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The relationship between ulcerative colitis activity and vitamin D, mean platelet volume and platelet distribution width

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ABSTRACT

Aim: In our study, we aimed to show the relationship between ulcerative colitis activity and vitamin D, platelet distribution width, and mean platelet volume.

Material and Method: Our study was conducted at the Internal Medicine Clinic. We planned to cross-sectionally investigate the severity of ulcerative colitis activity, vitamin D level, mean platelet volume, platelet distribution width and other laboratory parameters of patients admitted to the hospital. The Truelove and Witts' severity index was used to determine ulcerative colitis activity. In accordance with the guidelines, serum 25-OH vitamin D levels of >30 ng/ml were considered as sufficient vitamin D, 20-30 ng/ml as vitamin D insufficiency, <20 ng/ml as vitamin D deficiency, and <10 ng/ml as severe vitamin D deficiency.

Results: The study included 77 ulcerative colitis patients. Of the patients with severe ulcerative colitis activity, 10% had vitamin D deficiency and 90% had severe vitamin D deficiency ($p<0.001$). The patients with mild ulcerative colitis activity had the highest mean platelet volume (9.5±0.44), while the patients with severe ulcerative colitis activity had the lowest mean mean platelet volume (7.1±1.52) ($p<0.001$). Likewise, the patients with mild ulcerative colitis activity had the highest mean platelet distribution width (17.9±1.04), while the patients with severe ulcerative colitis activity had the lowest mean platelet distribution width (14.8±2.04) ($p<0.001$).

Conclusion: This study with a high level of evidence supports that 25-OH vitamin D has an anti-inflammatory effect in inflammatory diseases and that 25-OH vitamin D levels decrease as the disease activity increases. Moreover, the negative correlation between ulcerative colitis activity and mean platelet volume, platelet distribution width is demonstrated.

Keywords: Ulcerative colitis, vitamin D, mean platelet volume, platelet distribution width

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory, edematous and ulcerative disease of the superficial parts of the colon mucosa and submucosa. Although various immune system mechanisms play a role in inflammatory bowel disease (IBD), especially cellular immunity is involved in the pathogenesis of IBD (1,2). In general, the first finding is bloody or non-bloody diarrhea; however, patients may also present with other complaints such as abdominal pain, nausea, and malaise. Despite frequent bowel movements, the fecal volume is low in UC. This is the result of rectal inflammation. Abdominal pain in all quadrants of the abdomen, especially in the lower quadrant, elevated fever, weight loss, the involvement of all segments of the colon, as well as local involvements occur (3). Vitamin D (VitD) precursors are found in our body and when the skin is exposed to certain wavelengths of the sun's ultraviolet rays, VitD is synthesized from these precursors to the body (4). Lack of VitD often leads to many factors such as lack of physical activity, malabsorption, low sunlight exposure, VitD deficiency due to diet, smoking and drinking alcohol (5). Serum VitD is measured using the most stable form of 25-hydroxyvitamin D (25-OH vitamin D). The level of serum 25-OH VitD reflects the level of VitD, sun exposure, dietary intake, supplementation and storage (6). When VitD forms, it is first converted into 25-OH VitD in the liver and then into 1,25-hydroxyvitamin D (1,25-OH vitamin D), an active VitD, in the kidney (7). Vitamin D deficiency causes osteoporosis and

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osteomalacia in adults and rickets in children and also plays a role in many autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (8). One of the most important indicators of platelet reactivity is the mean platelet volume (MPV). The platelet distribution width (PDW) showing the heterogeneity of the platelet volume is a sign of platelet activation. PDW levels have been shown to be associated with an increase in carotid artery stenosis and vascular dementia in patients with diabetes mellitus (DM) (9). Platelet indices such as platelet count, PDW and MPV are associated with cardiovascular diseases developing due to arterial thrombosis (10). There is uncertainty about the most accurate method for measuring MPV; however, the cheapest and simplest method is the hemogram test. Large platelets which are more active metabolically and enzymatically have more prothrombotic potential. Patients with DM, primer hypertension, hypercholesterolemia, and active smokers and obese patients exhibit higher MPV values (11). Vitamin D deficiency in patients with IBD is higher than the general population. The incidence of VitD deficiency in IBD patients varies between 16% and 95% (12). Some studies have shown that there may be a correlation between the level of VitD and the severity of UC activity (13). This study was conducted to determine the correlation between the severity of UC activity and serum VitD level, MPV and PDW.

