ORIGINAL ARTICLE

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Relationship Between Hematological Parameters and Follow-up and Diet Compliance in Celiac Patients

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Abstract

Objective: Celiac disease is a proximal small bowel disease developing due to persistent intolerance in people who are genetically susceptible to gluten and other gluten-like grain proteins in cereals such as mainly wheat, barley, rye, and oats. Treatment is a lifelong gluten-free diet. Strict adherence to this treatment is important for the prognosis of the disease. Since it is quite costly to follow-up of the disease, there is need to parameters that are easy to apply to reflect diet compliance and antibody level and do not require additional cost. In this study we aimed to determine whether hemogram parameters and albumin level can be used to evaluate the compliance of gluten-free diet in Celiac patients.

Methods: Fifty-seven of 133 Celiac patients whose disease was confirmed with anti-tissue transglutaminase-IgA (anti-tTG-IgA) levels were included to the study. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte distribution width (RDW) and albumin levels were compared in the periods when the anti-tTG-IgA levels of the patients were positive and negative. The relationship of these results with gluten-free diet compliance was evaluated.

Results: The mean age of the patients was 38.96 (19-66). RDW value, at anti-tTG-IgA positive the period was significantly higher compared to the period when it was negative (p=0.005). PDW (p=0.02) and albumin (p=0.035) values were significantly low. Although the PLR (p=0.074) value was found to be higher, this difference was not statistically significant. There was no difference in NLR (p=0.69) and MPV (p=0.12) values.

Conclusion: PDW, RDW, and albumin levels are more cost-effective, and can be used as an auxiliary parameter to evaluate dietary adherence and antibody levels in Celiac patients' follow-up.

Keywords: Celiac disease, hematological parameters, diet compliance

INTRODUCTION

Celiac disease is a proximal small bowel disease that develops persistent intolerance to gluten and other gluten-like grain proteins in cereals mainly caused by wheat, barley, rye and oats in genetically susceptible individuals (1). Its prevalence in the population is approximately 1% (1,2). However, those diagnosed with this disease constitute 1/10-1/7 of celiac patients in the whole population (3,4). Symptoms of Celiac disease can occur in any age group (5). Gliadin, which is formed as a result of the contact of gluten with alcohol, causing small intestinal epithelial destruction and intraepithelial lymphocyte activation via IL-15 expression play role in the pathogenesis of the disease.

Gliadin's presentation to CD4 T-cells via receptor results in tissue damage by causing cytokine release. As a result, small intestinal villus atrophy and crypt hyperplasia develop. In the clinical presentation, asymptomatic people and patients with mild symptoms are more common. However, when the disease is symptomatic, often signs of malabsorption (chronic diarrhea, weight loss, bloating, fatigue) are observed. In addition to those findings, many diseases and findings

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have also been published in the literature related to Celiac disease (6,7). This disease and findings can be divided into two group as gastrointestinal and extraintestinal system diseases and findings. Atrophic glossitis, recurrent aphthous ulcers, gastroesophageal reflux, eosinophilic esophagitis, pancreatitis, autoimmune hepatitis, steatohepatitis, primary sclerosing cholangitis, inflammatory bowel disease, increased transaminase levels are findings of the gastrointestinal tract diseases and anemia (iron/B12/folate defiency), osteopenia/osteoporosis, secondary hyperparathyroidism due to vitamin D deficiency, IgA deficiency, dermatitits herpetiformis, IgA nephropathy, peripheral neuropathy due to B12 deficiency, type 1 diabetes mellitus, autoimmune thyroiditis, epilepsy, depression, migraine, infertility, short stature, delayed puberty, myocarditis, dilated cardiomyopathy, Down syndrome, Turner syndrome are part of extraintestinal findings and diseases.

Serological tests used in the diagnosis of Celiac disease are anti-tissue transglutaminase-IgA (anti-tTG-IgA), anti-endomisium-IgA, anti-deamine gliadin peptide antibodies. Definitive diagnosis is reached by endoscopically multiple biopsies samples taken from the small intestine, demonstrating intraepithelial lymphocyte increase, crypt hyperplasia and villus atrophy (8). The only known treatment is lifetime compliance with a gluten-free diet (8). It is very important to obey strict adherence to treatment in terms of prognosis and prevention of future complications.

Since the follow-up of the disease is very costly, there is a need for biomarkers that can be applied more easily and do not require additional cost, which reflect the diet compliance and antibody level of the patients. In this study, we aimed to determine whether hemogram parameters and albumin levels can be used to evaluate adherence to a gluten-free diet in Celiac patients.

