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Thiol-Disulfide Balance in Fibromyalgia: A Case-Control Study

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Abstract

Aim. We aimed to examine the thiol-disulfide (SS) balance, a recognized marker of oxidative stress, in fibromyalgia syndrome (FMS).

Methods. The study comprised 98 female participants (61 newly diagnosed patients and 37 patients under treatment) with FMS, along with 82 apparently healthy female volunteers. In both groups, assessments were conducted using the Fibromyalgia Impact Questionnaire (FIQ), Visual Analogue Scale (VAS), Pittsburgh Sleep Quality Index (PSQI), Fatigue Severity Scale (FSS), Short Form-36 (SF-36), Tender Point Count, Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Native thiol (NT) and total thiol (TT) levels were measured, SS levels and SS/NT ratio were calculated.

Results. FMS patients demonstrated significantly lower NT levels, higher SS levels, and an elevated SS/NT ratio compared to the control group ($p < 0.05$ for all groups). In FMS patients, a statistically significant correlation was found between SS level and the SS/NT ratio, as well as the number of tender points (r=-0.24, p=0.02; r=-0.21, p=0.04), SF-36 pain subscales (r=0.22, p=0.032; r=0.21, p=0.04), and BAI scores (r=-0.22, p=0.01; r=-0.23 p=0.03). In the subgroup analysis, all health assessment scales were observed to exhibit statistically significant differences between the under-treatment group and newly-diagnosed group when compared to the control group ($p < 0.05$ for all groups). The FIQ, VAS, FSS, and BAI scores were found to be significantly lower in the under-treatment group as compared to the newly-diagnosed group ($p < 0.05$ for all groups). In the newly-diagnosed group, NT was significantly lower and the SS/NT ratio was significantly higher than those in the control group ($p < 0.05$). In the under-treatment group, SS levels and SS/NT ratio were significantly higher as compared to the control group ($p < 0.05$). In the multivariate regression analysis, which incorporated age, health assessment scales, patient subgroups, tender points, and duration of symptoms to predict the SS/NT ratio, variabes such as being in the under-treatment group, tender points, and BAI score were identified as significant predictors ($p < 0.05$).

Conclusions. The thiol-SS balance was observed to shift in the oxidative direction, and oxidative stress was higher in the FMS group. The absence of a significant difference between the under-treatment group and the newly-diagnosed group in terms of thiol-SS balance parameters suggests a shift to oxidative stress in patients, independent of the treatment status.

Keywords
Disulfide; Fibromyalgia; Oxidative Stress; Pain; Thiol

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Introduction

Fibromyalgia syndrome (FMS) is a clinical picture of an unknown etiology characterized by widespread body pain, fatigue, sleep disturbance, cognitive impairment, and anxiety. The prevalence of FMS is 2-4% worldwide. Potential causes in etiology include genetic, neurological, psychological, immunological factors, and sleep problems [1, 2]. Although the etiology of FMS remains unclear, significant advancements have occurred in understanding its origins in recent years. The neuroendocrine and autonomic nervous systems as well as genetic and psychosocial factors play a role in the pathophysiology of FMS. FMS is thought to develop in individuals with genetic predisposition if exposed to environmental, physiological, and psychological stresses [3].

Recent studies suggest that oxidative stress plays a role in the etiopathogenesis of FMS [4, 5]. The relation between the rate of formation of free radicals and the rate of their elimination is referred to as oxidative balance. An increase in the formation rate or a decrease in the elimination rate of these radicals causes the deterioration of this balance. Oxidative stress triggers a series of pathophysiological processes that lead to cellular toxicity [6]. Antioxidants can be classified into enzymatic and non-enzymatic structures. Glutathione peroxidase, superoxide dismutase (SOD), glutathione reductase, paraoxonase, arylesterase, and catalase (CAT) are enzymatic antioxidants, while glutathione (GSH), ascorbic acid, vitamin E, selenium, and uric acid are examples of non-enzymatic antioxidants [7]. Various studies on oxidative stress in FMS have explored antioxidant status with protein carbonyls, malondialdehyde, and nitric oxide; they have examined oxidative enzyme activities such as GSH, paraoxonase, arylesterase, CAT, and SOD. Studies have yielded varying results regarding oxidant stress and antioxidant status [4, 8–10].

