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The relationship between the changes in inflammatory parameters and response to treatment in major depression patients starting antidepressant treatment

Antidepresan tedavi başlanan major depresyon hastalarında inflamatuar parametrelerdeki değişikliklerin tedavi yanıtı ile ilişkisi

Abdullah Burak Uygur[1*], Şeyda Çankaya[2]

1.Medical School of Alaaddin Keykubat University, Department of Psychiatry, Alanya/Antalya, Turkey
2.Medical School of Alaaddin Keykubat University, Department of Neurology, Alanya/Antalya, Turkey

ABSTRACT

Aim: Changes in inflammatory parameters such as cytokines, stress hormones and C reactive protein that occur in depression, are important in understanding the pathophysiology of depression and developing new treatment approaches. The main purpose of this study was to determine the changes in inflammatory markers in patients with major depression, before and after antidepressant treatment, as well as to determine the effect of antidepressant treatment types on these changes.

Methods: This study was a single center, retrospective study. According to the retrospective records of the last five years in the psychiatry outpatient clinic of Alanya Alaaddin Keykubat University Training and Research Hospital, the patients diagnosed with Major Depressive Disorder (MDD), started on single antidepressant treatment for the first time and who used antidepressant treatment for at least 6-8 weeks, were included in the study. Patients whose Hamilton Depression Rating Scale (HDRS), complete blood count, C reactive protein and cortisol values were reached from the system during MDD treatment, constituted the sample of the study.

Results: In the present study, after the antidepressant treatment, while HDRS scores decreased significantly in patients with Major Depression compared to before treatment (p<0,001), no significant correlation was found between the changes in inflammatory parameters and the response to treatment (p>0,05). This condition was independent of the type of antidepressant used in the treatment (p>0,05 in the SSRI treatment group, p>0,05 in the SNRI treatment group). In addition, it was observed that the decrease in depression scores was not associated with the type of antidepressant (p=0,001, in the SSRI treatment group, p=0,005, in the SNRI treatment group).

Conclusion: Results to support the inflammatory hypothesis in Major Depressive Disorder were not conclusive in this study. Considering that the pathophysiology of depression is quite complex, it could be argued that a single group of blood tests may not be sufficient to explain the link between inflammation and depression. Considering all the limitations of the study, a future a prospective study to prove the inflammatory hypothesis in MDD, including the detailed blood, BOS tests, along with more comprehensive neuroimaging parameters on the brain pathways, might provide more effective results.

Keywords: major depressive disorder, inflammation, inflammatory parameters, antidepressant treatment, antidepressant type, treatment response

ÖZ

Amaç: Depresyonda meydana gelen sitokinler, stres hormonları ve C reaktif protein gibi inflamatuvar parametrelerin değişimi, depresyonun patofizyolojisinin anlaşılması ve yeni tedavi yaklaşımlarının geliştirilmesi açısından önem taşımaktadır. Bu çalışmanın temel amacı, major depresyon hastalarında antidepresan tedavi öncesi ve sonrasında inflamatuvar belirteçlerde nasıl bir değişiklik olduğunu tespit etmek ve antidepresan tedavi türünün bu değişiklikler üzerindeki etkisini belirlemektir.

Yöntem: Tek merkezli, retrospektif olarak gerçekleştirilen çalışmada, Alanya Alaaddin Keykubat Üniversitesi Eğitim ve Araştırma Hastanesi psikiyatri polikliniğinde son beş yıla ait geriye dönük incelenen kayıtlara göre, Majör Depresif Bozukluk (MDB) tanısı konulup, ilk kez tekli antidepresan tedavisine başlanan ve en az 6-8 hafta antidepresan tedavi kullanmış, tedavi öncesi ve sonrası Hamilton Depresyon Derecelendirme Ölçeği (HDDÖ), tam kan sayımı, C reaktif protein, kortizol değerlerine ulaşılabilen hastalar çalışmanın örneklemini oluşturmuştur.

Bulgular: Çalışmamızda, antidepresan tedavi sonrası, HDDÖ puanları Majör Depresyonlu hastalarda tedavi öncesine göre anlamlı olarak azalırken (p<0,001), inflamatuar parametrelerdeki değişiklikler ile tedaviye yanıt arasında anlamlı bir ilişki belirlenmemiştir (p>0,05). Bu durum, tedavide kullanılan antidepresan ilaç türünden bağımsızdır (SSRI tedavi grubunda p>0,05, SNRI tedavi grubunda p>0,05). Ayrıca depresyon puanlarındaki azalmanın da, antidepresan ilaç türü (SSRI-SNRI) ile ilişkili olmadığı belirlenmiştir (SSRI tedavi grubunda, p=0,001, SNRI tedavi grubunda, p=0,005).