MATERIAL AND METHOD

This study was approved by the Balıkesir University Medical Faculty Clinical Studies Ethics Board (Date: 26/07/2017, Decision No: 2017/65). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from each individual who participated in the study.

Our study was conducted at the Internal Medicine Clinic of Our University, Faculty of Medicine. We planned to cross-sectionally investigate the severity of UC activity, vitamin D level, MPV, PDW and other laboratory parameters of patients admitted to the hospital. The diagnosis of UC was made using the guideline of the European Crohn's and Colitis Organization. The Truelove and Witts' severity index was used to determine UC activity (14). Serum 25-OH VitD level was measured with the spectrophotometric method using a Beckman Coulter AU 680 (California, USA) device. In accordance with the guidelines, serum 25-OH VitD levels of >30 ng/ml were considered as sufficient VitD, 20-30 ng/ml as VitD insufficiency, <20 ng/ml as VitD deficiency, and <10 ng/ml as severe VitD deficiency (15). Patients with any other comorbidities and on calcium and VitD supplements due to other conditions such as osteoporosis were excluded from the study.

Statistical Analysis

The statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) Version 23.0 software. Normality of variables was tested with histogram charts and the Kolmogorov-Smirnov test. They were compared using Fisher's Exact test in 2x2 tables. One-Way analysis of variance (ANOVA) test was used in the comparison of normally distributed (parametric) PDW data while evaluated between UC activity severities. The Kruskal Wallis Test was used in the comparison of non-normally distributed parameters (non-parametric) while evaluated between MPV, 25-OH VitD, and UC activity severities. P <0.05 values were considered to be statistically significant.

RESULTS

The study included 77 UC patients. Of the patients, 44 (57%) were male and 33 (43%) were female. The mean duration of disease was 2.8±2 years (0.3-10 years). The mean age of the patients was 39±5 years; the mean age of female patients was 37±4 and the mean age of male patients was 41±5. It was found that the rate of VitD deficiency (<20 ng/mL) was as 70.1% and the rate of severe VitD deficiency (<10 ng/ml) was 25.9% (p=0.001).

The VitD groups were compared according to UC activity of the patients with UC. 94.12% of the patients with mild UC activity and 90.91% of the patients with moderate UC activity had VitD deficiency. Of the patients with severe UC activity, 10% had VitD deficiency and 90% had severe VitD deficiency (p<0.001). In post-hoc analysis, it was determined that UC activation was significantly higher in patients with severe VitD deficiency than in patients with moderate VitD deficiency and normal VitD levels (p<0.001). However, no significant difference was found between the other groups. As the severity of UC activity increased, the levels of VitD decreased (**Figure 1**). The MPV, PDW, and VitD values of the patients with UC were compared according to their UC activity severity. As UC activity increased, the values of MPV and PDW decreased (**Figure 2**).

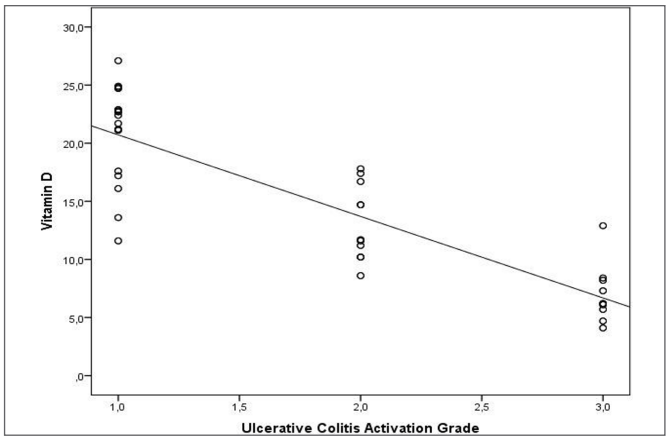

Figure 1. Correlation between severity of ulcerative colitis activity and vitamin D