Thiols are organic sulfur analogs of alcohol compounds containing a sulfhydryl group attached to a carbon atom [11]. The plasma thiol pool includes albumin, protein, and low-molecular-weight thiols, some of which are formed of cysteine, cysteinyl glycine, and γ-glutamyl cysteine [12]. Thiol groups of proteins, thiol groups of low-molecular-weight compounds, cysteine residues, and other thiol groups are oxidized by environmental oxidant molecules and turn into reversible covalent disulfide (SS) bond structures. The SS bond structures formed can be reduced back to thiol groups. Thus, the thiol-SS balance can be maintained; this balance plays a role in detoxification, antioxidant protection, apoptosis, signal transduction, regulation of enzymatic activity, transcription factors, and cellular signaling mechanisms [13]. In the context of oxidative stress, this balance shifts in favor of SS, while serum thiols, one of the main antioxidant buffers of the body, decrease. Abnormal thiol-SS balance levels are involved in the pathogenesis of many diseases, such as diabetes mellitus, cardiovascular diseases, cancer, rheumatic diseases, chronic kidney failure, neurological diseases, and liver diseases [13]. For evaluating the thiol-SS balance, both variable levels can be measured separately and additively with the automatic measurement method developed by Erel and Neselioglu [14]. This is an easy, inexpensive, practical, fully automated, and optionally manual spectrophotometric process that evaluates SS homeostasis [14]. Research on the thiol-SS balance in fibromyalgia is limited, and conflicting results have been reported [10, 15–17].

Numerous studies have demonstrated the presence of oxidative stress in FMS, using different parameters [5]; however, the findings from studies on the thiol-SS balance are still contradictory [10, 17]. We primarily **aimed to** evaluate thiol-SS homeostasis in patients with FMS compared to healthy controls. Our secondary objectives were to elucidate the association between the thiol-SS balance and clinical parameters in FMS and to compare thiol-SS balance parameters between newly diagnosed patients and those undergoing treatment.

Materials and Methods

Study Design and Participants

This case-control study was conducted at Ankara Training and Research Hospital, Physical Medicine and Rehabilitation outpatient clinic, Ankara, Turkey, between June and December 2017. Participants included 98 female FMS patients who met the 2016 revised FMS diagnostic criteria and 82 apparently healthy female volunteers.

Eligibity Criteria of Participants

Exclusion criteria were systemic diseases such as uncontrolled diabetes mellitus, renal diseases, atherosclerotic heart disease, metabolic syndrome, a history of malignancy, acute and chronic infection, pregnancy, cognitive impairment, and absence of patient consent. The control group comprised apparently healthy females matched for age and gender. Socio-demographic characteristics of patients and controls were recorded.

Health Assessment Scales

The **Fibromyalgia Impact Questionnaire** (FIQ) is a specific scale that assesses physical function and health status in fibromyalgia. High scores indicate low functional outcomes [18].

The **Short Form-36** (SF-36) consists of eight subscales: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, mental health, social functioning, bodily pain, and general health perceptions. Low scores are associated with poor functional outcomes [19].

Pain intensity was evaluated with the **Visual Analogue Scale** (VAS) [20].

The **Beck Depression Inventory** (BDI) and **Beck Anxiety Inventory** (BAI) were used to measure depression and anxiety levels. High scores indicate increased depression or anxiety symptoms [21, 22].

The **Pittsburgh Sleep Quality Index** (PSQI) was used to assess sleep quality. High scores indicate poor sleep quality [23].

