ORIGINAL ARTICLE

Subclinical organ damage in perimenopausal women with essential hypertension

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KEY WORDS

hypertension, menopause, subclinical organ damage

ABSTRACT

INTRODUCTION Hypertension and its complications are more common in postmenopausal women than before menopause. However, whether this is due to the effect of age or menopause is still unknown.

OBJECTIVES The aim of the study was to assess the effect of menopause on blood pressure (BP), left ventricular and vascular structure and function, as well as kidney function in perimenopausal women.

PATIENTS AND METHODS The study involved 192 women aged 40 to 60 years (mean age, 51.73 ±1.82 years), including 152 with newly diagnosed essential hypertension and 40 normotensive controls matched for age. In all subjects, 24-hour BP monitoring was performed. Echocardiographic examination with the assessment of left ventricular mass (LVM) and systolic and diastolic function, as well as carotid ultrasound with the measurement of intima-media thickness (IMT) in the common carotid artery were performed. Carotid-femoral pulse wave velocity (PWV) was measured. Glomerular filtration rate (eGFR) was calculated and urinary albumin-creatinine ratio (UACR) was measured.

RESULTS The study group was divided according to hypertension and menopausal status into 4 subgroups: normotensive premenopausal, normotensive postmenopausal, hypertensive premenopausal, and hypertensive postmenopausal women. Menopause did not affect BP or LVM. Differences in LVM between pre- and postmenopausal women were dependent on age and the body mass index. Hypertensive postmenopausal compared with hypertensive premenopausal women had significantly higher IMT (0.72 ±0.34 mm vs. 0.59 ±0.30 mm, $P = 0.001$) and a lower ratio of early to late mitral inflow velocity (E/A, 1.04 ±0.32 vs. 1.32 ±0.33, $P = 0.01$). PWV was higher in hypertensives compared to controls (9.7 ±1.6 m/s vs. 8.4 ±1.2 m/s, $P = 0.001$), without differences between premenopausal and postmenopausal women. Menopause did not affect eGFR and UACR either in the hypertensive or normotensive group.

CONCLUSIONS Left ventricular diastolic function and carotid IMT are independently associated with menopausal status in both normo- and hypertensive women. Menopause per se did not affect BP in the examined group.

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INTRODUCTION Cardiovascular diseases are the leading cause of mortality and morbidity worldwide. Each year, 82,000 men and up to 91,000 women die from cardiovascular diseases, which constitutes 43% of all-cause male and 55% of all-cause female mortality.[1] Cardiovascular diseases are the most common cause of death in women; also, a constant increase of morbidity from cardiovascular diseases is observed, which can only partly be explained by population aging.

Epidemiology, symptoms, and progression of cardiovascular disease are different in women than in men. Typically, women are about 10 years older than men when they develop cardiovascular disease, and its annual incidence varies according to the menopausal status.[2] However, it remains controversial whether menopause affects the risk of coronary heart disease. Numerous studies have demonstrated an increase in the prevalence of coronary heart disease and atherosclerosis after menopause, but because physio-

logical menopause is highly correlated with age, as is the incidence of heart disease, this association may well be spurious.

Hypertension is one of the major risk factors for the development of coronary heart disease and a major cardiovascular risk factor possibly explaining high cardiovascular morbidity and mortality in postmenopausal women. The relationship between menopause and blood pressure (BP) remains unclear.[3] Women show a sharper increase in systolic BP after menopause, but whether this is due to the effect of age or menopause is still debated, because cross-sectional and longitudinal studies provided discrepant results.[4-6]

The reappraisal of the European Society of Hypertension (ESH) guidelines considers subclinical organ damage to be a particularly important criterion in assessing global cardiovascular risk, given the fact that asymptomatic alterations of the cardiovascular system and the kidneys are crucial intermediate stages in the disease continuum that links risk factors such as hypertension to cardiovascular events and death.[7] In both hypertensive patients and the general population, the presence of left ventricular hypertrophy (LVH) documented on echocardiography, carotid plaque or intima thickening, increased arterial stiffness, a reduced estimated glomerular filtration rate (eGFR) or microalbuminuria substantially increase global cardiovascular risk, usually moving hypertensive patients into the high absolute risk group.

The aim of our study was to elucidate the impact of menopause on BP and subclinical organ damage in middle-aged women.

