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The relationship between vitamin 25(OH)D level and hematological parameters in newly diagnosed women with fibromyalgia syndrome

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Ethics Committee Approval
The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Clinical Trials Ethics Committee (11.04.2018/ 2011-KAEK-25 2018 / 04-10).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Chronic inflammation may play a role in the pathogenesis of fibromyalgia syndrome (FMS). Several hematological markers are prothrombotic, and markers of systemic inflammation. Vitamin D (VitD) level can affect FMS and has an anti-inflammatory effect. The aim of this study is to investigate the relationship between hematological parameters and VitD in FMS and its effect on disease severity.

Methods: The prospective case-control study included 90 newly diagnosed female patients with FMS (group 1) and 90 healthy volunteers (group 2). Pain and fatigue were evaluated by visual analogue scale (VAS). Disease severity was evaluated by FMS Impact Questionnaire (FIQ) in FMS. Neutrophils, lymphocytes, platelets, platelet distribution width (PDW) and mean platelet volume (MPV) were obtained from complete blood count results in both groups. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. 25(OH)D concentration was measured. Patients were divided into 3 groups according to vitamin D levels (VitD < 10 ng/ml, 10-30 ng/ml and >30 ng/ml.)

Results: The mean MPV and vitamin D levels were significantly higher in group 2 (P=0.001, P<0.001 for both), whereas median PDW was significantly higher in group 1 (P<0.001). Among FMS patients grouped according to VitD levels, only PLR level was significantly different (P=0.049). In subgroup analysis, PLR was significantly higher in the group with VitD < 10 ng/ml compared to the group with vitD levels between 10-30 ng/dl (P=0.024). There was no significant relationship between VitD levels and clinical and laboratory parameters (P>0.05). There was a significant inverse relationship between FIQ and PLR (P=0.022).

Conclusion: VitD deficiency may be a risk factor for FMS (cut-off is<14.6 ng/ml). In FMS, high PDW and high PLR in patients with VitD<10 ng/ml are indicative of a prothrombotic condition which can be aggravated by inflammation. We think that complete blood count and VitD levels can support the diagnosis and predict cardiovascular risk in FMS.

Keywords: Fibromyalgia, Inflammation, Platelet activation, Platelet distribution width, Vitamin D

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Introduction

Fibromyalgia Syndrome (FMS) is a chronic painful syndrome characterized by widespread pain and tender points, accompanied by a group of symptoms including sleep disturbance, morning stiffness, fatigue, irritable bowel [1]. FMS can be observed alone or as a comorbidity accompanying other rheumatic diseases [2]. It affects 2-4% of the population worldwide and is predominant among women [3]. The etiology and pathogenesis of FMS has not yet been clearly explained, however, central, and autonomic nervous system dysfunction, cytokines, neurotransmitters, hormones, immune system, and environmental stress factors were held responsible. It is thought that chronic inflammatory process may play a role in the pathogenesis of fibromyalgia [4], but there are no reliable laboratory markers that indicate disease activity or severity in fibromyalgia. Recently, studies in FMS have focused on markers of inflammation derived from complete blood counts because they are cheap and easily accessible [5,6]. Simple hematological markers such as neutrophil/lymphocyte ratio (NLR), platelet distribution width (PDW), mean platelet volume (MPV) and platelet/lymphocyte ratio (PLR) have been identified as markers of systemic inflammatory response and have been reported to support the diagnosis in FMS [7]. Platelet count, PDW and MPV are also predictors of platelet activation and have been associated with an increased risk of cardiovascular disease due to arterial thrombosis. Inflammation may increase arterial and venous thrombus formation [5,8]. Few studies in this area have reported conflicting results regarding these parameters in patients with FMS when compared to healthy individuals [5, 9, 10].

Vitamin D mainly affects calcium homeostasis and bone structure [11]. However, recent research has shown that it also influences tissues other than bone tissue. It has been assumed that vitamin D has anti-inflammatory properties which contribute to pain relief. In the studies, a relationship was shown between vitamin D deficiency and chronic pain. FMS symptoms such as fatigue, diffuse muscle pain and weakness have also been observed in individuals with vitamin D deficiency [12].

