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Research Article

Evaluation of hematologic inflammatory markers in Graves' disease

Graves hastalığında hematolojik inflamatuar belirteçlerin değerlendirilmesi

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Abstract

Introduction: The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) have been used as new inflammatory markers in certain autoimmune diseases to assess the severity of inflammation. The current study aimed to evaluate the changes in neutrophil and lymphocyte series in hyperthyroid patients and to investigate whether NLR, PLR, and SII may be markers of inflammation.

Methods: This cross-sectional study was conducted with 207 Graves' patients and 120 healthy controls between 2018-2022 years. Hematologic parameters, thyroid function tests, age and gender were recorded. The NLR, PLR and SII values of all subjects were calculated. Firstly, groups were composed as Graves' group and participants without thyroid disorder as control group. Secondly, Graves' patients composed as two groups before treatment and after antithyroid treatment. These groups were compared with each other in terms of descriptive data and hematological parameters.

Results: The patient and control groups were similar in terms of gender (p=0.522) and age (p=0.051). Graves' patients had a significantly lower NLR than the control group (p=0.004). There was no significant difference between the groups in terms of PLR (p=0.120) and SII (p=0.577). Patients' baseline TSH-receptor antibodies (TRAb) levels had a significant positive correlation with fT3 (r:0.283, p<0.001), fT4 (r:0.252, p<0.001) and Thyroid stimulating immunoglobulin (TSI) (r:0.673, p<0.001). There was no significant correlation between TRAb and TSI levels, inflammatory markers, and hematological parameters.

Conclusions: Graves' patients had lower NLR compared to the control group. The patient and control groups did not have a significant difference with regard to PLR and SII. Thyroid autoantibody levels and inflammatory markers did not have a significant correlation.

Keywords: Hyperthyroidism, inflammation, neutrophils, lymphocytes

Öz

Giriş: Nötrofil-lenfosit oranı (NLO), platelet-lenfosit oranı (PLO) ve sistemik immün inflamasyon indeksi (SII), bazı otoimmün hastalıklarda inflamasyonun şiddetini değerlendirmek için yeni inflamatuar belirteçler olarak kullanılmıştır. Bu çalışma, hipertiroidi hastalarında nötrofil ve lenfosit serilerindeki değişiklikleri değerlendirmeyi ve NLO, PLO ve SII'nin inflamasyon belirteçleri olup olmadığını araştırmayı amaçladı.

Yöntem: Bu kesitsel çalışma, 2018-2022 yılları arasında 207 Graves hastası ve 120 sağlıklı kontrol ile yürütülmüştür. Hastaların hematolojik parametreleri, tiroid fonksiyon testleri, yaş ve cinsiyetleri kaydedildi. NLO (nötrofil/lenfosit), PLO (platelet/lenfosit) ve SII hesaplandı. Öncelikle olgular Graves grubu ve tiroid hastalığı olmayan sağlıklı kontrol grubu olarak ikiye ayrıldı. İkinci olarak, Graves hastaları tedavi öncesi ve antitiroid tedavisi sonrası olmak üzere iki grup oluşturdu. Bu gruplar tanımlayıcı veriler ve hematolojik parametreler açısından birbirleriyle karşılaştırıldı.

Bulgular: Hasta ve kontrol grubu cinsiyet (p=0,522) ve yaş (p=0,051) açısından benzerdi. Graves hastalarının NLO'su kontrol grubuna göre anlamlı derecede düşüktü (p=0,004). Gruplar arasında PLO (p=0,120) ve SII (p=0,577) açısından anlamlı fark yoktu. Hastaların bazal TRAb düzeyleri fT3 (r:0,283, p<0,001), fT4 (r:0,252, p<0,001) ve TSI (r:0,673, p<0,001) ile anlamlı pozitif korelasyona sahipti. TRAb ve TSI seviyeleri, inflamatuar belirteçler ve hematolojik parametreler arasında anlamlı bir ilişki yoktu.

