Zeynep Kamil Med J 2021;52(2):82–85
DOI: 10.14744/zkmj.2021.57855

ORIGINAL ARTICLE

The role of functional platelet indices in dietary monitoring of children with celiac disease

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ABSTRACT

Objective: Determining the value of platelet count, mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) on histologic disease stage and compliance to gluten-free diet (GFD) in children with celiac disease (CD).

Material and Methods: Children diagnosed as CD and healthy subjects were recruited. CD patients were classified into two groups: Newly diagnosed and on GFD for over 1 year. CD patients on GFD were further divided into two groups according to their dietary adherence determined by anti-tissue transglutaminase IgA levels. Samples for complete blood count were obtained from all participants.

Results: A total of 236 CD patients (60 newly diagnosed, 83 with good GFD adherence, and 93 with poor GFD adherence, mean age: 11±3.9 years, 59.3% female) and 92 healthy subjects (mean age: 10.7±3.8 years, 52.2% female) were studied. Platelets, MPV, PCT, and PDW values of newly diagnosed CD and poor GFD adherence cases were statistically similar ($p>0.05$) while they were statistically higher than the controls and good GFD adherents ($p<0.01$). In ROC analysis, MPV had the highest area under the curve (0.758). The sensitivity and the specificity of MPV were 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Only PCT was found correlated with modified Marsh stage in newly diagnosed CD patients (r^2: 0.302, $p<0.05$).

Conclusion: This is the first report about platelet functions in children with CD. Functional platelet indices, especially MPV and PCT, would be a promising tool for indirect determination of GFD adherence and villous atrophy stage, respectively, at a low cost compared to other modalities.

Keywords: Celiac disease, children, gluten-free diet, mean platelet volume, plateletcrit.

Cite this article as: Bayrak NA, Volkan B. The role of functional platelet indices in dietary monitoring of children with celiac disease. Zeynep Kamil Med J 2021;52(2):82–85.

Received: April 04, 2021 **Accepted:** May 04, 2021 **Online:** June 18, 2021

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INTRODUCTION

Celiac disease (CD) is an autoimmune condition triggered by gluten and other environmental factors in genetically susceptible individuals. Permanent gluten ingestion eventually results in progressive lymphocytosis, villous atrophy, and inflammation in the small intestine, which leads to small intestinal malabsorption. Dietary elimination of gluten is the only approved therapeutic approach at the moment. Reversal of malabsorptive signs and symptoms can be achieved by a strict gluten-free diet (GFD). However, a reliable marker quantifying dietary compliance does not exist.[1] The gold standard is repetitive duodenoscopies which are too invasive and impractical. Despite their high accuracy for individuating the subjects needing a diagnostic biopsy, serological tests lack reliability after diagnosis. The autoantibody titers do not correlate well with histological amelioration or CD patients' symptoms on a GFD.[2] Immunoglobulin (Ig)A- and IgG-class tests usually take up to 24 months to normalize after gluten elimination from the diet.[3] The autoantibodies' somewhat long half-life can explain whether these titers reflect the immune response to gluten rather than the direct intestinal injury. Moreover, small, infrequent, or intermittent exposures to gluten cannot be detected by such serological tests in the clinical setting.[4]

Cytokines such as interleukin (IL)-3 and IL-6 induce megakaryocytes to produce young platelets during inflammation.[5] Young platelets are more reactive and more prominent in size. An elevation in serum IL-6 levels was reported previously in CD, which was highly correlated with mucosal injury severity.[6] In this context, elevated IL-6 would trigger the young platelet synthesis. Consequently, as well as the platelet quantity, qualitative platelet indices such as mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution with (PDW) will be affected. These parameters are frequently provided in the complete blood count (CBC) examination reports; nevertheless, they are still overlooked by most clinicians. A recent study suggests MPV as a promising biomarker for monitoring dietary compliance in CD adults.[7] Pediatric data do not exist. Our purpose is to investigate the relationship between qualitative platelet indices and mucosal damage, and compliance to GFD in CD children.

