Original Article

Frequency of Audiological Complaints in Patients with Fibromyalgia Syndrome and its Relationship with Oxidative Stress

TT Koca, M Seyithanoğlu[1], S Sagiroglu[2], E Berk, H Dağlı[1]

Departments of Physical Medicine and Rehabilitation, [1]Clinic Biochemistry and [2]Otorhinolaryngology, Faculty of Medicine, Sütçü İmam University, Kahramanmaraş, Turkey

Abstract

Aim: Central sensitization-related neuroaudiological symptoms are frequently seen in patients with fibromyalgia syndrome (FMS). This study aimed to evaluate the audiological signs and symptoms in patients with FMS and explore their relationship with oxidative stress markers. **Methods:** This prospective controlled cross-sectional study compared the serum myeloperoxidase, superoxide dismutase, glutathione peroxidase (GPx), nitric oxide (NO), and malondialdehyde (MDA) concentrations in 44 patients with FMS diagnosed according to the 2010 American College of Rheumatology criteria and 44 healthy volunteers. FMS severity was assessed using the visual analog scale and Fibromyalgia Impact Questionnaire. An audiological assessment including vocalizations, vertigo, balance problems, and hearing problems was done to all participants. **Results:** The two groups were of similar age (P = 0.24), gender (P = 0.40), and weight distribution (P = 0.6). Vertigo, tinnitus, hearing, and balance complaints (P = 0.01/P = 0.00/P = 0.00/P = 0.01) were significantly higher in the FMS group. All subunits and total scores of dizziness handicap inventory were significantly higher (P = 0.00/P = 0.00/P = 0.01/P = 0.01) in the FMS group. An antioxidant GPx and oxidant parameters such as NO and MDA were found to be significantly higher (P = 0.00/P = 0.01/P = 0.02). The hearing assessments at frequencies between 250 and 12,000 Hz showed a significant difference between the two groups (high hearing frequencies in the FMS group) in audiometry. No significant difference was found between the two groups in terms of the presence of stabilo-acoustic reflex, intraaural pressure, and compliance (P = 0.18/P = 0.33/P = 0.41) in tympanogram. **Conclusions:** Patients with FMS have high levels of oxidative stress markers (GPx, NO, and MDA), highly frequent audiological symptoms with high hearing frequencies in audiometry, independent of disease severity.

Keywords: *Audiologic disorders, fibromyalgia, oxidative stress*

Date of Acceptance:
18-Jun-2018

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by diffuse muscle pain, poor sleep, and fatigue with an unknown etiology and limited treatment options. The estimated prevalence of FMS in the general population varies globally between approximately 2% and 11%, depending on the population.[1,2] The prevalence is higher in women than men (9:1) increasing with age.[2] FMS is often accompanied by nonspecific symptoms and comorbidities, such as memory and concentration problems, sleep disturbances, stomach ache, depressive symptoms and headache, and disorders such as irritable bowel syndrome, chronic fatigue syndrome, interstitial cystitis, and temporomandibular disorder. Multiple

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_95_18

Address for correspondence: Dr. TT Koca, Department of Physical Medicine and Rehabilitation, Sütçü Imam University, Kahramanmaras, Turkey.
E-mail: tuba_baglan@yahoo.com

How to cite this article: Koca TT, Seyithanoğlu M, Sagiroglu S, Berk E, Dağlı H. Frequency of audiological complaints in patients with fibromyalgia syndrome and its relationship with oxidative stress. Niger J Clin Pract 2018;21:1271-7.

factors such as genetic factors, substance P, serotonin, hypothalamic–pituitary–adrenal axis, metabolic dysfunction, reactive oxygen species, and reactive nitrogen samples were found to be related to FMS pathophysiology. Oxidative stress is thought to be crucial in the pathophysiology of FMS.[3,4]

Electron-accepting molecules are called free radicals in biological systems.[5] Active oxygen derivatives of these free radicals are also called oxidants. Some studies have explored the role of free radicals in the etiology of diabetes mellitus, ischemia–reperfusion injury, cancer, aging, and muscular diseases due to their damaging properties.[6]

Oxidative stress is determined by measuring blood plasma levels of lipid peroxide (LPO) and protein carbonyl and also antioxidative parameters such as catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR).[5,6] Previous studies have investigated the role of oxidative stress in patients with FMS and shown conflicting results. Oxidative stress and nitric oxide (NO) are involved in the pathophysiology of FMS.[1-4] This study investigated the role of oxidative stress markers associated with the severity of disease and audiological complaints in patients with FMS.

