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Effects of oral hormone replacement therapy on mean platelet volume in postmenopausal women

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Background/aim: To examine the effects of hormone replacement therapy (HRT) on mean platelet volume (MPV), lipid profile, and C-reactive protein (CRP) levels in postmenopausal women who have a high risk and incidence of cardiovascular disease.

Materials and methods: This study was performed retrospectively. Twenty-seven healthy postmenopausal women received 1 mg estradiol and 2 mg drospirenone orally for 6 months. Twenty-eight healthy postmenopausal women not taking any HRT were admitted to the study as the control population.

Results: Time effect (independent from group effect) was statistically significant for the MPV variable (P = 0.025), but there was no significant change in MPV levels and other cardiovascular disease risk markers in women receiving HRT compared to women in the control group.

Conclusion: Younger postmenopausal women taking HRT and women who initiated hormone therapy close to menopause are not at increased risk of cardiovascular disease.

Key words: Mean platelet volume, menopause, cardiovascular risk, hormone replacement therapy, lipid profile

1. Introduction

Cardiovascular disease (CVD) is the most common cause of female death worldwide. While CVD is rare in premenopausal women, its incidence markedly increases after menopause. This has been partly attributed to the decline in circulating levels of estrogen (1). Observational studies have also shown that hormone replacement therapy (HRT) reduces the risk of CVD in postmenopausal women. However, large randomized, controlled trials have not recommended HRT for CVD treatment during menopause (2). Nevertheless, there is emerging evidence that initiation of HRT in close proximity to menopause may reduce the risk of CVD (3). Overall, there are conflicting reports, and it is important to clarify whether HRT prevents or promotes CVD.

Platelets are important for the integrity of normal homeostasis, and mean platelet volume (MPV), an accurate measure of platelet size, is an indicator of platelet function. Large platelets with high MPV values are metabolically and enzymatically more reactive than small platelets and produce more prothrombotic factor thromboxane A2, increasing the propensity for thrombosis (4). A high MPV level is a new and independent risk factor for atherothrombosis and CVD. It has been shown to be high in acute myocardial infarction, cerebral ischaemia, and transient ischaemic attacks (5). Moreover, measuring MPV is a cost-effective and simple procedure.

So far there has been insufficient knowledge about why young or premenopausal women are safe from CVD, and why postmenopausal women do not benefit from HRT.

The aim of the present study is to investigate the effect of low-dose combined oral hormone replacement therapy on MPV, lipid profile, and C-reactive protein (CRP) levels in postmenopausal women.

2. Materials and methods

This study was performed retrospectively between January 2007 and August 2009 at the Medical School of

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Turgut Özal University, Department of Obstetrics and Gynecology, Ankara, Turkey. Fifty-five healthy, nonobese postmenopausal women between the ages of 43 and 52, without any known cardiovascular risk factors, were included in this study. Patients were excluded from the study if they had cardiovascular disease, thromboembolic disease, hypertension, thyroid disease, diabetes mellitus, acute or chronic inflammatory or infective diseases, anemia, or alcohol abuse. All subjects were nonsmokers and had not taken any drugs that affect platelet aggregation. This information was obtained from the patient care computer system.

Twenty-seven healthy postmenopausal women receiving 1 mg estradiol and 2 mg drospirenone (Angeliq tablet; Bayer Ilaç, İstanbul) for 6 months were placed in the hormone treatment group. The indications for hormone replacement were vasomotor symptoms and dyspareunia caused by vaginal atrophy. Twenty-eight healthy postmenopausal women not taking any hormone treatment were admitted to the study as the control population. All participants had been amenorrheic for 1–3 years or had serum follicle-stimulating hormone concentration of >25 IU/L. No women had received HRT for at least 3 months before the study. All subjects were evaluated for the effect of HRT use for 6 months before and after the study.

Venous blood samples were obtained from the participants through routine full blood count tests. Samples were collected in Becton Dickinson Vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA) containing tripotassium EDTA. Complete blood count (CBC) analyses were performed in a Beckmann Coulter analyzer model LH within 1 h. MPV analyses were performed as part of each CBC. The MPV reference range in our clinic is 7.8–11.1 fL. The other parameters measured in fasting blood samples were glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and CRP.

Continuous variables were inspected for normality of statistical distribution both graphically and by Shapiro–Wilk test. Data are reported as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Considering that some clinical variables are influenced by subject age and menopausal age, HRT and control groups were standardized with respect to these 2 covariates. The Mann–Whitney U test was used to perform the statistical analysis of the variables without normal distribution. To evaluate group, time, and group × time interaction effects on clinical variables, 2-way repeated ANOVA was used with Bonferroni adjustment. Type-I error rate was taken as $\alpha = 0.05$. Statistical analysis was performed using the SPSS 20 (SPSS Inc., Chicago, IL, USA).

