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ORIGINAL STUDY

Evaluation of the relationship between plasma viscosity and selected menopausal symptoms using the Menopause Rating Scale

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Abstract

Objective: The aim of this study was to investigate whether whole blood viscosity and plasma viscosity are associated with the severity of postmenopausal symptoms using the Menopause Rating Scale (MRS).

Methods: This study included 108 postmenopausal women admitted to menopause clinics. Participants were divided into two groups according to their MRS scores. Groups 1 (n = 52) and 2 (n = 56) were composed of healthy postmenopausal women with MRS scores of <14 and ≥14 points, respectively. The clinical findings and hemorheological parameters were compared between the two groups.

Results: Comparing plasma viscosity levels between the two groups showed that group 1 had 1.25 ± 0.08 centipoise, whereas group 2 had 1.30 ± 0.10 centipoise ($P = 0.03$). The difference in plasma viscosity between the two groups persisted after adjustment for age (1.24 ± 0.08 vs 1.31 ± 0.10; $P < 0.001$). Plasma viscosity was also significantly correlated with age ($r = 0.384$, $P < 0.001$), menopausal duration ($r = 0.362$, $P < 0.001$), and urogenital symptoms ($r = 410$, $P < 0.001$).

Conclusions: Increased plasma viscosity levels were significantly associated with selected postmenopausal symptoms, independent of age.

Key Words: Hemorheology – Menopausal symptoms – Menopause Rating Scale – Plasma viscosity – Urogenital symptoms.

Menopause is defined as the permanent cessation of spontaneous menses for 12 months. Most women worldwide reach menopause between 49 and 52 years of age.[1] With life expectancy increasing in developed countries, most women can expect to live a third of their lives after menopause.[2] Symptoms of menopause are experienced by most women during the menopausal period and can significantly affect their quality of life.[3] Hot flashes are usually observed in late perimenopause and the first few years after menopause. However, some women continue to experience vasomotor symptoms for years after menopause.[4] In addition, sleep disorders are very common in the menopausal period and are often attributed to night sweats and frequent arousal due to psychological factors.[5] Menopause does not cause mood disorders, such as depression and anxiety; however, women prone to these disorders may experience their first attack or a relapse during the transition to menopause.[6] In addition, muscle and joint pains are common symptoms in the menopausal period,[7] and hot flashes and depressed mood disorders are often experienced.[8]

Different scales have been used to determine the severity of menopausal symptoms. In this study, we utilized the commonly used Menopause Rating Scale (MRS).[9] The MRS aims to compare the menopausal symptoms of women with different conditions, determine the severity of their symptoms over time, and compare the conditions before and after treatment.[10] The MRS is an internationally accepted scale that has been translated into various languages and used in several studies.[11]

Viscosity is defined as the ratio of shear stress to shear rate. Plasma viscosity has a normal value between 1.10 and 1.35 centipoise (cp) at 37°C.[12] Blood is a biphasic fluid; its fluidity at a given shear rate and temperature is determined by the rheological properties of plasma, cellular phases, and hematocrit. A change in plasma viscosity directly affects blood viscosity because it does not contain cellular elements from the blood. Whole blood viscosity (WBV) is closely related to the hematocrit. In addition, the hematocrit in a person is not constant and is a dynamic parameter that can change rapidly and significantly as a part of the physiological, pathophysiological, and even psychosomatic processes. For example, an acute increase in hematocrit may

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result from a relative increase in erythrocyte mass in the circulatory system because of decreased intravascular fluid volume.[13]

