ORIGINAL RESEARCH

Disease activation and laboratory parameters in Fibromyalgia Syndrome: Relationship with C-reactive protein/albumin ratio, neutrophil/lymphocyte ratio, mean platelet volume

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Abstract

Fibromyalgia syndrome (FMS) is a chronic, widespread painful disease with unexplained etiopathogenesis and somatic-psychic findings. Unlike inflammatory rheumatic diseases, there are no specific laboratory parameters in FMS. In our study, we aimed to investigate the relationship between inflammatory markers and FMS activation scales. Eighty patients aged 18-65 years, diagnosed with FSM according to the American College of Rheumatology (ACR) 1990 criteria, were evaluated retrospectively. 61 healthy controls matched for sex, age, and body mass index (BMI) constituted the control group. In addition to the demographic data of the patients, the fibromyalgia impact questionnaire (FIQ) score, visual analog scale (VAS) fatigue score, VAS pain score, number of tender points, C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, and complete blood count values were evaluated and compared statistically. FIQ, VAS pain, and VAS fatigue score, number of tender points were significantly higher in the patient group (p<0.001). The mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), CRP values of the patient group were not statistically different from the control group. Patients' FIQ, VAS pain and VAS fatigue scores, number of tender points, and MPV, NLR, and CRP albumin ratio (CAR) parameters were not significant according to the correlation analysis. FIQ, VAS pain, VAS fatigue scores, and the number of tender points were statistically higher in the patient group, MPV, NLR, and CAR parameters were not different. Contrary to studies stating that FMS may be of inflammatory origin, no statistically significant difference was found in inflammatory disease activation parameters between patients with FMS and the control group in our study.

Keywords: Fibromyalgia syndrome (FMS), C-reactive protein/albumin ratio (CAR), neutrophil lymphocyte ratio (NLR), mean platelet volume (MPV)

Introduction

Fibromyalgia Syndrome (FMS) is a disease in which widespread pain in the body is accompanied by somatic and cognitive symptoms (fatigue, sleep, memory, and mood disturbance), and its etiopathogenesis has not been fully elucidated [1]. The prevalence of the syndrome ranges from %2 to %8. It is twice as common in women [2]. Biochemical, metabolic, genetic, epigenetic, and immune regulatory mechanisms play role in pathophysiology [3]. The central sensitization mechanism is the most examined one among the mechanisms explaining pain. However, no biomarker has been indicated to explain the functional and chemical processing disorder that causes peripheral nociceptive stimulation and the perception of this pain in the brain [3-5]. To monitor and treat the disease effectively and to evaluate disease activation accurately, the pathophysiology should be better understood and laboratory markers showing activation should be defined.

During the activation period of inflammatory rheumatic diseases, the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, which are the acute phase reactants (APR), increase [6]. However, these values occasionally may be insufficient to indicate the activation of rheumatic disease and even if the disease is active APR can be monitored normally. CRP is an APR synthesized by the effect of proinflammatory cytokine interleukin-6 (IL-6) [7]. Albumin is a negative acute-phase reactant, and its low levels are associated with the severity of inflammation [8]. The CAR is better than CRP alone in showing the activation status in inflammatory conditions, including rheumatic diseases [9, 10]. In addition, It has been reported in previous studies that neutrophil-lymphocyte ratio (NLR) is associated with markers of inflammation

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during the active period of ankylosing spondylitis, polymyalgia rheumatica, systemic lupus erythematosus, and Behçet's disease. [11-16]. NLR has been clearly shown to be associated with systemic inflammation, and we included this parameter in our study that we investigated the relationship between fibromyalgia activity measures and systemic inflammation. Mean platelet volume (MPV) is a parameter associated with platelet function and activity, and it is negatively correlated with the activation of many inflammatory diseases [17-19].

