Thyroid Autoimmunity may Affect Mean Platelet Volume

Tiroid Otoimmünitesi Ortalama Trombosit Hacmini Etkileyebilir

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ABSTRACT

Objective: Mean platelet volume (MPV) has been associated with autoimmune diseases and is considered a potentially useful parameter to assess platelet activity and subclinical inflammation. In the present study, we aimed to investigate the effects of thyroid autoimmunity on MPV.
Methods: 84 patients with newly diagnosed Hashimoto's thyroiditis (HT), including 44 euthyroid (EHT, mean age 41.4±10.8 years) and 40 hypothyroid (HHT, mean age 44.6±13.2 years) patients, 61 patients with newly diagnosed Graves' disease (GD, mean age 42.8±12.4 years) and 57 euthyroid control subjects (age-matched 46.4±11.6 years) were included in the study. Patients were not taking antithyroid medication or levothyroxine. Thyroid hormones and platelet parameters were determined in all study participants.
Results: The MPV of the patients was significantly higher than that of the control group (p:0.008). There was no association between MPV and age, sex, or TSH (p:0.06, p:0.4, and p:0.9, respectively). MPV increased in chronic autoimmune thyroid disease regardless of age, sex, and TSH.
Conclusion: Our results suggest that autoimmunity, rather than thyroid hormone levels, affects MPV in GD and HT.

Key Words: Graves' disease, hashimoto's thyroiditis, mean platelet volume, platelets, thyroid, thyroid-stimulating hormone

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ÖZET

Amaç: Ortalama trombosit hacmi (MPV), otoimmün hastalıklarla ilişkilendirilmiş olup trombosit aktivitesini ve subklinik inflamasyonu göstermede yararlı bir parametre olarak kabul edilmektedir. Bu çalışmada tiroid otoimmünitesinin MPV üzerine olan etkisini araştırmayı amaçladık.
Yöntem: Yeni tanı almış 84 Hashimoto tiroiditi (HT) hastası [44'ü ötiroid (EHT, ortalama yaş 41.4±10.8 yıl) ve 40'ı hipotiroid (HHT, ortalama yaş 44.6±13.2 yıl)], yeni tanı almış 61 Graves hastası (GD, ortalama yaş 42.8±12.4 yıl) ve 57 ötiroid kontrol olgusu (yaş eşleştirilmiş 46.4±11.6 yıl) çalışmaya dahil edildi. Hastalar antitiroid ilaç veya levotiroksin almıyordu. Tüm katılımcıların tiroid hormonları ve trombosit parametreleri değerlendirildi.
Bulgular: Hastaların MPV'si kontrol grubuna göre anlamlı derecede yüksek bulundu (p:0.008). MPV ile yaş, cinsiyet veya TSH arasında anlamlı ilişki saptanmadı (sırasıyla p:0.06, p:0.4 ve p:0.9). MPV, kronik otoimmün tiroid hastalığında yaş, cinsiyet ve TSH'den bağımsız olarak artmıştı.
Sonuç: Sonuçlarımız, GD ve HT'de MPV'yi, tiroid hormon düzeylerinin değil otoimmünitenin etkilediğini göstermektedir.

Anahtar Sözcükler: Graves hastalığı, hashimoto tiroiditi, ortalama trombosit hacmi, trombositler, tiroid, tiroid uyarıcı hormon

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INTRODUCTION

Autoimmune thyroid diseases, including Hashimoto's thyroiditis (HT) and Graves' disease (GD), are common, especially in women. The etiology is multifactorial. Both genetic and environmental factors are involved in the pathogenesis. Microscopic examination usually reveals varying degrees of lymphocytic infiltration of the thyroid gland. This infiltration is caused by autoantibodies against thyroid tissue and leads to destruction of thyroid follicles (1). Thyroid hormones play an essential role in the metabolism and proliferation of blood cells. Thyroid dysfunction has various effects on blood parameters such as anemia, erythrocytosis, leukopenia, and thrombocytopenia (2,3). Platelets play a critical role in the pathophysiology of atherosclerotic disease. The association between increased platelet activity and atherosclerotic disease, including coronary artery disease, is well documented (4). Mean platelet volume (MPV) is a potentially useful parameter to assess platelet activity (5). Larger platelets are metabolically more active than smaller ones and have a higher prothrombotic potential. We have recently shown that MPV levels tend to be higher in Hashimoto's patients than in healthy controls, even in the euthyroid state (6). In the present study, we aimed to investigate the relationship between MPV and autoimmune thyroid diseases, including GD and HT.

