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Vital roles of age and metabolic syndrome-associated risk factors in sex-specific arterial stiffness across nearly lifelong ages: Possible implication of menopause and andropause

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ABSTRACT

Background and aims: Postmenopausal status is correlated with increased metabolic syndrome (MetS) and cardiovascular risks. However, the vital roles of age and MetS-associated risk factors in sex-specific arterial stiffness remain unclear.

Methods: In this population-based cross-sectional study of the general population, we enrolled in our Health Examination Program 9812 adult participants who were measured for brachial-ankle pulse wave velocity (baPWV) to assess arterial stiffness. Piecewise linear regression models were used to survey predefined ages associated with menopause and andropause in relation to arterial stiffness. Multivariate linear regression analyses were used to evaluate independent determinants.

Results: Across gender, stepwise increases in baPWV corresponded to increased MetS-associated risk scores (MetSRS) and aging (all p for trend < 0.001), while a turning point was found at 50 years of age (50age). The incremental ratios of baPWV presented inverse U curves with aging, whereas the highest R^2 values and incremental ratios of baPWV were found at 50age across gender. Comparing men with women, a 1.4-fold higher incremental ratio of baPWV was observed before 50age, compared to a 1.3-fold after 50age, respectively. MetS risk group and over 50age were associated with stepwise increased baPWV across gender (both p for trend < 0.001). Before 50age, the determinants did not include hs-CRP for women compared with men, while MetSRS was lost as a determinant across gender. In contrast with men, in women after 50age, HDL-C was an additional determinant and triglyceride was not, while MetSRS remained a determinant across gender.

Conclusions: Arterial stiffness increased with aging across nearly lifelong ages more in women than in men. While menopause and andropause may both play a role, 50age was the most critical factor across gender. The sex-specific differences in determinants of arterial stiffness may remind us of sex-specific targets for further interventional studies associated with arterial stiffness.

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1. Introduction

While cardiovascular disease (CVD) is traditionally regarded as a male disease, CVD remains the number one killer of women globally, especially in high-income countries [1,2]. Since the 1980s, in the United States the annual CVD mortality rate has been higher for women than for men, and the number of subjects living with and dying of CVD is greater for women than for men [3]. Some reports highlight the sex-specific CVD differences from biological factors, especially female reproductive concerns, and psychosocial gender differences affected by environmental, social, and community factors [4]. Additionally, postmenopausal status and early menopause are even independent risk factors for CVD [5]. However, given that sex-specific research gaps still exist, we believe investigating the sex-specific CVD differences to better understand and reduce CVD morbidity and mortality is an urgent priority.

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Metabolic syndrome (MetS) is prevalent worldwide. It was shown that in the United States, MetS was present in 22.8% and 22.6% of men and women, respectively, and postmenopausal status was associated with an increased odds of MetS [6]. In our previous study, we showed that MetS was present in 31.0% and 22.2% of Taiwanese men and women, respectively, and the prevalence of MetS increased dramatically with aging in women, but not in men [7]. While menopause clearly plays a key role in MetS-associated risk factors (MetSRF), the role of subtle andropause remains unclear.

Overall, central obesity and insulin resistance are associated with a cluster of cardiometabolic risk factors well-known as MetS [8], which is correlated with CVD and type 2 diabetes mellitus [9]. High-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker, is also associated with insulin resistance [10], type 2 diabetes mellitus [11], CVD and all-cause mortality [12]. However, few studies have combined MetSRF for arterial stiffness [13] and mortality prediction [14].

Pulse wave velocity (PWV) indicating arterial stiffness has been well-studied as a risk predictor of coronary artery disease [15] and all-cause mortality [16] among the general population. Although some progress on CVD has been achieved, the associations between the sex-specific arterial stiffness and MetSRF have not yet been elucidated. This study was, therefore, designed to simultaneously investigate the possible implication of menopause and andropause with MetSRF in sex-specific arterial stiffness.

