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Original article

An Overview of the Hematological Picture with Antithyroid Therapy in Graves' Disease

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SUMMARY

Aim: Graves' disease is an autoimmune thyroid disease that is the most common cause of hyperthyroidism. Peripheral blood cell parameters such as neutrophils, lymphocytes, and platelets play a role in inflammation control. Several studies have proven that neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio are indicators of chronic subclinical inflammation in various diseases. In our study, we aimed to review the peripheral blood picture by evaluating these parameters before and after antithyroid treatment in patients with Graves' disease.

Patients and methods: A total of 120 patients (93 female, 27 male) between the ages of 18 - 65 were included. Demographic data, hemogram and biochemical data of the patients were recorded retrospectively at the time of diagnosis and after euthyroidism was achieved with medical treatment.

Results: During the treatment, there was an increase in hemoglobin, lymphocytes, neutrophils and red cell distribution width, while a decrease in monocytes was observed. There was no significant difference between white blood cell, platelet and mean platelet volume. In addition, while there was no statistically significant difference between neutrophil-lymphocyte ratio ($p = 0.8$) and thrombocyt-lymphocyte ratio ($p = 0.078$) after euthyroid state, a statistically significant difference was found in favor of a decrease in monocyte-lymphocyte ratio ($p = 0.006$).

Conclusion: Changes in hematopoiesis are relatively common in patients with newly diagnosed Graves' disease, and initiation of antithyroid therapy leads to improvement in these parameters. Although neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio are accepted as new, non-invasive markers in clinical evaluation, in our study only a significant decrease in monocyte-lymphocyte ratio levels was observed after euthyroidism was achieved with antithyroid treatment.

Keywords: **Graves' disease, neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio, platelet-lymphocyte ratio, mean platelet volume**

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INTRODUCTION

Graves' disease (GD) is the most common cause of hyperthyroidism and is an autoimmune thyroid disease. Its prevalence is estimated to be 0.23% in men and 2.5% in women. The clinical manifestations of the disease cause thyrocyte hyperplasia (goiter) and excessive thyroid hormone synthesis, reflecting hyperstimulation of the gland. It may be accompanied by extrathyroidal involvement, especially in orbital and pretibial regions. The exact etiology of GD is not clear. However, the development of this autoimmune process is thought to be multifactorial, caused by the complex interaction between genetics and environmental factors such as high dietary iodine intake, stress, smoking, and pregnancy (1).

The onset of GD refers to the disruption of immune tolerance to the thyroid through an autoimmune multifactorial process. The fact that about 70% of genes that correlate with GD risk are associated with T cell function, with known effects, indicating the importance of T lymphocytes in the pathogenesis of autoimmune thyroid disease. Therefore, infiltration of thyroid antigen-specific T cells occurs into tissues expressing the thyroid stimulating hormone receptor (TSH-R). The autoimmune reaction causes the production of thyrotropin receptor antibodies (TRAb) by the infiltrating B cell clones. These circulating autoantibodies bind to and stimulate the TSH-R, resulting in hyperthyroidism and goiter.

Lymphocytes especially have the main role in the autoimmune process. When immune tolerance is impaired, the balance of pro- and anti-inflammatory cytokine functions is disturbed (2, 3). Activated T cells secrete many cytokines such as interleukin-1, tumor necrosis factor alpha, and interferons, resulting in increased proinflammatory cytokines (4). Both thyrotoxicosis and the underlying autoimmunity of GD affect multiple tissues and their functions, including hematopoesis and liver function. These abnormalities may revert once antithyroid drug (ATD) therapy has started, but may also occur and persist in some patients due to side effects of treatment (5).

In the last decade, easily accessible, cost-effective parameters available from a complete blood count (CBC) have received widespread attention. Peripheral blood cells involved in the immune system, such as lymphocytes, neutrophils, and platelets play a role in inflammation control. Neutrophils are active components of inflammation, while lymphocytes are involved in regulatory and protective pathways. Many studies have proven that neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR) are novel biomarkers of chronic subclinical inflammation in coronary artery disease, diabetes mellitus, and different types of malignancies (6). In addition, MLR is thought to be an indicator of systemic inflammatory response (7).

There are three methods of treatment: pharmacological treatment with ATDs, I-131 treatment and thyroidectomy. The goal of treatment is to control symptoms and make the patient permanently euthyroid. The most commonly used ATD group in patients with GD is thionamides, including methimazole (MMI), propylthiouracil (PTU), and carbimazole (CBZ) (8). Antithyroid therapy can sometimes cause severe and life-threatening neutropenia. Although the medicine CBZ is generally well tolerated, it can have serious side effects, such as agranulocytosis and hepatotoxicity, which are uncommon but can be fatal (9).