Sonuç: Graves hastalarında kontrol grubuna kıyasla daha düşük NLO değerleri saptandı. Hasta ve kontrol grupları arasında PLO ve SII açısından anlamlı fark yoktu. Tiroid otoantikor seviyeleri ile inflamatuar belirteçler arasında anlamlı bir korelasyon yoktu.

Anahtar kelimeler: Hipertiroidizm, inflamasyon, nötrofil, lenfosit

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Key Points

1. NLR levels may be lower in Graves' patients.
2. Hematological inflammatory markers are not useful in predicting inflammation in Graves' disease.
3. Hematological inflammatory markers are insufficient to predict the severity and treatment response of Graves' disease.

Introduction

Graves' disease (GD), which is an autoimmune disorder of the thyroid gland, is also the most common cause of hyperthyroidism. In Graves' disease, TSH-receptor antibodies (TRAb) are responsible for a clinical picture of hyperthyroidism. The annual incidence of the disease is approximately 40/100.000 [1]. It most frequently occurs in females and in the 30-50 age group. Clinically, findings of hyperthyroidism may be accompanied by Graves' orbitopathy (GO), dermopathy, and pretibial myxedema. Graves' disease is caused by the induction of an autoimmune process by environmental and endogenous factors in genetically predisposed individuals [2, 3].

The primary complaints of Graves' patients include various serious symptoms such as hyperthyroidism-related palpitations, tremor, heat intolerance, weight loss and anxiety. There are medical, radioactive iodine therapy and surgical treatment options for symptoms of hyperthyroidism. Another important issue for these patients concerns recurrence and Graves' orbitopathy. Inflammatory processes have been implicated in the Graves' orbitopathy pathology. Previous data from the literature have revealed the importance of cytokines and chemokines in the pathogenesis of GD and GO. Mingqian et al. reported proinflammatory cytokines to be associated with both severe hyperthyroidism and the active phase of GO in newly diagnosed Graves' patients [4]. Wang et al. demonstrated an increase in CD4+ cytotoxic T lymphocytes that are characterized by inflammatory properties in Graves' orbitopathy (GO), which is the most severe form of Graves' hyperthyroidism (GH) [5].

Recently, the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), and the systemic inflammation index (SII) have been used as new inflammatory markers in certain autoimmune diseases to assess the severity of inflammation. An earlier study reported higher NLR values in GO patients compared to the control group [6]. Yüksel et al. reported higher NLR, MLR, mean platelet volume (MPV), and SII in both GO and Graves' patients compared to the control group [7]. In contrast with these results, Dağdeviren et al. reported that NLR and lymphocyte levels were not significantly different in hyperthyroid patients compared to the control group [8]. Meanwhile, Szydełko et al. stated that NLR could be useful in predicting the risk for the development of GO in the follow-up of Graves' patients as this patient group has NLR values that are generally high [9].

Complete blood count indices (NLR, PLR, SII), which are cost-effective, easily accessible and widely used, may be employed as a marker of inflammation in patients with hyperthyroidism, which is an inflammatory disease. Although hyperthyroidism is known to cause changes in a series of hematological parameters, its relationship with the above-mentioned parameters has not been adequately elucidated. Therefore, the present study aimed to evaluate the changes in neutrophil and lymphocyte series in hyperthyroid patients and to investigate whether NLR, PLR, and SII may be markers of inflammation.