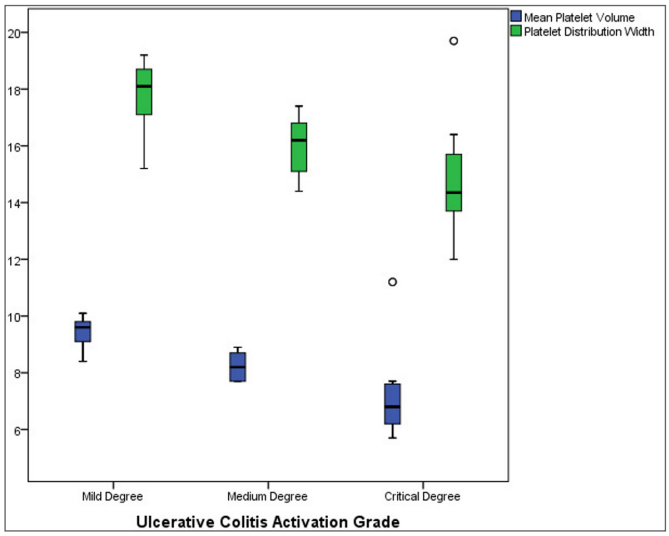

Figure 2. Boxer graph showing the correlation between mean platelet volume and platelet distribution width and ulcerative colitis activity

The patients with mild UC activity had the highest mean MPV (9.5±0.44), while the patients with severe UC activity had the lowest mean MPV (7.1±1,52) (p<0,001) (**Table 1**). Likewise, the patients with mild UC activity had the highest mean PDW (17.9±1.04), while the patients with severe UC activity had the lowest mean PDW (14.8±2.04) (p<0.001). Considering the mean values of 25-OH VitD, the patients with mild UC activity had the highest value (20.9±4.18), while the patients with mild UC activity had the lowest value (7.0±2.42) (p<0.001) (**Table 1**).

The MPV levels of the UC patients were compared according to the severity of UC activity (**Figure 3**). While MPV value was within normal limits in all patients with mild UC activity, this rate decreased to 72.23% in patients with moderate UC activity and to 10% in patients with severe UC activity (p<0.001). The PDW levels of the UC patients were compared according to the severity of UC activity (**Figure 4**). While PDW was high in all patients with mild and moderate UC activity, it was 50% higher in patients with severe UC activity (p<0.001) (**Table 2**). Considering the levels of VitD, 94,12% of the patients with mild UC activity and 90,91% of the patients with moderate UC activity had VitD deficiency, while this rate was 10% in the patients with severe UC activity and 90% of them had severe VitD deficiency (p<0.001) (**Table 2**).

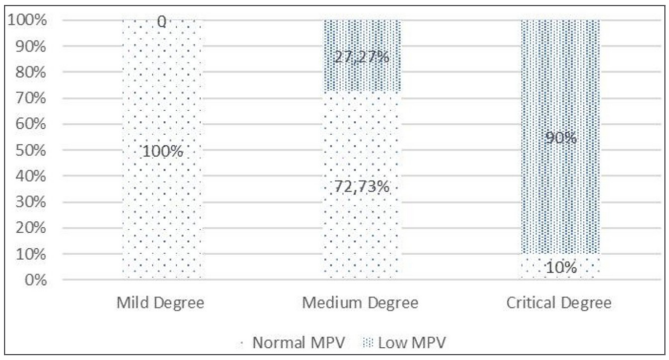

Figure 3. Distribution of mean platelet volume groups according to the severity of ulcerative colitis activity

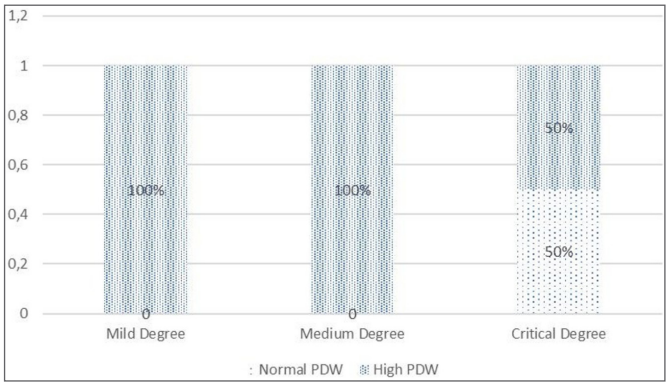

Figure 4. Distribution of platelet distribution width groups according to the severity of ulcerative colitis activity

