# Relationship between mean platelet volume and vitamin D deficiency in fibromyalgia.

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## Abstract

**Objective: To investigate whether vitamin D deficiency is associated with high mean platelet volume (MPV) in fibromyalgia (FMS) compared to healthy controls.**

**Methods: Ninety-nine patients with fibromyalgia and ninety-nine age- and sex-matched healthy female control subjects were included. Tenderness was evaluated by applying pressure (4 kg/cm$^2$) over 18 specific body points, and the number of tender points was recorded. FMS patients completed visual analog scales (VAS) to evaluate their level of pain and were evaluated with the FMS Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI). In all cases, platelet count and MPV were measure as part of each full blood count. Serum 25(OH)D3 levels were analyzed with Enzyme-Linked ImmunoSorbent Assay (ELISA). Patients were divided into three groups as follows: Group 1, vitamin D level of <10 ng/ml (n=33); Group 2, vitamin D level of 10–20 ng/ml (n=3); and Group 3, vitamin D level of >20 ng/ ml (n=33).**

**Results: MPV values were significantly higher in the vitamin group 1 compared to the control group. There was no significant difference between the vitamin group 3 and the controls. A negative correlation was determined between MPV and vitamin D status or 25 (OH) D level.**

**Conclusion: Vitamin D deficiency may contribute to an increase in MPV levels, which is a risk factor in cardiovascular disease (CVD) in FMS.**

## Introduction

Fibromyalgia (FMS) is a disease characterized by widespread pain accompanied by sleep disorders, affective impairments, chronic fatigue, functional deficiency, and emotional disorders [1]. However, the etiology of the disease is not fully understood. Several factors have been implicated in the pathophysiology of FMS, such as neuroendocrine dysfunction, genetic factors, psychosocial changes, and environmental stresses [2]. Further, many studies suggest that autonomic nervous system (ANS) dysfunction plays a role in the disease process [3,4]. FMS commonly presents with co-morbidities including psychiatric diseases, headache, irritable bowel syndrome, and interstitial cystitis [5]. However, FMS has been associated with cardiovascular disease (CVD) [6]. But the data are not fully understood regarding the risk of in FMS cases. The role of psychological distress and activation of the sympathetic nervous system, has been reported in FMS patients with CVD [7-13].

Higher mean platelet volume (MPV) values in FMS patients, which have been reported as a causative factor increasing the risk of CVD, have been shown in only one study [14]. Risk factors increasing MPV levels in FMS patients have not yet been evaluated. Platelets play an important role in the pathogenesis of atherosclerosis [8], and MPV is one of the most widely used biomarkers of platelet function [9]. Larger platelets with higher MPV values are hemostatically more reactive and produce higher amounts of the prothrombotic factor thromboxane A2, increasing the propensity to thrombosis [10]. Increased MPV has been reported in patients with CVD, atherosclerosis, cerebrovascular disease, venous thromboembolism, and several chronic inflammatory disorders [11-13].

Vitamin D deficiency is among the factors that cause an increase in MPV. The main role of vitamin D is in calcium metabolism and bone structure [15]. However, recent studies indicate that vitamin D has various clinical effects in non-bone tissues, such as in the brain and musculoskeletal system

[16-18]. An association between vitamin D and CVD has been reported in several studies [19-21]. Whether vitamin D deficiency or insufficiency is a risk factor for CVD is, however, currently unclear. Some studies have reported that low levels of circulating 25(OH)D are associated with CVD [22] while others have found no such association [23,24]. The levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 are found to be increased in vitamin D deficiency. Elevated cytokine levels lead to increased MPV [25-27]. However, vitamin D decreases the expression of the various adhesion molecules, thus preventing platelet activation and decreasing fibrinolysis and thrombosis [28]. In patients with vitamin D deficiency, the combined effect of elevated TNF-α and IL-6 levels and increased release of adhesion molecules may lead to increased MPV.