Methods

Study design and sample

The population of this cross-sectional study was composed of patients followed-up for a diagnosis of Graves' diseases in the Endocrinology clinic of Batman Training and Research Hospital between 2018-2022. The calculation of the sample size considered the NLR values reported by Turan [10]. The minimum sample size required to detect a significant difference was calculated as 46 per group and 92 in total using the Independent Samples t-Test with a Type I error (alfa) of 0.05, test power of (1-beta) 0.8, effect size of 0.59 and a two-tailed alternate hypothesis (H1) for the sample estimation. This study included 207 patients diagnosed with Graves' disease without co morbid disease and acute or chronic inflammation and 120 age- and gender-matched healthy controls. The exclusion criteria for the patient and control groups included; i) age younger than 18 years, ii) acute or chronic infections, iii) systemic autoimmune and inflammatory diseases, iv) hematologic diseases, v) malignancies, vi) pregnancy, vii) history of immunosuppressive or glucocorticoid therapy in the last 6 months, and vii) toxic nodular goitre.

Definition of Graves' disease

The diagnosis of Graves' disease was confirmed in all patients by a positive history of Graves' disease accompanied by clinical symptoms of hyperthyroidism, presence of orbitopathy and dermopathy in some patients, thyroid scintigraphy consistent with hyperthyroidism, raised free thyroxine (fT4) and free triiodothyronine (fT3) levels with suppressed thyroid stimulating hormone (TSH) and positivity of TRAb [11].

Data collection

Participants' sociodemographic characteristics (age and gender) were recorded. Concentrations of TSH, fT3, fT4 were evaluated to determine the thyroid status in both the patient and control groups. In addition, TRAb and TSI concentrations were also measured in the patient group. Neutrophil, lymphocyte, platelet counts of both groups were recorded to evaluate inflammation. The neutrophil-lymphocyte ratio (neutrophil/lymphocyte) and platelet lymphocyte ratio (platelet/lymphocyte) were calculated for both groups. Systemic Immune-Inflammation Index (SII) was calculated for both groups using the formula "platelet count x neutrophil count/lymphocyte count." In the patient group, those who achieved euthyroid state after treatment, had a change in TRAb and TSI status from positive to negative, and remained euthyroid after cessation of medical treatment were considered as remission. NLR, PLR, SII, and TRAb and TSI levels were measured again in remission. In participants in the patient group that achieved remission; thyroid function tests, the TRAb level, and hematological parameters were measured again in remission. The levels of NLR, PLR, and SII were evaluated again in patients in remission.

Ethical approval, informed consent and permissions

The study was approved by Batman Training and Research Hospital Ethics Committee (Decision: 356/21.06.2023). The research was conducted in accordance with Good Clinical Practice (Declaration of Helsinki of 1975). Written consent form was obtained from all participants.

Statistical Analysis

Study data were analyzed using the SPSS 22 (IBM Corporation, Armonk, New York, USA) software package. The distribution of continuous variables was analyzed with the Shapiro-Wilk test. For descriptive statistics; frequency and percentage values were given for categorical data and median (minimum-maximum) were given for non-normally distributed continuous data. The analysis of categorical data used Pearson's chi-squared or Fisher's exact test. The Mann-Whitney U test was used for comparison of non-normally distributed continuous data. The Wilcoxon Signed Ranks test was used for the comparison of inflammatory and hematological parameters before and after the treatment. The relationship between continuous variables was analyzed with Spearman's correlation. p values < 0.05 were considered statistically significant.

Results

This study included 207 Graves' patients and 120 healthy controls. The patient and control groups were similar in terms of gender (p=0.522) and age (p=0.051). The control group had a higher neutrophil count than the patient group (p=0.023). On the other hand, Graves' patients had a higher platelet count than the control group (p=0.001). Graves' patients had lower TSH (p<0.001) levels, and higher fT3 (p<0.001) and fT4 (p<0.001) levels compared to the control group. Graves' patients had a significantly lower NLR than the control group (p=0.004). (Table 1)

Table 1. Comparison of baseline characteristics between Graves' patients and controls.