Furthermore, a link between hypovitaminosis D and cardiovascular risk has been established. Vitamin D exerts its effect on the cardiovascular system by regulating inflammatory, oxidant and immune processes leading to the progression of atherosclerosis [13]. Vitamin D may also have a regulatory effect on platelets, for Vitamin D receptors have been identified in platelets. Vitamin D deficiency has been associated with endothelial dysfunction [14].

In the light of this information, we thought that there may be a relationship between hematological parameters known as markers of subclinical inflammation, prothrombotic state and serum vitamin D levels in fibromyalgia, which may affect the severity of the disease. However, we could not reach sufficient data in the literature review.

In this study, we aimed to investigate the relationship between hematological parameters and serum vitamin D level in newly diagnosed female patients with Fibromyalgia syndrome and its effect on disease severity.

Materials and methods

The study was conducted between November 2018 - April 2019 in Physical Medicine and Rehabilitation outpatient department of Bursa Yuksek Ihtisas Training and Research Hospital. It was approved by local ethics committee (Bursa Yuksek Ihtisas Training and Research Hospital Clinical Trials Ethics Committee /11.04.2018/ 2011-KAEK-25 2018 / 04-10). All participants were informed about the study and signed a written consent form.

Female patients aged 18-65 years newly diagnosed with FMS according to the ACR 2013 revised form [15] were included in the study. Chronic systemic disease, inflammatory rheumatic disease (AS, RA, SLE), having clinically or laboratory proven acute or subacute infection, hypertension, and dyslipidemia, those with psychiatric, neurological, endocrinological and hematological diseases, patients with disorders of the calcium metabolism, pregnant or breastfeeding patients, and Vitamin D, nonsteroidal anti-inflammatory and anticoagulant drug users were excluded from the study.

The study group consisted of 90 female patients (Group 1) diagnosed with primary FMS, while the control group consisted of 90 age and gender matched healthy volunteers (Group 2). Age, body mass index (BMI) (kg/m^2) and demographic data of all participants were recorded. Tenderness in FMS patients was assessed by applying 4 kg/cm^2 pressure on 29 specific body points. Pain and fatigue levels were evaluated by visual analogue scale (VAS) and disease severity was evaluated by FMS Impact Questionnaire (FIQ).

FIQ is a valid and reliable method for assessing the impact of the disease on daily life in patients with FMS [16]. The Turkish version of the FIQ was validated by Sarmer et al. [17]. This scale measures 10 distinctive parameters: Physical function, well-being, inability to work, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The maximum score for FIQ is 100 and higher scores indicate increased disease severity. In the intensity analysis, total FIQ scores between 0-38 represent low impact, those between 39-58 represent moderate impact, and those between 59-100 indicate severe impact.

Five milliliters of venous blood samples were collected from all participants from the antecubital region at 08.00 AM after one night of fasting into tubes with tripotassium ethylenediamine tetra acetic acid (EDTA) and studied within two hours of collection. Hematological indices were analyzed by a Mindray BC 6800 Haematology Analyser (M68LHLYSE, Nanshan Shenzhen, China). Neutrophils, lymphocytes, platelets, PDW and MPV values obtained from complete blood count were recorded. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. 25-hydroxyvitamin D [25(HO)D] concentration was measured by the ELISA method. Patients with FMS were divided into 3 groups based on 25(HO)D concentration, as follows: <10 ng/ml: Severe insufficiency, 10-30 ng/ml: moderate insufficiency, > 30 ng/ml: Normal [18].

Statistical analysis

The suitability of continuous variables to normal distribution was examined by Shapiro Wilk test. Normally and non-normally distributed continuous variables were expressed as

mean (standard deviation), and median (minimum-maximum), respectively. Categorical variables were reported as n (%). Mann Whitney U test and independent samples t-test were used for comparisons of continuous and discrete variables between the FMS and control groups, and chi-square test was used for comparisons of categorical variables. Kruskal Wallis or ANOVA tests were used in comparisons between vitamin D groups. After the Kruskal Wallis test, the groups were compared in pairs using Dunn test. The correlation between hematological parameters and vitamin D level, pain VAS, fatigue VAS and FIQ total score were examined using correlation analysis and Spearman correlation coefficient was calculated. Internal consistency of the FIQ scale was examined by reliability analysis and Cronbach alpha coefficient. Receiver operator characteristic (ROC) curve analysis was performed to estimate the sensitivity and specificity of vitamin D level for predicting the presence of FMS. The Cronbach α value for the overall scale was α = 0.79. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and $P<0.05$ was considered statistically significant.

