MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

ARAŞTIRMA MAKALESİ
RESEARCH ARTICLE
CBU-SBED, 2025, 12 (1): 125-133

The Relationship Between Inflammatory Parameters in Hemogram and Thyroid Stimulating Immunoglobulin (TSI) Levels at the Beginning and the 6th Month of Treatment in Graves' Disease

Graves Hastalığında Başlangıç ve Tedavinin 6. Ayında Hemogramdaki İnflamatuar Parametreler ile Tiroid Stimulan İmmunglobulin (TSI) Düzeyi Arasındaki İlişki

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Gönderim Tarihi / Received:18.11.2024
Kabul Tarihi / Accepted: 26.12.2024
DOI: 10.34087/cbusbed.1593450.

Öz

Giriş ve Amaç: Tirotoksikozun ayırıcı tanısında, hastalık nüksü ve aktivitesini göstermede TSI kullanılmaktadır. Ancak ulaşılabilirlik ve maliyet TSI kullanımını sınırlandırmaktadır. Çalışmamızda GH tanı ve takibinde TSI yerine kullanılabilecek ve kolay ulaşılabilen belirteç varlığı araştırılmıştır. Hastaların başlangıç ve antitiroidal tedavi sonrası 6. aydaki tam kan sayımından elde edilen NLO, MLO, TLO, SII indeks, PIV gibi inflamatuar belirteçler ile TSI düzeyleri arasındaki ilişkinin değerlendirmesi amaçlanmıştır.

Gereç ve Yöntemler: Graves hastalığı tanılı 162 hasta retrospektif olarak incelendi. Serbest T4 düzeyine göre hastalar, hafif, orta, ağır şiddetli hastalık olarak 3'e ayrıldı. Hastaların tanı anındaki ve 6 ay antitiroid tedavi sonrasındaki tiroid fonksiyon testleri, hemogram parametreleri ve TSI değerleri karşılaştırıldı. İstatistiksel olarak anlamlı bulunan parametrelerin TSI ile korelasyonu her grup için ayrı ayrı incelendi.

Bulgular: Tedavi sonrası başlangıca göre hemoglobin (p=0.009), lökosit (p=0.001), nötrofil (p=0.002), lenfosit (p=0.002), eozinofil (p=0.033), bazofil (p=0.001) ve TSH (p=0.001) anlamlı artış varken; monosit (p=0.003), trombosit (p=0.010), TLO (p=0.001), MLO (p=0.001), sT3 (p=0.001), sT4 (p=0.001) düzeylerinde anlamlı azalma izlendi. İstatistiksel olarak anlamlı bulunan bu parametrelerin TSI ile korelasyonu incelendi. Tüm hastalarda başlangıç ve tedavi sonrası 6. ay değerleri incelendiğinde; TSI ile monosit ve MLO arasında pozitif yönde çok zayıf korelasyon ve sT3 ile pozitif yönde zayıf korelasyon tespit edildi. Ağır şiddetli hastalık grubunda TSI ile RDW ve sT3 arasında pozitif yönde zayıf korelasyon saptandı.

Sonuç: Graves hastalığı takibinde TSI'ya alternatif olarak kullanılabilecek güvenilir bir belirteç saptanmamış olsa da monosit, MLO ve ağır şiddetli hastalarda RDW'nin hastalık takibinde aktivasyonu göstermede fikir verebileceği düşünülmüştür.

Anahtar kelimeler: Graves hastalığı, İnflamatuar parametreler, Tiroid Stimülan İmmünglobulin

Abstract

Aim: Thyroid stimulating immunoglobulin (TSI) is used in the differential diagnosis of thyrotoxicosis and disease recurrence and activity. However, the accessibility and the cost can limit the use of TSI. In our study, we investigated the existence of easily accessible markers that can be used instead of TSI in the diagnosis and follow-up of Graves' disease (GD). The aim was to evaluate the relationship between TSI levels and inflammatory markers such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (TLR), systemic immune inflammation (SII) index, pan-immune inflammation value (PIV) obtained from the complete blood count of the patients at the beginning and 6 months after anti-thyroid treatment.

