

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Role of Oxidants/Antioxidants, Mitochondrial Dysfunction, and Autophagy in Fibromyalgia

Alejandra Guillermina Miranda-Díaz and
Simón Quetzalcóatl Rodríguez-Lara

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.70695>

Abstract

Fibromyalgia (FM) is a syndrome that presents primarily in women and is characterized by generalized pain, muscle rigidity, poor quality of sleep, fatigue, cognitive dysfunction, anxiety, episodes of depression, overall sensitivity, and deterioration in the performance of day-to-day activities. In the pathophysiology of fibromyalgia neuroendocrine factors, anomalies of the autonomous nervous system, genetic characteristics, and environmental and psychosocial factors are implicated. Alterations to the cells of the central nervous system that are present in fibromyalgia are due to the toxic effects of free radicals by the high concentrations of polyunsaturated fatty acids of the membranes that are easily oxidized and the low level of protective antioxidant enzymes. In FM, defects are produced in any part of the cycle in the generation of adenosine-5'-triphosphate (ATP) by the mitochondria, which can alter energy production by the mitochondria and cause the characteristic symptoms of FM. The degradation of the mitochondria dependent on autophagy or mitophagy is an important process for maintaining the critical integrity of the mitochondria and limiting the production of reactive oxygen species (ROS). Therefore, the deregulation of autophagy and mitochondrial dysfunction could represent key aspects in the pathophysiology of FM. Management with antioxidants, vitamins, coenzyme Q10, and melatonin, in addition to the antidepressants and structural analogs of the gamma-aminobutyric acid, could modify the florid symptomatology that patients with FM have.

Keywords: fibromyalgia, oxidative stress, mitochondrial dysfunction, autophagy, antioxidants, antioxidant vitamins

1. Introduction

1.1. Fibromyalgia

Fibromyalgia (FM) is a syndrome characterized by generalized pain, muscle rigidity, poor quality of sleep, fatigue, cognitive dysfunction, anxiety, episodes of depression, overall sensitivity, and deterioration in the performance of day-to-day activities [1, 2]. The incidence of FM is higher in women than in men in all decades of life, and it generally appears between 30 and 35 years of age [3, 4]. The prevalence of FM increases with age, reaching a maximum peak around the seventh decade. Fibromyalgia affects about 5% of the population worldwide [5]. According to the classification of the American College of Rheumatology, the definition of FM encompasses two variables: (a) bilateral pain above and below the waist with centralized pain and (b) chronic generalized pain for 3 months with pain on palpation in at least 11 of 18 specific body sites (sensitive spots) [6]. In the presentation of FM alterations to the central and autonomous nervous system, and alterations to the neurotransmitters, hormones, the external immune system, psychiatric conditions, and stress factors are involved [7]. Along with pain there are frequent disturbances in sleep, fatigue, morning rigidity, a subjective sensation of the accumulation of bodily fluids, paresthesias of the extremities, depression, headache, dizziness, and intestinal disturbances, which cause a decrease in quality of life [8]. The current review describes the oxidative stress, mitochondrial alterations, autophagy, antioxidants, and alternatives to the pharmacological management of FM.

1.2. Etiology

The etiology and the pathophysiological mechanisms of FM are still unknown and continue to be a challenging clinical entity for researchers and clinicians [9]. Some studies suggest that the involvement of the hypothalamus-pituitary-adrenal axis and the autonomic nervous system in response to stress is present in patients who are vulnerable to suffering with FM or its symptoms [10]. Neuroendocrine factors, anomalies of the autonomic nervous system, genetic characteristics, environmental changes, psychosocial changes, and oxidative stress are involved in the pathophysiology of FM [11]. There is a high prevalence of FM among relatives of patients who also suffer from it, which is attributed to the combination of environmental and genetic factors [12]. Genetic studies suggest that the association with polymorphisms of the serotonergic, dopaminergic, and catecholaminergic pathways found is implicated in the transmission and modulation of pain [11]. One theory of etiology suggests that infections are capable of activating inflammatory cytokines that could modify the central and peripheral perception of pain in FM. FM is characterized by chronic pain of unknown origin. Evidence suggests that sensitized neurons in the spinal cord of the dorsal horn are responsible for processing increased pain from peripheral nociceptive signals, glial activation, apparently by cytokines and excitatory amino acids that could play a role in the initiation and perpetuation of the pain due to acute or repetitive tissue injury [13]. Three FM subgroups have been described based on the predominant symptoms, depending on the following domains: psychosocial (depression/anxiety), cognitive (catastrophic/pain control), and neurobiology (sensitivity) [14]. The proportion of new patients with FM varies between

10 and 20% in clinics for patients with rheumatic diseases, while in clinics not specialized for rheumatic illnesses the prevalence is >2.1–5.7% [15]. Amitriptyline is the most common prescription drug for the management of FM. Amitriptyline has the ability to influence the autonomic nervous system [16].

2. Oxidative stress

Oxygen is used by the eukaryotic cells for metabolic transformations and the production of energy by the mitochondria. Under physiologic conditions, there is a beneficial endogenous production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that interact as signaling molecules in multiple physiological mechanisms (**Figure 1**). The ROS have bactericide activity of the phagocytes, act in the transduction of signals, and in the regulation of cellular growth and the redox state of the cell, among other mechanisms [17]. When the ROS or RNS are produced in excess or are not eliminated by the antioxidants, the oxidative stress with the capacity to damage the macromolecules (carbohydrates, proteins, lipids, DNA, and organelles) is produced [18, 19]. In relation to FM, it is important to mention that the cells of the central nervous system are highly vulnerable to the toxic effects of free radicals when

