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Original Research Article

Influence of metabolic syndrome and its components on subclinical organ damage in hypertensive perimenopausal women

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ABSTRACT

Purpose: We investigated the association between metabolic syndrome (MS), its components and the presence of subclinical organ damage in hypertensive perimenopausal women.
Patients/methods: 152 women with newly diagnosed, untreated arterial hypertension (mean age 51.0 ± 3.5 years) were included in the study. In all subjects anthropometrical measurements, 24-hr blood pressure monitoring, echocardiographic examination, and carotid ultrasound were performed. Carotid-femoral pulse wave velocity (PWV) was measured to obtain data on vascular compliance. As the index of early kidney damage both glomerular filtration rate was calculated and albumin/creatinine ratio in the urine sample was measured. A fasting blood sample was taken to measure glucose and lipid concentration.
Results: MS was found in 41% of patients. Patients with MS exhibited elevated left ventricular mass index (LVMI 84.7 vs. 78.8 g/m$^{2.7}$, $p = 0.03$), higher intima-media thickness (IMT 0.67 vs. 0.62 mm, $p = 0.003$), greater prevalence of LV hypertrophy (30% vs. 13%, $p = 0.01$), and carotid plaques (24% vs. 15%, $p = 0.01$). The multivariate regression analysis revealed that components of MS (systolic blood pressure and waist circumference) are stronger predictors of LVM than MS itself. The relationship between MS and LVMI lost its significance when BMI was included in the model, and remained significant for IMT.
Conclusion: In hypertensive perimenopausal women components of MS are stronger predictors of subclinical organ damage than MS itself. Left ventricular mass and hypertrophy are more strongly correlated with increasing body weight than with the presence of MS. MS, independently of BMI, influences the level of subclinical atherosclerosis in the study group.

1. Introduction

Metabolic syndrome (MS) is a complex of interrelated risk factors for cardiovascular disease and diabetes that arises from insulin resistance accompanying abnormal adipose tissue deposition and function. These factors include raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, glucose metabolism abnormalities, and obesity (particularly central adiposity). Although controversy exists regarding its pathogenesis and the appropriateness of considering it a distinct state, prospective observations indicate that MS has been reported to be a strong predictor of cardiovascular events [1].

MS carries a fourfold higher risk of cardiovascular events in females than in males [1]. MS has a continuously increasing prevalence in industrialized countries, driven largely by and increasing incidence of obesity and a sedentary lifestyle. In last decade in Poland, the prevalence of obesity and MS significantly increased, especially in women [2].

Hypertension is one of the key features of MS. The reciprocal relationship between hypertension and MS is well known. Prevalence of hypertension in patients with MS is significantly increased, and in patients with hypertension the presence of MS is higher than in the general population [3].

Prevalence of MS increases with age, and in women it significantly increases with menopause. During the transition from the premenopause to postmenopause state, many women experience weight gain and central fat deposition [4].

It is likely that the enhanced cardiovascular risk in postmenopausal women is associated with MS. In a hypertensive female this risk may be partially mediated through an increased prevalence of hypertension-induced preclinical cardiovascular and renal damage. Data regarding the influence of MS on target organ damage are inconsistent [5–9] although the concept of the MS is wildly

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accepted, recent data elicited some doubts as to whether its components are not more predictive of cardiovascular events and organ damage than MS itself. Criticism regarding the MS definition is related with its inherent limitations such as use of discrete thresholds to define abnormalities which discards crucial information about the magnitude of the risk factor. From the clinical point of view it seems to be interesting to analyze the influence of single but highly correlated measures that comprise the MS definition and MS itself on cardiovascular risk and organ damage.

The aim of this study was to investigate the relationship between MS and its components, and the presence of subclinical organ damage in hypertensive perimenopausal women.

2. Patients and methods

We recruited 152 women aged 40–60 years with newly diagnosed, untreated mild to moderate hypertension, that were referred to the Outpatient Clinic of the 1st Department of Cardiology and Hypertension.

All subjects underwent a clinical assessment; a detailed history was taken using a standardized questionnaire and a physical examination with anthropometric measurements was performed. Body weight and height were measured and body mass index (BMI) was calculated. Waist circumference (measured between the lowest rib margin and the iliac crest, in a patient standing and breathing normally) and hip circumference (measured at the level of the greater trochanters) was determined, and the waist to hip ratio (WHR) was calculated. Office blood pressure measurements were performed using semiautomatic, validated, oscillometric monitors in accordance with ESC and ESH guidelines [10]. In all subjects 24-hr ABPM (SpaceLabs 90210, SpaceLabs Inc., Redmond, WA, USA), with blood pressure readings every 15 min during the day and every 20 min during the night, was performed.

