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The Level of Serum C-Reactive Protein and Neutrophil Lymphocyte Ratio According to Thyroid Function Status

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ABSTRACT

Objective: We aimed to investigate neutrophil lymphocyte ratio (NLR), leukocyte count (WBC), mean platelet volume (MPV) and C-reactive protein levels (CRP) as inflammatory markers according to thyroid function status in hypo-hyperthyroidism patients.

Methods: Data of patients (n=454, age>18) who applied to the Eskisehir Osmangazi University Hospital between March 2018 and December 2018 were evaluated retrospectively. There were 79 patients in hyperthyroidism group (TSH<0.27 µIU/ml, group I), 297 patients in euthyroid group (TSH=0.27-4.2 µIU/ml, group II) and 78 patients in hypothyroidism group (TSH>4.2 µIU/ml, group III).

Results: Serum TSH, fT4, fT3, anti-TG and anti-TPO levels were found statistically different between groups (p<0.001) but there were no significant difference in WBC, NLR and MPV between groups. There was a positive correlation between the NLR and CRP (r=0,295, p<0.01). In addition, NLR was positively correlated with WBC (r=0,412, p<0.001). Serum CRP levels were statistically higher in group I (3.5 mg/L [1.50-11]) than group II (2.1 mg/L [0.86-5.42]), (p<0.001). Although CRP levels were higher in group III (2.5 mg/L [1.18-5.73]) than group II, there was no significant difference. CRP showed weak positive correlation with fT4 (r=0,118, p<0.05) and negative correlation with TSH (r=-0,108, p<0.05).

Conclusion: High CRP levels may play an important role in the evaluation of hyperthyroidism in terms of thyroid dysfunction observed in the present study.

Keywords: Hyperthyroidism, hypothyroidsm, inflammation, TSH, CRP.

1. INTRODUCTION

The thyroid gland is an important endocrine organ that regulates basal metabolism and metabolic activity, secreting two major hormones triiodothyronine (T3) and thyroxin (T4). The secretion of these hormones are regulated by thyroid stimulating hormone (TSH) in the pituitary gland controlled by thyrotropin-releasing hormone (TRH) in the hypothalamus (1). Hyperthyroidism, hypothyroidism, and thyroid nodules are the most common disorders of the thyroid gland (2). The lack or absence of thyroid hormones (THs) causes hypothyroidism, and the excess of these hormones causes hyperthyroidism (3).

THs play a crucial physiological role and regulate human hematopoiesis. A study was performed in which all hematological parameters were normal in euthyroid state (4). In the evaluation of white blood cells and platelets, total leukocyte count and neutrophil levels decreased slightly in hypothyroid patients. Furthermore, total leukocyte count and neutrophil levels were found to be high, normal or mild in hyperthyroid patients (5).

The effects of THs were observed on the immune system in experimental research (6). TSH has been shown to be both produced and used by leukocytes as well as controlling thyroid hormone production and metabolic function (7). Moreover, lymphoid and myeloid cells also have a TSH receptor. There are studies showing the ability of TSH to influence lymphocyte function and it has been shown to have an enhancing effect on the proliferation of lymphocytes (8). Apart from these effects, T3 and T4 hormones may indirectly affect the immune system. Immune dysfunction has been demonstrated in cells with low TSh levels (9). The presence of a thyroid hormone receptor was also showed on haematopoietic progenitor cells (10).

Neutrophil/lymphocyte ratio (NLR) has been recently researched and is a marker of inflammation that can be easily

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identified in the follow-up of the inflammatory process in patients with hyperthyroidism (11). One of the most commonly used acute phase reactants (APRs) is C-reactive protein (CRP) in the case of inflammation; a rapid increase is observed in the rate of damage and quickly returns to normal in recovery (12). Although thyroid disorders appear to cause changes in a large number of hematological parameters and the relationship between NLR and inflammation, there is inconsistent data on hypo-hyperthyroidism. In addition, many thyroid diseases involve inflammation processes, but so far, CRP is not used as a significant biomarker in thyroid diseases.

In the present study, the levels of hematological parameters (leukocyte, neutrophil, lymphocyte counts and mean platelet volume), serum inflammation markers (CRP) and their association with thyroid function tests (Serum free T4, free T3, TSH, anti-thyroglobulin and anti-thyroid peroxidase antibody) were evaluated in hypo-hyperthyroidism.

