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Original Article

Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio in the Patients with Euthyroid Hashimoto's Thyroiditis

Ötiroid Hashimoto Tiroiditi Hastalarında Nötrofil-lenfosit Oranı ve Trombosit-lenfosit Oranının Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to compare the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values in patients with euthyroid Hashimoto's thyroiditis (HT) with healthy control subjects.

Methods: This was a single-center, retrospective, cross-sectional study conducted on obese patients aged 18 years and over. The medical records of patients who presented with complaints of being overweight at the obesity clinic between April 2017 and May 2019 were examined. Patients and healthy individuals were included in the study consecutively until the sample sizes reached saturation. Patients with diabetes, cardiovascular disease, chronic inflammatory disease, and malignancy were excluded from the study. The patients' anthropometric measurements, smoking status, blood examination, and thyroid ultrasounds were evaluated. The difference in means between the groups was calculated using the Mann-Whitney U test.

Results: The study included 179 participants, consisting of 93 patients and 86 healthy controls. The mean age was 46.6±14.1 years, with most females (91.6%). Although the NLR and PLR values in patients were higher than those in the control group, the difference did not reach statistical significance (p=0.427 and p=0.089, respectively). Furthermore, no significant difference was observed in NLR (p=0.191) and PLR (p=0.668) values between levothyroxine-treated and untreated patients. Correlation analysis revealed weak positive associations between C-reactive protein and thyroid peroxidase antibodies (p<0.05), neutrophils (p<0.01), platelets (p<0.01), and NLR (p<0.05).

Conclusions: The findings of this study suggest that NLR and PLR may not serve as effective indicators of systemic inflammation in patients with euthyroid HT, nor do they adequately assess the impact of levothyroxine usage on systemic inflammation.

Keywords: Hematological indices, systemic inflammation, hypothyroidism

ÖZ

Amaç: Bu çalışmanın amacı, ötiroid Hashimoto tiroiditi (HT) hastalarında nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (PLO) değerlerinin sağlıklı kontrol grubuyla karşılaştırılmasıdır.

Yöntemler: Bu tek merkezli, retrospektif, kesitsel çalışma 18 yaş ve üzeri obez hastalar ile gerçekleştirildi. Nisan 2017 ile Mayıs 2019 tarihleri arasında obezite kliniğine kilo fazlalığı şikayeti ile başvuran hastaların tıbbi kayıtları tarandı. Örneklem boyutları doygunluğa ulaşana kadar ötiroid HT ve kontrol grubundan kişiler ardışık olarak çalışmaya dahil edilmeye devam edildi. Diyabet, koroner arter hastalığı, kronik enflamatuvar hastalığı ve malignite öyküsü olan hastalar çalışmaya alınmadı. Hastaların yaş, cinsiyet, boy, kilo, sigara içme durumu, laboratuvar ve tiroid ultrasonografi sonuçları değerlendirildi. Değişkenlerin ortalamalarının gruplar arasındaki farklılığı, Mann-Whitney U testi kullanılarak hesaplandı.

Bulgular: Çalışmaya, 93 ötiroid HT ve 86 sağlıklı kontrol olmak üzere toplam 179 kişi dahil edildi. Ortalama yaş 46,6±14,1 yıl olarak bulundu ve kadınlar çoğunluktaydı (%91,6). HT olan hastalarda NLO ve PLO değeri kontrol grubuna göre daha yüksek olsa da iki grup arasındaki fark istatistiksel anlama ulaşmadı (sırası ile p=0,427, p=0,089). Ayrıca, levotiroksin tedavisi alan ve almayan hastalar arasında da NLO (p=0,191) ve PLO (p=0,668) değerlerinde anlamlı bir fark gözlenmedi. Korelasyon analizi, C-reaktif protein ile tiroid peroksidaz antikorlar (p<0,05), nötrofiller (p<0,01), trombositler (p<0,01) ve NLO (p<0,05) arasında zayıf pozitif ilişkileri ortaya çıkardı.

Sonuçlar: Çalışmanın bulguları, NLO ve PLO'nun ötiroid HT hastalarında sistemik enflamasyonun etkili göstergeleri olmadığını ve levotiroksin kullanımının sistemik enflamasyon üzerindeki etkisini yeterince değerlendiremediklerini düşündürmektedir.

Anahtar kelimeler: Hematolojik indeksler, sistemik enflamasyon, hipotiroidi

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INTRODUCTION

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease characterized by elevated levels of thyroid autoantibodies and distinct sonographic features. The incidence of HT is estimated to be between 0.3 and 1.5 cases per 1000 individual, with a female to male predominance of 7-10 to 1[1,2].