3. Results

There were no differences in age, gravida, parity, menopausal age, menopausal time, and BMI values between the analyzed groups. Table 1 shows the clinical characteristics of the subjects in all groups. Group, time, and group × time interaction effects were analyzed for clinical variables. In the HRT group, while the MPV level was 7.92 ± 0.68 fL at baseline, after 6 months it increased to 8.04 ± 0.64 fL. In the control group, while the MPV level was 8.22 ± 0.90 fL at baseline, after 6 months it decreased to 8.16 ± 0.73 fL. Time effect (independent from group effect) was statistically significant for the MPV variable ($P = 0.025$). Group and group × time interaction effect were not statistically significant for the MPV variable ($P = 0.273$ and $P = 0.152$, respectively) (Table 3).

The group × time interaction effect was statistically significant for hemoglobin (Hb) and hematocrit (Htc) values ($P = 0.002$ and $P = 0.037$, respectively). The difference between baseline and 6-month Hb values for the control group was statistically significant ($P = 0.004$). The difference between baseline and 6-month Htc values for

Table 1. The demographic properties of the study and control groups.

	HRT (n = 27) Median (IQR)	Control (n = 28) Median (IQR)	P
Age (years)	49 (5)	50	0.94
Gravidity	3 (3)	4 (1.5)	0.74
Parity	2 (4)	2 (1)	0.34
Menopause age (years)	47 (6)	48 (4.5)	0.79
Menopause time (years)	1 (2)	2 (1.5)	0.53
BMI-0 (kg/m^2)	24.14 (3.91)	26.56 (30.44)	0.08
BMI-6 (kg/m^2)	24.35 (4.04)	26.56 (3.74)	0.68

HRT: hormone replacement therapy, BMI-0: pretreatment body mass index, BMI-6: body mass index after 6 months, IQR: interquartile ranges.

Table 2. Baseline and 6-month data for subjects.

		HRT		Control	
		Mean ± SD	n	Mean ± SD	n
Hb (g/dL)	Baseline	13.78 ± 0.74	27	13.99 ± 0.76	28
	6-month	13.94 ± 0.77	27	13.70 ± 0.80	28
Htc (%)	Baseline	40.74 ± 2.18	27	41.35 ± 2.61	28
	6-month	41.02 ± 2.18	27	40.46 ± 2.13	28
Plt ($\times 10^3/\mu L$)	Baseline	287.15 ± 63.31	27	288.36 ± 66.57	28
	6-month	286.00 ± 63.25	27	275.18 ± 72.74	28
MPV (fL)	Baseline	7.92 ± 0.68	27	8.22 ± 0.90	28
	6-month	8.04 ± 0.64	27	8.16 ± 0.73	28
PDW (%)	Baseline	16.05 ± 0.41	27	16.28 ± 0.72	28
	6-month	16.12 ± 0.44	27	16.18 ± 0.61	28
FG (mg/dL)	Baseline	85.86 ± 8.81	11	89.60 ± 7.17	21
	6-month	89.15 ± 6.04	11	89.90 ± 7.32	21
TC (mg/dL)	Baseline	211.15 ± 338.96	11	218.34 ± 36.56	21
	6-month	213.20 ± 29.42	11	212.18 ± 31.27	21
LDL (mg/dL)	Baseline	115.09 ± 32.94	11	128.99 ± 31.60	21
	6-month	124.64 ± 29.88	11	124.06 ± 35.48	21
HDL (mg/dL)	Baseline	62.33 ± 15.86	11	68.73 ± 19.89	21
	6-month	58.67 ± 16.14	11	66.73 ± 19.91	21
TG (mg/dL)	Baseline	112.72 ± 44.94	11	103.42 ± 59.98	21
	6-month	130.17 ± 50.12	11	105.69 ± 58.10	21
CRP (mg/L)	Baseline	3.19 ± 3.26	11	3.58 ± 2.54	21
	6-month	2.01 ± 1.61	11	2.81 ± 3.37	21

HRT: hormone replacement therapy, Hb: hemoglobin, Htc: hematocrit, Plt: platelet, MPV: mean platelet volume, PDW: platelet distribution width, FG: fasting glucose, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, CRP: C-reactive protein.

the control group was statistically significant (P = 0.024) (Table 3). Group, time, and group × time interaction effects were not statistically significant for other clinical variables. Table 2 shows the baseline and 6-month data for the subjects.

4. Discussion

In this study, we found a statistically significant increase in MPV levels from baseline to 6 months. However, there was no significant difference in MPV levels and other CVD risk markers between women receiving oral combined continuous 1 mg estradiol plus 2 mg drospirenone and the control group.

Postmenopausal women have a high risk and incidence of CVD, which is attributed to a decline in estrogen levels. Despite the potential beneficial effects of estrogen for cardioprotection, including an improvement in lipid profiles, endothelial function (6,7), and insulin sensitivity, it also has adverse effects, such as an increase in serum triglyceride levels, and effects on vascular inflammatory markers such as CRP and prothrombotic marker (8).