Methods

This prospective, cross-sectional study included 44 patients (42 females and 2 males) who were in the age range of 21–68 years and diagnosed with FMS in the physical medicine and rehabilitation clinic, according to 2010 American College of Rheumatology criteria. Control group consisted of 44 healthy volunteers (39 females and 5 males). The severity of FMS in the study group was detected using the Fibromyalgia Impact Questionnaire (FIQ) forms, which contains 10 self-administered instruments covering physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. A visual analog scale (VAS: from 0 = no pain to 10 = the worst pain) was used to measure pain score. The age, sex, and body mass index (BMI) of both groups were recorded. The participants were questioned regarding balance disorder, vertigo, tinnitus, and hearing problems, and dizziness handicap inventory (DHI) was applied to those with vertigo/dizziness complaint.

The serum levels of myeloperoxidase (MPO), superoxide dismutase (SOD), GPx, NO, and malondialdehyde (MDA) were measured in all participants. Tympanogram, stapedial acoustical reflex, tubal residual function tests, pure-tone audiometry, and speech audiometry (including high frequencies) were evaluated in the audiology clinic. Those with chronic inflammatory disease, malignancy, and infection were excluded from the study.

Fibromyalgia Impact Questionnaire

To evaluate the functional status of patients, disease progression and outcomes, FIQ was used of which the Turkish validity study was performed by Sarmer *et al*.[7] It is the scale used to follow-up the conditions and outcomes of patients with FMS. The first item consists of 10 Likert-type questions. In the second and third items, it is asked to tick the days to allow for the determination of "disease exposure" and "absence from work." The scores obtained are adapted to 10. The remaining seven questions are based on marking the corresponding points in the equivalent visual scale. The score interval is 0–100. High scores indicate severe illness.

Oxidative/antioxidative marker measurement

Venous blood samples were obtained from the antecubital area by phlebotomy. After these samples were allowed to clot, they were centrifuged for 10 min at 3000 g. The sera were separated and stored at −80°C until the analysis.

The concentration of serum lipid peroxidation (total MDA) was determined as described by Ohkawa *et al*. with slight modifications. MDA results were expressed in nanomoles per milliliter (nmol/ml).[8]

SOD activity was determined as described by Beyer and Fridovich. This method employs xanthine and xanthine oxidase to generate superoxide radicals, which react with 2-(4 iodophenyl)-3-(4-nitro phenol-s-phenyl tetrazolium chloride) to form a red formazan dye. SOD activity is then measured by the degree of inhibition of this reaction.[9]

MPO activity was determined by a modification of the O-dianisidine method. The assay mixture, in a cuvette of 1 cm path length, contained 0.3 mL 0.1 M phosphate buffer (pH 6.0), 0.3 mL 0.01 M hydrogen peroxide (H_2O_2), 0.5 mL 0.02 M O-dianisidine (freshly prepared) in deionized water, and 10 µL serum in a final volume of 3 mL. The serum was added last, and the change in absorbance at 460 nm was monitored for 10 min. All measurements were carried out in duplicate. One unit of MPO is defined as that giving an increase in absorbance of 0.001/min, and specific activity is given as U/mL.[10]

The Beutler method was used for glutathione peroxidase (GSH-Px) activity measurement. The role of GSH-Px is to catalyze the oxidation of reduced glutathione (GSH) to oxidized glutathione (GSSG) by means of H_2O_2. In the presence of H_2O_2 with t-butyl hydroperoxide, GSSG formed by GSH-Px is reduced to