The gradual onset of hypothyroidism in HT occurs because of the atrophy of the thyroid parenchyma caused by autoimmune processes in lymphoid follicles. HT may cause systemic inflammation at the cellular level in the body[3]. Recent studies indicate that the inflammation associated with HT may not be confined to the thyroid gland, even in patients with normal thyroid function[4-6].

Markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count are commonly used to indicate the level of systemic inflammation. Recently, studies have been conducted on the use of hematological indices as indicators of inflammation. The monocyte-to-lymphocyte ratio, monocyte-to-high-density lipoprotein ratio, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are used for this purpose[7-11]. Among them, NLR and PLR have been widely recognized as indicators of systemic inflammatory response because of their easy availability, affordable cost, and ability to be calculated from complete blood counts. There are conflicting results in studies examining the usefulness of these hematological indices as indicators of systemic inflammation in patients with euthyroid HT. This study aims to compare NLR and PLR values in patients with euthyroid HT treated with levothyroxine or those who are untreated with healthy control subjects.

MATERIALS and METHODS

Study Population

This was a single-center, retrospective, cross-sectional study conducted in accordance with the principles of the Helsinki Declaration. This study was approved by the Clinical Research Ethics Committee of the Istanbul Medeniyet University Goztepe Training and Research Hospital on November 18, 2020 (decision no: 2020/0665).

The medical records of patients aged 18 years who presented with complaints of overweight at the obesity clinic between April 2017 and May 2019 were screened to identify those diagnosed with HT. Patients with a history of diabetes, cardiovascular disease, chronic inflammatory disease, chronic kidney disease, malignancy, or those who were pregnant or breastfeeding were excluded from the study. Euthyroid HT patients were consecutively included in the study until the sample size reached saturation. In addition, healthy individuals who presented to the same obesity clinic with similar complaints during the same period were recruited as the control group. Furthermore, the HT patients were divided into subgroups of patients receiving levothyroxine treatment and those not receiving any treatment.

Clinical Assessment

The records of patients in the obesity clinic and hospital electronic information system (Nucleus®) were examined to collect data on patients' age, gender, height, body weight, smoking status, levothyroxine treatment status, and full blood count, biochemical test results, and thyroid ultrasounds.

Height and weight measurements were taken using a height scale and weight machine (SECA 799+220, SECA GmbH & co, Germany), and the body mass index (BMI) was calculated using the weight in kilograms divided by the height in meters squared.

Complete blood counts were performed using venous blood samples on a Mindray BC-6800 (Mindray BioMedical Electronics Co., Ltd., Shenzhen, China) device. Thyroid function tests and autoantibodies were analyzed on the Roche Cobas e801 (Roche Diagnostics, Basel, Switzerland) module, whereas CRP was analyzed on the c702 module of the same brand. ESR was measured using an Alifax TEST 1 (Alifax SpA, Polverara, Italy) device. Thyroid ultrasound was performed using the Toshiba Aplio 500 device (Toshiba Medical Systems, Tokyo, Japan). NLR and PLR were calculated using the neutrophil count divided by the lymphocyte count and the platelet count divided by the lymphocyte count, respectively.

Statistical Analysis

Descriptive statistics of the characteristics measured in the study participants were tabulated as mean, standard deviation, quartiles (25^{th}, median, 75^{th}), and number and percentage frequencies. The compatibility of the numerical characteristics with the normal distribution was examined using the Kolmogorov-Smirnov test.

When the assumptions for parametric tests were met, an independent samples t-test was conducted, and when the assumptions were not met, a Mann-Whitney U test was performed to compare the means between the two groups. Pearson's chi-square test and, when necessary, Yates correction were used to analyze categorical variables. The relationship between continuous variables

was examined using the Pearson correlation test. Data were analyzed using IBM SPSS Statistics 18 ©Copyright SPSS Inc. 1989, 2010 software. The level of statistical significance was set at 0.05

RESULTS

A total of 179 participants were included in the study, of whom 93 (52%) were patients and 86 (48%) were controls. Of the participants, 15 (8.4%) were male and 164 (91.6%) were female, with a mean age of 46.63±14.09 years and a mean BMI of 34.24±2.59 kg/m^2. The percentage of patients who smoked was 26.8%.

Table 1 shows the clinical and laboratory characteristics of the patients and healthy participants. The two groups had similar gender distribution and mean age (p=0.075 and p=0.295, respectively). In the patient group, thyroid stimulating hormone (TSH) (p=0.001), thyroid peroxidase antibodies (anti-TPO), and anti-thyroglobulin antibodies (anti-TG) values were higher (both p<0.001), and lymphocyte levels were lower (p=0.048). No significant relationship was found between other laboratory values and the study groups.

Of the 93 patients in the study group, 39 (42%) were receiving LT4 treatment, whereas 54 (58%) were not. It was observed that patients receiving LT4 treatment had higher levels of free thyroxine (sT4) (p<0.001) and platelets (p=0.016), whereas their anti-TG values were lower (p=0.037). No significant differences were found in the other laboratory values (Table 2).

