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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

Evaluation of Inflammatory Markers in Fibromyalgia Syndrome

Fibromiyalji Sendromunda İnflamatuvar Belirteçlerin Değerlendirilmesi

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ABSTRACT

Objective: It was aimed to demonstrate the presence of inflammation in fibromyalgia syndrome(FMS) and healthy subjects by evaluating hematological indices and ratios associated with inflammation.

Method: A total of 187 participants (98 FMS; 89 healthy controls) were included in the retrospective-cross-sectional study, and participants' neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are hematological indices showing inflammation in the last 6 months, were calculated.

Results: Mean age of the participants was 37.3±5.05 years for FMS, and 37.2±5.2 years for healthy controls. There were statistically significant differences between both groups in terms of NLR (p=0.034), MPV (p<0.001), CRP (p=0.001), and ESR (p<0.001). There was no difference in PLR between the two groups (p>0.05).

Conclusion: Proinflammatory hematological indices were significantly changed in FMS compared to healthy controls. In addition, the results supported inflammatory pathogenesis of FMS.

Keywords: Fibromyalgia, inflammation, mean platelet volume, neutrophile-lymphocyte ratio, platelet-lymphocyte ratio

ÖZ

Amaç: Çalışmada, fibromiyalji sendromu (FMS) ve sağlıklı bireylerde inflamasyonu gösteren hematolojik indeksler ve oranlar değerlendirilerek inflamasyon varlığının gösterilmesi amaçlanmaktadır.

Yöntem: Retrospektif kesitsel olarak planlanan bu çalışmaya toplam 187 katılımcı (98 FMS tanısı almış katılımcı, 89 sağlıklı kontrol) dahil edildi ve katılımcıların nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), ortalama trombosit hacmi (OTH), eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) düzeyleri hesaplandı.

Bulgular: Katılımcıların yaş ortalaması, FMS'li katılımcılar için 37,3±5,05 yıl, sağlıklı kontroller için 37,2±5,2 yıl olarak hesaplandı. NLO (p=0,034), OTH (p<0,001), CRP (p=0,001) ve ESH (p<0,001) açısından her iki grup arasında istatistiksel olarak anlamlı fark saptandı. İki grup arasında PLO açısından anlamlı fark bulunmadı (p>0,05).

Sonuç: Sağlıklı kontrollere kıyasla FMS'de proinflamatuvar hematolojik indeksler önemli düzeyde artmıştır. Ayrıca, bu sonuçlar FMS'nin inflamatuvar patogenezini desteklemektedir.

Anahtar kelimeler: Fibromiyalji, inflamasyon, nötrofil/lenfosit oranı, ortalama platelet hacmi, platelet/lenfosit oranı

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by fatigue, mood disorders, cognitive dysfunction, and sleep disturbance.[1] The prevalence of FMS ranges from 0.4% to 11%, and it is more common in females.[2]

Etiology of this syndrome is not fully understood. Although genetic, hormonal, environmental, neural and immunological factors have been defined, no specific cause has been identified yet.[3] Recent studies have shown that inflammatory process may play a role in the etiology of FMS.[4,5] Inflammatory markers of rheumatological diseases are usually negative, but it is found that hematological indices associated with inflammation has been changed in FMS.[6]

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are accepted as hematological indices that show inflammation in some diseases.[7,8] NLR has been used to investigate the severity of systemic inflammation in cardiovascular diseases, malignancies, and diabetes mellitus as an easily predictable and inexpensive indicator.[6] Moreover, it is used as an indicator of immune system, inflammation and adaptive immune balance in peripheral blood.[9] Mean platelet volume (MPV) and platelet distribution width (PDW) are also frequently used as systemic inflammatory markers.[5] Several studies have reported a correlation between MPV and active inflammatory diseases.[10–12] In this study, it was aimed to determine whether there was a difference in terms of hematological indices (NLR, PLR, MPV), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) between FMS patients and healthy controls, and to reveal the inflammatory process in pathogenesis of FMS.

METHOD

This retrospective, cross-sectional study included female participants, aged 18–45 years, who applied to the Istanbul Kanuni Sultan Suleyman Training and Research Hospital Physical Medicine and Rehabilitation outpatient clinic between January 2020-December 2021 with chronic widespread pain and diagnosed with FMS and healthy controls.

Participants aged 18–45 years admitted to the outpatient clinic with fatigue, sleep disturbance and widespread chronic pain, and diagnosed with FMS according to AAPT diagnostic criteria[13] in the last two years were included in the study. Participants in the healthy control group were selected among hospital staff who applied to our outpatient clinic in the last 3 months, had hemogram, ESR, CRP levels analysis, did not have any chronic or inflammatory disease, and met the inclusion criteria. The exclusion criteria were male sex, having another systemic inflammatory disease, and receiving treatment for FMS within the last 6 months.

NLR (absolute neutrophil count/ absolute lymphocyte count), PLR (absolute platelet count/ absolute lymphocyte count), MPV (mean platelet volume), ESR, and CRP levels in the blood test of the participants included in the study were calculated.

Institutional ethics committee approved the study under the Helsinki Declaration (under number: KAEK/2022.02.35).

Statistical Analysis

Statistical analysis was performed using SPSS software version 23.0 (MacOs, IBM Corp., Armonk, NY, USA). The sample size was calculated using G*Power software (G*Power version 3.1.9, Germany) based on the change in NLR. According to the calculation of sample size, in order to achieve $\alpha<0.05$ and $\beta=95\%$, it was calculated that a minimum of 78 participants would be required for each group as described by Al-Nimer et al.[14]

Normal distribution of the variables was controlled by Shapiro-Wilk test and histogram. Descriptive statistics were presented as mean±standard deviation, minimum and maximum values. For inter-group analysis, Mann Whitney-U test or student independent t test were used according to the distribution of the variables. Confidence interval was 95%, and p-values of <0.05 were considered as significant.