METHODS

Eighty-four patients with newly diagnosed HT, including 44 euthyroid (EHT) (mean age 41.4±10.8 years) and 40 hypothyroid (HHT) (mean age 44.6±13.2 years) patients, and 61 patients with newly diagnosed GD (mean age 42.8±12.4 years) were included in the study. Patients were not receiving antithyroid or levothyroxine therapy. The diagnosis of HT was based on the detection of circulating autoantibodies, mainly anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG), and decreased echogenicity, heterogeneous or coarsened parenchyma, accompanied by a mostly micronodular pattern on thyroid ultrasound. Hypothyroidism was defined as elevated TSH concentrations (greater than 4.5 U/ml) with decreased concentrations of free thyroxine (FT4) and free triiodothyronine (FT3) with clinical symptoms of hypothyroidism. The diagnosis of GD was based on the presence of an enlarged thyroid gland, elevated thyroid hormones with positive TSH receptor antibodies (TRAB), or high uptake of radioactive iodine on thyroid scintigraphy. Fifty-seven age-matched euthyroid control subjects (46.4±11.6 years) without thyroid disease or a history of thyroid medication were included in the study. Anti-TPO and anti-TG antibodies were analyzed, all of which were negative in the control subjects.

The inclusion criteria were as follows:

- 18-65 years old
- Patients who had no history of thyroid surgery or RAI treatment
- Patients who had no history of antithyroid medication or levothyroxine use

The exclusion criteria were as follows:

- < 18 years old or > 65 years old
- Patients who had a history of thyroid surgery or treatment with RAI
- Patients with known pre-existing conditions such as cirrhosis, chronic kidney disease, cancer, cardiovascular disease, diabetes mellitus and severe obesity (body mass index (BMI) > 35kg/m2), infections, chronic inflammatory diseases such as collagen tissue disease, and inflammatory bowel disease, hematologic diseases such as hemoglobinopathy and blood coagulation disorders.
- Patients treated with diuretics, antihyperlipidemics, anticoagulants and corticosteroids.
- Patients taking antithyroid medication or levothyroxine
- Smokers

Written informed consent was obtained from participants. All study populations were assessed by hormonal and platelet parameters. TSH, FT3, and FT4 and complete blood count (CBC) were analysed.

Laboratory Analysis

In each patient a venous blood sample was drawn from the antecubital vein without venous stasis via a 19-gauge scalp-vein needle at 8:30 – 9:00 AM after 12–15 hours of overnight fasting. All complete blood count (CBC) analyses were performed in the hematology laboratory of our hospital. Three mL K_2EDTA (5.4 mg) based anticoagulated blood samples were drawn and kept for 10 minutes at room temperature. All measurements were performed within 2 hours after blood collection using an automatic hematologic analyzer, the Beckman Coulter LH 750 (Beckman Coulter, USA). The platelet count (PC), neutrophil count, lymphocyte count, mean platelet volume (MPV), platelet distribution width (PDW) and *plateletcrit (*PCT), hemoglobin (Hbg), hematocrite (Hct) were evaluated. The reference values of hematological parameters for our laboratory are as follows: Hemoglobin (Hgb) in the range of 12-17 g/dL, hematocrit (Hct) in the range of 36-50%, white blood cells (WBC) in the range of 4.0-10.5 × 103/µL, platelets (PLT) in the range of 150-450 × 103/µL, MPV in the range of 6.0-10.0 fL, PDW in the range of 15.0-18.0%, and PCT in the range of 0.108-0.300%. FT3, FT4, and TSH in serum were measured by electrochemiluminescence immunoassay (Siemens Advia Centaur® XP Immunoassay System (Siemens Medical Solutions Diagnostics Tarrylown NY 10591-5097 USA). TSH reference range is 0.27 - 4.2 mIU/ L, FT4 reference range is 1-1.6 ng/dL, FT3 reference range is 2 - 4.4 pg/mL in our hormone laboratory. Serum anti-TPO and anti-TG levels were measured by chemiluminescence. The reference range for anti-TPO is 0-9 u/ml, for anti-TG the reference range is 0-4 u/ml.

Ethics Committee Approval

This study entitled "Thyroid autoimmunity may affect mean platelet volume" was approved by the Clinical Research Ethics Committee of Kırıkkale University on December 15, 2014 under number 28/02.

Statistical analysis

SPSS 17 was used for statistical analysis. All results were expressed as mean±standard deviation (SD). The multiple comparison analysis with ANOVA was used for comparison of the control and patient groups. A p-value less than 0.05 was considered statistically significant.

