ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Assessment of Mean Platelet Volume in Children with Celiac Disease on a Gluten-Free Diet

Glutensiz Diyet Uygulanan Çölyak Hastalığı Olan Çocuklarda Ortalama Trombosit Hacminin Değerlendirilmesi

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Abstract

Introduction: Celiac disease (CD) is a systemic disorder due to gluten in genetically susceptible individuals and characterized by an immune-mediated response. Gluten, triggers a chronic inflammatory response that leads to progressive atrophy of the small intestine in individuals with CD. Mean platelet volume (MPV) is a marker of platelet activation and function, and is considered a marker of inflammation. The objective of our study was to investigate whether MPV values change after introducing a gluten-free diet (GFD) in children with CD.

Materials and Methods: The pediatric patients with CD admitted to our pediatric gastroenterology clinic at Konya Training and Research Hospital between November 2013 and May 2016 were enrolled retrospectively. In all of the cases, demographic characteristics complete blood count parameters, including hemoglobin, white blood cell, platelet count, MPV, mean corpuscular volume, neutrophil, lymphocyte, and vitamin B12 values were recorded. The values were evaluated at the time of diagnosis and after six months of a GFD for the children with CD and healthy control subjects.

Results: Thirty-three pediatric patients with CD and 44 healthy children with no history of CD in their families or relatives were enrollled. Although the MPV values of patients with CD were slightly higher after a GFD, in the comparison of the values at diagnosis and after a GFD, the difference was not statistically significant (p=0.068). No statistically significant difference was detected between the MPV values of patients with CD at diagnosis and the healthy children (p=0.851). A statistically significant increase was detected in the comparison of hemoglobin, vitamin B12, and MCV values at diagnosis and after a GFD in patients with CD (p<0.001, p=0.002, and p=0.027, respectively). A comparison of the platelet counts at the time of diagnosis and after a GFD revealed a statistically significant decrease (p=0.011).

Conclusion: MPV may not be a useful biomarker for monitoring GFD in children with CD.

Keywords
Children, mean platelet volume, gluten-free diet, celiac disease

Anahtar kelimeler
Çocuk, ortalama trombosit hacmi, glutensiz diyet, çölyak hastalığı

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Öz

Giriş: Çölyak hastalığı (ÇH) genetik olarak duyarlı bireylerde glutene bağlı ortaya çıkan immün aracılı sistemik bir hastalıktır. Gluten, ÇH olan bireylerde ince bağırsakta progresif atrofiye yol açan kronik bir enflamatuvar yanıtı tetikler. Ortalama trombosit hacmi (OTH), trombosit aktivasyonu ve fonksiyonunun bir göstergesidir, ve bir enflamasyon belirteci olarak kabul edilmektedir. ÇH tanısı konulmuş çocuklarda glutensiz diyet uygulandıktan sonra MPV değerlerinin değişip değişmediğini araştırmayı amaçladık.

Gereç ve Yöntem: Kasım 2013 ile Mayıs 2016 tarihleri arasında Konya Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Kliniği'ne başvuran ÇH tanısı alan çocuk hastalar retrospektif olarak incelendi. Tüm vakaların demografik özellikleri, hemoglobin, beyaz küre, trombosit sayısı, MPV, ortalama korpusküler hacim, nötrofil, lenfosit ve vitamin B12 değerleri kaydedildi. Sağlıklı kontrollerin ve hastaların tanı anındaki ve glutensiz diyetten 6 ay sonraki değerleri değerlendirildi.