The fluidity of blood mainly depends on the volumetric ratio of the cellular elements of blood (hematocrit) and its rheological properties (eg, plasma viscosity, erythrocyte aggregation, and erythrocyte deformability). Plasma acts as a carrier for cellular elements in the blood; hence, a change in the fluidity of plasma directly affects the blood viscosity. When blood viscosity increases, tissue perfusion decreases,[14] and tissues with impaired or decreased blood supply cannot be expected to perform physiological functions. Clinical and experimental studies have clearly shown that blood flow behavior is an important determinant of optimum tissue perfusion.[15,16] Moreover, increased blood viscosity is related to ischemic heart disease, stroke, metabolic syndrome, and diabetes mellitus, which are all associated with chronic inflammation.[17-19] Several studies report the association of conditions such as mean arterial blood pressure increase and osteoporosis with increased hematocrit in the postmenopausal period and therefore an increase in blood viscosity.[20,21] However, no studies have investigated the relationship between WBV or plasma viscosity and selected postmenopausal symptoms using the MRS. Demonstrating the existence of such a relationship may help in improving the quality of life of women in the postmenopausal period. Therefore, in this study, we investigated whether both WBV and plasma viscosity are associated with the severity of postmenopausal symptoms using the MRS.

METHODS

Study design

This study included 108 postmenopausal women between 40 and 70 years who were admitted consecutively to the menopause clinic. This study fulfilled the requirements of good clinical practice according to the Declaration of Helsinki and was approved with number 2020/143 by the Gazi University Ethics Committee for Clinical Research, Ankara, Turkey. All participants provided written informed consent to participate in the study.

Women in the postmenopausal period with the following criteria were excluded: those who had undergone menopause surgically (oophorectomy) or medically due to chemotherapy; those with chronic diseases such as diabetes, hypertension, chronic kidney disease, blood diseases such as hemoglobinopathy, chronic inflammatory disease, cardiovascular or cerebrovascular disease, and malignancy; those receiving any medical treatment such as hormone therapies (HTs) or anticoagulant agents; those who were smokers or alcohol abusers; and those who had a COVID-19 infection.

In the design stage of this study, two independent groups were determined to evaluate MRS scores and hemorheological tests. Whereas an independent gynecologist performed the MRS scoring of the participants, physiologists who were not aware of MRS scores performed the hemorheological tests.

Study questionnaire

The data collected included self-reported age, height, weight, duration of menopause, history of smoking and alcohol consumption, and general medical history. Menopausal symptoms were assessed using the MRS, including 11 questions about somatic, urogenital-sexual, and psychological problems.[11] For each item, the women were assigned a score ranging from 0 to 4 for the intensity of the symptom (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The total score corresponded to the sum of the values obtained for each item on the scale. The women were divided into two groups according to their total score: group 1, <14 points; and group 2, ≥14 points. An MRS score of ≥14 indicated the need to receive therapy for climacteric symptoms.[10]

Hemorheological measurements

Venous blood samples were collected from the participants between 9:00 AM and 11:00 AM, after a 12-hour overnight fast. For WBV and plasma viscosity measurements, blood samples were collected from the participants and transported immediately to the physiology laboratory without any delay. Whole blood and plasma viscosities were measured using a Vilastic Bioprofiler (Vilastic Scientific, Inc, Austin, TX). For WBV measurement, 0.5 mL whole blood was used, and for plasma viscosity measurement, approximately 3 mL of blood was centrifuged at 1,500*g* for 5 minutes. All measurements were performed at a constant temperature achieved by operating the device at a constant temperature for at least 30 minutes before conducting the measurements. All samples were evaluated within a fixed time after blood samples were collected to eliminate the effect of the time interval between blood sampling and viscosity measurements. Because hematocrit is a determining parameter for WBV, all measurements were made at a 45% hematocrit value. The hemogram results were obtained, and all blood samples were corrected with their hematocrit values and recalculated using the Vilastic Bioprofiler computer program, as described by the manufacturer. The viscosity results are given as a centipoise unit.

The hemogram parameters were determined using an autoanalyzer (Abbott Cell-Dyn Sapphire, Abbott Diagnostics, Santa Clara, CA). Blood samples for measuring the hemogram were collected simultaneously with blood samples for measuring viscosity. In the design stage of this study, two independent groups were determined to evaluate the MRS scores and hemorheological tests. While MRS scoring of the participants was performed by an independent gynecologist, hemorheological tests were performed by physiologists who were not aware of MRS scores.

