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ARAŞTIRMA / RESEARCH

Higher mean platelet volume is accompanied with hyperthyroidism in patients with Graves' disease

Yüksek ortalama platelet hacmi Graves hastalarında hipertiroidizme eşlik etmektedir

Gülay Şimşek Bağır[1], Melek Eda Ertörer[1]

[1]Baskent University, Faculty of Medicine, Departmant of Endocrinology and Metabolism, Adana. Turkey

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Abstract

Purpose: Graves' disease (GD) is an autoimmune disease that is the most common cause of thyrotoxicosis. Thyrotoxicosis can cause a decrease in platelet survival time. Inflammation is an important stimulus for platelets and mean platelet volume (MPV) could be used a diagnostic marker which is an important determinant of platelet activity. In this study we aimed to evaluate whether MPV would be a useful inflammatory marker for evaluation of disease activity in patients with Graves' disease.

Materials and Methods: Two hundred twenty-nine patients (GD patients (Group 1); n=102 and patients with euthyroid nodular goiter (Group 2); n= 127) were included in this retrospective study. Serum TSH, fT3, fT4 and MPV levels were recorded at presentation and at first euthyroid period under ATD treatment in GD patients and at presentation in patients with euthyroid nodular goiter.

Results: The mean age was 40.3±13.5 in Group 1 and 50.2±11.6 in Group 2. Mean initial MPV level did not differ between groups; 8.3±1.2 fL and 8.3±1.1 fL, respectively (p=0.9). We found that mean initial MPV was higher than the first euthyroid period MPV in Group 1; Graves' group (8.3±1.2 fL vs 8.0±1.3 fL, p= 0.02).

Conclusion: Higher initial MPV levels in Graves patients and significant drop following the restoration of hyperthyroidism may be due to hypermetabolism of hyperthyroidism.

Keywords:. Graves' disease, mean platelet volume, autoimmunity, thyrotoxicosis

Öz

Amaç: Graves hastalığı, tirotoksikozun en sık nedeni olup, otoimmün bir hastalıktır. Tirotoksikoz, trombosit yaşam süresinde azalmaya neden olan bir durumdur. İnflamasyonun trombositler için önemli bir uyaran olduğu bilinmektedir. Ortalama trombosit hacmi (MPV) ise trombosit fonksiyonlarının önemli bir belirleyicisi olup, çeşitli inflamatuar hastalıklarda tanısal bir belirteç olarak kullanılabileceği söylenmektedir. Bu çalışmada MPV'nin, Graves hastalarında, hastalık aktivitesini değerlendirmede yararlı bir inflamatuar belirteç olup olmadığını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya 229 hasta (Graves hastalığı olanlar (Grup 1); n=102 ve ötiroid nodüler guatr hastaları (Grup 2); n= 127) dahil edildi. Graves hastalarında başlangıçta ve antitiroid ilaç tedavisi ile ilk ötiroid oldukları anda, ötiroid noduler guatr hastalarında ise başlangıçta ölçülen serum TSH, fT3, fT4 and MPV değerleri kaydedildi.

Bulgular: Hastaların ortalama yaşı Grup 1'de 40.3±13.5 ve Grup 2'de 50.2±11.6 idi. Başvuru anındaki ortalama MPV düzeyi gruplar arasında farklı değildi; sırasıyla 8.3±1.2 fL ve 8.3±1.1 fL, (p=0.9). Graves hastalarında (Grup 1), başlangıç MPV düzeyini, ilk ötiroid oldukları andaki MPV düzeyine göre daha yüksek olarak saptadık (8.3±1.2 fL vs 8.0±1.3 fL, p= 0.02).

Sonuç: Graves hastalarında başvuru anındaki yüksek MPV düzeyinde hipertiroidizmin düzelmesi ile izlenen anlamlı düşüş, hipertiroidizm ilişkili platelet yıkımının artışına bağlı olabilir.