RESULTS

The clinical characteristics and laboratory test results of the patients and controls are shown in Table 1. The anti-TPO and anti-TG levels of the patients in the control group were within the reference range. The mean anti-TPO level in the EHT group was 281±534 u/ml (12-4000 u/ml, median: 141 u/ml), 414±747 u/ml (54-5000 u/ml, median: 301 u/ml) in the HHT group, and 242±441 u/ml (10-3040 u/ml, median: 517 u/ml) in the GD group. Mean serum anti-TPO levels were significantly higher in all study groups (EHT, HHT, GD) than in control subjects (p:0.01, p:0.0001, and p:0.04, respectively). The mean anti-TG value was 394±488 u/ml (10-2444 u/ml, median: 255 u/ml) in the EHT group, 797±1116 u/ml (111-4000 u/ml, median: 400 u/ml) in the HHT group, 188±466 u/ml (10-3001, median=188 u/ml) in the GD group. Mean serum anti-TG levels were significantly higher in all study groups (EHT, HHT, GD) than in control subjects (p:0.002, p:0.0001, and p:0.02, respectively).

Table 1. The clinical characteristics and laboratory test results of Hashimoto's thyroiditis patients, Graves' disease patients and controls

	Euthyroid Hashimoto's thyroiditis	Hypothyroid Hashimoto's thyroiditis	Graves' Disease	Control group	p
N	44	40	61	57	
Age (years)	41.4±10.8	44.6±13.2	42.8±12.4	46.4±11.6	0.07
Sex (M/F)	6/38	12/28	10/51	18/39	0.08
FT3 (pg/ml)	2.7±0.3	2.8±0.4	6.9±4.4	2.9±0.3	0.03*
FT4 (pg/ml)	1.4±0.1	1.0±0.3	2.1±1.3	1.2±0.1	0.02*
TSH (uIU/ml)	2.2±1.0	10.1±4.1	0.05±0.1	1.7±0.7	0.009*
Anti -TPO	281±534	414±747	224±441	0.6±0.3	0.0001*
Anti -TG	394±488	797±1116	188±466	1.7±0.7	0.008*

TSH, thyroid-stimulating hormone; FT3, free T3; FT4, free T4; anti-TPO, anti-thyroid peroxidase; anti-TG, anti-thyroglobulin. *p<0.05 is statistically significant

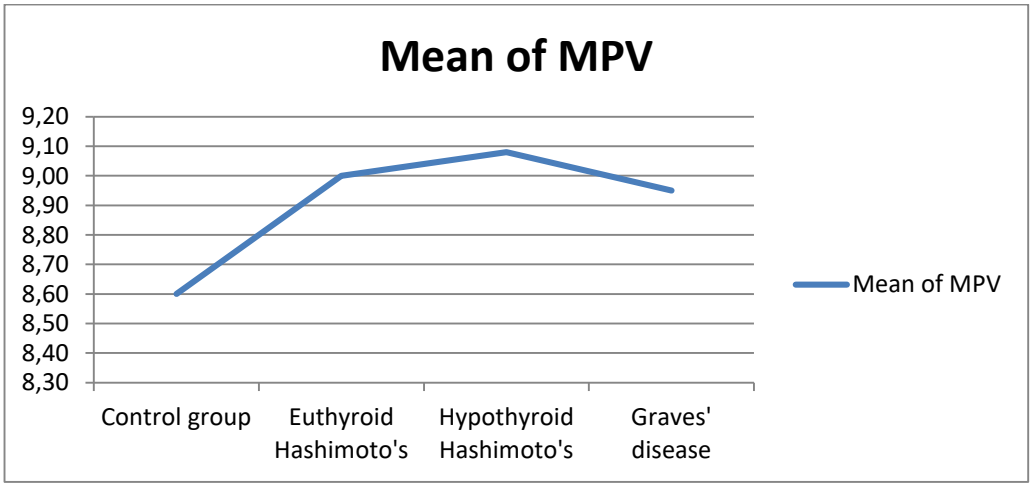
The MPV of the patients was significantly higher than that of the control group (p:0.008), as shown in Table 2 and Figure 1. In subgroup analyses, the MPV values of EHT, HHT, and GD were significantly higher than those of the control group (p:0.03, p:0.04, and p:0.01, respectively).

No statistically significant differences in MPV values were found between the groups of EHT and HHT (p:0.8), EHT and GD (p:0.9), HHT and GD (p:0.8). No statistically significant differences were found between the other parameters such as platelet count, platelet distribution width and plateletcrit as shown in Table 2.

