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Original article

The effects of metabolic syndrome and its components on arterial stiffness in relation to gender

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ABSTRACT

Objectives: The influence of gender-dependent metabolic risk factors on arterial stiffness has not been fully determined. This study was performed to investigate the relationship between components of metabolic syndrome and brachial-ankle pulse wave velocity (baPWV) according to gender.
Methods: A total of 537 subjects (54.4 ± 7.5 years and 70.6% men) who underwent baPWV measurement during routine check-ups were analyzed.
Results: BaPWV was 1363 ± 229 cm/s in men and 1387 ± 269 cm/s in women ($p = 0.313$). The prevalence of metabolic syndrome was not different according to gender (23% in men versus 27% in women, $p = 0.335$). In multiple linear regression analyses, after adjustment for age, baPWV was significantly associated with systolic and diastolic blood pressures, fasting glucose, and triglyceride in both genders. Waist circumference was associated with baPWV in women but not in men. High-density lipoprotein levels were not associated with baPWV in either gender. Subjects with metabolic syndrome had a higher baPWV than those without metabolic syndrome for women aged <55 years, but not for all men and women aged ≥55 years. As the number of the components of metabolic syndrome increased, baPWV increased proportionally in both genders. However, this correlation was more strong in women than that in men ($\beta = 0.408$ versus $\beta = 0.146$ after adjustment for age).
Conclusion: In middle-aged Koreans, women showed stronger associations between each component of metabolic syndrome and baPWV than men. The association of each component of metabolic syndrome to arterial stiffness may differ between men and women.

Introduction

Metabolic syndrome is associated with increased risk of mortality, cardiovascular disease, and diabetes [1–3]. It has been reported that about one-quarter of adults have metabolic syndrome, and that its prevalence is increasing persistently [4]. Therefore, metabolic syndrome is a big public health burden worldwide.

Arterial stiffness reflects vascular aging and atherosclerosis [5]. Increased arterial stiffness has been advocated as an independent risk factor for cardiovascular mortality and morbidity [6–9]. Arterial stiffness can be measured using pulse wave velocity (PWV). Although carotid-femoral PWV (cfPWV) is considered as the gold standard measure of arterial stiffness, difficulty in performing the test limits its clinical use, whereas, brachial-ankle PWV (baPWV) is performed more easily than cfPWV, so that it has been used as an effective tool for screening vascular damage and cardiovascular risk in various populations [10–14], and its usefulness was demonstrated in a meta-analysis [6].

Metabolic risk factors lead to an increase in arterial stiffness. There have been many studies on the association between metabolic syndrome and arterial stiffness [15,16]. However, the impact of gender on the association between metabolic syndrome and arterial stiffness has not yet been fully assessed. This study was performed to investigate the relationship between each component of metabolic syndrome and baPWV according to gender.

Methods

Study subjects

Between October 2009 and July 2013, a total of 537 consecutive subjects underwent baPWV measurement as a part of self-paid health examination at Seoul National University Boramae Medical

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Center (Seoul, Korea) and their data were retrospectively reviewed. There were no exclusion criteria. All study subjects were relatively healthy and medically stable at the time of examination. Information on medical history, including hypertension, diabetes, dyslipidemia, stroke, and coronary artery disease, and smoking habits, were obtained using a standardized questionnaire. All subjects underwent measurement of body weight, height, and waist and hip circumference. Body fat composition was also obtained using a bioimpedance spectroscopy analyzer (InBody 720; Biospace Co., Ltd., Seoul, Korea), and was presented as percentages (%). Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m). Blood pressure was measured on the right upper arm using an automatic digital blood pressure monitor. Venous blood was collected from the antecubital vein in the morning after overnight fasting. The blood levels of hemoglobin, fasting glucose, uric acid, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, serum creatinine, and C-reactive protein were measured. Estimated glomerular filtration rate (eGFR) was calculated using following formula: eGFR = 175 × serum creatinine (mg/dL) − 1.154 × age − 0.203 (×0.742, if woman) [17]. Approval for the study protocol was obtained from the Institutional Review Board of Seoul National University Boramae Medical Center (Seoul, Korea).

