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Investigation of the Relationship between Inflammation and Oxidative Stress Markers and Treatment Response in First-Attack Major Depression Patients: A Follow-Up Study

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ABSTRACT

Objective: There is a need to biomarkers for major depression (MD). The goals of this study are to compare serum levels of oxidative stress markers malondialdehyde (MDA) and F2-isoprostane and inflammation markers tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) between patients with first-episode MD and healthy controls, to investigate the change of these markers after treatment and to investigate the relationship between levels of these markers and treatment response.

Method: Our study was performed in 30 first-episode MD patients and 30 healthy volunteers. During the clinical evaluation Hamilton Depression Rating Scale and Clinical Global Impression Scale were applied to the participants. Serum levels of markers were measured at the baseline and after 8 weeks of treatment.

Results: Compared to the control group, first-episode MD patients had significantly higher IL-6, CRP and MDA levels and lower F2-isoprostane levels. There was no difference between the groups in terms of TNF-α levels. TNF-α, IL-6, MDA and F2-isoprostane levels decreased significantly after treatment, whereas there was no significant change in CRP levels with treatment. Baseline F2-isoprostane levels were found to be significantly higher in treatment responders than non-responders ($p<0.05$).

Conclusion: In our study, it was shown that there are irregularities related to inflammatory processes and oxidative stress in MD, even in patients who had their first-episode and did not take medication, and these irregularities can be resolved after treatment. While there was a relationship between treatment response and baseline F2-isoprostane levels, there was no relationship with other biomarkers.

Keywords: Biomarkers, depression, inflammation, oxidative stress, treatment response

INTRODUCTION

Major depression (MD) is an important public health problem and it directly affects 322 million people worldwide (World Health Organization 2017). Its prevalence is higher in females than males. While its prevalence in women is 5.1% worldwide, its prevalence in men has been reported to be 3.6% (World Health Organization 2017). In Turkey, the prevalence of depressive disorders has been reported to be 7.2% (9.8% in women, 3.9% in men) (Erol et al. 1998). Depression can lead to suicide, being more common in moderate and severe depressions and prolonged periods of illness, and it is among the most important causes of disability (World Health Organization 2017, Öztürk and Uluşahin 2015). Early and accurate diagnosis, and the most appropriate treatment and follow-up of patients are very important in determining the course of depression (Öztürk and Uluşahin 2015). Almost 60% of the patients do not respond to the treatment with the first use of antidepressants, and 20% of these patients are also unresponsive to other treatments (Mora et al. 2018). For these reasons, it is important to develop methods that can predict the response to treatment and determine the best medication for each patient, thus providing personalized medication selection (Mora et al. 2018).

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Today, there are no biological markers among the diagnostic criteria of any psychiatric disease, including depression (Gadad et al. 2018, Hacımusalar and Eşel 2018). Detection of biomarkers for depression will help with providing more accurate treatments, ensuring efficacious treatment and complete well-being, as well as determining new targets for the development of new antidepressant medicines (Mora et al. 2018, Gadad et al. 2018, Hacımusalar and Esel 2018).

The immune system is a complex structure with many cells and secretory factors that regulates inflammation in all tissues (Medina-Rodriguez et al. 2018). It has been suggested that inflammation is important in the etiopathogenesis of major depression and that inflammation markers can be used as markers for the diagnosis and treatment response to depression (Hacımusalar and Eşel 2018). Although changes in immune response elements in major depression have been shown by many studies, no consensus has been reached on the change in cytokine levels (Mora et al. 2018, Hacımusalar and Eşel 2018). In many studies, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) levels were found to be significantly higher in both blood and cerebrospinal fluid of depression patients compared to healthy controls (Medina-Rodriguez et al. 2018). In addition, it has been reported that peripheral blood levels of many proinflammatory cytokines are higher in depression patients compared to healthy controls, and cytokine levels change with antidepressant treatment (Mora et al. 2018). In a study, it was reported that there was a significant correlation between treatment resistance, as assessed by number of failed antidepressant treatments and increased plasma TNF, tumor necrosis factor receptor-2 (sTNF-R2), IL-6 and C-reactive protein (CRP) concentrations (Haroon et al. 2018). According to the results of a meta-analysis, IL-6, TNF-α, interleukin-10 (IL-10) and CC chemokine ligand 2 (CCL-2) levels were found to be significantly higher in major depression patients compared to healthy controls, and it has been shown that there is a significant decrease in IL- 6, TNF-α, IL-10 and CCL-2 levels after antidepressant treatment (Kohler et al. 2018).

Oxidative stress is a condition associated with the deterioration of the balance between antioxidants and pro-oxidants in favor of pro-oxidants, and it has been suggested that oxidative stress plays a role in the pathophysiology of depression (Lopresti et al. 2014, Liu et al. 2015). There are studies reporting that the levels of lipid peroxidation products such as malondialdehyde (MDA) increase in depression patients, and that MDA levels decrease and return to normal with antidepressant treatment (Hacımusalar and Eşel 2018). Köhler et al. (2018) found that the first-episode depression patients had increased MDA and decreased superoxide dismutase (SOD) levels compared to healthy controls. According to the results of a meta-analysis, it was found that lipid peroxidation markers are elevated in depression patients, there is a relationship between the levels of these products and the severity of depression, and the levels of these markers decrease with antidepressant treatment (Mazereeuw et al. 2015).

