J Atheroscler Thromb, 2018; 25: 178-185.
http://doi.org/10.5551/jat.39388

Original Article

Age-Specific Determinants of Pulse Wave Velocity among Metabolic Syndrome Components, Inflammatory Markers, and Oxidative Stress

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***Aim*: Pulse wave velocity (PWV) is thought to have different relationships with metabolic syndrome (MS) components, inflammatory markers, and oxidative stress, according to age. However, age-specific determinants of PWV have not yet been studied. We investigated age-dependent relationships among PWV and MS components, inflammatory markers, and oxidative stress.**

***Methods*: A total of 4,318 subjects were divided into 4 groups: 19–34 y (n=687), 35–44 y (n=1,413), 45–54 y (n=1,384), and 55–79 y (n=834). MS components, brachial-ankle PWV (baPWV), high-sensitivity C-reactive protein (hs-CRP), and oxidative stress markers were measured.**

***Results*: There were age-related increases in MS, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic BP (DBP), triglycerides, glucose, hs-CRP, oxidized low-density lipoprotein (LDL), 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), and baPWV. BaPWV was significantly associated with sex and elevated BP in the 19–34 y group; with age, sex, BMI, elevated BP and triglycerides in the 35–44 y group; with age, sex, elevated BP, fasting glucose, hs-CRP and oxidized LDL in the 45–54 y group; and with age, BMI, elevated BP, fasting glucose and oxidized LDL in the 55–79 y group.**

***Conclusions*: Our results show that age-related increases in baPWV are associated with age-related changes in MS components, inflammatory markers, and oxidative stress. However, each of these factors has an age-specific, different impact on arterial stiffness. In particular, oxidative stress may be independently associated with arterial stiffness in individuals older than 45 y.**

Key words: Arterial stiffness, baPWV, Metabolic syndrome, Oxidative stress

Introduction

Metabolic syndrome (MS) is a phrase that refers to a cluster of several cardiovascular risk factors, including abdominal obesity, impaired glucose tolerance, dyslipidemia, and hypertension[1, 2]. MS is associated with a marked increase in the risk of atherosclerotic cardiovascular disease. MS affects 24% of adults in the US and 18.8% of adults in Korea[3, 4]. MS and age are major risk factors for arterial stiffness, a marker of arterial damage. Moreover, oxidative stress was recently reported to be a marker of metabolic risk in the general population, and it has been suggested that it is associated with the pathogenesis underlying arterial stiffness[5, 6]. Increases in arterial stiffness have been associated with an increased risk of experiencing a cardiovascular event[7].

Brachial ankle pulse wave velocity (baPWV) is an effective index of the arterial stiffness of large arteries that is widely used for noninvasive assessments of vas-

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Received: December 11, 2016
Accepted for publication: June 5, 2017

cular function[8]. In a community-based population, baPWV has been shown to be significantly higher in asymptomatic individuals with composite coronary and carotid atherosclerotic changes, as determined by coronary CT and carotid ultrasonography, demonstrating its good diagnostic potential for atherosclerosis[9]. In addition, many previous studies have shown that ba-PWV is a useful marker for the management of atherosclerotic cardiovascular disease and/or its risk factors, including screening, diagnosis, prognostication, and treatment[10].

It is thought that PWV may have different relationships with different MS components, inflammatory markers, and oxidative stress that may vary according to age. However, age-specific determinants of PWV have not yet been studied. Therefore, in the present study, we investigate the age-dependent relationships between pulse wave velocity and MS components, inflammatory markers, and oxidative stress.