Correlation analysis was performed between CRP, ESR, NLR, and PLR and other laboratory parameters, and the findings are presented in Table 3. A weak positive association was detected between CRP and anti-TPO values (r=0.168; p<0.05), neutrophils (r=0.277; p<0.01), platelets (r=0.287; p<0.01), and NLO (r=0.186; p<0.05), while a moderate positive correlation was observed between CRP and ESR (r=0.327; p<0.01).

A weak positive association was found between ESR and platelet count (r=-0.281; p<0.01), and between PLR (r=-0.148; p<0.05), whereas a moderate positive association was found between NLR and PLR (r=0.496; p<0.01).

DISCUSSION

In our study, although NLR and PLR values in patients with HT were higher than those in the control group, the difference between the two groups was not statistically significant. Patients treated with LT4 had significantly higher sT4 levels and significantly lower anti-TG antibody levels than the untreated euthyroid group. A significant correlation was observed in the same direction between CRP and anti-TPO and NLR, ESR and PLR, and NLR and PLR.

An increase in circulating neutrophil and platelet counts and a decrease in lymphocyte count serve as markers of inflammatory diseases. Thus, NLR and PLR parameters have been investigated in many studies as indicators of systemic inflammation and prognostic factors

Table 1. Comparison of the clinical and laboratory characteristics of the control and patient groups.

Variables	n1/n2	Control	Patients	p-value
Age, mean ± SD	86/93	45.47±15.93	47.68±12.11	0.295
BMI (kg/m^2),	86/93	34 (32-36)	34 (33-36)	0.267
Smoker (n), (%)	86/93	23 (26.7)	25 (26.9)	0.983
TSH	86/93	1.48 (1.14-2.25)	2.24 (1.25-3.1)	**0.001**
sT4, mean ± SD	86/93	0.95±0.009	0.96±0.13	0.300
Anti-TPO	86/93	0.5 (0.5-0.58)	204.7 (73.42-559.87)	**<0.001**
Anti-TG	86/93	1.09 (0.85-1.41)	24.19 (7.33-99.93)	**<0.001**
Neutrophil	86/93	4.5 (3.8-5.2)	4.4 (3.5-5)	0.336
Thrombocyte	86/93	263.5 (232-333)	270 (236-309)	0.952
Lymphocyte	86/93	2.55 (2.18-3.12)	2.4 (2.04-2.81)	**0.048**
NLR	86/93	1.73 (1.37-2.06)	1.76 (1.42-2.13)	0.427
PLR	86/93	107.47 (86.8-130.25)	113.82 (93.09-144.5)	0.089
CRP	85/93	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.195
ESR	85/93	13 (8-25)	15 (8-22)	0.509

SD: Standard deviation, BMI: Body mass index, TSH: Thyroid stimulating hormone, sT4: Free thyroxine, Anti-TPO: Thyroid peroxidase antibodies, Anti-TG: Anti-thyroglobulin antibodies, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Results are shown as median and interquartile range scores unless otherwise stated

in cardiovascular diseases, infections, inflammatory diseases, and various types of cancer[12-15].

Thyroid pathologies have also been evaluated on the basis of these parameters in recent years. In a study, Cengiz et al.[16] showed that patients with subacute thyroiditis exhibited high NLR and PLR values during the active phase of the disease, which subsequently normalized with recovery. These values were positively associated with the commonly used acute phase reactants.

Studies support the development of systemic inflammation in patients with HT, even in the absence of hypothyroidism[17,18]. Keskin et al.[19] compared euthyroid HT patients who did not receive replacement therapy with healthy controls and found that NLR and PLR were higher and lymphocyte counts were lower in HT patients. They also reported a positive correlation between NLR and PLR[19]. In a study conducted with children and adolescents with euthyroid HT, it was shown that there was no difference in NLR compared with healthy controls, but PLR was increased[20]. In another study conducted with euthyroid adult patients, NLR and PLR were found to be higher and lymphocyte count was lower in the HT group than in the healthy control group[21].

However, there are also studies in the literature that do not find a relationship between NLR, PLR levels

Table 2. Comparison of laboratory results of patients with Hashimoto's thyroiditis treated with and without levothyroxine.

