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The role of oxidative stress in the relation between fibromyalgia and obstructive sleep apnea syndrome

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Abstract. – OBJECTIVE: The aim of this study is to examine the involvement of oxidative and antioxidative parameters and to evaluate the relation between fibromyalgia (FMS) and obstructive sleep apnea syndrome (OSAS).

PATIENTS AND METHODS: Oxidative stress was determined by measuring the levels of malondialdehyde (MDA) and antioxidative parameters (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) in 131 randomly selected patients with OSAS. The control group was composed of 129 subjects with no clinical OSAS symptoms. OSAS was diagnosed by polysomnographic tests. All patients underwent overnight polysomnographic recording. The diagnosis of fibromyalgia was made following the diagnostic criteria of the American College of Rheumatology. The FMS patients used visual analog scales (VAS) to evaluate their pain, and they completed the FMS Impact Questionnaire (FIQ). All subjects completed the 36-item Short Form Health Survey (SF-36) and the Beck Depression Inventory (BDI).

RESULTS: In the OSAS + FMS group, CAT, SOD, and GDX were found to be statistically significantly lower and MDA was found to be statistically significantly higher than in both the control group and the OSAS group (p = 0.0001). A significant difference was found about gender between the OSAS group and the OSAS+FMS group (p = 0.0001). In the OSAS + FMS group, BDI was found to be statistically significantly higher than in both the control group and the OSAS group (p = 0.0001). In the OSAS + FMS group, SF 36 was found to be statistically significantly higher than in both the control group and the OSAS group (p = 0.0001). No differences were observed between the groups about AHI, minimum O_2 saturation, or total sleep time values. About the presence of FMS presence, no differences were detected among the mild, moderate, and severe OSAS groups (p = 0.831). A negative correlation was determined between AHI and VAS and total sleep and sensitive points (p = 0.0001). A negative correlation was shown between CAT and GPX, SOD and apnea/hypopnea index (AHI) (p = 0.0001). A positive correlation was shown between CAT, GPX and SOD (p = 0.0001). A minimum O_2 saturation was detected. A positive correlation between MDA and AHI (p = 0.0001), and a negative correlation between MDA and O_2 saturation (p = 0.0001) were found.

CONCLUSIONS: OSAS and FMS were highly prevalent, which indicated that oxidative stress might play a role in the pathophysiology of both diseases, especially if they co-exist in the same patient.

Key Words:
Fibromyalgia, Obstructive sleep apnea syndrome, Oxidative stress, Antioxidants.

Introduction

Fibromyalgia (FMS) is characterized by widespread pain, emotional dysregulation, chronic fatigue, and dysfunction accompanied by sleep disorder[1]. Various factors, such as neuroendocrine and autonomic nervous system abnormalities, genetic features, psychosocial changes, and environmental stress, were found responsible for the pathophysiology of FMS[2]. In recent years, oxidative stress was included as a major factor in the pathogenesis of FMS[3,4]. Obstructive sleep apnea syndrome (OSAS) is frequently manifested as a decrease (hypopnea) or a complete cessation (apnea) of airflow, which causes an increase in inspiratory effort. OSAS is characterized by the collapse of the extrathoracic airway, a temporary decrease in oxyhemoglobin saturation, hypercapnia, and related hyperventilation[5]. In OSAS patients, repetitive intermittent hypoxia and oxygen desaturation occur due to the cessation of inspiration. These metabolic alterations trigger oxidative stress and systemic inflammation, which causes the release of inflammatory indicators, antioxidant enzymes,