In our study, we aimed to review the peripheral blood picture by evaluating NLR, PLR, MLR and mean platelet volume (MPV) before and after treatment in patients using methimazole, an antithyroid treatment in GH. To the best of our knowledge, this is the first study to collectivelly evaluate these novel inflammatory parameters before and after antithyroid therapy in GD.

MATERIAL AND METHODS

The hospital records of 120 GD patients of both sexes, aged 18 - 65 years, followed in our Ankara Training and Research Hospital Endocrinology outpatient clinic were retrospectively analyzed. Demographic characteristics of the patients, treatment modalities, biochemical data at the time of diagnosis and after becoming euthyroid after ATD were recorded. The diagnosis of GD was confirmed by the presence of traditional symptoms of hyperthyroidism associated with a widely enlarged goiter, elevated free tri-iodothyronine and free thyroxine levels, and low thyroid stimulating hormone (TSH) level and positive TRAb, and, if present, evidence of diffuse increased activity on thyroid scintigraphy.

Inclusion criteria: Patients aged 18 - 65 years diagnosed with GD hyperthyroidism and followed up with medical treatment. Exclusion criteria: Preg-

nant or patients with malignancy, severe kidney or liver disease, ongoing infection or chronic inflammatory disease, or any other autoimmune disease, or a history of chronic drug use.

NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte number, and PLR is calculated by dividing the absolute platelet count by the absolute lymphocyte number, and MLR is calculated by dividing the absolute monocyte count by the absolute lymphocyte count. Analysis was performed on ARCHEM H3000 device with Cell Counter (Flowcytometry method using semiconductor laser) method.

The study complied with the Declaration of Helsinki and was approved by Ankara Training and Research Hospital ethics committee (41/419-2018).

STATISTICAL ANALYSIS

IBM SPSS Statistics version 21 was used for statistical analysis. Tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk) were used. Descriptive data were expressed as mean ± SD for normally distributed parameters, and as median ± interquartile range for non-normally distributed parameters. Paired Samples T-Test was performed to find out the significance of the difference between the means. Wilcoxon Signed Ranks Test was performed for parameters that did not fit the normal distribution. $P < 0.05$ was considered to be a statistically significant difference.

RESULTS

A total of 120 patients, 93 women (77.5%) and 27 (22.5%) men, aged 18 - 65 years were included in the study. The median age of the participants was 38 (28 - 47 IQR).

Table 1. *Laboratory characteristics of participants before and after antithyroid treatment*

	Pretreatment	Post-treatment	p
WBC ($x10^9$/L)[a]	7.27 ± 1.75	7.7 ± 1.91	0.06
Hb (g/dL)[a]	13.67 ±1.18	14.03 ± 1.36	**< 0.001**
Neutrophil ($x10^9$/L)[b]	3.89 (3.2 - 4.8)	4.25 (3.5 - 5.3)	**0.003**
Lymphocyte ($x10^9$/L)[a]	2.3 ± 0.65	2.47 ± 0.68	**0.004**
Monocyte ($x10^9$/L)[b]	0.7 (0.5 - 0.8)	0.53 (0.40 - 0.65)	**< 0.001**
MPV (fL)[b]	9.2 (8.6 - 10.3)	9.4 (8.6 - 10.5)	0.436
RDW (%)[b]	13.2 (12.5 - 14)	14.1 (13.2 - 14.9)	**< 0.001**
PLT ($x10^9$/L)[a]	264.88 ± 65.73	270.81 ± 66.61	0.096
TSH (mIU/L)[b]	0.01 (0.01 - 0.02)	0.5 (0.02 - 2.13)	**< 0.001**
fT3 (ng/L)[b]	11.01 (7.26 - 18.16)	3.19 (2.94 - 3.61)	**< 0.001**
fT4 (ng/dL)[b]	3.19 (2.07 - 4.6)	0.93 (0.74 - 1.1)	**< 0.001**
TRab (U/L)[b]	29.85 (18.3 - 58.2)	9.82 (7.1 - 20.5)	**< 0.001**
Anti-TPO (IU/mL)[b]	278.6 (53.2 - 986.3)	58.6 (20.5 - 300)	**0.036**
NLR [a]	1.97 ± 1.17	1.94 ± 0.79	0.800
MLR [a]	0.13 ± 0.29	0.06 ± 0.05	**0.006**
PLR [a]	123.91 ± 48.58	117.46 ± 43.21	0.078

a. Results are expressed as mean ± SD; Paired Samples T-Test is used

b. Results are expressed as median (IQR 25 - 75); Wilcoxon Signed Ranks Test is used

* $p < 0.05$ was considered to be a statistically significant difference.

