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ORIGINAL ARTICLE

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Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder?

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Abstract The role of free radicals in fibromyalgia is controversial. In this study, 85 female patients with primary fibromyalgia and 80 age-, height-, and weight-matched healthy women were evaluated for oxidant/antioxidant balance. Malondialdehyde is a toxic metabolite of lipid peroxidation used as a marker of free radical damage. Superoxide dismutase is an intracellular antioxidant enzyme and shows antioxidant capacity. Pain was assessed by visual analog scale. Tender points were assessed by palpation. Age, smoking, body mass index (BMI), and duration of disease were also recorded. Malondialdehyde levels were significantly higher and superoxide dismutase levels significantly lower in fibromyalgic patients than controls. Age, BMI, smoking, and duration of disease did not affect these parameters. We found no correlation between pain and number of tender points. In conclusion, oxidant/antioxidant balances were changed in fibromyalgia. Increased free radical levels may be responsible for the development of fibromyalgia. These findings may support the hypothesis of fibromyalgia as an oxidative disorder.

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Introduction

Fibromyalgia is a chronic musculoskeletal syndrome characterized by diffuse pain, stiffness, and tenderness of specific anatomic sites which are called tender points. Fatigue, headache, sleep disturbances, irritable bowel syndrome, and depression usually accompany the disease [1]. The prevalence is 1–2%, and most of the patients are female (89%) [2]. The etiology of fibromyalgia is still unknown. Recently, local hypoxia was postulated as playing an etiologic role in the development of the symptoms, and clinical, morphologic, and biochemical investigations seem compatible with this theory [3].

Free radicals or reactive oxygen species are produced as a consequence of redox reactions and controlled by antioxidative defense mechanisms. Antioxidants are enzymatic, as with superoxide dismutase, glutathione peroxidase, and catalase, or nonenzymatic, as with ascorbic acid, alpha tocopherol, and glutation. Many conditions such as lipid peroxidation, protein degradation, and DNA damage leading to tissue destruction and changes in membrane permeability might result from imbalances between free radicals and antioxidant levels [4]. Free radicals are blamed for the etiopathogenesis of aging, atherosclerosis, carcinogenesis, infarction, osteoporosis [5], and muscle diseases [6].

Malondialdehyde (MDA) is the end product of lipid peroxidation and has been used widely as a marker of free radical damage on lipid molecules [7]. Malondialdehyde levels may affect the mitochondrial oxidation chain reaction, cell membrane permeability, and cell excitability. Dib [8] suggested that MDA might be used as a biological marker for neurodegenerative disease. The toxic effect of MDA was neutralized by antioxidants. Superoxide dismutase (SOD) enzyme presents in all cells and catalyzes the conversion of superoxide free radicals to oxygen and hydrogen peroxide. It is the most

powerful antioxidant produced by the body and has been used as a marker of antioxidant defense [9].

The role of the oxidant/antioxidant balance in fibromyalgia is unknown. Evidence has been shown of oxidative metabolism disorder of muscle in chronic fatigue syndrome (CFS) and fibromyalgia complex. Biochemical evidence for anaerobic metabolism and lactosis was also found in CFS-fibromyalgic patients [10].

In this study, we investigated the oxidant/antioxidant status in patients with fibromyalgia. We designed it thinking that, if a balance discordance were found, fibromyalgia might be an oxidative disorder.

Materials and methods

Eighty-five female patients diagnosed with primary fibromyalgia according to American College of Rheumatology criteria and 80 healthy, age-, weight-, and height-matched women were evaluated. Patients with thyroid function disorders, hypertension, diabetes mellitus, liver and renal dysfunction, anemia, osteoporosis, or inflammatory arthritis were excluded. All patients' routine blood, sedimentation, C-reactive protein, thyroid, liver, and kidney function tests and sex hormone profiles were evaluated. The pain was assessed by visual analog scale (VAS) [11]. Tender points were assessed by digital/thumb palpation (4 kg) on specific points of the muscle, and the numbers of tender points was recorded along with body mass index (BMI), smoking, and duration of disease.

Determination of serum malondialdehyde

The MDA levels were determined by thiobarbituric acid reaction according to Hiroshi and Yagi [12]. The principle of this reaction depends on measurement of the pink color produced by interaction of the barbituric acid with malondialdehyde elaborated as a result of lipid peroxidation. The colored reaction 1,1,3,3 tetraetoxypropane was used as the primary standard.

Determination of serum superoxide dismutase

Pyrogallol auto-oxidizes rapidly in aqueous solution to produce a yellow color that can be read at 420 nm. This process is dependent on the presence of superoxide anions. The SOD enzyme inhibits the auto-oxidation of pyrogallol by catalyzing the breakdown of superoxide. The inhibition of pyrogallol oxidation by SOD is monitored at 420 nm, and the amount of enzyme producing 50% inhibition was defined as one unit of enzyme activity [13].