Statistical analysis

A post hoc power analysis was conducted with a power of 81.38%, and statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to determine the distribution of the variables. Normally distributed variables were compared using an independent-samples *t* test and expressed as mean ± SD. Variables that were not normally distributed were evaluated using the Mann-Whitney *U* test and expressed as median (min-max). Multiple regression analysis was used to analyze the relationship between the corrected data, and univariate analysis of variance was used to compare the mean plasma viscosity after adjusting for age. Pearson correlation analyses were used to determine the degree of association of parametric

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TABLE 1. *Clinical characteristics and blood parameters of participants (n = 108)*

Age, y	57.7 ± 8.1
BMI, kg/m^2	30.5 ± 2.3
MD, y	8.4 ± 4.9
Plasma viscosity, cp	1.28 ± 0.09
WBV, cp	4.22 ± 0.75
WBC, 10^3/μL	7.2 (1.9-18.4)
RBC, M/μL	4.77 ± 0.58
Hemoglobin, g/dL	13.0 ± 1.6
Hematocrit, %	40.8 ± 4.6
MCV, fL	87 (66-95)
MCH, pg	27.8 (20-31.3)
MCHC, %	31.9 ± 1.2
RDW, %	13 (10.9-18)
ESR, mm/h	12.7 ± 8.8

BMI, body mass index; cp, centipoise; ESR, erythrocyte sedimentation rate; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MD, duration of menopause; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell; WBW, whole blood viscosity.

data. The results were evaluated using a 95% confidence interval, and $P < 0.05$ was considered significant.

RESULTS

The mean age of the participants was 57.7 ± 8.1 years, BMI was 30.5 ± 2.3 kg/m^2, and the mean duration of menopause was 8.4 ± 4.9 years. In addition, the mean plasma viscosity level was 1.28 ± 0.09 cp, and WBV was 4.22 ± 0.75 cp. The clinical and blood parameters of the participants are shown in Table 1.

Whereas 93.5% of the women included in the study experienced hot flushes and sweating symptoms, 6.5% of them did not. Therefore, these symptoms were the most commonly observed in the women included in this study. Muscle and joint discomfort was the least common symptom (63.9%) in the participants. The prevalence and intensity of all symptoms found in women according to the MRS are shown in Table 2.

According to the MRS score, there was a significant difference in terms of age (60.4% ± 6.4% vs 55.4% ± 8.9%, $P = 0.011$) and plasma viscosity (1.25% ± 0.08% vs 1.30% ± 0.10%, $P = 0.03$; Fig. 1) among the two groups. The difference in plasma viscosity between the two groups persisted after adjusting for age (1.24 ± 0.08 vs 1.31 ± 0.10, $P < 0.001$). A comparison of the clinical characteristics and blood parameters between the two groups is shown in Table 3.

Plasma viscosity was significantly correlated with age ($r = 0.384$, $P < 0.001$), menopausal duration ($r = 0.362$, $P < 0.001$), and erythrocyte sedimentation rate ($r = 0.426$, $P = 0.06$). The total MRS score was not significantly correlated with plasma viscosity. However, plasma viscosity significantly correlated with the total score of urogenital symptoms when the MRS score was divided into three groups in terms of somatic, psychological, and urogenital symptoms ($r = 0.410$, $P < 0.001$; Fig. 2).

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the relationship between the MRS and the severity of selected menopausal symptoms and plasma viscosity. Healthy postmenopausal women were compared with women with MRS scores of <14 and ≥14 points in relation to plasma viscosity, WBV, and complete blood parameters. The results revealed that the plasma viscosity level was higher in women with MRS ≥14 and is related with the score of urogenital symptoms. We also found a significant correlation between the duration of menopause and plasma viscosity, with data suggesting that plasma viscosity may play a role in postmenopausal symptoms.