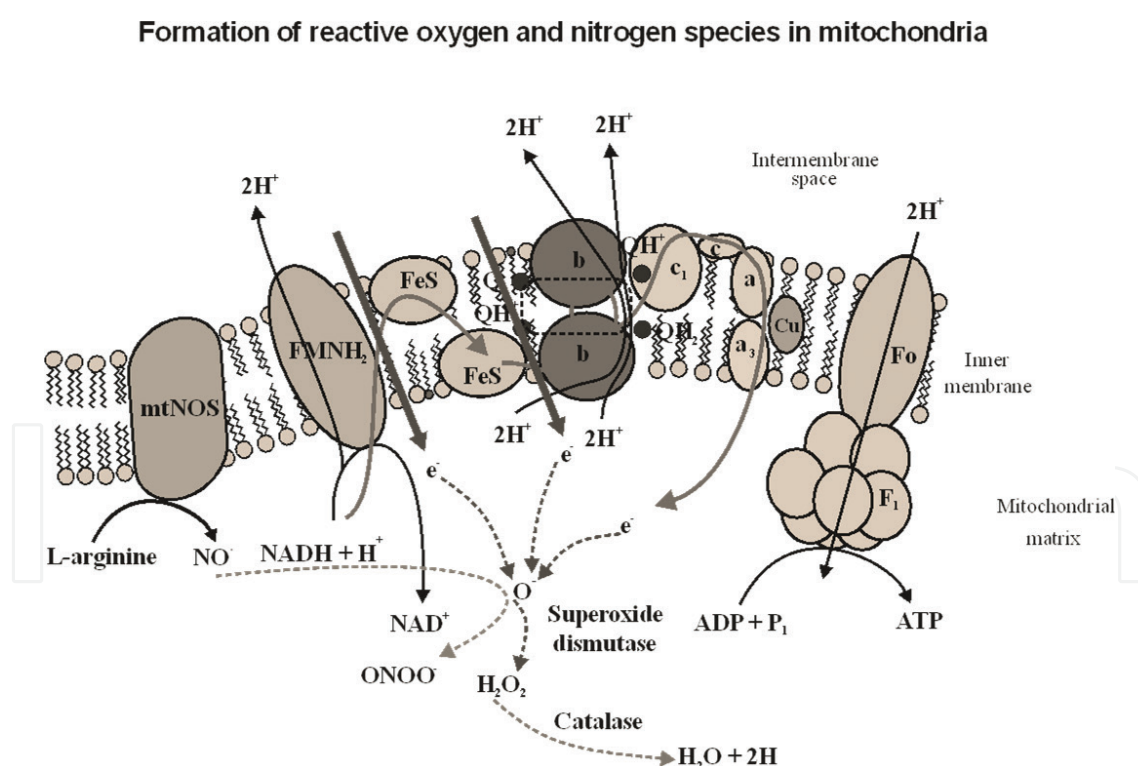


Figure 1. Formation of reactive oxygen and nitrogen species in mitochondria. The process is mediated by oxidative phosphorylation and the activity of the mitochondrial NO synthase: In physiological conditions, the production of ROS and RNS is reduced by multiple enzymatic scavengers that involved SOD, GPx, and catalase. When the mitochondria suffer an insult, the increase of the leakage of electrons to the matrix leads to an overload to the capacity of the enzymatic systems and leads to toxicity of the cell. Vectors of reactions and products. The physiological pathway for formation of oxidative stress. Leakage of electron to matrix. Pathophysiological pathway for formation of ROS and RNS.

compared to other organs in the body because they have a high index of oxidative metabolic activity and a low level of protector antioxidant enzymes, with an anatomical neuronal network that is vulnerable to interruption and high concentrations of polyunsaturated fatty acids of the membrane that are easily oxidized [20]. One of the primary enzyme sources of the superoxide anion (O^{2-}) is the xanthine oxidase. The purine nucleotides are degraded where the phosphate group is lost by the action of the 5'-nucleotidase. The adenosine is deaminated to inosine by the adenosine deaminase (ADA). The inosine is hydrolyzed to produce the purine base hypoxanthine, which is subsequently oxidized to xanthine and later to uric acid by the xanthine oxidase. The xanthine oxidase is an important enzyme that contains iron and molybdenum. The enzyme exists primarily in the form of xanthine dehydrogenase and can convert into xanthine oxidase through diverse conditions including proteolysis, homogenization, and the oxidation of sulfhydryl [21]. Oxidative stress appears to be involved in the severity of symptoms in FM; thus, the antioxidant therapy should be investigated as a possible alternative to adjunct management of FM. Blockage of the production of ROS by the mitochondria offers a new therapeutic strategy to diminish the symptoms of FM and other inflammatory states.

2.1. Lipoperoxides in fibromyalgia

The overproduction of ROS favors lipid peroxidation (LPO) that leads to the oxidative destruction of the polyunsaturated fatty acids, components of the cellular membranes, and favors the production of cytotoxic metabolites and aldehyde reactives [malondialdehyde (MDA) and 4-hydroxynonenal (HNE)] [22]. The MDA and HNE produced in relatively large quantities have an important capacity for diffusion from their site of origin and attack distant objects to form covalent bonds with diverse molecules [23]. Measuring MDA is one popular method in the search for LPO in bodily fluids or cell lysates. In one study reported in 2011, the authors found increased levels of LPO in mononuclear cells associated with the plasma levels of LPO and clinical symptoms of FM, within the pathophysiology of FM [24]. Research in LPO is highly important since the deleterious effects of oxidative stress could be prevented through control of the underlying pathology and the administration of antioxidants or free radical scavengers.

2.2. Nitric oxide in fibromyalgia

The production of nitric oxide (NO) occurs from the L-arginine by the nitric oxide synthase (NOS) (**Figure 2**). The NOS has four isoforms: neuronal (nNOS), inducible (iNOS), endothelial (eNOS), and mitochondrial (mtNOS) [25]. The NO is implicated in physiological processes like: vasodilation, modulation of nociception, immune function, neurotransmission, and excitation-contraction coupling [26]. The NO is considered an atypical neurotransmitter and a second messenger in the nervous system [27] or as a hormone [28]. The majority of the effects of NO are mediated through the activation of the guanylate-cyclase enzyme that produces cyclic guanosine-3,5-monophosphate (cGMP) [29]. The NO has pro-nociceptor properties in the neural crest and in the dorsal root ganglia that positively regulate as a result of cutaneous or visceral inflammation and by the peripheral lesions of the fibers. This effect could be

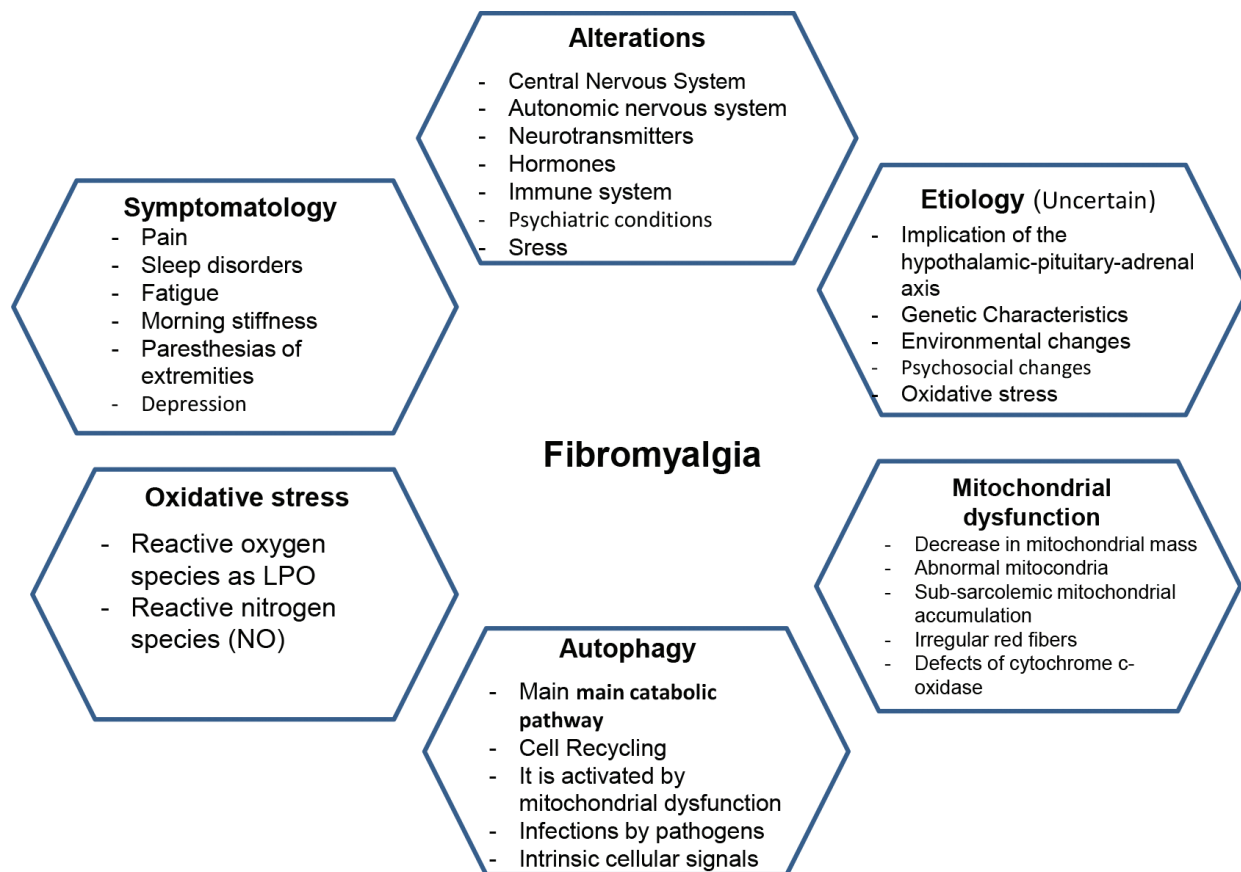


Figure 2. Mechanisms involved in the presentation of fibromyalgia. The alterations involved in the presentation of fibromyalgia. The etiology and symptomatology of the appearance of fibromyalgia and events may be the cause or consequence of having FM.