Sonuç: Çalışmamızda, MDB'de inflamatuar hipotezi destekleyecek sonuçlar belirlenmemiştir. Depresyonun patofizyolojisinin oldukça karmaşık olduğu düşünüldüğünde, inflamasyon ve depresyon arasındaki bağlantıyı açıklamak için yalnızca bir grup kan testinin yeterli olmayabileceği düşünülebilir. Çalışmamızdaki tüm sınırlılıklar göz önünde bulundurulduğunda, gelecekte daha kapsamlı kan, BOS testleri ile beraber beyin yolaklarına ilişkin nörogörüntüleme parametrelerini de içeren prospektif çalışmalar, MDB'de inflamatuar hipotezi kanıtlamak için daha etkili sonuçlar sağlayabilir.

Anahtar sözcükler: major depresif bozukluk, inflamasyon, inflamatuar parametreler, antidepresan tedavi, antidepresan türü, tedavi yanıtı

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*Corresponding author: Abdullah Burak Uygur. Medical School of Alaaddin Keykubat University, Department of Psychiatry, Alanya/Antalya, Türkiye. +905446482594 burak.uygur@alanya.edu.tr

ORCID: 0000-0001-7056-7553

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INTRODUCTION

According to the World Health Organization, depression is the leading cause of disability and worldwide, in excess of 350 million people are affected [1]. Major Depressive Disorder (MDD) is the most severe among the depressive disorder subgroups and it is conventionally treated with antidepressants. Despite numerous treatment options, complete remission cannot be achieved in many patients with major depression [1]. In recent years, researchers have focused on identifying the reasons for the unresponsiveness of MDD therapy. The inflammation and inflammatory responses play a role in depression and its pharmacological treatment. Psychosocial stress reveals an immune response that ends in inflammation [2]. Increased inflammation increases the probability of developing depression [3]. This hypothesis has been based on the idea that chronic inflammation may contribute to serotonergic, noradrenergic and dopaminergic dysfunction [4].

Historically, the "monoamine-depletion hypothesis" pointed to an imbalance, principally between serotonergic and noradrenergic neurotransmission, however this suggestion offers no explanation why current antidepressants are not helpful for a number of patients. It has been suggested that depression relapses and lack of therapeutic benefits from antidepressants might be associated with overall activation of the inflammatory response [5]. Therefore, immune dysregulation or chronic inflammation might be present in resistance to therapy of MDD [6]. In this context, cerebrospinal fluid (CSF) and inflammatory blood markers have been detected. Increased levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), and C reactive protein (CRP) are found in MDD patients [7-11].

Previous studies with small samples showed that the neutrophil lymphocyte ratio (NLR), a common biomarker for systemic inflammatory condition, is associated with MDD and that NLR is significantly increased in Major Depression patients, compared to healthy controls [12]. In a study by Kasama et al., high NLR levels were found to be related with increased oxidative stress and inflammatory cytokines [13]. However, the relationship between major depression and inflammation remains problematic, notwithstanding the fact that a great proportion of patients show no significant inflammation sign [14].

In light of the existing data suggesting a possible link between inflammation and depression, the main purpose of this study was to determine the changes in inflammatory markers in patients with major depression, before and after antidepressant treatment, and to determine the effects of antidepressant treatment types on these changes. Studies in this field are important in understanding the pathophysiology of depression and developing new treatment approaches.

MATERIAL AND METHODS

Ethics committee approval

Ethics committee approval of the study was obtained from Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Research Ethics Committee, with the decision number 20-26 dated 18.06.2020.

