



Evaluation of Monocyte/HDL and Neutrophil/Lymphocyte Ratios in Patients with Hashimoto's Thyroiditis

Hashimoto Tiroiditi Hastalarında Monosit/HDL ve Nötrofil/Lenfosit Oranlarının Değerlendirilmesi

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ABSTRACT

Aim: Systemic inflammation related to Hashimoto's thyroiditis (HT) is thought to increase oxidative stress, endothelial dysfunction, and the risk of cardiovascular diseases. In this study, we aimed to indirectly evaluate this risk increase through easily measurable and cost-effective parameters such as the neutrophil/lymphocyte ratio (NLR) and monocyte/high-density lipoprotein ratio (MHR).

Materials and Methods: In this retrospective study, the laboratory data of patients aged between 18 and 80 who were diagnosed with hypothyroidism were reviewed. A total of 325 individuals who met the inclusion criteria were included in the study. Of these, 203 were diagnosed with HT and were divided into two subgroups: overt hypothyroidism (OH) and subclinical hypothyroidism (SH). These data were compared with those of 122 individuals in the healthy control group (CG).

Results: The mean age of the control and patient groups was similar. In the evaluation of inflammatory parameters, no significant differences were observed in C-reactive protein and sedimentation values between OH, SH, and the healthy CG. There were no statistically significant differences in terms of NLR and MHR between OH, SH, and CG (p: 0.507, p: 0.064, respectively). Additionally, no correlation was found between autoantibodies and NLR or MHR parameters in the OH, SH, and CG groups.

Conclusion: Parameters such as NLR and MHR could serve as practical tools in assessing oxidative stress, endothelial dysfunction, and cardiovascular disease risk in autoimmune and chronic inflammatory diseases like HT. However, further large-scale studies are needed to validate the clinical applicability of these parameters.

Keywords: Hashimoto's thyroiditis, neutrophil/lymphocyte ratio, monocyte/HDL ratio

ÖZ

Amaç: Hashimoto tiroiditi (HT) ile ilişkilendirilen sistemik enflamasyon artışının; oksidatif stres, endotel disfonksiyonu ve kardiyovasküler hastalık riskini artırdığı düşünülmektedir. Bu çalışmada, HT hastalarında risk artışını indirekt olarak değerlendirebilmek için, nötrofil/lenfosit oranı (NLR) ve monosit/yüksek yoğunluklu lipoprotein oranı (MHR) gibi kolay ve ucuz ölçülen parametreler incelenmiştir.

Gereç ve Yöntem: Bu retrospektif çalışmada HT tanısı almış 18-80 yaş aralığındaki hastaların laboratuvar verileri incelenmiştir. Çalışmaya alınma kriterlerine uyan toplam 325 kişi çalışmaya dahil edilmiştir. Dahil edilen bireylerin 203'ü HT hastası olup; aşikar hipotiroidi (AH) ve subklinik hipotiroidi (SH) olmak üzere iki alt gruba ayrılmıştır, bu veriler sağlıklı kontrol grubu (KG) olan 122 birey ile kıyaslanmıştır.

Bulgular: Kontrol ve hasta gruplarının yaş ortalaması benzerdi. Enflamasyon parametreleri açısından yapılan değerlendirmede AH, SH ve KG arasında C-reaktif protein ve sedim değerleri açısından benzerlik gözlemlenmiştir. AH, SH ve KG arasında NLR ve MHR parametreleri bakımından istatistiksel olarak anlamlı bir fark bulunmamıştır (sırasıyla p: 0,507, p: 0,064). Ayrıca, AH, SH ve KG de otoantikörler ile NLR ve MHR parametreleri arasında herhangi bir ilişki saptanmamıştır.

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Sonuç: NLR ve MHR gibi parametreler, HT gibi diğer otoimmün ve kronik enflamatuvar hastalıklarda oksidatif stres artışı, endotel disfonksiyonu ve kardiyovasküler hastalık riskini belirlemede pratik birer parametre olabilir. Bununla birlikte, bu parametrelerin klinik kullanımıyla ilgili daha geniş ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Hashimato tiroiditi, nötrofil/lenfosit oranı, monosit/HDL oranı

INTRODUCTION

Hashimoto's thyroiditis (HT) is the most common chronic autoimmune disease of the thyroid gland, first described by Hakaru Hashimoto in 1912 as "struma lymphomatosa¹." Patients with HT are often asymptomatic but may present with euthyroid, subclinical hypothyroidism (SH), overt hypothyroidism (OH), and rarely hyperthyroidism clinical manifestations². If the diagnosis of SH is missed, the condition may progress to OH, leading to complications such as dyslipidemia, endothelial dysfunction, coronary artery disease, heart failure, and metabolic syndrome³.