potentiated or inhibited by the NO donors [29]. In addition, a decrease in capillary volume of the blood vessels, structural disorganization of the capillary endothelium, and structural abnormalities of the mitochondria in histopathology studies of muscles have been reported in FM [30]. The structural damages can contribute to poor oxygen diffusion, less oxidative phosphorylation, and a decrease in the synthesis of ATP, which can increase oxidative stress and LPO of the membrane [31]. Abnormal microcirculation of the skin above sensitive spots in patients with FM has been reported with the use of the laser Doppler flowmetry technique [32]. The results support that local hypoxia and the possible decrease in concentrations of high-energy phosphate result in oxidative stress and LPO of the membrane. Therefore, abnormal microcirculation can be a result of the abnormal regulation of capillary blood flow [33].

3. Mitochondrial alterations in fibromyalgia

Mitochondrial myopathies are disturbances that are characterized by morphological anomalies of the mitochondria in muscles. Mitochondrial problems are found in the most common inherited metabolic illnesses. The patients who suffer from mitochondrial myopathies can

present symptomatology characterized by muscle weakness, pain, fatigue, and exercise intolerance that progressively worsen over time, similar to what happens in patients with FM [34]. Defects in any part of the cycle in the generation of ATP by the mitochondria can alter mitochondrial energy production and cause symptoms [35]. Oxidative stress is implicated in the pathogenesis of FM, which indicates that mitochondrial dysfunction can be associated with FM [36]. In fact, a decrease in the quantity of mitochondrial mass and the coenzyme Q10 (CoQ10) in the production of mitochondrial ROS in mononuclear blood cells has been detected in patients who suffer from FM [37]. Reports of muscle biopsies from the trapezius muscle have shown inflammatory markers, abnormal mitochondria, accumulation of sub-sarcolemma mitochondria, higher incidence of irregular red fibers, and defects of the cytochrome-c oxidase (Complex IV of oxidative phosphorylation) [38]. In addition, the implication of mitochondrial oxidative stress in peripheral nociception described as a predominant symptom mediated by the inflammatory state in FM has been previously reported [39].

4. Autophagy

Autophagy is the process of cellular recycling that promotes energy efficiency through the generation of ATP and mediates damage control through the elimination of organelles and nonfunctional proteins, in regulating the degradation of cytosolic components by the lysosomes [40]. Autophagy is the main catabolic pathway through which macromolecules and organelles of the eukaryotic cells are degraded and recycled. This pathway is activated under conditions of environmental stress and during the development of diverse pathologic situations. Autophagy plays an essential role in the cellular differentiation, development, and response to stress. It is activated during amino acid deprivation and is associated with neurodegenerative illnesses, cancer, pathogenic infections, and myopathies [41]. Autophagy can be induced by diverse causes: mitochondrial dysfunctions, infections of intracellular pathogens, and intrinsic cellular signals. Folded or damaged proteins, the organelles, and the intracellular pathogens are isolated by double membrane vesicles forming autophagosomes, which, on fusing with the lysosomes, convert into autolysosomes to be degraded [42]. Autophagy is an active process that plays the role of cleansing in maintaining the integrity of the intracellular organelles and proteins; however, autophagy is strongly induced by starvation, as in the case of cellular hypoxia, and is a key component in the adaptive response of the cells and organisms to the lack of nutrients, in order to promote cellular survival until the nutrients are made available once more [43]. Thirty-two different genes have been identified in relation to autophagy, obtained by genetic screening in yeasts. Many of these genes can be found in mold, plants, worms, flies, and in mammals, emphasizing, through phylogeny, the importance of the autophagy process in response to starvation [44]. Three types of autophagy that promote proteolytic degradation of the cytosolic components in lysosomes have been defined:

- a. *Macroautophagy*: the cytoplasmic load is given to the lysosomes through a vesicle with a double-layered membrane called an autophagosome, which fuses with the lysosome to form the autolysosome. Macroautophagy is capable of engulfing large structures through selective and nonselective mechanisms.

- b. *Microautophagy*: the cytosolic components are absorbed directly by the lysosome through engulfment by the lysosomal membrane. In microautophagy, large structures can also be ingested through selective and nonselective mechanisms.
- c. *Chaperone-mediated autophagy*: targeted proteins are translocated through the lysosomal membrane forming a complex with protein chaperones (i.e., Hsc-70) that are recognized by the membrane protein 2A associated with the lysosomes of the lysosomal membrane, causing unfolding and degradation [45].

The autophagy mechanism begins with an isolation membrane (phagophore), probably derived from the lipid bilayer originating in the endoplasmic reticulum (ER), and/or through the Golgi apparatus and endosomes [46]. The phagophore expands to engulf intracellular components, isolating protein aggregates, organelles and ribosomes, and forming an autophagosome with a double membrane. The autophagosome matures through fusion with the lysosome, promoting the degradation of the autophagosome content by acidic lysosome proteases. The lysosomal permeases and transporters export amino acids and by-products of degradation to the cytoplasm, where they can be reused for the construction of macromolecules and for metabolism [47]. Selective degradation of the mitochondria mediated by autophagy is called mitophagy [48]. It seems the absence of functional mitochondria produced by metabolic deregulation and autophagy obligates the muscle cells to gain energy without the participation of the Krebs cycle, in comparison to intact mitochondria. The mitochondrial degradation dependent on autophagy or mitophagy is an important process to maintain the critical integrity of the mitochondria and to limit the production of ROS [49]. The deregulation of autophagy and mitochondrial dysfunction could represent key aspects in the pathophysiology of FM [50]. The authors demonstrate that CoQ deficient fibroblasts exhibit increased levels of lysosomal markers (beta-galactosidase, cathepsin, LC3, and Lyso Tracker), and enhanced expression of autophagic genes at both transcriptional and translational levels, indicating the presence of autophagy [51]. CoQ10 deficiency apparently induces autophagy activation in mononuclear blood cells (BMCs) of FM patients by finding increased levels of acid vacuoles in BMCs identified by LysoTracker fluorescence and flow cytometry analysis. The authors suggest restoring mitochondrial functionality with CoQ10 supplementation as demonstrated in *in vitro* studies with decreased lysosomal activity following treatment with CoQ10 [52]. Autophagy is an attractive, strategic target for investigation of bodily fluids or muscle biopsies in patients who suffer FM (**Figure 2**).

5. Managing fibromyalgia

Treatment for FM is a challenge and often requires nonpharmacological and pharmacological treatment [53]. The dietary habits of FM patients are important, and diverse studies have demonstrated improvement of symptoms with the ingestion of healthy, balanced diets [54]. However, the heterogeneity of symptoms that presents in FM deserves individualized treatment. Therapy should include physiotherapy, psychotherapy, pharmacotherapy, and educate the patient on the pathology of FM [55].