Method: 162 patients diagnosed with Graves' disease were retrospectively investigated. According to the free T4 level, the patients were divided into 3 groups as mild, moderate, and severe disease. Thyroid function tests, hemogram parameters, and TSI values of the patients at the time of diagnosis and after 6 months of anti-thyroid treatment were compared. The correlation of the statistically significant parameters with TSI was studied separately for each group.

Results: While there was a significant increase in hemoglobin (p=0.009), leukocyte (p=0.001), neutrophil (p=0.002), lymphocyte (p=0.002), eosinophil (p=0.033), basophil (p=0.001) and TSH (p=0.001) levels after treatment compared to the baseline, there was a significant decrease in monocyte (p=0.003), platelet (p=0.010), TLR (p=0.001), MLR (p=0.001), freeT3 (p=0.001), freeT4 (p=0.001) levels. The correlation of these statistically significant parameters with TSI was observed. When the baseline and 6th month post-treatment values were investigated in all patients; a weak positive correlation was detected between TSI and monocytes and MLR, and a weak positive correlation was detected with freeT3. A weak positive correlation was detected between TSI and RDW and freeT3 in the severe disease group.

Conclusion: Although a reliable marker that can be used as an alternative to TSI in the follow-up of Graves' disease has not been available, monocyte level, MLR and RDW in patients with severe Graves' disease may predict an activation in the follow-up of the disease.

Keywords: Graves' disease, Inflammatory parameters, Thyroid Stimulating Immunoglobulin

1. Introduction

Thyrotoxicosis is a clinical syndrome characterized by an increase in thyroid hormone levels. The most common cause of thyrotoxicosis is Graves' disease. Graves' disease is an autoimmune thyroid disorder characterized by hyperthyroidism, goiter, ophthalmopathy (exophthalmos), and dermopathy. It is approximately five times more common in women than in men. Although it can occur at any age, its incidence peaks between the ages of 20-40 and affects about 0.5-1% of the population [1]. T lymphocytes are sensitized to antigens within the thyroid gland and stimulate B lymphocytes to produce antibodies. These antibodies, known as thyroid-stimulating antibodies or thyroid-stimulating immunoglobulins (TSI), target the thyroid-stimulating hormone (TSH) receptor, thereby increasing the thyroid gland's function [2]. TSI is used in the differential diagnosis of thyrotoxicosis and in evaluating relapse and remission after antithyroid treatment [3].

Although the exact mechanism of Graves' disease has not been fully explained, it is known to affect various organs and systems, including blood cell metabolism and proliferation [1]. The effects of thyrotoxicosis on blood cells are often not clinically apparent. Hyperthyroidism is recognized as an inflammatory disease and is therefore thought to cause changes in hematological parameters. Indices derived from complete blood counts, such as the systemic immune-inflammation (SII) index, pan-immune-inflammation value (PIV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have been studied on as indicators of mortality, prognosis, and disease activity in cardiovascular diseases, infections, inflammatory conditions, and certain malignancies [4–6].

Hyperthyroidism is thought to cause changes in inflammatory parameters through the direct toxic effects of thyroid hormones as well as humoral and cellular mechanisms during the maturation and differentiation processes of hematopoiesis [7,8]. Antithyroid therapy (ATT) is expected to improve hematological parameters by reducing suppression on hematopoiesis. Various studies have reported increases

in hemoglobin, leukocyte, neutrophil, lymphocyte, and NLR levels following ATT [1].
TSI, used in the differential diagnosis of thyrotoxicosis and in assessing disease recurrence and activity, has limitations in terms of cost and accessibility. Our study aimed to investigate the potential for an easily accessible marker that could replace TSI in the diagnosis and follow-up of Graves' disease. We planned to evaluate the relationship between inflammatory markers derived from complete blood counts at the onset and the 6th month of antithyroid therapy and TSI levels.