Elevated total cholesterol and low-density lipoprotein (LDL) levels are prone to oxidation and, under the effect of reactive oxygen species, accelerate lipid peroxidation. This process leads to increased oxidative stress, endothelial dysfunction, and increased peripheral resistance. The combination of arterial hypertension due to increased peripheral resistance and elevated cholesterol levels in thyroid hormone deficiency poses a significant risk for atherosclerotic cardiovascular disease (CVD) and cerebrovascular disease. Additionally, bradycardia and reduced ventricular contractility result in decreased cardiac output, predisposing to heart failure⁴.

Recently, low-cost and easily measurable parameters such as neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-high-density lipoprotein ratio (MHR) have gained popularity in assessing systemic inflammatory response⁵. Previous studies have indicated that NLR may serve as an independent predictor of CVD and mortality in acute heart failure⁶. Additionally, research suggests that NLR can be used as a marker of subclinical inflammation in non-cardiac conditions. For example, NLR has been reported as a helpful parameter in determining prognosis and guiding treatment decisions in cancer patients⁷. The association between NLR and rheumatologic diseases such as systemic lupus erythematosus and familial Mediterranean fever has also been investigated, revealing a significant correlation between NLR and disease prognosis⁸. Similarly, MHR has been found to be associated with various diseases including Parkinson's disease, hypertension, obstructive sleep apnea syndrome, ulcerative colitis, and vitiligo. In these conditions, increases in these parameters have been observed alongside elevated mortality⁹.

In HT, the development of hypothyroidism alongside increased systemic inflammation constitutes a significant risk factor for endothelial dysfunction and atherosclerotic processes¹⁰. While

previous studies have investigated the relationship between HT and NLR, no studies have, to our knowledge, examined the association between HT and MHR. In this study, we aimed to evaluate oxidative stress in patients with OH and SH due to HT by assessing NLR and MHR parameters.

MATERIALS AND METHODS

Data and Sources

This retrospective study reviewed data from patients diagnosed with hypertension based on ICD code screening via the hospital automation system, who visited the Internal Medicine Outpatient Clinics at Tekirdağ Namık Kemal University Hospital between January 1, 2020, and February 10, 2023. Approval for this study was obtained from the Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine, with the (protocol number: 2023.28.02.16, date: 28.02.2023). This article is derived from a thesis completed in 2024, registered under number 906166.

Patient Selection

Individuals under the age of 18 or over the age of 80, as well as those with CVD, pregnant women, individuals with active infections or chronic illnesses, those with autoimmune or rheumatologic diseases, and patients with immunosuppressive conditions who were using steroids were excluded from the study.

Laboratory Diagnostic Criteria

The diagnosis of HT was established based on anti-thyroid peroxidase (TPO) levels above 34 IU/mL and Anti-Tg levels above 115 IU/mL. Patients diagnosed with HT were divided into two groups according to their thyroid hormone levels: OH and SH. In the OH group, patients had a TSH level above 4.20 mIU/L, a free triiodothyronine (T3) level below 2.0 pg/mL, and a free thyroxine (T4) level below 0.93 ng/dL. In the SH group, patients had a TSH level above 4.20 mIU/L, a free T3 level between 2.0-4.4 pg/mL, and a free T4 level between 0.93-1.7 ng/dL.

Distribution of Groups

OH group included 99 patients, while the SH group consisted of 104 patients. As the control group (CG), 122 healthy individuals with normal levels of anti-TPO, anti-Tg, TSH, free T4, and free T3 were included in the study. No euthyroid or hyperthyroid individuals were identified among the HT patients.

Laboratory Methods

Laboratory results for all participants, including TSH, T3, T4, C-reactive protein (CRP), sedimentation rate, anti-TPO, anti-Tg, NLR, MHR, cholesterol, triglycerides, HDL, and LDL, were recorded. NLR and MHR were calculated as the ratios of neutrophils to lymphocytes and monocytes to HDL, respectively. The obtained results were compared among the OH, SH, and CG.

Thyroid function tests and autoantibody measurements were performed using the electrochemiluminescence immunoassay method on Roche COBAS 8000 analyzers. HDL cholesterol, total cholesterol, and triglycerides were also analyzed on the same device using spectrophotometric biochemical reactions. LDL cholesterol values were calculated manually using the Friedewald formula ($\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides} / 5$).