The **Fatigue Severity Scale** (FSS) was used to assess fatigue status. High scores on the scale indicate increased fatigue [24].

Tender Point Count. In tender point assessment, approximately 4 kg of pressure, defined as the blanching of the nail bed color after thumb pressure, is applied to the 18 tender points. Pain elicited during palpation of the tender point was considered indicative of a positive tender point [25].

Biochemical Analysis

After collecting 5 ml of blood from the patients into a biochemistry tube, the tubes were centrifuged at 1500 g for 10 minutes after a 30-minute incubation period in the biochemistry laboratory of our hospital. Subsequently, the serums were transferred to Eppendorf tubes, and the samples were stored at -80 degrees Celsius until the day of analysis. On the day of analysis, all samples were thawed, and the blood thiol-SS homeostasis parameters were measured using the automated measurement method developed by Erel and Neselioglu with an autoanalyzer (Cobas c501, Roche, Mannheim, Germany) [14]. In this method, native thiol (NT) levels of the sample were measured with 5, 5'-dithiobis (2-nitrobenzoic acid) (DTNB). Subsequently, the SS content of the sample was reduced by sodium borohydride ($NaBH_4$) to generate free thiol groups. Formaldehyde was used to deactivate excess unused $NaBH_4$. Following that, total thiol (TT) levels, including both reduced thiols from SSs and NT, were determined using DTNB. The amount of SS was determined by taking half of the difference between serum TT and NT levels. After the determination of NT and TT levels, SS and SS/NT percent ratios were calculated [14].

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., NY, USA). The normality of the data was assessed with the Shapiro-Wilk test. Nominal (categorical) data were presented as numbers and percentages (%). Parametrically distributed data were presented as mean ± standard deviation, while data showing non-parametric distribution were shown as median (25^{th}-75^{th} percentile) values. The significance of the difference between groups, based on mean values, was compared with Student's t-test. For comparing more than two groups, one-way ANOVA with a post hoc Bonferroni test was used. For variables without a normal distribution, the Mann-Whitney U test was used to compare two groups, and the Kruskal-Wallis test was utilized to compare more than two groups. Spearman's correlation analysis was used for non-parametric variables, and Pearson's correlation analysis was used for parametric variables to investigate the relationship between variables. The predictive value of parameters were evaluated by multivariate regression analysis. For $p < 0.05$, the results were considered statistically significant.

Results

Ninety-eight individuals with FMS (61 newly diagnosed patients and 37 patients under treatment) and 82 apparently healthy volunteers were included in the study. In the under-treatment group, 27 patients were taking duloxetine, 8 patients were taking pregabalin, 1 patient was taking both duloxetine and pregabalin, and 1 patient was taking amitriptyline.

The median age of the FMS group was 44 (37-51) years, and the median age of the control group was 44 (32-53.25) years (p=0.80). The median number of tender points in patients was 12.5 (9-16). The median duration of symptoms was 36 (12-72) months. The mean duration of taking medications among patients under treatment was 6 (1-12) months. The score of the FMS group was found to be statistically significantly higher ($p < 0.001$) on the FIQ, VAS, PSQI, FSS, BDI, and BAI. Additionally, the FMS group scores were significantly lower for each subscale of the SF-36 questionnaire ($p < 0.001$) (Table 1).

NT levels of the FMS group were significantly lower than those in the control group ($p < 0.01$). TT levels were

Table 1. Comparison of health assessment scales and oxidative stress biomarkers in the fibromyalgia and control group.