2. Method

This study was conducted with the approval of the Clinical Research Ethics Committee of Manisa Celal Bayar University, dated 09.10.2023, with decision number 563. In our study, 162 patients diagnosed with Graves' disease (GD) and followed up at the Endocrinology and Metabolism Diseases Divison of Manisa Celal Bayar University Faculty of Medicine between June 2018 and June 2023 were retrospectively analyzed. Patients with acute or chronic infections, hematologic or rheumatologic diseases, malignancy history, pregnant patients, and those who did not attend follow-up visits were excluded from the study.

The patients diagnosed with Graves' disease were classified into three groups according to disease severity: mild, moderate, and severe. Free T4 (fT4) levels were used to determine the groups. Those with fT4 levels up to 1.5 times the upper normal limit were classified as mild, 1.5–2 times as moderate, and those with more than 2 times as severe. According to our hospital's laboratory, patients with fT4 ≤1.95 were categorized as mild, those with fT4 between 1.96–2.6 as moderate, and those with fT4 >2.6 as severe [9]. In the mild disease group, 81 patients were included, in the moderate group, 22 patients, and in the severe group, 59 patients were included in the study.

Thyroid function tests (TSH, fT4, fT3), hemogram parameters (hemoglobin, leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils, MPV, NLR, PLR, MLR, SII index, PIV), and TSI levels at diagnosis and after 6 months of antithyroid therapy were compared. Statistically significant parameters were analyzed for correlation with TSI separately for each group.

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, PLR by dividing the absolute platelet count by the absolute lymphocyte count, and MLR by dividing the absolute monocyte count by the absolute lymphocyte count. The SII index was calculated by dividing the product of platelet count and neutrophil count by the lymphocyte count, and PIV was obtained by multiplying the SII index by the monocyte count.

The normality of the data distribution was tested using the Shapiro-Wilk test. Data were expressed as mean ± standard deviation for normally distributed parameters and median (range) for non-normally distributed parameters. The values at baseline and after 6 months were compared using the paired t-test for parameters that followed a normal distribution, and the Wilcoxon signed-rank test for parameters that did not show a normal distribution. Spearman's correlation test was used to examine the degree of correlation between TSI and other variables. A type 1 error rate of 0.05 was considered statistically significant.

3. Findings and Discussion

3.1 Findings

A total of 162 patients diagnosed with Graves' disease (GD) and followed up at the Endocrinology Division of Manisa Celal Bayar University Faculty of Medicine between 2018 and 2023 were included in the study, consisting of 108 women (66.7%) and 54 men (33.3%). The ages of these patients ranged from 18 to 83 years, with a mean age of 42.68 ± 15.33 years.

After treatment, there were significant increases in hemoglobin (p=0.009), leukocytes (p=0.001), neutrophils (p=0.002), lymphocytes (p=0.002), eosinophils (p=0.033), basophils (p=0.001), and TSH (p=0.001), whereas significant decreases were observed in monocytes (p=0.003), platelets (p=0.010), platelet-to-lymphocyte ratio (PLR) (p=0.001), monocyte-to-lymphocyte ratio (MLR) (p=0.001), free T3 (fT3) (p=0.001), and free T4 (fT4) (p=0.001) (**Table 1**).

Table 1. The comparison of parameters at the time of diagnosis and after 6 months of antithyroid treatment for all patients

	At the time of diagnosis	**6th month of treatment**	**p value**
Hemoglobin (gr/dL)	13.5 (7.5-17.6)	13.65 (9.7-17.8)	**0.009** *
Leukocytes (10^3/uL)	6.765 (3.92-16.15)	7.32 (3.09-18.72)	**0.001** *
Neutrophils (10^3/uL)	3.67 (1.58-11.15)	4.01 (1.25-13.67)	**0.002** *
Lymphocytes (10^3/uL)	2.34±0.77	2.501±0.80	**0.001** **
Monocytes (10^3/uL)	0.542±0.187	0.500±0.164	**0.003** **