In the literature, there are only few studies that investigates the relationship between treatment response and markers of inflammation and oxidative stress in depression patients together. In one of these studies, the relationship between oxidative stress and inflammation and treatment response was investigated in depression patients, and the initial F2-isoprostane (F2-iso) levels were found to be significantly lower in those who responded to treatment (Lindqvist et al. 2017).

There are some inconsistencies in the results of studies which investigate inflammation markers and oxidative stress markers together. It is believed that the reasons for this situation are the differences in the methods and patient group characteristics of the studies (Gadad et al. 2018). Detection of biomarkers is important in the diagnosis of depression, in determining which treatment method is more convenient in which patient and predicting the possible response to treatment. Therefore, there is a need for studies in this field especially in patient clusters with similar clinical characteristics (Gadad et al. 2018, Hacımusalar and Eşel 2018).

The goals of this study are as the following: (a) to determine the serum levels of oxidative stress markers (MDA and F2-isoprostane) and inflammation markers (TNF-α, IL-6 and CRP) in first-episode major depression patients and to compare them with those in the healthy control group, (b) to investigate whether the levels of these markers in the patient group changed after 8 weeks of treatment compared to pre-treatment, (c) and whether the baseline levels of these markers were associated with treatment response. The first hypothesis of the study is that peripheral blood levels of oxidative stress and inflammation markers will be higher in first-episode major depression patients compared to healthy controls. The second hypothesis is that the levels of these markers will decrease after treatment. The third hypothesis is that there will be a difference between those who respond to treatment and those who do not, in their pre-treatment levels of these markers. We believe that this study will contribute to both the clarification of the pathophysiology of depression and to the identification of biomarker candidates that can be used to diagnose depression and/or predict treatment response.

METHODS

Before starting the research, an application was made to the Çanakkale Onsekiz Mart University Rectorate Clinical Research Ethics Committee and ethics committee approval was obtained with the date of 28.11.2018 and decision number 21-10.1.2018.

For this study, the patient group was formed among the patients who applied to the outpatient clinics of Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Psychiatry between 28 May 2019 and 4 December 2019, was diagnosed with MD according to the DSM-5 diagnostic criteria, were diagnosed with MD according to DSM-5 diagnostic criteria and decided to use a member of the selective serotonin reuptake inhibitors (SSRI) group in treatment. Among the 64 patients who were between the ages of 18-65 and met the inclusion criteria, 42 patients who volunteered to participate were included in the study. After the informed consent of the participants was obtained, a detailed clinical evaluation was made and the sociodemographic data form, Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression Scale (CGI) were applied for each patient. After the initial interviews were completed and the blood sample was taken, the predetermined treatment was started, and the study was completed with 30 patients as a result of 12 patients leaving the study during the 8-week follow-up period, which included a total of 2 interviews conducted every 4 weeks. After 8 weeks of treatment, blood samples were taken again from the patient group and the response to treatment was evaluated. The control group was formed with 30 healthy volunteers who were matched one-on-one with each patient who completed the study in terms of gender and smoking and after clinical evaluations were made and sociodemographic data form, HAM-D and CGI were applied, blood samples were taken.

Exclusion criteria for both patient and control groups are as the following: Having a history of any psychiatric disease that requires treatment; risky use of alcohol or alcohol use disorder, substance abuse; acute or chronic infectious disease or inflammatory disease, neurological disease, eating disorder, other chronic medical diseases (obesity, cancer, cardiovascular diseases, diabetes mellitus, thyroid diseases, etc.), being pregnant for female participants, using psychotropic medications and/or medicine that will affect the endocrine system or with anti-inflammatory or antioxidant properties in the last 6 months, a situation that prevents them from continuing the clinical interview and filling the scales (mental retardation, dementia, significant comprehension and speech difficulties due to previous cerebrovascular diseases, etc.). In addition, the condition of not having any comorbid psychiatric disease and not having depression with psychotic features was required for the patient group, while the condition of not having any psychiatric disease was sought for the control group. In order to minimize the possible undesirable effects on the results due to the different mechanisms of action of the medications, patients who were started on an antidepressant medication other than SSRI or who were recommended to use an additional medication for any reason were not included in the study.

All blood samples were taken between 09:00 and 11:00 in the morning after 12 hours of fasting and after 30 minutes of rest, and the serum samples obtained were stored at -40 °C until analysis. TNF α, IL-6, CRP, MDA and F2-isoprostane levels were measured in serum samples of all participants using ready-made kits by ELISA method. TNF α, IL-6, CRP and F2-isoprostane levels were calculated in ng/L (nanogram/liter), MDA levels were calculated in nmol/ml (nanomoles/milliliter). All clinical evaluations and blood sampling of the participants were completed on February 28, 2020. Those who showed a 50% or more decrease in their total score after 8 weeks of treatment compared to the initial HAM-D total score were considered as "treatment responders" while those with a HAM-D score of less than 7 and a CGI-Severity score of 1 after 8 weeks of treatment were considered to have shown "improvement".

Data Collection Tools

Sociodemographic Data Form: A questionnaire asking about the age, gender, educational status, occupation, marital status, medical background, alcohol and substance use status and medical family background of the individuals were developed by the researchers.

