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## Research Article

# THE CORRELATION BETWEEN ULCERATIVE COLITIS ACTIVITY AND MAGNESIUM, MEAN PLATELET VOLUME AND PLATELET DISTRIBUTION WIDTH

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### ABSTRACT

Ulcerative colitis (UC) is a chronic and recurrent inflammatory process that requires continuous treatment, so can affect the biochemical and hematological parameters. In this study, we aimed to investigate the correlation between UC activity and magnesium (Mg), mean platelet volume (MPV) and platelet distribution width (PDW). This study was conducted in a Gastroenterology Clinic. The patients' records between 2010 and 2017 were reviewed. The diagnosis of UC was made according to the guidelines for European Crohn's and Colitis Organization. The severity of Truelove and Witts was used to determine the severity of UC activity. MPV, PDW, and Mg values were compared according to the severity of UC activity of the patients with UC. The study included 77 inflammatory bowel disease male patients. Patients with mild UC activity had a higher MPV ( $9.5 \pm 0.44$ ), while the patients with severe UC activity had a lower MPV ( $7.1 \pm 1.52$ ) ( $p < 0.001$ ). Likewise, the patients with mild UC activity had the highest mean PDW ( $17.9 \pm 1.04$ ), while the patients with severe UC activity had the lowest mean PDW ( $14.8 \pm 2.04$ ) ( $p < 0.001$ ). As the severity of UC activity increased, the mean Mg value decreased. The Mg levels of the patients with mild UC activity ( $1.9 \pm 0.14$ ) were higher compared to that of other groups, while the Mg levels of the patients with severe UC activity ( $1.6 \pm 0.09$ ) were lower ( $p < 0.001$ ). Mg has an anti-inflammatory effect in inflammatory diseases and that Mg levels decrease as the disease activity increases, moreover the negative correlation between UC activity and MPV, PDW is demonstrated.

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### INTRODUCTION

Ulcerative colitis (UC) is a chronic and recurrent inflammatory process that requires continuous treatment, inflammatory bowel disease (IBD) and gastrointestinal tract disease. IBD, which is common in developed countries such as Europe and North America, affects 0.5% of the general population.<sup>[1]</sup> 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 IBD, especially cellular immunity is involved in the pathogenesis of IBD.<sup>[2]</sup> Magnesium (Mg) is the fourth most commonly found cation in human.<sup>[3]</sup> Since Mg plays a part in the regulation of ion channels, it has a role in basic physiological functions. It acts as a cofactor in enzymatic reactions for protein synthesis and is naturally linked to mineral and bone metabolism.<sup>[4]</sup> It plays an active role in the biochemical and cellular pathways regulating the cardiovascular system. It has important roles in vascular muscle tone, endothelial cell function stimulability of

the myocardium. Therefore, it plays a role in the pathogenesis of cardiovascular diseases such as coronary artery disease, congestive heart failure and cardiac arrhythmias.<sup>[5]</sup>

One of the most important indicators of platelet reactivity is the mean platelet volume (MPV). The platelet distribution width (PDW) is a marker of platelet activation, indicating the heterogeneity of platelet volume. PDW levels have been shown to be associated with an increase in carotid artery stenosis and vascular dementia in patients with diabetes mellitus (DM).<sup>[6]</sup> Platelet indices such as platelet count, PDW and MPV are associated with cardiovascular diseases developing due to arterial thrombosis.<sup>[7]</sup> 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.<sup>[8]</sup>

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**METHODS**

Our study was conducted in a Gastroenterology Clinic. The patients' records between 2010 and 2017 were retrospectively reviewed. The diagnosis of UC was made using the demographic, laboratory, endoscopic, radiological, and pathological and other clinical data of the patients in line with the guideline of the European Crohn's and Colitis Organization. Patients without data of serum Mg level, patients who have comorbid diseases (kidney failure, liver disease, malabsorption) that affects serum Mg level, those who are on medications that may affect Mg level (Mg supplements, vitamin D) were excluded from the study. Serum Mg level was measured with Beckman Coulter AU 680 (California, USA) device using the spectrophotometric method. The Truelove and Witts' severity index was used to determine UC activity level (Table 1).<sup>[9]</sup> The statistical analyses were carried out using the Statistical Package for the Sociale Sciences (SPSS) Version 17.0 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 UC activity severities. Spearman's correlation test was used in the analysis of measurable data. P value < 0.05 was considered statistically significant. Ethics Committee approved the present study in accordance with the Declaration of Helsinki. Written informed consent was obtained from each individual who participated in the study.