		FMS group (n=98)	Control group (n=82)	p value
Fibromyalgia Impact Questionnaire (FIQ)		66.9 (56.4-76.9)	20.7 (10.0-28.3)	<0.001
Visual Analogue Scale (VAS)		72.5 (60-90)	0 (0-17.5)	<0.001
Pittsburgh Sleep Quality Index (PSQI)		9 (6.5-12)	4 (3-6)	<0.001
Fatigue Severity Scale (FSS)		5.2 (3.9-6.1)	3 (1.5-4)	<0.001
Beck Depression Inventory (BDI)		14 (10-23)	4 (2.5-8)	<0.001
Beck Anxiety Inventory (BAI)		18 (10.5-28.5)	5 (3-12)	<0.001
SF-36 subscales	Physical functioning	55 (45-70)	90 (77.5-95)	<0.001
	Role limitations due to physical problems	25 (0-56.3)	100 (87.5-100)	<0.001
	Role limitations due to emotional problems	0 (0-33.3)	100 (100-100)	<0.001
	Vitality	25 (15-40)	65 (50-75)	<0.001
	Mental health	48 (32-65)	76 (64-84)	<0.001
	Social functioning	62.5 (49.4-75)	87.5 (68.8-100)	<0.001
	Bodily pain	32.5 (12.5-45)	77.5 (60-90)	<0.001
	General health perception	35 (25-50)	65 (50-90)	<0.001
Native thiol (μmol/L)		394.4±52.4	418.1±50.0	<0.01
Total thiol (μmol/L)		429.6 (384.5-468)	441 (417.2-475.9)	0.05
Disulfide (μmol/L)		17.5 (13.6-23.4)	14.8 (9.1-19.5)	<0.01
Disulfide/native thiol (%)		4.5 (3.4-5.9)	3.5 (2.2-4.7)	<0.001

Table 2. Comparison of health assessment scales and oxidative stress biomarkers in the fibromyalgia and control group.

	Newly diagnosed patients (n=61)	Patients under treatment (n=37)	Control group (n=82)	p value*
Age, years	43.0 (34.5-50.5)	45.0 (39.0-51.5)	44.0 (32.0-53.3)	0.44
Duration of medication use, months		6 (1-12)		
Duration of symptoms, months	30 (12-60)	48 (20-105)		0.04**
Tender points	13 (9-16)	12 (7-14)		0.23**
Fibromyalgia Impact Questionnaire (FIQ)	70.8 (61.4-78.8)[a]	57.3 (50.4-67.1)[b]	20.7 (10.0-28.3)[c]	<0.001
Visual Analogue Scale (VAS)	80 (70-90)[a]	60 (45-80)[b]	0 (0-17.5)[c]	<0.001
Pittsburgh Sleep Quality Index (PSQI)	9.0 (7.0-12.5)[a]	8.0 (5.3-11.8)[a]	4.0 (3.0-6.0)[b]	<0.001
Fatigue Severity Scale (FSS)	5.6 (4.6-6.2)[a]	4.4 (3.3-5.8)[b]	3.0 (1.5-4.0)[c]	<0.001
Beck Depression Inventory (BDI)	15 (10-23)[a]	12 (9.3-22.3)[a]	4 (2.5-8)[b]	<0.001
Beck Anxiety Inventory (BAI)	22 (13.5-30.5)[a]	12.5 (8.3-23.5)[b]	5 (3-12)[c]	<0.001
SF-36 subscales:				
· Physical functioning	55 (35-70)[a]	60 (52.5-80)[a]	90 (77.5-95)[b]	<0.001
· Role limitations due to physical problems	25 (0-50)[a]	25 (0-75)[a]	100 (87.5-100)[b]	<0.001
· Role limitations due to emotional problems	0 (0-33.3)[a]	0 (0-50)[a]	100 (100-100)[b]	<0.001
· Vitality	25 (15-40)[a]	25 (12.5-42.5)[a]	65 (50-75)[b]	<0.001
· Mental health	48 (32-64.5)[a]	48 (32-66.5)[a]	76 (64-84)[b]	<0.001
· Social functioning	62.5 (48.8-75)[a]	62.5 (43.8-75)[a]	87.5 (68.8-100)[b]	<0.001
· Bodily pain	22.5 (12.5-35)[a]	37.5 (28.8-57.5)[b]	77.5 (60-90)[c]	<0.001
· General health perception	35 (25-50)[a]	40 (25-55)[a]	65 (50-90)[b]	<0.001
Total thiol (μmol/L)	429.5 (383-469.2)	430.8 (392.2-472.4)	441 (417.2-475.9)	0.14
Native thiol (μmol/L)	384.2 (351.9-428.6)[a]	387.6 (358.4-423.4)[a,b]	416.6 (381.3-444.7)[b]	0.01
Disulfide (μmol/L)	17.2 (13.8-21.3)[a,b]	18.3 (13.5-28.1)[b]	14.8 (9.1-19.5)[a]	0.01
Disulfide/native thiol (%)	4.4 (3.5-5.9)[a]	4.6 (3.3-7.1)[a]	3.5 (2.2-4.7)[b]	<0.001

