Chapter 2

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

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Additional information is available at the end of the chapter

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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 serotoninergic, 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

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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

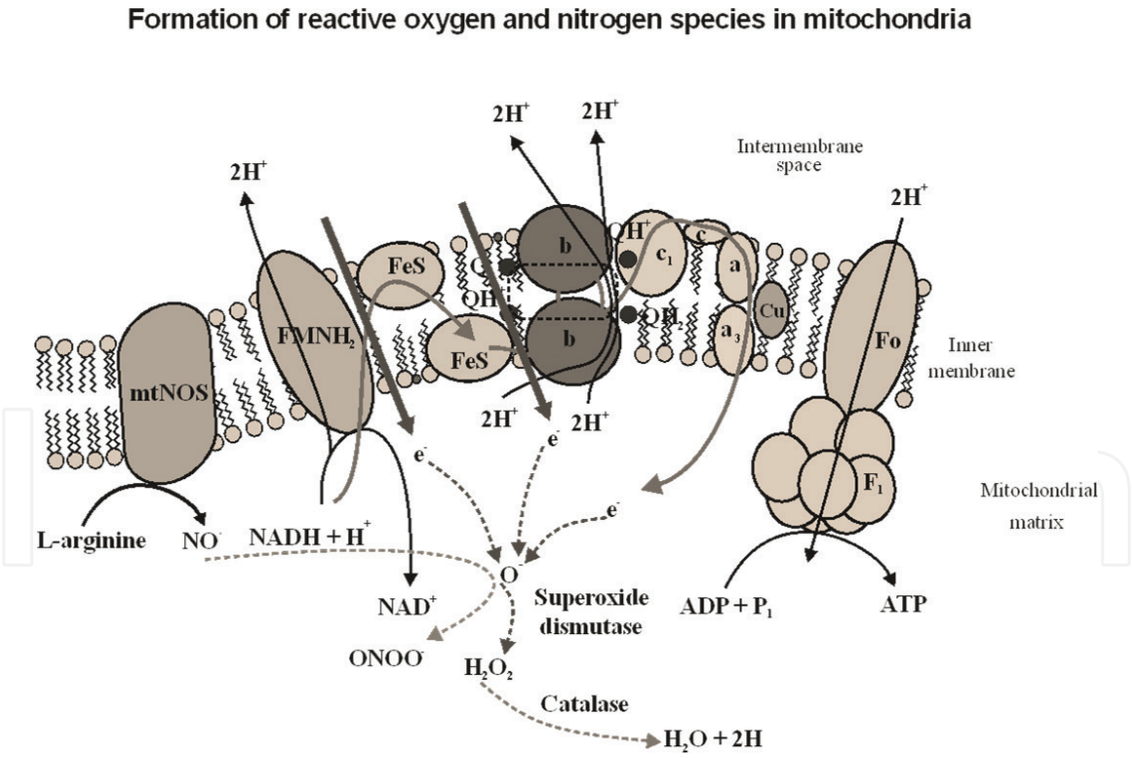

Figure 1. Formation of reactive oxygen and nitrogen species in mitochondria. The process is mediated by oxidative phosphorylation and the activity of the mitochondrial NO synthase: In physiological conditions, the production of ROS and RNS is reduced by multiple enzymatic scavengers that involved SOD, 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

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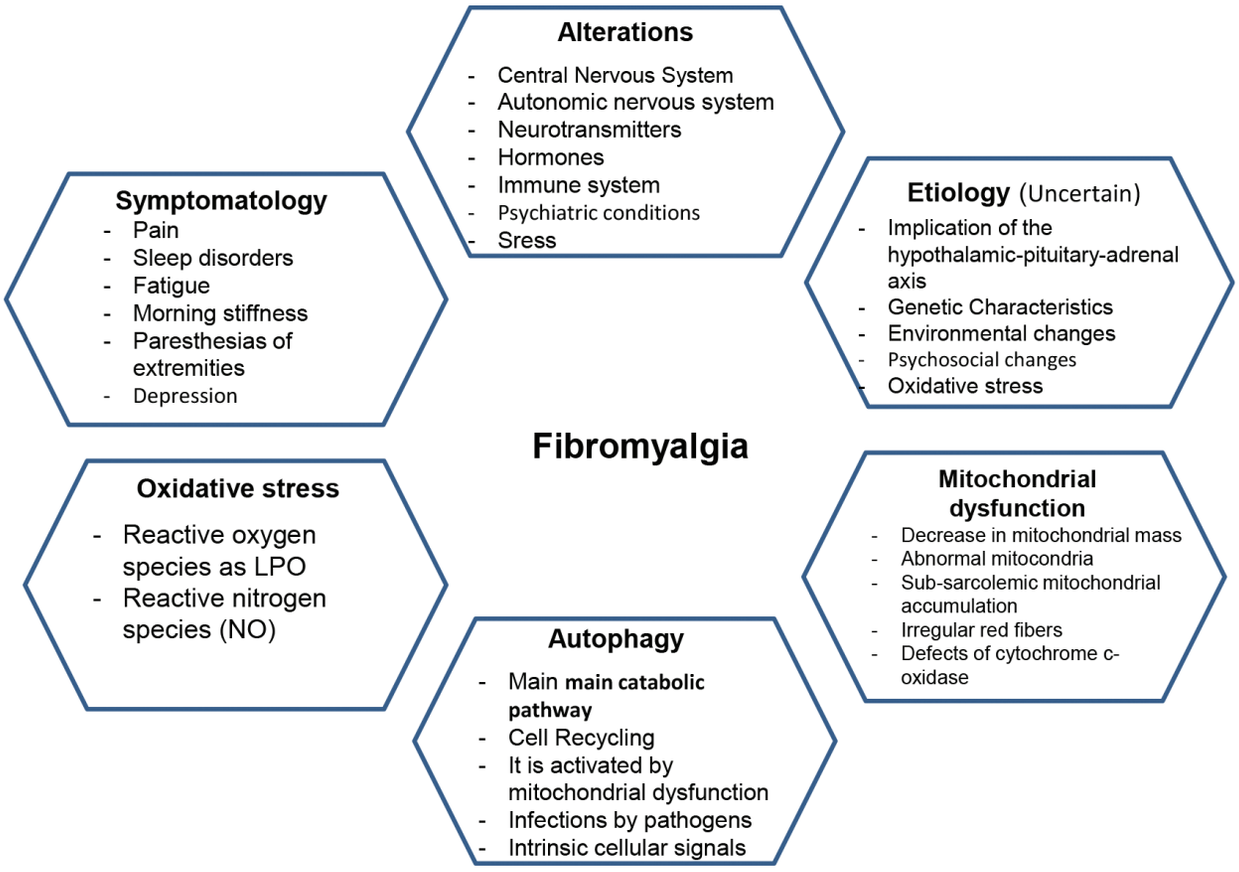

Figure 2. Mechanisms involved in the presentation of fibromyalgia. The alterations involved in the presentation of fibromyalgia. The etiology and symptomatology of the appearance of fibromyalgia and events may be the cause or consequence of having FM.

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 liposomes [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 exhibite 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,

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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 defiecincy 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-} 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-} 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) 2D3) 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.

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