2. METHODS

Before obtaining the data, the research protocol was approved by Eskişehir Osmangazi University Non-invasive Clinical Research Ethics Committee (decision number:30, 30.04.2019) and handled according to the declaration of Helsinki.

Data of patients (n=454, age>18) who applied to the Eskişehir Osmangazi University Hospital between March 2018 and December 2018 were evaluated retrospectively. Patients with known chronic inflammatory disease, such as diabetes mellitus, with malignancy, hematological disease and acute infection were excluded from the study. The causes of hypothyroidism and hyperthyroidism such as chronic autoimmune response (Hashimoto thyroiditis), iodine status, genetic, drug-induced, transient thyroiditis, thyroid infiltration and escalated stimulation, Graves disease like secondary to TSH receptor antibodies were not specifically evaluated in our study.

TSH levels were used to detect the thyroid disorder group of all participants. There were 79 patients in hyperthyroidism group (TSH<0.27 µIU/ml, group I), 297 patients in euthyroid group (TSH=0.27-4.2 µIU/ml, group II) and 78 patients in hypothyroidism group (TSH>4.2 µIU/ml, group III)

Complete blood count (CBC), inflammation and thyroid function test parameters of the patients who visited our laboratory for routine control and were not included in the exclusion criteria were used in the study. fT4, fT3, TSH, anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase antibody (anti-TPO) levels for thyroid function tests; leukocyte (WBC), neutrophil (Neu), lymphocyte (Lym) counts, mean platelet volume (MPV) and CRP were recorded for all patients. NLR was calculated by dividing neutrophil counts by lymphocyte counts.

Sysmex XN-9000 (Sysmex Co., Kobe, Japan) automatic analyzer was used for hematological analyses. Thyroid hormone levels, CRP, anti-TG and anti-TPO levels were analyzed by Roche Cobas 8000 (Roche, Mannhaim, Germany). The original kits provided by the manufacturer were used for all analyzes.

2.1. Statistical analysis

All data were evaluated statistically with SPSS software (SPSS 21.0; SPSS Inc., Chicago, IL, USA). The results were evaluated using Kolmogorov-Simirnov and Shapiro Wilk normality tests. The data were performed according Kruskal-Wallis One Way Analysis of Variance on Ranks, Median (%25-%75) and p<0.05 values were considered significant.

3. RESULTS

There were 454 patients between the ages of 32-66 who were classified according to TSH levels. Hyperthyroidism patients (group I, n=79) mean age was 47.0 years (37.0, 66.0), euthyroid patients (group II, n=298) mean age was 44.5 (33.0, 57.0) and hypothyroidism patients (group III, n=78) mean age was 46.5 years (32.75, 58.25).

As shown in Table 1, TSH, fT3 and fT4 were significantly varied between groups (p<0.001). TSH levels were significantly higher in group III than group I and group II (p<0.001). The median serum anti-TPO values in group III was also significantly higher when compared with the group I and group II (p<0.001). The mean serum anti-TG levels were similar in group I and group II. However, serum anti-TG levels in group III were significantly higher in comparison with group II.

Table 1. *Thyroid function test and thyroid autoantibody levels between groups*

Thyroid Function Tests	Groups	Median (%25-%75)	P	Pairwise Comparisons
TSH (µIU/mL)	Group I	0,01 (0,01-0,07)	<0.001	1-3, 1-2, 2-3
	Group II	1,81 (1,04-2,62)		
	Group III	6,50 (5,28-9,51)		
fT3 (pg/mL)	Group I	3,94 (3,08-5,72)	<0.001	1-3, 1-2, 2-3
	Group II	3,10 (2,79-3,35)		
	Group III	2,77 (2,40-3,17)		
fT4 (ng/dL)	Group I	1,82 (1,48-2,31)	<0.001	1-3, 1-2, 2-3
	Group II	1,24 (1,13-1,37)		
	Group III	1,09 (0,92-1,24)		
Anti-TPO (IU/mL)	Group I	16,8(11,6-88,2)	<0.001	1-3, 2-3
	Group II	16,1 (11,5-35,9)		
	Group III	140 (13,3-235)		
Anti-TG (IU/mL)	Group I	15,2 (11,3-227)	<0.001	2-3
	Group II	13,4 (10,4-43,6)		
	Group III	64,78 (11,99-365,03)		

p<0.05 is significant, Kruskall Wallis Test

TSH: Thyroid stimulating hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-TG: Anti-thyroglobulin

Table 2 summarizes levels of inflammation-related blood count parameters and CRP in hypothyroid and hyperthyroid patients. There were no significant differences for Neu, Lym, NLR, MPV and WBC between groups. In group I, NLR were slightly higher than other groups. However, no statistical difference was observed (p=0.485). Serum CRP levels were statistically higher in group I than group II (p<0.001). Although CRP values were higher in group III than group II, no significant difference was noted (p=0.342) (Table 2).