GSH with the help of GR and NADPH. GSH-Px activity is determined by reading the difference of absorbance spectrophotometrically at 340 nm during the oxidation of NADPH to NADP.[11]

NO production was quantified by measuring nitrite, a stable oxidation end product of NO. Briefly, nitrite production was determined by mixing 50 µl of the assay buffer with 50 µl of Griess reagent 1.5% sulfanilamide in 1 M HCl plus 0.15% N-(1-naphthyl) ethylenediamine dihydrochloride in distilled water (v/v). After 10 min of incubation at room temperature, the absorbance at 540 nm was determined and nitrite concentrations were calculated from the sodium nitrite standard curve.[12] All parameters were calculated according to the standard curve graphs that were run.

The dizziness handicap inventory

The DHI is used in clinical work and in research to assess the impact of dizziness on quality of life. The self-report questionnaire was originally designed to quantify the handicapping effect of dizziness imposed by vestibular system disease but has also been used for persons with dizziness of other origins. The DHI contains 25 items, and a total score (0–100 points) is obtained by summing ordinal scale responses, higher scores indicating more severe handicap. The scale was developed to capture various subdomains of self-perceived handicap and comprises 7 physical, 9 functional, and 9 emotional questions.[13]

Audiological evaluation

Tympanogram, stapes acoustic reflex, and Toynbee and Valsalva maneuvers were applied using Interacoustics AZ 26 (226 Hz, Interacoustics, DK-5610 Assens, Denmark) impedance meter for the participants. The pure voice and speech audiometry tests were performed using the Interacoustics AC40 Pure Tone Audiometer. Tympanometric results were classified as Type A, B, or C tympanograms. Acoustic reflexes were simultaneously recorded and evaluated. Evaluations were performed at 250-Hz and 12,000-Hz intervals in the pure audio test. For each set of tests, the mean values of air and bone conduction at each frequency value were calculated for both groups.

Patients were excluded if they had a history of any systemic or chronic disease, chronic use of any medications, a previous history of otologic disease, a family history of early-onset hearing loss, hearing loss due to other causes, or a history of high-risk noise exposure or ototoxic drug therapy.

Statistical analysis

IBM SPSS for Windows, version 21.0, software (IBM Corporation, NY, USA) was used for data analysis. Descriptive data were presented as mean ± standard deviation and median scores. The *t*-test was used to analyze normally distributed data; the Mann–Whitney U-test was used to analyze the abnormally distributed data. The Spearman's correlation analysis was used to analyze the levels of correlation between the variables. The coherence of variables to normalization (normality) was analyzed using the Kolmogorov–Smirnov test. $P < 0.05$ was considered statistically significant. The study was approved by the Regional Committee for Ethics (no: 147) in accordance with the criteria of Medical Research and Helsinki.

Results

The descriptive data of the FMS and control groups are summarized in Table 1. The FMS group comprised 44 patients aged 21–68 years (42 ± 10 years). Of these 44 patients, 42 patients (95.5%) were female and 2 were male. The mean VAS value was 5.5 ± 1.1 cm, mean BMI was 29.9 ± 8.3 kg/m^2, and FIQ value was 60.6 ± 10.6. The mean DHI total score was 24.6 ± 23.7, emotional score was 5.6 ± 6.9, functional score was 9.5 ± 9.9, and physical score was 9.6 ± 8.3 [Table 1].

The two groups were of similar age ($P = 0.24$), gender ($P = 0.40$), and weight distribution ($P = 0.6$).

Table 1: Descriptive data for the groups

	Mean±SD		*P*
	FMS (*n*=44)	Control (*n*=44)	
Age (year)	42±10	38±13	0.24
VAS (cm)	5.5±8.3	-	
BMI (kg/m^2)	29.9±8.3	27.2±5.8	0.6
Gender (f/m)	42/2	39/5	0.4
FIQ	60.6±10.6	-	
DHI total*	24.6±23.7	11.7±17.1	0.01
DHI emotional*	5.6±6.9	1.9±4.4	0.00
DHI functional*	9.5±9.9	5.4±7.8	0.00
DHI physical*	9.6±8.3	4.3±5.7	0.01