Variables		Graves' disease (n=207) median (min-max)	Control (n=120) median (min-max)	p value
Gender n (%)				
	Female	160 (77.3)	89 (74.2)	0.522[a]
	Male	47 (22.7)	31 (25.8)	
Age		35.0 (18.00-65.00)	32.5 (18.00-60.00)	0.051[b]
Neutrophil		3.96 (1.30-15.06)	4.19 (2.27-7.97)	***0.023[b]***
Lymphocyte		2.31 (0.74-4.82)	2.23 (1.03-4.85)	0.569[b]
Platelet		275.00 (123.00-540.00)	251.00 (131.00-404.00)	***0.001[b]***
TSH		0.01 (0.01-0.08)	1.43 (0.64-5.13)	***<0.001[b]***
fT3		8.95 (2.03-30.35)	3.21 (2.30-4.17)	***<0.001[b]***
fT4		2.84 (0.96-12.78)	1.18 (0.88-1.68)	***<0.001[b]***
NLR		1.67 (0.64-9.47)	1.87 (0.66-4.65)	***0.004[b]***
PLR		115.15 (37.13-462.16)	105.99 (49.20-271.14)	0.120[b]
SII		454.61 (126.21-3049.89)	452.19 (139.92-1581.82)	0.577[b]

[a] Pearson Chi-square test; [b] Mann-Whitney U test; TSH, thyroid stimulating hormone; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, Systemic immune-inflammation index;

Of the 207 Graves' patients included in the study, 52 (25.1%) achieved remission with treatment. In the study population, malignancy was determined with surgery in 3 patients (Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in 1 patient; Thyroid papillary microcarcinoma in 2 patients) in total. TRAb levels were lower in remission compared to the pre-treatment period with statistical significance (p<0.001). The neutrophil count was higher after the treatment compared to the pre-treatment period (p=0.031). (Table 2).

Table 2. Comparison of hematological and inflammatory parameters from before and after treatment in Graves' patients with remission

Variables	Graves' disease before treatment (n=52) median (min-max)	Graves' disease after treatment (n=52) median (min-max)	p value*
TRAb	3.53 (1.04-86.25)	0.45 (0.05-1.71)	***<0.001***
Neutrophil	3.34 (1.30-9.14)	4.15 (1.33-7.30)	***0.031***
Lymphocyte	2.26 (1.13-4.46)	2.52 (1.05-4.73)	0.053
Platelet	269.50 (162.00-540.00)	277.00 (146.00-421.00)	0.702
NLR	1.61 (0.64-3.33)	1.66 (0.49-3.86)	0.273
PLR	113.94 (51.12-253.98)	115.52 (62.79-193.45)	0.168
SII	453.50 (135.00-1185.99)	468.84 (108.73-1145.48)	0.265

* Wilcoxon Signed Ranks Test; TRAb, thyroid-stimulating hormone receptor antibodies; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, Systemic immune-inflammation index;

Patients' baseline TRAb levels had a significant positive correlation with fT3 (r:0.283, p<0.001), fT4 (r:0.252, p<0.001) and TSI (r:0.673, p<0.001). No significant correlation was found between TRAb, TSI levels and inflammatory markers, hematological parameters (Table 3).