5.1. Amitriptyline in fibromyalgia

Amitriptyline is a tricyclic antidepressant known to inhibit the reuptake of serotonin and norepinephrine, and it has been used for a long period of time in the management of neuropathic pain and FM [56]. Amitriptyline is the pharmacological treatment with the most solid evidence in FM management, although exhaustive follow-up for secondary effects is recommended [57]. The administration of the medication is recommended for short periods to control pain. It was previously reported that the administration of 50 mg/day of amitriptyline at bedtime, for 9 weeks, in patients with FM, significantly improved pain, muscle rigidity, and sleep, compared to patients treated with placebo [58]. In another study, 62 patients with FM received 25 mg/day of amitriptyline at bedtime with an additional 500 mg of naproxen x2 daily, or a placebo for 6 weeks. Those who received amitriptyline had significant improvements in pain, sleep disturbances, and fatigue on waking, compared to those who received placebo. The authors did not find significant differences in improvement of pain among patients who only received amitriptyline or amitriptyline with naproxen [59]. The guidelines of the European League Against Rheumatism (EULAR) suggest that the management of FM with low doses of amitriptyline of 25 mg/day improves pain, sleep, and fatigue at 6–8 weeks without finding evidence that the use of 50 mg/day was superior [60]. However, the toxicity induced by amitriptyline implies the early activation of the mitofagia that subsequently changes to apoptosis. Amitriptyline induces mitochondrial dysfunction and oxidative stress in HepG2 cells. Amitriptyline specifically inhibits mitochondrial complex III activity that is associated with decreased mitochondrial membrane potential ($\Delta\Psi_m$) and increased ROS production. Transmission electron microscopy studies revealed structurally abnormal mitochondria that were engulfed by double membrane structures resembling autophagosomes. Pharmacological or genetic inhibition of autophagy exacerbated the deleterious effects of amitriptyline on hepatoma cells and leads to increased apoptosis. These results suggest that mitophagy acts as a mechanism of initial adaptation of cell survival. However, persistent mitochondrial damage induces extensive and lethal mitophagy, autophagic stress, and autophagic permeabilization leading to cell death by apoptosis [61].

5.2. Pregabalin

The postsynaptic NMDA receptors can alter the presynaptic transport of the vesicles that contain neurotransmitters through the NO pathway that diffuses to the presynaptic membrane and alters traffic of the vesicles [67].

5.3. Co-enzyme Q10 (CoQ10)

The CoQ10, a small lipophilic molecule located in the internal mitochondrial membrane, transfers reducing equivalents of the complexes I and II to the complex III of the mitochondrial respiratory chain. The CoQ10 is crucial for the efficiency of the mitochondrial chain, and there is existing evidence that reports CoQ10 as affecting the expression of genes involved in the inflammatory pathways [62]. The presence of mitochondrial dysfunction has been proposed as a relevant fact in the pathogenesis of FM [63]. The mitochondria generate energy primarily in the form of an electrochemical proton gradient that fuels the production of ATP,

ion transport, and metabolism. The mitochondria are the primary sources of ROS in the complexes I and III, together with CoQ10 [64]. Management with CoQ10 could be useful as an alternative treatment in FM; however, more studies are needed to confirm whether the beneficial effect is real. More detailed studies through analysis in double blind placebo-controlled clinical trials are required on the effect of CoQ10 in bodily fluids and/or muscle biopsies [65]. In a study by Alcocer-Gomez E et al. included four patients with FM who measured the visual analogue scale (pain, fatigue and sleep), the Generalized Pain Index, the symptom severity scale and the Scl-90-R using the FM Impact Questionnaire. High-performance liquid chromatography the CoQ10 content of patients with FM, and the authors found that CoQ10 in the four patients had deficiency before the treatment, and after the treatment with CoQ10 patients showed significant improvement in clinical symptoms [66].

6. Antioxidants

Antioxidants, like the superoxide dismutase (SOD), catalase, and the glutathione peroxidase (GPx), are enzymes of the defense system that work to prevent oxidative stress through inactivation of the ROS. The SOD enzyme eliminates the damaging effects of the free radicals through the conversion of the radical $O_2^{\cdot-}$ into hydrogen peroxide (H_2O_2), and the GPx converts H_2O_2 into oxygen and water [67]. The principle intracellular antioxidant enzymes, copper, zinc-SOD (Cu-Zn-SOD) in the cytoplasm, and the manganese-SOD (MnSOD) in the mitochondria, specifically reduce the $O_2^{\cdot-}$ radicals to H_2O_2 . Normally, there is an equilibrium between the ROS and the antioxidants in the cell, in the membranes, and in the extracellular space. However, the antioxidants are overwhelmed by the excessive production of ROS. The ROS attack the polyunsaturated fatty acids of the membrane producing LPO, resulting in alteration to the membrane permeability and changes to the membrane potential. The measurement of thiobarbituric acid reactive substances (TBARS), MDA, or 4-hydroxynonenal is the most common method applied to measure LPO [68]. The central nervous system is especially sensitive to ROS due to its high content of lipids compared to other areas of the body (Figure 1) [34].

6.1. Melatonin

Pain is a dynamic phenomenon resultant of the activity of the endogenous system of excitation and inhibition of pain. The efficiency of the system in FM has been related to the quality of sleep [69]. The relationship between pain and quality of sleep is supported on a neurobiological basis by the neurotransmitters involved: norepinephrine, serotonin, and dopamine [70]. The effect of melatonin on pain has been demonstrated in studies on inflammatory pain in experimental animals with neuropathic pain [71, 72] and in acute and chronic pain in clinical studies [73, 74]. Since the most frequent complaints in patients with FM are sleep alterations, fatigue, and chronic pain, these symptoms could be a consequence of the disruption of melatonin secretion [75]. Additionally, there is information that the serum levels of the precursors to melatonin (tryptophan and serotonin) are diminished in patients with FM [76]. The deficiency of melatonin in FM could explain the lack of reparative sleep and could be a

mechanism involved in the regulation of dysfunctional pain [77]. There have been reports of studies which suggest that melatonin increases the effect of the descending pain inhibitory system, which involves anatomical connections between cortical regions and the brainstem in the human brain [78]. Therefore, the restoration of melatonin could be an additional mechanism to explain the discrepancy of its effect compared to amitriptyline. In a phase II randomized controlled clinical trial, it was demonstrated that the exogenous administration of 10 mg every 24 h of melatonin augmented the endogenous inhibitory system of pain regulation, evaluated by a numerical scale (0–10), and demonstrated that the association between melatonin with amitriptyline gave better results than the amitriptyline alone, as determined by the visual analog pain scale [79]. Another randomized trial demonstrated that the administration of melatonin alone or in combination with fluoxetine (3–5 mg/day) was efficient in treating FM [80]. However, clear and conclusive evidence from clinical trials or prospective cohorts with prolonged follow-up on the effect of melatonin in patients suffering from FM is still lacking. Melatonin behaves as a free radical scavenger and therefore as a potent antioxidant. Melatonin has physical–chemical advantages over other antioxidant molecules. It is a hormone that is found naturally in the body. Melatonin molecules enter all subcellular organs and compartments. Melatonin detoxifies up to 10 Free Radicals [81]. Compared with other antioxidants, melatonin has equal or better efficacy in the protection of tissues from oxidative lesions such as vitamin C and E. Another inherent feature of melatonin is mitochondrial membrane selectivity and may be the most interesting advantage of pineal hormone [82]. Even melatonin is an effective antioxidant in the prevention of hepatotoxicity induced by amitriptyline [83].

7. Vitamins

Vegetarian diets seem to alleviate some symptoms of FM due to a low content of fat and proteins, high levels of fiber, vitamin C, beta-carotenes, minerals (magnesium, potassium, zinc, and selenium), and antioxidants [49].