*Statistically significant difference, $P<0.05$. FMS=Fibromyalgia syndrome; VAS=Visual analog scale; BMI=Body mass index; DHI=Dizziness handicap inventory; FIQ=Fibromyalgia Impact Questionnaire; SD=Standard deviation

Table 2: Laboratory data of the groups

Parameter/group	Mean±SD		*P*
	FMS (*n*=44)	Control (*n*=44)	
SOD	15.3±6.4	14.9±6.7	0.79
GPx*	5.8±2.8	4.1±1.9	0.00
MPO (U/mL)	163.0±79.8	243.8±154.2	0.10
NO*	0.46±0.23	0.38±0.19	0.02
MDA (nmol/ml)*	18.6±7.6	17.3±6.4	0.02

*Statistically significant difference, $P<0.05$. Yellow=antioxidant; Red=oxidantant. MPO=Myeloperoxidase; SOD=Superoxide dismutase; Gpx=Glutathione peroxidase; NO=Nitric oxide; MDA=Malondialdehyde; SD=Standard deviation; FMS=Fibromyalgia syndrome

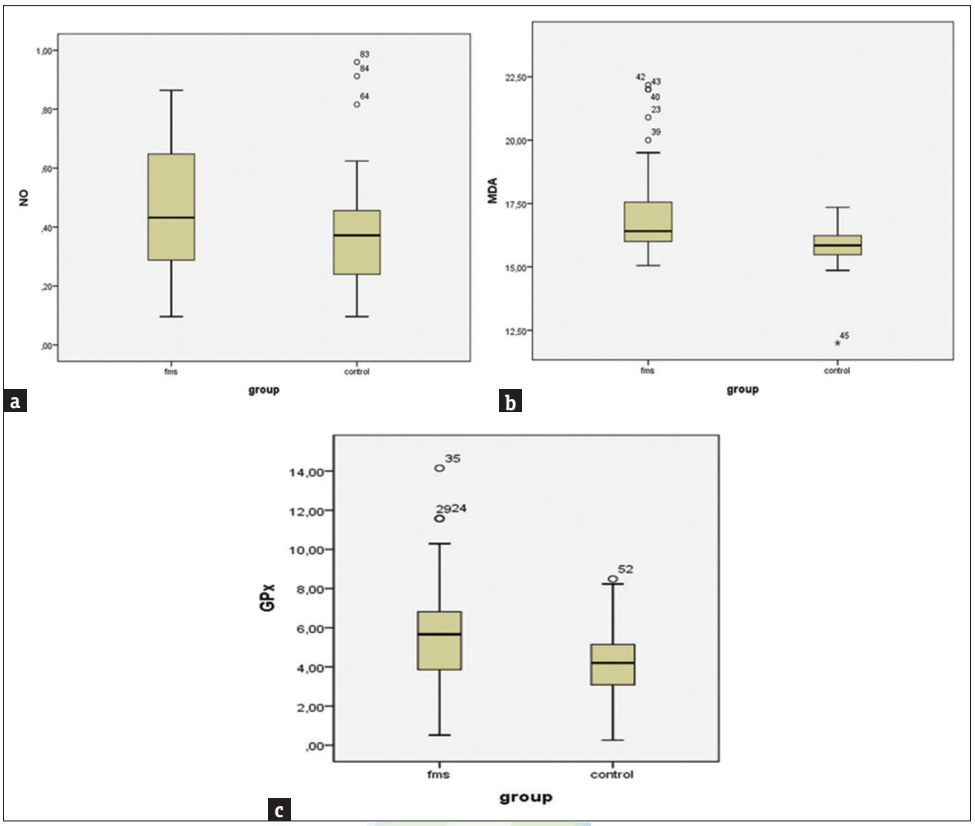

Figure 1: (a-c) Boxplot of oxidative stress markers according to the groups. fms = Fibromyalgia, Gpx = Glutathione peroxidase, NO = Nitric oxide, MDA = Malondialdehyde