Eosinophils (10^3/uL)	0.14 (0-0.57)	0.15 (0-0.59)	**0.033** *
Basophils (10^3/uL)	0.02 (0-0.11)	0.03 (0-0.11)	**0.001** *
Platelets (10^3/uL)	277.5 (117-522)	271.5 (118-518)	**0.010** *
RDW (%)	13.5 (11.4-20.3)	13.6 (11.7-25)	0.053 *
MPV (fL)	9.8±1.04	9.8±1.02	0.503 **
NLR	1.61 (0.62-17.72)	1.596 (0.65-8.37)	0.622*
TLR	121.89 (58.03-1549.11)	107.79 (52.17-332.53)	**0.001***
MLR	0.23 (0.09-2.37)	0.189 (0.08-0.6)	**0.001***
SII index (10^3)	433.273 (140.1-6149.9)	435.688 (105.9-2311.08)	0.684*
PIV (10^3)	225.37 (48.32-3259.47)	205.118 (22.25-1493.65)	0.101 *
fT3 (ng/L)	6.2 (3-29.8)	3.6 (1.3-16.7)	**0.001***
fT4 (ng/L)	1.99 (0.42-5.77)	0.78 (0.07-2.92)	**0.001** *
TSH (mIU/L)	0.1 (0.01-2.42)	1.41 (0.01-46)	**0.001***
TSI (mIU/L)	4.92 (0.56-40)	2.14 (0.1-40)	**0.001***
***Results are given as median with the range (minimum and maximum values). Wilcoxon Signed Ranks test was used. ****Results are given as mean ± SD. Paired samples t-test was used. p<0.05 was considered statistically significant.			
RDW: Red Cell Distribution Width, **MPV**: Mean Platelet Volume, **NLR**: Neutrophil-to-Lymphocyte Ratio, **TLR**: Platelet-to-Lymphocyte Ratio, **MLR**: Monocyte-to-Lymphocyte Ratio, **SII index**: Systemic Immune-Inflammation Index, **PIV**: Pan-Immune Inflammation Value, **fT3**: Free Triiodothyronine, **fT4**: Free Thyroxine (Tetraiodothyronine), **TSH**: Thyroid Stimulating Hormone, **TSI**: Thyroid Stimulating Immunoglobulin			

Patients diagnosed with Graves' disease were divided into three groups based on the severity of the disease: mild, moderate, and severe. The fT4 level was used to determine the groups. Those with a free T4 level up to 1.5 times the upper limit of normal were categorized as mild, 1.5–2 times as moderate, and more than 2 times as severe disease [9].

In the mild disease group (n=81), after 6 months of antithyroid treatment, there were statistically significant increases in leukocyte (p=0.003), neutrophil (p=0.012), basophil (p=0.001), and TSH (p=0.001) levels compared to baseline, while statistically significant decreases were observed in platelet (p=0.004), TLR (p=0.001), fT3 (p=0.003), and TSI (p=0.001) levels.

In the moderate disease group (n=22), after 6 months of antithyroid treatment, statistically significant increases in basophil (p=0.024), MPV (p=0.008), and TSH (p=0.001) levels were observed compared to baseline, while statistically significant decreases were detected in TSI (p=0.002) and fT3 (p=0.001) levels.

In the severe disease group (n=59), after 6 months of antithyroid treatment, statistically significant increases in hemoglobin (p=0.001), leukocyte (p=0.010), lymphocyte (p=0.002), eosinophil (p=0.008), basophil (p=0.001), RDW (p=0.002), and TSH (p=0.001) levels were observed compared to baseline, while statistically significant decreases were seen in monocyte (p=0.001), TLR (p=0.005), MLR (p=0.001), PIV (p=0.031), fT3 (p=0.001), and TSI (p=0.001) levels **(Table 2).**

Table 2. The comparison of parameters at diagnosis and after 6 months of antithyroidal treatment in the mild, moderate, and severe disease groups