Hamilton Depression Rating Scale (HAM-D): Validity and reliability studies of this scale, which is applied by the clinicians, have been carried out in our country as well. It is a scale that measures the level of depression and changes in severity in the patient. The scale includes 17 questions, where each question is scored between 0 and 4. The total scale score is formed by adding the scores (Akdemir et al. 1996). According to the total scale score, the cut-off point was determined as 7. The total score is evaluated in favor of mild depression between 8-13, moderate between 14-18, severe depression between 19-22, and very severe depression above 23.

Clinical Global Impression Scale (CGI): In this scale, the severity of the disease is graded by the clinician between 1 (normal, not sick) and 7 (most severely ill) (Busner and Targum 2007). There is no study for the validity and reliability of the scale in our country.

Statistical Analysis

Data collected were analyzed using SPSS 19 statistical package program. Categorical variables were given as numbers and percentages. Whether the variables violated the normal distribution was evaluated with both analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) and visual data (histogram and probability graphs). The mean and standard deviation values were given for the numerical variables that fit the normal distribution. The median, interquartile range and minimum (lowest)- maximum (highest) values were given for the numerical variables that did not fit the normal

distribution. Pearson Chi-Square test, Continuity correction and Fisher Exact test were used when necessary in order to compare categorical variables between the patient and control groups. In cases where at least one of the variables did not fit the normal distribution or to determine the relationships between ordinal variables, correlation coefficients and statistical significance were determined using the Spearman Test. The Mann-Whitney U test was used for pairwise comparison of numerical variables between the control and patient groups, and the Wilcoxon test was used for the comparison of numerical variables before and after treatment in the patient group. BackWard logistic regression analysis was used to determine the factors affecting the treatment response. The level of significance was accepted as $p<0.05$.

RESULTS

The gender distribution was balanced in the patient and control groups of the study, and 80% (n=48) of all participants were female. It was observed that 33.3% (n=20) of all participants were smokers, and the distribution of smokers by gender was the same across the two groups. None of the participants had a history of substance use or suicide attempt. Some sociodemographic and clinical data of the participants are summarized in Table 1.

It was examined whether there was a significant difference in serum inflammation markers (TNF-α, IL-6 and CRP) and oxidative stress markers (MDA and F2-isoprostane) levels between the patient and control groups. The results are summarized in Table 2, Figure 1 and Figure 2.

For the HAM-D total scores of the participants in the patient group at the first examination, the median value was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 6.75. According to the baseline HAM-D total scores of the patients, 40% were mild, 30% moderate, and 30% severe/very severe. The median CGI scale-disease severity scores of the patients in the patient group at the first examination were 4, the lowest value was 4, the highest value was 5, and the difference between quartiles was 0.25. It

Table 1. Comparison of age, Body Mass İndex, Smoking, Alcohol Use, and Some Sociodemographic Characteristics Between Groups

	Patient Group (n:30) Median (min-max) Interquartile range	**Control Group (n:30) Median (min-max) Interquartile range**	**p**
Age*	42.5 (20-59) 20.5	29 (23-64) 13.25	0.005
Total years of education*	12 (5-20) 9	18 (5-20) 8	< 0.001
Body Mass Index*	23.2 (18.6-24.9) 2.7	21.7 (18.7-24.9) 3.8	0.093
Living in urban area**	63.3% (19)	100% (30)	< 0.001
Living in rural area	36.7% (11)	0% (0)	
Employed**	26.7% (8)	73.3% (22)	< 0.001
Unemployed	73.3% (22)	26.7% (8)	
Lives alone**	10% (3)	36.7% (11)	0.015
Lives with relatives	90% (27)	63.3% (19)	
Family history of psychiatric disease**	23.3% (7)	16.7% (5)	0.519
No family history of psychiatric disease	76.7% (23)	83.3% (25)	
Alcohol **	16.7% (5)	33.3% (10)	0.136
No alcohol	83.3% (25)	66.7% (20)	
Smoker	33.3% (10)	33.3% (10)	
Non-smoker	66.6% (20)	66.6% (20)	
Other medical disease	3.3% (1)	3.3% (1)	
No other medical disease	96.7% (29)	96.7% (29)	
On medication	3.3% (1)	3.3% (1)	
Non-medicated	96.7% (29)	96.7% (29)	

*Mann-Whitney U Test was used. Min: lowest value, Max: highest value
** Chi-square test was used.

Table 2. Comparison of the Levels of Markers of Inflammation and Oxidative Stress Between Groups

	Patient Group (n:30) Median (min-max) Interquartile range	Control Group (n:30) Median (min-max) Interquartile range	p *
CRP	13.66 (4.95-15.36) 2.51	13.38 (3.49-14.38) 2.95	0.044
IL-6	70.15 (41.15-1265.27) 404.59	59.52 (5.13-139.12) 95.90	0.015
TNF- α	44.45 (20.14-833.93) 224.62	42.26 (2.89-84.97) 68.29	0.055
MDA	6.49 (0.07-118.55) 42.15	4.75 (0.20-13.34) 6.58	0.03
F2-iso	86.19 (56.46-1288.39) 404.90	642.12 (71.04-1434.27) 1039.12	0.0004