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and reactive oxygen species (ROS)[6]. The role of oxidative stress in OSAS was reported in several publications[7]. In patients with OSAS, characteristic polysomnography findings are increased in superficial sleep (NREM stage 1 and stage 2) and decreased in deep sleep (NREM stage 3). It was shown that the absence of the fourth phase of sleep causes FMS-like symptoms in healthy individuals[8]. Similar to OSAS patients, sleep disorders in FMS patients are commonly reported in the literature[9]. Disorders in sleep patterns were indicated as an important factor in pathogenesis[10]. Abnormalities in slow wave sleep-delta wave sleep were observed in the deep sleep phase (non-rapid eye movement [NREM] phase 3) in patients with FMS. Therefore, the presence of similar sleep patterns in OSAS and FMS patients and OSAS patients suffering from frequent sleep interruptions. These patients do not enter the deep sleep phase, which inhibits their physical rest, indicating that these two conditions may be related[11]. Studies evaluating the relationship between OSAS and FMS have been conducted in very small patient groups. However, the results are controversial[12]. In addition, as far as we know, no study has investigated the role of oxidative stress in the relationship between OSAS and FMS.

To contribute to closing this gap in the literature, we performed an FMS evaluation in a large OSAS group of patients. Our aim was to determine the participation of oxidative parameters (malondialdehyde [MDA]) and antioxidative parameters (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) in both FMS and OSAS.

Patients and Methods

Patient Selection

This study was performed using 131 randomly selected patients with OSAS. The control group was composed of 129 subjects with no clinical OSAS symptoms. The ethical approval for the study was obtained from the Ethics Committee of Namik Kemal University. Written informed consent was obtained from all participants before the study. Body mass index, age, and demographic characteristics of all patients and controls were recorded. All patients and controls underwent a general physical examination by the same investigator. Individuals with metabolic, inflammatory, infectious and collagen tissue disorders and thyroid, chronic renal, pulmonary and cardiac diseases, and individuals who had used opioid analgesics, antidepressants, anticonvulsive and non-steroidal anti-inflammatory drug were excluded from the study.

Polysomnographic Testing and Diagnosis of OSAS

All patients underwent overnight polysomnographic testing (Embla N 7000, Embla Systems, Inc., Broomfield, CO, USA) and were diagnosed with OSAS based on the results. The polysomnography included the following: electroencephalogram, electrooculogram, chin and leg electromyography, electrocardiography, snoring, oronasal thermistor, nasal pressure transducer, finger pulse oximeter, thoracic and abdominal respiratory movements, and body position. The scoring was based on the criteria of the American Academy of Sleep Medicine (AASM), which were published in 2007. Apnea was defined as a ≥90% decrease from baseline in the oronasal thermistor signal amplitude for at least 10 s. Hypopnea was defined as ≥ 50% decrease from baseline in the nasal cannula signal amplitude at least for 10 s, and a decrease in oxygen saturation was defined as ≥ 3% decline or presence of arousal. The apnea/hypopnea index (AHI) is defined as the number of occurrences of apnea/hypopneas per hour (/h) during sleep. Patients with apnea/hypopnea index (AHI) ≥ 5/h are considered to have OSAS. The AHI of 5-15/h is considered mild, AHI of 15-30/h is considered moderate, and AHI ≥ 30/h is considered OSAS. In our study, the OSAS group consisted of patients whose symptoms of OSAS had started at least one year before the study and who had not received any treatment for OSAS. The control group and their bed partners were interviewed together. They were questioned about the presence of major and minor symptoms of OSAS. They were excluded from the study if they had symptoms of OSAS.

Diagnosis of FMS

FMS was diagnosed based on the criteria of the American College of Rheumatology[13]. Tenderness was evaluated by applying pressure (4 kg/cm^2) over 18 specific body points, and the number of tender points was recorded. To evaluate their pain, the FMS patients used visual analog scales (VAS), and they completed the FMS Impact Questionnaire (FIQ). The validated version of FMS Impact Questionnaire (FIQ)[14] is a specific instrument used to assess the impact of the disease on the daily lives of FMS patients. This instrument measures "physical functioning," "overall impact" (e.g., missed days of work and job difficulty), and

"symptoms" (depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being over the past week). The maximum score for the FIQ is 100, and higher values indicate greater severity. In the severity analysis, a total FIQ score from 0 to <39 was found to represent mild effects; ≥39 to <59, moderate effects; and ≥59 to 100, severe effects[15]. The Turkish version of FIQ was validated by Sarmer et al[16].