PATIENTS AND METHODS

Study population

We recruited 192 women aged 40 to 60 years: 152 consecutive patients referred to the Hypertension Outpatient Clinic between June 2004 and November 2008, with newly diagnosed untreated mild and moderate hypertension, and 40 normotensive, healthy controls matched for age, who met the inclusion criteria and were selected from a population-based study conducted in our department. Diagnosis of hypertension was based on at least 2 office BP measurements on different occasions and confirmed by 24-hour ambulatory BP monitoring (ABPM). We excluded patients with surgical menopause, women on hormone replacement therapy or oral contraceptives, those with secondary hypertension, chronic kidney disease, diabetes mellitus, and current smokers. The definition of menopause was based on 2 criteria: self-reported menstrual characteristics (last menstruation >1 year ago) confirmed by follicle-stimulating hormone (FSH) level (>40 IU/l). The study protocol was approved by the local ethics committee (KBET/378/B/2003 and KBET/51/B/2007).

Study design

All subjects underwent clinical assessment with a detailed history based on the standardized questionnaire and physical examination. Body weight and height were measured and the body mass index (BMI) was calculated. Waist and hip circumference was measured and the waist-to-hip ratio calculated. Office BP measurements were performed with semiautomatic, validated, oscillometric monitors (OMRON 715-IT, Kyoto, Japan) in accordance with the European Society of Cardiology and ESH guidelines.[8] In all subjects, 24-hour ABPM (SpaceLabs 90 210, SpaceLabs Inc., Redmond, Washington, United States), with BP readings every 15 minutes during the day and 20 minutes during the night, was performed.

Echocardiographic examination

Echocardiographic measurements were performed by one experienced investigator, using a digital ultrasound system GE Vivid 7 equipped with a 3.5-MHz transducer (General Electric Vingmed Ultrasound, Horten, Norway). Left ventricular internal diameter and interventricular septal and posterior wall thickness were measured at end-diastole according to the recommendations of the American Society of Echocardiography.[9] Left ventricular mass (LVM) was indexed to body surface area and height$^{2.7}$.[10] LVH was defined as LVM index >110 g/m^2 or 45 g/m$^{2.7}$.[8,10] As a measure of systolic function, dimensional fractional shortening was computed. For evaluation of diastolic function, mitral inflow velocities were recorded with pulsed-wave Doppler sonography. Three consecutive cardiac cycles were averaged to measure peak velocities reached in early diastole (E-wave) and after atrial contraction (A-wave), and to calculate the E/A ratio. We also measured E wave deceleration time and isovolumetric relaxation time.[11] Color-coded tissue Doppler images were acquired for the lateral and septal segments of the mitral annulus. Peak velocities during systole (Sm), early diastole (Em), and late diastole (Am) were measured. The ratio of mitral annulus diastolic velocities (Em/Am) was calculated.[12] All measurements were done by the same examiner, who was blind to the hypertension and menopausal status of the examined subject. The intraobserver intersession reproducibility coefficient, computed according to the Bland and Altman's method, was 2.5% for LVM and 2.0% for the E/A ratio.

Carotid intima-media thickness

Carotid artery ultrasound with high resolution ultrasound scanner was performed with a high frequency (7 MHz) linear array transducer (GE Vivid 7 General Electric Vingmed Ultrasound, Horten, Norway). The images of the common carotid artery and carotid bifurcation were recorded and subsequently measured off-line. The automated intima-media thickness (IMT) package from Vivid 7 was used. IMT was measured in the far wall of the common carotid artery at a 1-cm distance from carotid bifurcation in a single frame during the end-diastolic phase between the P and Q wave of the electrocardiogram (ECG). Whenever atherosclerotic plaques (defined as a focal thickening >1.3 mm in any

segment of carotid arteries) were detected, their number, location, maximal thickness, and foot were assessed.[13] The presence of at least 1 carotid atherosclerotic plaque or diffuse IMT (the average common carotid wall thickness >0.9 mm) was chosen as evidence of vascular abnormalities.

Pulse wave velocity The measurement of carotid-femoral pulse wave velocity (PWV) was performed using the SphygmoCor system (AtCor Medical, Sydney, Australia, Model MM3, Software version 6.31). Arterial waveforms were obtained with high-fidelity SPC-301 micromanometer (Millar Instruments, Inc., Houston, Texas, United States) interfaced with a computer running SphygmoCor software. Arterial PWV was determined by the foot-to-foot flow wave velocity method. The time delay was measured between the feet of the flow waves recorded at these different points and designated as pulse transmit time. ECG gating permitted the time lapse between pulse waves at the carotid and femoral sites to be calculated from sequential measurements. PWV was calculated as the distance to transit time ratio and expressed as meters per second.[14] Examination was performed by an experienced observer blinded to the hypertension and menopausal status.