Variables	Patients without treatment (n=54)	Patients receiving levothyroxine treatment (n=39)	p-value
TSH, mean ± SD	2.33±1.06	2.16±1.1	0.460
sT4, mean ± SD	0.91±0.1	1.04±0.13	**<0.001**
Anti-TPO	161.47 (54.25-416.15)	267.91 (106.5-837.86)	0.085
Anti-TG	31.57 (13.04-142.77)	17.45 (5.44-44.25)	**0.037**
Neutrophil	4.5 (3.4-5.4)	4.2 (3.5-5)	0.580
Thrombocyte	254.5 (227-304)	290 (263-311)	**0.016**
Lymphocyte, mean ± SD	2.36±0.58	2.57±0.67	0.116
NLR	1.84 (1.42-2.29)	1.71 (1.36-1.99)	0.191
PLR	108.53 (92.12-144.5)	115.35 (93.54-144.62)	0.668
CRP	0.3 (0.1-0.5)	0.2 (0.1-0.5)	0.771
ESR	14 (7-20)	16 (10-26)	0.156

SD: Standard deviation, BMI: Body mass index, TSH: Thyroid stimulating hormone, sT4: Free thyroxine, Anti-TPO: Thyroid peroxidase antibodies, Anti-TG: Anti-thyroglobulin antibodies, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Results are shown as median and interquartile range (IQR) scores unless otherwise stated

Table 3. Correlation analysis of the laboratory results of all participants.

Pearson's correlation (r)	CRP	ESR	NLR	PLR
TSH	-0.055	-0.064	-0.105	-0.052
sT4	-0.088	-0.52	-0.125	-0.041
Anti-TPO	0.168*	0.062	0.020	0.122
Anti-TG	-0.118	-0.053	0.031	0.039
Neutrophil	0.277**	0.112	0.640**	-0.030
Thrombocyte	0.287**	0.281**	0.010	0.530**
Lymphocyte	0.042	0.019	-0.515**	-0.671**
NLR	0.186*	0.077	1	0.496**
PLR	0.134	0.148*	0.496**	1
CRP	1	0.327**	0.186*	0.134
ESR	0.327**	1	0.077	0.148*

SD: Standard deviation, BMI: Body mass index, TSH: Thyroid stimulating hormone, sT4: Free thyroxine, Anti-TPO: Thyroid peroxidase antibodies, Anti-TG: Anti-thyroglobulin antibodies, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

*p<0.05, **p<0.01

and thyroid disease. In their study comparing overt and subclinical hypothyroidism groups with a control group, Günes et al.[22] found NLR to be similar in all groups. In concordance with our study findings, Pekgör et al.[23] reported that NLR and PLR levels were similar in patients with hypothyroidism and healthy controls, and they also found a positive association between these two markers. Although the patient group showed higher values of NLR and PLR in our study, the difference did not reach statistical significance. One possible reason for this outcome could be that the number of patients was relatively low. Another reason could be the unequal distribution of confounders that could affect the level of inflammation between the patient and control groups. Specifically, despite excluding individuals with diabetes mellitus, cardiovascular disease, chronic inflammatory diseases, and malignancies, both the patient and control groups included individuals with obesity who were not evaluated for prediabetes, which is known to be associated with inflammation. It is plausible that patients with euthyroid HT received regular follow-up from endocrinology clinics, whereas healthy participants did not. Therefore, the control group may have had a higher proportion of individuals with prediabetes.

Studies have shown that levothyroxine replacement therapy in patients with hypothyroidism reduces oxidative stress and systemic inflammation by decreasing proinflammatory cytokines and increasing anti-inflammatory cytokines[24,25].

In their study on patients with euthyroid HT, Bilge et al.[21] found that in the levothyroxine treatment group, despite having higher TSH values, they had lower levels of NLR and PLR compared with those not receiving treatment. In contrast to this study, Elmaoğullari et al.[20] did not find a significant difference in the NLR and PLR associated with levothyroxine use in their study on children and adolescents with euthyroid HT. Similarly, we did not find a significant difference in NLR and PLR between patients receiving levothyroxine replacement therapy and those not receiving therapy. Our findings suggest that NLR and PLR parameters may not be an effective method for evaluating the effect of levothyroxine use on systemic inflammation.

The exclusion of chronic diseases that could cause inflammation and the division of the patient group into subgroups based on treatment status are the strengths of our study. However, the retrospective design of the study, single-center experience, relatively small study group consisting entirely of obese individuals, lack of evaluation of prediabetes status and lipid levels, and unknown disease onset durations are limitations of our study.

CONCLUSION

In conclusion, while NLR and PLR may exhibit good correlation with other inflammation markers, they may not be reliable markers of systemic inflammation in individuals with euthyroid HT. In addition, they do not sufficiently evaluate the effects of levothyroxine treatment on systemic inflammation. To support the findings of this study, more comprehensive and prospective research is required.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the Istanbul Medeniyet University Goztepe Training and Research Hospital on November 18, 2020 (decision no: 2020/0665).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: H.N.R., Concept: M.T., Design: H.N.R., M.T., Data Collection and/or Processing: H.N.R., M.T., Analysis and/or Interpretation: H.N.R., C.T., Literature Search: H.N.R., C.T., Writing: H.N.R., C.T.

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

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