Anahtar kelimeler: Graves hastalığı, ortalama trombosit hacmi, otoimmünite, tirotoksikoz

Yazışma Adresi/Address for Correspondence: Dr. Gülay Şimşek Bağır, Baskent University, Faculty of Medicine, Departmant of Endocrinology and Metabolism, Adana. Turkey E-mail: gulaysimsekbagir@yahoo.com.tr
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INTRODUCTION

Graves' disease (GD) is an autoimmune disease characterized by increased thyroid hormone production and secretion via thyroid receptor auto-antibodies that stimulate TSH receptors[1-3]. It is the most common cause of thyrotoxicosis and is an inflammatory disease accompanied with thyroid orbitopathy and rarely infiltrative dermopathy. Antithyroid drugs (ATD) are used to treat hyperthyroidism caused by Graves' disease[4]. Thyrotoxicosis can cause an increase in megakaryocytes and a decrease in platelet survival time that is is thought to be due to enhanced splenic sequestration[5-7].

Euthyroid nodular goiter is characterized by nodular or multinodular enlargement of the thyroid gland that is not associated with thyrotoxicosis or underlying autoimmune or inflammatory process. Thyroid nodules are common entities, frequently discovered in radiological and clinical practice. Thyroid fine needle aspiration biopsy (FNAB) is the main test to differentiate benign lesions from malignant ones. The indication for FNAB should be based primarily on the sonographic features rather than the nodule size[8,9]. If the cytological results are benign and there are no local compression, physical examination and ultrasonography findings should be considered for euthyroid patient management[8].

Mean platelet volume (MPV) is an indicator of platelet size. It is an important determinant of platelet activity. It is known that inflammation is an important stimulus for platelets. Large platelets are relatively young and metabolically and enzymatically active than smaller ones. Therefore, in conditions that involve increased platelet activation, an increase in the percentage of young platelets is expected. Recent studies demonstrated that MPV could be used as a diagnostic marker for inflammatory disorders[10-12]. The purpose of our study was to examine whether MPV would be a useful inflammatory marker in patients with Graves' disease.

MATERIALS AND METHODS

This retrospective study was performed at the Outpatient Endocrinology Clinic of Baskent University Faculty of Medicine, Adana hospital between 2016-2018. Graves' disease patients (Group 1, n=102) and patients with euthyroid nodular goiter (Group 2, n= 127) were recruited to the study and their medical records were collected.

Serum TSH, fT3, fT4 and MPV levels were recorded at presentation and at first euthyroid period under ATD treatment in GD patients and at presentation in patients with euthyroid nodular goiter.

Graves' disease was diagnosed on the basis of standard clinical and laboratory criteria, including clinical symptoms of hyperthyroidism, thyroid ultrasound findings, increased concentrations of free thyroxine (fT4), free triiodothyronine (fT3) and suppressed TSH concentrations in all patients. Additionally, measurement of thyrotropin receptor antibodies (TRAbs), determination of high radioactive iodine uptake and/or diffuse uptake at thyroid scintigraphy were performed in some patients[4].

Thyroid biopsy was performed according to the guidelines of American Thyroid Association and European Thyroid Association. Patients whose results were benign or patients with no indication for FNAB were recruited to study[8,9].

Our study excluded patients with known histories of the following conditions: cirrhosis, chronic kidney disease, cancer, cardiovascular disease, diabetes mellitus, severe obesity (body mass index (BMI) >35kg/m^2), infections, chronic inflammatory diseases, haematological diseases such as haemoglobinopathy, and blood coagulation disorders. Furthermore, patients undergoing treatment with diuretics, antihyperlipidemic agents, anticoagulants, and corticosteroids were also excluded. Smokers were not included, as well.

In order to measure patients complete blood count (CBC), a venous blood sample was obtained and collected in K- ethylenediaminetetraacetic acid (EDTA) tubes and measured by Siemens Advia 2120i Haematology System (Siemens Healthcare Inc. Tarrytown, NY USA). The MPV measurements were performed immediately in our laboratory with a reference value for MPV of 7.0-12 fL. Automated chemiluminescent immunoassays performed by the Advia Centaur XP Immunoassay system (Siemens Healthcare İnc. Tarrytown, NY USA) were used to measure fT4 (normal range:11.5-22.7 pmol/L), fT3 (normal range:3.5-6.5 pmol/L) and TSH (normal range:0.35-4.94 uIU/ml). The study was approved by the Local Ethics Committee of Baskent University, Project no: KA 17/50).