	Severity of disease	**At the time of diagnosis**	**6th month of treatment**	**p value**
Hemoglobin (gr/dL)	Mild	13.7 (10-17.6)	13.6 (9.7-17.8)	0.761*
	Moderate	13.16 ±1.42	13.03 ± 1.52	0.543**
	Severe	13.2 (7.5-16.2)	13.9 (10.1-16.9)	**0.001***
Leukocytes (10^3/uL)	Mild	6.83 (3.92-12.37)	7.330 (3.94-14.15)	**0.003***
	Moderate	6.19 (4.17-11.49)	6.88 (3.89-11.55)	0.115*
	Severe	6.760 (3.97-16.15)	7.5 (3.09-18.72)	**0.010***
Neutrophils (10^3/uL)	Mild	3.82 (1.58-8.07)	3.9 (1.87-10.2)	**0.012***
	Moderate	3.21 (1.85-8.29)	3.6 (2.08-8)	0.426*

	Severe	3.77 (1.81-11.15)	4.27 (1.25-13.67)	0.123*
Lymphocytes (10^3/uL)	Mild	2.363±0.642	2.478±0.712	0.055**
	Moderate	2.05 (1.25-4.28)	2.41 (1.14-3.86)	0.399*
	Severe	2.274 ± 0.883	2.552±0.933	**0.002****
Monocytes (10^3/uL)	Mild	0.493±0.146	0.489±0.141	0.787**
	Moderate	0.51 (0.27-1.13)	0.46 (0.27-0.76)	0.432*
	Severe	0.614 ± 0.217	0.512±0.198	**0.001****
Eosinophils (10^3/uL)	Mild	0.15 (0-0.51)	0.16 (0-0.58)	0.754*
	Moderate	0.184 ± 0.112	0.196 ± 0.119	0.457**
	Severe	0.11 (0-0.57)	0.14 (0-0.59)	**0.008***
Basophils (10^3/uL)	Mild	0.02 (0-0.09)	0.03 (0-0.11)	**0.001***
	Moderate	0.025 (0.01-0.11)	0.035 (0.01-0.09)	**0.024***
	Severe	0.02 (0-0.08)	0.03 (0.01-0.11)	**0.001***
Platelets (10^3/uL)	Mild	273 (117-479)	270 (118-518)	**0.004***
	Moderate	285.318 ± 89.771	278.59 ± 89.891	0.649**
	Severe	281 (136-480)	283 (128-394)	0.567*
RDW (%)	Mild	13.5 (11.8-18.7)	13.5 (11.9-25)	0.644*
	Moderate	13.65 (11.7-18.3)	13.85 (11.8-16.4)	0.371*
	Severe	13.5 (11.4-20.3)	13.7 (11.7-20.9)	**0.002***
MPV (fL)	Mild	9.88 ± 1.08	9.93 ± 1.06	0.431**
	Moderate	9.57 ±0.741	9.91 ± 0.837	**0.008****
	Severe	9.81±1.08	9.7 ± 1.04	0.221**
NLR	Mild	1.60 (0.62-5.5)	1.974 (0.65-8.37)	0.428*
	Moderate	1.435 (0.89-4.55)	1.611 (0.8-5.84)	0.709*
	Severe	1.807 (0.69-17.72)	1.559 (0.83-5.82)	0.502*
TLR	Mild	117.511 (59.46-232.88)	106.425 (52.17-332.53)	**0.001***
	Moderate	117.948 (67.52-286.81)	125.044 (72.28-209.49)	0.211*
	Severe	127.69 (58.03-1549.11)	106.069 (58.23-302.38)	**0.005***
MLR	Mild	0.20 (0.09-0.59)	0.189 (0.1-0.57)	0.098*
	Moderate	0.216 (0.13-0.62)	0.212 (0.09-0.55)	0.291*
	Severe	0.268 (0.11-2.37)	0.187 (0.08-0.6)	**0.001***
SII index (10^3)	Mild	461.009 (175.8-6149.9)	428.361 (105.96-1430.26)	0.394*
	Moderate	379.332 (193.8-2377.6)	421.901 (192.9-1675.9)	0.961*
	Severe	461.009 (175.8-6149.9)	428.361 (105.9-1430.2)	0.394*
PIV (10^3)	Mild	205.2 (48.32-1608.2)	206.8 (63.606-1493.655)	0.441*
	Moderate	190.853 (81.414-2686.7)	194.923 (52.107-1273.693)	0.808*
	Severe	407.807 (52.762-3259.4)	211.686 (22.25-1479.406)	**0.031***
fT3 (ng/L)	Mild	4.6 (3-10.5)	3.6 (2.3-7.1)	**0.001***
	Moderate	6.6 (4.8-13.1)	3.65 (2.7-4.7)	**0.001***
	Severe	14.5 (4.4-29.8)	3.8 (1.3-16.7)	**0.001***
TSH (mIU/L)	Mild	0.01 (0.01-2.42)	1.64 (0.01-15.67)	**0.001***
	Moderate	0.01 (0.01-0.03)	1.43 (0.01-10.6)	**0.001***
	Severe	0.1 (0.01-1)	0.68 (0.01-46)	**0.001***
TSI (IU/L)	Mild	3.55 (0.56-40)	2.21 (0.1-40)	**0.001***
	Moderate	2.45 (0.8-33.3)	1.18 (0.1-40)	**0.002***
	Severe	13.45 (1.09-40)	2.42 (0.23-40)	**0.001***