Results

A total of 90 female patients with FMS aged between 22-56 years (median 37.50) and 90 healthy female volunteers aged between 21-55 years (median 41) were included in this study. The groups were similar in terms of age, BMI, smoking and marital status (Table 1).

There was no significant difference between the two groups in terms of leukocyte, neutrophil, lymphocyte, platelet values and NLR. The mean MPV level was significantly higher and mean PDW level was significantly lower in the control group ($P=0.001$, $P<0.001$, respectively), while Vitamin D levels were significantly lower in the patient group ($P<0.001$) (Table 1).

Only PLR significantly differed between FMS patient subgroups categorized according to vitamin D levels ($P=0.049$). In subgroup analysis, PLR level was significantly higher in the group with vitamin D level < 10 ng/ml compared to the group with vitamin D levels between 10-30 ng/ml ($P=0.024$). There was no significant difference between the groups with vitamin D levels>30 ng/ml and <10 ng/ml according to PLR level ($P=0.152$ and $P=0.557$, respectively) (Table 2).

A significant correlation was found between vitamin D level and age. Vitamin D levels increased with increasing age ($P=0.029$). There was no significant relationship between vitamin D levels and clinical and laboratory parameters ($P>0.05$). There was an inverse significant relationship between FIQ score and PLR level (r=-0.024, $P=0.022$) (Table 3).

Receiver operator characteristic curve analysis was performed to estimate the sensitivity and specificity of vitamin D for predicting the presence of FMS, and the cut-off point for vitamin D was determined as ≤14.66 ng/ml. The area under the curve for vitamin D was 0.72 (sensitivity 75.56%, specificity 61.36%, $P<0.001$), showing that a vitamin D ≤14.66 ng/ml was significantly related to an increased risk of FMS (Figure1).

Table 1: Demographic, clinical, and laboratory characteristics of the FMS and control groups

	FMS n=90	CONTROL n=90	*P*-value
Age (year)	37.50(22-56)	41(21-55)	0.114[a]
BMI (kg/cm^2)	25.47(18.31-41.53)	25.95(19.72:38.63)	0.940[a]
Smoking	16(27.10%)	24(27.90%)	0.917[b]
Marital status			
Single	9(10.10%)	17(19.10%)	
Married	75(84.30%)	67(75.30%)	0.233[b]
Widow	5(5.60%)	5(5.60%)	
FIQ	59(20-94)	-	-
Pain VAS	7(0-0)	-	-
Fatigue VAS	8(0-10)	-	-
WBC (K / uL)	7.43(4.10-12.07)	7.13(3.32-12.71)	0.408[a]
NEU (× 10 ^{3} / uL)	4.35(1.40-8.32)	4.10(1.69-9.31)	0.320[a]
LYM (× 10 ^{3} / uL)	2.21(1.20-4.50)	2.25(0.42-4.26)	0.463[a]
PLT (× 10 ^{3} / uL)	275(163-444)	262(149-469)	0.402[a]
PCT (%)	0.25(0.15-2.89)	0.26(0.15-0.39)	0.253[a]
PDW (%)	16.20(15.30-17.40)	16(15.10-16.80)	<0.001[a]
MPV (fL)	9.37(1.58)	9.94(1.02)	0.001[c]
NLR	1.81(0.48-3.86)	1.73(0.78-10.69)	0.851[a]
PLR	114.53(52.67-263.85)	115.96(55.40-428.33)	0.782[a]
Vitamin D (ng/dl)	8.50(4.20-52.85)	17.11(4.20-58.89)	<0.001[a]

Data are presented as mean (standard deviation), median (minimum- maximum) and n%. a: Mann Whitney U Test, b: Chi-Square Test, c: Independent samples t-test, MPV: Mean platelet volume, PDW: Platelet distribution width, NLR: Neutrophil-lymphocyte ratio, PCT: Plateletcrit, PLR: Platelet-lymphocyte ratio, NEU: Neutrophil count, LYM: Lymphocyte count, PLT: Platelet count, WBC: White blood cell

Table 2: Clinical and laboratory parameters according to 25(OH)D levels in patients with FMS