Table 2. Comparison of severity of ulcerative colitis activity and MPV, PDW and vitamin D groups

	Severity of ulcerative colitis activity						p
	Mild		Moderate		Severe		
	n	%	n	%	n	%	
MPV							<0.001
Normal	34	(100)	16	(72.73)	2	(10)	
Low	0	(0)	6	(27.27)	18	(90)	
PDW							<0.001
Normal	0	(0)	0	(0)	10	(50)	
High	34	(100)	22	(100)	10	(50)	
Vitamin D							<0.001
Severe deficiency	0	(0)	2	(9.09)	18	(90)	
Moderate deficiency	32	(94.12)	20	(90.91)	2	(10)	
Normal	2	(5.88)	0	(0)	0	(0)	

MPV= mean platelet volume; PDW= platelet distribution width

Table 1. Comparison of MPV, PDW, vitamin D values with severity of ulcerative colitis activity

	Severity of ulcerative colitis activity						p
	Mild		Moderate		Severe		
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
MPV	9.5±0.44	9.6	8.3±0.47	8.2	7.1±1.52	6.8	<0.001
PDW	17.9±1.04	18.1	16.0±0.96	16.2	14.8±2.04	14.4	<0.001
25 OH-D	20.9±4.18	22.4	13.2±3.14	11.7	7.0±2.42	6.2	<0.001

MPV= mean platelet volume; PDW= platelet distribution width; SD= standard deviation; OH-D= hydroxy D vitamin

DISCUSSION

This study demonstrated the negative correlation between the severity of disease activity and VitD, PDW, and MPV levels of the patients with UC. One of the important parameters of platelet function and activation parameters is PDW. The importance of PDW has been discovered recently. In retrospective studies on PDW, it was found that PDW could be used as a predictor for thrombolysis failure and ST-segment elevation myocardial infarction (16). High MPV levels have been associated with diseases such as myocardial infarction, acute ischemic stroke, and DM (17). In a study conducted in Poland, it was shown to be a practical predictive parameter for left ventricular failure developing in patients with the acute coronary syndrome (18). It is also supported by the study that it is also a predictive parameter in terms of preeclampsia and acute appendicitis for those with similar results (19,20). In clinical hematology, MPV can be used as a marker of platelet function and activation. It can also be used as a marker of inflammation (21). There is a negative correlation between MPV and rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis (22). In two studies with a limited number of patients on the correlation between decreased MPV value and severity of UC activity, Kapsoritakis et al. (23) proposed to use MPV as an effective marker of activity in IBD, but did not analyze the sensitivity and specificity. In a study conducted by Jaremo et al. (24), a negative correlation was found with MPV in 18 UC patients.

It was thought that VitD could be a part of the immune-regulatory system due to the determination of VitD receptor in the immune response-related cells and demonstration of VitD synthesis from the activated dendritic cells. Exposure of CD4 T lymphocytes to 1.25 (OH)2 VitD3 (1.25-Dihydroxyvitamin D3) inhibits Th1 lymphocyte proliferation and cytokine production by decreasing IL-2 and IFN-D secretion of CD4 lymphocytes. IL-6 expression, which is an important component of the autoimmune reaction, is inhibited by 1.25 (OH)2 VitD3 (25). The cause of low MPV in IBD is unclear. Some authors have suggested that decreased MPV may result from the depletion or sequestration of activated platelets in the intestinal vessels (26). Another reason for the decreased MPV may be the existence of a defect in the regulation of thrombopoiesis in IBD (27). In individuals with autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and IBD, T lymphocytes steer the immune system to induce the inflammatory response in the internal organs and peripheral tissues of individuals. When women were divided into 5 groups according to their VitD intake in the "Nurses Health Study I and II", a large society study, it was found that multiple sclerosis developed 40% less among women in the highest group (28). Experimentally, it has been shown that VitD deficiency exacerbates IBD and multiple sclerosis, and VitD suppresses multiple sclerosis and IBD in rats. Interestingly, the administration of VitD even if VitD is sufficient has been shown to inhibit autoimmunity in animals. In the US, the incidence of systemic lupus erythematosus (SLE) has increased threefold in African Americans and is seen in earlier ages, and the morbidity and mortality rates are higher than that of whites. On the other hand, the fact that the prevalence of the disease is not high among blacks who live in western Africa cannot explain that the prevalence of high SLE is only due to genetic reasons in black people in the USA (29). This difference may be related to low VitD concentrations resulted from reduced exposure to sunlight compared to black race living in western countries due to the penetration of ultraviolet rays through the skin with excess pigment. This hypothesis is also supported by other studies with the discovery of significantly lower levels of 25 OH VitD3 in patients newly diagnosed with SLE compared to controls. There is a correlation between low VitD levels and the severity of the disease, and therefore the treatment of VitD deficiency in SLE patients gains importance (29).