2. Materials and methods

2.1. Study design and population

In this population-based cross-sectional study, we enrolled participants from our self-paid Health Examination Program at the Health Care Center of Chang Gung Memorial Hospital, Taoyuan branch, from January 2005 to December 2007. Compared with today, there was a relatively lower prevalence of lipid lowering drug use in those years to minimize the interference. All participants were required to be afebrile and to have undergone a standardized protocol, including structured questionnaires covering their personal and family history of chronic diseases and lifestyle, as well as measurements of blood pressure, body weight, and height. The inclusion criteria were older than 20 years of age with a standardized vascular assessment of brachial-ankle PWV (baPWV) measurement. We excluded participants with ankle-brachial index below 0.9. These participants were categorized by gender, specific ages, and MetS risk groups to correlate with baPWV. All participants provided their written informed consent. This study was approved by the Ethics Committee of the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 102–4175B) and performed according to the ethical principles of the Declaration of Helsinki.

2.2. Pre-defined ages during menopause and andropause

For Taiwanese women, the mean age of menopause was 49.5 years [17], so we pre-defined the ages of 30, 50 (50age), and 70 years to evaluate the relationship of menopause with arterial stiffness. In men, unlike menopause, a subtler drop of androgen from 40 to 75 years of age with a high degree of inter-individual variability causes difficulty in precisely defining andropause [18], therefore, we pre-defined the ages of 30, 40, 50, 60, 70, and 80 years to evaluate the relationship of andropause with arterial stiffness.

2.3. MetS risk groups classified by MetS-associated risk score (MetSRS)

MetSRF were determined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria [19] and the American College of Endocrinology Position Statement on Insulin Resistance Syndrome [8]. The six criteria of MetSRF defined in the present study included: 1) increased body mass index (BMI) ($\geq$25 kg/m^2) [8,13]; 2) increased blood pressure (BP) ($\geq$130/85 mmHg); 3) increased fasting plasma glucose ($\geq$5.55 mmol/L); 4) reduced high-density lipoprotein cholesterol (HDL-C) level (<1.0 mmol/L in men or <1.3 mmol/L in women); 5) increased triglyceride level ($\geq$1.7 mmol/L); and 6) increased hs-CRP level ($\geq$3 mg/L) [8,13,14]. Individual criteria were each given a score, which were summed so that we could obtain a MetSRS for each participant. All participants were classified to MetS risk groups according to the range of MetSRS from 0 to 6, where low MetS was defined as from 0 to 2, moderate MetS from 3 to 4, and high MetS from 5 to 6.

2.4. Measurements

Eligible participants completed anthropometric measurements, and venous blood samples were collected in the morning after overnight fasting for 12 h. BMI was calculated as body weight (kg) divided by the square of body height (m). The biochemical tests included assessments of fasting glucose, triglyceride, HDL-C, and hs-CRP at the central laboratory of the Taoyuan Chang Gung Memorial Hospital.

2.5. Arterial stiffness as represented by pulse wave velocity

Measurements of baPWV were made using an automated apparatus (Colin VP-1000, Omron, Kyoto, Japan). The technicians from our single center were all similarly trained and accredited. We requested that participants avoided tobacco or any stimulant beverages, such as alcohol or coffee, overnight, before the examination. A standardized temperature was maintained in the examination room. Right and left baPWVs were calculated automatically as the length/transit time between the right arm and both ankles, and we calculated the mean of the right and left PWVs as the last representative baPWV.

2.6. Statistical analysis

Data were analyzed using SPSS 22.0 software for Windows 7 (SPSS Inc., Chicago, IL, USA) and expressed as the mean ± SD or frequency, as appropriate. All variables were tested for normal distribution using the Kolmogorov-Smirnov test. One-way analysis of variance was applied to compare differences in continuous variables, whereas categorical data were tested by using Pearson's Chi-square test. For female baPWV prediction, by using age, cut-off points of age_{30} or age_{50} or age_{70}, and their interactions as variables in models of piecewise linear regression analyses, while for males, by using age, cut-off points of age_{30} or age_{40} or age_{50} or age_{60} or age_{70} or age_{80}, and their interactions, we derived regression equations to survey the pre-defined ages associated with menopause and andropause in relation to arterial stiffness. The adjusted risk estimates for baPWV were calculated by using multivariate linear regression analyses in the pre-defined model, including prognostic risk factors from published observations [13,20]. The variance-inflation factor calculation was performed to address the issue of collinearity, and we did not find a serious risk of collinearity (all VIF < 4). All statistical tests were two-tailed, and a p value < 0.05 indicated statistical significance.

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