There is a study stating that patients with FMS whose inflammatory and rheumatic values are monitored differently than normal should be classified as a different subtype and there should be a different treatment approach for these patients [20]. In another study, in which a positive correlation between FMS symptom severity and CRP were determined, emphasized that this association should be evaluated together with body mass index (BMI) and accompanying comorbid conditions [21]. It was reported that there is a significant positive correlation between IL-6 and high sensitive CRP (hsCRP) but no dramatical increase in serum interleukin -6 (IL-6) levels of FMS patients and hsCRP levels can be affected by age and obesity in research which was conducted based on the knowledge that IL-6 is the main regulator of hsCRP production [22].

In light of the studies mentioned above in the literature, we believe that detecting laboratory parameters associated with disease or activity scales in FMS will help reduce controversial uncertainties in FMS, where there are no objective parameters in diagnosis and follow-up. Therefore, this study, it was aimed to evaluate the relationship between laboratory findings and disease activity scales in patients with FMS.

Materials and Methods

This study was planned retrospectively and patients who applied to the Physical Medicine and Rehabilitation clinic between January 2019 and December 2020 were included. The diagnosis of FMS was made according to the American College of Rheumatology (ACR) 1990 criteria [23]. Eighty patients (n=80) who did not use drugs in the last 1 year, aged 18-65 years, and 61 (n=61) healthy controls with similar age, sex, and BMI were recruited.

The exclusion criteria were set as follows: patients aged under 18 years, who were on psychiatric therapy, had a history of alcohol and substance abuse, other uncontrolled medical disorders, and mental retardation, and progressive central and peripheral neurological disorders.

Clinical Evaluation

Patient information from the hospital electronic system was evaluated retrospectively and age, gender, marital status, history of other diseases and medications, habits, complaints, and symptoms at presentation, visual analog scale (VAS) fatigue score, VAS pain score, number of sensitive points, fibromyalgia impact questionnaire (FIQ), laboratory data were recorded.

Laboratory parameters

CRP (normal range 0-5 mg/dL), ESH (0-20 mm/hour), albumin (g/dL) values were obtained from laboratory analyzes. Leukocyte

(K/uL), lymphocyte (K/uL), neutrophil (K/uL), platelet (K/uL) counts and MPV values were determined from the hemogram examination. The CAR value was calculated by dividing the CRP level by the albumin level and the NLR value by dividing the neutrophil count by the lymphocyte count.

Measurements

Fibromyalgia Impact Questionnaire (FIQ)

On this scale, 10 different characteristics are measured. This scale gives information about the functional status of the patient. It provides evaluation under the headings such as pain, fatigue, anxiety, and depression. Low scores indicate well-being. It is a questionnaire that we apply to our patients that we follow up routinely and gives information about the quality of life and functional status. The questionnaire was developed by Burchardt et al. for measuring functional status in patients with FMS [24]. Turkish validity and reliability have been demonstrated [25].

Measurement of Fatigue Severity - Visual Analogue Scale (VAS)

The scale created by Price et al. has been used in studies to identify fatigue, a subjective symptom such as pain [26-28]. The scale is a 10-cm ruler that says "I do not feel tired" (0 points) at the one end, and "I feel very tired" (10 points) on the other. The patients were informed that the "0" on the scale means "I do not feel tired", that the increasing numbers indicate an increase in severity of fatigue, and that "10" means "I feel very tired", and asked to mark the fatigue they felt at the moment on the scale.

Measurement of Pain Severity-VAS

For pain severity according to the VAS, "no pain" is usually graded as 0 points and "worst pain imaginable" as 10 points (10 cm scale) [29]. Ranges for pain intensity; 6 indicated severe pain [30].

Tender Point Count (TPC)

Tender point count was determined by applying pressure of <4 kg to 18 symmetrical points on both sides of the body. If the participants felt pain, the tender point was considered positive. The total number of tender points was recorded as the TPC score. The maximum score of TPC was 18.

Study protocol

All evaluations in both groups were made and compared with each other.

Statistical analysis and method

SPSS V22.0 statistical software package was used for all data analyses. The Kolmogorov–Smirnov test was used to check the normality assumption of continuous variables. Descriptive statistics were presented as frequency (%), number and mean ± standard deviation (SD), or median (minimum-maximum). The independent-samples t-test was used for intergroup comparisons of normally distributed variables, while the Mann–Whitney's U test was used for non-normally distributed variables. χ^2 and Fisher's Exact test were used to compare nominal and categorical values

between groups. Spearman's correlation analysis (rho) was used for correlation analysis. The level of statistical significance was set at p<.05.