Materials and Methods

Study Population

Study participants were recruited from a cohort of 4,336 individuals (2,174 males and 2,162 females; age range 19–79 years old) who underwent a health examination at the National Health Insurance Corporation, Ilsan Hospital, in Goyang, Korea from January 2011 to December 2015. Among these participants, 4,318 (2,165 men and 2,153 women; age range 19–79 years old) met the study criteria and were included in the final analysis. The exclusion criteria were as follows: cardiovascular disease, cancer, liver disease, renal disease, pancreatitis, or psychiatric problems; pregnancy or lactation; and drug or alcohol abuse. The aim of this study was carefully explained to all participants, and each participant provided written informed consent. The Institutional Review Board of Yonsei University and Ilsan Hospital approved the study protocol, which complied with the Declaration of Helsinki.

Definition of Metabolic Syndrome

The definition of MS was based on A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity[11]. MS was defined as the presence of three or more of the following five criteria: waist circumference ≥ 90 cm in males and ≥ 80 cm in females (defined by the WHO Asian Region guidelines[12]); triglycerides (TG) ≥ 150 mg/dL (drug treatment for elevated TGs was used as an alternate indicator); high-density lipoprotein (HDL) cholesterol $<$40 mg/dL in males and $<$ 50 mg/dL in females (drug treatment for reduced HDL cholesterol was used as an alternate indicator); systolic blood pressure (SBP) ≥ 130 mmHg or diastolic BP (DBP) ≥ 85 mmHg (antihypertensive drug treatment was used an alternate indicator); and fasting glucose ≥ 100 mg/dL (drug treatment for elevated glucose was used as an alternate indicator).

Grouping Subjects According to Age and the Presence of Metabolic Syndrome

To determine the effects of age and MS on high-sensitivity C-reactive protein (hs-CRP), oxidative stress, and baPWV, the 4,318 healthy included subjects were divided into eight subgroups based on age and the presence of MS: 19–34 years old with no MS (n=635) and with MS (n=52), 35–44 years old with no MS (n=1,241) and with MS (n=172), 45–54 years old with no MS (n=1,087) and with MS (n=297), and 55–79 years old with no MS (n=548) and with MS (n=286).

Blood Pressure and baPWV

BP was measured using a random-zero sphygmomanometer (HM-1101, Hico Medical Co., Ltd., Chiba, Japan) with an appropriately sized cuff after a rest period during which the participant was seated for at least 20 minutes. BP was measured in both arms, and the higher of the two measurements was recorded. Three BP measurements were obtained at each visit, and the difference between the three systolic BP measurements was always $<$2 mmHg. The average values of the systolic and diastolic BP measurements were used. The participants were instructed not to smoke or drink alcohol for at least 30 minutes before each BP measurement. baPWV was measured using an automatic waveform analyzer (model VP-1000; Nippon Colin Ltd., Komaki, Japan) as previously described[13].

Clinical and Biochemical Assessments

Detailed information regarding the clinical and biochemical assessments performed in this study are provided elsewhere[14]. Body weight and height were measured, and body mass index (BMI) was calculated in units of kilograms per square meter (kg/m^2). Waist circumference (measured directly on the skin) was measured at the umbilical level after normal expiration using a plastic measuring tape with measurements to the nearest 0.1 cm while the subject was in an upright standing position. Blood samples were collected following an overnight fast of at least 12 hours. Fasting

Table 1. MS components, hs-CRP, oxidative stress and baPWV according to age group