In addition, this study found that women with selected menopausal symptoms requiring treatment according to the MRS score (MRS ≥14 points) had a significantly higher plasma viscosity than did those who did not require treatment. This result suggests that the reason for postmenopausal symptoms might be increased plasma viscosity. Moreover, plasma viscosity and WBV are parameters that determine tissue blood supply, and deterioration of physiological functioning is inevitable in tissues with insufficient blood supply. Teng et al[20] showed a negative correlation between bone mineral density and WBV in a study that included 163 participants with postmenopausal osteoporosis, 155 with osteopenia, and 163 control participants. Moreover, they emphasized that osteoporosis is associated with cardiovascular disease and has been shown to be an independent predictor of cardiovascular mortality.[20] The hypothesis that increased plasma viscosity may be one of the mechanisms linking conventional risk factors to the risk of cardiovascular disease and that appropriate lifestyle changes may decrease its incidence was proposed in a study by Bonithon-Kopp et al.[22] In addition, a study published in *Menopause* that evaluated postmenopausal women with glaucoma reported that plasma viscosity

TABLE 2. *Menopause Rating Scale % scores of participants (n = 108)*

	MRS score				
Symptoms (MRS)	Absent (0)	Mild (1)	Moderate (2)	Severe (3)	Very severe (4)
Hot flushes, sweating	6.5	53.7	21.3	16.7	1.9
Heart discomfort	14.8	52.8	26.9	4.6	0.9
Sleep problems	27.8	35.2	20.4	14.8	1.9
Muscle and joint discomfort	36.1	24.1	25	10.2	4.6
Depressive mood	21.3	40.7	25	9.3	3.7
Irritability	18.5	44.4	21.3	14.8	0.9
Anxiety	18.5	45.4	25.9	9.3	0.9
Physical and mental exhaustion	8.3	38.9	31.5	18.5	2.8
Sexual problems	15.7	38	29.6	15.8	0.9
Bladder problems	14.8	40.7	27.8	14.8	1.9
Vaginal dryness	15.7	43.5	27.8	12	0.9

MRS, Menopause Rating Scale.

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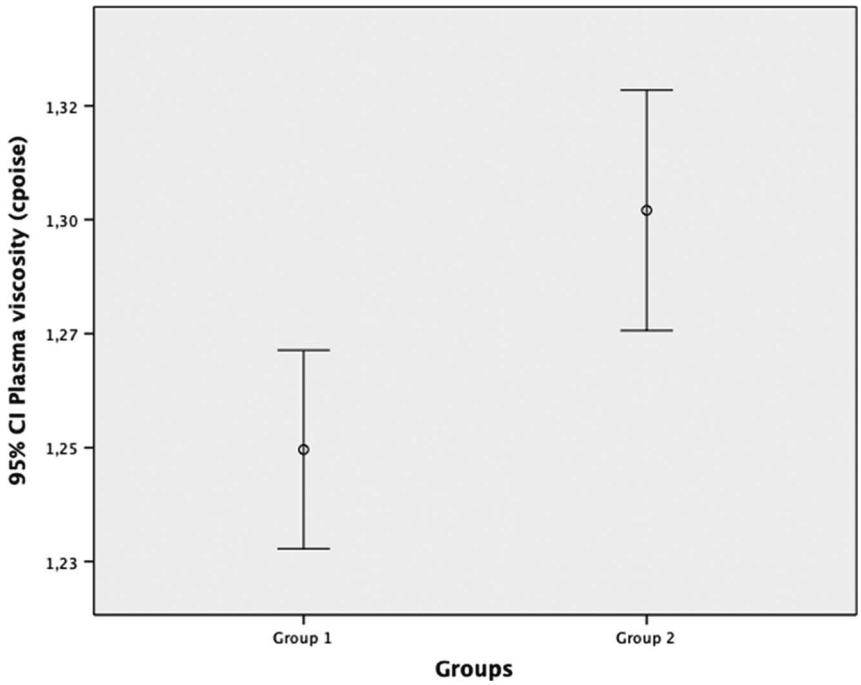