Statistical analysis

Statistical analysis was performed using the statistical package *SPSS* software (Version 17.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean±standard deviation (p>0.05 in Kolmogorov-Smirnov test or Shapira-Wilk (n<30)); however, if the continuous variables were not normal, they were described as the median. Groups of normally distributed data were compared using Student T test or One Way ANOVA for normally distributed data, while Mann Whitney U test or Kruscall Wallis tests were used for groups of data not normally distributed. The categorical variables between the groups were analysed using the Chi square test or Fisher Exc. test. Pre-post measures data were analysed using the Paired T test or Wilcoxson test. Values of $p < 0.05$ were considered statistically.

RESULTS

Two hundred twenty-nine patients (Group 1, n=102 and Group 2, n= 127) were included in the study. The mean age was 40.3±13.5 in Group 1 and 50.2±11.6 in Group 2 (Table 1).

According to our findings, mean initial MPV level did not differ between groups; 8.3±1.2 fL and 8.3±1.1 fL, respectively (p=0.9). We found that mean initial MPV was higher than the first euthyroid period MPV in Group 1; Graves' group (8.3±1.2 fL vs 8.0±1.3 fL, p=0.02). There was no significant difference in euthyroid MPV levels between the two groups (8.0±1.3 vs 8.3±1.1, p=0.05, Table 2).

When we used age and BMI as covariate variables in the univariate model, it was found that the MPV levels between the groups was not statistically different (p=0.24). The rate of thyroid nodule was 22.5 % (n=23) in GD patients. FNAB was performed in 10 (9.8 %) of GD patients with nodule, where as it was 81 (63.8 %) in euthyroid nodular goiter patients.

Table 1. General characteristics of patients

	Group 1 (n=102)	**Group 2** (n=127)	**p**
Age (years)	40.3±13.5	50.2±11.6	0.00
Gender, F (%)	61 (59.8)	105 (82.7)	0.00
BMI (kg/m2)	24.0±3.1	27.1±4.2	0.00

Group 1: Graves' disease patients
Group 2: Euthyroid nodular goiter patients
Values are mean ± SD

Table 2. ,Comparison of laboratory values of groups according to disease outcome

At presentation	**GD patiens** (n=102)	**Euthyroid nodular goiter patiens** (n=127)	***p***
Initial MPV (fL)	8.3±1.2	8.3±1.1	0.9
Initial TSH (uIU/ml)	0.04±0.1	1.6 ±0.9	0.00
Initial fT3 (pmol/L)	7.2 (2-36)	4.5±0.9	0.00
Initial fT4 (pmol/L)	19.8 (12-87)	15±1.5	**0.00**
	GD patiens (n=102)		
	At presentation	**At first euthyroid period**	***p***
MPV(fL)	8.3±1.2	8.0±1.3	0.02
TSH (uIU/ml)	0.04±0.1	1.9±1.3	0.00
fT3 (pmol/L)	7.2 (2-36)	4.5±0.9	0.00
fT4 (pmol/L)	19.8 (12-87)	12.6±2.6	0.00
	At first euthyroid period in GD patients (n=102)	**Euthyroid nodular goiter patiens** (n=127)	***p***
MPV (fL)	8.0±1.3	8.3±1.1	0.05
TSH (uIU/ml)	1.9±1.3	1.6±0.9	0.04
fT3 (pmol/L)	4.5±0.9	4.5±0.9	0.7
fT4 (pmol/L)	12.6±2.6	15±1.5	0.00

MPV, Mean platelet volume GD; Graves' Disease Initial MPV; MPV at initial diagnosis in both groups Initial TSH-fT3-fT4; TSH-fT3-fT4 at initial diagnosis in both groups
Values are the mean ± SD or median (minimum-maximum)

DISCUSSION

Mean platelet volume is a marker of platelet function that is calculated by automatic blood count equipment during routine blood counts. Thyroid hormone receptors are present on hematopoietic stem cells and thyroid hormone may modulate the production of platelets[13,14]. An increase in number of mega karyocytes and decrease in platelet survival time are observed in hyperthyroid patients. In this study investigating MPV as an indicator of disease activity in GD patients, we found that the difference in MPV levels were statistically insignificant between GD patients and euthyroid nodular goiter cases regardless of thyroid hormone status. However, MPV levels were higher in Graves cases with hyperthyroidism and dropped following euthyroidism.