Psychological Status and Functional Status

All subjects completed the 36-item Short Form Health Survey (SF-36) and the Beck Depression Inventory (BDI). The BDI is a self-report inventory that is used to measure the severity of depression[17]. The BDI includes 21 items scored between 0 and 3. The Turkish version of the BDI was validated by Hisli[18]. The SF-36 distinguishes eight areas that are used measure physical health and mental health. These include physical health problems, physical functioning (PF), role disability due to physical problems (RP), bodily pain (BP), and general health perceptions (GH). Mental health consists of vitality (VT), social functioning (SF), role disability due to emotional problems (RE), and mental health (MH). The scores range from 0 to 100; higher scores indicate better functioning[19].

Biochemical Assay

Fasting blood samples were taken by venipuncture, placed in vacutainer tubes, and then centrifuged for 10 min at 3,000 rpm to obtain serum. The harvested serum samples were frozen at -70°C until they were assayed. The serum samples were used to measure the levels of Cu/Zn superoxide dismutase (Cu/Zn-SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA). Before the analysis, the frozen serum samples were brought gradually to room temperature and then mixed gently. The samples were diluted by sample buffer as appropriate. All analyses were performed in duplicate on the same day. The levels of human serum Cu/Zn-SOD, CAT, GSH-Px, and MDA were measured using commercial ELISA kits (Cu/Zn-SOD, eBioscience, San Diego, CA, USA; CAT, Cayman, Ann Arbor, MI, USA; GSH-Px and MDA, SunRedBio, Shanghai, China) according to the manufacturers' instructions.

Measurement of Serum Zn/Cu SOD, GSH-Px, and MDA Levels

Briefly, the standard and serum samples were added to microwells that were pre-coated with human Zn/Cu SOD monoclonal antibody and then incubated for 1 hr. Then washing was carried out to remove the unbound Zn/Cu SOD enzymes. Then HRP-conjugated anti-human Cu/Zn-SOD antibody was added, followed by incubation for 1 hr to form immune complex Cu/Zn-SOD enzyme [the monoclonal antibody] was HRP-conjugated anti-human Cu/Zn-SOD antibody complex. Incubation and washing were carried out again to remove the unbound HRP-conjugated anti-human Cu/Zn-SOD antibodies. Then, a chromogen solution was added and incubated for 10 min until the color of the liquid in the microwells became blue. The reaction was terminated by the addition of acid, and the blue color became yellow. The absorbance of the yellow liquid was measured at 450 nm using a microplate reader. The absorbance of the resulting yellow color was directly proportional to the level of human Cu/Zn-SOD present in the serum samples. The serum GSH-Px and MDA levels were measured in the manner described above.

Measurement of Serum CAT Levels

Catalase activity was measured in the serum of patients using the Catalase Assay Kit (Cayman), which included a colorimetric test based on the capacity of catalase to produce formaldehyde after hydrolyzing hydrogen peroxide (H_2O_2). The experimental procedures were carried out according to the manufacturer's protocol. Briefly, the samples of standard, control, and serum were mixed with diluted assay buffer and methanol in a 96-well microtiter plate. The reaction was initiated by adding diluted hydrogen peroxide, and the plate was incubated for 20 min with constant shaking, after which formaldehyde occurred in the wells containing the serum and the control. Then, diluted potassium hydroxide solution was added, followed by 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (Purpald®) as the chromogen. The plate was incubated immediately for 10 mins with constant shaking. Potassium hydroxide was added to stop the formation of formaldehyde. Purpald® specifically forms a colorless bicyclic heterocycle with aldehydes, which, upon oxidation, changes to a purple color. Finally, potassium periodate was added, followed by 5 min of incubation with constant shaking. The absorbance of the purple liquid was measured at 450 nm using a microplate reader. The absorbance of the resulting purple liquid was directly proportional to the level of human CAT present in

the serum samples.