Notes: Descriptive statistics expressed as median (1st-3rd quartile) values.

*Kruskal-Wallis test: there was no statistically significant difference between the groups with the same letter in exponential expressions according to the Dunn-Bonferoni pairwise comparison test. Groups that share same letters are non significant, while different letters represent significantly different groups.

**Mann-Whitney U test was used, with the control group excluded from comparison.

not significantly different in the FMS group as compared to the control group (p=0.05). SS levels and SS/NT ratio were statistically significantly higher in the FMS group than in the control group ($p < 0.01$) (Table 1).

Table 2 shows the comparisons of health assessment scales and oxidative stress biomarkers in the under-treatment group, newly-diagnosed group, and control group. In the subgroup analysis, all health assessment scales were observed to exhibit statistically significant differences between the under-treatment group and newly-diagnosed group when compared to the control group ($p < 0.05$ for all groups). The FIQ, VAS, FSS, and BAI scores were found significantly lower in the under-treatment group as compared to the newly-diagnosed group ($p < 0.05$ for all groups). In the newly-diagnosed group, NT was significantly lower and the SS/NT ratio was significantly higher than those in the control group ($p < 0.05$). In the under-treatment group, SS levels and SS/NT ratio were significantly higher as compared to the control group ($p < 0.05$). While NT values were higher in patients under treatment as compared newly diagnosed patients, no difference was observed in SS values. The SS/NT ratio remained oxidative in both patients under treatment and newly diagnosed patients (Table 2).

In the FMS group, a statistically significant correlation was found between SS level and the SS/NT ratio, as well as the number of tender points (r=-0.24, p=0.02; r=-0.21, p=0.04), SF-36 pain subscales (r=0.22, p=0.03; r=0.21, p=0.04), and BAI scores (r=-0.22, p=0.01; r=-0.23 p=0.03). No additional correlations with other parameters were identified.

A multiple regression analysis was conducted to predict the SS/NT ratio, considering variables such as age, health assessment scales, patient subgroups, tender points, and duration of symptoms. Variables such as being in the under-treatment group, tender points, and BAI scores were found as statistically significant predictors ($p < 0.05$) (Table 3).

Discussion

In our study, we observed lower levels of antioxidant components of the thiol-SS balance in the FMS group as compared to the control group. In contrast, oxidative indicators were found to be higher in the FMS group. In addition, while SS values were significantly higher in the under-treatment group compared to the control group, no statistically significant difference was found in the newly-diagnosed group compared to the control and under-treatment groups. This suggested that the elevation in SS observed in the newly-diagnosed group, which was not statistically significant compared to the control group, became significantly higher than that in the control group with the subsequent increase in SS following treatment. Upon evaluation with clinical scales, we found predominantly weak correlations between the number of tender points, SF-

Table 3. Multiple regression analysis to predict the disulfide/native thiol ratio.