**Table 1** Truelove and Witts' Score for Clinical Severity of Ulcerative Colitis

Activity	Mild	Moderate	Severe
Bloody stools per day (N)	<4	4-6	>6
Pulse (beats/minute)	normal	intermediate	>90
Temperature (°C)	normal	intermediate	>37.8
Hemoglobin (g/dL)	normal	intermediate	<10.5
Erythrocyte sedimentation rate (mm/h)	<20	20-30	>30

**RESULTS**

The study included 77 IBD male patients. The mean duration of disease was 2.8 ± 2 years (0.3-10 years). The mean age of the patients was 39 (± 5) years. MPV, PDW, and Mg values were compared according to the severity of UC activity of the patients with UC. UC activity increased, the mean values of MPV and PDW decreased (Figure 1). The patients with mild UC activity had a higher MPV (9.5 ± 0.44), while the patients with severe UC activity had a lower MPV (7.1 ± 1.52) (p<0.001) (Table 2). 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) (Table 2). As the severity of UC activity increased, the mean Mg value decreased (Figure 2). The Mg levels of the patients with mild UC activity (1.9 ± 0.14) were higher compared to that of other groups, while the Mg levels of the patients with severe UC activity (1.6 ± 0.09) were lower (p<0.001) (Table 2). When the correlation between the severity of UC activity and Mg was analyzed, it was found

that there was a significant correlation between Mg and the severity of disease activity (Figure 3). There was a very strong negative correlation between the severity of UC activity and Mg (r: -0,825). Accordingly, it was observed that the Mg value decreased as the severity of UC activity increased (p <0.001) (Table 2). The MPV, PDW and Mg groups were compared according to the severity of UC activity of the patients with UC. There was a significant correlation between the MPV groups according to the severity of UC activity (Figure 4). All patients with mild UC activity had a normal MPV, while this rate decreased to 72.23% in patients with moderate UC activity and decreased to 10% in patients with severe UC activity (p <0.001). There was a significant correlation between the PDW groups according to the severity of UC activity (Figure 5). All patients with mild and moderate UC activity had a high PDW, while it was 50% higher in patients with severe UC activity (p<0.001). All patients had normal Mg levels (Table 3).

**Table 2** Comparison of MPV, PDW, Mg values with Severity of Ulcerative Colitis Activity

	The 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
Mg	1.9 ± 0.14	1.8	1.7 ± 0.16	1.7	1.6 ± 0.09	1.6	<0.001

MPV= mean platelet volume; PDW= platelet distribution width; SD = standard deviation; Mg= Magnesium

**Table 1** Comparison of Severity of Ulcerative Colitis Activity and MPV, PDW and Mg groups

		The severity of Ulcerative Colitis Activity						p
		Mild		Moderate		Severe		
		n	%	n	%	n	%	
MPV	Normal	34	(100)	16	(72.73)	2	(10)	<0.001
	Low	0	(0)	6	(27.27)	18	(90)	
PDW	Normal	0	(0)	0	(0)	10	(50)	<0.001
	High	34	(100)	22	(100)	10	(50)	
Mg	Normal	34	(100)	22	(100)	20	(100)	<0.001

MPV= mean platelet volume; PDW= platelet distribution width; Mg= Magnesium

**DISCUSSION**

This study showed the negative correlation between the severity of disease activity and Mg, PDW, and MPV levels of the patients with UC. One of the important parameters of platelet function and activation parameters is PDW. Despite the increased significance, it has recently been associated with the progression of other diseases. 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.<sup>[10]</sup> Numerous studies in the literature have accepted MPV level and the neutrophil-to-lymphocyte ratio as markers of inflammation.<sup>[11]</sup> MPV is a parameter of routine blood count which is usually ignored by many clinicians.<sup>[12]</sup> One of the important parameters of platelet function and activation parameters is MPV.<sup>[13]</sup> In clinical hematology, MPV can be used as a marker of platelet function and activation. Several studies have investigated the correlation of MPV value with inflammation. Smyth *et al.* reported that a low MPV value was associated with inflammation, but that its level increased with anti-inflammatory therapy.<sup>[14]</sup> Recent studies have shown that platelets play a role in inflammation, angiogenesis, thrombosis, and immunity.<sup>[15]</sup> High MPV levels have been associated with