Research Ethics

The approval for the study was obtained from Malatya Clinical Research Ethics Committee. (Approval number: 2021/73).

Results

Eighty female patients diagnosed with FMS and 61 female healthy controls similar to the patients in terms of age and BMI were included in the study (p=.23 and p=.87, respectively). Table 1 shows the demographic findings of patients with FMS and healthy controls.

FIQ, VAS pain, VAS fatigue questionnaires, and the number of tender points were statistically significantly higher in the patient group compared to the control group. (For all p<.001). When the laboratory parameters MPV, NLR, and CAR were evaluated, there was a significant difference between the patient and control groups. The comparison of the questionnaire score and laboratory values between the control and patient group is shown in Table 2. No significant correlation was found according to the correlation analysis of the FIQ scale, VAS pain, VAS fatigue, and tender point number, and MPV, NLR, and CAR parameters of the patient group [Table 3].

Table 1. Demographic and clinical characteristics of the patient and control groups

		Patients (n=80)	Controls (n=61)
Age, year, mean ± SD		41.4±7.6	39. ±10.5
BMI, kg/m², mean ± SD		26. ±3.8	26.6±5.8
Marital Status, n (%)	Single	5 (6.3)	11 (18)
	Married	74 (92.5)	48 (78.7)
	Divorced	1 (1.3)	2 (3,3)
Main complaint, n (%)	No complaints	0	17 (27.9)
	Widespread Pain	59 (73.8)	7 (11.5)
	Pain in legs	5 (6.3)	5 (8.2)
	Pain in arms	7 (8.8)	5 (8.2)
	Low back pain	4 (5.0)	8 (13.1)
	Neck pain	5 (6.3)	19 (31.1)

SD: Standard deviation; BMI: Body mass index.

Table 2. Comparison of questionnaire and laboratory values between patient and control group

	Patients (n=80)	Controls (n=61)	P
FIQ	68.1 (46.2-99.3)	39 (0-91.1)	<0.001^m
VAS pain	8 (5-10)	6 (0-9)	<0.001^m
VAS fatigue	9 (2-10)	5 (0-8)	<0.001^m
Tender Points	14 (4-18)	0 (0-5)	<0.001^m
MPV, mean±SD	10.0 ± 0.9	9.9 ± 1.1	0.660^t
NLR	1.8(0.6-4.9)	1.7 (0.4-3.9)	0.2641^m
CAR	0.07 (0-1.43)	0.05 (0-0.05)	0.113^m

Unless otherwise stated, values are presented as median (min-max).
SD: standad deviation; FIQ: Fibromyalgia impact questionnaire; VAS: visual analogue scale;; NLR: Neutrophil lymphocyte ratio; MPV: mean platelet volume, CAR: CRP albumin ratio
^{t}: Independent simple T test, ^{m}: Mann-Whitney-U test

Table 3. Spearman's rho correlation analysis of FIQ scale, VAS pain, VAS fatigue and tender point number(TPC) and MPV, NLR and CAR parameters in the patient group

	FIQ		VAS Pain		VAS Fatigue		TPC	
	rho	p	rho	p	rho	p	rho	p
MPV	-.04	.73	-.007	.95	-.088	.49	.08	.46
NLR	.05	.65	-.102	.37	.12	.31	.18	.10
CAR	-.20	.07	.026	.82	-.01	.97	-.15	.18

FIQ: Fibromyalgia impact questionnaire; VAS: visual analogue scale; MPV: mean platelet volume; NLR: Neutrophil lymphocyte ratio; CAR: CRP albumin ratio, TPC: tender point number

Discussion

In this retrospective study, the relationship between MPV, NLR, and CAR values, which are frequently used to determine disease activation in inflammatory diseases, and disease activation scores of patients with FMS was evaluated. FIQ, VAS pain, VAS fatigue scores, and the number of tender points were statistically significantly higher in the patient group than in the control group. However, the MPV, NLR, and CAR parameters were not different.