Metabolic syndrome

Metabolic syndrome was defined as a waist circumference level ≥85 cm in women and ≥90 cm in men and 2 or more of the following four risk factors: (1) an elevated systolic/diastolic blood pressure of ≥130/85 mmHg, or previously diagnosed hypertension, (2) an elevated triglyceride level of ≥150 mg/dL, or specific treatment of this lipid abnormality, (3) a reduced HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women, and specific treatment of this lipid abnormality, and (4) an elevated fasting glucose level of ≥100 mg/dL or previously diagnosed type 2 diabetes mellitus [18].

baPWV measurement

The baPWV measurement protocol has been described previously [19]. All study subjects had received no drug treatment on the day of measurement. Patients were examined in the supine position after resting for five or more minutes. BaPWV was measured using a volume-plethysmographic apparatus (VP-1000; Colin Co., Ltd., Komaki, Japan) in accordance with the manufacturer's instructions. Cuffs were wrapped on both arms and ankles. Phonogram, pulse volume waveform, blood pressure, and heart rate were simultaneously recorded. PWV was calculated by measuring the time for the pulse wave to travel between the brachial and posterior tibial arteries (velocity = distance/time). The mean value between left and right baPWV was used for study analysis. All measurements were performed by the same experienced operator blinded to patients' information.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were expressed as percentages. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using the Chi-square test between both genders. Pearson's correlation analysis and scatter plots were used to show the association between two continuous parameters. Multiple linear regression analyses were performed to assess associations between baPWV and each component of metabolic syndrome, independent of age. The interactions between the number of metabolic components and gender in relation to baPWV were assessed using cross-product term in the regression model. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 18.0 (Chicago, IL, USA).

Table 1
Baseline characteristics of study subjects.

	Men (n = 379)	Women (n = 158)	p
Age (years)	53.8 ± 7.5	55.9 ± 7.5	0.004
Body mass index (kg/m^2)	24.4 ± 3.1	24.2 ± 3.4	0.570
Body fat (%)	23.2 ± 5.2	33.8 ± 6.0	<0.001
Waist circumference (cm)	84.4 ± 7.7	77.5 ± 9.1	<0.001
Hip circumference (cm)	95.1 ± 5.6	93.5 ± 6.5	0.003
Hypertension, *n* (%)	125 (34.5)	44 (29.1)	0.236
Diabetes, *n* (%)	39 (10.8)	13 (8.6)	0.459
Dyslipidemia, *n* (%)	74 (20.4)	39 (25.8)	0.180
Current smoking, *n* (%)	125 (38.0)	8 (6.5)	<0.001
Previous CAD, *n* (%)	11 (3.0)	2 (1.3)	0.363
Previous stroke, *n* (%)	5 (1.4)	3 (2.0)	0.699
SBP (mmHg)	123 ± 13	118 ± 16	<0.001
DBP (mmHg)	82.3 ± 9.7	78.5 ± 10.0	<0.001
Hemoglobin (g/dL)	15.3 ± 0.9	13.2 ± 0.8	<0.001
Fasting plasma glucose (mg/dL)	98.3 ± 18.5	96.1 ± 18.3	0.209
Uric acid (mg/dL)	5.76 ± 1.29	4.44 ± 1.09	<0.001
Total cholesterol (mg/dL)	191 ± 32	200 ± 41	0.012
LDL cholesterol (mg/dL)	119 ± 31	125 ± 39	0.141
HDL cholesterol (mg/dL)	48.7 ± 11.9	54.9 ± 12.0	<0.001
Triglyceride (mg/dL)	113 ± 61	103 ± 54	0.059
Estimated GFR (mL/min/1.73 m^2)	81.6 ± 13.1	83.0 ± 14.9	0.254
C-reactive protein (mg/dL)	0.12 ± 0.20	0.15 ± 0.29	0.306
baPWV (cm/s)	1363 ± 229	1387 ± 269	0.313

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GFR, glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity.

Results

Baseline characteristics

Of the enrolled subjects, 379 (70.6%) were men. Baseline clinical characteristics according to gender are shown in Table 1. Women were older than men (55.9 ± 7.5 years versus 53.8 ± 7.5 years, p = 0.004). BMI was similar between both genders. Waist and hip circumferences were greater in men than in women. The percentage of body fat was higher in women than in men. The prevalence of traditional risk factors, including hypertension, diabetes, dyslipidemia, previous coronary artery disease, and stroke, were similar in both genders. The proportion of current smokers was significantly higher in men than in women. Systolic and diastolic blood pressures were higher in men than in women. Laboratory test results showed that men had a higher level of uric acid and a lower level of HDL cholesterol than women. Total cholesterol level was higher in women than in men. BaPWV values were 1363 ± 229 cm/s in men and 1387 ± 269 cm/s in women (p = 0.313). The distributions of baPWV of men and women are shown in Fig. 1.