	Vit D< 10 n=51	Vit D 10-30 n=34	Vit D >30 n=5	*P*-value [d]
FIQ	56(20-90)	59(21-94)	57(24-83)	0.966[d]
Pain VAS	7(3-10)	7(0-10)	8(1-10)	0.948[d]
Fatigue VAS	8(2-10)	8(0-10)	8(1-10)	0.962[d]
WBC (K / uL)	7.47(4.66-10.20)	7.26(4.32-12.07)	6.90(4.10-11.10)	0.971[d]
NEU (× 10 ^{3} / uL)	4.64(2.49-7.37)	4.08(1.40-8.32)	4.70(2.40-7.60)	0.613[d]
LYM (× 10 ^{3} / uL)	2.20(1.20-4.50)	2.42(1.30-4.38)	1.77(1.40-3)	0.063[d]
PLT (× 10 ^{3} / uL)	281(163-444)	264(174-371)	254(191-283)	0.225[d]
MPV (fL)	9.30(7-12.30)	9.70(6.90-11.60)	9.30(7.90-11.20)	0.396[d]
PCT (%)	0.25(0.15-0.40)	0.25(0.16-2.89)	0.22(0.18-0.28)	0.337[d]
PDW (%)	16.30(15.50-17.40)	16.20(15.40-17.20)	16.20(15.30-17.30)	0.299[d]
NLR	1.90(1-3.86)	1.66(0.48-3.48)	2.53(1.64-3.53)	0.068[d]
PLR	122.31(52.67-263.85)	105.57(60.29-215.38)	143.50(79-171.88)	0.049[d]

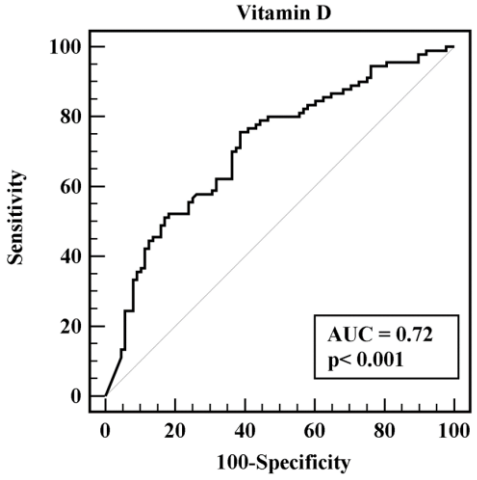
Data are given as mean (standard deviation), median (minimum- maximum) and n%. d: Kruskal Wallis Test

Table 3: The relationship between 25(OH)D levels and clinical and laboratory parameters in patients with FMS

	Vit D		Pain VAS		Fatigue VAS		FIQ	
n=90	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value
AGE	0.23	0.029	-0.11	0.293	-0.10	0.332	-0.09	0.379
WBC	-0.08	0.427	0.02	0.873	-0.05	0.615	0.02	0.845
NEU#	-0.15	0.160	0.02	0.877	-0.11	0.288	-0.02	0.839
LYM#	0.08	0.446	0.06	0.572	0.12	0.273	0.16	0.144
PLT	-0.08	0.446	-0.17	0.116	-0.11	0.315	-0.14	0.197
MPV	0.05	0.665	0.17	0.101	0.14	0.178	0.12	0.278
PCT	-0.04	0.724	-0.02	0.872	0.06	0.552	-0.01	0.922
PDW	-0.08	0.435	-0.09	0.427	-0.05	0.611	-0.13	0.240
NLR	-0.13	0.236	-0.05	0.625	-0.18	0.096	-0.17	0.112
PLR	-0.12	0.276	-0.17	0.118	-0.16	0.129	-.024	0.022
VIT D	-	-	-0.04	0.747	0.01	0.995	0.03	0.793

r_s: Spearman correlation coefficient

Figure 1: Receiver-operator characteristic (ROC) curves for determining the presence of FMS status. The area under the curve (AUC) for vitamin D is 0.72 with $P<0.001$.



Discussion

Our results showed that serum vitamin D levels were lower in patients with FMS compared to healthy subjects and did not affect the clinical activation findings, but PLR level, one of the markers of subclinical inflammation / thrombotic activation, increased in patients with Vitamin D levels below 10 ng/ml. Although the results of this study showed that serum PDW level was higher in patients with FMS compared to healthy controls, it did not correlate with

disease activity.