Table 2. *Levels of inflammation-related blood count parameters and CRP between groups*

Blood Count Patameters and CRP Levels	Groups	Median (%25-%75)	P	Pairwise Comparisons
Neu (10^3/uL)	Group I	3,95 (3,00-5,40)	>0.05	NS
	Group II	4,10 (3,20-5,00)		
	Group III	3,93 (3,10-5,20)		
Lym (10^3/uL)	Group I	1,90 (1,50-2,30)	>0.05	NS
	Group II	2,01 (1,61-2,50)		
	Group III	2,05 (1,59-2,40)		
NLR	Group I	2,00 (1,54-2,85)	>0.05	NS
	Group II	1,94 (1,46-2,56)		
	Group III	1,91 (1,56-2,83)		
MPV (fL)	Group I	9,20 (8,40-10,60)	>0.05	NS
	Group II	9,30 (8,50-10,20)		
	Group III	9,50 (8,55-10,20)		
WBC (10^3/uL)	Group I	6,60 (5,60-8,20)	>0.05	NS
	Group II	6,93 (5,80-8,26)		
	Group III	6,70 (5,30-8,45)		
CRP (mg/L)	Group I	3,50 (1,50-11,00)	<0.001	1-2
	Group II	2,10 (0,86-5,43)		
	Group III	2,50 (1,18-5,73)		

p<0.05 is significant, Kruskall Wallis Test; NS: Non significant. CRP: C-reactive protein levels, NLR: Neutrophil / lymphocyte ratio, MPV: Mean platelet volume, *WBC: Leukocyte count, CRP: C-reactive protein levels.*

We determined that there was a positive correlation between the NLR and CRP levels (r=0,295) as shown in Table 3. CRP levels were positively correlated with fT4 (r=0,118, p<0.05) and had a weak negative correlation with TSH (r=-0,108, p<0.05). No statistical difference was observed in the correlation of CRP with other parameters (p>0.05). In addition, NLR was positively correlated with WBC (r=0,412, p<0.001).

Table 3. *Correlation analyses between the variables in all groups.*

Spearman's rho		Neu	Lym	NLR	MPV	WBC	CRP	AntiTG	Anti TPO	fT3	fT4	TSH
NLR	Correlation Coefficient	,712**	-,538**	1,000	-,058	,412**	,295**	-,048	-,054	-,008	,041	-,076
	Sig. (2tailed)	,000	,000	.	,217	,000	,000	,311	,253	,872	,385	,108
CRP mg/L	Correlation Coefficient	,406**	,016	,295**	-,024	,381	1,000	-,004	-,054	-,090	,118*	-,108*
	Sig. (2-tailed)	,000	,731	,000	,606	,000	.	,938	,248	,055	,012	,021

**p<0.05, **p<0.01*

NLR: Neutrophil / lymphocyte ratio; CRP: C-reactive protein levels; MPV: Mean platelet volume, WBC: Leukocyte count; TSH: Thyroid stimulating hormone; Anti-TPO: Anti-thyroid peroxidase antibody; Anti-TG: Anti-thyroglobulin

4. DISCUSSION

Thyroid dysfunctions, which are identifiable and treatable endocrine diseases, can cause serious metabolic problems when ignored (13). Despite advanced laboratory techniques and increased awareness of the disease, there are still cases of excessive dysfunction. (14, 15). Hypo – and hyperthyroidism are usually caused by pathological processes in the thyroid gland, but may be caused by hypothalamus or pituitary (central hypothyroidism) or functional thyroid disorders in certain situations (16). In our study, CRP levels were found to be increased in patients with hyperthyroidism when compared with hypothyroidism and euthyroid patients. As far as we know this is the first reported relationship between hypo-hyperthyroidsm and inflammation such as NLR and CRP parameters.