Association between age and baPWV

Although it is not a component of metabolic syndrome, age has been reported to be one of the most powerful indicators of arterial stiffness [20]. Our results also showed that there were significant positive linear correlations between age and baPWV in both genders (r = 0.411 in men and 0.495 in women, $p < 0.001$ for each) (Fig. 2).

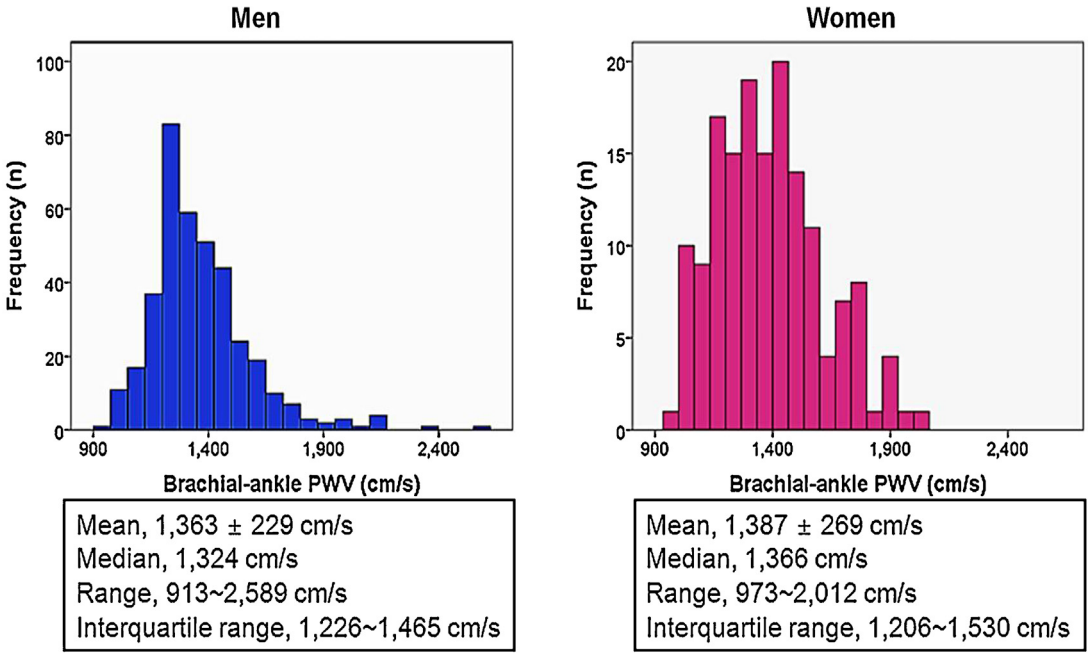

Fig. 1. Distribution of brachial-ankle PWV of study subjects. PWV, pulse wave velocity.

Associations between baPWV and each component of metabolic syndrome

Multiple linear regression analyses were used to control the effect of age on baPWV (Table 2). Systolic ($\beta = 0.333$, $p < 0.001$) and diastolic ($\beta = 0.262$, $p < 0.001$) blood pressures, fasting plasma glucose ($\beta = 0.138$, $p = 0.003$), HbA1c ($\beta = 0.128$, $p = 0.007$), and triglyceride ($\beta = 0.109$, $p = 0.021$) were significantly associated with baPWV in men. Waist circumference was not associated with baPWV in men ($\beta = -0.026$, $p = 0.576$). In women, waist circumference ($\beta = 0.388$, $p < 0.001$), systolic ($\beta = 0.487$, $p < 0.001$) and diastolic ($\beta = 0.329$, $p < 0.001$) blood pressures, fasting plasma glucose ($\beta = 0.227$, $p = 0.002$), HbA1c ($\beta = 0.163$, $p = 0.029$), and triglyceride ($\beta = 0.190$, $p = 0.010$) were significantly associated with baPWV. HDL cholesterol was not associated with baPWV in either gender ($p > 0.05$ for each). Simple linear correlations between waist circumference and baPWV according to gender are shown in Fig. 3.