Table 3. Correlation between continuous variables at diagnosis

		Baseline-TRAB (IU/L)REF. 0-1.5	Baseline-TSI (IU/L) (0-0.1)	Baseline-NLR	Baseline-PLR	Baseline-SII
Baseline-neutrophil	r	-0.094	-0.004	0.693**	-0.111	0.653**
	p value	0.188	0.962	***<0.001***	0.112	***<0.001***
Baseline-lymphocyte	r	-0.013	0.059	-0.493**	-0.743**	-0.355**
	p value	0.858	0.476	***<0.001***	***<0.001***	***<0.001***
Baseline platelet	r	0.011	0.094	0.047	0.546**	0.520**
	p value	0.879	0.261	0.505	***<0.001***	***<0.001***
Baseline TSH	r	-0.010	0.003	0.058	0.013	0.014
	p value	0.894	0.969	0.408	0.849	0.839
Baseline fT3	r	0.283**	0.283**	-0.217**	-0.049	-0.169*
	p value	***<0.001***	***0.001***	***0.002***	0.480	***0.015***
Baseline fT4	r	0.252**	0.319**	-0.202**	-0.012	-0.168*
	p value	**<0.001**	**<0.001**	***0.004***	0.860	***0.016***
Baseline-TRAB (IU/L)REF. 0-1.5	r	1.000	0.673**	-0.051	0.009	-0.041
	p value	.	***<0.001***	0.481	0.904	0.572
Baseline-TSI	r	0.673**	1.000	-0.053	-0.019	-0.021
	p value	***<0.001***	.	0.524	0.820	0.800
Baseline-NLR	r	-0.051	-0.053	1.000	0.420**	0.845**
	p value	0.481	0.524	.	***<0.001***	***<0.001***
Baseline-PLR	r	***0.009***	-0.019	0.420**	1.000	0.635**
	p value	0.904	0.820	***<0.001***	.	***<0.001***
Baseline-SII	r	-0.041	-0.021	0.845**	0.635**	1.000
	p value	0.572	0.800	***<0.001***	***<0.001***	.

TRAb, thyroid-stimulating hormone receptor antibodies; TSI, Thyroid stimulating immunoglobulin NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, Systemic immune-inflammation index; *: significant mild correlation; ** significant moderate correlation; *** significant strong correlation

Discussion

The present study focused on the comparison of baseline hematological parameters and inflammatory markers of Graves' patients with those of healthy controls, as well as the effects of the treatment of this disease on these markers. In the present study, Graves' patients had a lower neutrophil count and a higher platelet count compared to the control group. Graves' patients and the control group were not significantly different in terms of the lymphocyte count. Thyroid diseases exhibit various effects on blood cells. According to previous data from the literature, hyperthyroidism may result in a mild decrease in the total white blood cell count, as well as neutropenia and thrombocytopenia. The effects of hyperthyroidism on leukocytes are variable. In hyperthyroidism, the total white blood cell count may be higher, lower or normal [11]. Agarwall et al. reported the prevalence of neutropenia as 14.1% in newly diagnosed Graves' patients. They showed the neutrophil count to increase with antithyroid drug therapy [12]. A meta-analysis reported neutropenia in approximately 10% of the cases in Graves' disease [13]. The present study and data from the literature show that neutropenia may occur in Graves' patients. We recommend that clinicians assess the neutrophil count at diagnosis in Graves' patients. The platelet count is also variable in thyroid diseases. It is known from the literature that platelet abnormalities may be encountered in autoimmune thyroid diseases, however that there is not a single type of disorder. Particularly, high platelet counts have been reported in autoimmune hypothyroidism. Meanwhile, especially in Graves' disease, studies have indicated increases in mean platelet volume [12]. However, multiple studies have suggested that autoimmune thrombocytopenia may be present in autoimmune thyroid patients [13, 14]. In a study conducted on a large cohort in China, thyroid functions were not associated with platelet count [15]. Current findings are insufficient to explain the effects of Graves' disease on platelet count. In addition, platelet function may be impaired even in the presence of a normal platelet count in autoimmune thyroid diseases. A previous study showed elevated expression of GPIIb/IIIa, which is an integrin receptor responsible for platelet aggregation in thyroid patients, resulting in increased platelet aggregation [13]. All of these data suggest that there may be changes in the platelet count and function in Graves' patients and that these require attention in patient management. In the present study, Graves' patients and the control group were not different in terms of lymphocyte count. T-lymphocyte activation was described to play a role in the pathophysiology of autoimmune thyroid diseases by triggering inflammatory and autoimmune mechanisms [16]. Graves' patients were shown to have more CD4 T lymphocytes in thyroid tissue at diagnosis. In addition, it has been reported that fT3 levels and CD4 T lymphocyte are positively correlated, and that the CD4 T lymphocyte count can be a prognostic predictor [17]. Wang et al. emphasized the potential relationship of CD4 T lymphocytes with Graves' orbitopathy and disease recurrence [5]. Turan reported that Graves' patients had a higher total lymphocyte count in peripheral blood compared to the control group [10]. In the present study, lymphocyte counts of Graves' patients were compared with the control group based on complete blood count and could not be assessed at the thyroid tissue level. Studies with large populations are needed to determine the differences in the baseline total lymphocyte count and lymphocyte subset counts in Graves' patients.