The patients with fT4 up to 1.5 times the upper limit of normal (fT4≤1.95) were included in the mild disease group.
The patients with fT4 1.5-2 times the upper limit of normal (fT4 1.96-2.6) were included in the moderate disease group.
The patients with fT4 more than 2 times the upper limit of normal (fT4 >2.6) were included in the severe disease group.
* Wilcoxon Signed Ranks ** Paired samples T test

When the baseline and 6th month post-treatment values were examined in all patients; a very weak positive correlation (p=0.012, r=0.197), (p=0.003, r=0.234) was found between TSI and monocytes/MLR and a weak positive correlation (p=0.001, r=0.372) was found between TSI and RDW/fT3 in the severe disease group (p=0.019, r=0.303; p=0.002, r=0.403, respectively). No statistically significant correlation was found between TSI and other parameters in the mild and moderate disease group (**Table 3**).

Table 3. The correlation between statistically significant parameters detected in hemogram and TSI

	Mild disease (n=81)	**Moderate disease (n=22)**	**Severe disease (n=59)**	**All patients (n=162)**
Hemoglobin (gr/dL)			p: 0.999 r: 0.001	p: 0.145 r: -0.115
Leukocytes (10^3/uL)	p:0.780 r:-0.32		p: 0.776 r: -0. 38	p: 0.753 r: 0.025
Neutrophils (10^3/uL)	p:0.972 r:-0.004			p: 0.437 r: 0.061
Lymphocytes (10^3/uL)			p: 0.706 r: 0.050	p: 0.291 r: -0.083
Monocytes (10^3/uL)			p: 0.941 r: -0.10	**p: 0.012** **r: 0.197**
Eosinophils (10^3/uL)			p: 0.279 r: 0.143	p: 0.766 r: -0.024
Basophils (10^3/uL)	p:0.409 r:-0.093	p: 0.358 r: -0.206	p: 0.539 r: 0.082	p: 0.216 r: -0.098
Platelets (10^3/uL)	p: 0.806 r: 0.028			p: 0.868 r: -0.013
RDW (%)			**p: 0.019** **r: 0.303**	
MPV (fL)		p: 0.728 r: -0. 79		
TLR	p:0.799 r:0.029		p: 0.218 r: 0.163	p: 0.453 r: 0.059
MLR			p: 0.949 r: 0.009	**p: 0.003** **r: 0.234**
fT3 (ng/L)	p:0.167 r:0.156	p: 0.784 r: 0.064	**p: 0.002** **r: 0.403**	**p: 0.001** **r: 0.364**
TSH (mIU/L)	p:0.239 r:-0.132	p: 0.128 r:-0.335	p: 0.618 r: -0.066	p: 0.457 r:- 0.059
PIV			p:0.618 r:0.066	
Spearman correlation test				