Blood and urine samples All blood samples were taken during the follicular phase of the menstrual cycle in premenopausal women and arbitrarily in postmenopausal women. The sampling was performed between 7:30 and 8:30 a.m., after an overnight fast and 30-minute rest in horizontal position, using a previously placed intravenous cannula. After centrifuging, the samples were stored at –70°C until analysis. The levels of FSH and estradiol were measured using the MEIA kits, (Abbott, United States) with a sensitivity level at 1 ng/ml for estradiol and 0.5 mIU/ml for FSH).

Routine laboratory methods were applied to measure basic biochemical parameters. The creatinine level was determined using the Jaffe method, with a double-blind probe. The GFR was estimated from the Modification of Diet in Renal Disease (MDRD) formula. The levels of cholesterol were measured using an enzymatic method (CHOD-PAP), low-density lipoprotein (LDL) cholesterol using the Friedewald formula, and triglycerides using an enzymatic method (GPO-PAP). All measurements were made using Modular P, Roche device, and appropriate Roche kits.

Urine samples were taken twice at 2-week intervals. Urine creatinine (Jaffe reaction) and urine albumin concentration (by immunoturbidimetry)[15] were determined using the Cobas Mira Plus analyser (Roche Diagnostics). The urine albumin to creatinine ratio was averaged from 2 independent samples.

Statistical analysis The results were compared between the analyzed groups of patients. The data were expressed as mean values and standard deviations. The STATISTICA 7.0 software was used for data management and statistical analysis. Analysis of variance was used to compare means and the Pearson χ^2 test to compare proportions. Stepwise regression analysis was performed to evaluate and classify the determinants of the analyzed variables. Multivariate linear regression analysis was applied when necessary to correct between-group differences for the effects of confounding variables.

RESULTS Clinical characteristics of the hypertensive and normotensive groups, including anthropometric parameters, are presented in TABLE 1. The age of patients did not differ between groups. Hypertensive women had significantly higher BMI, waist circumference, and serum triglyceride level. The other classification of the studied group was based on the menopausal status. Clinical characteristics of premenopausal and postmenopausal women, irrespective of hypertension status, is shown in TABLE 2. After the assessment of the menopausal status, the studied group was further subdivided into 4 subgroups: normotensive premenopausal, normotensive postmenopausal, hypertensive premenopausal, and postmenopausal women (TABLE 3). Postmenopausal women, both normo- and hypertensive, were significantly older, thus subsequent analyses were adjusted to age. Hypertensive premenopausal women had significantly higher waist circumference and BMI compared with premenopausal normotensive women. The difference in BMI between postmenopausal hypertensive and postmenopausal normotensive women was not statistically significant (TABLE 3). We did not observe any effect of menopausal status on body mass or the indices of visceral obesity.

The effect of menopause on blood pressure There were no differences in BP from 24-hour ABPM between pre- and postmenopausal women in the groups of hypertensive subjects and normotensive controls (TABLE 3). The association of BP and age, BMI, waist circumference, pulse rate, and sex hormone level was tested using a multiple regression analysis. These models explained a rather small proportion of BP variation in perimenopausal women (coefficient of determination R^2 = 0.22), where the closest, but not significant, correlation with BP was found for BMI (multiple regression coefficient 0.29, P = 0.09).

The effect of menopause on subclinical organ damage **Heart** In the examined group, hypertensive postmenopausal women had higher LVM index compared with premenopausal women. After adjustment for age, this difference lost its significance. In the multiple regression analysis, 56% of LVM variation could be explained by age (multiple regression coefficient 0.10, P = 0.35), BMI (multiple regression coefficient 0.33, P = 0.03), waist circumference (multiple regression coefficient 0.31, P = 0.04), systolic BP (multiple