WBC, white blood cell count; Hb, hemoglobin; MPV, mean platelet volume; RDW, red cell distribution width; PLT, platelet; TSH, thyroid stimulating hormone, fT3, free triiodothyronine; fT4, free thyroxine; TRab, thyrotropin receptor antibodies; Anti-TPO, anti-thyroid peroxidase antibody; NLR,neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio

A statistically significant difference was found in Hb (< 0.001), lymphocyte, neutrophil, red cell distribution width (RDW) ($p < 0.001$), and TSH before and after ATD treatment, and all of them increased after treatment. The findings are presented in Table 1.

Monocytes, free triiodothyronine (fT3), free thyroxine (fT4), TRab, and anti-thyroid peroxidase antibody (anti-TPO) were found to be significantly different between before and after ATD treatment, and they all decreased after treatment.

There was no significant difference between white blood cell count (WBC) ($p = 0.06$), thrombocyte ($p = 0.096$) and MPV ($p = 0.436$) values before and after treatment.

While there was no difference between NLR ($p = 0.8$) and TLR ($p = 0.078$) before and after ATD treatment, a significant difference was found in MLR ($p = 0.006$), which decreased after treatment.

DISCUSSION

To the best of our knowledge, our study is the first in the literature with this design. In our study, in which we evaluated the peripheral blood cells before and after ATD treatment in GD patients, after the treatment, there was an increase in Hb, lymphocyte, neutrophil and RDW, while a decrease in monocytes was observed. There was no significant difference between WBC, platelet and MPV values before and after treatment. Also, no difference was found between NLR and TLR after the euthyroid state, but a significant difference was found in MLR in favor of reduction after treatment. As expected, fT3, fT4, TRab and anti-TPO decreased after treatment, while TSH increased.

Although hematopoietic system involvement in hyperthyroidism does not usually result in a bad outcome, changes may occur in all three blood cell lineages (10). Thyroid hormones stimulate the production of erythropoietin; however, abnormally high thyroid hormone levels interfere with effective erythropoiesis and inactivate the use of iron in the bone marrow. Despite increased demand, anemia can also occur if there is a deficiency of folate, iron, and vitamin B12. Different studies have conflicting results regarding the incidence of hematopoiesis disorders in GD patients, but anemia appears to be the most common, with an estimated incidence of 10-34%, and the incidence of leukopenia and thrombocytopenia is estimated to be less than 10% (11). Although pancytopenia and autoimmune hemolytic anemia may rarely follow, none of the patients in our study had anemia. In addition, there was no accompanying leukopenia, neutropenia, lymphopenia or thrombocytopenia at the time of diagnosis and during the treatment process. In a study by Artemniak-Wojtowicz et al., anemia was observed in 22% at the time of diagnosis of GD, an increase of 15.3% was observed in RDW before treatment, and an increase was observed in both parameters after ATD (12). Reddy et al. found that the most common peripheral blood abnormality in patients with uncomplicated thyrotoxicosis was microcytosis at a rate of 37% (13). Geetha and Srikrishna showed that RDW values were significantly increased in both hypo- and hyperthyroid patients, while MCV was significantly decreased in hyperthyroidism and increased significantly in hypothyroidism. The authors concluded that abnormal thyroid hormone levels can significantly alter the size of circulating RBC (14). Our analysis also confirmed the changes in RDW values, and although there was no anemia, an increase was observed in RDW and Hb after ATD. Aiming to elucidate the exact mechanism of the action of thyroid hormones on human hematopoiesis, Kawa et al. showed that in both hypo- and hyperthyroidism, gene expression of thyroid hormone receptors is altered in hematopoietic progenitor cells (HPCs) *in vivo*. They noted an increased frequency of apoptotic CD34 (+) -enriched HPCs in both hypo- and hyperthyroidism via modulation of apoptosis-related genes. They suggested that the molecular mechanism by which thyroid hormones affect hematopoiesis will open up new therapeutic approaches in thyroid diseases. (15).