In this study, we aimed to investigate the association of vitamin D deficiency with high MPV in FMS.

# Methods

## Patient selection

Ethical approval for the study was obtained from the Ethics Committee of the Namik Kemal University. Written informed consent was obtained from all study participants prior to the study.

Inclusion criteria, according to revised American College of Rheumatology (ACR) preliminary diagnostic criteria [29], were diagnosis as primary FMS and acceptance to participate in the study.

Exclusion criteria were chronic inflammatory disorders, hypertension, hypercholesterolemia, or diabetes, to be undergoing anti-coagulant therapy, or being predisposed to thrombotic or bleeding disorders and calcium metabolic disorders. All included patients were nonsmokers and were not taking calcium or vitamin D supplements, consuming alcohol, or using drugs.

Ninety-nine patients diagnosed with primary FMS comprised the study group while the control group was composed of ninety-nine healthy, age-matched subjects. Body mass index, age, and demographic characteristics were recorded for all patients and controls. Tenderness was evaluated by applying pressure (4 kg/cm$^2$) over 18 specific body points, and the number of tender points was recorded. FMS patients completed visual analog scales (VAS) to evaluate their level of pain and were evaluated with the FMS Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI).

The validated version of the FIQ [30] is a specific instrument assessing disease impact on daily living in FMS patients. This instrument measures "physical functioning," "overall impact" (missed work days and job difficulty), and "symptoms" (depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being over the past week). The maximum score for the FIQ is 100, with higher values indicating greater severity.

In the severity analysis, a total FIQ score from 0 to <39 was found to represent a mild effect, from ≥ 39 to <59 a moderate effect, and from ≥ 59-100 a severe effect [31].

The Turkish version of the FIQ was validated by Sarmer [32]. The BDI is a self-report inventory that measures the severity of depression [33]. It includes 21 items, which are scored between 0 and 3. The Turkish version of the BDI was validated by Hisli [34].

## Blood samples

In all cases, platelet count and MPV were measured as part of each full blood count. Samples were taken by antecubital venipuncture into tubes containing tripotassium ethylenediaminetetraacetic acid (EDTA). All samples were analyzed using an automated analyzer (Sysmex SE 9500; Roche, Indianapolis, IN). The samples were rapidly processed (within less than 1 h) in order to minimize platelet swelling in the test tubes. The MPV reference range was determined as 7.8-11.0 fl. Strict quality control procedures were adopted: tri-level controls and external quality assurance programs were used on a regular basis to ensure the accuracy and precision of the instrument. The best indicator of vitamin D status is serum 25(OH)D3 concentration because it reflects both dietary intake and coetaneous synthesis of vitamin D. Therefore, we examined serum 25(OH)D3 concentration. The serum 25(OH)D3 levels were analyzed with the ELISA (EUROIMMUN, D-23560 Lübeck, Seekamp 31, Germany) method.

The definition of serum vitamin D status was summarized as severe, deficient, and insufficient when the concentration of 25-hydroxyvitamin (OH)-D <10, 10-20, >20 , ng/ml respectively [35]. Thus we divided patients into three groups as follows: Group 1, vitamin D level of <10 ng/ml (n=33); Group 2, vitamin D level of 10–20 ng/ml (n=33); and Group 3, vitamin D level of >20 ng/ml (n=33).

## Statistical analyses

SPSS for Windows version 17.0 software was used for statistical analyses of our study data. Mean +/- standard deviations (SD) were used to identify the data related to the continuous variables, and the number was used to identify the ones related to the categorical variables. The Kolmogorov-Smirnov normalizing test was used to determine whether the continuous variable data fit the normal distribution. The comparison of the variables with normal distribution was tested with an unpaired t-test, and the comparison of the variables without normal distribution was tested with a Mann–Whitney U test. The categorical variables were compared with Pearson's chi-square test, and the relation among continuous variables was studied with Spearman rank correlation analysis. A p-value < 0.05 was considered statistically significant.