Recently, NLR has been evaluated as a simple systemic inflammation indicator in experimental and observational studies in different clinical situations (17). In a study examining inflammation in different thyroid diseases it was found that NLR correlates with the size of thyroid tumors and functions (18). When compared with the healthy control group, patients with Hashimoto's thyroiditis (HT) had significantly lower TSH levels (control: 1.9±1; HT: 1.2±1) associated with this increased NLR (control: 1.9 [0.6-3.3]; HT: 2.1 [1.3-5.8]) (19). Keskin et al. (11) concluded that NLR was statistically elevated in euthyroid Hashimoto patients, but also positively correlated with NLR and autoantibody levels. Dagdeviren et al. found that NLR did not increase in hyperthyroid patients and this rate decreased in Graves' disease patients. They found a negative correlation between fT3 and NLR in hyperthyroid patients (r=-0.28, p=0.001). Oguzhan et al. found that NLR levels were higher in HT patients than the control group (HT: 2.37 ± 1.46, control: 1.80 ± 0.67; p<0.003). In the same study, they found a negative but not statistically significant correlation between NLR and anti-TG and anti-TPO antibodies (20). According to Turan's study, NLR decreased in untreated Graves' patients (21). Although previous studies have shown a negative relationship between the fT3 level and NLR (22, 23), we found no statistically significant correlation in our study (r=-0,008, p= 0,872). It is observed in the studies that NLR can be used as an inflammatory marker in thyroid diseases and other diseases. However, in our study, there was no statistically significant difference between the groups in the presence of an increased NLR in hyperthyroidism, but no significant correlation was observed with thyroid function tests (p>0.05).

There are some studies reporting changes in lymphocyte levels in thyroid diseases (24, 25). In one of these studies, there was no significant difference in lymphocyte levels between the hypo-hyperthyroid groups (p>0.05). This ratio is parallel to the data obtained in our study. However, we observed that these studies have inadequate and inconsistent results. We have shown that NLR is not an appropriate parameter in hypo-hypertyroid patients. The change in parameters (WBC) is also associated with thyroid dysfunction. According to the results of Dorgalaleh and colleagues, they did not observe a statistically significant difference in WBC levels in hypothyroidism and hyperthyroidism groups in a similar way to our results (p>0.05) (2). In another study, WBC levels in the euthyroid and hyperthyroid groups were slightly higher than those in the hypothyroid group. Although different results were obtained at the WBC levels between the groups, the underlying mechanism is unknown. These inconsistencies are largely attributable to differences in exclusion criteria and origin of thyroid dysfunction.

CRP responds quickly to inflammatory processes and is one of the best known inflammatory markers. Several studies have shown that NLR is correlated with CRP (26, 27). Steven et al. found this correlation value as r=0.438, whereas in our study it was found to be r=0.295 (26). Lee and colleagues found that CRP levels in hypothyroidism (0.99±0.36) were significantly higher than control (0.93 ± 0.37) and hyperthyroidism (0.43±0.08) groups. However, they did not find a direct correlation between CRP and fT4 (r=0.062) and TSH levels (r=0.038) (28). Thus, they concluded that there was a weak relationship between thyroid status and CRP. On the other hand, we concluded that CRP increased in the case of hyperthyroidism (3.50 mg/L [1.50-11.0]) and showed a weak correlation with fT4 and TSH in our results. According to the Savas and his friends' findings, CRP levels were significantly higher in both hypothyroidism (5.62±4.75 mg/L) and hyperthyroidism (5.62±4.75 mg/L) compared to the control group (3.59±0.87 mg/L) (p<0.001), but there was no statistically significant difference in the case of autoimmune (HT and Graves's disease) and non-autotoimmune thyroid dysfunctions (p=0.087) (29). In the same study of these researchers, they found that MPV levels of hypothyroid, hyperthyroid and non-autoimmune patients were minor compared to the controls (30). In our findings, there was no change in MPV levels between the groups. In contrast to our results, MPV levels increased in both hypothyroidism and hyperthyroidism patients in different studies evaluating thyroid functions (30-32). In a comprehensive study by Pearche et al., no statistically significant difference was detected in the distribution of high CRP levels (>10 mg/L) in different thyroid diseases, before and after treatment (33). However, we were unable to find any significant differences in CRP levels according to thyroid function status. These results show that CRP levels are limited in the evaluation of thyroid function states.

5. CONCLUSION

According to the data we obtained, patients with hyperthyroidism and hypothyroidism should be able to follow CRP and NLR changes regularly. Failure to include all risk factors for hypothyroidism and hyperthyroidism has limited our study. Elevated levels of CRP for thyroid function status observed in current study confirm that inflammation has an important role in pathogenesis of hyperthyroidism. The effect of inflammation parameters on thyroid dysfunction requires further investigation

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