Original Article

The relationship of mean platelet volume with endogenous sex hormones and cardiovascular risk parameters in postmenopausal women

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Abstract. Evaluation of the relationship among mean platelet volume (MPV) and endogenous sex hormones and cardiovascular (CV) risk parameters.

We designed a retrospective study in postmenopausal women. Patient charts were reviewed for the results of mean platelet volume, hormonal and biochemical parameters.

MPV correlated only with white blood cell and platelet counts (r=-0.270, p=0.023 and r=-0.558, p=0.001 respectively). There was no statistically significant difference in MPV of patients with and without metabolic syndrome.

We could not detect any relationship between MPV and endogenous sex hormones and parameters indicating higher CV risk.

Key words: Endogenous sex hormones, postmenopausal women, mean platelet volume, cardiovascular disease

1. Introduction

Cardiovascular (CV) events increase in the postmenopausal period. Previous epidemiological studies suggested a risk reduction with hormone replacement therapy (HRT) in postmenopausal women (1), but the results of Women's Health Initiative (WHI) study showed an increased risk of CV events in the first 2 years of HRT and the risk of venous thrombosis also increased in women using combined HRT when compared to women using estrogen replacement therapy (ERT) alone (2). Epidemiological studies also showed an increased risk of CV events related to increased platelet count (3) and mean platelet volume (MPV) (4). MPV is a marker used to calculate the volume of platelets and also to determine the functions of platelets. Larger platelets are more active and secrete more Thromboxane A2 which increases the risk of thrombosis (5). Estrogen and androgen receptors were detected on megakaryocytes and platelets (6). Autocrine estrogens were shown to promote change of megakaryocytes to platelets (7). Postmenopausal women with lower estradiol levels had lesser platelet activation when compared to premenopausal women (8). In addition, it was reported that HRT increased MPV (9) and platelet activity (10). These findings suggest an association between increased risk of CV events and platelet activity in the postmenopausal period. Does the hormonal differences of postmenopausal period lead to increased CV events by changing platelet activity? The aim of this study was to evaluate

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the relationship among MPV and endogenous sex hormones and cardiovascular risk parameters in postmenopausal patients.

2. Materials and methods

Subjects for this retrospective study were recruited from the archives of our gynecology outpatient clinic. Charts of postmenopausal women attending to a previous study were searched and those with a documented complete blood count (CBC) analysis and sex steroids were included. Postmenopausal status was defined as no menses for more than twelve months in the presence of natural menopause or at the time of bilateral salpingoophorectomy in addition to a follicle stimulating hormone (FSH) level >30mIU/mL. We excluded the women who had undergone hysterectomy without salpingoophorectomy and the women using hormone replacement therapy. Only postmenopausal women without any systemic diseases such as uncontrolled diabetes mellitus (fasting serum glucose>150mg/dL), previous thromboembolic diseases (such as coronary artery disease, stroke), autoimmune diseases, chronic renal failure, hepatic diseases, malignancy, Cushing syndrome and congenital adrenal hyperplasia were included. Women using anticoagulant and antithrombotic drugs or those continuously using non-steroidal anti-inflammatory agents were excluded. The study protocol was in confirmation with the ethical guidelines of the Declaration of Helsinki.

Hip circumference (HC) and waist circumference (WC), weight, height and body mass index (BMI) of the subjects were obtained from patient charts. Levels of fasting blood glucose, insulin, total cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL), triglycerides (TG), Luteinizing hormone (LH), FSH, free testosterone (FT), estradiol (E2), sex-hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS) and C-reactive protein (CRP), hemoglobin, white blood cell count (WBC), hematocrite, platelet count, MPV were measured. Insulin resistance was determined by homeostasis model assessment (HOMA) of insulin resistance with the formula: HOMA-IR = fasting insulin (mU/mL) x fasting glucose (mg/dL)/405.

Table 1. Demographic and biochemical features of the patients

(n =71)	Mean ± SD (range)
Age (years)	56.77 ± 4.5 (47 - 69)
Height (cm)	159.39 ± 5.59 (147 - 175)
Weight (kg)	71.48 ± 11.53 (48 - 116)
Waist (cm)	94.78 ± 10.14 (70 - 119)
Hip (cm)	107.46 ± 9.24 (90 - 132)
BMI (kg/m^2)	8.31 ± 5.39 (1 - 24)
Duration of menopause (years)	28.14 ± 4.74 (20.42 - 44.2)
Waist-to-Hip Ratio	0.88 ± 0.07 (0.64 - 1.05)
Hemoglobin (mg/dL)	13.22 ± 0.85 (11.7 - 15.6)
Hematocrite (%)	39.13 ± 2.31 (34.7 - 45.5)
Mean Platelet Volume (f/L)	10.22 ± 1.03 (8.4 - 12.7)
White Blood Cell Count (mm^3)	5841.97 ± 1378.3 (3370 - 9760)
Platelet Count (mm^3)	230408.45 ± 48220.79 (127000 - 340000)
Fasting Blood Glucose (mg/dL)	98.59 ± 9.46 (78 - 143)
Low Density Lipoprotein (mg/dL)	142.26 ± 34.3 (66 - 218)
High Density Lipoprotein (mg/dL)	67.17 ± 18.98 (37 - 113)
Triglyceride (mg/dL)	102.48 ± 51.67 (45 - 375)
C-Reactive Protein (μ/dL)	0.49 ± 0.97 (0.02 - 7.5)
Insulin (uU/mL)	9.51 ± 4.67 (2.51 - 24.6)
Estradiol (pg/mL)	8.72 ± 5.12 (5 - 28.21)
Follicle Stimulating Hormone (mIU/mL)	79.23 ± 29.62 (29.29 - 163.3)
Dehydroepiandrosterone Sulfate (ug/dL)	87.36 ± 53.1 (15.75 - 251.4)
Free Testosterone (ng/mL)	0.23 ± 0.17 (0.03 - 0.77)
Sex Hormone Binding Globulin (nmol/mL)	50.42 ± 21.28 (18 - 100.2)
HOMA-IR	2.37 ± 1.38 (0.48 - 8.68)
Luteinizing Hormone (mIU/mL)	27.63 ± 11.19 (7.08 - 63.79)