METHODS

Study Design

Patients with a definitive clinical, endoscopically, and pathologically diagnosis of Celiac disease who were followed up at University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital enrolled to the study. Fifty-seven of the 133 patients with positive anti-tTG-IgA levels who attended their scheduled follow-ups and had confirmed diet adherence were included. All patients gave their informed consent. Beside the demographic and descriptive features of patients, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratios (PLR), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte distribution width (RDW) and albumin levels were compared retrospectively in periods when anti-tTG-IgA levels were positive vs. negative and their relationship with gluten-free diet compliance was evaluated.

Ethical Principles

The study was carried out after receiving approval from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee (E-48670771-514.99), which was granted in accordance with the Helsinki Declaration of Ethical Principles.

Statistical Analysis

Data were analyzed using STATA, version 13. Mean, standard deviation, median, frequency, ratio, minimum, and maximum values were calculated and reported when applicable. Paired t-test were used for pairwise analysis of repeated measures coinciding with specific periods of the disease, and logistic regression analysis and receiver operating characteristic (ROC) analysis techniques were used for significant data associated with the disease. In addition, $p<0.05$ was considered statistically significant when interpreting the results.

RESULTS

Out of 133 Celiac patients, 76 patients did not come to regular follow-up or did not have hemogram and albumin parameters in periods when anti-tTG-IgA levels are both negative and positive. Having no definite data on dietary compliance to reflect this period was excluded from the study. Demographic and descriptive characteristics of 57 patients included in the study are shown in Table 1.

RDW value ($p=0.005$) was significantly higher during the period when the patients were anti-tTG-IgA positive, compared to the period when they were negative; PDW ($p=0.02$) and albumin ($p=0.035$) values were found to be significantly lower. PLR ($p=0.074$) value was higher however, this difference was not statistically significant. No difference was observed in MPV ($p=0.12$) and NLR ($p=0.69$) values.

Comparison of hemogram parameters and albumin levels in patients at both anti-tTG-IgA positive and negative periods are shown in Table 2.

Logistic regression analysis was performed to understand whether PDW, RDW and albumin results can predict the periods when patients' anti-tTG-IgA levels are positive and negative. The results were statistically significant at p value <0.05 significance level (*p value $=0.027$ for PDW, *p value $=0.017$ for RDW, and *p value $=0.021$ for albumin). As a result, PDW, RDW and albumin

values of the patients were found to be independent risk factors for predicting dietary compliance.

ROC analysis was performed to find the optimal cut point value of PDW, RDW, and albumin levels predicting patients' dietary compliance. In Figure 1, this ROC analysis results for parameters are shown. Area under the curve (AUC) was 0.6175 for PDW estimating dietary compliance in Celiac patients and cut-off was 15.85 (fL); for RDW, AUC was 0.6273 and cut-off was 14.25 (%); and for albumin, AUC was 0.6787 and cut-off was 44.45 (g/L).

According to these calculated cut-off values, sensitivity was 46% and specificity was 39% for PDW estimating the dietary compliance of Celiac patients. The sensitivity was 51%, the specificity was 82% for RDW; and the sensitivity was 39% and the specificity was 53% for albumin.

DISCUSSION

Clinical manifestations of Celiac disease are comparable to those of numerous other disorders. This similarity may cause a delay in the diagnosis if the disease is not suspected. Serological tests and endoscopic interventions used to evaluate dietary compliance during follow-up of patients are high-cost examinations that cannot be performed in every clinic. In this study, we aimed to determine whether hemogram parameters and albumin level can be used for the follow-up of the diet compliance of patients with Celiac disease.

Although hemogram parameters may show changes according to the etiology of the primary disease and accompanying comorbidities, they can still be utilized to forecast mortality, prognosis, disease activation, or complications that may arise in

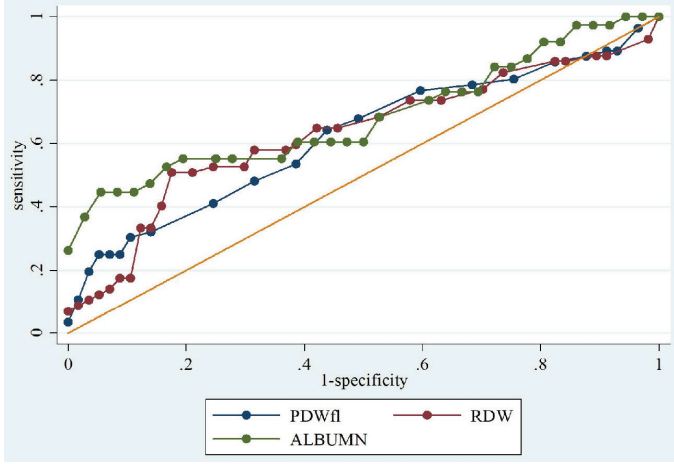

Figure 1. ROC analysis results for PDW, RDW and albumin
PDWfl: Platelet distribution width fentoliter, ALBUMN: Albumin, RDW: Erythrocyte distribution width, ROC: Receiver operating characteristic