Predictor		$\beta \pm$SE	Standardized β (95% CI)	p value
Group	Newly diagnosed patients	1.692±1.130	0.732 (-0.234 to 1.698)	0.14
	Patients under treatment	2.299±0.980	0.995 (0.157 to 1.832)	0.02
	Controls (reference)	-	-	-
Age, years		0.009±0.016	0.040 (-0.109 to 0.190)	0.59
Tender points		-0.158±0.057	-0.458 (-0.782 to -0.133)	0.01
Duration of symptoms, months		-0.001±0.004	-0.022 (-0.199 to 0.154)	0.80
Fibromyalgia Impact Questionnaire(FIQ)		0.029±0.018	0.335 (-0.066 to 0.735)	0.10
Visual Analogue Scale (VAS)		0.015±0.013	0.227 (-0.143 to 0.628)	0.27
Pittsburgh Sleep Quality Index (PSQI)		0.044±0.063	0.079 (-0.143 to 0.301)	0.48
Fatigue Severity Scale (FSS)		-0.098±0.149	-0.077 (-0.155 to 0.310)	0.51
Beck Depression Inventory (BDI)		0.000±0.033	0.001 (-0.247 to 0.245)	0.99
Beck Anxiety Inventory (BAI)		-0.050±0.021	-0.263 (-0.479 to -0.047)	0.02
SF-36 subscales:				
· Physical functioning		-0.005±0.012	-0.049 (-0.277 to 0.178)	0.67
· Role limitations due to physical problems		-0.005±0.007	-0.087 (-0.335 to 0.160)	0.49
· Role limitations due to emotional problems		-0.010±0.006	-0.188 (-0.417 to 0.040)	0.11
· Vitality		0.008±0.015	0.093 (-0.231 to 0.418)	0.57
· Mental health		-0.005±0.014	-0.050 (-0.309 to 0.209)	0.70
· Social functioning		0.018±0.010	0.200 (-0.018 to 0.418)	0.07
· Bodily pain		0.019±0.014	0.245 (-0.116 to 0.607)	0.18
· General health perception		0.003±0.013	0.030 (-0.247 to 0.307)	0.83

Notes: R^2=0.25, β – Regression Coefficient, SE – Standart Error, CI – Confidence Interval.

36 pain subscales, BAI scores, and thiol-SS components; however, no correlations were identified for the FIQ, which is considered the primary scale for assessing FMS.

Despite numerous studies investigating the etiopathogenesis of FMS, uncertainties persist regarding its etiopathogenesis [26]. Oxidative stress has been a focus of investigation in recent decades, with the idea that it may be related to the etiopathogenesis and severity of clinical symptoms [5]. There is mention that local hypoxia may be a contributing factor in the development of FMS [27]. The mechanism suggested for the relationship between pain sensitivity and oxidative stress in FMS involves an elevation in superoxide and lipid peroxidation products due to a reduction in mitochondrial membrane potential attributed to decreased levels of coenzyme Q10, coupled with a decrease in the rate of free radical elimination owing to impaired mitochondrial function. Consequently, this triggers cell autophagy, leading to cell damage and increased oxidative damage in FMS patients [5]. In addition, abnormal pain processing in the central nervous system and dysregulation in modulatory pathways are thought to contribute to the manifestation of FMS [26]. The central nervous system is one of the most vulnerable tissues to free radical damage due to its high lipid content [27]. Oxidative stress markers such as hydroperoxides and aldehydes are produced by lipid peroxidation reactions. Lipid peroxidation products have been shown to be elevated in FMS patients and correlated with clinical scales [8]. Consequently, oxidative stress and mitochondrial dysfunction are thought to be actively involved in pain pathways by triggering free radical and inflammatory cytokine increase [28].