Considering α=0.05 1-β (power)=0.80 in the power analysis, it was calculated in the study titled 'Relationship between mean platelet volume and vitamin D deficiency in fibromyalgia' that at least 99 subjects should be taken from each group so that the

mean variation of Vitamin D in the FMS group in comparison to the control group can be 0.6 units.

## Results

The data from 99 FMS patients (80 female) and 99 healthy controls (77 female) were analyzed. Demographic characteristics as well as clinical and laboratory features of the patients are summarized in Table 1. 25 (OH) D levels in the FMS group were significantly lower compared to the control group.

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

| Variables | FMS (n: 99) Mean ± SD | Control (n: 99) Mean ± SD | p |
|---|---|---|---|
| Age | 49.4 ± 9.2 | 50.8 ± 8.8 | 0.34 |
| 25 (OH) D levels | 15.7 ± 7.2 | 20.6 ± 6.1 | <0.001 |
| MPV | 8.2 ± 0.6 | 7.9 ± 0.5 | 0.008 |
| Tender points | 11 ± 3.6 | | |
| Fatigue | 7.4 ± 1.6 | | |
| VAS | 7.1 ± 1.6 | | |
| FIQ | 62.9 ± 17.7 | | |
| Depression | 18 ± 11.0 | | |
| Gender E/K | 18/80 | 21/77 | 0.567 |

FMS: Fibromyalgia; MPV: Mean Platelet Volume; VAS: Visual Analog Scales; FIQ: FMS Impact Questionnaire

**Table 2.** *MPV parameters according to 25 (OH) D levels in FMS and controls.*

| According 25 (OH) D levels to groups of | MPV in FMS group Mean ± SD | MPV in control group Mean ± SD | p |
|---|---|---|---|
| 25 (OH) D ≤ 10 (n: 33) | 8.7 ± 0.7 | 7.6 ± 0.3 | <0.001 |
| 25 (OH) D 10-20 (n: 33) | 8.0 ± 0.4 | 7.9 ± 0.5 | 0.512 |
| 25 (OH) D>20 (n: 33) | 7.9 ± 0.5 | 7.9 ± 0.5 | 0.65 |

25 (OH) D levels categorized by MPV values are shown in Table 2. MPV values were significantly higher in the 25 (OH) D levels ≤ 10 group compared to the control group. There was no significant difference between the 25 (OH) D levels >20 group and the controls (Table 2).

A negative correlation was found between MPV and 25 (OH) D levels (Table 3). There was no significant correlation between MPV and VAS, fatigue, FIQ, and depression (Table 3). There was no significant correlation between and 25 (OH) D, VAS, fatigue, FIQ, and depression (Table 3).

**Table 3.** *An examination of the relationship between clinical and laboratory variables of the patient group.*

| Parameters | r | p |
|---|---|---|
| MPV-25 (OH) D | -0.17 | 0.017 |
| MPV-VAS | -0.046 | 0.65 |
| MPV-Fatigue | -0.061 | 0.54 |
| MPV-FIQ | 0.02 | 0.84 |
| MPV-Depression | 0.134 | 0.23 |
| VAS-Fatigue | 0.919 | <0.001 |
| VAS-FIQ | 0.471 | <0.001 |
| VAS-Depression | 0.08 | 0.45 |
| 25 (OH) D-VAS | 0.104 | 0.3 |
| 25 (OH) D-Fatigue | 0.125 | 0.22 |
| 25 (OH) D-FIQ | 0.122 | 0.28 |
| 25 (OH) D-Depression | -0.04 | 0.97 |
| Fatigue-FIQ | 0.454 | <0.001 |
| Fatigue-Depression | 0.12 | 0.29 |
| FIQ-Depression | 0.467 | <0.001 |