3.2 Discussion

Various studies have shown that hyperthyroidism affects the hematopoietic system. In a study by Aggarwal et al. involving 206 hyperthyroid patients, neutropenia was detected in 14% and thrombocytopenia in 4.3% of cases. In another study on hyperthyroid patients, 18% had neutropenia accompanied by lymphocytosis and eosinophilia, and 34% had anemia [10,11]. In our study, anemia was detected in 19.13% of the patients, thrombocytopenia in 3.08%, thrombocytosis in 1.8%, and leukocyte count changes (leukocytosis 6.7%, leukopenia 1.2%) in 7.9%. Although the pathogenesis is not fully understood, the most likely causes are humoral and cellular mechanisms. Excess thyroid hormones are thought to have a direct toxic effect on hematopoietic system maturation and differentiation [12]. Experimental molecular studies have also provided evidence that abnormal T3 levels in hypothyroidism and hyperthyroidism affect hematopoietic cell series and induce apoptosis [13].

Parameters obtained from complete blood counts, such as NLR, TLR, MLR, SII index, and PIV, have been suggested to predict prognosis, mortality, and disease activation in various conditions such as diabetes mellitus, hypertension, rheumatic diseases, and malignancy [14]. In a study by Cindoglu et al. on 103 patients with Graves' disease, hemogram parameters at diagnosis were compared with those after 3–6 months of antithyroid treatment. Significant increases in leukocyte, neutrophil, lymphocyte, and NLR values were detected after treatment compared to baseline [1]. Similarly, a study by Peng et al. on patients with GD (n=39) reported an increase in neutrophil levels after treatment, consistent with other studies [1,15,16]. Another study involving 120 GD patients compared values at diagnosis and after achieving euthyroidism with treatment, finding increases in hemoglobin, neutrophil, and lymphocyte levels [17]. In our study, significant increases in leukocyte, neutrophil, and lymphocyte levels were observed after antithyroid treatment (p=0.001, p=0.002, p=0.001, respectively). The cause of this increase is thought to be a disruption

in the maturation process of pluripotent stem cells due to autoimmune system activation and the bone marrow suppression caused by hyperthyroidism, which is alleviated with antithyroid treatment. Both neutrophil and lymphocyte counts showed a significant increase with antithyroid therapy; however, this increase was not found to cause a significant change in the neutrophil-to-lymphocyte ratio (NLR).

Significant increases in hemoglobin, eosinophil, and basophil levels were also observed after antithyroid treatment compared to baseline (p=0.009, p=0.033, p=0.001, respectively). This supports the reduction in bone marrow suppression with antithyroid treatment in hyperthyroidism. In a study by Turan et al. comparing 37 pre-treatment and 49 post-treatment patients with euthyroid GD, platelet counts were significantly lower in the post-treatment euthyroid group [16]. In another study on patients with GD comparing baseline and 3–6 months' post-treatment values, no significant changes in platelet counts were observed. Although a decrease in TLR was noted after treatment, it was not statistically significant [1]. In our study, significant decreases in TLR and platelet counts were observed after antithyroid treatment compared to baseline (p=0.001, p=0.010, respectively). This decrease is thought to occur due to the suppression of inflammation and mediators involved in the megakaryopoiesis by antithyroid treatment.

The volume of circulating platelets increases in inflammation, leading to an early rise in MPV, which later decreases as platelets migrate to and degrade in the inflammation site [18]. In a study by Lippi et al. on approximately 1000 healthy individuals, a positive correlation between MPV and TSH was found [19]. Similarly, a meta-analysis by Cao et al. evaluating MPV levels in autoimmune thyroid diseases found significantly higher MPV levels in GD patients compared to control patients [20]. In our study, a statistically significant increase in MPV was observed only in the moderate disease group after treatment (p=0.008). This may be related to non-linear changes in MPV based on the duration of inflammation.