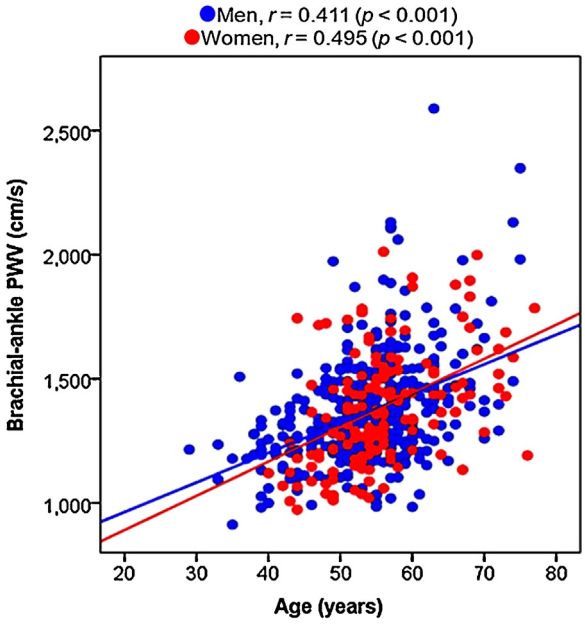

Fig. 2. Associations between brachial-ankle PWV and age according to gender. PWV, pulse wave velocity.

Associations between baPWV and metabolic syndrome and its components according to gender

The prevalence of metabolic syndrome was 22.7% in men ($n = 86$) and 26.6% ($n = 42$) in women ($p = 0.335$). Study subjects were stratified according to their mean age (<55 versus ≥55 years) and gender, and we compared baPWV value in relation to metabolic syndrome and its components. For the whole subjects, those with metabolic syndrome had a higher baPWV than those without metabolic syndrome regardless of their ages. The same was seen for women aged <55 years but not for all men and women aged ≥55 years (Fig. 4). High blood pressure was associated with elevated baPWV in both genders, and central obesity was associated with elevated baPWV in women aged <55 years but not in all men and women aged ≥55 years. High plasma glucose level was associated with elevated baPWV in men but not in women. HDL and triglyceride were not associated with baPWV in either gender in these analyses (Fig. 5). As the number of the components of metabolic syndrome increased, baPWV increased proportionally in both genders ($p < 0.001$ for each). However, this correlation was more significant in women than in men ($\beta = 0.408$

Table 2
Multiple linear regression analyses showing gender-specific correlations between brachial-ankle pulse wave velocity and each component of metabolic syndrome after controlling for age.

Variable	Men		Women	
	β	p	β	p
Waist circumference	−0.026	0.576	0.388	<0.001
Systolic blood pressure	0.333	<0.001	0.487	<0.001
Diastolic blood pressure	0.262	<0.001	0.329	<0.001
Fasting plasma glucose	0.138	0.003	0.227	0.002
Hemoglobin A1c	0.128	0.007	0.163	0.029
Triglyceride	0.109	0.021	0.190	0.010
High-density lipoprotein cholesterol	0.057	0.228	−0.020	0.782