Statistical Analysis

Statistical analyses were performed using SPSS for Mac, version 26. The normality of the distribution of variables was assessed using both visual methods (histograms and probability plots) and analytical tests (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics for normally distributed variables were presented as means and standard deviations. For normally distributed numerical data, comparisons between independent groups were made using one-way ANOVA with Bonferroni post-hoc analysis. For non-normally distributed data, the Mann-Whitney U test and Kruskal-Wallis test (with Mann-Whitney U post hoc analysis) were used. Spearman's correlation analysis was performed for non-normally distributed variables. Nominal variables were presented using cross-tabulations, and group comparisons were made using the chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 99 individuals with OH, 104 with SH, and 122 healthy individuals in the CG were included in the study. Among the participants, 67 (20.6%) were male and 258 (79.4%) were female. The mean age of the patients was 50.5 ± 12.9 years in the OH group, 48.7 ± 12.6 years in the SH group, and 47.1 ± 14.7 years in the CG. No statistically significant difference in age was found between the groups ($p: 0.175$). When the patient and CG were evaluated in terms of gender, it was observed that female gender predominated in all groups, and this difference was statistically significant ($p: 0.001$) (Table 1).

Figures 1 and 2 present the distributions of NLR and MHR across the OH, SH, and CGs, respectively.

When the lipid profiles of the OH, SH, and CG groups were compared, total cholesterol and HDL levels were found to be

significantly higher in both the OH and SH groups compared to the CG ($p: 0.016$, $p: 0.011$, respectively). However, no statistically significant difference was found between the OH and SH groups in terms of these parameters. When triglyceride and LDL cholesterol levels were evaluated, no significant difference was observed between the OH, SH, and CG groups, and their values remained at similar levels ($p: 0.315$, $p: 0.234$, respectively).

In the comparison of the patient groups with OH and SH and CG in terms of the NLR parameter, no statistically significant difference was found between the groups ($p: 0.507$). Similarly, the MHR parameter showed similar results across these three groups ($p: 0.064$). Anti-TPO and anti-Tg levels were found to be higher in the OH and SH groups than in the CG ($p: 0.001$ and $p: 0.001$, respectively). However, no statistically significant difference was found between the OH and SH groups in terms of these parameters. In the SH group with HT, a significant correlation was observed between NLR and MHR (Table 2), whereas no significant correlation was detected in the OH group (Table 3) ($p: 0.018$ and $p: 0.719$, respectively). Furthermore, when the relationships between antibodies and NLR and MHR were examined, no significant correlation was found between NLR and MHR in either patient group.

DISCUSSION

Certain parameters obtained from routine blood tests can provide valuable insights into disease prognosis and inflammatory processes¹¹. This study aimed to evaluate the increased risk of CVD and cardiovascular and cerebrovascular disease which may result from enhanced oxidative stress and endothelial dysfunction associated with chronic inflammation in patients with HT, through the assessment of NLR and MHR parameters. By evaluating NLR and MHR together, the study sought to contribute to a better understanding of this pathophysiological process. When NLR and MHR parameters were compared among healthy control subjects and those in the OH and SH groups, no statistically significant differences were observed. However, a positive correlation between NLR and MHR ($p: 0.018$) was identified in the SH group, whereas no such correlation was found in the other groups. No significant correlation was found between thyroid autoantibodies and these parameters. Moreover, no significant correlation was observed between these parameters and other inflammatory markers such as erythrocyte sedimentation rate (ESR) and CRP. In the literature, parameters such as NLR and MHR have been reported to be associated with inflammatory diseases including cancer, lupus, psoriasis, and rheumatoid arthritis, and to be related to disease activity, inflammation severity, and prognosis. These findings indicate that inflammation plays an important role in various disease processes and suggest that these parameters may serve as potential biomarkers for