*Mann-Whitney U Test was used. Min: lowest value, Max: highest value

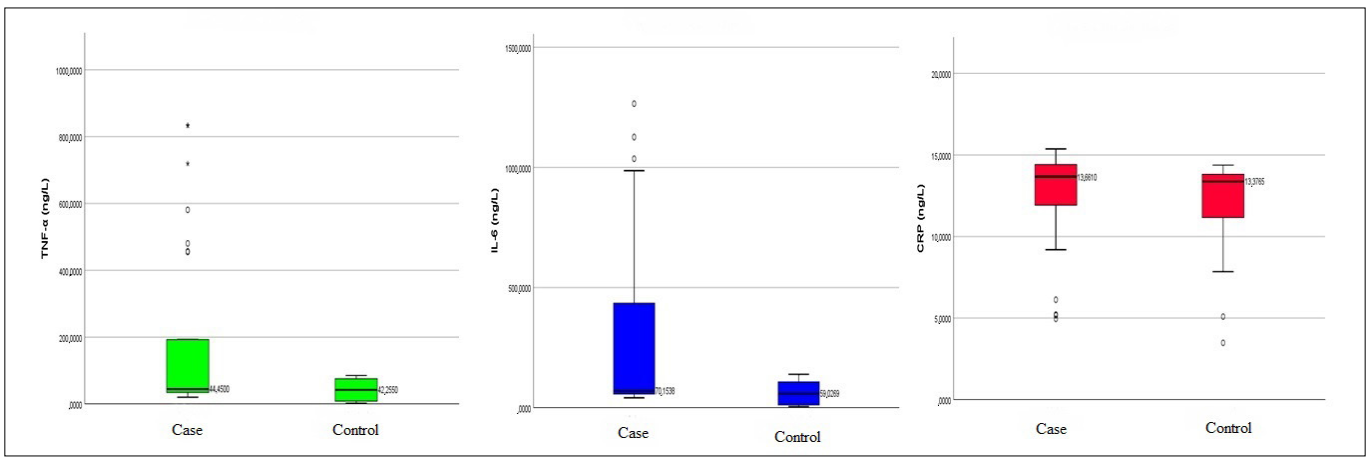

Figure 1. Comparison of TNF-α, IL-6 and CRP levels in the case and control groups.

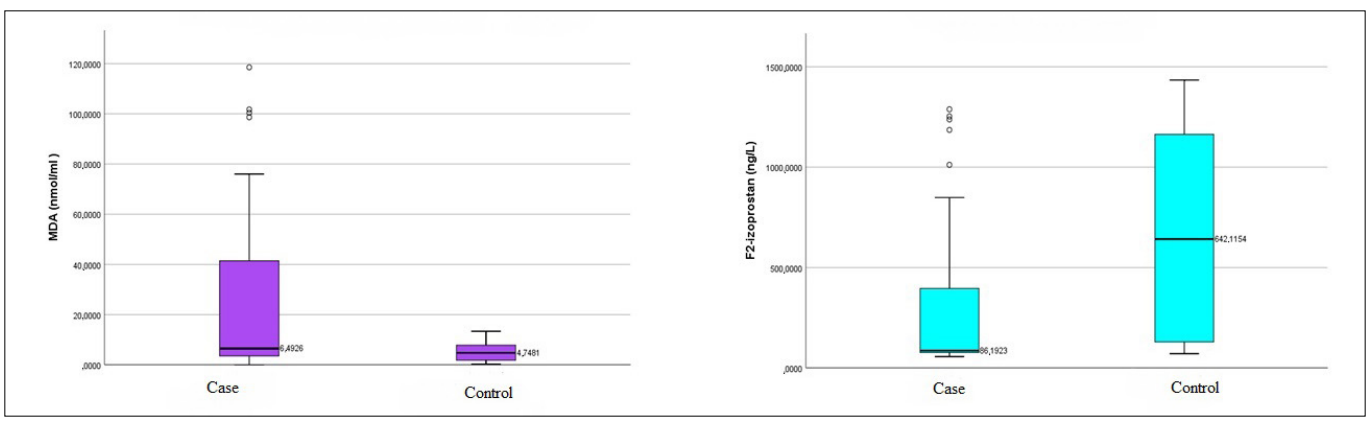

Figure 2. Comparison of MDA and F2-isoprostane levels in case and control groups.

was observed that the participants in the healthy control group did not have any depressive symptoms and all of them scored 0 on the HAM-D scale. The CGI scale-disease severity score for each healthy control was also assessed as 1 (normal, not sick).

The relationship between the variables of the patients was examined and as a result of the correlation analysis. Significant correlations were found between the treatment response and gender (rho=0.582, p<0.01), alcohol use status (rho=-0.447, p<0.05), and initial F2-isoprostane level (rho=-0.391, p<0.05). Accordingly, a positive correlation was found between responding well to treatment and being female, while a negative correlation was found between alcohol use and initial F2-isoprostane levels (see Table 3).

It was investigated whether there was a difference between the levels of inflammatory markers (TNF-α, IL-6 and CRP) and oxidative stress markers (MDA and F2-isoprostane) in the serum obtained from the blood samples taken before the treatment and the blood samples taken 8 weeks after the treatment of the first-episode depression patients (see Table 4, Figure 3, and Figure 4 for the summary of the results).

