rheumatol Int.* 28, 7, (May) (685-91); ISSN 0172-8172.

Tiano, L.; Padella, L.; Santoro, L.; Carnevali, P.; Principi, F.; Brugè, F.; et al. (2011). Prolonged coenzyme Q(10) treatment in Down syndrome patients, effect on DNA oxidation. *Neurobiol Aging*. Pp., ISSN 0197-4580.

Turrens, J.F. (2003). Mitochondrial formation of reactive oxygen species. *J Physiol*. 552, Pt 2, (Oct) (335-44), ISSN 0022-3751.

Turunen, M.; Olsson, J. & Dallner, G. (2004). Metabolism and function of coenzyme Q. *Biochim Biophys Acta*. 1660, 1-2, (Jan) (171-99), ISSN 0006-3002.

Tsutsumi, S.; Tsuji, K.; Ogawa, K.; Ito, T. & Satake, T. (1988). Effect of dietary salt and cholesterol loading on vascular adrenergic receptors. *Blood vessels*. 25, 5, (209-16), ISSN 0303-6847.

Uçeyler, N.; Valenza, R.; Stock, M.; Schedel, R.; Sprotte, G. & Sommer, C. (2006). Reduced levels of ntiinflammatory cytokines in patients with chronic widespread pain. *Arthritis Rheum*. 54, 8, (Aug) (2656–2664), ISSN 0004-3591.

Vecchiet, J.; Cipollone, F.; Falasca, K.; Mezzetti, A.; Pizzigallo, E.; Bucciarelli, T.; et al.(2003). Relationship between musculoskeletal symptoms and blood markers of oxidative stress in patients with chronic fatigue syndrome. *Neuroscience letters*. 335, 3, (Jan) (151-4), ISSN 0304-3940.

Wallace, D.J.; Linker-Israeli, M.; Hallegua, D.; Silverman, S.; Silver, D. & Weisman, M.H. (2001). Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology (Oxford)*. 40, 7, (Jul) (743-9), ISSN 1462-0324.

Wallace, D.J. (2006). Is there a role for cytokine based therapies in fibromyalgia. *Curr Pharm Des*. 12, 1, (17-22), ISSN 1381-6128.

Wang, Z.Q.; Porreca, F.; Cuzzocrea, S.; Galen, K.; Lightfoot, R.; Masini, E.; et al. (2004). A newly identified role for superoxide in inflammatory pain. *J Pharmacol Exp Ther*. 309, 3, (Jun) (869-78), ISSN 0022-3565.

Werle, E.; Fisher, H.; Muller, A.; et al. (2001). Antibodies against serotonin have no diagnostic relevance in patients with fibromyalgia syndrome. *J Rheumatol*. 28, 3, (Mar) (595–600, ISSN 0315-162X.

Whaley-Connell, A.; McCullough, P.A. & Sowers JR. (2011). The role of oxidative stress in the metabolic syndrome. *Rev Cardiovasc Med*. 12, 1, (21-9), ISSN 1530-6550.

Wiseman, H. (1993). Vitamin D is a membrane antioxidant. Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. *FEBS Lett*. 326, 1-3, (Jul) (285-8), ISSN 0014-5793.

Wolfe, F.; Smythe, H.A.; Yunus, M.B.; Bennett, R.M.; Bombardier, C.; et al. (1990) The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 33, 2, (Feb) (160-72), ISSN 0004-3591.

Yunus, M.; Masi, A.T.; Calabro, J.J.; et al. (1981). Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Semin Arthritis Rheum*. 11, 1, (Aug) (151-71), ISSN 0049-0172.

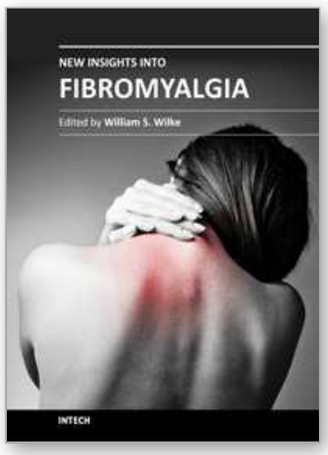
Yunus, M.B.; Kalyan-Raman, U.P.; Kalyan-Raman, K. & Masi, A.T. (1986). Pathologic changes in muscle in primary fibromyalgia syndrome. *Am J Med*. 81, 3A, (Sep) (38-42), ISSN 0002-9343.

Yunus, M.B.; Kalyan-Raman, U.P. & Kalyan-Raman, K. (1988). Primary fibromyalgia syndrome and myofascial pain syndrome: clinical features and muscle pathology. *Arch Phys Med Rehabil*. 69, 6, (Jun) (451-4), ISSN 0003-9993.

Zhang, R. & Naughton, D.P. (2010). Vitamin D in health and disease: current perspectives. *Nutr J*. 8, 9, (Dec) (65), ISSN 1475-2891.

Zhou, C.; Huang, Y. & Przedborski, S. (2008). Oxidative stress in Parkinson's disease: a mechanism of pathogenic and therapeutic significance. *Ann N Y Acad Sci*. 1147, (Dec) (93-104), ISSN 0077-8923.

Zorov, D.B.; Juhaszova, M. & Sollott, S.J. (2006). Mitochondrial ROS-induced ROS release: an update and review. *Biochim Biophys Acta*. 1757, 5-6, (May-Jun) (509-17), ISSN 0006-3002.




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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 Berkley 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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