MLR, an inflammatory parameter obtained by dividing monocyte count by lymphocyte count, has been studied for its role in systemic inflammatory responses in conditions like diabetes mellitus, cardiovascular diseases, and malignancy [21]. In a retrospective study by Li et al. on approximately 1500 nasopharyngeal cancer patients, a lower pre-treatment MLR value was associated with disease-free survival and was suggested to predict prognosis [22]. In a study by Gokce et al. on 120 GH patients, MLR values significantly decreased after treatment compared to baseline [17]. In our study, significant decreases in monocyte count and MLR values were observed post-treatment compared to baseline (p=0.003, p=0.001, respectively). A weak positive correlation between TSI and monocyte/MLR values was also detected (p=0.012, r=0.197; p=0.003, r=0.234). Monocyte and MLR values may provide insights into disease activation in centers where TSI cannot be measured.

RDW, reflecting the variability in erythrocyte size, significantly increased six weeks after treatment compared to baseline in a study by Dorota et al. involving patients with 59 GD [23]. In another study comparing patients with 50 GD with 50 healthy control patients, RDW was significantly lower in patients with GD [24]. Unlike other inflammatory diseases, changes in RDW may be attributed to reduced erythrocyte lifespan and defects in erythropoiesis due to thyrotoxicosis. In our study, RDW significantly increased after antithyroid treatment in the severe disease group compared to baseline (p=0.002). A weak positive correlation between TSI and RDW was found in the severe disease group (p=0.019, r=0.303). RDW may be thought to indicate inflammation and disease activation in the severe disease group compared to mild and moderate groups.

The SII index, calculated as neutrophil-to-lymphocyte ratio multiplied by platelet count, and PIV, calculated as the product of monocyte count and platelet count, are considered more reliable in determining disease prognosis than other inflammatory markers (NLR, TLR, MLR) due to their inclusion of more parameters [25,26]. However, no studies have examined the relationship between SII index, PIV, and Graves' disease so far. In our study, PIV significantly decreased after six months of antithyroid treatment in the severe disease group compared to baseline (p=0.031). PIV may be a suitable marker for monitoring patients with high disease activity. No significant changes in the SII index were observed (p=0.684), as both neutrophil and lymphocyte counts increased proportionally with treatment.

Several limitations of our study can be mentioned. Firstly, as this is a cross-sectional study, only the laboratory parameters at the baseline and the sixth month of treatment were analyzed. A study with longer-term data could yield statistically more significant results. Additionally, while longer use of antithyroid treatment is recommended for remission in Graves' disease, our study evaluated data at the time of diagnosis and after six months of antithyroid treatment. Therefore, the results may have been influenced by evaluations conducted before the disease entered remission. Another limitation is the uneven distribution of patients across the severity-based disease groups.

In light of all these findings, when comparing inflammatory parameters derived from hemograms at the time of diagnosis and after six months of antithyroid therapy in Graves' disease, statistically significant increases were observed in hemoglobin, leukocytes, neutrophils, lymphocytes, eosinophils,

basophils, and TSH values. Conversely, statistically significant decreases were found in monocytes, platelets, TLR, MLR, fT3, and fT4 levels. Correlations of these statistically significant parameters with TSI were examined. A very weak positive correlation was identified between TSI and monocytes/MLR, while a weak positive correlation was found between TSI and fT3. In the severe disease group, weak positive correlations were observed between TSI and RDW/fT3.

4. Conclusion

In the conclusion of our study, although no reliable marker was identified as an alternative to TSI in follow-up of Graves' disease, monocyte, MLR, and RDW in severe disease cases are thought to provide insights into disease activation. However, further multicenter, long-term studies with larger patient populations are needed to confirm these findings.

5. Acknowledgements

None declared.

6. References

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