Table 3. Correlation Analyzes of Patients' Baseline Marker Levels, Gender, Alcohol Use Status, and Treatment Response Variables

	Gender	Alcohol use	CRP	IL-6	TNF- α	MDA	F2-iso	Treatment response
Cinsiyet	1.000	-0.447*	0.010	-0.106	0.000	0.000	-0.125	0.582**
Alcohol use	-0.447*	1.000	0.078	-0.160	-0.243	-0.367*	-0.098	-0.488**
CRP	0.010	0.078	1.000	0.027	0.133	0.060	-0.076	-0.155
IL-6	-0.106	-0.160	0.027	1.000	0.903**	0.622**	0.823**	-0.189
TNF- α	0.000	-0.243	0.133	0.903**	1.000	0.668**	0.834**	-0.214
MDA	0.000	-0.367*	0.060	0.622**	0.668**	1.000	0.605**	-0.147
F2-iso	-0.125	-0.098	-0.076	0.823**	0.834**	0.605**	1.000	-0.391*
Treatment response	0.582**	-0.488**	-0.155	-0.189	-0.214	-0.147	-0.391*	1.000

Spearman correlation analysis was applied. The numbers represent the Spearman correlation coefficient (rho).
* p<0.05 ** p<0.01

Table 4. Comparison of Inflammation and Oxidative Stress Markers Levels Before and After Treatment

	Pre-treatment (n:30) Median (min-max) Interquartile range	Post-treatment (n:30) Median (min-max) Interquartile range	p *
CRP	13.66 (4.95-15.36) 2.51	14.02 (2.23-15.03) 3.20	0.894
IL-6	70.15 (41.15-1265.27) 404.59	66.67 (19.92-1177.12) 354.673	0.032
TNF- α	44.45 (20.14-833.93) 224.62	39.06 (15.88-842.05) 261.13	0.041
MDA	6.49 (0.07-118.55) 42.15	5.72 (0.00-105.83) 24.31	0.001
F2-iso	86.19 (56.46-1288.39) 404.90	77.15 (36.92-1207.89) 373.59	0.00026

*Two-sided p-value determined using the Wilcoxon test. Min: lowest value, Max: highest value

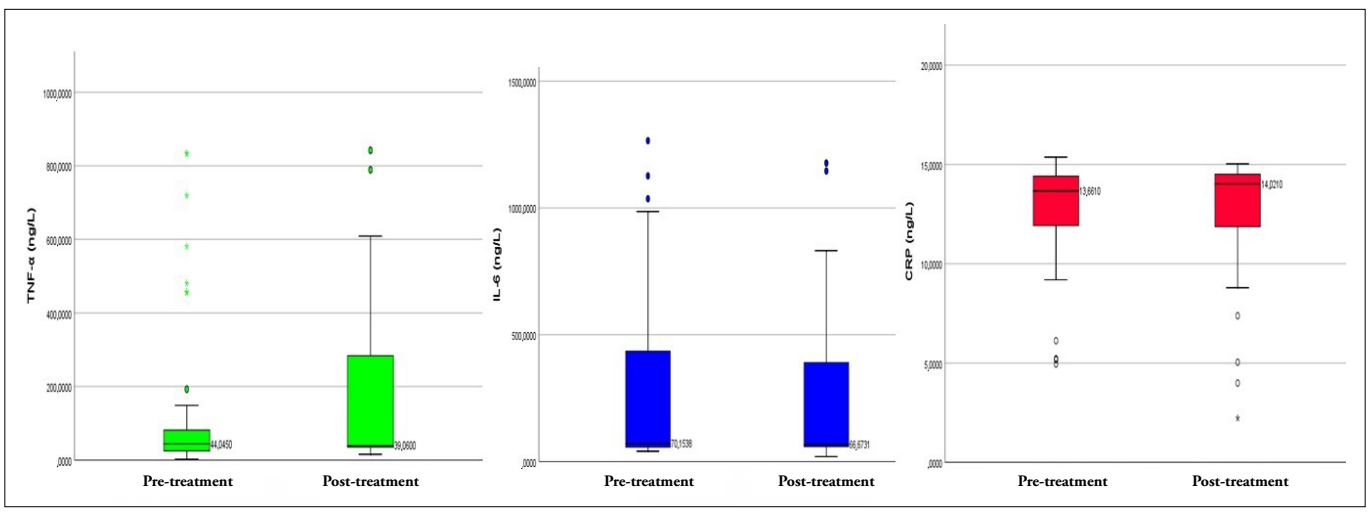

Figure 3. Comparison of TNF-α, IL-6 and CRP levels before and after treatment.