Bulgular: ÇH tanısı konulmuş 33 çocuk hasta ve ailelerinde veya akrabalarında ÇH öyküsü olmayan 44 sağlıklı çocuk çalışmamıza dahil edilmiştir. ÇH tanısı konulan hastaların OTH değerleri glutensiz diyet sonrasında biraz daha yüksek olsa da, tanı anındaki ve glutensiz diyet sonrasındaki OTH arasında istatistiksel olarak anlamlı fark yoktu (p=0,068). Yeni tanı almış hastalar ile sağlıklı kontrol grubu kıyaslandığında MPV değerleri arasında istatistiksel olarak anlamlı bir fark saptanmadı (p=0,851). ÇH tanısı alan hastaların hemoglobin, B12 vitamini ve MCV değerleri tanı anında ve glutensiz diyet sonrasında karşılaştırıldığında istatistiksel olarak anlamlı bir artış tespit edilmiştir (sırasıyla p<0.001, p=0.002 ve p=0.027). Tanı anındaki ve glutensiz diyet sonrasındaki trombosit sayıları karşılaştırıldığında istatistiksel olarak anlamlı bir düşüş saptanmıştır (p=0.011).

Sonuç: OTH, ÇH olan hastalarda glutensiz diyet yanıtını izlemek için yararlı bir biyobelirteç olmayabilir.

Introduction

Celiac disease (CD) is a systemic disorder triggered by gluten in genetically susceptible individuals and characterized by an immune-mediated response (1). Gluten, a protein complex found in barley, wheat, and rye, triggers a chronic inflammatory response that leads to progressive atrophy of the small intestine in individuals who suffer from CD (1,2). CD diagnosis is made based on the presence of clinical manifestations, human leukocyte antigen DQ2 or DQ8 haplotypes, and CD-specific antibodies as well as histological analysis of duodenal biopsies (3). CD-specific antibodies comprise endomysial antibodies, including autoantibodies against tissue transglutaminase type 2, and antibodies against deamidated forms of gliadin peptides (3). The modified Marsh classification is used for the histopathological diagnosis of CD (3). A lifelong gluten-free diet (GFD) is the fundamental aspect of CD treatment and requires follow-up (4). Early diagnosis and regular follow-up are crucial to protect against complications that can manifest in untreated patients with CD (1,5). Regarding follow-up, there are some limitations. The histological findings on a diet that includes gluten remain the gold standard for patients with CD, but it is an invasive method and is difficult to implement in children for routine follow-up (6). At present, celiac-specific serological tests constitute the first-line investigations for CD screening; however, there are certain limitations associated with their use in routine clinical practice (6). The antiendomysial antibody test is only conducted in laboratories with the requisite expertise, and the results are dependent on subjective interpretation of the test results (6). In the literature, the specificity of anti-tissue transglutaminase type 2 antibody varies considerably (even from kit to kit) from 89.5% to 98.8% (7).

Mean platelet volume (MPV) is a parameter assessed as part of a complete blood count, and generally, it is not noticed by physicians. Furthermore, MPV in a complete blood count represents a cost-effective marker. For diseases characterized by systemic or local inflammation, platelets play a significant role in their pathogenesis (8). MPV is a marker of platelet activation and function, and it has been demonstrated that larger platelets are more active (8). Furthermore, MPV is considered a marker of inflammation (8). In recent years, MPV has been established as an inflammatory marker with a demonstrated role in various systemic and gastrointestinal disorders, including amoebiasis (9), ulcerative colitis (10), allergic proctocolitis (11), acute appendicitis (12), irritable bowel syndrome (13), Crohn's disease (14), rotavirus gastroenteritis (8), and familial Mediterranean fever (15).

The objective of our study was to investigate whether MPV values change after introducing a GFD, as this may prove to be a useful biomarker in the diagnosis or follow-up of patients with CD. Therefore, we evaluated MPV values in patients with CD during diagnosis and after treatment with a GFD.