Table 1. Demographic and descriptive characteristics

Variables		n	%
Age (years)	Min-max (median)	19-66 (39)	
	Mean ± SD	38.96±11.28	
Gender	Woman	39	68.4
	Male	18	31.6
BMI (kg/m^2)	Min-max (median)	16.6-34 (24.85)	
	Mean ± SD	24.69±3.78	
Disease (year)	Min-max (median)	0.66-21 (4)	
	Mean ± SD	4.78±4.42	

SD: Standard deviation, BMI: Body mass index, kg/m^2: Kilogram/square meter

Table 2. Comparison of hemogram parameters and albumin levels in patients at both anti-tTG-IgA positive and negative periods

Variables	Anti-tTG-IgA positive	Anti-tTG-IgA negative	*p<0.05
	Mean ± SD	Mean ± SD	p value
NLR	2.06±1.24	2.0±0.85	0.69
PLR	0.14±0.07	0.13±0.07	0.074
MPV (fL)	9.88±1.2	10.06±1.2	0.12
PDW (fL)	15.09±2.06	15.82±1.09	*0.02
RDW (%)	15.15±3.48	13.85±1.57	*0.001
Albumin (g/L)	38.48±13.24	44.68±2.62	*0.035

Anti-tTG-IgA: Anti-tissue transglutaminase-IgA, SD: Standard deviation, fL: Fentoliter, g/L: gram/Liter, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, PDW: platelet distribution width, RDW: Erythrocyte distribution width

a many diseases. The relationship between NLR and PLR levels, which are used as markers of inflammation, with prognosis and mortality in some malignancies (9-11), Coronavirus disease-2019 infection (12,13), in the postoperative period (14,15) and in diseases acute coronary syndrome (16,17), acute ischemic stroke (18), pulmonary embolism (19) and chronic renal failure (20) has been demonstrated by meta-analysis. RDW showing anisocytosis in peripheral blood is one of the first parameters to be evaluated in the distinction between iron deficiency anemia and thalassemia. Moreover, it has been proven that increased RDW also shows poor prognosis and mortality in many diseases (21-25). Many studies have been reported in the literature demonstrating MPV and PDW which show platelet functions and activity as markers of mortality and morbidity (26-30).

There are studies about these parameters which are routinely used in practice having quite low cost compared to the serological and invasive interventions in Celiac disease.

Sarikaya et al. (31) compared 76 Celiac patients and 86 functional dyspepsia patients and reported that NLR is a sensitive test in the diagnosis and follow-up of Celiac disease. Palmacci et al. (32) examined the relationship between NLR, dietary compliance and osteoporosis in Celiac patients. Although they could not show NLR as a significant determinant of gluten-free diet adherence, they reported that it is significantly higher in Celiac patients with osteoporosis (32). In the study of Brusco et al. (33) evaluating 126 Celiac patients, increased RDW detected in 57.9% of patients as the most common hematological disorder in patients and RDW was found to be decreasing trend in 37 of 43 patients after gluten free diet. Sategna Guidetti et al. (34) reported that high RDW level despite normal hemoglobin concentration can be a reliable indicator of Celiac disease in patients with strong clinical suspicion.

CONCLUSION

In our study, we observed that PDW and RDW as hemogram parameters and albumin values which are less cost and frequently used in clinical practice can be used to evaluate the dietary compliance and antibody levels of Celiac patients during follow-up. However, there is a need for further prospective studies with a larger number of participants investigating NLR, PLR and MPV levels.

Ethics

Ethics Committee Approval: The study was carried out after receiving approval from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee (E-48670771-514.99), which was granted in accordance with the Helsinki Declaration of Ethical Principles.

Informed Consent: All patients gave their informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S.P., Y.G., Concept: A.S.P., Y.G., Design: A.S.P., Y.G., Data Collection or Processing: A.S.P., Y.G., Analysis or Interpretation: A.S.P., Y.G., Literature Search: A.S.P., Y.G., Writing: A.S.P., Y.G.

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