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Editorial

Oxidative Stress in Fibromyalgia: Pathophysiology and Clinical Implications☆

Estrés oxidativo en la fibromialgia: fisiopatología e implicaciones clínicas

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In general, oxidative stress is defined as the imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and antioxidant defense mechanisms. These toxic molecules become highly reactive in their formation because of their altered number of unpaired valence electrons. It corresponds to the mitochondria to be the main producer of ROS, generating the bulk of the respiratory chain complexes I and III, following the flow of electrons between the two complexes. However, the production of ROS under physiological conditions becomes essential for maintaining life and a baseline level of ROS are involved in numerous mechanisms such as bactericidal activity of phagocytes or signal transduction, regulation of cell growth or the redox state of cells, including others.[1] High levels of oxidative stress have been implicated as the primary and/or secondary event in numerous diseases such as rheumatoid arthritis, Parkinson's, Alzheimer's, atherosclerosis, cardiovascular diseases and diabetes mellitus.[2]

Oxidative Stress in Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome accompanied by other symptoms such as depression, anxiety, fatigue or sleep disturbances. The diagnosis is based on the classification criteria established by the American College of Rheumatology 1990 (ACR). In Spain it has a high prevalence: 2.4% of the population over 20 years and a greater presence in women than in men, with a ratio of 21:1.[3] Despite its high prevalence, its etiology is still unknown and there are no effective treatments.

In recent years oxidative stress has taken a leading role in the pathophysiology of FM.

Lipid peroxidation (LP) and carbonylated proteins, end products of membrane damage induced by ROS, are increased in the plasma of patients with FM.[4,5] Furthermore, total antioxidant capacity or antioxidant enzymes such as superoxide dismutase (SOD) and catalase are decreased in the plasma of patients with FM.[4–6] Research has been directed to the plasma or serum of patients as a study model, with a need for cellular models, as this is the place where activation and control of the ROS-producing machinery occur. In this regard, hydrogen peroxide (H_2O_2), as one of the free oxygen radicals that results from the oxygen of the ROS, has been found increased in neutrophils of patients with FM. Similarly, high levels of superoxide of mitochondrial origin (O_2^-) have been observed in the peripheral blood mononuclear cells of patients with FM7. In this model, patients had low levels of CoQ_{10}, a vital element in the mitochondrial respiratory chain whose primary mission is the electron transport from complexes I and II to III, in addition to regulating the coupling of proteins, the pore transition and mitochondrial β-oxidation of fatty acids, an important antioxidant and membrane, so that a deficiency of the cell induces a drop in the activity of complex II + III, complex III, and complex IV, plus reduces the expression of mitochondrial proteins involved in oxidative phosphorylation, decreases mitochondrial membrane potential and increases the production of ROS.[7]

But, from a physiological point of view, what relationship exists between oxidative stress and the symptoms of FM? It is known that the PL reflects the intracellular production of ROS, and it is known that ROS are involved in the etiology of one of the major symptoms of fibromyalgia: pain. The superoxide radical plays an important role in the development of pain on one side by peripheral and central nervous system sensitization and thus induces an alteration of nociception, and on the other hand contributes to it through the activation of several cytokines such as TNF-α, IL-1β, and IL-68. The role of cytokines in FM has been widely discussed, although not as an etiologic mechanism, but as a factor in the worsening of symptoms.[8,9] Although the mechanisms by which oxidative stress can alter muscle sensitivity are still unknown, it is possible that oxidative damage interferes with the muscles by reducing local nociceptors, which causes a decrease in the pain[10] threshold. On the other hand, PL has been associated

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with a typical symptom of FM: fatigue. High levels of LP, as well as an interesting correlation with this symptom, have been demonstrated in chronic fatigue syndrome, a disease with a high rate of comorbidity with FM.[8] Another characteristic of FM symptoms: depression, has shown a high correlation between LP in erythrocytes of patients with major depression and values obtained on the Hamilton depression[8] scale, a result consistent with those obtained in FM[4]. Interestingly, significant correlations are observed between the levels of antioxidants in both plasma and serum with respect to the score on a visual analogue pain scale, and the degree of morning stiffness by patients.[5,6] On the other hand, LP in serum has demonstrated a high degree of correlation with the level of depression presented by patients with FM4, which shows the relationship between the balance of oxidants/antioxidants and symptoms of fibromyalgia.

Clinical Implications of Oxidative Stress in Fibromyalgia

From a clinical standpoint, we want to focus on one aspect of FM which still is largely uncertain and is one of the main problems of this disease: lack of effective treatments. This leads the specialists to treat the symptoms of the disease rather than its causes, sometimes leading to a worsening of the disorders side-effects, and in many cases, these drugs induce an increase in oxidative stress. CoQ_{10} has been shown in in vitro experiments with peripheral blood mononuclear cells of patients with FM, either through its antioxidant role or by offsetting the deficit significantly, to reduce ROS levels and to induce a mitochondrial degradation pathway known as autophagic mitophagia.[7] This result, in spite of being an in vitro finding, could provide insights into the beneficial effect obtained in patients after administration of CoQ_{10} along with Gingko biloba shown by a pilot study in which there was a significant improvement in quality of life of patients.[11] Fatigue, one of the most typical symptoms of FM, has been reduced by treatment with CoQ_{10} in both animal and human physical fatigue models after exercise.[12,13] It should also be noted that CoQ_{10} has been shown to reduce muscle pain induced by statins in patients,[14] and animal models have proven an anti-inflammatory and antinociceptive effect,[15] and CoQ_{10} has recently been observed to regulate the expression of certain pro-inflammatory cytokine genes such as TNF-α,[16] whose role has already been described in FM.[9] On the other hand, melatonin, an important molecule endogenously synthesized by the body and with antioxidant properties, has been shown to reduce pain levels in FM, as well as more complex and typical symptoms of this disease such as depression, anxiety or sleeping disturbances.[17]

Antioxidant therapies have proven effective in many pathological processes in which oxidative stress plays an important role both primarily as secondarily. CoQ_{10}, Vitamin E or alpha-tocopherol, vitamin C or ascorbic acid, melatonin, SOD, vitamin A or retinol, glutathione, N-acetylcysteine, etc., are some of the antioxidants used in randomized trials of patients with a variety of diseases or co-treatment with drugs that induce side-effects, such as chemotherapy. CoQ_{10} has been applied successfully in clinical trials in pathological processes such as Parkinson,[18] Alzheimer,[19] Friedreich's ataxia,[20] migrane,[21] human disorder due to deficiency of CoQ_{10},[22] cardiomyopathy[23] or statin induced myopathies.[14] The lack of results showing negative side-effects or some degree of interference with other treatments in a good way to endorse the use of antioxidant therapies. However, in the case of FM, there are still no double blind and placebo controlled trials in which the possible mechanisms demonstrate the benefits of these therapies in general and of CoQ_{10} in particular. The sheer complexity of this disease makes it difficult to assess effectiveness of a single treatment, thus requiring a multidisciplinary therapeutic approach in which the use of antioxidants would acquire a role as co-treatment. Although oxidative stress in the FM is an accepted fact, its role in the disease from a physiological point of view is not yet clear, and the mechanism by which high levels of free radicals, low levels of antioxidants or both processes simultaneously can have effects on the worsening of symptoms is still unknown. Therefore, further studies are necessary in this regard, as well as the design of controlled trials on the therapeutic effect of antioxidants.

Conflict of Interest

The authors have no conflict of interest to declare.

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