FIG. 1. Plasma viscosity levels in groups 1 and 2 ($P = 0.03$).

and Doppler parameters (ophthalmic artery mean improvements of pulsatility index, peak systolic blood flow velocity, and time-averaged maximum velocity) were significantly improved after 6 months of HT.[23] Another study that included 753 men and 821 women between the ages of 25 and 74 years showed that postmenopausal women have higher blood viscosity, hematocrit, corrected blood viscosity, plasma viscosity, and fibrinogen levels than premenopausal women; these findings are associated with cardiovascular disease. Moreover, it has been suggested that each of these differences is completely or partially eliminated by using HT.[24] Although many studies have suggested that whole blood and plasma viscosity may be associated with various diseases,[25-27] no study has directly investigated their relationship with postmenopausal symptoms. However, few studies have examined the relationship between plasma viscosity and HT, which is recommended for treating estrogen deficiency and is often blamed for postmenopausal symptoms. Spengler et al[28] showed that plasma viscosity and WBV decreased significantly after 6 months of using HT, compared with before treatment. Moreover, Rosenson et al[29] claimed that the use of HT in postmenopausal women reduced the risk of cardiovascular disease by reducing plasma viscosity. Another study performed by Mancini et al[30] used Doppler flow modifications at the uterine, internal carotid, ophthalmic, and bladder wall arteries to evaluate the effects of transdermal HT on certain biological cardiovascular risk factors. Mancini et al[30] showed that the use of transdermal HT for 6 months caused a significant decrease in plasma viscosity in both nonsmokers and heavy smokers. In summary, these study findings and our study findings strengthen the idea that plasma viscosity may play an important role in postmenopausal symptoms.

TABLE 3. *Clinical characteristics and blood parameters of the two groups determined according the MRS score (n = 108)*

	Group 1 (<14 points) (n = 52)	Group 2 (≥14 points) (n = 56)	*P*
Age, y	60.4 ± 6.4	55.4 ± 8.9	**0.011**[a]
BMI, kg/m^2	29.0 (27.9-33.3)	30.8 (27.1-35.2)	NS
MD, y	10.0 ± 2.5	7.1 ± 6.2	NS
Plasma viscosity, cp	1.25 ± 0.08	1.30 ± 0.10	**0.003**[a]
Plasma viscosity (adjustment for age), cp	1.24 ± 0.08	1.31 ± 0.10	**<0.001**[a]
WBV, cp	4.5 ± 0.69	4.0 ± 0.8	NS
WBC, 10^3/μL	7.39 (5.72-10.02)	5.89 (1.89-18.38)	NS
RBC, M/μL	4.87 ± 0.39	4.69 ± 0.70	NS
Hemoglobin, g/dL	13.5 ± 1.4	12.6 ± 1.8	NS
Hematocrit, %	41.7 ± 3.9	40.0 ± 5.1	NS
MCV, fL	85.6 (78.6-95.0)	88.2 (66.6-93.4)	NS
MCH, pg	27.6 (25.3-31.3)	28.3 (20.0-31.1)	NS
MCHC, %	32.4 ± 0.7	31.6 ± 1.4	NS
RDW, %	12.2 (10.9-15.4)	13.0 (11.6-18.0)	NS
ESR, mm/h	13.7 ± 6.2	11.9 ± 10.7	NS

BMI, body mass index; cp, centipoise; ESR, erythrocyte sedimentation rate; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MD, duration of menopause; NS, nonsignificant; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell; WBV, whole blood viscosity.
[a]Group 1 versus group 2.