Clinical studies have shown inconsistent association among thyroid hormone levels, MPV and autoimmunity. The pathological processes responsible for autoimmunity are lymphocytic infiltration at the target organ and the presence of antigen-reactive T and B cells to thyroid antigens in Graves' disease, which is similar to other autoimmune diseases[15-17]. It is known that platelets have significant roles in inflammation and immune response. There are several studies about the association between MPV and autoimmunity in the literature but the results are contradictory[18-20]. In the development and progression of cancer, inflammation is an essential process. There are clinical studies investigating the association between MPV levels in thyroid cancer and benign goiter patients. Some report significantly higher MPV levels in thyroid cancer[18,19], whereas in another; Yaylacı et al found no significant relationship inbetween[20].

High MPV levels measured during thyrotoxic period in GD are proposed to be due to hyperthyroidism rather than autoimmunity[5,6,21]. Okada et al have found higher MPV levels in patients with untreated Graves' disease that have become lower after treatment with antithyroid agents[5]. Similarly, Panzer et al have found significantly lower MPV levels in Graves' disease patients 3 weeks after ATD therapy. They have shown that platelet lifespan is significantly shortened in patients with hyperthyroidism, and higher MPV levels are proposed to be a metabolically rather than immunologically, mediated phenomena[6]. A significant drop in MPV levels with ATD therapy may be due to prolonged platelet survival that is observed with restoration of euthyroidism.

In a study on thyrotoxic toxic adenoma patients, higher MPV levels have been reported before RAI (radioactive ^{131}I) treatment. Because toxic adenoma is a nonautoimmune thyroid disease, it has been clearly demonstrated that MPV levels are associated with TSH levels, not with autoimmune mechanisms[22]. Accordingly, a study to investigate the possible relationship among haematological parameters and the presence and size of thyroid nodules has shown no difference between MPV and thyroid nodules[7]. Accordingly, in our study, it is hard to explain why our thyrotoxic Graves patients and euthyroid nodular goiter patients exhibit similar levels of MPV, even though the latter were both older and heavier. Moreover, our univariate analysis reported the insignificant impact of age and body weight on MPV levels. One may propose that it may not be appropriate to compare two originally different clinical states; Graves disease and euthyroid nodular thyroid disease when MPV, a parameter that is affected by many factors, is the case. There also may be some silent patients with thyroid autoimmune disease in euthyroid nodular goiter group, which we were unable to detect as we did not measure the autoimmune antibodies.

The retrospective design and not measuring the thyroid autoimmune markers in euthyroid nodular goiter are limitations of our study.

In conclusion, MPV levels were higher in Graves cases with hyperthyroidism and returned to normal levels following the restoration of hyperthyroidism. This finding may be due to hypermetabolism of hyperthyroidism.

Yazar Katkıları: Çalışma konsepti/Tasarımı: GŞB, MEE; Veri toplama: GŞB, MEE; Veri analizi ve yorumlama: GŞB, MEE; Yazı taslağı: GŞB, MEE; İçeriğin eleştirel incelenmesi: GŞB, MEE; Son onay ve sorumluluk: GŞB, MEE; Teknik ve malzeme desteği: GŞB, MEE; Süpervizyon: GŞB, MEE; Fon sağlama (mevcut ise): yok.
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REFERENCES