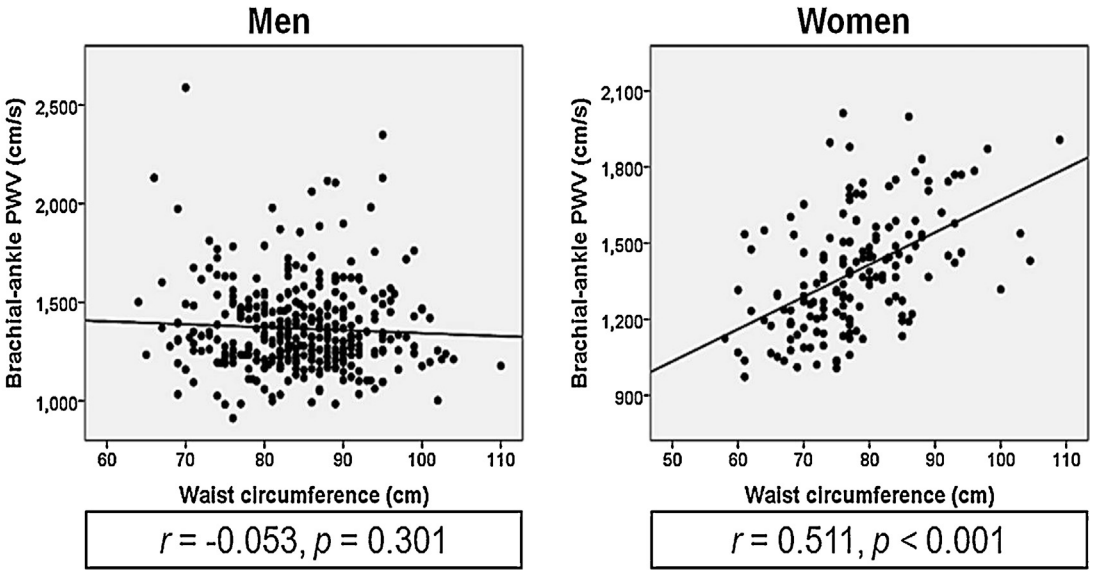

Fig. 3. Simple linear correlations between waist circumference and brachial-ankle PWV according to gender. PWV, pulse wave velocity; *r*, correlation coefficient.

versus $\beta = 0.146$ after adjustment for age) (Fig. 6A). There was significant interaction between the number of metabolic components and gender in relation to baPWV (p for interaction = 0.004), indicating that the associations were stronger in women than in men (Fig. 6B).

Discussion

Our results showed that elevated baPWV is associated with metabolic syndrome in both genders; however, each component of metabolic syndrome has a different impact on baPWV according to gender. Women have a stronger association of baPWV with metabolic syndrome and its components than men.

Associations between baPWV and metabolic syndrome

There have been many studies showing a positive association between elevated baPWV and metabolic syndrome [15,16]. Each component of metabolic syndrome plays a role as a risk factor of cardiovascular disease by promoting inflammation, thrombosis, and atherosclerosis [21]. These unfavorable effects lead to vascular damage and consequent poor cardiovascular outcome, which is reflected by increased arterial stiffness. In addition, it has been reported that there is close interaction between metabolic derangement and endothelial dysfunction, which is a hallmark of atherosclerosis [22]. Therefore, in the setting of metabolic syndrome, it is possible to predict that elevated baPWV is potentially caused by cumulative effects of risk factors of metabolic syndrome. This study also demonstrates a positive relationship between high baPWV and metabolic syndrome: subjects with metabolic syndrome had a higher baPWV than those without, and as the number of the components of metabolic syndrome increased, baPWV value also increased proportionally in both genders. Our results add to the body of evidence that metabolic syndrome is a risk factor of arterial stiffening.

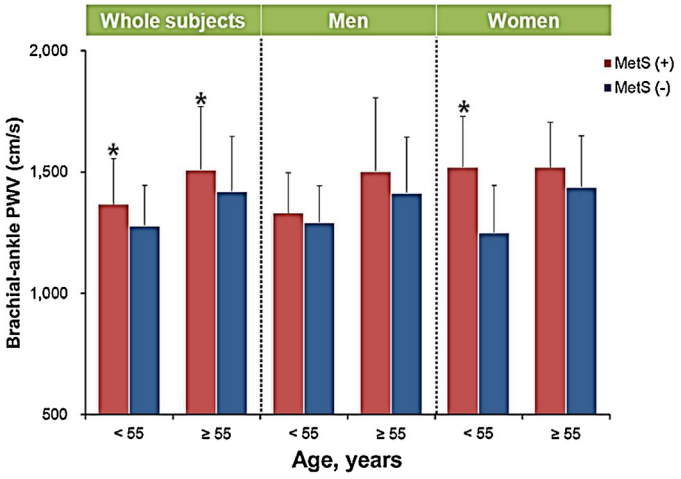

Fig. 4. Associations between brachial-ankle PWV and metabolic syndrome according to gender and ages. PWV, pulse wave velocity; MetS, metabolic syndrome. $^{*}p < 0.05$ versus MetS (−).