Nowadays, MPV is thought to play a significant role in coronary artery disease, diabetes, atherosclerosis, hypertension, and other vascular insufficiency states (4). Platelets play an important role in the integrity of normal homeostasis. Large platelets contain denser granules and are hemostatically more reactive; therefore, they are more thrombogenic. MPV, an accurate measure of platelet size, reflects the activity of platelets (4). Moreover, increased MPV is now emerging as an independent risk factor for CVD (5).

Several scientific reports have shown sex-related differences in platelet count and MPV, which seem to reflect hormonal profiles. In 1994 Tarantino et al. discovered the

Table 3. Two-way repeated analysis of variance test results for each clinical parameter.

	Effect					F	df	P
		HRT		Control				
Hb	Group × time	Baseline	6-month	Baseline	6-month	11.049	1	0.002
		13.8 ± 0.14	13.94 ± 0.15	13.99 ± 0.14*	13.70 ± 0.15			
		HRT		Control				
Htc	Group × time	Baseline	6-month	Baseline	6-month	4.572	1	0.037
		40.74 ± 0.46	41.01 ± 0.42	41.35 ± 0.46†	40.46 ± 0.41†			
		HRT	Control					
	Group	7.98 ± 0.14	8.19 ± 0.14			1.229	1	0.273
		Baseline	6-month					
MPV	Time	8.07 ± 0.11	8.1 ± 0.09			5.318	1	0.025
	Group × time	HRT		Control				
		Baseline	6-month	Baseline	6-month			
		7.92 ± 0.15	8.04 ± 0.13	8.22 ± 0.15	8.16 ± 0.13	2.114	1	0.152

*Difference between baseline and 6-month HB values for control group is statistically significant (P = 0.004)
†Difference between baseline and 6-month HCT values for control group is statistically significant (P = 0.024)

presence of functional estrogen receptors in megakaryocytes and blood platelets in vitro (9). Butkiewicz et al. (10) showed higher platelet count and lower MPV levels in women due to menstrual blood loss. While Bain suggested a similar correlation (11), other research found no correlation and no statistically significant differences in MPV between sexes (12). In another study, platelet count was lower in postmenopausal women compared to young menstruating women. However, MPV values were similar in both groups (13). When evaluating the effect of hormone treatment, Ranganath et al. (6) showed an increase in platelet count (not significant) and platelet volume (MPV) ($P < 0.05$) after 6 weeks of hormone therapy (conjugated equine estrogen 0.625 mg daily combined with L-norgestrel 75 mg daily, from days 17 to 28 of a 28-day cycle). Teede et al. (7) noted no difference in MPV within 6 months of 2 mg estradiol plus 1 mg of norethisterone exposure; yet, they noted a trend towards increased platelet aggregation in the HRT group. In other studies, the effects of HRT on platelet function were evaluated by measuring platelet aggregation, fatty acid composition of platelet membranes, and urinary thromboxane B2 excretion (14,15). While Saraç et al. (14) found no difference in platelet function in postmenopausal women with HRT (transdermal estradiol, estradiol 17-valerate/cyproterone acetate, or tibolone) after 6 months, Yoshimura et al. (15) discovered significant reduction in the activity of platelet-activating factor acetylhydrolase (PAF-AH) within 2 weeks of a 10-week conjugated equine estrogen treatment.

Despite its importance, there are limited reports about the effect of hormone replacement therapy on MPV levels. Other platelet aggregation methods have been evaluated more frequently. However, there are many differences in hormonal preparations with regard to type and dose of estrogen and type of progestin combination. An important point to consider is that the measurement of MPV is a cost-effective and simple procedure compared to other procedures. The MPV value can improve the follow-up and management of postmenopausal women taking HRT. It may aid the detection of CVD and may decrease future complications of HRT use. Early detection of possible CVD complications will increase the quality of life of the patient and their chance of survival. To achieve these results, a longer-term follow-up of the subjects and larger series are necessary. One limitation of our study is the moderate sample size and the 6-month follow-up period. Additionally, the women in our study were healthy and were not at risk of the conditions associated with HRT use. After 6 months, we did not observe any change in CVD risk markers such as MPV, lipid profile, and CRP levels. These results suggest that younger postmenopausal women taking HRT and women who initiated hormone therapy close to menopause are not at increased risk of CVD. Our findings are consistent with the study of Rossouw et al. (3), which is a secondary analysis of the Women's Health Initiative's randomized controlled trials of hormone therapy.

In conclusion, menopause is an important phase in a woman's life, and postmenopausal women have a high risk and incidence of CVD. It is suggested that initiation of HRT close to menopause and at a younger age is associated with

a lower incidence of CVD. MPV is a new and independent risk factor for CVD, and the measurement of MPV is a cost-effective and simple procedure that can be used in the preassessment phase at the start of the treatment. High MPV levels can be cautionary, even if the patient does not carry any risk factors for CVD. Further studies with larger series and a longer-term follow-up of cases are needed to confirm these results.

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