There are many laboratory parameters used to measure disease activation in inflammatory rheumatic diseases. Although FMS is not considered to be an inflammatory rheumatic disease, studies suggesting that inflammation is effective in the perception and formation of pain in the periphery, as well as central sensitization in the formation and perception of pain, reported that a low-grade inflammatory response was observed in patients with FMS [31]. Many studies are reporting that this inflammatory response may be effective on pain perception and processing disorders [31-34]. In a meta-analysis, IL-6, interleukin-4 (IL-4), and interleukin-17A (IL-17A) levels were found to be high in patients with FMS [32]. In the study investigating the relationship between the severity of FMS-related pain, fatigue, anhedonia, anxiety, cognitive dysfunction symptoms, and cytokine levels, it was observed that the level of interleukin-10 (IL-10), which blocks the perception of pain, decreased, and the level of IL-6 and interleukin 1R (IL1R) increased [31, 35]. Cytokine levels were examined in these studies, but the association of these cytokine levels with acute phase reactants that would determine their effects in peripheral blood has not been reported. IL-6 is a cytokine involved in the synthesis of CRP, which is one of the indicators of inflammation in the peripheral blood, and an increase in CRP levels can be expected in patients with high IL-6 levels.

In healthy people, a triple response develops as a result of mechanical or chemical stimulation of the skin [36, 37]. This response is called neurogenic inflammation and is produced by the release of proinflammatory peptides from peripheral nerves terminating in peptidergic C fibers. Activation of these neuroinflammatory mechanisms is important in the early stages of fibromyalgia and may continue to contribute to ongoing core symptoms [38, 39]. Substance P, calcitonin gene related peptide (CGRP) and neurokinin A play an important role in the functioning of this mechanism. These neuropeptides increase skin blood flow, increase vascular permeability, and increase the extravasation of leukocytes and polymorphonuclear cells, which is the main feature of neurogenic inflammation [40]. Substance P and CGRP activate innate (mast cells, keratinocytes, dendritic cells) and adaptive (T lymphocytes) immune system cells. Mast cells are localized near sensory neurons and blood vessels and when activated lead to the release of neuroactive and vasoactive substances such as bradykinin, histamine, prostaglandin, TNF [40]. These substances cause an increase in neuroinflammation by stimulating nociceptive receptors [41].

In the studies of patients with FMS; It has been reported that these local reactions are seen at high (64%) rates with a mechanical stimulation [42, 43]. The sympathetic nervous system interacts with this process through upregulation of α¬ adrenergic receptors in local inflammation [44]. This may be the reason why there was no difference in the blood parameters evaluated in our study.

In a study examining the association between FMS and CRP level, it was reported that there was a statistically significant relationship after all demographic and lifestyle adjustments were made, but this significant relationship weakened when adjusting regarding BMI and other comorbid conditions [21]. In another study, an increase in BMI was associated with an increase in CRP levels in patients with FMS [22]. Although some studies have found that blood inflammatory indicators represented by CRP are high in patients with FMS, it has been concluded that this is due to comorbid conditions, especially BMI. In some studies examining interleukin levels, it has been reported that proinflammatory cytokines, especially IL-6, are increased and anti-inflammatory cytokine levels are decreased in patients with FMS [31]. In this study, we examined MPV, NLR, and CAR values in patients with FMS, whose relationship with inflammation has recently been reported, and we evaluated the relationship of these values with disease activation. In contrast to previous studies that claimed that FMS is an inflammatory disease, no statistically significant difference in the values indicating the activation status of inflammatory disease between patients with FMS and the control group was found in our study.

In our study, it was aimed to compare laboratory parameters and disease activity in patients with FMS, and to determine a specific biomarker that can be easily accessed in clinical practice, to provide patients with the chance to apply more effective treatments.

Conclusion

Unfortunately, the results of our study do not show an indicator that can be used in FMS diagnosis and activation follow-up. Broader, multicenter follow-up studies are needed to better understand the inflammatory aspect of FMS.

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