Statistical Analysis

The statistical analysis of our study data were performed using SPSS for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Mean standard deviation (SD) was used to identify the data related to the continuous variables, and numbers were used to identify the data related to the categorical variables. The Kolmogorov-Smirnov normalizing test was used to determine whether the continuous variable data fit a normal distribution. The comparison of the variables with normal distribution was performed using an unpaired *t*-test. The comparison of the variables without normal distribution was performed using the Mann-Whitney U test. The comparison of categorical variables was performed using Pearson's x^2 test. The relation among continuous variables was determined using the Spearman rank correlation analysis. $p < 0.05$ was considered statistically significant.

Results

Differences between the groups regarding CAT, GPX, SOD, and MDA levels were observed ($p = 0.0001$). CAT, SOD, and MDX were statistically lower in the OSAS group compared with the control group ($p = 0.0001$). In the OSAS + FMS group, they were statistically significantly lower than in both the control group and the OSAS group ($p = 0.0001$). MDA was statistically higher in the OSAS group compared with the control group ($p = 0.0001$). In the OSAS + FMS group, they were statistically significantly higher than in both the control group and the OSAS group (Table I).

No differences were observed about gender in the OSAS group and the control group ($p = 0.10$). However, a difference was found about gender between the OSAS group and the OSAS+FMS group ($p = 0.0001$) (Table I).

BDI was statistically significantly higher in the OSAS group compared with the control group ($p = 0.0001$). In the OSAS + FMS group, it was statistically significantly higher than in both the control group and the OSAS group ($p = 0.0001$) (Table I).

No differences in SF-36 were found between the OSAS and the control group ($p = 0.643$). In the OSAS + FMS group, the SF-36 was statistically significantly higher than in both the control group and the OSAS group ($p = 0.0001$). No differences were observed between the groups about AHI, minimum O_2 saturation, or total sleep time values (Table I).

Discussion

Previous studies[20-24] were conducted to evaluate the frequency of FMS in small groups of OSAS patients; however, the results were controversial. In our study, we evaluated 131 OSAS patients, among which FMS was diagnosed in 50. When gender was evaluated, it was observed that the number of male subjects was higher in the OSAS group and the number of female subjects was higher in the FMS group. In a previous study, May

Table I. Comparison of demographic, polysomnographic, clinical, and laboratory data.

Variables	OSAS (no. 131) mean ±SD	OSAS+FMS (no. 50) mean ±SD	Control (no. 129)	*p*
Age (years)	48.8±8.8	50.6±10.3	48.9±8.4	0.476
Gender (M/F)	58/23	16/34	78/51	0.0001
BDI	10.0±9.4	15.7±10.2	4.71±2.7	0.0001
SF36	45.8±29.9	82.6±19.1	39.8±11.1	0.0001
CAT	10.0±0.8	5.15±1.4	16.2±1.5	0.0001
SOD	8.93±1.4	3.16±1.8	13.6±1.5	0.0001
GPX	11.00±0.8	6.82±1.7	17.07±1.5	0.0001
MDA	12.01±0.9	18.02±1.3	7.14±1.4	0.0001
AHI	33.8±28.7	39.9±34.8	-	0.441
Minimum O2 Saturation %	0.80±0.10	0.79±0.11	-	0.44
Total sleep time (min)	353.7±76.29	358.65±69.88	-	0.908

Abbreviations: SOD = superoxide dismutase; CAT = catalase; GPX = glutathione peroxidase; MDA = malondialdehyde; BDI = Beck Depression Inventory; SF-36 = 36-item Short Form Health Survey; AHI = Apnea-Hypopnea Index

Table II. Comparison of patients with FMS and without FMS by OSAS severity.