Cytokines released by inflammatory and immune cells are hypothesized to play a role in the etiopathogenesis of autoimmune thyroid diseases. Especially in Graves' disease, an increase in serum levels of inflammatory cytokines has been reported [18]. In Graves' disease, inflammation is associated with disease severity, remission, and complications. An autoimmune-mediated inflammatory process characterized by fibroblast activation, adipogenesis and enlargement of extraocular muscles is implicated in the etiopathogenesis of Graves' orbitopathy. In light of this information, the present study investigated inflammatory markers in Graves' patients. Graves' patients had lower NLR values than the control group. The patient and control groups were not different in terms of PLR and SII. Turan determined lower NLR in the patient group. The same study did not report a difference in PLR between the patient and control groups [10]. Meanwhile, Szydełko et al. reported that both NLR and PLR were higher in Graves' disease [9]. An increase in inflammatory cells has been previously reported at the tissue level in Graves' disease. The inflammation in Graves' disease is attributed to lymphocytes. In this case, a decrease in NLR would be an expected finding. Previous studies and the present results have determined lower NLR in Graves' disease [8, 10]. In contrast to these results, there are also studies reporting high NLR in Graves' disease and Graves' orbitopathy [6, 19, 20]. Our opinion is that the data from the present study and data from previous literature are not sufficient to explain the relationship between hematological inflammatory markers and Graves' disease. Prospective studies with large populations are needed for stronger evidence. The present study did not identify a significant relationship between SII, which is another inflammatory marker, and Graves' disease. In the literature, studies investigating the relationship between Graves' disease and SII are limited. Certain studies have reported higher SII in thyroid patients [21, 22]. Subacute thyroiditis is an inflammatory disease with a high inflammatory burden and this result is expected. The local inflammatory process in Graves' disease may explain the unchanged levels of SII in the present study population. In the present study, the inflammatory parameters from before and after treatment were not significantly different in patients that achieved remission. Turan also did not find a difference in inflammatory parameters from before and after treatment. In the present study, systemic inflammatory markers at diagnosis were not different between the Graves' group and the control group. This result explains the unchanged levels of inflammatory markers after treatment. TRAb levels did not have a significant correlation with inflammatory markers in this study, which may also explain why the treatment did not cause a change in inflammatory markers. Two other studies have reported that TRAb levels and inflammatory markers are not significantly correlated [23, 24].

Limitations

The current study has certain limitations. This study cannot be generalized to the general population due to its cross-sectional design. In the study population, inflammation was evaluated only with hematological parameters. Parameters that indicate systemic inflammation such as CRP, erythrocyte sedimentation rate (ESR), TNF-α, IL-1β, IL-6 were not examined.

Conclusion

In the current study, Graves' patients had lower NLR compared to the control group. The patient and control groups did not have a significant difference with regard to PLR and SII. Thyroid autoantibody levels and inflammatory markers did not have a significant correlation. The present study did not find a relationship between hematological inflammatory markers and Graves' disease. We think that more comprehensive studies are needed to elucidate the role of hematological markers in Graves' disease.

Conflict of interest: The authors declared no conflict of interest.

	Author Contributions	**Author Initials**
SCD	Study Conception and Design	HA, RD
AD	Acquisition of Data	HA, RD
AID	Analysis and Interpretation of Data	HA, RD
DM	Drafting of Manuscript	HA, RD
CR	Critical Revision	HA, RD

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