The median value of the HAM-D total scores at the first examination of the patient group was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 6.75. In the control examination performed 4 weeks later, the median value of HAM-D total scores was 6.5, the lowest value was 1, the highest value was 16, and the interquartile range was 6. In the control examination performed after 8 weeks, the median value for HAM-D scores was 3, the lowest value was 0, the highest value was 13, and the interquartile range was 6.25. At the end of eight weeks, it was observed that all 21 patients who responded to the treatment (HAM-D total scores decreased by 50% or more from baseline) also showed 'improvement' (HAM-D total scores of 7 or lower). While the median value of HAM-D total score at the first examination of the responders was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 8.5; the median for those who did not respond to treatment was 14, the lowest value was 12, the highest value was 21, the interquartile range was 5.5. This difference was not statistically significant (p=0.41). It was examined whether the

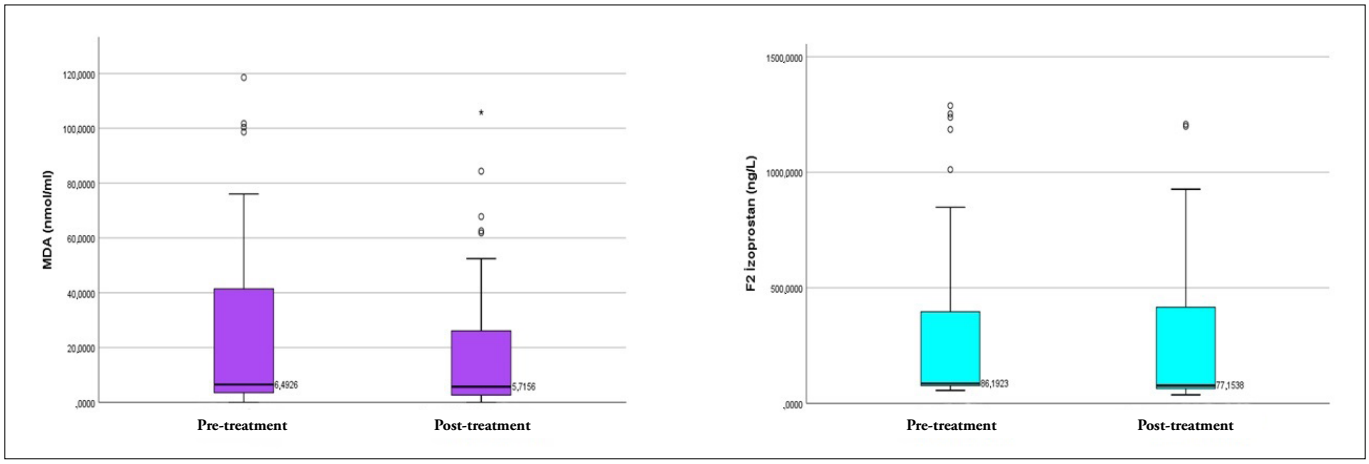

Figure 4. Comparison of MDA and F2-isoprostane levels before and after treatment.

Table 5. Comparison of Pre-treatment Levels of Markers Between Treatment Responders and Non-responders

	CRP	IL-6	TNF- α	MDA	F2-iso
Treatment responders (n= 21)					
Median	14.02	77.23	46.33	7.06	92.58
Minimum	5.22	41.15	23.88	1.100	56.46
Maximum	15.37	1265.27	833.93	118.55	1288.39
Interquartile range	1.83	748.14	431.32	58.29	791.115
Non-responders (n= 9)					
Median	13.33	63.15	42.44	5.93	76.77
Minimum	4.95	48.08	20.14	0.0074	61.35
Maximum	14.83	539.85	456.72	76.05	848.77
Interquartile range	8.88	59.87	64.6	37.52	171.29
p*	0.402	0.309	0.249	0.428	0.035

*Mann-Whitney U Test was used.

Table 6. Logistic Regression (backward) Analysis Model Examining the Effects of Gender, IL-6 and MDA Levels on Treatment Response

	BETA	Standard error	P	Odds Ratio (OR)	95% Confidence Interval for OR
Gender	6.037	3.388	0.70	418.757	0.604-290429.659
IL-6	-0.012	0.006	0.032	0.988	0.977-0.999
MDA	0.097	0.048	0.044	1.102	1.002-1.211

Nagelkerke R^2=0.654

baseline levels of the markers differed between patients who responded to treatment (n:21) and non-responders (n:9) and the results are shown in Table 5.

When the initial serum values are compared; TNF-α, IL-6, CRP and MDA levels did not show a statistically significant difference between those who responded to treatment and those who did not. Baseline F2-isoprostane values were significantly higher in responders compared to nonresponders (p=0.035).

The gender variable, which was found to be significantly correlated (p<0.05), with univariate analyses of the factors that may be associated with the response to treatment of first-episode depression patients, some variables associated with Type I error level p<0.25 (IL- 6, CRP and MDA) were evaluated with the logistic model and the model including gender, IL-6 and MDA was found to be valid. As a result of the logistic regression (backward) analysis, it was determined that the risk of not responding to treatment increased 1.102 times with a 1-unit increase in MDA. It was observed that the probability of responding to treatment increased by an increase in IL-6 value (OR=0.988, 95% CI=0.977-0.999). As a result of logistic regression analysis (Backward), the CRP variable included in the model was not associated with treatment response (Table 6).

DISCUSSION

In our study, IL-6, CRP and MDA levels were found to be significantly higher and F2-isoprostane levels were lower in first-episode MD patients compared to the healthy control group, but there was no significant difference between the groups in terms of TNF-α levels. Thus, it has been shown that there are some changes in the inflammatory system and oxidative stress in first-episode MD patients. While significant decreases were observed in TNF-α, IL-6, MDA, and F2-isoprostane levels after treatment with one of the medications in the SSRI group for 8 weeks in first-episode MD patients, there was no statistically significant change in CRP levels between before and after treatment measurements. With these findings, attention was drawn to the effect of treatment with an antidepressant from the SSRI group on the levels of this biomarker in first-episode MD patients. When the initial serum values were compared between those who responded to 8 weeks of treatment and those who did not; TNF-α, IL-6, CRP and MDA levels were not statistically significantly different, whereas baseline F2-isoprostane levels were significantly higher in responders compared to non-responders. No statistically significant correlation was found between baseline TNF-α, IL-6, MDA, and CRP levels and treatment response.

