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Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio Changes During Follow-up in Celiac Patients

Çölyak Hastalarında Takip Sırasında Nötrofil/Lenfosit Oranı ve Trombosit /Lenfosit Oranı Değişiklikleri

ABSTRACT

Objective

Compare the Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) ratios of pre-diagnosis and diet-adherent follow-up patients with Celiac disease (CD) and to evaluate the cost-effective parameters that can be used in future follow-up.

Material and Methods

Patients admitted to the Pediatric Gastroenterology clinic between 2020 and 2023 and diagnosed with celiac disease were retrospectively analyzed for the study. Patients with heart failure, peripheral vascular disease, acute or chronic infection, cancer, hematologic, liver disease and chronic drug use (nonsteroidal anti-inflammatory, anticoagulant) were excluded.

Results

A total of 287 patients were included in the study. After treatment, the control complete blood count value was checked at the earliest 3 months and at the latest 10 months (mean 5.4 ± 1.6 months). Neutrophil values showed a significant decrease in CD patients on gluten-free diet. The mean platelet value decreased during follow-up, but the result was not significant. It was analyzed that lymphocyte values increased with gluten free diet. Pre-diagnosis and follow-up NLR (2.4 ± 1.3 vs 1.9 ± 1.1; $P < 0.001$) and PLR (141 ± 65 vs 119 ± 56; $P < 0.001$) values of CD patients treated with gluten-free diet showed a significant decrease.

Conclusion

NLR, PLR rates decrease during follow-up in CD patients adhering to a gluten-free diet. It may be possible to follow-up celiac disease with NLR and PLR values obtained from complete blood count, which are low cost and routinely used.

Key Words

Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Celiac Patients

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ÖZ

Amaç

Çölyak hastalığı (ÇH) ön tanılı ve diyetle takip edilen hastaların nötrofil lenfosit oranı (NLO) ve trombosit lenfosit oranı (PLR) oranlarını karşılaştırmak ve gelecekte kullanılabilecek maliyet etkin parametreleri değerlendirmek takip etmek.

Gereç ve Yöntemler

Çalışma için 2020-2023 yılları arasında Çocuk Gastroenteroloji kliniğine başvuran ve çölyak hastalığı tanısı alan hastalar retrospektif olarak analiz edildi. Kalp yetmezliği, periferik damar hastalığı, akut veya kronik enfeksiyon, kanser, hematolojik, karaciğer hastalığı ve kronik ilaç kullanımı (nonsteroid antiinflamatuar, antikoagülan) olan hastalar çalışma dışı bırakıldı.

Bulgular

Çalışmaya toplam 287 hasta dahil edildi. Tedavi sonrasında en erken üçüncü ayda ve en geç onuncu ayda (ortalama 5,4±1,6 ay) kontrol tam kan sayımı değerlerine bakıldı. Glutensiz diyet uygulayan ÇH hastalarında nötrofil değerleri anlamlı bir düşüş gösterdi. Ortalama trombosit değeri takip sırasında düştü ancak sonuç anlamlı değildi. Glutensiz diyetle lenfosit değerlerinin arttığı analiz edildi. Glutensiz diyetle tedavi edilen ÇH hastalarının ön tanı ve takip NLR (2,4 ± 1,3 / 1,9 ± 1,1; P < 0,001) ve PLR (141 ± 65 / 119 ± 56; P < 0,001) değerlerinde anlamlı bir azalma gösterdi.

Sonuç

Glutensiz diyet uygulayan ÇH hastalarında takip sırasında NLR, PLR oranları azalmaktadır. Maliyeti düşük ve rutin olarak kullanılan tam kan sayımından elde edilen NLR ve PLR değerleri ile çölyak hastalığının takibi mümkün olabilir.