In the first controlled pilot study to establish the safety and feasibility of intravenous treatment of micronutrients based on water-soluble vitamins and minerals in FM (Myer's cocktail), the authors reported that the majority of subjects experienced alleviation compared to baseline symptomatology, but they did not observe significant differences between the therapy and the placebo, considering the relationship uncertain between the placebo and micronutrients in FM [84]. According to the Brazilian Society of Rheumatology, the ingestion of sugar, salt, fat, and alcohol should be reduced, and the ingestion of fiber, fruits, vegetables, and fluids increased, in order to avoid the appearance of chronic degenerative illnesses and obesity [85]. Specific micronutrients like calcium (Ca) and magnesium (Mg) are important for proper muscular contraction, and the increase in tryptophan intake can be beneficial in the synthesis of serotonin [86]. The combination of vitamins and minerals can reduce the doses of analgesics and improve the sensation of pain in patients with FM [87]. In the majority of subjects with FM, an inadequate intake of vitamin C is observed. In 2003, Richard et al. demonstrated that the prolonged use of analgesics can augment the excretion of potassium and

vitamin C causing anemia from iron deficiency [88]. In the study by Sakarya et al., the authors evaluated blood levels of antioxidant vitamins and Mg in FM patients, and they correlated them with clinical parameters without finding a correlation between the levels of vitamins A, C, E, and Mg with pain severity, functional capacity, and depression. The authors suggest that based on the results, the poor intake of these nutrients does not necessarily signify low blood levels [89]. Folate and vitamin B12 are essential for the regulation of the central nervous system, and their deficiency can result in peripheral neuropathic pain. Vitamin C deficiency can cause myalgia and bone pain, and a deficiency of vitamin D can cause muscle-skeletal pain [90]. The fatigue present in FM seems to have similarities to the manifestations of mild thiamine deficiency [91]. Various similarities have been reported between FM and thiamine deficiency, which include irritability, frequent headache, fatigue, muscular weakness, irritable bowel syndrome, and sleep disturbances. Studies have been published where anomalies in thiamine metabolism have been demonstrated in FM, and investigating thiamine deficiency together with the consumption of alcohol has been suggested in FM patients [92]. The administration of large quantities of oral thiamine increases the blood concentration to levels where the passive transport restores the normal glucose metabolism, and then the normal glucose metabolism of all the organs returns to normal values and symptoms are reduced. It is recommended to prescribe the permanent use of high doses of thiamine in FM [93]. Vitamins A, E, and C are potent nonenzymatic antioxidants [94]. Vitamins A and E are essential fat-soluble vitamins, are the primary chain antioxidants in body tissues, are considered the first line of defense against LPO, they protect the cell membranes early on when the activity of free radicals increases [95]. Vitamin C is the main water-soluble vitamin and is a free radical purifier that transforms vitamin E to its active form [96]. Magnesium (Mg) is a mineral that plays an important role in ATP synthesis and functions in adequate muscle metabolism [97]. Serum levels of Mg have been investigated in FM to reveal etiopathology [98]. Vitamin C is capable of accelerating the degradation of intra- and extracellular proteins targeting lysosomal lumen by autophagic and heterophagic pathways. Vitamin C decreased and stabilized the intra-lysosomal acid pH at values that resulted in maximal activation of the lysosomal hydrolases [99].

7.1. Vitamin D

Vitamin D is a hormone essential for maintaining homeostasis of the muscle-skeletal system. Vitamin D deficiency has been proposed as a factor associated with generalized chronic pain. The majority of vitamin D is produced naturally in the skin after exposure to ultraviolet B light (UVB) producing 25-hydroxyvitamin D (25-OHD). Vitamin D undergoes hydroxylation of the active form 1,25-dihydroxyvitamin D (1,25-OHD) in the liver and kidneys. Age, latitude, time of day, season, skin pigmentation, adiposity, smoking, and amount of exposure to sunlight directly affect the production of vitamin D in the skin [100]. People who are at risk of vitamin D deficiency include people with dark skin, obesity, the elderly, those with chronic degenerative illnesses, or those with disabilities who have little exposure to sunlight [101]. The active form of vitamin D, 1,25-OHD, acts in the cell nucleus (genomic effects caused by gene over-regulation) and the cell membranes (nongenomic effects that cause rapid response) in more than 30 tissues and organs [102]. The muscles are a target organ for the metabolites of vitamin D because they contain receptors for vitamin D identified in the muscle tissues in

humans and animals on producing genomic effects that alter calcium, phosphate, and the metabolism of phospholipids [103]. These changes are important for the normal, functional development of the skeletal musculature. There is evidence that the ingestion of vitamin D improves muscle strength and functional capacity. It should be considered that vitamin D decreases in elderly populations, and supplementation is necessary [104]. Recent studies have centered on the potential therapeutic implications of vitamin D and its deficiency, in the regulation of chronic pain processing in FM, through the interactions of central and peripheral complexes. The primary functional scenario of the interaction is based on the presence of the vitamin D receptor and the 1α -hydroxylase (enzyme that converts the 25-hydroxyvitamin D by hydroxylation to the active 1,25 di-hydroxyl-vitamin D (1,25 (OH) $2D_3$) in many areas of the human central nervous system, among which are: the prefrontal cortex, the amygdala, the raphe, the gelatinous substance, the cerebellum, the hippocampus, the cingulate cortex, the substance *nigra*, the thalamus, and the hypothalamus [105]. Both the receptor and the enzyme have been found in neuronal and glial cells [106]. The general characteristics of hypovitaminosis D are body pain, especially in the shoulder, the thoracic cavity, and lumbar and pelvic regions. The biological relationship between generalized chronic pain and vitamin D deficiency continues to be an interesting investigative topic. Patients with FM could have vitamin D deficiencies due to the characteristics of their pain, poor mobility, or the associated depression that decreases free time exposed to sunlight, or by the increase in adiposity that favors the decrease in vitamin D synthesis. Therefore, the participation of the 1,25-OHD in the regulation of the immune system could be involved in vitamin D deficiency and muscular pain [107]. A systematic review that sought evidence of an association between FM and vitamin D deficiency was inconclusive, without finding improvement in muscular pain after supplementation. However, patients with concurrent risk factors between FM and other pathologies like osteoporosis should be tested in case a vitamin D deficiency is found that would favor muscle strength [108]. The search between vitamin D deficiency and the presence of FM remains an inconclusive matter.

8. Conclusion

In conclusion, oxidative stress, mitochondrial dysfunction, autophagy, multivitamin deficiencies, and the imbalance between oxidants and antioxidants are an intriguing and clinically attractive topic to elucidate the state and progression of FM. Pharmacological treatment alone is insufficient for the majority of patients who suffer from FM syndrome. It is recommended to approach treatment in a multidisciplinary way in clinical practice. Moderate physical activity and the supplementation/ingestion of antioxidants could be beneficial in regulating the oxidative state.

Conflicts of interest

There are no conflicts of interest to report.

This study did not receive any funding.