It was found that IL-6, CRP and MDA levels were statistically significantly higher in first-episode MD patients compared to the control group. These results are consistent with the knowledge that the levels of inflammation markers (Osimo et al. 2020, Hashimoto 2015) and oxidative stress markers (Lopresti et al. 2014, Liu et al. 2015, Mazereeuw et al. 2015, Lindqvist et al. 2017, Palta et al. 2014) increase in depression patients, which has been found in many existing studies and meta-analyses. In the study reported, there were no statistically significant differences between the patient and control groups in terms of TNF-α levels. Although most studies and meta-analyses in the literature have shown that TNF-α levels significantly increase in depressed patients, this is not true for all studies, and there are studies reporting that there is no increase in TNF-α levels in depressed patients compared to healthy controls (Himmerich et al. 2019, Köhler et al. 2017). It can be suggested that among the possible reasons for the conflicting findings related to TNF-α in depression is the presence of confounding factors such as chronic diseases, the different biochemical measurement methods, and the lack of clinical homogeneity of the patients (first-episode or recurrent episode, presence of other medical problems, taking medication, type of depression, etc.) participated in the studies. It is possible that the younger age group of the healthy control group compared to the patients in our study affected the results. It is reported in the literature that as age increases, CRP (Cattaneo et al. 2015), TNF-α and IL-6 (Himmerich et al. 2019) levels also increase. Although there is information that MDA levels do not change with age (Tsikas 2017), and that F2-isoprostane levels are not associated with age (Czerska et al. 2015), it can be thought that age may have affected the levels of these markers. Due to this age difference between the patient and control groups in our study, it is thought that the results, especially the findings related to inflammatory markers, may have been affected.

In this study, it was observed that F2-isoprostane levels were significantly lower in the patient group compared to the healthy control group. Contrary to this result, previous studies that evaluated F2-isoprostane levels in patients with depression reported higher levels in the patient group compared to the control group (Lopresti et al. 2014, Liu et al. 2015, Mazereeuw et al. 2015, Lindqvist et al. 2017, Palta et al. 2014). In a study, it has been reported that oxidative stress markers, especially F2-isoprostane levels, change in parallel with estradiol concentrations during the menstrual cycle (Schisterman et al. 2010). It was thought that the reasons such as 80% of the participants in our study were women and the healthy control group was younger than the patient group, lack of data on the stage of the menstrual cycle and estrogen levels of female participants at the time of sampling, may be among the possible reasons for the higher F2-isoprostane levels in the healthy control group. It is thought that the inconsistent findings from time to time in studies evaluating oxidative stress markers may also play a role in the failure to evaluate the levels of menstrual cycle and reproductive hormones (Schisterman et al. 2010) Future studies designed by taking this into account are much needed.

As a finding similar to the decrease in TNF-α and IL-6 levels after treatment in our study, in a meta-analysis, it was reported that TNF-α and IL-6 levels were decreased with antidepressant treatment (Köhler et al. 2018). It has been reported that TNF-α, IL-6 and CRP levels, which were elevated in depression patients, returned to normal with antidepressant treatment (Hacımusalar and Esel 2018, Park et al. 2019). As a result of a meta-analytical evaluation, it was reported that there was no change in the levels of many markers, including IL-6 and CRP, after treatment, while TNF-α levels decreased only in those who responded to treatment (Liu et al. 2020). In the light of all this information, although it has been reported that inflammatory markers, especially TNF-α, IL-6 and CRP, decrease after antidepressant treatment in a significant part of other studies, there are also studies reporting a decrease in some markers, while no significant change was observed in some. In the previous studies, it is seen that there are results that show a significant change between antidepressant treatment and CRP levels, but there are also study results that did not show any difference (Hashimoto 2015). In our study, while TNF-α and IL-6 levels were found to decrease with antidepressant treatment, no significant change was observed in CRP levels.

In a significant number of studies, it was reported that MDA levels decreased and returned to normal following antidepressant drug treatment (Lopresti et al. 2014, Liu et al. 2015), and F2-isoprostane levels decreased with antidepressant treatment (Lindqvist et al. 2017). Although findings similar to our study, such as a decrease in MDA and F2-isoprostane levels after treatment, were obtained in previous studies, there are also studies that did not detect a decrease in oxidative stress markers with treatment. It can be thought that the heterogeneity in the design of the studies, such as the sample sizes of the studies, the clinical characteristics of the participants, the status of the confounding factors, the biochemical measurement methods used, the duration of the treatment or the medications used, may have caused this situation (Palta et al. 2014). Although the results of studies investigating the effects of antidepressant treatment on the levels of inflammation and oxidative stress markers are not consistent, there is strong evidence that the levels of these markers decrease with treatment (Hacımusalar and Eşel 2018, Haroon et al. 2018, Liu et al. 2015). In our study, there was a significant decrease in TNF-α, IL-6, MDA and F2-isoprostane levels after treatment, but no significant difference was found in CRP levels. Based on this information, it can bethought that inflammatory processes and oxidative stress are associated with depression and antidepressant treatment, but it is seen that there may still be other mechanisms and interactions that need to be explained about the direction and nature of this relationship.