TABLE 1 Clinical characteristics of the studied patient groups

	Normotensive controls n = 40	Hypertensive women n = 152	*P*
age, y	51.0 ±2.8	51.1 ±5.5	0.98
BMI, kg/m^2	25.2 ±4.1	27.1 ±3.2	0.006
waist circumference, cm	81.7 ±9.2	89.7 ±8.8	<0.001
office SBP, mmHg	128.7 ±14.0	158.2 ±17.2	<0.001
office DBP, mmHg	77.8 ±8.4	91.6 ±11.5	<0.001
24-h SBP, mmHg	112.6 ±6.2	134.4 ±10.1	<0.001
24-h DBP, mmHg	70.8 ±5.0	81.3 ±8.7	<0.001
pulse rate, beats/min	73.4 ±7.8	76.1 ±10.9	0.36
fasting blood glucose, mmol/l	5.13 ±0.80	5.15 ±0.46	0.96
serum TC, mmol/l	5.94 ±1.2	5.95 ±1.1	0.99
serum LDL-C, mmol/l	3.54 ±0.9	3.74 ±1.0	0.65
serum HDL-C, mmol/l	1.66 ±0.4	1.54 ±0.4	0.46
serum triglicerydes, mmol/l	1.22 ±0.52	1.91 ±0.84	0.04
FSH, IU/l	45.2 ±36.1	42.2 ±35.1	0.71
LVMI, g/m^2	82.0 ±13.5	78.9 ±13.0	0.21
LVMI height, g/m$^{2.7}$	38.8 ±6.7	36.5 ±7.3	0.06
LVH, n (%)	2 (5)	33 (22)	0.07
PWV, m/s	9.7 ±1.6	8.4 ±1.2	<0.001
IMT, mm	0.64 ±0.14	0.59 ±0.12	0.03
plaques, n (%)	3 (7.5)	47 (31)	0.001
UACR, mg/mmol	0.78 ±0.51	0.78 ±0.44	0.96
eGFR, ml/min/1.73 m^2	100.6 ±14.0	95.2 ±16.7	0.07

Data are expressed as mean values ± SD; *P*-values refer for the Student's t-test for continuous variables and χ^2 test for proportions

Abbreviations: BMI – body mass index, DBP – diastolic blood pressure, eGFR – estimated glomerular filtration rate, FSH – follicle-stimulating hormone, HDL-C – high-density lipoprotein cholesterol, IMT – intima–media thickness, LDL-C – low-density lipoprotein cholesterol, LVH – left ventricle hypertrophy, LVMI – left ventricular mass index, PWV – pulse wave velocity, SBP – systolic blood pressure, SD – standard deviation, TC – total cholesterol, UACR – urinary albumin-creatinine ratio

regression coefficient 0.14, $P = 0.09$), heart rate (multiple regression coefficient 0.27, $P = 0.01$), and serum FSH levels (multiple regression coefficient 0.18, $P = 0.09$).

Postmenopausal women in both normotensive and hypertensive groups had significantly lower values of the E/A ratio compared with premenopausal subjects. In the multiple regression analysis, 36% of the E/A variation could be explained by age (multiple regression coefficient –0.30, $P = 0.01$), BMI (multiple regression coefficient –0.27, $P = 0.16$), heart rate (multiple regression coefficient –0.26, $P = 0.01$), systolic BP (multiple regression coefficient –0.06, $P = 0.55$), and LVM (multiple regression coefficient –0.14, $P = 0.34$). Parameters of mitral annulus velocities describing left ventricular diastolic function (Em/Am), adjusted to confounding variables, were also significantly lower in postmenopausal women (TABLE 3).

Arteries Hypertensive women, irrespective of the menopausal status, had higher PWV than normotensive controls. We did not observe any effect of the menopausal status on carotid-femoral PWV (TABLE 3).

Women with arterial hypertension had higher IMT in the common carotid artery compared with normotensive controls (TABLE 1). Postmenopausal women in both normotensive and hypertensive groups had significantly higher IMT than premenopausal women (TABLE 3).

Kidneys The GFR, estimated according to the MDRD formula, showed a tendency to lower values in postmenopausal women in both hypertensive and normotensive groups (TABLE 3). In the multiple regression analysis, the coefficient of determination for eGFR (R^2) was 26%. Among the studied variables (age, BMI, waist, heart rate, BP, FSH level), the most significant correlation with eGFR was found for heart rate (multiple regression coefficient –0.24, $P = 0.03$).

DISCUSSION

An important finding of our study is the lack of effect of menopause on BP. The main factor affecting BP in middle-aged women is body weight and waist circumference. Cross-sectional and longitudinal studies that investigated the relationship between menopause and hypertension have provided conflicting results. Although several studies[4,5] have reported an association

TABLE 2 Clinical characteristics of the studied patients according to the menopausal status