Author details

Alejandra Guillermina Miranda-Díaz* and Simón Quetzalcóatl Rodríguez-Lara

*Address all correspondence to: kindalex1@outlook.com

Department of Physiology, Institute of Clinical and Experimental Therapeutics, University Health Sciences Centre, University of Guadalajara, Guadalajara, Jalisco, México

References

- [1] Gerdle B, Björk J, Cöster L, Henriksson K, Henriksson C, Bengtsson A. Prevalence of widespread pain and associations with work status: A population study. *BMC Musculoskeletal Disorders*. 2008;**9**:102
- [2] Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskeletal Disorders*. 2007;**8**:27
- [3] Heymann RE, Paiva Edos S, Helfenstein M Jr, Pollak DF, Martinez JE, Provenza JR, Paula AP, Althoff AC, Souza EJ, Neubarth F, Lage LV, Rezende MC, de Assis MR, Lopes ML, Jennings F, Araújo RL, Cristo VV, Costa ED, Kaziyaama HH, Yeng LT, Iamamura M, Saron TR, Nascimento OJ, Kimura LK, Leite VM, Oliveira J, de Araújo GT, Fonseca MC. Brazilian consensus on the treatment of fibromyalgia. *Revista Brasileira de Reumatologia*. 2010;**50**:56-66
- [4] Tornero MJ, Sanmartí SR, Rodríguez VV, Martín ME, Marenco-de la Fuente JL, González AI, Muñoz FS, Gómez-Reino CJ, Carreño PL, Batlle GE, Balsa CA, Andreu JL, Alvaro-Gracia JM, LJA M, Loza SE. Update of the consensus statement of the Spanish Society of Rheumatology on the management of biologic therapies in rheumatoid arthritis. *Reumatologia Clinica*. 2010;**6**(1):23-36
- [5] Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism*. 1995;**38**:19-28
- [6] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis and Rheumatism*. 1990;**33**:160-172
- [7] Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE, Blonna D. Fibromyalgia syndrome: Etiology, pathogenesis, diagnosis, and treatment. *Pain Research and Treatment*. 2012;**2012**:426130
- [8] Gavi MB, Vassalo DV, Amaral FT, Macedo DC, Gava PL, Dantas EM, Valim V. Strengthening exercises improve symptoms and quality of life but do not change autonomic modulation in fibromyalgia: A randomized clinical trial. *PloS One*. 2014;**9**(3):e90767

- [9] Ozgocmen S, Ozyurt H, Sogut S, Akyol O. Current concepts in the pathophysiology of fibromyalgia: The potential role of oxidative stress and nitric oxide. *Rheumatology International*. 2006;**26**(7):5855-5897
- [10] Buskila D, Sarzi-Puttini P. Biology and therapy of fibromyalgia: Genetics aspects of fibromyalgia síndrome. *Arthritis Research & Therapy*. 2006;**8**:218-222
- [11] Bradley LA. Pathophysiology of fibromyalgia. *The American Journal of Medicine*. 2009;**122**:1-13
- [12] Yunus MB, Khan MA, Rawlings KK, Green JR, Olson JM, Shah S. Genetic linkage analysis of multicase families with fibromyalgia syndrome. *The Journal of Rheumatology*. 1999;**26**:408-412
- [13] Staud R. Fibromyalgia pain: Do we know the source? *Current Opinion in Rheumatology*. 2004;**16**(2):157-163
- [14] Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: Presented at the Third World Congress of World Institute of Pain, Barcelona 2004. *Pain Practice*. 2005;**5**(2):85-94
- [15] Wolfe F. Fibromyalgia: The clinical syndrome. *Rheumatic Diseases Clinics of North America*. 1989;**15**:1-18
- [16] Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. Effect of low-dose amitriptyline on autonomic functions and peripheral blood flow in fibromyalgia: A pilot study. *Pain Medicine*. 2012;**13**(1):131-136
- [17] Davies KJ. Oxidative stress: The paradox of aerobic life. *Biochemical Society Symposium*. 1995;**61**:1-31
- [18] Sánchez A, Calpena AC, Clares B. Evaluating the oxidative stress in inflammation: Role of melatonin. *International Journal of Molecular Sciences*. 2015;**16**(8):16981-17004
- [19] Rodríguez-Lara SQ, Cardona-Muñoz EG, Ramírez-Lizardo EJ, Totsuka-Sutto SE, Castillo-Romero A, García-Cobián TA, García-Benavides L. Alternative interventions to prevent oxidative damage following ischemia/reperfusion. *Oxidative Medicine and Cellular Longevity*. 2016;**2016**:1-16. DOI: 10.1155/2016/7190943
- [20] Evans PH. Free radicals in brain metabolism and pathology. *British Medical Bulletin*. 1993;**49**:577-587
- [21] Buskila D, Cohen H, Neumann L, Ebstein RP. An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. *Molecular Psychiatry*. 2004;**9**:730-731
- [22] Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radical Biology & Medicine*. 1991;**11**:81-128
- [23] Clot P, Tabone M, Arico S, Albano E. Monitoring oxidative damage in patients with liver cirrhosis and different daily alcohol intake. *Gut*. 1994;**35**:1637-1643

- [24] Cordero MD, Alcocer-Gómez E, Cano-García FJ, De Miguel M, Carrión AM, Navas P, Sánchez Alcázar JA. Clinical symptoms in fibromyalgia are better associated to lipid peroxidation levels in blood mononuclear cells rather than in plasma. *PloS One*. 2011;**6**(10):e26915
- [25] Ghafourifar P, Cadenas E. Mitochondrial nitric oxide synthase. *Trends in Pharmacological Sciences*. 2005;**26**(4):190-195
- [26] Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: Effect of training in health and cardiovascular disease. *The FASEB Journal*. 2000;**14**(12):1685-1696
- [27] Schulman H. Nitric oxide: A spatial second messenger. *Molecular Psychiatry*. 1999;**2**:296-299
- [28] Ghasemi A, Zahediasl S. Is nitric oxide a hormone? *Iranian Biomedical Journal*. 2011;**15**(3):59-65
- [29] Millan MJ. The induction of pain: An integrative review. *Progress in Neurobiology*. 1999;**57**:1-164
- [30] Lindman R, Hagberg M, Bengtsson A, Henricksson KG, Thornell LE. Capillary structure and mitochondrial volume density in the trapezius muscle of chronic trapezius myalgia, fibromyalgia, and healthy subjects. *J Musculoskelet Pain*. 1995;**3**:5-22
- [31] Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. *Scandinavian Journal of Rheumatology*. 1986;**15**:165-173
- [32] Jeschonnek M, Graohmann G, Hein G, Sprott H. Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia. *Rheumatology*. 2000;**39**:917-921
- [33] Gronemann ST, Ribel-Madsen S, Bartels EM, Danneskiold-Samsøe B, Bliddal H. Collagen and muscle pathology in fibromyalgia patients. *Rheumatology*. 2004;**43**:27-31
- [34] Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, Taylor RW, Bindoff LA, Turnbull DM. The epidemiology of pathogenic mitochondrial DNA mutations. *Annals of Neurology*. 2000;**48**:188-193
- [35] DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *The New England Journal of Medicine*. 2003;**348**:2656-2668
- [36] Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, Cotán D, Gómez Izquierdo L, Bonal P, Campa F, Bullon P, Navas P, Sánchez Alcázar JA. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: Implications in the pathogenesis of the disease. *Arthritis Research & Therapy*. 2011;**12**:R17
- [37] Cordero MD, Moreno-Fernández AM, deMiguel M, Bonal P, Campa F, Jiménez-Jiménez LM, Ruiz-Losada A, Sánchez-Domínguez B, Sánchez Alcázar JA, Salvati L, and Navas P. Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. *Clinical Biochemistry*. 2009;**42**:732-735