In our study, after 8 weeks of treatment, 'improvement' was observed in all of the patients who responded to the treatment at the same time. There was no significant difference between those who responded to treatment and those who did not in terms of initial levels of TNF-α, IL-6, CRP and MDA. It was found that F2-isoprostane levels before treatment were significantly higher in treatment responders than in non-responders. This finding is not consistent with a previous similar study reporting that F2-isoprostane levels were found to be lower in responders (Lindqvist et al. 2017). On the other hand, Lindqvist et al., in their study, stated that it is remarkable that they found a relationship between high F2-isoprostane levels and poor response to treatment, but also they stated that it should be considered as a preliminary finding and stated that since the treatment response was evaluated with a small number of patients, it is necessary to confirm the results with larger-scale repeated studies (Lindqvist et al. 2017). Again, in the same study, it was reported that no significant relationship was found between the treatment response and the initial levels of CRP, IL-6, and TNF-α, and this may be due to the small sample size (Lindqvist et al. 2017). In our study, it is possible that reasons such as the fact that most of the patients were female and that menstrual cycle periods or reproductive hormone values were not evaluated, may create an important limitation especially by affecting F2-isoprostane levels. Therefore, new studies designed by considering all confounding factors are needed.

There are many studies, meta-analyses and reviews reporting that the high level of markers such as IL-1, IL-6, TNF-α and CRP seen in depression patients is associated with treatment unresponsiveness to antidepressants (Hacımusalar and Eşel 2018, Syed et al. 2018, Eller et al. 2008). On the other hand, there are also studies reporting results that are inconsistent with these findings. For example, in a study, it was reported that basal plasma IL-6 levels were found to be significantly higher in those who responded to treatment with SSRI than in those who did not (Yoshimura et al. 2013). In another study, it was reported that there is a relationship between good response to amitriptyline in long-term treatment and high pre-treatment CRP levels (Harley et al. 2010). These findings suggest that the use of inflammatory biomarkers in the clinic requires further validation in larger samples (Mora et al. 2018). In our study, in the logistic regression (backward) analysis performed to examine the variables that may be related to the response to treatment of first-episode depression patients: included gender, IL-6 and MDA. The model was found valid. It was seen that the risk of not responding to treatment increased by 1.102 times with a 1-unit increase in MDA, and the probability of responding increased 1.012 times in case of an increase in IL-6 value. These findings suggest that even if the markers alone are not sufficient to predict treatment response, models that evaluate multiple markers together can predict treatment response.

It is known that both inflammation markers and oxidative stress markers can be affected by many conditions such as Acute (such as infectious diseases) and chronic diseases (especially obesity, cancer, cardiovascular diseases, diabetes mellitus, thyroid diseases, etc.), medicine use, smoking, substance use, heavy alcohol use, and previous psychiatric illness (Liu et al. 2015, Himmerich et al. 2019, Ambrosio et al. 2018, Czerska et al. 2015). For this reason, these characteristics were taken into account in the determination of both first-episode depression patients and healthy volunteers to participate in the study. Although it was aimed to match one-to-one regarding age, this goal could not be achieved because the study had to be completed quickly in order not to affect the results of the study due to the Covid-19 pandemic during the conduct of the study. The volunteers in the healthy control group were younger than the patients, and this is the most important limitation of our study. Although it is known that depression is more common in women than men, the fact that the majority of the participants were women can be considered as another limitation of the study. The fact that female participants are in the majority leads to a significant limitation as the stage of the menstrual cycle and reproductive hormone levels of the participants are not evaluated when

blood samples are taken, and it can be thought that this situation may have affected especially F2-isoprostane levels. In order to clarify this issue, studies with large samples are needed, in which the ratio between male and female patients is similar to that in the population, and the menstrual cycle and reproductive hormone levels in female participants are taken into account. Despite these limitations, the strength of our study is recruting the evaluation of first-episode MD patients (patients who have not had any psychiatric disease and have not been treated before), which constitutes the patient group, and thus, enabling the examination of the relationship between MD and inflammatory and oxidative processes without the effect of recurrent depression episodes.

Another strength of our study is that the markers of inflammation and oxidative stress were evaluated together. The findings obtained as a result of examining the inflammation and oxidative stress status both before and after treatment, as well as evaluating the relationship between treatment response and inflammation and oxidative stress, especially in first-episode depression patients, contribute to the elucidation of the pathophysiology of depression and the detection of possible biomarkers that could be used in the diagnosis and determination of treatment.

In conclusion, in the light of the findings of our study, it was determined that there are irregularities in terms of inflammatory processes and oxidative stress in major depression patients, even during the first-episode and without any medicine. These irregularities can be improved by treating the disease with antidepressant medicine, and it seems promising in terms of finding markers that can be associated with treatment response. However, there are still many issues to be clarified in this area. In order to reveal how and to what extent inflammatory and oxidative stress markers can be used as biomarkers in the diagnosis and treatment process, future studies with large sample sizes, evaluating all possible confounding factors, investigating many markers together, and including diagnosis and treatment processes with long follow-up periods are needed.

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