Changes in WBC and platelet (PLT) pictures occur less frequently than RBC abnormalities in patients with GD. The incidence of neutropenia in thyrotoxicosis is thought to be 2.5-18%. One study showed that WBC and neutrophil counts decreased more frequently than PLT counts in untreated GD patients (12). It was also found that the PLT count returned to normal faster than the WBC count when ATD treatment was started. They also noted that one-third of the children had a (mostly mild) decrease in neutrophil counts prior to initiation of treatment, which mostly returned to normal during ATD treatment, and slightly decreased in one-tenth of the patients (12). In our study, although neutropenia was not found at the beginning, an increase in neutrophil count was observed after ATD. Also, our findings are consistent with the previous

results of Dorgalaleh et al., who confirmed significant changes in red blood cell parameters such as Hb and RDW, but found no statistically significant difference in WBC or PLT counts in hyperthyroid and hypothyroid patients (16). Noting a decreased PLT count in patients with GD, the authors suggest that thrombocytopenia may be associated with increased sequestering potency of the thyroid hormone-induced reticuloendothelial phagocyte system (17). Although Hb level and RBC, WBC and PLT counts usually normalize with the initiation of ATD treatment, it should be kept in mind that neutropenia and agranulocytosis may also occur as side effects of treatment in GD patients (18). Our study was also in line with the study of Peng Y et al. which reported increased neutrophil counts in Graves patients who were euthyroid with treatment compared with untreated Graves' patients (19).

Although neutrophilia and lymphocytopenia are usually seen in tissue damage and inflammation, unlike other inflammation-related diseases, GD may be accompanied by leukopenia, absolute and relative neutropenia, and relative lymphocytosis. In a study by Dağdeviren et al., although not statistically significant, lymphocyte counts were found to be higher in the GD group than in the controls (20). On the contrary, in another study, a significantly lower lymphocyte count was found in GD patients compared to the control group (21). However, the mechanisms responsible for the changes are not yet clear. The same investigators showed that neutrophil counts and NLR values were significantly increased in Grave's ophthalmopathy (GO) patients compared to those without GO or healthy individuals. Additionally, their study found statistical differences in WBC, lymphocyte counts, and MLR between all groups (21). It has been suggested that almost all subpopulations of WBC and platelets are involved in the pathogenesis of this disease. Activation of T cells has a very important role in the development of autoimmunity. Stimulation of T lymphocytes to B lymphocytes also leads to the production of autoreactive antibodies. Activated T cells are also known to secrete cytokines such as interleukin 1 β (IL-1β), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and interleukin (IL-17), which is accompanied by increased production of neutrophils and macrophages. This hypothesis may be a partial explanation for the neutrophilia, increased monocyte count and MLR values in the GD course in the literature (22).

In Turan's study, an increase was observed in the neutrophil-lephocyte ratio with ATD, while no change was observed in the platelet-lymphocyte ratio (23). In the same study, there was a decrease in monocyte level after treatment, but no change in lymphocyte count. Similarly, in our study, while the number of monocytes decreased, an increase was observed in the number of lymphocytes after treatment. NLR has been associated with disease activity in inflammatory diseases in the literature. In line with this, Celik's study provides evidence that NLR values are higher in patients with active thyroid ophthalmopathy than in inactive patients (24).

Another thing to be aware of in thyrotoxic patients is a decrease in platelet count, usually without clinical manifestations. Although rare, it is probably caused by autoantibodies produced separately from thyroid stimulating immunoglobulin. Pancytopenia in GD was linked to primary immune thrombocytopenia (25), Evans syndrome (26) and thrombotic thrombocytopenic purpura (27). Studies have also shown that platelet survival time is shortened due to hyperthyroidism and that the reticuloendothelial phagocyte system is activated, increasing platelet sequestration. An increase in megakaryocytes may be seen in the bone marrow (10). Therefore, while the MPV value is expected to increase in hyperthyroidism, no change was observed in the MPV value in our study both at the beginning and after the treatment in accordance with the stability in the platelet count. Some studies have shown an improvement in platelet survival and an increase in platelet count after treatment for hyperthyroidism. ATD treatment often causes improvement in pancytopenia, but acute plasma exchange may be required in thrombotic thrombocytopenic purpura (27).

There is also a tendency for platelet adhesion and aggregation in GD, accompanied by increased serum concentrations of intercellular and vascular cell adhesion molecules, selectins, tumor necrosis factor-alpha and interleukin-6 (28).

Lymphocytes and platelets mutually regulate their reciprocal functions, namely platelet-lymphocyte crosstalk. Platelets increase lymphocyte function through direct cell-cell contact and/or soluble mediators, increasing T-helper (TH), T-cytolytic (TC) adhesion of platelets, natural killer (NK) and B cells, and cell migration.