diseases such as myocardial infarction, acute ischemic stroke, and DM.<sup>[16]</sup> 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.<sup>[17]</sup> High MPV levels have been detected in immune thrombocytopenic purpura, congenital giant thrombocytopathy and myelodysplastic syndrome (MDS). MPV levels were low in MDS cases with degranulated platelets. MPV may be a promising predictive parameter in these patients.<sup>[18]</sup> In active disease phases of patients with rheumatoid arthritis and ankylosing spondylitis, MPV value has been shown to be low, and increase with anti-inflammatory treatment. In two studies with a limited number of patients on the correlation between decreased MPV value and severity of UC activity, Kapsoritakis *et al.* proposed to use MPV as an effective marker of activity in IBD, but did not analyze the sensitivity and specificity.<sup>[19]</sup> In a study conducted by Jaremo *et al.*, a negative correlation was found with MPV in 18 UC patients.<sup>[20]</sup> Mg is a basic cofactor for multi-enzyme pathways involved in energy metabolism.<sup>[21]</sup> About 99% of magnesium, an important electrolyte in our body, is found in bone, muscle and soft tissue.<sup>[22]</sup> It is found only about 0.3-1% in serum and the mean Mg concentration is about 0.85 mmol/L. 70%-80% of this exist in free ionized form and the rest is bound to proteins, phosphate, citrate and other compounds.<sup>[23]</sup> Mg loss may be caused by numerous mechanisms. Distribution between extracellular and intracellular space, decrease in Mg intake with diet, decrease in intestinal absorption, increase in gastrointestinal loss and increase in Mg loss through the kidney. As Mg deficiency is usually secondary to pathological conditions or drugs, a primary disease may mask the discovery of Mg deficiency.<sup>[24]</sup> Regulation of glucose uptake has been associated with inflammation and endothelial dysfunction.<sup>[25]</sup> Mg deficiency has been found to be a risk factor in women with type 2 diabetes mellitus (T2DM). Low levels of Mg are known to be linked to the pathogenesis of T2DM, particularly through insulin. By establishing the cause-effect relationship of low Mg levels, it was found that insulin secretion caused resistance.<sup>[26]</sup> The retrospective cohort study by Goyal *et al.* investigated the correlation between admission and post-admission Mg levels. There was a correlation between Mg levels and the spread of bleeding in patients with intracerebral hemorrhage. Due to low levels of Mg, increased severity of hepatic encephalopathy and poorer functional outcomes were found, which was associated with large hematoma volume caused by Mg deficiency.<sup>[27]</sup> The symptoms associated with Mg deficiency are cramps, bone pain, delirium, fatigue, depression, cardiac anomalies, urolithiasis, impaired healing, and colonic motility disorders. Urolithiasis is a CD complication associated with circulating Mg concentrations. It is recommended to use Mg potassium and citrate to prevent stone formation.<sup>[28]</sup> Mg deficiency is common in IBD. It has been reported in 13%-88% of cases. Recently, newly diagnosed CD and UC patients had lower serum Mg levels than the healthy population.<sup>[29]</sup> Decreasing physical performance is a common condition in CD; these individuals had more muscle fatigue in a study with the control group, and patients with decreased physical performance were found to have lower Mg levels. In general, Mg can be supplemented intravenously in acute complicated cases and with oral medications or Mg-rich diets in cases of chronic deficiency. In patients with IBD, the need for parenteral Mg is

at least 120 mg/day or more, depending on fecal or stomach loss. Oral replacement therapy may be given up to a maximum of 700 mg/day depending on the severity of the absorption disorder.<sup>[30]</sup>

The limitations of our study are that it is a single-center study, included only UC patients from IBD patients, and inflammatory parameters such as cytokines and acute phase reactants were not studied. The superiority of our study to the other studies is that it is the first study in terms of evaluation of the correlation between UC activity and Mg and that our patient sample was larger than other studies.

## CONCLUSION

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

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