Table 1. Demographic and biochemical characteristics of the study participants

	Control group	Subclinical hypothyroidism	Overt hypothyroidism	p
Age (years)	47.1±14.7	48.7±12.6	50.5±12.9	0.175
Gender (female %)	74	92	92	0.001
TSH (mIU/L)	1.74±0.8	6.82±3.62	11.22±12.81	0.001
T3 (pg/mL)	3.10±0.48	2.84±0.47	2.49±0.51	0.001
T4 (ng/dL)	1.2±0.26	1.09±0.17	1.01±0.33	0.001
Anti-TPO (IU/dL)	11.04± 5.22	260.04±218.39	281.98±237.76	0.001
Anti-TG (IU/dL)	15.51±9.44	470.16±903.79	475.90±722.84	0.001
Cholesterol (mg/dL)	198.34± 46.61	214.2±45.17	212.17±44.28	0.016
HDL (mg/dL)	50.35±14.29	54.13±14.5	54.96±13.2	0.011
Triglyceride (mg/dL)	142.11±80.36	136.46±85.14	150.86±83.31	0.315
LDL (mg/dL)	122.11±60.36	116.08±44.93	135.46±43.31	0.234
Monocyte (10 ³ /uL)	0.48±0.18	0.45±0.15	0.48±0.21	0.274
MHR	10.53±5.17	8.95±4.25	9.34±5.83	0.064
Neutrophil (10 ³ /uL)	4.34±1.17	4.12±1.62	4.08±1.62	0.399
Lymphocyte (10 ³ /uL)	2.3±0.80	2.27±0.80	2.25±0.90	0.497
NLR	2.01±0.90	1.88±0.85	1.93±0.88	0.507
CRP (mg/L)	3.80±5.33	3.09±3.69	3.22±4.44	0.882
Sediment (mm/hour)	24.80±12.15	19.19±14.46	24.61±11.11	0.104

TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, Anti-TPO: Antithyroid peroxidase, Anti-TG: Anti-thyroglobulin, HDL: High-density lipoprotein, MHR: Monocyte-high-density lipoprotein ratio, NLR: Neutrophil-lymphocyte ratio, CRP:C-reactive protein

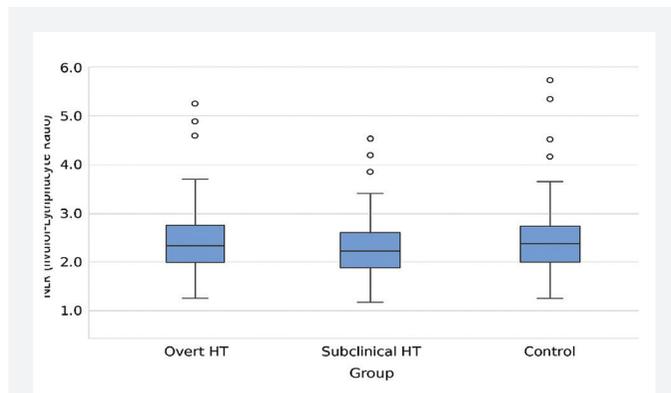


Figure 1. Representation of NLR between OH, SH and CG

NLR: Neutrophil-lymphocyte ratio, OH: Overt hypothyroidism, SH: Subclinical hypothyroidism, HT: Hashimoto’s hyroiditis, CG: Control group

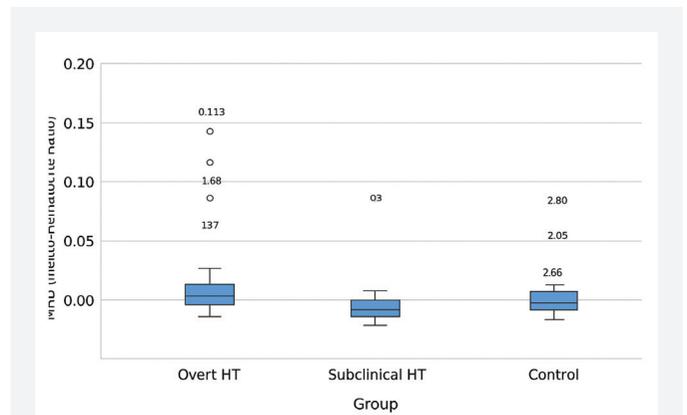


Figure 2: Representation of MHR between OH, SH and CG

MHR: Monocyte-high-density lipoprotein ratio, OH: Overt hypothyroidism, SH: Subclinical hypothyroidism, HT: Hashimoto’s thyroiditis, CG: Control group

clinical assessment^{7,8,12,13}. When previous studies examining the NLR parameter in HT patients are considered, Acay et al.¹⁴ and Aksu et al.¹⁵ reported, similar to our findings, that there was no statistically significant difference in NLR values between HT patients and CG (p: 0.23). Furthermore, consistent with our study, no significant relationship was found between autoantibodies and NLR1.