Sample Selection and Study Design

This study is a single-center, retrospective study. Routine tests such as hemograms are performed for patients who are referred to the psychiatry outpatient clinic by other departments, or who will be prescribed medication for the first time and are repeated in the controls, as a result of possible side effect of the drug. Following a retrospective examination of the records of the last five years from the psychiatry outpatient clinic of Alanya Alaaddin Keykubat University (ALKU) Training and Research Hospital (TRH), the patients diagnosed with Major Depressive Disorder (MDD), who were started on a single antidepressant treatment for the first time and used antidepressant treatment for at least 6-8 weeks, were included in the study. The records of a total of twenty-four MDD patients, three males and twenty-one females, between the ages of 18-41, were examined for the purpose of the study. Patients whose Hamilton Depression Rating Scale (HDRS), C reactive protein (CRP), cortisol, and complete blood count [Lymphocyte, neutrophil, platelet, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red cell

distribution width (RDW), immunoglobulin (IG)] values were reached during MDD treatment, constituted the sample of the study.

Patients with a history of autoimmune disease that may affect inflammatory parameters, a history of hematologic diseases, chronic inflammatory diseases, leukocyte value suggestive of infection, those using antidepressant drugs and those with diagnoses of alcohol or substance addiction, mental retardation and organic brain disease, were all excluded from the study.

Despite diligent efforts, differences may be found in some characteristics in independent groups. In biological subjects, including human patients, the variations in traits such as height, body weight and other factors, are very pronounced. As a result of these disadvantages of working with independent groups, the present study was designed as a "before-after" type: the inflammatory values of patients with major depressive disorder, before and after antidepressant treatment, were compared. The patients' antidepressant agents (SSRI or SNRI), age and gender were also recorded.

Data Collection Tools

Hamilton Depression Rating Scale (HDRS): HDRS administered by the clinician, aims to measure the severity of depressive symptoms. It was developed by Hamilton et al. in 1960 [15]. The Turkish validity and reliability study conducted by Akdemir et al. in 1996 [16].

Statistical Analysis

Number, minimum, maximum and median values were used as descriptive statistical methods in the evaluation of the data. The Related-Samples Wilcoxon Signed Ranks Test was used to compare the variables forming two dependent groups. The data was evaluated with the SPSS 22,0 statistical program and the level of $p \leq 0,05$ was accepted for statistical significance [17].

RESULTS

The inflammatory parameter values and Hamilton Depression Rating Scale scores of the Major Depressive Disorder patients, before and after antidepressant treatment, as well as their sociodemographic characteristics are shown in Table 1. The study sample consisted of 24 Major Depressive Disorder patients, aged between 18 and 41. The median age of the MDD patients group was 33,50 consisting of 21 female and 3 male. While 13 patients were on SSRI therapy, 11 patients received SNRI therapy. The comparison of inflammatory parameter values and depression scores of MDD patients, again before and after antidepressant treatment, is also shown in Table 1. The median of the CRP level was 0,100 mg / L. before the antidepressant treatment, it was 0,200 mg / L. after the treatment ($p = 0,074$). The median of the cortisol level was 8,08 mcg / dL. before the antidepressant treatment, it was 7,47 mcg / dL. after the treatment ($p = 0,511$). The median of the Neutrophil level was 4625 -10^3/uL. before the antidepressant treatment, it was 4280 -10^3/uL. after the treatment ($p = 0,511$). The median of the Lymphocyte level was 2570 -10^3/uL. before the antidepressant treatment, it was 2180 -10^3/uL. after the treatment ($p = 0,284$). The median of the Platelet level was 283000 -10^3/uL. before the antidepressant treatment, it was 279000 -10^3/uL. after the treatment ($p = 0,148$). The median of the RDW-CV was 13,50%, before the antidepressant treatment, it was 13,30% after the treatment ($p = 0,807$). The median of the RDW-SD was 39,35%, before the antidepressant treatment, it was 39,35% after the treatment ($p = 0,807$). The median of the IG was 0,025 -10^3/uL before the antidepressant treatment, it was 0,020 -10^3/uL. after the treatment ($p = 0,761$). The median of the Neutrophil-Lymphocyte ratio was 2,12 before the antidepressant treatment, it was 1,87 after the treatment ($p = 0,932$). The median of the Platelet-Lymphocyte ratio was 123,44 before the antidepressant treatment, it was 120,22 after the treatment. ($p = 0,549$).

The median of the Hamilton Depression Rating Scale points was 20,00 before the antidepressant treatment, and it was 8,00 after the treatment ($p < 0,001$, Related-Samples Wilcoxon Signed Ranks Test, Table 1).