Materials and Methods

In this study, pediatric patients with CD admitted to our pediatric gastroenterology clinic at Konya Training

and Research Hospital between November 2013 and May 2016 were enrolled retrospectively. The inclusion criteria were children with CD aged 17 years and below who came for regular follow-up visits. The control group comprised healthy children with no history of CD in their families or relatives. The diagnosis of CD was made according to the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (3). Patients with CD who did not come for follow-up after treatment and whose data were missing were excluded from the study group. The following datas were collected by using a computerized patient database: demographic characteristics (age and sex) and laboratory parameters, including white blood cell, hemoglobin, platelet count, MPV, mean corpuscular volume (MCV), neutrophil, lymphocyte, and vitamin B12 values. The values were recorded at the time of diagnosis and after six months of a GFD for the children with CD and healthy control subjects. The analysing of complete blood count parameters were conducted using the same coulter analyzer (Sysmex XE-2100, Sysmex Corporation, Kobe, Japan), on which general maintenance was performed and it was checked at regular intervals in the hospital's laboratory. Blood samples were taken in constant quantities in ethylenediaminetetraacetic acid–containing tubes. The samples were analyzed within two hours. Vitamin B12 titers were determined using the ADVIA Centaur XP (Siemens Diagnostics, Tarrytown, NY, USA) immunoassay autoanalyzer. The study was conducted in accordance with the principles outlined in the Helsinki Declaration and reviewed by the Selçuk University Ethical Review Board, and ethical approval was obtained from the Institutional Review Board (date: 09.06.2016, approval number: 2016/181).

Statistical Analysis

We analyzed the obtained data by using the IBM SPSS Statistics for Windows (version 22.0) program. The data are reported as mean ± standard deviation. The distribution of the parameters was controlled with the Kolmogorov-Smirnov test. We used the Mann-Whitney U test or Student's t-test to compare the groups. Regarding the study group, the Wilcoxon test or paired t-test was used to compare the parameters at the time of diagnosis and after introducing a GFD. The associations between parameters were assessed using Pearson's or Spearman's correlation test. The results were accepted to be significant when $p<0.05$.

Results

In this study, 33 patients with CD, comprising 21 girls (63.6%) and 12 boys (36.4%), were enrolled. There were 44 healthy children, consisting of 30 girls (68.1%) and 14 boys (31.9%), in the control group. The mean age of the children with CD was 9.7±0.7 years, while for the healthy children group, it was 9.5±0.8 years. There was no statistically significant difference in age between the healthy subjects and the children with CD (p=0.834).

Although the MPV values of children with CD were slightly higher after a GFD, in the comparison of the values at diagnosis and after a GFD, the difference was not statistically significant (p=0.068). No statistically significant difference was demonsrated between the MPV values of patients with CD at diagnosis and the healthy children (p=0.851) and similarly, there was no statistically significant difference between the children with CD after a GFD and the healty control group (p=0.171). On the other hand, a statistically significant increase was detected in the comparison of hemoglobin, vitamin B12, and MCV values at diagnosis and after a GFD in patients with CD ($p<0.001$, p=0.002, and p=0.027, respectively). A comparison of the platelet counts at the time of diagnosis and after a GFD revealed a statistically significant decrease (p=0.011). The laboratory and demographic features of children with CD at diagnosis and after a GFD are shown in Table 1. The laboratory and demographic features of the controls and the comparison with the CD group are shown in Table 2.

Discussion

CD has a multifactorial etiology, including environmental and genetic factors and an abnormal immune response (16). In the pathogenesis of CD, an abnormal immune response plays a crucial role, as such a response to deamidated gluten peptides stimulates inflammation and epithelial damage (16). In recent studies, researchers have demonstrated that platelets may be significant in the development of the adaptive immune response and have linked platelet activation to the pathophysiology of diseases characterized by inflammation (17,18). MPV

Table 1. The demographic and laboratory characteristics of patients at the time of diagnosis of CD and after gluten-free diet