Table 3: Audiometry and tympanogram results of the groups

Frequency of hearing test	Mean±SD		*P*
	FMS	Control	
Mean 250*	11.2±3.3	8.2±4.3	0.001
Mean 500	11.4±3.5	10.3±2.2	0.121
Mean 1000*	13.3±4.9	10±1.6	0.001
Mean 2000*	14.6±6.9	9.8±1.4	0.000
Mean 4000*	18.0±11.6	11.3±7.2	0.007
Mean 6000*	23.7±15.4	13.6±10	0.002
Mean 8000*	25.3±17.0	13.0±9.6	0.001
Mean 10,000*	42.9±26.7	17.1±15.7	0.000
Mean 12,000*	56.7±25.1	22.1±21.0	0.000
SAR, *n* (%)	35/79.5	39/88.6	0.18
Pressure	−37.3±21.1	−32.9±15.3	0.33
Compliance	1.3±4.4	0.6±0.3	0.41

*Statistically significant difference, $P<0.05$. FMS=Fibromyalgia syndrome; SAR=Stabilo-acoustic reflex; SD=Standard deviation

The frequency of tinnitus (63.6%), vertigo (84%), imbalance (61.3%), and hearing problems (45.4%) was significantly higher in the FMS group ($P = 0.00/P = 0.01/P = 0.01/P = 0.00$). The prevalence of audiological assessment of tinnitus, vertigo, balance problems, and hearing problems was 27.2%, 29.5%, 13.6%, and 13.6%, respectively, in the control group. All subunits (emotional, functional, physical) and total scores of DHI were significantly higher ($P = 0.00/P = 0.00/P = 0.01/P = 0.01$) in the FMS group [Table 1].

The scores of oxidant–antioxidant parameters in the FMS group are summarized in Table 2. An antioxidant GPx and oxidant parameters, such as NO and MDA, were found to be significantly higher in the FMS group ($P = 0.00/0.02/0.02$) [Figure 1a-c]. A positive correlation was found between SOD and imbalance complaint ($r = 0.49/P = 0.04$). No laboratory values were associated with VAS and FIQ values. A positive correlation was found between BMI and NO values ($r = 0.278/P = 0.01$).

The hearing assessments at frequencies between 250 and 12,000 Hz showed a significant difference between the two groups (high hearing frequencies in the FMS group) in audiometry. No significant difference was found between the two groups in terms of the presence of stabilo-acoustic reflex, intraaural pressure, and compliance ($P = 0.18/0.33/0.41$) in tympanogram. The tympanogram results of the patients were evaluated as Type A normal [Table 3].

Discussion

A general description of oxidative stress is that the

prooxidant–antioxidant balance leading to potential cellular damage due to a shift in the direction of prooxidant.[5] Therefore, the assessment of antioxidant consumption, decrease in the amount of antioxidants, or increase in the amount of their metabolites are used as biomarkers of oxidative stress.[5,6,14,15]

Oxidative stress is usually determined by measuring the levels of various enzymes, such as MDA as an end product of lipid peroxidation, 8-hydroxy-2'-deoxyguanosine as a DNA damage indicator, protein oxidation, SOD, GPx, CAT, Glutathione-S-transferase, GR, and some antioxidants, including alpha-tocopherol, ascorbic acid, glutathione, ubiquinone, and cysteine.[14,15]

FMS is an entity with multiple concomitant disorders, rather than a single disorder. The common symptoms of FMS include sleep disorders, affective disorders, chronic generalized pain, and fatigue. The pathophysiology of FMS has not been elucidated yet, and no treatment is available for relieving all of the symptoms.[16,17]

Many neuroaudiological complaints, such as dizziness, tinnitus, hearing loss, and vertigo are frequently seen in patients with FMS in correlation with the severity of the disease. These symptoms are explained by central hypersensitivity and dysregulation of the nervous system, which causes a change in perception. A small number of studies demonstrated that audiological complaints were not correlated with objective findings.[18-20] İt is believed that audiologic complaints develop due to an abnormal presentation of stimuli from internal or external circulation due to neural disintegration, events related to neural mediators, or systemic dysregulation related with FMS. Not only pain but also alterations in perception and other sensory stimuli and proprioceptive disorders are often seen in FMS.[21-23] Rosenhall *et al*.[22] showed the frequency of vertigo/dizziness and sensorineural hearing loss to be 72% and 15%, respectively, in patients with FMS. In the present study, the vertigo prevalence was found high with 84% frequency in FMS group.