Statistical analysis

All statistic analyses were performed using version 9.0 SPSS software (SPSS, Chicago, Ill., USA), and the results were given as means ± SD. Levene's test was used to investigate the variance homogeneity between groups. Student's *t*-test was used compare means of MDA and SOD levels between the patient and control groups. Pearson's correlation test was used to investigate the relationship between age, BMI, disease duration, VAS, number of tender points, and MDA and SOD levels. $P < 0.05$ was accepted as significant.

Results

There was no difference between patient and control age or BMI according to Levene's test. The characteristic findings of both groups are presented in Table 1. The number of tender points was 11–15 in 70% of the patients, and the number of smokers was 14. Malondialdehyde levels were significantly higher ($P = 0.000$) and SOD levels significantly lower ($P = 0.000$) in fibromyalgia patients than controls. No relationship was found between VAS, number of tender points, and MDA or SOD levels ($P > 0.05$). Also, MDA and SOD levels did not correlate with age, BMI, or duration of disease ($P > 0.05$).

Discussion

In this study, we found that serum malondialdehyde levels were higher and superoxide dismutase levels lower in patients with fibromyalgia. These results suggest that an imbalance exists in oxidant/antioxidant levels in fibromyalgia.

In recent years, oxidant/antioxidant balance and its effects on the organism have gained much attention. The increase in toxic reactive oxygen metabolites and decrease in antioxidant defense mechanisms are defined as oxidative stress and have resulted in local tissue injury, organ dysfunction, and many disorders such as inflammation, carcinogenesis, lung and pancreatic diseases, diabetes mellitus, rheumatoid arthritis, peptic ulcer, and atherosclerosis [14, 15].

Recently, the role of free radical-mediated oxidative damage was investigated in the etiopathogenesis of fibromyalgia. Fassbender [16] suggested that muscle tender points in fibromyalgia result from local hypoxia. Lund [17] showed abnormal oxygen pressure at the muscle surface above trigger points. Jeschonneck [18] also described microcirculatory disturbances in tender points. Bengtsson [19] investigated oxidative metabolism and found that adenosine diphosphate and phosphoryl creatine levels decreased and adenosine monophosphate and creatine levels increased in fibromyalgic patients. The different methods used in the above studies lead to the emphasis on oxidative stress as a basic pathologic process in fibromyalgia.

There are limited data about the oxidant/antioxidant status in fibromyalgia. This issue was investigated only by Eisinger [20, 21]. He examined malondialdehyde

Table 1 Characteristic findings of the patient and control groups

	Fibromyalgia ($n = 85$)	Control ($n = 80$)	P*
Age (years)	39.32 ± 7.66	37.76 ± 5.84	0.146
BMI (kg/m^2)	26.02 ± 3.68	25.05 ± 3.73	0.098
Duration of disease (years)	4.11 ± 3.55		
VAS	5.16 ± 2.3	0.5 ± 0.85	
N tender points	11.79 ± 3.02	3.2 ± 2.1	
MDA (nmol/ml)	4.33 ± 1.00	2.1 ± 0.59	0.000
SOD (U/l)	11,862.1 ± 1,354.2	14,181.45 ± 2,462.48	0.000

*$P < 0.05$ accepted as significant

levels, protein carbonyls, and antioxidant status in 23 female patients with fibromyalgia. Although he was able to show protein peroxidation in them, he found no difference in malondialdehyde levels between patient and control groups. However, the significance of his study is limited because of the small number of patients. In another study, lower levels were shown of adenosine triphosphate and lactate dehydrogenase, a muscular isoenzyme in fibromyalgic patients [22]. Findings from these studies, although unable to demonstrate any significant differences in MDA levels, are important to support our hypothesis of fibromyalgia as an oxidative stress disorder. There are no data about SOD levels in fibromyalgia, and their decrease in our study also supports this theory.

The cause of the imbalance between oxidant and antioxidant levels in fibromyalgia is unknown. Many factors such as aging, smoking, stress, and hormones may increase free radicals and decrease antioxidant levels [23]. In our study group, there was no relationship found between age, BMI, duration of disease, and MDA or SOD levels. All patients' thyroid and sex hormone profiles were normal. The number of smokers among the patients was 14, and MDA and SOD levels were found to be unrelated to smoking. Therefore these findings might suggest an oxidant/antioxidant imbalance related to the disease process, and the increase in free radical levels may be responsible for the development of fibromyalgia.

Pain is the major symptom of fibromyalgia. The number of tender points is also important. We thought that oxidative stress might affect the disease symptoms. We investigated this issue but found no correlation between pain, number of tender points, and MDA and SOD levels. This may be due to the patients selected, because the number of tender points was < 15 in most of them. Studies of patients with higher numbers of tender points might prove this relation. Also, pain assessment was subjective in our study. To assess this relation, an objective pain measurement method such as dolorimetric evaluation may apply better in this condition.

In conclusion, our study suggests an oxidant/antioxidant imbalance in fibromyalgia. The increase in MDA levels and decrease in SOD levels show that fibromyalgia disease is related to free radical-mediated disorders. In light of previous studies, ours supports the hypothesis that fibromyalgia is an oxidative disorder. Further studies with larger series are needed to prove this hypothesis.

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