Characteristics	Patients at the time of diagnosis of CD	Patients with CD after gluten-free diet	p-value
Number of patients	33		
Age, years (mean)	9.7±0.7		
Male: female ratio	12/21		
WBC (/mm^3)	8302.1±478.5	7652.7±452.3	0.088
Hb (gr/dL)	12.0±0.3	13.3±0.2	**<0.001**
MCV (fL)	76.7±1.5	79.5±0.9	**0.027**
Platelet count (/mm^3)	361818.2±16204.1	316909.1±11821.9	**0.011**
MPV (fL)	9.9±0.2	10.2±0.2	0.068
Neutrophile (/mm^3)	4328.7±334.3	3927.2±341.1	0.231
Lymphocyte (/mm^3)	3033.6±185.5	2946.6±185.9	0.308
Vit B12 (pg/mL)	394.8±33.0	479.1±25.5	**0.002**

CD: Celiac disease, WBC: White blood cell, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, Vit B12: Vitamin B12. Parametric values are expressed as means with standard deviation. Significance is determined by p<0.05 and shown with bold character

Table 2. The demographic and laboratory characteristics of controls and comparison with the CD group

		p-value	p-value
Characteristics	**Healthy controls**	**Control vs. patients with at the time of diagnosis of CD**	**Control vs. patients with after gluten-free diet**
Number of patients	44		
Age, years	9.5±0.8		
Male: female ratio	14/30		
WBC (/mm^3)	7927.2±455.2	0.649	0.555
Hb (gr/dL)	12.7±0.2	**0.035**	**0.037**
MCV (fL)	80.2±0.7	**0.042**	0.562
Platelet count (/mm^3)	321727.3±13734.4	**0.037**	0.878
MPV (fL)	9.9±0.2	0.851	0.171
Neutrophile (/mm^3)	4353.0±412.1	0.748	0.317
Lymphocyte (/mm^3)	2915.5±207.4	0.530	0.842
Vit B12 (pg/mL)	388.7±22.2	0.724	**0.010**

CD: Celiac disease, WBC: White blood cell, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, Vit B12: Vitamin B12. Parametric values are expressed as means with standard deviation. Significance is determined by p<0.05 and shown with bold characters

indicates platelet activation and is used as a measure of platelet size (19,20). Research has demonstrated MPV's importance as a marker for disease activity, inflammation, and the efficacy of anti-inflammatory treatment in various chronic inflammatory disorders (18). MPV reflects proinflammatory conditions involving various inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha (18). Overproduction of proinflammatory cytokines can suppress thrombocytes size by affecting megakaryopoiesis, resulting in the release of smaller thrombocytes by the bone marrow (18). On the other hand, in diseases associated with inflammation, it is thought that early platelet activation following inflammation leads to an increase in the release of young thrombocytes from the bone marrow into the bloodstream, thereby causing elevated MPV levels (12). It has been suggested that cytokine levels may

play a part in CD (21,22). In Manavalan et al. (21) study, individuals with active CD had higher levels of IL-1β, TNF-alpha, and IL-6 than healthy controls. Additionally, Kapoor et al. (22) demonstrated that IL-6 levels were significantly higher in newly diagnosed cases of CD than in healthy subjects and in patients with CD on a GFD. In children with CD, systemic levels of the cytokines IL-1β, IL-6, IL-8, IL-10, IL12p70, IL13, and TNF-alpha were increased compared to controls, but none of the systemic cytokines measured differed between the children with CD on a GFD and the controls (23). According to our hypothesis, we thought that MPV values might change due to reduced inflammation with GFD in CD and also MPV might be a beneficial biomarker in treatment follow-up.

Numerous studies have explored MPV as a marker in gastrointestinal disorders. In a study of 76 children with amoebiasis, MPV levels were significantly higher than in controls, and Çelik et al. (9) noted that MPV could be useful as an acute phase reactants. In 151 pediatric patients presenting with rotavirus gastroenteritis, Tanju et al. (8) found MPV values to be lower than in the control group, highlighting that MPV may be useful as a negative acute phase reactant. Furthermore, Chen et al. (10) found ulcerative colitis disease activity was negatively correlated with MPV, and they suggested that MPV is a potential biomarker for ulcerative colitis disease activity. However, Liu et al. (14) emphasized that MPV, a controversial marker in Crohn's disease, has no distinctive value in disease activity.