Anahtar Kelimeler

Nötrofil/lenfosit oranı, Trombosit/lenfosit oranı, Çölyak Hastalığı

INTRODUCTION

Celiac disease (CD) is a genetically based autoimmune small bowel disease that causes malabsorption. It causes destruction of villi as a result of an inflammatory reaction to gluten-containing foods such as wheat, barley, rye and oats (1). Crypt hyperplasia and lymphocytosis are observed on pathologic examination (1). Serology measurements of antigliadin antibody (AGA), antiendomysial antibody (EMA) or tissue transglutaminase (tTG) antibodies are used in the diagnosis. Delayed diagnosis can lead to the development of complications such as osteoporosis due to severe digestive and absorption deficiencies due to malabsorption (2). Early diagnosis is of great importance to prevent the development of complications (osteopenia/osteoporosis and vitamin and mineral deficiencies due to malabsorption, T-cell lymphoma) (3). Elimination of gluten from the diet provides clinical, laboratory and histopathologic improvement. Activation of gluten-restricted T cells through HLA-DQ2 antigen presentation and the resulting T helper cells type 1 response is the main pathophysiologic mechanism (1).

Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been shown in some studies to be useful in the diagnosis and more importantly in the follow-up of inflammatory conditions and malignancies. Its advantages are that it is obtained from the commonly used complete blood count and does not involve additional costs. Platelets play an important role in inflammation (2). Research on low-cost laboratory parameters that can be used in the follow-up of celiac disease continues. In this study, we aimed to compare the NLR and PLR ratios of pre-diagnosis and diet-adherent follow-up patients with CD and to evaluate the cost-effective parameters that can be used in future follow-up.

MATERIAL and METHODS

Patients admitted to the Pediatric Gastroenterology clinic between 2020 and 2023 and diagnosed with celiac disease were retrospectively analyzed for the study. This study was approved by the Local Ethics Committee (Date: 18/01/2024, No: 3121). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Hemogram, routine biochemical examinations, endoscopic findings, ultrasound findings, duodenal biopsy and histopathologic evaluation findings in Marsh classification, anti-gliadin and endomysium antibody levels were retrospectively analyzed in the study patients. Patients with heart failure, peripheral vascular disease, acute or chronic infection, cancer, hematologic, liver disease and chronic drug use (nonsteroidal anti-inflammatory, anticoagulant) were excluded. In our clinic, the diagnosis of CD is based on typical clinical symptoms, serum antibodies to endomysium or gliadin, and the presence of histopathologic Marsh criteria from duedenal biopsies (including pathognomonic findings such as the presence of intraepithelial lymphocytes, villus atrophy and crypt hyperplasia) (4). A gluten-free diet was recommended to all patients and the importance of adherence was emphasized in terms of treatment. Patients who adhered

to the gluten-free diet were included in the study, while those who did not adhere to the diet at all or those who broke the diet in between were excluded from the study.

After the diagnosis of celiac disease, gluten-free diet treatment was started and compliance with the diet was questioned and laboratory tests (hemoglobin and biochemistry) were checked at the first follow-up visit 3 months later. All complete blood count analyses at both admission and follow-up were performed within 2 hours of blood sample collection using a Beckman Coulter (High Wycombe, United Kingdom) Gen-S automated analyzer. If more than one complete blood count was available before diagnosis, analysis was based on the value closest to the endoscopy procedure.

Upper gastrointestinal endoscopy was performed in all patients. Biopsy specimens were obtained from the duodenal bulb and the second part. The specimen was fixed in formalin and embedded in paraffin wax. Slides were stained with hematoxylin and eosin. Histological patterns were evaluated according to the Marsh-Oberhuber classification: type 0 indicates a normal histology, type I (infiltrative) is characterized by an increased number of IELs, type II (hyperplastic) also shows crypt hyperplasia, type III (destructive) is also characterized by partial (IIIa), subtotal (IIIb) or total (IIIc) villous atrophy, and type IV is represented by villous atrophy only (5). If there was clinical uncertainty about the diagnosis of CD, the patient was excluded from the study.

EMA values obtained from anti-tTGA and serologic tests were analyzed. Anti-tTG IgA titer was measured with Alisei model Seac device and EMA titer was measured with Aesku kit and Helmed device. Test results were expressed in IU/mL.