In contrast to our findings, Aktas et al.¹⁶ reported that NLR levels were higher in patients with HT. The researchers suggested that NLR may serve as an indicator of inflammation, particularly in cases of complicated hypertension. Similarly to our study, Güneş et al.¹⁷ divided HT patients into two groups as OH and SH.

Consistent with our findings, no statistically significant difference in NLR values was observed among the OH, SH, and CG. When reviewing previous studies, no research was found that specifically examined the relationship between MHR and disease status in patients with HT. Therefore, our study is among the first to investigate the association between the MHR parameter and HT. Examining studies that have explored the relationship between MHR and other diseases, Gembillo et al.¹⁸ investigated the role of MHR in patients with resistant hypertension and found that MHR levels were higher in the resistant hypertension group. In addition, that study reported a positive correlation between MHR and CRP levels. In the study conducted by Demirbaş et al.¹⁹ on patients with vitiligo, MHR values were found to be higher compared to the healthy CG, whereas the NLR parameter was found to be similar between the groups. Similarly, in the study by Yalçın et al.²⁰ on patients with ulcerative colitis, MHR, NLR, ESR, and CRP values were observed to be higher in the active disease group compared to the remission group.

The relationship between antibody titers and the degree of inflammation has gained importance as a current topic of research. In the literature, there are conflicting results regarding the association between antibody titers and the NLR and MHR parameters. For instance, in the studies by Aksu et al.¹⁵ and Acay et al.¹⁴ similar to our findings, no significant correlation

was found between NLR and autoantibody levels. On the other hand, Keskin et al.²¹ reported a positive correlation between autoantibodies and NLR; however, no relationship was identified between NLR and thyroid autoantibodies.

The effects of hypothyroidism on serum cholesterol levels are well established. Previous studies have indicated that elevated TSH levels lead to an increase in serum cholesterol concentrations²². In our study, total cholesterol and HDL cholesterol levels were found to be significantly higher in both the OH and SH groups compared to the CG (p: 0.016 and p: 0.011, respectively). However, no statistically significant difference in these parameters was observed between the AH and SH groups. Regarding triglyceride and LDL levels, no statistically significant differences were detected among the AH, SH, and CG.

Study Limitations

The present study has several limitations. Since the data were retrospectively obtained from the hospital information system, it is possible that not all medications received by the patients were recorded in the database. This limitation may affect the completeness of the data and, consequently, the reliability of the results. To further evaluate inflammation in HT patients and to ensure the consistency and applicability of parameters such as NLR and MHR, prospective studies with larger patient populations are needed.

CONCLUSION

It is thought that in patients diagnosed with HT, concomitant hypothyroidism may lead to increased systemic inflammation, resulting in elevated endothelial dysfunction and oxidative stress. In this context, when NLR and MHR parameters were evaluated in hypertensive patients with OH and SH, these parameters were found to be similar among the groups. Although some studies have demonstrated an association between these parameters and atherosclerotic processes, further research and large-scale clinical studies are required to obtain more reliable and comprehensive results.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine, with the (protocol number: 2023.28.02.16, date: 28.02.2023).

Informed Consent: This is retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Y., A.Ç., Concept: B.B., Design: B.B., Data Collection or Processing: D.Y., Analysis or Interpretation: D.Y., B.B., Literature Search: D.Y., Writing: D.Y.

Table 2. Correlations of NLR and MHR in the SH group

	NLR		MHR	
	r	p	r	p
NLR	1	.	0.232	0.018
CRP	0.142	0.151	0.154	0.117
Sediment	0.03	0.763	0.177	0.072
Anti-TPO	0.102	0.301	-0.095	0.338
Anti-TG	0.082	0.407	0.065	0.514

SH: Subclinical hypothyroidism, MHR: Monocyte-high-density lipoprotein ratio, NLR: Neutrophil-lymphocyte ratio, CRP: C-reactive protein, Anti-TPO: Antithyroid peroxidase, Anti-TG: Anti-thyroglobulin

Table 3. Correlations of NLR and MHR in the OH group

Parametre	NLR		MHR	
	r	p	r	p
NLR	1	.	0.037	0.719
CRP	0.081	0.426	0.161	0.112
Sediment	0.158	0.118	0.006	0.953
Anti-TPO	0.035	0.728	0.091	0.368
Anti-TG	-0.04	0.692	0.152	0.134

NLR: Neutrophil-lymphocyte ratio, MHR: Monocyte-high-density lipoprotein ratio, OH: Overt hypothyroidism, Anti-TPO: Antithyroid peroxidase, Anti-TG: Anti-thyroglobulin

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