Even though fibromyalgia is not known as an inflammatory disease, secondary systemic symptoms are difficult to explain. There are no reliable laboratory markers indicating fibromyalgia disease activity or severity. However, recent studies have shown that inflammatory mechanisms play a key role in pathogenesis. Cytokines and neurotransmitters, such as IL-6, IL-8 and TNF-α, which are biochemical mediators of inflammation, are abnormal in FMS patients [4, 19]. In clinical practice, these markers cannot be used for diagnostic purposes. Therefore, studies in FMS have focused on markers of inflammation derived from complete blood counts because they are cheap and easily accessible [5,9].

It has been shown that simple hematological markers such as MPV, PDW, NLR, platelet (PCT) and PLR reflect inflammatory burden and disease activity in various diseases [7,20-22].

In FMS, increased platelet count, MPV and PDW have been identified as risk factors for cardiovascular disease, but studies have shown conflicting results. When compared with the control group, Aktürk et al. [5] found that MPV value was significantly higher and PDW value was lower in patients with FMS. On the contrary, Molina et al. [10] found PDW values higher and MPV values lower in patients with FMS. Al-Nimer et al. [23] found a significant increase in both MPV and PDW values in newly diagnosed women with FMS. It is thought that these contradictory results may be caused by differences in the characteristics of the working groups. Our results showed that there was no significant difference in platelet counts in women with FMS compared with healthy controls; however, PDW values were significantly higher and MPV values were significantly lower. This result was consistent with the results of Molina et al. [24] PDW is a measure of variability in platelet size and increases during platelet activation. PDW is used to identify fractions of large platelets that are more enzymatically and metabolically active. MPV is associated with platelet size, platelet activity and function. Larger platelets are more active than smaller ones [25]. It is thought that PDW is more specific than MPV as an indicator of platelet reactivity because it is not affected by single platelet distension caused by platelet swelling [10]. Our results may suggest platelet hyperactivation, which may contribute to the prothrombotic status of FMS patients by showing a high PDW value. Oxidative stress promotes platelet hyperactivation and consequently increases the risk of arterial thrombosis [26]. Studies have shown that oxidative stress increases in patients with FMS, and patients with FM may be prone to a prothrombotic state in which oxidative stress may contribute [27].

NLR and PLR have been described as a prognostic marker of systemic inflammatory response [10]. Elevated blood NLR has been shown to be associated with increased disease activity in many systemic, rheumatologic diseases [20, 22]. Aktürk et al. [5] found that NLR levels were higher in patients with FMS compared to healthy controls and argued that the diagnosis was supportive. Molina et al. [10] found that PLR levels were high in patients with FMS compared with healthy controls and emphasized that increased inflammation triggers prothrombotic status. However, neither of those studies evaluated the relationship between markers of inflammation and clinical activation findings such as pain, fatigue, daily living activity in FMS. There are few studies evaluating this relationship in the literature. El-Nimer et al. [6] showed that NLR and PLR were significantly higher in patients with FMS and significantly correlated with the total revised FIQ score. On the contrary, Yıldırım et al. [28] evaluated only MPV in patients with FMS and found no association between MPV and pain, fatigue, and FIQ. Our results showed no significant difference between the groups in terms of NLR and PLR values. In our study, we examined all hematological markers such as MPV, PDW, NLR, PCT, PLR, and found only an inverse relationship between FIQ score and PLR.

Many studies have shown that low serum 25 (OH) vitamin D levels increase the risk of cardiovascular disease [29] by altering platelet and endothelial functions, increasing oxidative stress, and activating inflammatory pathways [30]. A study showed that vitamin D levels <20 ng/ml were associated with increased cardiac risk and that MPV levels were significantly higher in the vitamin D ≤10 ng/ml group compared with healthy controls [31].

In the literature, there are many studies about FMS and vitamin D deficiency in chronic pain with contradictory results. While there are studies showing that vitamin D levels are significantly lower in FMS patients compared to healthy controls [32, 33], there are also studies that cannot find a relationship between vitamin D deficiency and FMS [34,35]. The large heterogeneity between the studied groups and the low power of most studies have been shown as the reasons for this inconsistency [36]. Our results showed statistically significantly lower vitamin D values in patients with FMS compared with the healthy control group. According to Roc analysis, we found an increased risk for FMS incidence in patients with vitamin D < 14.6 ng/ml. We categorized vitamin D levels as <10 ng/ml, 10-30 ng/ml and <30 ng/ml and observed that the clinical activation we evaluated with pain VAS, fatigue VAS and FIQ was not affected by vitamin D levels. We also observed that only the PLR level, one of the inflammatory/prothrombotic markers, was statistically significantly higher in the vitamin D <10 ng/ml group compared to the group with vitamin D levels between 10-30 ng/ml. When VitD <10 ng/ml group and VitD >30 ng/ml were compared, we did not observe a significant difference. This may be due to the small number of patients in the VitD >30 ng/ml group. However, in our study, we found no correlation between vitamin D level and clinical and laboratory activation. Yıldırım et al. [29] showed that vitamin D deficiency may increase MPV values, which is a risk factor in cardiovascular