RESULTS

One hundred and eighty-seven female participants were included in the study according to the inclusion criteria: ninety-eight of them were diagnosed with FMS (FMS Group) and eighty-nine were healthy controls (Control Group). Mean age of the participants was 37.3±5.05 years for the FMS Group and 37.2±5.2 years for the Control Group. Demographic characteristics and laboratory parameters are shown in Table 1.

Upon comparison of the FMS and Control Groups according to hematologic indices, there were statistical differences between both groups in terms of NLR (p=0.034), MPV (p<0.001), CRP (p=0.001), and ESR (p<0.001). There was no significant difference in PLR (p=0.195) between the two groups (Table 2).

DISCUSSION

This study is important to demonstrate the presence of an inflammatory process in the pathogenesis of FMS. According to the results of the study, NLR, MPV, CRP and ESR levels were found to be higher in participants with FMS compared to healthy controls.

The reasons of FMS are not clarified yet. It was not known as an inflammatory disease; however, recent studies have

Table 1. Demographic characteristics and laboratory parameters of the participants

Variable	FMS group (n=98)	Control group (n=89)	p
Age (years), Mean±SD	37.3±5.05	37.2±5.2	0.332
Age, n (%)			
25–35 years	23 (23.5)	31 (34.8)	0.087
36–45 years	75 (76.5)	58 (65.2)	
BMI (kg/m^2)	29.7±3.9	26.9±4.1	0.587
Neutrophils (x10^9/L)	4.5±1.2	3.8±0.9	0.115
Lymphocytes (x10^9/L)	2.3±0.6	2.2±0.5	0.675
Platelets (x10^9/L)	287.5±60.9	256.4±51.3	0.333

FMS: Fibromyalgia syndrome; SD: Standard deviation; BMI: Body-mass index

shown that the inflammatory process may play a role in the pathogenesis of FMS.[15,16] Based on recent studies, inflammatory cytokines, such as substance-p, IL-6, and IL-8, have been found to be higher in FMS.[17] In addition, proinflammatory cytokines, such as IL-1 and TNF- α, may cause sleep disturbance, fatigue or depression.[18,19] Bote et al.[20] have revealed that anti-inflammatory treatment modalities improved and changed neutrophile functions in FMS. These results support the inflammatory process in the pathogenesis of FMS.

NLR is a prognostic marker revealing systemic inflammatory response, and it has been found that levels of NLR increased in some systemic diseases.[6,7] Al-Nimer et al.[14] have found that NLR and PLR levels of FMS patients were higher than healthy controls. Additionally, they have reported it would be possible to estimate disease severity and prognosis of FMS by calculating hematological indices. Similarly, Akturk et al.[5] have stated the NLR levels were statistically significantly higher in FMS patients than healthy controls. The present study also supported the findings of the aforementioned study results. In a study, NLR has been compared between healthy controls and FMS patients, and no significant difference has been found between them.[21] This result may be associated with the small number of participants.

PLR is also a new marker that indicates the presence of inflammation. PLR has been studied in many systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and cancers.[22,23] Several studies have found FMS patients had higher mean values of PLR than healthy individuals.[14,24,25] Contrarily, in the current study, there was no difference in PLR values between both groups.

MPV is an indicator of platelet function.[5] Delgado-Garcia et al.[11] have reported a relation between MPV and inflammatory diseases. MPV is also one of the hematological inflammatory markers found to be high in FMS in the literature. Akturk et al.[5] have found higher MPV values in FMS compared to healthy controls. In one cross-sectional study, based on the fact that MPV is an independent risk factor in cardiovascular disease, MPV values have been evaluated between healthy subjects and FMS patients, and it has been found that MPV values were higher in participants with FMS.[26] According to the present and aforementioned study results, MPV is supported to be a predictive value for FMS.

In Toker et al.'s[19] study evaluating CRP and ESR levels in 52 patients with FMS and 32 healthy individuals, they have found significantly higher CRP and ESR values in FMS patients when compared with controls. Xiao et al.[16] have found that CRP levels were higher than healthy controls, while ESR levels were similar. In the current study, in accordance with the literature, ESR and CRP levels were found to be higher in FMS patients compared to healthy controls. These results reveal the inflammatory process in the pathogenesis of FMS.

Table 2. Inter-group analysis of hematological indices

Hematological indices	FMS group			Control group			p
	Mean	Lower bound	Upper bound	Mean	Lower bound	Upper bound	
NLR	2.0	1.9	2.2	1.8	1.7	1.9	0.034*
PLR	130	121.7	138.5	122.4	115.3	130.5	0.195
MPV	10.2	9.9	10.5	9.6	9.4	9.8	<0.001*
CRP (mg/L)	2.7	2.2	3.3	1.7	1.4	2.1	0.001*
ESR (mm/L)	9.7	8.2	11.2	6.0	5.1	7.1	<0.001*

P<0.05 was considered significant for inter-group analysis. FMS: Fibromyalgia syndrome; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; MPV: mean platelet volume; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

Limitations of the Study

Owing to the retrospective study design, pain intensity of the participants was not known, and the relation between disease activity and mean values of the hematological indices was not revealed. Furthermore, larger number of participants can be effective to generalize the results.

CONCLUSION

Proinflammatory hematological indices were significantly changed in FMS compared to healthy controls. These indices and ratios can serve as useful markers for diagnosing FMS and considering treatments to reduce inflammation in treatment of FMS. However, multicenter studies with large sample numbers should be conducted to determine the cut-off values of these hematological indices and ratios in FMS.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (No: KAEK/2022.02.35, Date: 10/02/2022).

Informed Consent: Written informed consent was obtained from all patients.

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