Statistical analysis

The categorical factors are summarised using frequencies and percentages. The categorical data were compared with the aid of the Chi-square test. Numerical parameters are given as Mean±SD and compared with the Student-T test. Since the same patients were used in the comparison of pre-diagnosis and follow-up NLR and PLR data, it was defined as a dependent group. Paired-T test was used to compare these values. Data recording and statistical analyses were performed using SPSS (statistical package for the social sciences) software (version 17, SPSS, Inc, Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 287 patients were included in the study. Patients underwent complete blood count before diagnosis. After treatment, the control complete blood count value was checked at the earliest 3 months and at the latest 10 months (mean 5.4 ± 1.6 months). The age range of the patients was 12-212 months (mean 96.5 ± 51.8 months). All patients underwent upper gastrointestinal endoscopy, biopsy and histopathologic examination. When Marsh evaluation was performed, it was observed that the patients were most commonly diagnosed at Marsh stage 3B (120, 41.8%). It was observed that 66.6% of the patients were female. When the laboratory values were analyzed, the mean values of EMA and tGA were 182 ± 119 and 184 ± 144, respectively. EMA was positive in 75.3% of the patients. Clinical and pathologic characteristics of the patients are given in Table I.

Table I. General clinical and laboratory data of the study group

	Patients (n= 287)
Age (Month), Mean ± StD	96.5 ± 51.8
Gender, n (%) **- Male** **- Female**	 96 (33.4%) 191 (66.6%)
EMA (IU/mL), Mean ± StD	182 ± 119
Positive EMA, n (%)	216 (75.3%)
tGA (IU/mL), Mean ± StD	184 ± 144
Marsh, n (%) **- 1** **- 2** **- 3A** **- 3B** **- 3C** **- 4**	 6 (2.1%) 3 (1.0%) 69 (24.0%) 120 (41.8%) 80 (27.9%) 9 (3.1%)
Follow-up period (Month), Mean ± StD	5.4 ± 1.6

EMA= Antiendomysial antibody, tGA= Tisue antigliadin antibody, StD= Standard deviation

Neutrophil, platelet, lymphocyte, NLR and PLR values obtained from the control complete blood counts of the patients before and 3-10 months after diagnosis are given in Table II. Neutrophil values showed a significant decrease in CD patients on gluten-free diet. The mean platelet value decreased during follow-up, but the result was not significant. It was analyzed that lymphocyte values increased with gluten free diet. Pre-diagnosis and follow-up NLR (2.4 ± 1.3 vs 1.9 ± 1.1; P < 0.001) and PLR (141 ± 65 vs 119 ± 56; P < 0.001) values of CD patients treated with gluten-free diet showed a significant decrease.

Table II. Comparison of neutrophil, platelet, lymphocyte, NLR and PLR values before diagnosis and at follow-up

	Pre-diagnosis	**In follow-up**	**P**
Neutrophil	5115 ± 1722	4716 ± 1549	0.003
Platelet, *10^3	288 ± 73	285 ± 69	0.636
Lymphocyte	2254 ± 660	2658 ± 793	<0.001
Neutrophil Lymphocyte Ratio	2.4 ± 1.3	1.9 ± 1.1	<0.001
Platelet Lymphocyte Ratio	141 ± 65	119 ± 56	<0.001

DISCUSSION

In our study, a significant decrease in NLR and PLR values was observed in patients diagnosed with celiac disease who complied with a gluten-free diet and then followed up. Complete blood count can be used in the diagnosis and follow-up of patients with low cost and routinely used in the clinic. In the literature, NLR and PLR values are investigated in cancer and other inflammatory diseases.

In the study conducted by Karacaer et al. NLR, mean platelet volume (MPV) and PLR values were analyzed to evaluate compliance with gluten-free diet (4). NLR values were found to be significantly lower in patients who complied with the diet (1.5 vs 2.3; p < 0.001). MPV and PLR values were not significantly different in the diet-adherent and non-adherent groups. According to receiver operating characteristic (ROC) curve analysis, the sensitivity and specificity rates were 87% and 52%, respectively, when the ideal cut-off value for NLR indicating dietary compliance was 1.5 (4). When NLR values