	Premenopausal women n = 99	Postmenopausal women n = 93	*P*
age, y	49.4 ±3.2	52.5 ±3.0	<0.001
BMI, kg/m²	26.5 ±3.6	26.8 ±3.3	0.45
waist circumference, cm	84.2 ±8.8	86.1 ±8.6	0.07
office SBP, mmHg	143.0 ±21.9	144.0 ±22.0	0.84
office DBP, mmHg	84.0 ±11.7	85.1 ±13.5	0.69
24-h SBP, mmHg	128.4 ±10.8	129.0 ±10.9	0.62
24-h DBP, mmHg	79.4 ±8.4	79.8 ±9.5	0.75
pulse rate, beats/min	74.7 ±8.9	75.1 ±9.2	0.86
fasting blood glucose, mmol/l	5.00 ±0.53	5.02 ±0.56	0.93
serum TC, mmol/l	5.31 ±0.82	5.73 ±0.97	<0.001
serum LDL-C, mmol/l	3.06 ±0.75	3.46 ±0.86	<0.001
serum HDL-C, mmol/l	1.52 ±0.33	1.57 ±0.37	<0.001
serum triglicerydes, mmol/l	1.64 ±1.09	1.55 ±0.86	0.55
FSH, IU/l	11.2 ±9.7	72.3 ±21.6	<0.001
LVMI, g/m²	78.3 ±13.2	84.2 ±13.1	<0.01
PWV, m/s	8.95±1.47	9.18 ±1.42	0.69
IMT, mm	0.58 ±0.11	0.69 ±0.14	<0.01
UACR, mg/mmol	0.72 ±0.45	0.85 ±0.61	0.18
eGFR, ml/min/1.73 m²	99.2 ±16.2	93.3 ±15.8	0.02

Data are expressed as mean values ± SD; *P*-values refer for the Student's t-test
Abbreviations: see TABLE 1

TABLE 3 Blood pressure, pulse rate, glucose, and lipids according to the menopausal status

	Normotensive controls		*P*	Hypertensive women		*P*
	NT-pre	NT-post		HT-pre	HT-post	
n	21	19		78	74	
age, y	46.3 ±2.7	55.6 ±3.2	<0.001	50.1 ±2.8[a]	51.9 ±2.5[b]	<0.001
BMI, kg/m²	24.6 ±4.7	25.7 ±3.5	0.46	27.0 ±3.1[a]	27.1 ±3.3	0.81
waist circumference, cm	81.1 ±7.7	82.4 ±10.2	0.67	84.6 ±8.3[a]	87.8 ±8.3[b]	0.02
office SBP, mmHg	113.8 ±5.0	111.9 ±7.3	0.42	133.4 ±8.1[a]	132.8 ±6.3[b]	0.82
office DBP, mmHg	71.0 ±4.3	70.7 ±5.2	0.84	82.5 ±6.7[a]	81.8 ±8.7[b]	0.68
pulse rate, beats/min	78.2 ±8.4	78.7 ±8.5	0.87	80.7 ±9.6	82.0 ±8.7	0.67
fasting blood glucose, mmol/l	4.82 ±0.33	5.10 ±0.61	0.15	5.05 ±0.35	5.01 ±0.55	0.39
serum TC, mmol/l	5.11 ±0.71	6.00 ±0.97	0.02	5.36 ±0.84	5.66 ±1.01	0.05
serum LDL-C, mmol/l	3.03 ±0.72	3.83 ±0.86	0.003	3.07 ±0.77	3.36 ±0.84	0.03
serum HDL-C, mmol/l	1.50 ±0.36	1.60 ±0.30	0.37	1.52 ±0.32	1.57 ±0.39	0.48
serum triglicerydes, mmol/l	1.26 ±0.63	1.26 ±0.61	0.99	1.74 ±1.42[a]	1.63 ±0.78[b]	0.55
FSH, IU/l	11.08 ±9.0	75.6 ±20.8	<0.001	11.20 ±9.9	71.4 ±27.2	<0.001

The data are expressed as mean values ± SD; *P*-values refer for the Student's t-test for continuous variables and χ^2 test for proportions

a $P < 0.05$ vs. NT-pre, **b** $P < 0.05$ vs. NT-post

Abbreviations: HT-post – hypertensive postmenopausal, HT-pre – hypertensive premenopausal, NT-pre – normotensive premenopausal, NT-post – normotensive postmenopausal, others – see TABLE 1

between menopause and higher BP values, a number of other studies failed to demonstrate a significant menopause-related difference,[6,16,17] and a few studies have even shown a lower BP associated with menopause.[18] The relationship between menopause and BP is difficult to elucidate mainly because arterial stiffness and BP as well as serum lipids and glucose tolerance tend to worsen with aging.[19] This could actually explain the supposed cardiovascular adverse effects of menopause and conflicting results of several studies. In a number of studies a BP increase at menopause has been attributed to age, BMI, or a combination of both. In our study, body mass and waist