MATERIAL AND METHODS

The current study evaluated the medical CD database of the Pediatric Gastroenterology outpatient clinic of the University of Health Sciences, Zeynep Kamil Women and Children's Training and Research Hospital, between January 2018 and 2021. The study protocol was approved by the hospital's Ethics Committee (17.03.2021, decision no:77). The CD diagnosis was established following the recommendations of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; therefore, "no biopsy" approach was not utilized.[8] Demographic, clinical, and laboratory data of CD children were extracted from the database. Newly diagnosed cases and subjects under GFD for a minimum period of 1 year were included in the study group. Subjects under GFD were further classified according to their GFD compliance. Serum tissue transglutaminase (TTG) IgA (Anti-TTG IgA ELISA kit, Euroimmun AG, Lübeck, Germany) level under 20 RU/mL was accepted as a marker of good GFD compliance. The control group was generated by otherwise healthy and non-CD siblings and/or cousins of the newly diagnosed CD subjects. Their laboratory data were obtained during family screening. Platelet count, MPV, PCT, and PDW data were extracted from CBC reports, analyzed by a Beckman Coulter analyzer.

The CD's severity was graded histologically by the modified Marsh classification (Marsh) in newly diagnosed individuals.[9] The study's exclusion criteria include inadequate patient data, potential CD, selective IgA deficiency, current fever or acute/chronic inflammatory/infectious state, diabetes mellitus, giardiasis, cerebral palsy, and the presence of any hepatic, metabolic, cardiac, or renal disease.

Data were analyzed using SPSS software (IBM SPSS version 20, IBM Corp., New York, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as numbers or percentages. The Shapiro–Wilk test tested the normality of the data. The one-way analysis of variance or Mann–Whitney U-test was used to compare groups where appropriate. For metric variables, Pearson's correlation coefficients were computed. Calculated $p<0.05$ indicated statistical significance.

RESULTS

Among 374 individuals, 328 cases (236 CD cases and 92 controls) fulfilling the inclusion criteria were studied. The excluded subjects were: Eight with inadequate data, three with potential CD, six with giardiasis, four with selective IgA deficiency, 14 with fever or acute/chronic inflammation, six with diabetes mellitus, and five cases with a chronic disease were excluded from the study. The mean age and the gender distribution were indifferent between the study group and the controls (11.0±3.9 years vs. 10.7±3.8 years, 59.3% vs. 52.2%, $p>0.05$, respectively). In the study group, 60 cases were newly diagnosed, and 176 were under GFD for more than 1 year. According to serum TTG IgA levels, the dietary compliance was classified as "good" in 83 and "poor" in 93 cases.

Mean thrombocyte, MPV, PCT, and PDW values of the groups are shown in Table 1. Thrombocytes, MPV, PCT, and PDW values of the newly diagnosed CD cases and individuals with poor GFD compliance were statistically similar ($p>0.05$). These values were also similar when the control group was compared with individuals with good GFD compliance ($p>0.05$). In contrast, a statistical difference was present when we compared newly diagnosed and poor GFD compliant cases with the control group and good GFD compliant cases, one by one ($p<0.01$). In ROC analysis, MPV had the highest area under the curve (0.758). The sensitivity and the specificity of MPV were 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Only PCT was found correlated with the modified Marsh stage of newly diagnosed CD patients (r^2: 0.302, $p< 0.05$).