1. Rosenbaum JT, Choi D, Wong A, Wilson DJ, Grossniklaus HE, Harrington CA et al. The role of the immune response in the pathogenesis of thyroid eye disease: a reassessment. PLoS One. 2015;15:10.
2. Penta L, Muzi G, Cofini M, Leonardi A, Lanciotti L, Esposito S. Corticosteroids in moderate-to-severe Graves' ophthalmopathy: oral or intravenous therapy? Int J Environ Res Public Health. 2019;16:155.
3. Song RH, Qin Q, Wang X, Yan N, Meng S, Shi XH, et al. Differential cytokine expression detected by protein microarray screening in peripheral blood of patients with refractory Graves' disease. Clin Endocrinol (Oxf). 2015;84:402-7.
4. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343-1421.
5. Okada M, Kamiya Y, Ito J, Yoshimata T, Kawaguchı M, Shibata H, et al. Platelet epidermal growth factor in thyroid disorders. Endocr J. 1998;45:83-8.
6. Panzer S, Haubenstock A, Minar E. Platelets in hyperthyroidism: studies on platelet counts, mean platelet volume, 111-indium-labeled platelet kinetics, and platelet-associated immunoglobulins G and M. J Clin Endocrinol Metab. 1990;70:491-96.
7. Erdogan Yucel E, Demiral Sezer S. Relationship between the neutrophil to lymphocyte ratio and the presence and size of thyroid nodules. Cureus. 2019;11:e3866.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133.
9. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: The EU-TIRADS. Eur Thyroid J. 2017;6:225-37.
10. Park BJ, Shim JY, Lee HR, Jung DH, Lee JH, Lee YJ. The relation ship of platelet count, mean platelet volume with metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists: a focus on gender differences. Platelets. 2012;23:45–50.
11. Demir Y, Üçler R, Sürücü E, Mahfuz T, Zekeriya B, Tarık Ş. Temporary changes in neutrophil-to-lymphocyte, platelet-to-lymphocyte ratios, and mean platelet volume reflecting the inflammatory process after radioiodine therapy. Nucl Med Commun. 2016;37:393-98.
12. Carlioglu A, Timur O, Durmaz SA, Ayhan ME. Mean platelet volume in euthyroid patients with Hashimoto's thyroiditis. Blood Coagul Fibrinolysis. 2015;26:282-4.
13. Chute JP, Ross JR, McDonnell DP: Minireview: nuclear receptors, hematopoiesis, and stem cells. Mol Endocrinol. 2010;24:1-10.
14. Ijaz SH, Jamal SM, Qayyum R. Relationship between thyroid hormone levels and mean platelet count and volume: quantitative assessment. Cureus. 2018;8;10:e3421.
15. Davies T, Laurberg P, Bahn R. Hyperthyroid Disorders, Graves Disease. In Williams Textbook of Endocrinology (Eds Melmed S, Polonsky K, Larsen P, Kronenberg H:373-95. Philadelphia, Elsevier-Saunders, 2016.
16. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726–38.
17. Morshed SA, Latif R, Davies TF. Delineating the autoimmune mechanisms in Graves' disease. Immunol Res. 2012;54:191-203.
18. Bayhan Z, Zeren S, Ozbay I, Kahraman C, Yaylak F, Tiryaki C et al. Mean platelet volume as a biomarker for thyroid carcinoma. Int Surg. 2016;101:50–3.
19. Baldane S, Ipekci S, Sozen M, Kebapcilar L. Mean platelet volume could be a possible biomarker for papillary thyroid carcinomas. Asian Pac J Cancer Prev. 2015;16:2671-74.
20. Yaylaci S, Tosun O, Sahin O, Genc AB, Aydin E, Demiral G et al. Lack of variation in inflammatory hematological parameters between benign nodular goiter and papillary thyroid cancer. Asian Pac J Cancer Prev. 2016;17:2321-3.
21. Bagir GS, Haydardedeoglu FE, Bakiner OS, Bozkirli E, Ertorer ME. Mean platelet volume in graves' disease: a sign of hypermetabolism rather than autoimmunity? Pak J Med Sci. 2017;33:871-75.
22. Simsek E, Timur O, Carlioglu A, Durmaz S, Demirci M, Sevimli H. Mean platelet volume in hyperthyroid toxic adenoma patients after radioactive 131i treatment. Adv Endocrinol. 2015;2015:436768