Gender-dependent associations between baPWV and each component of metabolic syndrome

There have been a few studies regarding the relationship between metabolic syndrome and arterial stiffness in relation to gender. Weng et al. [23] found that different metabolic variables and components of metabolic syndrome have distinct impacts on baPWV in age- and gender-dependent manners. They showed that linear associations between the number of the components of metabolic syndrome and baPWV are stronger in women than in men. Another study of 8300 Chinese subjects has also shown that the metabolic syndrome and its components affect arterial stiffness more severely in women than in men [24]. Nishida et al. [25] demonstrated similar findings that an increase in the number of clustering metabolic syndrome components is more significantly associated with worsening of baPWV. Consistent with these findings, our results showed that linear associations between the number of the components of metabolic syndrome and baPWV were stronger in women than in men suggesting more pronounced effects of metabolic syndrome on arterial stiffness in women than in men. In addition, we also showed different associations of metabolic syndrome and its components with baPWV according to age groups. In particular, baPWV was higher in young women (aged <55 years) with metabolic syndrome than those without; however, baPWV was not different by metabolic syndrome in older women (aged ≥55 years). The same result was shown in the

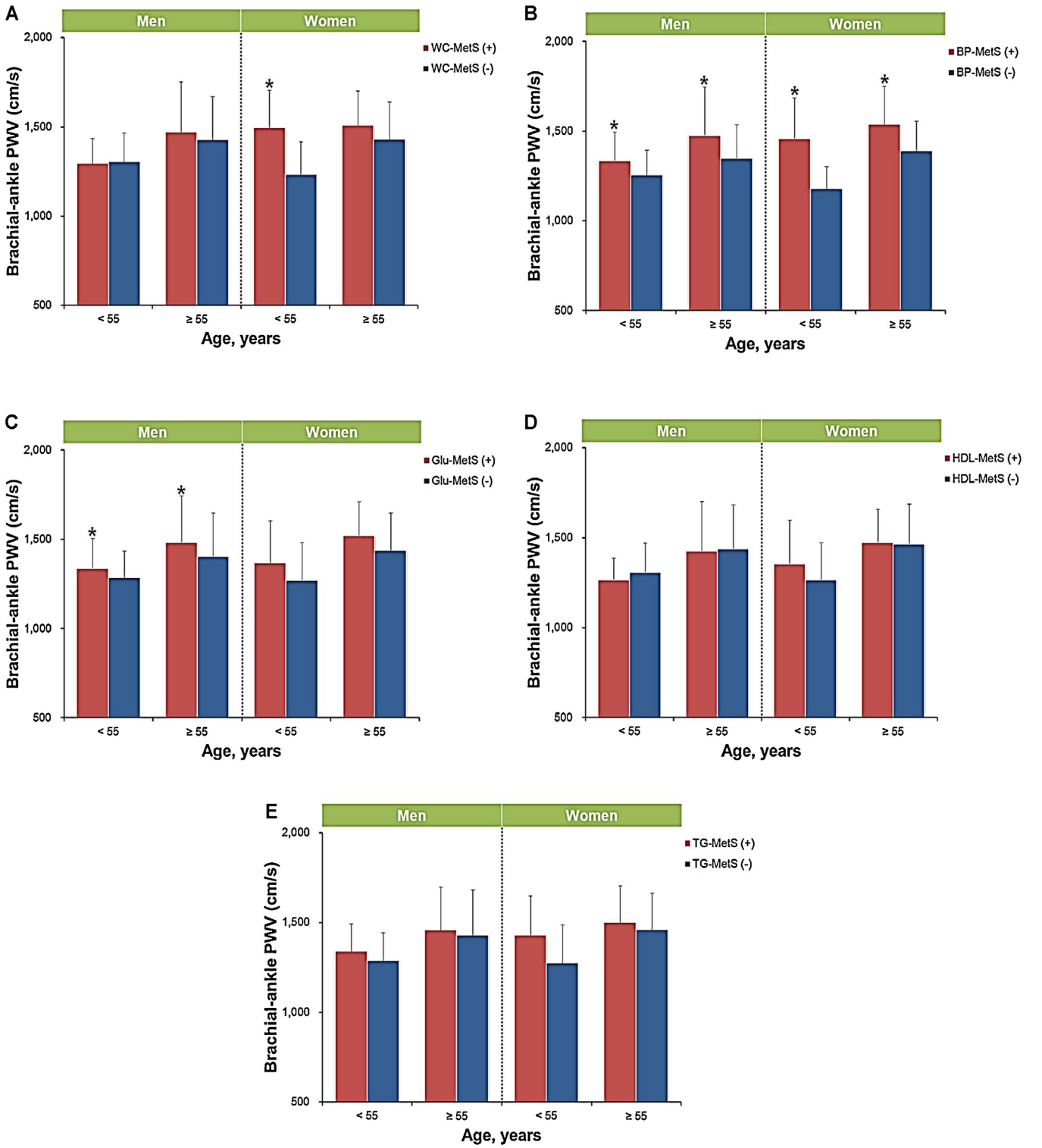

Fig. 5. Associations between brachial-ankle PWV and each component of metabolic syndrome according to gender and ages. Comparisons of baPWV values between subjects with and without waist circumference (A), blood pressure (B), fasting glucose (C), high-density lipoprotein cholesterol (D), and triglyceride (E) meeting diagnostic criteria of metabolic syndrome in relation to gender and ages. PWV, pulse wave velocity; MetS, metabolic syndrome; WC, waist circumference; BP, blood pressure; Glu, glucose; HDL, high-density lipoprotein; TG, triglyceride. $^{*}p < 0.05$ versus MetS (−).

association between waist circumference and baPWV. When we consider that most Korean women experience menopause around the age of 50 years [26], these results may suggest the important role of hormonal status on the associations between metabolic syndrome and arterial stiffness in women.

The mechanism on the gender-specific effects of metabolic syndrome and its components on arterial stiffness is uncertain. Traditionally, menopause and estrogen status have been proposed as the reason for gender difference in cardiovascular risk and complications [27,28]. Estrogen affects vascular structure and function [29] and hormonal replacement therapy reduces arterial stiffness in post-menopausal women [30]. Different mechanical properties of arteries between men and women have been reported [31]. Many investigations reported that women have a