It was found that rheumatoid arthritis severity and VitD serum concentration were related. In the study by Caraba et al. (30), VitD level, insulin resistance, IL-2 and endothelial dysfunction were analyzed in patients with cardiovascular complications due to rheumatoid arthritis, and healthy group was assigned as the control group; as a result of the analyses, it was found that the patient group had a decrease in VitD level and an increase in IL-2 level, impaired endothelial dysfunction, and increased insulin resistance despite the normal values in the healthy group (30). It was stated that VitD levels were negatively correlated with the presence of inflammation. The study by Carvallo et al. (31) included 32 dialysis patients with VitD levels of ≤20 ng/mL. These patients received a replacement with cholecalciferol 100.000 UI/week/3 months and 16 volunteers were included in the control group. This study showed that cholecalciferol replacement has an anti-inflammatory effect (31).

In our study, we attempted to use a similar correlation on UC patients. According to the Truelove-Witts's classification, there was an inverse correlation between the severity of UC and serum levels of 25-OH VitD, and it was found that patients with mild and moderate UC had lower levels of VitD compared to the society while patients with severe UC exhibited significantly lower levels of 25-OH VitD.

The study by Hassan et al. (32) found no significant correlation between UC activity and concentration of 25-OH VitD. However, 25-OH VitD levels were studied

in patients undergone colon resection due to UC and no correlation was found. We are of the opinion that this result is caused by the analysis methods and errors related to the patient selection method because the studies have found that 25-OH VitD is affected by many factors such as the location of the patients, the region where the patient live, climate, ethnicity, and the drugs used. The study by Limketkai et al. (33) found an increase in hospitalization and number of operations due to IBD in people with low exposure to ultraviolet light, and lower levels of 25-OH VitD in these patients (33). Thus, it was stated that there was a significant correlation between 25-OH VitD levels and inflammatory diseases. The study by Dolatshahi et al. (34) found an inverse correlation between UC activity and 25-OH VitD levels. As the severity of UC increased, 25-OH VitD levels decreased. The negative correlation between UC and VitD revealed in this study supports our study.

The limitations of our study are single-center design, the inclusion of only patients with UC, not studying inflammatory parameters such as cytokines and acute phase reactants, studying only 25-OH VitD level and not studying an active form of VitD. The superiority of our study is that our sample size was larger than other studies.

CONCLUSION

This study with a high level of evidence supports that 25-OH VitD has an anti-inflammatory effect in inflammatory diseases and that 25-OH VitD levels decrease as the disease activity increases. Moreover, the negative correlation between UC activity and MPV, PDW is demonstrated. There are few studies in this respect and our study supports this theory. If the correlation between the disease severity and the levels of 25-OH VitD, MPV and PDW are supported by further studies and the other processes that may affect these parameters can be revealed more clearly, the parameters of 25-OH VitD, MPV and PDW might be predictive of the severity of disease activity. Moreover, 25-OH VitD replacement can be given according to the severity of disease activity, and 25-OH VitD can be considered in the treatment of patients with UC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Medical Faculty Clinical Studies Ethics Board (Date: 26/07/2017, Decision No: 2017/65).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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