## Discussion

The present study represents the first attempt to evaluate the relationship between MPV and vitamin D in FMS. Our major finding is the presence of higher MPV values in FMS patients, although this is associated with decreased levels of vitamin D. The data are not fully understood regarding the risk of CVD in cases of FMS. Several lines of evidence could provide a

possible biological explanation to support this increased CVD risk. First, people with chronic widespread pain have been shown to have greater psychological distress. Previous reports indicated that people with chronic diseases such as FMS and CVD have a common history of childhood abuse [36]. The potential role of early psychosocial adversity in terms of vulnerability to FMS and CVD should be considered [37]. Second, FMS has been shown to be significantly associated with degree of stress [38], and chronic stress contributes to persistent activation of the sympathetic nervous system and hypothalamic–pituitary–adrenal axis. Autonomic dysfunction in patients with FMS is characterized by strong parasympathetic decline [39], which maintains patients in a state of sympathetic hyperactivity [40] and may lead to a greater risk of CVD. Third, only one study in the literature has determined an association between MPV and FMS [14], with results suggesting that individuals with FMS are susceptible to increased platelet activation and increased MPV values, which contribute to an increased risk of CVD [14].

Platelets play an important role in the pathophysiology of CVD [41]. MPV is an important platelet production index that may relate to platelet function. It has been shown that the size of platelets, measured as MPV, correlates with their reactivity [42]. Larger and hyper reactive platelets accelerate intracoronary thrombus formation, which leads to a cascade of clinical events including CVD [43]. In our study, MPV levels were significantly higher and vitamin D levels were significantly lower in patients with FMS compared to healthy controls. The association between vitamin D deficiency and adverse cardiovascular outcomes has been investigated in multiple observational studies. In the elderly population, serum 25(OH) vitamin D levels are correlated with cardiovascular mortality [44]. In the ARIC study, investigators also reported an increased risk of incident CVD in whites with lower serum 25(OH) vitamin D levels [45]. A meta-analysis considering previous case-control studies examining the association of circulating 25(OH)D concentration with CVD suggested that CVD patients have significantly lower circulating 25(OH)D concentrations than non-CVD controls [46]. Finally, the observed association could be attributable to confounding risk factors that are shared between CVD and low vitamin D levels. However, the question remains: How is vitamin D deficiency linked to cardiovascular health and disease?

Several hypotheses have been proposed to explain the relation between vitamin D deficiency and CVD [47-50]. Vitamin D deficiency can influence platelet and endothelial function [51]. The balance of body cytokines changes with decreased levels of vitamin D, and the release of cytokines increases TNF-α and IL-6 levels [25]. These cytokines are associated with increased oxidative stress, which contributes to platelet activation [26]. The induction of this event leads to the release of immature and activated platelets from bone marrow to the circulatory system, thus increasing MPV. Previous studies have shown that vitamin D decreases the expression of vascular cell adhesion molecule (VCAM)-1 and membrane type-1 matrix metalloproteinase (MT1-MMP), therefore preventing platelet activation and decreasing fibrinolysis and thrombosis [52].

Patients with vitamin D levels <10 ng/ml have vitamin D deficiency that is associated with a very high cardiac risk, and those with vitamin D levels <20 ng/ml have vitamin D insufficiency associated with only an increased cardiac risk [52]. In this study, patients were divided into three groups according to their vitamin D levels. MPV values were significantly higher in the vitamin D ≤ 10 group compared to the control group. There was no significant difference between the vitamin D>20 group and the controls.

This study has several limitations. First, the number of cases included in this study was relatively low and it was a cross-sectional study. Second vitamin D supplementation in vitamin D-deficient individuals may decrease MPV; however, it was not analyzed in our study. Third MPV is not the only indicator for future cardio vascular risk, and classic risk factors should not be ignored. Fourth the presence of cardiac disease was not analyzed when comparing MPV with vitamin D deficiency. In conclusion, we found that vitamin D deficiency was associated with high MPV in FMS. This may have predictive value in CVD risk estimation. This should be investigated in further prospective studies.

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