Variables	Mild OSAS	Moderate OSAS	Severe OSAS	Total	p
Without FMS	30 (37.0%)	13 (16.0%)	38 (46.9%)	81 (100%)	0.831
With FMS	17 (34%)	6 (12%)	27 (54%)	50 (100%)	
Total	47 (25.5%)	19 (14.5%)	65 (49.6%)	131 (100%)	

Note: FMS was observed in 50 of 131 OSAS patients. No differences were detected about FMS presence among the mild, moderate, and severe OSAS groups ($p = 0.831$).

Table III. The relationship of clinical parameters to polysomnographic and oxidative stress.

Variables		VAS	Sensitive point	FIQ	BDI	SF36
AHI	r	-0.442	-0.36	-0.184	-0.293	-0.101
	p	0.001	0.803	0.206	0.39	0.483
Minimum O_2 Saturation %	r	0.181	-0.07	0.91	0.237	0.232
	p	0.214	0.962	0.54	0.101	0.108
Total sleep time (min.)	r	-0.101	-0.51	0.04	-0.020	-1.45
	p	0.486	0.0001	0.979	0.89	0.314
CAT	r	-0.359	-0.73	-0.112	-0.126	0.052
	p	0.11	0.613	0.445	0.385	0.721
SOD	r	-0.456	-0.87	-0.24	-0.456	0.576
	p	0.24	0.46	0.12	0.34	0.24
GPX	r	-0.169	-0.61	-0.196	-0.197	0.176
	p	0.274	0.701	0.292	0.2	0.256
MDA	r	0.197	0.58	0.167	0.188	-0.169
	p	0.274	0.76	0.246	0.274	0.327

Abbreviations: SOD = superoxide dismutase; CAT = catalase; GPX = glutathione peroxidase; MDA = malondialdehyde; AHI = Apnea-Hypopnea Index
Note: Negative correlations are shown between AHI and VAS and total sleep and sensitive point ($p = 0.0001$).

Table IV. The relationship between polysomnographic findings and oxidative stress parameters.

Variables		AHI	Minimum O2 saturation %	Total sleep time (min)
CAT	r	-0.786	+0.543	+0.202
	p	0.0001	0.0001	0.160
SOD	r	-0.857	+0.674	+0.393
	p	0.0001	0.0001	0.24
GPX	r	-0.758	+0.624	+0.476
	p	0.0001	0.0001	0.342
MDA	r	0.654	-0.576	-0.246
	p	0.0001	0.0001	0.14

Abbreviations: SOD = superoxide dismutase; CAT = catalase; GPX = glutathione peroxidase; MDA = malondialdehyde; AHI = Apnea-Hypopnea Index
Note: A negative correlation is shown between CAT, GPX, and SOD and AHI ($p = 0.0001$). A positive correlation is shown between CAT, GPX, and SOD and minimum O2 saturation ($p = 0.0001$). A positive correlation is shown between MDA and AHI ($p = 0.0001$). A negative correlation is shown between MDA and O_2 saturation ($p = 0.0001$).

et al[12] showed that the frequency of sleep apnea was not significant in female patients with FMS, whereas the frequency was higher in male patients with FMS. It was concluded that FMS might be an indicator of sleep apnea in men.

In our study, a relationship between OSAS severity and FMS was not observed. However, a negative correlation was found among AHI, VAS, total sleep, and sensitive point. Germanowicx et al[11] compared groups about OSAS severity and FMS frequency; no significant difference was observed. In another study, 31 females with OSAS were evaluated, and FMS was detected in six patients. Although a relationship between OSAS severity and FMS was not found, a positive correlation was found between myalgic scores and mean O_2 saturation[25]. In our study, BDI was statistically significantly higher in the OSAS group. BDI was also statistically significantly higher in the OSAS + FMS group than in both the control group and the OSAS group. In a study of Terzi et al[25], the BDIs in OSAS, OSAS+FMS, and control groups were evaluated; no differences were found among the groups. However, this study was carried out using a small group of patients. In our work, depressive complaints increased with the presence of OSAS. Moreover, the presence of FMS accompanying OSAS in OSAS patients further increased depressive complaints. No difference was found between the OSAS and the control groups regarding SF36. Martinez-Garcia et al[26] observed that OSAS had little impact on quality of life in the elderly. The quality of life was statistically and significantly higher in the OSAS+FMS group compared with both the control group and the OSAS group. In our paper, we observed that OSAS alone did not affect patients' quality of life; however, when FMS accompanied OSAS, quality of life was impaired.