Patients with FMS generally have postural instability and imbalance, pain, muscle weakness, trigger points in the lower extremity, cognitive problems, depression, and sleep disturbances.[19,24,25] Despite normal neurological examination, dynamic objective postural sensory deficits may be seen on posturography.[20,26,27] Balance exercise and cognitive therapy should be applied together to these patients. The frequency of imbalance complaint was found 61.3% in the present study. A positive correlation was found between imbalance and antioxidant activity. As the intensity of the imbalance increases, the antioxidant activity increases. We can say that antioxidant activity plays a protective role in the body's balance. No correlation was found between other audiologic features and oxidative stress markers.

Fatima *et al*.[28] reported that the levels of oxidative stress markers were high and the levels of antioxidative markers were low in patients with FMS. A positive correlation was found between LPO and protein carbonyl levels and disease severity. Ranzolin *et al*.[29] observed elevated serum interleukin-10 (anti-inflammatory) levels in patients with FMS compared with the control group. They found no oxidative markers correlated with disease severity. Toker *et al*.[30] found that the MDA levels were significantly higher in patients with FMS and positively correlated with general health scores. La Rubia *et al*.[31] found high levels of oxidative DNA damage and protein carbon content and low activities of antioxidant enzymes, SOD, GPx, and CAT in patients with FMS.

In the present study, both antioxidant and oxidant enzyme activities were found to be high in FMS group independent of disease severity (VAS, FIQ). The antioxidant enzyme activities were presumed to increase in response to the increased oxidative stress activity.[32-35] This might be due to the activation of the nuclear factor (erythroid-derived-2)-like 2 transcription factor, which is activated in oxidative stress conditions and induces antioxidant response elements.[36-38] Oxidative markers were not correlated with disease severity, but some parameters (SOD-balance) were associated with audiological complaints. Hence, the imbalance complaint increased with an increase in SOD (antioxidant) levels. Furthermore, a positive correlation was found between BMI and NO (oxidant), supporting the high oxidative stress in obese individuals. High oxidative stress also adversely affects the health of patients with FMS through DNA and protein oxidation.[36] According to the current literature, pro-inflammatory cytokines and inflammatory markers are found high in obese individuals.[37]

Symptoms associated with the inner ear, such as tinnitus, hearing loss, vertigo, and dizziness, are correlated with NO/ONOO cycle illnesses. These cycle-slowing agents have been shown to be beneficial in treating tinnitus and related diseases.[38,39] Güçlütürk *et al*.[39] and Tsai *et al*.[40] showed that oxidative stress might contribute to the pathogenesis of benign positional progressive vertigo. Moreover, Raponi *et al*.[41] observed a significant improvement in patients with Meniere's disease treated with antioxidants compared with other treatments.[41,42] We found that the antioxidant parameter (SOD) was positively proportional to the imbalance complaint.

Limitation of the study

We should explain why there was no correlation between indices of severity and oxidative stress markers despite observing an overall difference in the two groups. Our study group consisted of patients from a wide age range (21–68 years). We know that oxidative stress increases with age. This may have affected the results of the study.

Conclusions

FMS is soft-tissue rheumatism characterized by chronic widespread musculoskeletal pain. Central sensitization-related neuroaudiological symptoms are frequently seen in patients with FMS. The role of oxidative stress in the etiopathogenesis of the disease has not been elucidated.

According to our study, patients with FMS have high levels of oxidative stress markers (GPx, NO, and MDA), highly frequent audiological symptoms with high hearing frequencies in audiometry, and independent of disease severity. İmbalance complaint was positively related with SOD levels. Antioxidant therapy may be used in the future for the treatment of FMS patients with audiological complaints.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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