They can reduce cytokine secretion and immunosuppressive response of TH cells, increase TC

cell proliferation and cytotoxicity, promote antibody production of B cells, and improve the cytolytic activity of NK cells. PLR is known as a marker of subclinical inflammation or a prognostic marker in various benign and malignant conditions, but it is not used much in benign thyroid diseases. In their study, Dasgupta et al. found that PLR was significantly lower in thyrotoxic patients compared to healthy controls and was a reliable screening tool to differentiate GD from subacute thyroiditis (29). There are not many studies dealing with PLR in hyperthyroidism in the literature and it is probably caused by the effect of thyroid tests, but the exact mechanisms underlying the PLR change still remains unclear. However, in our study, no change was observed in PLR with ATD.

Previous research has shown that anti-thyroid drugs alone can reduce microsomal and TSH receptor antibodies. Methimazole probably acts directly on autoantibody synthesis and regulates autoantibody levels independently of serum thyroxine levels (30). Consistent with this fact, in our study, while euthyroidism was achieved with methimazole treatment, a decrease in fT3, fT4, TRab and anti-TPO, and an increase in TSH were observed.

In various studies, peripheral blood cells have been used as an adjunct in the differential diagnosis of GD and as a prognostic factor in the course of the disease. Perhaps, over time, these parameters may become more used in daily practice because they are cheap, simple and easy to reach.

The limitations of our study are: retrospective design, absence of a control group, no patient with cytopenia, unknown levels of orbitopathy activities, unknown antithyroid doses, unknown duration of euthyroidism, absence of inflammation markers, no gender-stratified analysis, unknown smoking status.

CONCLUSION

Although NLR, MLR and PLR are considered to be new, non-invasive and widely accessible markers in the diagnostic approach and clinical evaluation, in our study, only a significant decrease in MLR levels was observed in patients with GD after euthyroidism was achieved with antithyroid treatment. Although thyroid hormones are known to increase erythropoiesis and megakaryocytogenesis, in our study, while thyroid hormones decreased after antithyroid treatment, no change was observed in platelet count and MPV, but an increase in hemoglobin and RDW was observed. Larger prospective studies are needed to fully evaluate the benefits of peripheral blood cells in Graves' patients.

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Pregled hematološke slike sa antitiroidnom terapijom kod Grejvsove bolesti

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SAŽETAK

Cilj. Grejvsova bolest je autoimuni poremećaj štitne žlezde i najčešći je uzrok hipertireoidizma. Ćelijski parametri periferne krvi, kao što su neutrofili, limfociti i trombociti, igraju ulogu u kontroli inflamacije. Više studija dokazalo je da su odnosi između neutrofila i limfocita, monocita i limfocita, kao i trombocita i limfocita, indikatori hronične subkliničke inflamacije kod različitih bolesti. Cilj naše studije bio je pregled krvne slike periferne krvi, kao i procena ovih parametara pre i nakon antitiroidne terapije kod bolesnika sa Grejvsovom bolešću.

Metode. U studiju je uključeno ukupno 120 bolesnika (93 ženskog i 27 muškog pola). Demografski podaci, hemogram i biohemijski podaci bolesnika beleženi su retrospektivno u vreme postavljanja dijagnoze i nakon što je eutiroidizam postignut terapijom.

Rezultati. U toku lečenja zabeležen je porast hemoglobina, limfocita, neutrofila kao i opseg rasporeda crvenih ćelija, dok je primećen pad monocita. Nije bilo značajne razlike između volumena belih krvnih zrnaca, trombocita i srednje vrednosti volumena trombocita. Iako nije bilo statistički značajne razlike između odnosa neutrofila i limfocita (p = 0,8) i odnosa između trombocita i limfocita (p = 0.078) nakon eutiroidnog stanja, statistički značajna razlika zabeležena je kod pada odnosa između monocita i limfocita (p = 0,006).

Zaključak. Promene u hematopoezi relativno su česte kod bolesnika sa tek dijagnostikovanom Grejvsovom bolešću i uvođenje terapije dovodi do poboljšanja ovih parametara. Premda se odnosi između neutrofila i limfocita, monocita i limfocita i trombocita i limfocita smatraju novim, neinvazivnim markerima u kliničkoj proceni, u našoj studiji zabeležen je značajan pad vrednosti u odnosu monocita i limfocita, nakon što je eutiroidizam postignut antitiroidnom terapijom.

Ključne reči: **Grejvsova bolest, odnos između neutrofila i limfocita, odnos između monocita i limfocita, srednja vrednost volumena trombocita**