We excluded from the study patients with surgical menopause, women using hormone replacement therapy or oral contraceptives, women with secondary hypertension, women with chronic kidney disease (defined as estimated glomerular filtration rate < 60 ml/min/1.73 m^2), women with diabetes mellitus, current smokers. The definition of menopause was based on two criteria: self-reported menstrual characteristics (last menstruation > 1 year ago) confirmed by blood follicle stimulating hormone level ($>$40 IU/l). The study protocol was approved by the local ethics committee (KBET/51/B/2007).

2.1. Laboratory measurements

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 min of rest in horizontal position, using a previously placed intravenous cannula. After centrifuging, the samples were stored at $-70\,^{\circ}C$ until analysis. The levels of FSH and estradiol were measured using MEIA kits, Abbott (sensitivity 1 ng/ml for estradiol and 0.5 mIU/ml for FSH).

Routine laboratory methods were applied for measurement of basic biochemical parameters. The creatinine level was determined using the Jaffe method, with a double blind probe. Glomerular filtration rate was estimated from CKD-EPI equation and creatinine clearance was calculated according to Cockroft-Gault formula and indexed to body surface area [11]. Cholesterol level was measured by an enzymatic method (CHOD-PAP); the level of LDL cholesterol fraction was calculated according to the Friedewald formula and the level of triglycerides was assessed by an enzymatic method (GPO-PAP). All measurements were made using Modular P, Roche device and appropriate Roche kits. Serum insulin concentrations were determined by radioimmunoassay (RIA-kit OriPI Swierk, Otwock, Poland) using a scintillation meter (LKB, Turku, Finland). The homeostasis model assessment HOMA index was calculated as the product of the fasting plasma insulin level (μU/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5 [12].

Urine samples were taken twice in the two week time intervals. Urine creatinine (Jaffe reaction) and urine albumin concentration (by immunoturbidimetry) were determined using a Cobas Mira Plus analyser (Roche Diagnostics) [13]. Urine albumin to creatinine ratio (UACR, mg/mmol) was averaged from two samples.

2.2. Metabolic syndrome definition

Metabolic syndrome was defined following the modified criteria of the International Diabetes Federation proposed in 2009 [1].

As all subjects included to the study were hypertensive, to diagnose MS at least two of the following factors had to be fulfilled: waist circumference > 80 cm; elevated triglyceride level ($\geq$1.7 mmol/l); decreased HDL cholesterol ($<$1.3 mmol/l); and/or elevated fasting glucose concentration ($\geq$100 mg%).

2.3. Assessment of subclinical organ damage

2.3.1. Echocardiographic examination

Echocardiographic measurements were performed by one experienced observer, 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 (LVID), interventricular septal (IVST) and posterior wall thickness (PWT) were measured at end-diastole; left ventricular mass was calculated according to the recommendations of the American and European Society of Echocardiography [14]. Left ventricular mass was indexed to body surface area and height$^{2.7}$. Left ventricular hypertrophy was defined as left ventricular mass exceeding 95 g/m^2 and/or 51 g/$m^{2.7}$ [14].

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. Pulsed Doppler spectral recordings were obtained from the apical four-chamber view with a sample volume positioned at the tips of the mitral leaflets. 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 [15]. Color coded tissue Doppler images were acquired for lateral and septal segments of mitral annulus. The sample volume was placed at the junction of the LV wall with the mitral annulus of the septal and lateral myocardial segments from the four-chamber view. Peak velocities during systole (S′), early diastole (E′), and late diastole (A′) were measured. The final value represented the average of two sites. The ratio of mitral annulus diastolic velocities (E′/A′) was calculated [15]. All measurements were taken by the same examiner, who was blind to the hypertension and menopause status of the examined subject. The intra-observer inter-session reproducibility coefficient for LVM, computed according to Bland and Altman's method, was 2.5%, and for E/A ratio 2.0%.

2.4. Carotid intima-media thickness measurements

Carotid arteries 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 acquired images of common carotid artery and carotid bifurcation were recorded for playback analysis with