diseases. The difference of our study is that we studied inflammatory/prothrombotic markers other than MPV.

Limitations

We performed this study on newly diagnosed female patients, but we did not distinguish between premenopausal and postmenopausal females. In our study, a significant correlation was found between age and vitamin D. This may be because postmenopausal women have been careful to use the natural source of vitamin D because of their high awareness of osteoporosis.

Conclusion

Our results showed increased PDW levels in FMS and confirmed that PDW was a predicting marker in FMS. At the same time, the results of our study showed that the incidence of FMS increases in patients with VitD <14.6 ng/ml, and there is an inflammatory condition associated with an increase in PLR levels in patients with VitD <10 ng/ml. Based on this, we thought that low VitD levels in patients with FMS may trigger inflammation and contribute to the risk of cardiovascular disease with a prothrombotic effect. In patients with FMS, complete blood count and vitamin D levels, which are easily accessible and inexpensive, can support the diagnosis and predict cardiovascular risk. The effect of VitD supplementation on hematological parameters in FMS needs to be investigated. We believe that larger-scale studies involving homogeneous groups are needed.

References

1. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014 Apr 16;311(15):1547-55.
2. Bennett RM, Russell J, Cappelleri JC, Bushmakin AG, Zlateva G, Sadosky A. Identification of symptom and functional domains that fibromyalgia patients would like to see improved: a cluster analysis. BMC Musculoskelet Disord. 2010 Jun 28; 11:134.
3. Berssaneti AA, Matsutani LA, Yuan SLK, et al. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed. 2017 57(4):356-363.
4. Coskun Benlidayi. Role of inflammation in the pathogenesis and treatment of fibromyalgia. Rheumatol Int. 2019;39(5):781-91.
5. Akturk S, Buyukavci R. Evaluation of blood neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol. 2017;36(8):1885–9.
6. Al-Nimer MSM, Mohammad TAM. Correlation of hematological indices and ratios derived from them with FIQR scores in fibromyalgia. Pak J Med Sci. 2018;34(5):1219–24.
7. Çintesun E, Akar S, Gul A, Çintesun FNI, Sahin G, Ezveci H, et al. Subclinical inflammation markers in hyperemesis gravidarum and ketonuria: A case-control study. J Lab Physicians. 2019;11(2):149-53.
8. Çetin MS, Özcan Çetin EH, Akdı A, Aras D, Topaloğlu S, Temizhan A, et al. Platelet distribution width and plateletcrit: novel biomarkers of ST elevation myocardial infarction in young patients. Kardiol Pol. 2017;75(10):1005-12.
9. Haliloğlu S, Carlioglu A, Sahiner E, Karaaslan Y, Kosar A. Mean platelet volume in patients with fibromyalgia. Z Rheumatol. 2014;73(8):742-5.
10. Molina F, Del Moral ML, La Rubia M, Blanco S, Carmona R, Rus A. Are patients with fibromyalgia in a prothrombotic state? Biol Res Nurs. 2019;21(2):224-30.
11. Baeke F, Gysemans C, Korf H, Mathieu C. Vitamin D insufficiency: implications for the immune system. Pediatr Nephrol. 2010;25:1597-606.
12. Çidem M, Karacan İ, Beytemur O, Kara S. Prevalence and risk factors for vitamin D deficiency in patients with widespread musculoskeletal pain. Turk J Med Sci. 2017 12;47(3):728-31.
13. Kiani A, Mohamadi-Nori E, Vaisi-Raygani A, Tanhapour M, Elahi-Rad S, et al. Vitamin D-binding protein, and vitamin D receptor genotypes and 25-hydroxyvitamin D levels are associated with development of aortic and mitral valve calcification and coronary artery diseases. Mol Biol Rep. 2019;29.
14. Verdoia M, Pergolini P, Nardin M, Rolla R, Negro F, Kedhi E. Vitamin D levels and platelet reactivity in diabetic patients receiving dual antiplatelet therapy. Vascul Pharmacol. 2019;7:106564.