In the study, two groups were created according to the antidepressant treatment types: SSRI treatment group and SNRI treatment group. The comparison of inflammatory parameter values and depression scores of Major Depressive Disorder patients before and after antidepressant

treatment in the SSRI treatment group, is shown in Table 2. In the SSRI treatment group: The median of the CRP level was 0,100 mg / L. before the antidepressant treatment, it was 0,100 mg / L. after the treatment (p = 0,527). The median of the cortisol level was 9,00 mcg / dL. before the antidepressant treatment, it was 7,56 mcg / dL. after the treatment (p = 0,345). The median of the Neutrophil level was 4730 -10^3/uL. before the antidepressant treatment, it was 4170 -10^3/ uL. after the treatment (p = 0,221). The median of the Lymphocyte level was 2590 -10^3/uL. before the antidepressant treatment, it was 2140 -10^3/ uL. after the treatment (p = 0,101). The median of the Platelet level was 293000 -10^3/uL. before the antidepressant treatment, it was 277000 -10^3/uL. after the treatment (p = 0,158). The median of the RDW-CV was 12,70%, before the antidepressant treatment, it was 13,00% after the treatment (p = 0,582). The median of the RDW-SD was 41,10%, before the antidepressant treatment, it was 39,20% after the treatment (p = 0,347). The median of the IG was 0,020 -10^3/uL before the antidepressant treatment, it was 0,020 -10^3/ uL. after the treatment (p = 0,357). The median of the Neutrophil-Lymphocyte ratio was 2,15 before the antidepressant treatment, it was 1,89 after the treatment (p = 0,889). The median of the Platelet-Lymphocyte ratio was 105,39 before the antidepressant treatment, it was 132,63 after the treatment (p = 0,701).

The median of the Hamilton Depression Rating Scale points was 21,00 before the antidepressant treatment, and it was 9,00 after the treatment in the SSRI treatment group (p = 0,001, Related-Samples Wilcoxon Signed Ranks Test, Table 2).

The comparison of inflammatory parameter values and depression scores of Major Depressive Disorder patients before and after antidepressant treatment in the SNRI treatment group, is shown in Table 3. In the SNRI treatment group: The median of the CRP level was 0,100 mg / L. before the antidepressant treatment, it was 0,300 mg / L. after the treatment (p = 0,068). The median of the cortisol level was 7,62 mcg / dL. before the antidepressant treatment, it was 7,38 mcg / dL. after the treatment (p = 0,859). The median of the Neutrophil level was 4520 -10^3/uL. before the antidepressant treatment, it was 4660 -10^3/ uL. after the treatment (p = 0,722). The median of the Lymphocyte level was 2550 -10^3/uL. before the antidepressant treatment, it was 2270 -10^3/ uL. after the treatment (p = 0,824). The median of the Platelet level was 271000 -10^3/uL. before the antidepressant treatment, it was 281000 -10^3/uL. after the treatment (p = 0,328). The median of the RDW-CV was 13,70%, before the antidepressant treatment, it was 13,70% after the treatment (p = 0,327). The median of the RDW-SD was 38,80%, before the antidepressant treatment, it was 39,40% after the treatment (p = 0,534). The median of the IG was 0,030 -10^3/uL. before the antidepressant treatment, it was 0,020 -10^3/ uL. after the treatment (p = 0,119). The median of the Neutrophil-Lymphocyte ratio was 2,12 before the antidepressant treatment, it was 1,53 after the treatment (p = 0,965). The median of the Platelet-Lymphocyte ratio was 131,60 before the antidepressant treatment, it was 105,15 after the treatment (p = 0,286).

The median of the Hamilton Depression Rating Scale points was 20,00 before the antidepressant treatment, and it was 7,00 after the treatment in the SNRI treatment group (p = 0,005, Related-Samples Wilcoxon Signed Ranks Test, Table 3).

DISCUSSION

In this study, it was aimed to evaluate the changes in inflammatory markers along with depression scores during the treatment of Major Depressive Disorder and to determine the effect of antidepressant type on these changes. Although it was found that Hamilton Depression Rating Scale scores decreased significantly after antidepressant treatment in patients with Major Depression, there was no significant relationship between inflammatory parameters and treatment response. This condition was independent of the type of antidepressant used in the treatment (SSRI or SNRI). In addition, it was observed that the decrease in depression scores was not associated with the type of antidepressant (SSRI or SNRI).