Oxidative stress caused by the impairment of the balance between ROS and the antioxidant defense system. Because ROS, which includes superoxide anions, hydrogen peroxide, and hydroxyl radical, has unpaired electrons, they are quite reactive molecules. Therefore, ROS cause various diseases that damage biomolecules such as proteins, lipids and nucleic acids[27]. CoQ functions as an antioxidant that protects cells by directly cleaning ROS. Therefore, the lack of CoQ causes low mitochondrial respiratory enzyme activity, elevated ROS production, decreased growth rate, and cell death. Excess mitochondrial ROS production may exceed cellular antioxidant defenses, and the cumulative damage may cause cell necrosis or apoptosis[28]. Antioxidant defense mechanism enzymes, such as SOD and GPX, prevent oxidative stress via ROS inactivation. SOD enzymes eliminate the damaging effects of free radicals by converting superoxide radicals to oxygen and hydrogen peroxide, as well as by means of the GPX enzyme, which converts hydrogen peroxide to water[29]. CAT is a common enzyme found in all living organisms. Their functions include catalyzing the decomposition of hydrogen peroxide to water and dioxygen[30]. CAT has the highest turnover rate among all enzymes, and a CAT molecule can convert millions of molecules of hydrogen peroxide to water and oxygen each second. Low CAT activity level damages primarily endoplasmic reticulum in cells[31]. MDA is an indicator of oxidative stress caused by lipid peroxidation[32]. Whether OSAS causes oxidative stress and inflammation or whether these changes occur because of accompanying metabolic co-morbidities remain controversial[33]. Controversial results were obtained in researches that investigated oxidative stress in OSAS. Some publications indicate high levels of oxidative stress in OSAS patients compared with healthy controls[34], whereas other authors showed that oxidative stress markers were similar in OSAS patients and controls[35]. OSAS increases the formation of ROS. The overproduction of ROS results in oxidative stress, which damages cellular structures that include lipids, membranes, proteins, and DNA[36]. OSAS patients have elevated levels of reactive oxygen metabolites in their blood, which may lead to cellular damage[37]. In a study by Yagihara et al[38], lipid peroxidation levels (MDA) in the OSAS group were initially high, and it was suggested that lipid peroxidation might be a major pathological event for these patients. In this report, continuous positive airway pressure (CPAP) treatment for six months increased the level of CAT activity. Based on the results, it was concluded that this treatment activated the antioxidant defense system, which decreased the levels of lipid peroxidation (MDA) levels in OSAS patients during the study period[38]. In another paper of hypoxic and non-hypoxic patients, no differences in GPX and CAT activities were observed. The study showed that high oxidative stress and the absence of DNA damage in patients with OSAS did not lead to oxidative stress production in the absence of significant co-morbidities. The findings of this work also showed that treatment with continuous positive airway pressure did not change the enzyme levels[39]. In an investigation conducted in severe OSAS patients, CAT and