- [38] Kalyan-Raman UP, Kalyan-Raman K, Yunus MB, Masi AT. Muscle pathology in primary fibromyalgia syndrome: A light microscopic, histochemical and ultrastructural study. *The Journal of Rheumatology*. 1984;**11**:808-813
- [39] Sánchez-Domínguez B, Bullón P, Román-Malo L, Marín-Aguilar F, Alcocer-Gómez E, Carrión AM, Sánchez-Alcazar JA, Cordero MD. Oxidative stress, mitochondrial dysfunction and, inflammation common events in skin of patients with fibromyalgia. *Mitochondrion*. 2015;**21**:69-75
- [40] Glick D, Barth S, Macleod KF. Autophagy: Cellular and molecular mechanisms. *The Journal of Pathology*. 2010;**2010**(221):3-12
- [41] Cuervo AM. Autophagy: In sickness and in health. *Trends in Cell Biology*. 2004;**14**:70-77
- [42] Scherz-Shouval R, Shvets E, Fass E, Shorer H, Gil L, Elazar Z. Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *The EMBO Journal*. 2007;**26**:1749-1760
- [43] Jin S. Autophagy, mitochondrial quality control and oncogenesis. *Autophagy*. 2006;**2**: 80-84
- [44] Nakatogawa H, Suzuki K, Kamada Y, Ohsumi Y. Dynamics and diversity in autophagy mechanisms: Lessons from yeast. *Nature Reviews. Molecular Cell Biology*. 2009; **10**:458-467
- [45] Saftig P, Beertsen W, Eskelinen EL. LAMP-2 a control step for phagosome and autophagosome maturation. *Autophagy*. 2008;**4**:510-512
- [46] Axe EL, Walker SA, Manifava M, Chandra P, Roderick HL, Habermann A, Griffiths G, Ktistakis NT. Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. *The Journal of Cell Biology*. 2008;**182**:685-687
- [47] Mizushima N. Autophagy: Process and function. *Genes & Development*. 2007;**21**: 2861-2287
- [48] Gomes LC, Scorrano L. Mitochondrial morphology in mitophagy and macroautophagy. *Biochimica et Biophysica Acta*. 1833;**2013**:205-212
- [49] Kim I, Rodriguez-Enriquez S, Lemasters JJ. Selective degradation of mitochondria by mitophagy. *Archives of Biochemistry and Biophysics*. 2007;**462**:245-253
- [50] Oezel L, Then H, Jung AL, Jabari S, Bonaterra GA, Wissniowski TT, Önel SF, Ocker M, Thieme K, Kinscherf R, Di Fazio P. Fibromyalgia syndrome: Metabolic and autophagic processes in intermittent cold stress mice. *Pharmacology Research & Perspectives*. 2016;**4**(5):e00248
- [51] Rodriguez-Hernandez A, Cordero MD, Salviati L, Artuch R, Pineda M, Briones P, Gomez Izquierdo L, Cotan D, Navas P, Sanchez-Alcazar JA. Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. *Autophagy*. 2009;**5**:19-32

- [52] Cordero MD De Miguel M, Fernández AMM, López IMC, Maraver JG, Cotán D, Izquierdo LG, Bonal P, Campa F, Bullon P, Navas P, Alcázar JAS Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: Implications in the pathogenesis of the disease. *Arthritis Research & Therapy*. 2010;**12**(1):R17
- [53] Hassett AL, Gevirtz RN. Nonpharmacologic treatment for fibromyalgia: Patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. *Rheumatic Diseases Clinics of North America*. 2009;**35**:393-407
- [54] Donaldson MS, Speight N, Loomis S. Fibromyalgia syndrome improved using a mostly raw vegetarian diet: An observational study. *BMC Complementary and Alternative Medicine*. 2001;**1**:7
- [55] Turk DC, Okifuji A, Sinclair JD, Starz TW. Differential responses by psychosocial subgroups of fibromyalgia syndrome patients to an interdisciplinary treatment. *Arthritis Care and Research*. 1998;**11**(5):397-404
- [56] Kia S, Choy E. Update on Treatment Guideline in fibromyalgia syndrome with focus on pharmacology. *Biomedicines*. 2017;**5**(2): pii:E20
- [57] Eich W, Häuser W, Friedel E, Klement A, Herrmann M, Petzke F, Offenbächer M, Schiltenswolf M, Sommer C, Tölle T, Henningsen P. Fibromyalgia syndrome. Definition, classification, clinical diagnosis and prognosis. *Zeitschrift für Rheumatologie*. 2008;**67**(8):665-666 668-672, 674-676
- [58] Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. *Arthritis and Rheumatism*. 1994;**37**:32-40
- [59] Scudds RA, McCain GA, Rollman GB, Harth M. Improvements in pain responsiveness in patients with fibrositis after successful treatment with amitriptyline. *The Journal of Rheumatology*. Supplement. 1989;**19**:98-103
- [60] Nishishinya B, Urrútia G, Walitt B, Rodriguez A, Bonfill X, Alegre C, Darko G. Amitriptyline in the treatment of fibromyalgia: A systematic review of its efficacy. *Rheumatology*. 2008;**47**:1741-1174
- [61] Villanueva-Paz M, Cordero MD, Pavón AD, Vega BC, Cotán D, De la Mata M, Oropesa-Ávila M, Alcocer-Gomez E, de Laveria I, Garrido-Maraver J, Carrascosa J, Zaderenko AP, Muntané J, de Miguel M, Sánchez-Alcázar JA. Amitriptyline induces mitophagy that precedes apoptosis in human HepG2 cells. *Genes & Cancer* 2016;**7**(7-8):260-277
- [62] Schmelzer C, Lindner I, Rimbach G, Niklowitz P, Menke T, Döring F. Functions of coenzyme Q10 in inflammation and gene expression. *BioFactors*. 2008;**32**:179-183
- [63] Cordero MD, de Miguel M, Moreno-Fernández AM. Mitochondrial dysfunction in fibromyalgia and its implication in the pathogenesis of disease. *Medicina Clínica (Barcelona)* 2011;**136**(6):252-256

- [64] Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. *Biochimica et Biophysica Acta*. 1990;2004:171-199
- [65] Quinzii CM, Lopez LC, Von-Moltke J, Naini A, Krishna S, Schuelke M, Salviati L, Navas P, Dimauro S, Hirano M. Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. *The FASEB Journal*. 2008;22:1874-1885
- [66] Alcocer-Gómez E, Cano-García FJ, Cordero MD. Effect of coenzyme Q10 evaluated by 1990 and 2010 ACR diagnostic criteria for fibromyalgia and SCL-90-R: Four case reports and literature review. *Nutrition*. 2013;29(11-12):1422-1425
- [67] Battin EE, Brumaghim JL. Antioxidant activity of Sulfur and selenium: A review of reactive oxygen species scavenging, glutathione peroxidase, and metal-binding antioxidant mechanisms. *Cell Biochemistry and Biophysics*. 2009;55:1-23
- [68] Söğüt S, Zoroğlu SS, Ozyurt H, Yilmaz HR, Ozuğurlu F, Sivasli E, Yetkin O, Yanik M, Tutkun H, Savaş HA, Tarakçıoğlu M, Akyol O. Changes in nitric oxide levels and antioxidant enzyme activities may have a role in the pathophysiological mechanisms involved in autism. *Clinica Chimica Acta*. 2003;331:111-117
- [69] Paul-Savoie E, Marchand S, Morin M, Bourgault P, Brissette N, Rattanaovong V, Cloutier C, Bissonnette A, Potvin S. Is the deficit in pain inhibition in fibromyalgia influenced by sleep impairments? *Open Rheumatology Journal*. 2012;6:296-302
- [70] Wood PB, Glabus MF, Simpson R, Patterson JC. Changes in gray matter density in fibromyalgia: Correlation with dopamine metabolism. *The Journal of Pain*. 2009;10:609-618
- [71] Laste G, Vidor L, de Macedo IC, Rozisky JR, Medeiros L, de Souza A, Meurer L, de Souza IC, Torres IL, Caumo W. Melatonin treatment entrains the rest-activity circadian rhythm in rats with chronic inflammation. *Chronobiology International*. 2013;30:1077-1088
- [72] Esposito E, Cuzzocrea S. Antiinflammatory activity of melatonin in central nervous system. *Current Neuropharmacology*. 2010;8:228-242
- [73] Caumo W, Torres F, Moreira NL, Auzani JA, Monteiro CA, Londero G, Ribeiro DF, Hidalgo MP. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesthesia and Analgesia*. 2007;105:1263-1271
- [74] Schwertner A, Conceição Dos Santos CC, Costa GD, Deitos A, de Souza A, de Souza IC, Torres IL, da Cunha Filho JS, Caumo W. Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial. *Pain*. 2013;154:874-881
- [75] Bazzichi L, Rossi A, Giacomelli C, Bombardieri S. Exploring the abyss of fibromyalgia biomarkers. *Clinical and Experimental Rheumatology*. 2010;28:S125-S130
- [76] Yunus MB. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis and Rheumatism*. 2007;36:339-356