There are inconsistencies in studies investigating changes in inflammation in Major Depressive Disorder in the literature. Many studies show the significant association between depression and inflammation [18-22]. A recent cumulative meta-

Table 1. Sociodemographic characteristics, inflammatory parameter values and Hamilton Depression Rating Scale scores of Major Depressive Disorder patients and the comparison of inflammatory parameter values and depression scores before and after antidepressant treatment

		Min.	Max.	N /	Z	p
Median						
N: 24	Age	18	41	33,50		
Gender	Female			21		
	Male			3		
AD Treatment Type	SSRI			13		
	SNRI			11		
HDRS Score	Before Treat.	12	27	20,00	-4,205	<0,001
	After Treat.	4	20	8,00		
CRP (mg/L.)	Before Treat.	0,00	1,3	0,100	-1,788	0,074
	After Treat.	0,00	1,7	0,200		
Cortisol (mcg/dL.)	Before Treat.	3,73	20,84	8,08	-0,657	0,511
	After Treat.	3,63	23,32	7,47		
Platelet (10^3/uL.)	Before Treat.	207000	460000	283000	-1,445	0,148
	After Treat.	192000	378000	279000		
Lymphocyte (10^3/uL.)	Before Treat.	1490	3420	2570	-1,071	0,284
	After Treat.	1390	3530	2180		
Neutrophil (10^3/uL.)	Before Treat.	1980	7960	4625	-0,657	0,511
	After Treat.	1940	8410	4280		
RDW-CV (%)	Before Treat.	11,8	24,6	13,50	-0,244	0,807
	After Treat.	12,0	22,3	13,30		
RDW-SD (%)	Before Treat.	34,5	62,3	39,35	-0,304	0,807
	After Treat.	33,8	48,7	39,35		
IG (10^3/ uL.)	Before Treat.	0,01	0,17	0,025	-1,740	0,761
	After Treat.	0,01	0,15	0,020		
Neutrophil-Lymphocyte Ratio	Before Treat.	1,15	3,82	2,12	-0,086	0,932
	After Treat.	0,98	4,26	1,87		
Platelet-Lymphocyte Ratio	Before Treat.	65,78	239,13	123,44	-0,600	0,549
	After Treat.	75,35	209,52	120,22		

N: Number of samples, SD: Standard Deviation, Min: Minimum, Max: Maximum, Treat: Treatment, AD: Antidepressant, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin and Noradrenaline Reuptake Inhibitor, CRP: C-reactive protein, HDRS: Hamilton Depression Rating Scale, Ig: Immunoglobulin, RDW: Red cell distribution width, CV: Coefficient of Variation, p: Statistical significance for Wilcoxon Signed Ranks Test, p ≤ 0,05

Table 2. The comparison of inflammatory parameter values and depression scores of Major Depressive Disorder patients before and after antidepressant treatment in the SSRI treatment group

		Min.	Max.	N /	Z	p
	Median					
N: 13	Age	18	41	27,00		
Gender	Female			11		
	Male			2		
HDRS Score	Before Treat.	12	26	21,00	-3,192	0,001
	After Treat.	4	15	9,00		
CRP (mg/L.)	Before Treat.	0,00	0,8	0,100	-0,632	0,527
	After Treat.	0,00	1,1	0,100		
Cortisol (mcg/dL.)	Before Treat.	4,77	20,84	9,00	-0,943	0,345
	After Treat.	4,31	17,08	7,56		
Platelet (10^3/uL.)	Before Treat.	207000	443000	293000	-1,412	0,158
	After Treat.	192000	378000	277000		
Lymphocyte (10^3/uL.)	Before Treat.	1490	2970	2590	-1,642	0,101
	After Treat.	1390	2850	2140		
Neutrophil (10^3/uL.)	Before Treat.	1980	7960	4730	-1,223	0,221
	After Treat.	1940	7640	4170		
RDW-CV (%)	Before Treat.	12,0	24,6	12,70	-0,550	0,582
	After Treat.	12,0	17,5	13,00		
RDW-SD (%)	Before Treat.	36,2	62,3	41,10	-0,941	0,347
	After Treat.	34,8	48,7	39,20		
IG (10^3/ uL.)	Before Treat.	0,01	0,04	0,020	-0,921	0,357
	After Treat.	0,01	0,05	0,020		
Neutrophil-Lymphocyte Ratio	Before Treat.	1,19	3,82	2,15	-0,140	0,889
	After Treat.	0,98	3,32	1,89		
Platelet-Lymphocyte Ratio	Before Treat.	78,98	239,13	105,39	-0,384	0,701
	After Treat.	93,08	209,52	132,63		