Table 2. Correlations among MPV and biochemical and hormonal parameters

	r	p
[1]Hemoglobin	-0.061	*0.614*
[1]Hemotocrite	0.015	0.899
[1]White Blood Cell Count	-0.270	**0.023***
[1]Platelet Count	-0.558	**0.001****
[1]Fasting Blood Glucose	0.168	0.163
[1]Low Density Lipoprotein	0.021	0.860
[1]High Density Lipoprotein	-0.056	0.646
[2]Triglyceride	0.050	0.677
[2]C-Reactive Protein	-0.134	0.267
[2]Insulin	0.158	0.192
[2]Estradiol	-0.001	0.994
[1]Follicle Stimulating Hormone	0.003	0.982
[2]Dehydroepiandrosterone Sulfate	-0.138	0.292
[2]Free Testosterone	0.044	0.719
[1]Sex Hormone Binding Globulin	0.140	0.256
[2]HOMA-IR	0.146	0.226
[1]Luteinizing Hormone	0.077	0.559

[1]r= Pearson Correlation Coefficient *p<0.05
[2]r= Spearman Correlation Coefficient **p<0.01

To define metabolic syndrome (MS) we used The Third Report of the National Cholesterol Education Program (NCEP) expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP-III). When ≥ 3 of the following criteria were present, patients were diagnosed with MS: 1. Systolic/Diastolic blood pressure ≥130/85mmHg or use of antihypertensive medications, 2. Waist circumference (WC) >88cm, 3. HDL-cholesterol < 50mg/dL, 4. Triglycerides ≥ 150mg/dL, 5. Fasting blood glucose ≥ 100mg/dL or use of hypoglycemic agents.

3. Results

There were 71 postmenopausal patients in the study group. Demographic and biochemical features of the patients were given in Table 1. Patients with MS (n=19) had a MPV of 10.17 ± 1.02 fL and patients without MS had a MPV of 10.23 ± 1.04 fL (p=0.818). MPV was not correlated with age (r=-0.071, p = 0.561), height (r = -0.044, p = 0.716), weight (r = 0.089, p=0.460), WHR (r = -0.036, p = 0.764), BMI (r=0.102, p=0.397) and duration of menopause (r=-0.156, p=0.194) in postmenopausal women.

The correlations among MPV, and biochemical and hormonal parameters were given in Table 2. MPV correlated with WBC (r=-0.270, p=0.023) and platelet count (r=-0.558, p=0.001). MPV correlated only with platelet count in patients with MS (r=-0.662, p=0.002).

4. Discussion

Mechanisms of arterial thrombosis and venous thrombosis are different. Arterial thrombosis develops by the adhesion of platelets to damaged endothelial surface, whereas venous thrombosis can develop without endothelial damage (11,12). The incidences of CV events are lower in premenopausal women when compared to men at the same age, but the rate increases after menopause. Platelet levels of men and women differ at every age group and decrease in both of them with aging (13). This oriented researchers to search the effects of hormones on platelet activity. Platelet aggregation changes in parallel to the changing estradiol levels of the menstrual cycle (14). Interruption of the natural menopause with HRT lead to an increase in platelet activity, microparticules originating from platelets increased (15). Another support to the relationship between platelets and hormones came from studies with selective estrogen receptor modulators, MPV increased in breast cancer patients using tamoxifen (16). These findings suggested sex hormones to have a role in CV events which might be related to platelet function instead of the coagulation cascade. To expect such an effect is logical because platelets contain both estrogenic and androgenic receptors (6). In this study we did not find a relationship between MPV, a marker of platelet activity and endogenous sex steroids and cardiovascular risk parameters and previous studies reported conflicting results about the effects of HRT on platelet functions (10-17). ERT was reported to increase MPV (9), both the estrogen and progesteron components of the oral contraceptives increased platelet aggregation (18). Our failure to detect a relationship might be due to different effects of endogenous and synthetic estrogen and progesteron on platelet functions, but in a previous study women with low levels of estradiol in the postmenopausal period had less platelet activation than premenopausal women (8).

In vitro studies showed human platelet aggregation to be enhanced by androgens (19). In vivo studies supported these findings, androgen therapy improved platelet counts in patients with myelodysplasia and thrombocytopenia (20) and

platelet production decreased with castration (21). DHEAS levels decrease with aging and CV events increase with aging. Women with polycystic ovary syndrome have a higher risk of CV events, they were reported to have a higher rate of MPV and their MPV correlated with DHEAS and FT levels (22). In an effort to decrease CV mortality, chronic DHEA supplementation was suggested, DHEA was expected to exert antiatherogenic effects, particularly in elderly subjects whom displayed low circulating levels of this hormone (23). In other reports physiologic doses of DHEAS prevented platelet activation and decreased risk of arterial thrombosis (24). When DHEAS was added to blood from postmenopausal women, platelet aggregation decreased (25). In our study neither DHEAS nor testosterone correlated with MPV. This suggests endogenous and synthetic hormones to exert different effects on platelets.

Limitations of this study might be the exclusion of postmenopausal women with systemic diseases, MPV might be higher in this group. The study group may be smaller to detect differences between the two groups.

In conclusion, we found no relationship among MPV and endogenous sex hormones and parameters indicating increased CV risk and we cannot suggest it as a marker of CV events in postmenopausal women.

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