DISCUSSION

According to our findings, platelet count, MPV, PCT, and PDW were significantly elevated in patients with newly diagnosed CD and poor GFD compliance compared to healthy controls and individuals with good GFD compliance. The main parameter was MPV, which had a sensitivity and specificity of 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Moreover, we found a correlation between the small intestinal mucosal injury and PCT. Since CD is a life-long chronic autoimmune disease, adequate adherence to GFD and rou-

Table 1: Mean thrombocyte, MPV, PCT, and PDW values of CD and control groups

Group	Thrombocytes (10^3/mL) (Mean±SD)	MPV (fL) (Mean±SD)	PCT (%) (Mean±SD)	PDW (fL) (Mean±SD)
Control	286.13±82.8	8.29±1.09	0.23±0.06	16.39±0.5
New diagnosed CD	380.12±98.7	9.23±1.34	0.26±0.05	15.2±1.6
CD good GFD compliance	288.14±66.3	8.48±1.03	0.24±0.04	16±0.9
CD poor GFD compliance	324.95±92.6	9.28±1.11	0.29±0.07	15.4±1.1

MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; CD: Celiac disease; GFD: Gluten-free diet; SD: Standard deviation.

tine outpatient follow-up are mandatory. Meanwhile, an established objective criterion to monitor dietary compliance is absent where the gold standard is the demonstration of histological improvement.[1–4] However, non-invasive methods such as serological tests are incapable of reflecting the actual histological injury status. One of the significant drawbacks of these antibody titers is the incapability of detecting small, infrequent, or intermittent exposures to gluten.[4] In some other autoimmune conditions, giardiasis, and other intestinal microbial disorders, the serology might be falsely positive and mimicking CD.[10] Quantifying gluten immunogenic peptides in CD patients' stool may help monitor adherence to a GFD.[10]

MPV, PCT, and PDW are straightforward indices that show the volume of platelets. These indices are obtained easily by a simple CBC order. Recently, many studies investigated a potential association between these platelet indices and inflammatory disorders such as systemic lupus erythematosus, Henoch-Schönlein purpura, hepatitis A, and acute bronchiolitis in children.[11–14] In these most recent pediatric studies, MPV was found elevated in systemic lupus erythematosus, Henoch-Schönlein purpura, and hepatitis A. In contrast, a reduction was present in cases with acute bronchiolitis. Despite these conflicting data, both high and low MPV levels might have a diagnostic and prognostic yield for disparate inflammatory disorders.

O'Grady et al.[15] compared the MPV levels between CD patients, splenectomized patients, and healthy controls. They discovered that CD patients with intact spleens had higher MPV values and platelet counts, similar to our results. However, the GFD adherence of the CD patients was not taken into account in that study. After three decades, Purnak et al.[7] studied MPV levels in newly diagnosed and under GFD CD subjects. They revealed that the elevated MPV values observed in newly diagnosed adult CD patients might reflect a continuing small intestinal mucosal injury. Moreover, they noticed a normalization in MPV levels with the introduction of GFD, which may specify a resolution in mucosal inflammation. Similar outcomes were achieved by extracting our data in children with CD. In addition, we found that PCT was elevated and correlated with mucosal damage in newly diagnosed CD children. This evidence should be further analyzed with prospective studies.

There are some limitations to this study that should be mentioned. Since this is a retrospective study, the results should be interpreted cautiously. Falsely elevated results induced by platelet-swelling should be avoided by studying the CBC samples within 2 h. However, we cannot guarantee this because of the retrospective nature of the study. Moreover, platelet indices might be affected by various factors which we excluded widely by our exclusion criteria. Therefore, we did not examine all patients for abnormal thyroid functions, hypercholesterolemia, and smoking which might affect the platelet size.

CONCLUSION

Our study suggests that measuring MPV levels exceptionally would be a practical, fast, and inexpensive choice to monitor children's dietary compliance with CD. Furthermore, a causal relationship between PCT and mucosal injury might exist, and oncoming prospective research is expected to clarify the exact mechanism's undisclosed pieces. We believe that together with serology, MPV and PCT might have a role in determining dietary adherence

Statement

Ethics Committee Approval: The Health Sciences University, Zeynep Kamil Women and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 17.03.2021, number: 77).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NAB, BV; Design – NAB, BV; Supervision – NAB, BV; Resource – NAB; Materials – NAB; Data Collection and/or Processing – NAB; Analysis and/or Interpretation – NAB, BV; Literature Search – NAB, BV; Writing – NAB, BV; Critical Reviews – BV.

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

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

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