N: Number of samples, SD: Standard Deviation, Min: Minimum, Max: Maximum, Treat: Treatment, SSRI: Selective Serotonin Reuptake Inhibitor, CRP: C-reactive protein, HDRS: Hamilton Depression Rating Scale, Ig: Immunoglobulin, RDW: Red cell distribution width, CV: Coefficient of Variation, p: Statistical significance for Wilcoxon Signed Ranks Test, p ≤ 0,05

Table 3. The comparison of inflammatory parameter values and depression scores of Major Depressive Disorder patients before and after antidepressant treatment in the SNRI treatment group

		Min.	Max.	N / Median	Z	p
N: 11	Age	20	40	34,00		
Gender	Female			10		
	Male			1		
HDRS Score	Before Treat.	13	27	20,00	-2,805	0,005
	After Treat.	4	20	7,00		
CRP (mg/L.)	Before Treat.	0,00	1,3	0,100	-1,823	0,068
	After Treat.	0,00	1,7	0,300		
Cortisol (mcg/dL.)	Before Treat.	3,73	16,98	7,62	-0,178	0,859
	After Treat.	3,63	23,32	7,38		
Platelet (10^3/uL.)	Before Treat.	209000	460000	271000	-0,979	0,328
	After Treat.	201000	378000	281000		
Lymphocyte (10^3/uL.)	Before Treat.	1680	3420	2550	-0,222	0,824
	After Treat.	1970	3530	2270		
Neutrophil (10^3/uL.)	Before Treat.	2110	6310	4520	-0,356	0,722
	After Treat.	2890	8410	4660		
RDW-CV (%)	Before Treat.	11,8	20,1	13,70	-0,981	0,327
	After Treat.	12,2	22,3	13,70		
RDW-SD (%)	Before Treat.	34,5	43,2	38,80	-0,622	0,534
	After Treat.	33,8	47,7	39,40		
IG (10^3/uL.)	Before Treat.	0,01	0,17	0,030	-1,561	0,119
	After Treat.	0,01	0,15	0,020		
Neutrophil-Lymphocyte Ratio	Before Treat.	1,15	3,07	2,12	-0,044	0,965
	After Treat.	1,19	4,26	1,53		
Platelet-Lymphocyte Ratio	Before Treat.	65,78	171,37	131,60	-1,067	0,286
	After Treat.	75,35	166,51	105,15		

N: Number of samples, SD: Standard Deviation, Min: Minimum, Max: Maximum, Treat: Treatment, SNRI: Serotonin and Noradrenaline Reuptake Inhibitor, CRP: C-reactive protein, HDRS: Hamilton Depression Rating Scale, Ig: Immunoglobulin, RDW: Red cell distribution width, CV: Coefficient of Variation, p: Statistical significance for Wilcoxon Signed Ranks Test, p ≤ 0,05

analysis has been shown that C reactive protein, IL-1, and IL-6 were positively associated with depression [23]. On the other hand, there are also many studies that did not find a relationship between inflammation and depression [24-26].

In the present study, changes in C reactive protein (CRP), a reliable marker of systemic inflammation during the MDD therapy were not associated with the response to treatment. In both the SSRI treatment group and the SNRI treatment group, there was no significant relationship between CRP levels and depression scores. In the study conducted by Uher et al., it was stated that the initial CRP levels could be an important factor in the choice of antidepressant treatment [27]. Individuals with low baseline CRP levels (< 1 mg. / L) have been shown to respond better to serotonergic antidepressants, and individuals with higher baseline CRP (> 1 mg. / L.) to noradrenergic antidepressants. The small sample size of the present study has not only prevented group formation according to the CRP levels, but may also have influenced findings of a significant relationship between CRP and different antidepressant types.