The dynamic thiol-SS balance is one of the main antioxidant buffers of the body and a powerful protective mechanism against oxidative stress [14]. This balance is disturbed in many diseases where oxidative stress is thought to be involved in the pathophysiological mechanisms [13]. Although various studies have evaluated the thiol-SS balance in FMS, the findings are contradictory, and conflicting results have emerged regarding its correlation with clinical scales of FMS [10, 15, 17]. Fidan *et al.* evaluated the thiol-SS balance in FMS and found a shift towards antioxidants in the FMS group [10]. That result was unexpected, as reviews evaluating oxidative stress in FMS generally reported a tendency towards increased oxidative stress in this balance [5]. Tuzcu *et al.* [15] evaluated the thiol-SS balance in FMS and found a shift in the oxidative direction, aligning with the findings of our study. In addition, they found a correlation between the FIQ scores and oxidative markers [15]. Ekinci *et al.* conducted a comparable evaluation of the thiol-SS balance in FMS and found a similar tendency towards the oxidative side [17]. We found that the thiol-SS balance shifted to the SS side, which is the oxidative side, in FMS patients. While we identified some correlations with clinical scales, no correlation was observed with the FIQ, which serves as the primary assessment scale in patients with FMS. This might be attributed to factors such as comorbidities, medications, and insufficient homogenization of patients in the study groups. Our study differs from previous research in comprehensive evaluation with numerous clinical scales, comparison of treatment and newly diagnosed groups, and presentation of regression analysis results. In the regression analysis, variables such as being in the under-treatment group, tender points, and BAI scores were significant predictors for the SS/NT ratio. This suggests that, beyond FMS itself, medication usage also exerts an effect on SS level.

The oxidant-antioxidant balance in the body is known to be affected by using various drugs [29]. In a study eval-

uating the effect of duloxetine, one of the most commonly used drugs in FMS, on oxidative stress, it was shown that duloxetine reduced the entry of calcium (Ca^{+2}) and reactive oxygen radicals into neuronal tissue via glutathione and had a neuroprotective effect [30]. Another study conducted on rats, investigating the hepatotoxic effects of hydroxylated and epoxide metabolites of duloxetine, reported that it could cause oxidative stress through the release of free radicals or reactive oxygen species [31]. In our study, we found a non-significant elevation in SS levels in the newly-diagnosed group compared to the control group, whereas this value was significantly higher in the under-treatment group than in the control group. Moreover, the significant prediction of the SS/NT ratio by being in the under-treatment group, along with tender point number and BAI score in our regression analysis, indicated that the treatment shifted this balance in favor of SS. This suggests that the antioxidant sites in albumin, the most important thiol-containing antioxidant molecule of serum, may have been affected, as albumin is the carrier of this drug in plasma [32]. Since this shift in favor of oxidants caused no significant increase compared to the newly-diagnosed group, and significant improvements in clinical scores of patients were observed, it is thought that oxidative stress can be mitigated through the use of thiol-containing antioxidant supplements in these patient groups and the possible supportive effect on recovery is worth investigating. Considering the regression of symptoms, significant improvement in clinical scales, and metabolic effects of the drugs, it appears challenging to attribute these outcomes to a single cause. We believe that conducting prospective follow-up studies within similar patient groups could prove beneficial in gaining further insights into this matter.

Limitations

The strengths of our study lie in the use of diverse clinical scales, a substantial number of participants, and the inclusion of treatment status details and regression analysis results. The limitations of the study encompass its exclusive focus on female patients and the relatively small number of subgroups included.

Conclusions

There was no difference in SS and NT levels in newly diagnosed patients and those undergoing treatment; however, significantly higher SS levels in the under-treatment group compared to the control group suggest a potential association with the binding of this drug to albumin. The treatment of FMS, the number of tender points, and anxiety levels were found to be correlated with the SS/NT ratio. Additionally, in FMS, there were weak correlations between the number of tender points, SF-36 pain subscales, BAI scores, and both SS levels and SS/NT ratio.

Ethical Statement & Informed Consent

The study was carried out according to the Helsinki declaration. The local ethical committee approval (93471371-771-E.8274) was obtained. Patients consent was obtained.

Data Availability

Data sets generated and/or analyzed during the current study will be provided by the corresponding author upon request of the editor or reviewers.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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