Table 2. MPV, platelet count, platelet distribution width and plateletcrit level of each groups

	Euthyroid Hashimoto's thyroiditis	Hypothyroid Hashimoto's thyroiditis	Graves' Disease	Control group	p
N	44	40	61	57	
MPV	9.01±0.6	9.0±0.8	8.9±0.9	8.5±0.7	0.006*
PLT	270±59	245±57	268±57	260±55	0.20
PDW	16.3±0.5	16.5±0.6	16.2±0.7	16.5±0.5	0.22
PCT	0.22±0.06	0.21±0.05	0.22±0.06	0.22±0.05	0.09

MPV, mean platelet volume; PLT, platelet count; PDW, platelet distribution width; PCT, plateletcrit; *p<0.05 is statistically significant



MPV, mean platelet volume

Figure 1. Mean platelet volume levels in control, Hashimoto's thyroiditis and Graves's disease group.

There was no association between MPV and age, sex, or TSH (p:0.06, p:0.4, and p:0.9, respectively) in chronic autoimmune thyroid disease. MPV increased independently of age, sex, and TSH. There was a significant correlation between MPV and anti-TPO levels (r=0.13, p:0.015).

DISCUSSION

Our results suggest that thyroid autoimmunity is associated with increased MPV and platelet activity. We also argue that patients with autoimmune thyroid disease are at risk for cardiovascular disease even in the euthyroid state. Platelets express many prothrombotic and inflammatory substances and play an essential role in atherothrombosis (4,7,8). Elevated MPV may influence the development and progression of cardiovascular disease. Larger platelets exhibit higher prothrombotic potential due to increased platelet aggregation, increased thromboxane A2 and B2 synthesis, and increased expression of adhesion molecules such as the glycoprotein IIb-IIIa receptor (9,10). Higher MPV is associated with greater aggregability in response to ADP (11). In addition, larger platelets are denser and contain more alpha-granules, which are associated with increased secretion of prothrombotic molecules such as P-selectin and platelet-derived growth factor (8). Increased MPV is observed in patients with cardiovascular risk factors: Diabetes mellitus (12), hypertension (13), hyperlipidemia (14), and smoking (15). In addition, increased MPV was observed in various cardiovascular diseases. Patients with established coronary artery disease were found to have a higher MPV than control subjects (16). Endler et al. reported that in subjects with established coronary artery disease, patients with higher MPV had a higher risk of acute myocardial infarction (17). Thyroid disease is one of the most common endocrine disorders worldwide. The effects of thyroid dysfunction on platelet function have been investigated in previous studies. Patients with thyroid dysfunction and autoimmune thyroid diseases have been found to have various alterations in the coagulation and fibrinolytic systems leading to thrombosis or bleeding (18,19). Thyroid hormones have a strong influence on the cardiovascular system (20). A previous study reported that serum MPV levels were significantly higher in patients with subclinical hypothyroidism, even when they became euthyroid. The contribution of elevated MPV levels to an increased risk of cardiovascular complications was also described in that study in patients with subclinical hypothyroidism (21). Erikci et al. studied 47 patients with subclinical hypothyroidism and reported higher MPV and PDW levels in patients than in controls (22). Çoban et al. reported higher MPV and platelet activation in patients with subclinical hypothyroidism (23). In this study, anti-TPO levels were positively correlated with MPV levels. Carlioglu et al. studied 51 patients with EHT and showed that MPV levels were higher than in the control group even in the euthyroid state. They also described a positive correlation between anti-TPO, anti TG and MPV levels (5). Several papers have been published on blood coagulation abnormalities in hyperthyroidism. Panzer S et al. and Şimşek E et al. studied platelets in hyperthyroidism and documented increased MPV in hyperthyroidism (24,25). However, in our study, increased MPV was documented in the GD group independent of serum thyroid hormone level and our study showed the association between MPV and GD independent of TSH level. MPV has been found to be associated with autoimmunity and chronic inflammation in several studies. In rheumatoid arthritis, a correlation between MPV and acute phase reactants was observed (26). Purnak T et al. described a correlation between increased MPV and disease activity (27). In some other immune-mediated inflammatory diseases, including chronic urticaria (28) and polymyositis (29), high MPV was observed in active disease. These observations suggest that MPV is associated with autoimmunity and could be used in the evaluation of some immune-mediated inflammatory diseases. In our study, all patients had higher anti-TPO levels than the control group, and a positive correlation was observed between MPV and anti-TPO levels. This study confirms an increase in MPV in chronic inflammation and autoimmunity. We conclude that autoimmune thyroid diseases are associated with higher MPV levels even in the euthyroid state and independently of TSH levels. New clinical trials could determine whether MPV is a factor contributing to the assessment of atherosclerosis risk.

Conflict of interest

No conflict of interest was declared by the authors.

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