To date, several studies involving adults have investigated the role of MPV as an inflammatory marker in patients with CD (24,25). Purnak et al. (24) emphasized that MPV may be a usable marker for monitoring dietary compliance in adult patients with CD, they found significantly higher MPV levels in the CD group compared to healthy adults and, after the introduction of a GFD, a significant decrease in MPV from baseline levels in the CD group. Eighty-one patients with CD were enrolled in another study, and significantly higher MPV levels were observed in patients with CD compared to healthy controls (25). Following the introduction of a GFD, MPV levels were significantly lower in patients demonstrating dietary adherence compared to those who were nonadherent (25). A study involving 66 pediatric patients with CD evaluated the effects of a GFD and found a significant decrease in MPV after GFD introduction (26). In our study, after introducing a GFD, we observed a modest increase in MPV values from 9.9±0.2 to 10.2±0.2 fL in patients with CD. Furthermore, MPV values were within normal limits both before and after GFD. Contrary to our hypothesis that MPV levels might change as a result of a reduction in inflammation with a GFD in CD, the results of this study did not consistent with the hypothesis; we found no statistically significant difference in MPV values between patients at diagnosis and after GFD introduction. In addition, no relationship was found between the MPV values of the patient (pre- and post treatment) and control groups.

Thrombocytosis in CD may occur due to a potential underlying factor such as platelet increase due to inflammatory mediators (26). Gerceker et al. (25) illustrated that platelet counts were significantly higher in the CD patients with activation compared to the CD patients in remission group and also in healthy controls. In another adult study they found that platelet values at initial diagnosis were significantly higher in the CD group compared to healthy controls (24). Terlemez and Tokgöz (26) observed a significant decrease in platelet values of pediatric patients with CD after a GFD. In the present study, we found that platelet levels were significantly higher in the CD group at the time of diagnosis when compared to the CD group after GFD, and also that platelet levels were within normal limits before and after GFD.

In CD, chronic inflammation damages the villi in the small intestine, leading to malabsorption, resulting in anemia and micronutrient deficiencies such as vitamin B12 (26,27). Terlemez and Tokgöz (26) observed a significantly increase in hemoglobin and MCV values of pediatric patients with CD after a GFD. Gerceker et al. (25) showed us a slightly higher hemoglobin in healthy controls compared to patients with CD, but there was no statistically significant difference. Deora et al. (27) assessed pediatric patients with CD for micronutrient deficiencies at the time of diagnosis and 18 months after introducing a GFD. The results indicated that the incidence of vitamin B12 deficiency decreased significantly from baseline to after 18 months on a GFD (27). In another study, 48 pediatric patients with CD were evaluated for different periods on a GFD, but the researchers did not observe any differences in hemoglobin or vitamin

B12 values between the subjects with CD and the non-CD controls (28). Likewise, an adult study comparing newly diagnosed patients with CD with non-CD individuals found no significant differences in hematocrit, and vitamin B12 levels (29). In our study we observed that hemoglobin, MCV, and vitamin B12 levels significantly increased after GFD treatment compared with the levels at the time of diagnosis; however, hemoglobin, MCV and vitamin B12 levels were within normal limits in patients with CD before and after GFD.

Study Limitations

Due to the retrospective nature of this study, a notable limitation is the relatively small number of patients included and the lack of data pertaining to the cytokine levels and acute phase reactants within the study group.

Conclusion

In conclusion, MPV may not be a useful biomarker for monitoring GFD in children with CD. More comprehensive studies are required to clarify this issue.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles outlined in the Helsinki Declaration and reviewed by the Selçuk University Ethical Review Board, and ethical approval was obtained from the Institutional Review Board (date: 09.06.2016, approval number: 2016/181).

Footnotes

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

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