	Total (n=4,318)				Comparisons					
	19-34 (n=687)	35-44 (n=1,413)	45-54 (n=1,384)	55-79 (n=834)	1-2	1-3	1-4	2-3	2-4	3-4
Age (year)	30.0±0.14	39.3±0.08	49.6±0.08	60.5±0.17	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Metabolic syndrome n (%)†, ‡	52 (7.6)	172 (12.2)	297 (21.5)	286 (34.3)	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
BMI (kg/m^2)	23.0±0.19	24.1±0.17	24.5±0.15	24.5±0.14	<0.001	<0.001	<0.001	0.438	0.441	1.000
Waist (cm)	80.7±0.34	82.0±0.22	83.2±0.20	86.0±0.26	0.002	<0.001	<0.001	<0.001	<0.001	<0.001
Systolic BP (mmHg)	115.7±0.50	116.2±0.36	119.9±0.39	124.4±0.54	1.000	<0.001	<0.001	<0.001	<0.001	<0.001
Diastolic BP (mmHg)	69.5±0.39	70.8±0.29	74.9±0.30	76.8±0.38	0.052	<0.001	<0.001	<0.001	<0.001	0.001
Triglyceride (mg/dL)§	92.5±2.43	105.8±1.72	117.8±2.03	126.4±2.58	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
HDL cholesterol (mg/dL)§	54.0±0.55	53.7±0.38	53.2±0.39	51.1±0.49	1.000	1.000	<0.001	1.000	<0.001	0.002
Glucose (mg/dL)§	88.1±0.45	91.6±0.33	93.7±0.44	96.0±0.59	<0.001	<0.001	<0.001	0.002	<0.001	0.001
hs-CRP (mg/L)§	0.89±0.06	0.95±0.05	1.09±0.06	1.35±0.08	0.489	0.011	<0.001	0.538	<0.001	<0.001
LDL particle size (nm)§	24.0±0.03	24.0±0.02	23.8±0.02	23.7±0.03	0.522	<0.001	<0.001	<0.001	<0.001	<0.001
Oxidized LDL (U/L)§	42.0±1.09	46.3±0.90	50.2±0.85	53.2±0.97	0.039	<0.001	<0.001	<0.001	<0.001	0.005
8-epi-PGF$_{2\alpha}$ (pg/mg creatinine)§	1489.4±28.1	1527±17.7	1601.4±21.2	1669.9±25.9	0.525	<0.001	<0.001	0.025	<0.001	0.055
Malondialdehyde (nmol/mL)§	8.05±0.12	8.5±0.09	9.26±0.10	9.53±0.13	0.143	<0.001	<0.001	<0.001	<0.001	0.384
baPWV (cm/s)§	1182.3±5.67	1230.5±4.07	1337.6±5.06	1512.9±9.44	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Mean±SE. §tested by logarithmic transformation. ANCOVA was used to calculate the p-values. p-values were adjusted for sex, smoking, and drinking. All alphabetical $p<0.05$ were derived from Bonferroni post hoc tests; a lack of a significant differences is marked with the same letter, and significant differences are marked with a different letter. †$p<0.001$, derived from Pearson's chi-squared test. ‡$p<0.001$, derived from linear-by-linear association test.

TGs; total, HDL, and low-density lipoprotein (LDL) cholesterol; glucose; serum hs-CRP; oxidized LDL; and LDL particle size were measured as previously described[14]. Plasma malondialdehyde (MDA) levels were measured from thiobarbituric acid-reactive substance (TBARS) levels using a TBARS assay kit (ZeptoMetrix Co., Buffalo, NY). The level of 8-epi-prostaglandin F$_{2\alpha}$ (8-epi-PGF$_{2\alpha}$) was measured using a Urinary Isoprostane ELISA kit (Oxford Biomedical Research Inc., Rochester Hills, MI).

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM/SPSS, Chicago, IL, USA). Analysis of covariance (ANCOVA) with a *Bonferroni* post hoc test was used to compare differences according to age. Independent *t*-tests were used to compare parameters between groups with and without MS in each age group. *Pearson's* chi-squared tests were performed to compare MS status according to age. Linear-by-linear association tests were used to determine whether there was a linear trend between the proportion of MS and age. *Pearson's* correlation coefficient was used to analyze the relationships between variables. A multiple linear regression analysis was performed to identify independent predictors of baPWV across all subjects, within each age group, and among the male and female groups. In the multiple linear regression model, MS components were included as binary variables according to the absence or presence of each MS component. A logarithmic transformation was performed on skewed variables. For descriptive purposes, the mean values are presented as untransformed values. The results are expressed as the means±standard error. A two-tailed p-value <0.05 was considered to indicate statistical significance.