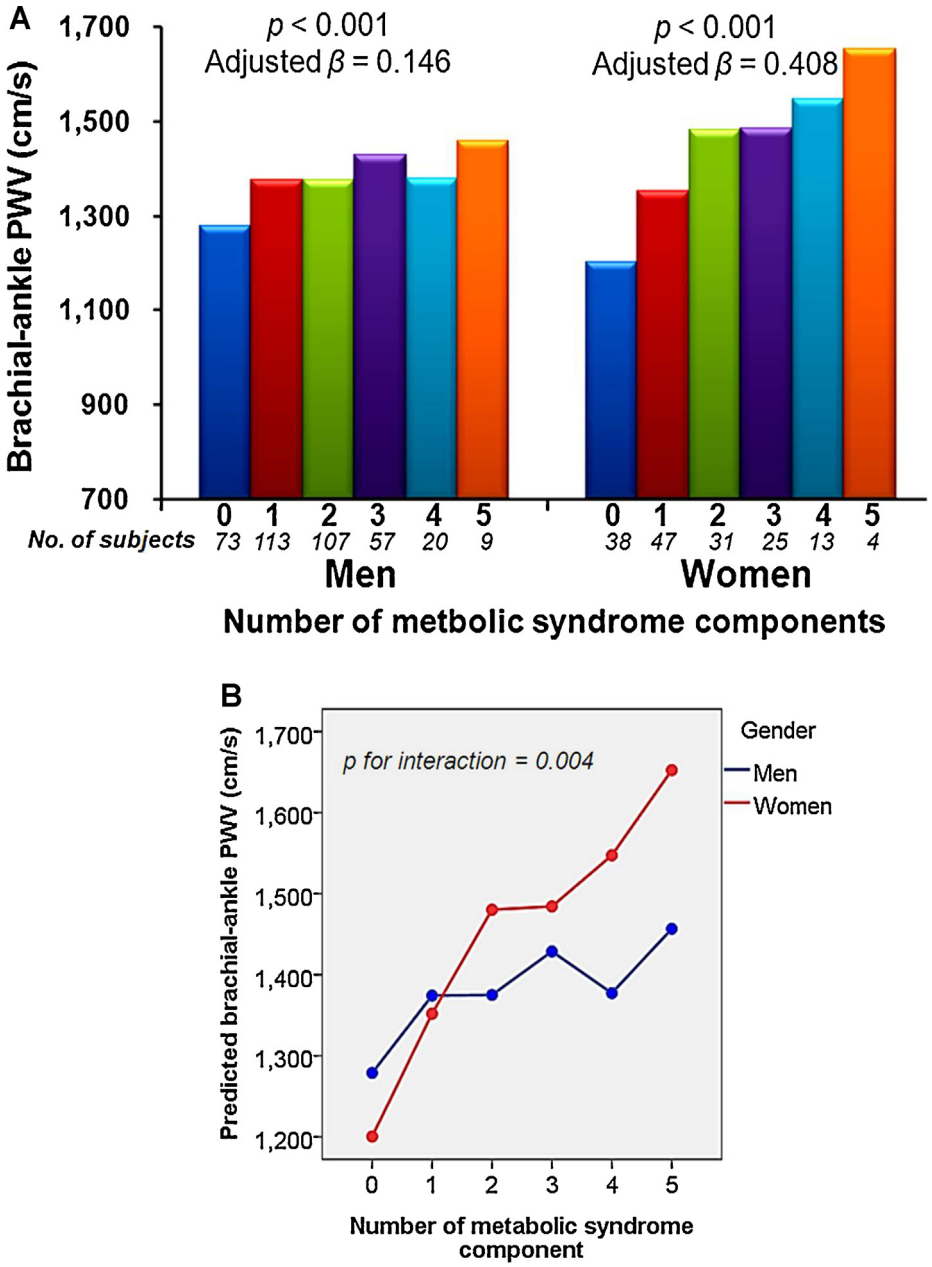

Fig. 6. Associations between brachial-ankle PWV and number of metabolic syndrome components according to gender. Age-adjusted associations between brachial-ankle PWV and number of metabolic syndrome components according to gender (A), and interaction between the number of metabolic syndrome components and gender in relation to brachial-ankle PWV (B). PWV, pulse wave velocity.

lower baPWV than men [23,32]. In our study, baPWV values were not different according to gender. The old age of our study population may explain this discrepancy. In the elderly, baPWV levels become similar because estrogen, which has a vascular protective effect, declines after menopause [24,30,33]. Regarding metabolic syndrome, it has been speculated that reduced accumulation of fat within the intra-abdominal area may play a protective role in young women. However, with aging, the decline in ovarian function reduces estrogen production which is responsible for menopause-related metabolic changes and central obesity [28]. Central obesity plays a pivotal role in the development of cardiometabolic disease, and is also an essential component for the diagnosis of metabolic syndrome. We found evidence of gender interactions in that central obesity was positively associated with arterial stiffness independently of age in women but not men, which is consistent with findings of a previous study [23]. The higher amount of hepatic-free fatty acid delivery derived from lipolysis of visceral adipose tissue and differences in adipokine secretion and synthesis have been suggested as another reason explaining gender difference [28,34]. Longevity and later onset of cardiovascular disease in women may also contribute to gender differences [28].

Clinical utility of baPWV