TABLE 4 Left ventricular mass index, indices of left ventricular diastolic function, carotid intima–media thickness, pulse wave velocity and estimated glomerular filtration rate and urinary albumin-creatinine ratio in the examined group

	Normotensive controls		*P*	Hypertensive women		*P*
	NT-pre	NT-post		HT-pre	HT-post	
n	21	19		78	74	
LVMI BSA, g/m^2	73.6 ±12.7	83.1 ±11.3	0.01	79.5 ±13.3[a]	84.4 ±13.5	0.03
LVMI BSA, g/m^2 (age- and SBP-adjusted)	76.6 ±20.2	81.0 ±17.4	0.35	80.1 ±13.7	83.3 ±13.8	0.12
LVMI height, g/m$^{2.7}$	33.8 ±6.7	38.2 ±7.1	0.02	37.8 ±6.4	40.3 ±6.8	0.04
LVMI height, g/m$^{2.7}$ (age-adjusted)	35.9 ±10.5	37.1 ±9.6	0.68	38.3 ±6.3	39.4 ±6.2	0.30
LVH, n (%)	1 (4.7)	1 (5.2)	0.99	12 (15.3)[a]	21 (28.4%)[b]	0.05
E/A	1.46 ±0.34	1.31 ±0.33	0.03	1.32 ±0.33	1.04 ±0.32[b]	0.01
E/A (age- and BMI-adjusted)	1.44 ±0.23	1.33 ±0.18	0.05	1.30 ±0.20	1.04 ±0.27[b]	0.02
Em/Am	1.35 ±0.35	1.06 ±0.33	0.001	1.02 ±0.39[a]	0.78 ±0.26[b]	0.001
Em/Am (age- and BMI-adjusted)	1.36 ±0.37	1.05 ±0.34	0.04	0.95 ±0.40[a]	0.79 ±0.35[b]	0.05
IMT, mm	0.54 ±0.14	0.64 ±0.11	0.01	0.58 ±0.13[a]	0.71 ±0.23[b]	0.001
IMT, mm (age- and BMI-adjusted)	0.58 ±0.19	0.61 ±0.18	0.16	0.59 ±0.30	0.72 ±0.34[b]	0.001
plaques, n (%)	1 (4.7)	2 (10.4)	0.53	10 (12.8)[a]	24 (32.4)[b]	0.13
PWV, m/s	8.43 ±1.26	8.35 ±1.29	0.93	9.40 ±1.52[a]	9.72±1.82[b]	0.81
PWV, m/s (age- and BMI-adjusted)	8.18 ±1.41	8.70 ±1.38	0.45	9.40 ±1.43[a]	10.1 2±1.9[b]	0.31
eGFR, ml/min/1.73 m^2	106.8 ±13.5	98.5 ±12.5	0.07	97.5 ±16.7[a]	92.8 ±16.5	0.08
UACR, mg/mmol	0.70 ±0.33	0.85 ±0.47	0.35	0.68 ±0.30	0.95 ±0.58	0.07

The data are expressed as mean values ± DS; *P*-values refer for the Student's t-test for continuous variables and χ^2 test for proportions; multiple regression analysis was used to adjust for confounding variables

a $P < 0.05$ vs. NT-pre, **b** $P < 0.05$ vs. NT-post

Abbreviations: E/A – ratio of early to late mitral inflow velocity, Em/Am – ratio of mitral annulus diastolic velocities, others – see TABLES 1 and 3

circumference seemed to be the most important factors in the pathogenesis of hypertension in middle-aged women. The effect of age should also be considered because postmenopausal women in our population were significantly older than premenopausal ones. This age stratification resulted from the menopause definition that we used, which was based on self-reported menstrual characteristics, confirmed by a FSH level, in women aged 40 to 60 years. A rather narrow age range also explains why we did not show any correlation of BP with age. Confounding effect of age differences between pre- and postmenopausal women was avoided in a prospective study of British cohort.[17] In this study, 1303 women aged 53 years were examined and categorized into 5 menopausal status groups. Authors found no differences in BP between groups defined on the basis of menopause stage; however, BMI, waist circumference, total and LDL cholesterol, varied between the menopausal status groups.

In another longitudinal study, menopause was not shown to affect BP.[16] The only parameter differentiating premenopausal and postmenopausal women was LDL cholesterol.[16] Our results are in agreement with the above prospective data, confirming that although menopause does not affect BP per se, it may influence patients' cardiovascular risk profile via its effect on cholesterol levels.