- [77] Wikner J, Hirsch U, Wetterberg L, Röjdmarm S. Fibromyalgia—a syndrome associated with decreased nocturnal melatonin secretion. *Clinical Endocrinology*. 1998;**49**:179-183
- [78] Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: A diffusion tensor imaging study in healthy controls. *Pain*. 2006;**123**:169-178
- [79] de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, Xavier F, de Souza IC, Deitos A, Torres IL, Caumo W. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: A phase II, randomized, double-dummy, controlled trial. *BMC Pharmacology and Toxicology*. 2014;**15**:1-14
- [80] Hussain SA, Al-Khalifa II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. *Journal of Pineal Research*. 2011;**50**:267-271
- [81] Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ. One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species. *Journal of Pineal Research*. 2007;**42**:28-42
- [82] Dragicevic N, Copes N, O'Neal-Moffitt G, Jin J, Buzzeo R, Mamcarz M, Tan J, Cao C, Olcese JM, Arendash GW, et al. Melatonin treatment restores mitochondrial function in Alzheimer's mice: A mitochondrial protective role of melatonin membrane receptor signaling. *Journal of Pineal Research*. 2011;**51**:75-86
- [83] Taziki S, Sattari MR, Dastmalchi S, Eghbal MA. Cytoprotective effects of melatonin against amitriptyline-induced toxicity in isolated rat hepatocytes. *Advanced Pharmaceutical Bulletin*. 2015;**5**(3):329-334
- [84] Ali A, Njike VY, Northrup V, Sabina AB, Williams AL, Liberti LS, Perlman AI, Adelson H, Katz DL. Intravenous micronutrient therapy (Myers' cocktail) for fibromyalgia: A placebo-controlled pilot study. *Journal of Alternative and Complementary Medicine*. 2009;**15**(3):247-257
- [85] Sociedade Brasileira de Reumatologia – SBR. Dieta. Available from: http://www.fibromialgia.com.br/novosite/index.php?modulo=pacientes_artigos&id_mat_mat=11&id_mat=10. [Accessed: June 16, 2017]
- [86] Kim YS, Kim KM, Lee DJ, Kim BT, Park SB, Cho DY, Suh CH, Kim HA, Park RW, Joo NS. Women with fibromyalgia have lower levels of calcium, magnesium, iron and manganese in hair mineral analysis. *Journal of Korean Medical Science*. 2011;**26**(10):1253-1257
- [87] Batista ED, Andretta A, de Miranda RC, Nehring J, Dos Santos Paiva E, Schieferdecker ME. Food intake assessment and quality of life in women with fibromyalgia. *Revista Brasileira de Reumatologia (English Edition)*. 2016;**56**(2):105-110
- [88] Rokyta R, Holecek V, Pekárkova I, Krejcová J, Racek J, Trefil L, Yamamotová A. Free radicals after painful stimulation are influenced by antioxidants and analgesics. *Neuro Endocrinology Letters*. 2003;**24**(5):304-309

- [89] Sakarya ST, Akyol Y, Bedir A, Canturk F. The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. *Clinical Rheumatology*. 2011;**30**(8):1039-1043
- [90] Bell RF, Borzan J, Kalso E, Simonnet G. Food, pain, and drugs: Does it matter what pain patients eat? *Pain*. 2012;**153**(10):1993-1996
- [91] World Health Organization. Thiamine deficiency and its prevention and control in major emergencies. Geneva: Department of Nutrition for Health and Development, WHO; 1999 Report No: WHO/NHD/99.13
- [92] Monroe BA. Fibromyalgia—A hidden link? *Journal of the American College of Nutrition*. 2013;**1998**:300-303
- [93] Lonsdale D. A review of the biochemistry, metabolism and clinical benefits of thiamin (e) and its derivatives. *Evidence-Based Complementary and Alternative Medicine*. 2013;**2006**:49-59
- [94] Nazıroğlu M, Şimşek M, Kutlu M. Moderate exercise with dietary vitamin C and E combination protects streptozotocin-induced oxidative damage to the blood and improves fetal outcomes in pregnant rats. *Clinical Chemistry and Laboratory Medicine*. 2004;**42**:511-517
- [95] Packer L, Landvik S. Vitamin E in biological systems. *Advances in Experimental Medicine and Biology*. 1990;**264**:93-103
- [96] Sies H, Stahl W. Vitamins E and C, β -carotene, and other carotenoids as antioxidants. *The American Journal of Clinical Nutrition*. 1995 Dec;**62**(6):1315S-1321S
- [97] Romano TJ, Stiller JW. Magnesium deficiency in fibromyalgia syndrome. *Journal of Nutritional Medicine*. 1994;**4**:165-166
- [98] Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. *Rheumatology International*. 2008;**28**:1117-1121
- [99] Martin A, Joseph JA, Cuervo AM. Stimulatory effect of vitamin C on autophagy in glial cells. *Journal of Neurochemistry*. 2002;**82**(3):538-549
- [100] Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, Ylikomi T. An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. *The American Journal of Clinical Nutrition*. 2007;**86**:714-717
- [101] McCabe PS, Pye SR, Mc Beth J, Lee DM, Tajar A, Bartfai G, Boonen S, Bouillon R, Casanueva F, Finn JD, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Pendleton N, Punab M, Vanderschueren D, Wu FC, O'Neill TW, EMAS Study Group. Low vitamin D and the risk of developing chronic widespread pain: Results from the European male ageing study. *BMC Musculoskeletal Disorders*. 2016;**17**:32

- [102] Norman AW. From vitamin D to hormone D: Fundamentals of the vitamin D endocrine system essential for good health. *The American Journal of Clinical Nutrition*. 2008;**88**:491S-4499
- [103] Ceglia L. Vitamin D and its role in skeletal muscle. *Calcified Tissue International*. 2013;**92**(2):151-156
- [104] Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis International*. 2009;**20**:315-322
- [105] Jirikowski GF, Kaunzner UW, Dief Ael E, Caldwell JD. Distribution of vitamin D binding protein expressing neurons in the rat hypothalamus. *Histochemistry and Cell Biology*. 2009;**131**:365-370
- [106] Shipton EA, Shipton EE. Vitamin D and pain: Vitamin D and its role in the aetiology and maintenance of chronic pain states and associated comorbidities. *Pain Research and Treatment*. 2015;**2015**:904967
- [107] Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hyppönen E. Vitamin D and chronic widespread pain in a white middle-aged British population: Evidence from a cross-sectional population survey. *Annals of the Rheumatic Diseases*. 2009;**68**:817-822
- [108] Daniel D, Pirotta MV. Fibromyalgia. Should we be testing and treating for vitamin D deficiency? *Australian Family Physician*. 2011;**40**(9):712-716

IntechOpen