Although cfPWV is considered the most reliable index of arterial stiffness, there is some strength of baPWV compared to cfPWV. BaPWV is easy to perform, and is well correlated with cfPWV [11] and aortic stiffness obtained by invasive recording [35]. In addition, the validity and usefulness of baPWV have been proved by applying it in the noninvasive assessment of atherosclerosis, and by employing it as a prognostic marker in the prediction of

future cardiovascular events in the general population and various subgroups with certain disease conditions [10–14]. In particular, because of its simplicity and short measurement time, baPWV is more suitable for screening a large population than other methods for arterial stiffness. Before the onset of overt cardiovascular disease, the metabolic syndrome is often present. Therefore, identification and management of the metabolic syndrome are crucial for the prevention of cardiovascular disease. From this point of view, baPWV would be a useful tool for the assessment of subclinical arterial alterations in metabolic syndrome.

Study limitations

In addition to the retrospective study design, our study has some limitations. First, our results do not infer causal relationships between metabolic syndrome and baPWV because of its observational and cross-sectional study design. Second, our study population consisted solely of middle-aged Koreans, so generalization to other populations is limited. Third, the study may have been underpowered to detect some gender differences because of the relatively small number of subjects. Finally, vasoactive drugs affecting baPWV values were not identified.

Conclusions

The effects of metabolic syndrome and its components on arterial stiffness are more pronounced in women than in men. When interpreting study results, this gender effect should be considered. In addition, more attention should be paid to women with metabolic syndrome. Prospective studies with a large sample size would be required to confirm these findings.

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