In our study, LVH was more frequently observed in postmenopausal hypertensive women compared with premenopausal subjects. Epidemiological data clearly show that LVH is a powerful predictor of cardiovascular morbidity and mortality, independent of BP and other cardiovascular risk factors.[20] Although women have a lower prevalence of LVH than men for any given level of BP, the available data indicate that both hypertension and LVH are stronger risk factors for stroke and heart failure in women than in men.[21] LVM increases progressively with older age and LVH becomes more common in postmenopausal women.[21] Also in our study, the effect of age cannot be excluded because postmenopausal women were older. When LVM was analyzed as a continuous variable, the crude data indicated significantly higher values of LVM in postmenopausal women in both normotensive

and hypertensive groups. After adjustment for age and BMI, the effect of menopause on LVM was no longer significant.

Only few studies investigated the effect of menopause on the structure of the left ventricle. In 2 studies, postmenopausal women were shown to have increased thickness of left ventricular septum and posterior wall compared with premenopausal subjects.[22,23] Our data are in agreement with those obtained by Schillaci et al.[24] In the cross-sectional study of 152 women aged 45 to 55 years, no significant increase in LVM was observed in postmenopausal subjects, although they tended to have more concentric left ventricular geometry pattern and reduced midwall fractional shortening.[24]

Although we did not confirm the effect of menopause on age-adjusted LVM, we observed significant differences in the parameters of left ventricular diastolic function in relation to the menopausal status. The current data are of particular interest, if we take into account that women are more likely to maintain a better left ventricular systolic function than men with similar heart failure symptoms, and heart failure due to diastolic dysfunction is more common in women than in men.[21]

The data on left ventricular diastolic function in perimenopausal women are limited. Similarly to our study, Kangro et al.[25] showed significantly lower values of conventional Doppler mitral inflow velocities in postmenopausal compared with premenopausal women. Duzenli et al.,[26] using both conventional Doppler and tissue Doppler derived indices of diastolic function, demonstrated that menopause negatively affected diastolic function of the left and right ventricles in normotensive women. Interesting data about the role of menopause in the pathogenesis of diastolic heart failure came from experimental animal studies. In ovariectomized rats, significant deterioration in diastolic function of the left ventricle was accompanied by increased cardiac interstitial fibrosis and higher circulating levels of aldosterone, 2 factors leading to reduced ventricular compliance.[27] In this regard, the depletion of ovarian hormones may promote cardiac growth factors to induce fibrosis and, in turn, lead to reductions in myocardial distensibility and diastolic dysfunction.[28]

Estrogen deficiency can affect arterial distensibility in a similar way. Prospective and cross-sectional studies have documented that arterial stiffness was increased disproportionately after menopause (either surgical or natural).[29-30] In a few clinical studies, hormonal replacement therapy after menopause was accompanied by a slower progression of arterial stiffness or improvement in vascular compliance.[31] In the current study, arterial compliance, assessed by carotid-femoral PWV, was significantly impaired in hypertensive women compared with normotensive controls, with no significant effect of menopause on vascular stiffness. However, in hypertensive women, menopause significantly influenced the parameters of arterial structure. This observation is in agreement with the data obtained by Muscelli et al.[32] In this cross-sectional study, early menopause was associated with common carotid artery remodeling, characterized by an increase in carotid IMT, independent of atherosclerotic risk factors and metabolic variables. On the basis of our result, we can presume that in hypertensive women in whom arterial compliance is decreased, menopause affects the process of subclinical atherosclerosis. Thus, menopause superimposed on hypertension accelerates vascular injury, which may represent an intermediate step between risk factors and cardiovascular events.

We did not find significant differences in the parameters of kidney function between pre- and postmenopausal women. Only the tendency to lower eGFR in postmenopausal women in both normotensive and hypertensive groups was observed, which resulted from age differences between the groups. However, in experimental studies on rats, females are protected from the age-dependent decline in GFR as compared with males.[33] The rate of progression of chronic renal disease is also faster in men than in premenopausal women,[34] and this protection disappears after menopause and can be restored by estradiol replacement.[35] The protective action of estrogens has been ascribed to their direct antigrowth effects on the glomerular mesangial cells and inhibition of mesangial extracellular matrix accumulation, typically observed in the development of glomerular sclerosis.[36]

Our results are limited by cross-sectional study design, which cannot provide information about cause-and-effect relationships between menopause and BP.