GPX levels were found to be low and MDA levels were found to be high[40]. The controversial results regarding the role of oxidative stemless in OSAS may have resulted from different pathways that might have been affected by metabolic, systemic, genetic, or inflammatory factors[39-41]. The relationship between aging and antioxidant capacity has not been determined, and a consensus regarding the effects of aging on antioxidant capacity has not been reached[42]. In our study, CAT, GPX, and SOD levels were statistically lower in the OSAS group than in the control group. MDA was statistically higher in the OSAS group than in the control group. These results indicate that OSAS may overload the antioxidant capacity of patients with increased CAT, GPX, and SOD activity. Nevertheless, the increase in antioxidant stress is inadequate to manage the oxidative stress resulting from OSAS. In our work, we excluded aging and the effects of metabolic, inflammatory, and co-morbid factors, which may cause ROS production on antioxidant capacity. CAT GPX levels were associated with polysomnographic indices, such as AHI, minimum oxygen saturation, and total sleep time[43]. In our study, a negative correlation between CAT, GPX, SOD and AHI, and a positive correlation between CAT, GPX, SOD and minimum O_2 saturation were detected. A positive correlation between MDA and AHI and a negative correlation between MDA and O_2 saturation were also found. The literature offers little information about oxidative stress in FMS. A few reports[44-46] have indicated that oxidative stress may play a role in the pathophysiology of FMS. Previous researches[47,48] have suggested that this process might play a role in the pathophysiology of the disease, and they have reported high levels of oxidative stress markers such as LPO and the lack of co-enzyme Q (CoQ) in FMS patients. It is known that ROS plays a role in the etiology of pain by triggering peripheral and central hyperalgesia[49]. Superoxide plays a major role in the development of pain via peripheral sensitization[50]. Even though the mechanisms by which elevated oxidative stress can affect muscle sensitivity specifically, they have to be investigated yet. Oxidative damage in these muscles might cause a local decrease in the threshold of nociceptors and thus alter nociception[51]. Oxidative stress was found to be high in patients with chronic fatigue syndrome[52]. Akkuş et al[53] reported that malondialdehyde (MDA), which is an indicator of lipid peroxidation, increased and that vitamin E, which prevents lipid peroxidation, decreased in FMS patients. Eisenger et al[54] studied the levels of MDA and of protein carbonyl, which is an indicator of protein peroxidation. According to their findings, MDA levels did not change in FMS patients, whereas their carbonyl levels decreased. Cordero et al[55] reported high levels of MDA in FMS patients. Ozgocmen et al[4] observed similar SOD enzyme activities in FMS and control groups.

Previous studies have also shown a relationship between oxidative stress and the severity of FMS. Significant correlations were observed between plasma and serum antioxidant levels, and pain and morning stiffness[56]. Ozgocmen et al[4] found a significant correlation between depression and LPO in serum; however, there was no correlation between biochemical parameters and pain, and clinical measurements of fatigue. Even though the etiology of FMS is not known, symptoms may be associated with an imbalance in oxidant and antioxidant states[57]. In a study by Fatima et al[58], increased LPO levels and decreased CAT and GPX were detected in FMS patients, which indicated an imbalance of oxidants and antioxidants in FMS. Also, this report showed that an increase in oxidative stress parameters was associated with the severity of FMS.

In our paper CAT, GPX, and SOD levels were statistically and significantly lower in the OSAS +FMS group compared with the control group and the OSAS group. MDA levels were statistically and significantly higher in the OSAS+FMS group compared with both the control group and the OSAS group. The higher CAT, GPX and SOD activity in OSAS+FMS patients may have resulted from the high exposure to oxidative stress. In our study, no relationships were found among CAT, GPX, SOD, MDA and VAS, sensitive point, and FIQ.

Conclusions

We evaluated a large cohort of OSAS patients. The prevalence of FMS in the OSAS patients is much higher than in the general population. The relationship between OSAS and FMS should be evaluated in large groups of patients, and more data regarding this matter should be analyzed and published. When the relationship between FMS and OSAS relationship is clarified, investigating the underlying pathogenesis will become important. Studies focusing on the relationship between oxidative stress and metabolic and clinical parameters help in understanding

the underlying pathogenesis, and they can be used for biomarker, diagnostic, prognostic, and therapeutical purposes. The high CAT, GPX, and SOD activities and low MDA found in this study indicate the importance of evaluating the oxidative stress markers in patients with OSAS and FMS accompanied by OSAS. Therefore, based on our findings, future research should focus on improving the antioxidant capacity in these patients.

Conflict of Interest

The authors declare no conflicts of interest.

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