in celiac disease and control groups were compared in the literature, it was analyzed that NLR value was significantly higher in the CD group (2.4 ± 1.2) compared to the control group (1.9 ± 0.5) (P < 0.019) (6). The cut-off value for NLR in CD detection was 2.3, sensitivity was 80% and specificity was 41% (6). When PLR was evaluated, it was significantly higher in the CD group (166 ± 71) compared to the control group (119 ± 36) (p < 0.001) (2). The cut-off value of PLR was 143 and the sensitivity and specificity rates were 80.2% and 53.9%, respectively (2). In our cohort, follow-up NLR and PLR values were analyzed for NLR (2.4 ± 1.3 vs 1.9 ± 1.1; P < 0.001) and PLR (141 ± 65 vs 119 ± 56; P < 0.001) values decreased when compared to the control value at least 3 months after starting gluten-free diet. These findings show promise for use in follow-up. In CD, while the villi structures in the intestine become dull and crypts hyperplasia occurs, there is infiltration of inflammatory leukocytes in the epithelium and lamina propria (7). T cells become dominant in the epithelial compartment (7, 8). Systemic effects may also occur as a result of cytokine release (7, 8). In CD, gluten exposure is responsible for the initial stage of these changes. We think that NLR and PLR rates evaluated with serum measurement, which is evaluated as inflammatory index, are rapidly affected by gluten diet due to this mechanism.

When celiac patients during activation and remission were evaluated, platelet and MPV values were significantly higher in the activated period (9). Other inflammatory biomarkers such as white blood count, erythrocyte sedimentation rate and C-reactive protein were similar between CD patients with activation and CD patients in remission (9). When dietary adherence was evaluated, it was found that platelet and MPV values were lower in the fully adherent group (9). Compared to the control group, platelet and MPV values were found to be higher in CD patients (9). In our study, it was analyzed that the neutrophil value decreased significantly (p= 0.003) in the control group, but there was no significant decrease in the platelet count (p= 0.636). CD is a chronic autoinflammatory disease and requires lifelong treatment and follow-up. The immune system in CD has an important role in intestinal damage (10). A gluten-specific T lymphocyte-mediated response occurs in the epithelial compartment leading to interferonγ overexpression (10). Inflammation is not limited to the duodenum but also affects other gastrointestinal mucosa. Thrombocytosis, thrombocytopenia, anemia and leukopenia may be observed in celiac disease due to malabsorption and villous atrophy (11). PLR and lymphocyte-to-monocyte ratio have been previously proposed as markers of inflammation in celiac disease (2, 12). No significant difference was found in anemia and PLR markers when celiac patients who consumed chocolate were compared with non-consuming patients (13). In one study, the NLR value was found to be lower in people with CD who ate chocolate (14).

In normal individuals, there is an inverse, non-linear relationship between platelet volume and platelet count. The human spleen plays an important role in platelet kinetics and impaired spleen function can be expected to affect the relationship between platelet count and platelet volume (15). Hyposplenism was found in 88% of celiac patients with platelet counts above 400 000 /l (15). There is a remarkable similarity in platelet counts between normosplenic celiac patients and normal subjects and severe hyposplenic celiac patients and splenectomized subjects (15). MPV value was found to be increased in CD patients compared to healthy control group (3, 16). In the CD group followed with a gluten-free diet, mean MPV values tended to normalize over time (16). In the literature, although vitamin D and calcium deficiency occurred due to gluten free diet, bone mineral density and parathormone levels were not affected (17).

The study has some shortcomings. First of all, it was retrospective. Secondly, if more objective questionnaires could have been used in questioning the dietary compliance of the patients, it would have been possible to discuss the changes in NLR and PLR values more objectively. Some factors that may have been overlooked and may have caused changes in daily complete blood count values, such as subclinic infections, may not have been noticed, even if only a small number, due to the retrospective nature of the study. However, despite these shortcomings, the evaluation of low-cost and routinely used complete blood count parameters with a sufficient number of patients and a homogeneous patient group adds importance to the study.

CONCLUSION

In conclusion, it may be possible to follow-up celiac disease with NLR and PLR values obtained from complete blood count, which are low cost and routinely used. Even compliance with treatment can be evaluated more clearly. Prospective studies are needed to investigate the parameters that can be used in the follow-up of celiac disease.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Kayseri City Education and Research Hospital Ethical Committee (approval number: 2024/3121).

Informed Consent

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions

Concept - A.G., D.G.T.; Design – A.G.; Supervision – D.G.T.; Resources – A.G.; Materials - A.G., D.G.T.; Data Collection and/or Processing - A.G., D.G.T.; Analysis and/ or Interpretation – A.G.; Literature Search – A.G.; Writing Manuscript - A.G.; Critical Review – D.G.T

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

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