Besides showing that women with severe menopausal symptoms had higher plasma viscosity, ours was the first study that found a significant relationship between menopausal duration and plasma viscosity. In other words, as the duration of menopause increases, the plasma viscosity also increases. In a single study performed by Larsson et al,[31] blood viscosity was measured in postmenopausal women twice, with a 2-week interval, and there was no reported change. The same study determined a significant difference in blood viscosity measured at the beginning of the menstrual cycle and on the 21st day in women during the reproductive period.[31]

When we evaluated the women in our study without dividing them into groups according to the severity of their symptoms,

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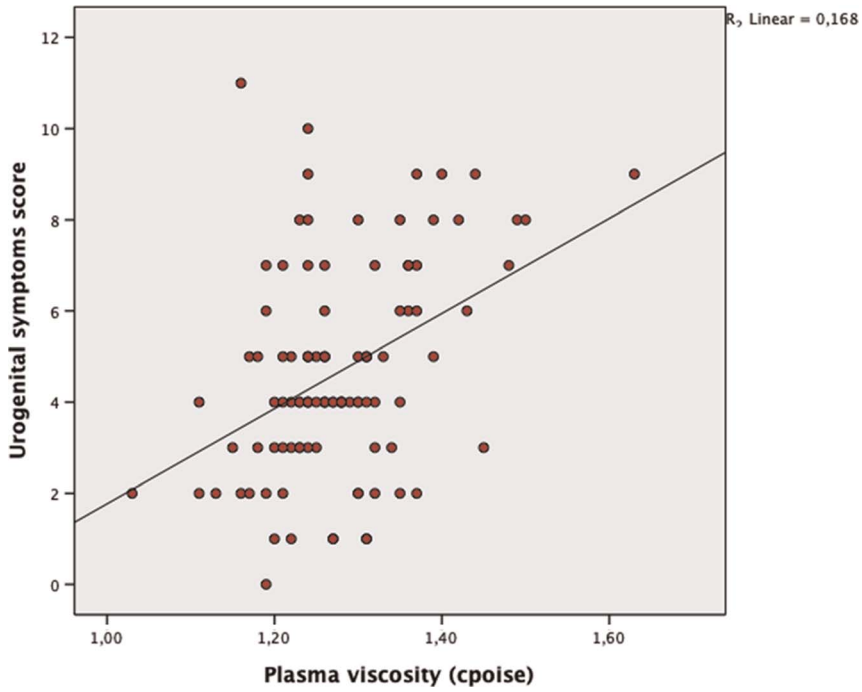


FIG. 2. Correlation of plasma viscosity and urogenital symptoms score ($r = 0.410$, $P < 0.001$).

we found that urogenital symptoms (sexual problems, bladder problems, and vaginal dryness) positively correlated with plasma viscosity. This study evaluated somatic, urogenital, and psychological symptoms using the MRS. We attribute the correlation of plasma viscosity with urogenital symptoms alone to the increased severity of urogenital symptoms in the late menopausal period.

Our study has several limitations. First, although the power of our study was 81.38%, the relatively small number of participants included was an important limitation of our study. Second, the fact that the data collected were hospital-based rather than population-based may have caused bias in case selection. However, we attempted to include healthy individuals by establishing wide exclusion criteria. Third, this study did not evaluate some problematic postmenopausal conditions such as cognitive decline, osteoporosis or bone loss, metabolic syndrome, increased risk/incidence of cancer, and cardiovascular disease. Finally, although causal inference cannot be established with the results of this study, this is a helpful cross-sectional study to help understand the burden and set up hypotheses. Despite these limitations, the prospective nature of the study and using an internationally accepted questionnaire such as the MRS to evaluate symptoms are strengths of the study. In addition, blood samples were also collected simultaneously from the participants after a 12-hour overnight fasting period to prevent variations in the WBV and plasma viscosity measurement due to various factors.

CONCLUSION

This novel study that examined the relationship between plasma viscosity and the severity of menopausal symptoms revealed that plasma viscosity was higher with MRS score ≥14 than that with MRS score <14. Moreover, plasma viscosity levels were correlated with urogenital symptom scores in the late stage of the postmenopausal period.

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