Studies investigating the changes in Neutrophil-Lymphocyte ratio (NLR) and Platelet-Lymphocyte ratio during MDD therapy have reported conflicting results. In the present study, changes in the NLR during antidepressant treatment were not associated with the response to treatment. In line with this study, no significant differences were found between major depression patients and healthy controls in terms of complete blood count levels, including NLR during MDD therapy, in a study carried out by Maes et al. [25]. On the other hand, Demircan et al.'s study

showed that compared to normal controls, NLR levels were accompanied by relief of depressive symptoms during the antidepressant treatment in MDD patients [20]. In a study investigating the relationship between NLR and geriatric depression in the elderly population in China, it was shown that increased NLR is associated with depression in young and middle-aged Chinese adult females. However, in the same study, the relationship of increased NLR with depressive symptoms in males could not be determined [28]. Changes in platelets, which are fractions produced by megakaryocytes, remain unclear in MDD. In the present study, changes in the Platelet-Lymphocyte ratio (PLR) during antidepressant treatment were also not associated with the response to treatment. Contrary to our results, in the study of Cai et al., the MDD group showed a significantly higher PLR compared to healthy controls [12]. The small sample size of the present study may be one of the factors that affected the findings of a significant relationship between NLR and PLR, with the response to treatment and depression scores. On the other hand, considering that the pathophysiology of depression is quite complex, it could be argued that a single group of blood tests may not be sufficient to explain the link between inflammation and depression.

In the literature, inconsistent results were found in studies investigating the relationship between antidepressant treatment response and depression severity with cortisol, one of the hypothalamus-pituitary-adrenal (HPA) axis hormones secreted in response to stress. Some studies have found significant changes in serum cortisol levels, before and after antidepressant therapy [29]. In the present study there was no relationship between the changes in cortisol levels and treatment response during MDD therapy. Consistent with this study, the findings by Alenko et al. did not show an association between serum cortisol levels and treatment response to SSRI [30]. There are many parameters in the measurement of cortisol and other stress hormones that are very difficult to control, such as sample collection time and exercise. The fact that this study was retrospective may have resulted in deficiencies in the details that may affect cortisol levels, therefore a significant result may not be found in the relationship between these and antidepressant treatment response.

In general, the present study did not reveal a relationship between changes in inflammatory parameters and antidepressant treatment response, as well as the type of antidepressant used in the treatment. In line with these results, a recent work using network psychometrics to examine the existing data from the database of the Netherlands Study of Depression and Anxiety, found no direct link between depression and inflammation. Nevertheless, this study has revealed important insights into the effects of individual symptoms and lifestyle factors [24]. Conflicting results have been obtained in studies conducted to understand the effects of anti-inflammatory and antidepressant agents on depression and inflammation. In a randomized study performed by Raison et al., with treatment-resistant depression patients, Anti-Tumor Necrosis Factor (TNF) infliximab or a saltwater placebo revealed no differences in terms of their antidepressant effect. Nevertheless, the inflammation group did respond to infliximab [26]. Many biological studies suggest that inflammatory mediators might have divergent effects on brain regions with different functions such as motivation, reward, fear, anxiety and mood regulation. However, the idea that anti-inflammation therapy might relieve depression symptoms has not been consistently demonstrated with clinical studies [31, 32].

Limitations of the Study:

Despite the interesting findings, the present study had some limitations. First, the sample size available was small. Second, this study only examined some specific inflammation related hematological parameters, C-reactive protein and cortisol. It may be useful if more sensitive inflammatory markers such as highly sensitive CRP or interleukins, were used to investigate the relationship between depression and inflammation, namely since those inflammatory markers could also reveal the subclinical (low grade) inflammation. Third, there was no healthy control group used to allow further comparison. Finally, the present study was designed as a retrospective study and as with all non-prospective designs, a causal relationship cannot be established with the results that have been obtained.

CONCLUSION

In conclusion, our understanding of the immunology underlying the inflammation in depression is limited to a small number of human studies [33]. For instance, despite the question being asked repeatedly, there yet remains no explicit knowledge about the percentage of patients suffering with depression, in whom inflammation plays a pivotal role. Results to support the inflammatory hypothesis in Major Depressive Disorder were not conclusive in this study. Considering all the limitations in the study and in order to prove the inflammatory hypothesis in Major Depressive Disorder, a future prospective study including detailed blood, BOS tests, along with more comprehensive neuroimaging parameters on the brain pathways, might provide more conclusive results.

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Author / ORCID	Authorship Contrubition
Abdullah Burak Uygur 0000-0001-7056-7553	Consept, design, materials, data collection, analysis, interpretation, literature search, manuscript writing, final approval, critical review
Şeyda Çankaya 0000-0001-5309-0351	Consept, analysis, literature review, manuscript writing, final approval, critical review