15. Bennett RM, Friend R, Marcus D, Bernstein C, Han BK, Yachoui R, et al. Criteria for the diagnosis of fibromyalgia: validation of the modified 2010 preliminary American College of Rheumatology criteria and the development of alternative criteria. Arthritis Care Res (Hoboken). 2014;66(9):1364-73.
16. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol. 2009;36:1304-11.
17. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int. 2000;20:9-12.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30.
19. Xiao Y, Haynes WL, Michalek JE, Russell IJ. Elevated serum high-sensitivity C-reactive protein levels in fibromyalgia syndrome patients correlate with body mass index, interleukin-6, interleukin-8, erythrocyte sedimentation rate. Rheumatol Int. 2013;33(5):1259–64.
20. Uslu AU, Deveci K, Korkmaz S, Aydın B, Senel S, Sancakdar E, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res Int 2013:185317.
21. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine. 2008;75(3):291–4.
22. Mercan R, Bitik B, Tufan A, Bozbulut UB, Atas N, Ozturk MA, et al. The Association Between Neutrophil/Lymphocyte Ratio and Disease Activity in Rheumatoid Arthritis and Ankylosing Spondylitis. J Clin Lab Anal. 2016;30(5):597–601.
23. Al-Nimer MSM, Mohammad TAM, Alsakeni RA. Serum levels of serotonin as a biomarker of newly diagnosed fibromyalgia in women: Its relation to the platelet indices. J Res Med Sci. 2018;23:71.
24. Vagdatli E, Gounari E, Lazaridou et al. Platelet distribution width: a simple, practical, and specific marker of activation of coagulation. Hippokratia 2010; 14:28–32
25. Kosus N, Kosus A, Turhan NO. Relationship of ovarian volume with mean platelet volume and lipid profile in patients with polycystic ovary syndrome. Exp Ther Med. 2011;2:1141–4.
26. Santhakumar AB, Bulmer AC, Singh I. A review of the mechanisms and effectiveness of dietary polyphenols in reducing oxidative stress and thrombotic risk. Journal of Human Nutrition and Dietetics. 2014;27:1–21.
27. La Rubia M, Rus A, Molina F, Del Moral ML. Is fibromyalgia-related oxidative stress implicated in the decline of physical and mental health status? Clinical and Experimental Rheumatology. 2013;31:S121–7.
28. Yildirim T, Solmaz D, Akgol G, Ersoy Y. Relationship between mean platelet volume and vitamin D deficiency in fibromyalgia. Biomedical Research. 2016;27(4):1265-70.
29. Nsengiyumva V, Fernando ME, Moxon JV, Krishna SM, et al. The association of circulating 25-hydroxyvitamin D concentration with peripheral arterial disease: A meta-analysis of observational studies. Atherosclerosis. 2015;243:645-51.
30. Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE. Vitamin D deficiency and coronary artery disease: a review of the evidence. Am. Heart J. 2014;167:283-391.
31. Correia LC, Sodré F, Garcia G, Sabino M, Brito M, Kalil F, et al. Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. Am J Cardiol. 2013;111:324-7.
32. Okyay R, Kocyigit BF, Gursoy S. Vitamin D levels in women with fibromyalgia and relationship between pain, tender point count and disease activity. Acta Medica Mediterranea. 2016;32(1):243–7.
33. Olama SM, Senna MK, Elarman MM, Elhawary G. Serum vitamin D level and bone mineral density in premenopausal Egyptian women with fibromyalgia. Rheumatol Int. 2013;33(1):185–92.
34. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain 2014;155(2):261–8.
35. Mateos F, Valero C, Olmos JM, Casanueva B, Castillo J, Martinez J, et al. Bone mass and vitamin D levels in women with a diagnosis of fibromyalgia. Osteoporosis Int. 2014;25(2):525–33.
36. Ellis SD, Kelly ST, Shurlock JH, Hepburn ALN. The role of vitamin D testing and replacement in fibromyalgia: a systematic literatüre review BMC Rheumatol. 2018;2:28.

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