Another important limitation is a relatively small sample size, especially the subgroup analysis with unproportionally smaller normotensive group. The primary outcome variable of the study was BP. The power of the study was calculated to be 80% for 200 subjects included, to detect 5 mmHg BP difference between pre- and postmenopausal women. Because the observed difference of BP was lower than expected, the number of subjects should be doubled to achieve sufficient power of the study. Considering these limitations, the study results should be interpreted as preliminary data.

In conclusion, in our well-described population of middle-aged women, menopause affected global cardiovascular risk via metabolic changes and the effect on subclinical organ damage. A decrease in left ventricular diastolic function observed in postmenopausal women as well as subclinical atherosclerosis may link the complex relationship between menopause, hypertension, aging, and cardiovascular morbidity in the population of women. Further studies focused on better understanding of the relationships between menopause and BP are needed.

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ARTYKUŁ ORYGINALNY

Subkliniczne zmiany narządowe u kobiet z nadciśnieniem tętniczym w okresie okołomenopauzalnym

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SŁOWA KLUCZOWE

menopauza, nadciśnienie tętnicze, subkliniczne zmiany narządowe

STRESZCZENIE

WPROWADZENIE Nadciśnienie tętnicze i jego powikłania są częstsze u kobiet po menopauzie niż u tych przed menopauzą. Nie wiadomo jednak, czy wynikają one ze zmian związanych z wiekiem, czy z samej menopauzy.

CELE Celem pracy była ocena wpływu menopauzy na ciśnienie tętnicze, strukturę i czynność lewej komory serca oraz naczyń, a także na czynność nerek u kobiet w okresie okołomenopauzalnym.

PACJENCI I METODY Do badania włączono 192 kobiety w wieku 40–60 lat (średni wiek 51,73 ±1,82 roku), w tym 152 z nowo rozpoznanym, dotychczas nieleczonym nadciśnieniem tętniczym oraz 40 zdrowych kobiet dobranych pod względem wieku. U wszystkich badanych wykonano 24-godzinną rejestrację ciśnienia tętniczego krwi. Przeprowadzono badanie echokardiograficzne z oceną masy lewej komory serca, funkcji skurczowej i rozkurczowej oraz ultrasonograficzny pomiar grubości kompleksu intima–media (*intima-media thickness* – IMT) w obrębie dalszej ściany tętnicy szyjnej wspólnej. Wykonano ocenę podatności tętnic za pomocą pomiaru prędkości aortalno-udowej fali tętna (*pulse wave veolocity* – PWV). Obliczono szybkość przesączania kłębuszkowego (*estimated glomerular filtration rate* – eGFR) oraz oznaczono stosunek stężenia albuminy do kreatyniny (*urinary albumin-creatinine ratio* – UACR) w porannej próbce moczu.

WYNIKI Badaną grupę podzielono na 4 podgrupy w zależności od obecności nadciśnienia i menopauzy: kobiety z prawidłowym ciśnieniem przed i po menopauzie oraz pacjentki z nadciśnieniem tętniczym przed i po menopauzie. Nie stwierdzono wpływu menopauzy na ciśnienie tętnicze ani na masę lewej komory serca. Różnice w masie lewej komory serca u kobiet przed i po menopauzie są zależne od wieku oraz wskaźnika masy ciała. U pacjentek z nadciśnieniem tętniczym po menopauzie, w porównaniu do chorych przed menopauzą obserwowano istotnie większą wartość IMT (0,72 ±0,34 mm *vs* 0,59 ±0,30 mm; $P = 0{,}001$) oraz mniejszy wskaźnik E/A prędkości napływu mitralnego opisującego funkcję rozkurczową lewej komory serca (1,04 ±0,32 *vs* 1,32 ±0,33; $P = 0{,}01$). Stwierdzono istotnie wyższe wartości PWV u kobiet z nadciśnieniem w porównaniu z badanymi z prawidłowym ciśnieniem (9,7±1,6 m/s *vs* 8,4 ±1,2 m/s; $P = 0{,}001$), nie obserwując różnic w PWV zależnych od menopauzy. Nie stwierdzono różnic w eGFR i UACR zależnych od menopauzy ani w grupie z nadciśnieniem, ani w grupie kontrolnej.

WNIOSKI Funkcja rozkurczowa lewej komory serca oraz grubość kompleksu IMT w tętnicy szyjnej wykazują niezależny związek z menopauzą zarówno u kobiet z nadciśnieniem tętniczym, jak i u tych z normalnym ciśnieniem. W badanej grupie nie stwierdzono wpływu menopauzy *per se* na ciśnienie tętnicze.

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