Results

MS Components, hs-CRP, Oxidative Stress, and baPWV According to Age

Table 1 shows the MS components, hs-CRP, oxidative stress, and baPWV according to the age groups after adjusting for gender distribution, smoking, and drinking. The MS proportion, waist circumference, serum TGs, serum glucose, plasma oxidized LDL, and baPWV progressively and significantly increased with age. The mean value for BMI was the lowest in the youngest group (19–34 y). SBP and DBP increased with age, although there was no significant difference between the 19–34 y group and the 35–44 y group. The mean value for HDL cholesterol was lowest in the oldest group (55–79 y). The hs-CRP level was highest in the oldest group, and the mean value in the 45–54 y group was higher than the value in the 19–34 y group. LDL particle size decreased with age, although there was no significant difference between the 19–34 y group and the 35–44 y group. The mean

Table 2. BaPWV, hs-CRP, and oxidative stress in non-MS and MS subjects according to age group

	Non-MS (n=3,511)				Comparisons					
	19-34 (n=635)	35-44 (n=1,241)	45-54 (n=1,087)	55-79 (n=548)	1-2	1-3	1-4	2-3	2-4	3-4
baPWV (cm/s)§	1177.0±5.81	1219.0±4.23	1313.5±5.29	1471.0±11.1	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
hs-CRP (mg/L)§	0.86±0.06	0.88±0.05	1.00±0.07	1.37±0.10	0.763	0.044	<0.001	0.891	<0.001	<0.001
LDL particle size (nm)§	24.1±0.03	24.0±0.02	23.9±0.03	23.8±0.03	1.000	0.002	<0.001	0.042	<0.001	0.294
Oxidized LDL (U/L)§	41.1±1.10	44.8±0.95	49.5±0.95	51.7±1.11	0.212	<0.001	<0.001	<0.001	<0.001	0.110
8-epi-PGF$_{2\alpha}$ (pg/mg creatinine)§	1487.9±26.4	1508.1±19.4	1569.1±19.0	1609.8±27.9	1.000	0.004	<0.001	0.027	0.001	0.838
Malondialdehyde (nmol/mL)§	8.03±0.12	8.32±0.09	9.03±0.10	9.18±0.14	0.148	<0.001	<0.001	<0.001	<0.001	1.000
	MS (n=807)				Comparisons					
	19-34 (n=52)	35-44 (n=172)	45-54 (n=297)	55-79 (n=286)	1-2	1-3	1-4	2-3	2-4	3-4
baPWV (cm/s)§	1248.7±22.1	1313.8±11.7	1425.7±12.2	1591.8±16.4	0.204	<0.001	<0.001	<0.001	<0.001	<0.001
hs-CRP (mg/L)§	1.23±0.16	1.49±0.14	1.40±0.11	1.33±0.09	1.000	1.000	1.000	1.000	1.000	1.000
LDL particle size (nm)§	23.3±0.11	23.4±0.06	23.4±0.05	23.2±0.06	1.000	1.000	1.000	1.000	0.193	0.053
Oxidized LDL (U/L)§	52.1±4.72	56.0±2.47	53.4±1.91	57.8±1.92	1.000	1.000	0.082	1.000	0.473	0.093
8-epi-PGF$_{2\alpha}$ (pg/mg creatinine)§	1507.8±179.0	1664.7±36.9	1722.0±70.4	1793.2±53.6	0.002	<0.001	<0.001	1.000	0.197	0.676
Malondialdehyde (nmol/mL)§	8.29±0.49	9.83±0.36	10.2±0.28	10.5±0.26	0.250	0.028	0.003	0.812	0.039	0.675

Mean±SE. §tested by logarithmic transformation. ANCOVA was used to calculate the p-values. p-values were adjusted for sex, smoking, and drinking. All alphabetical $p<0.05$ were derived from Bonferroni post hoc tests; a lack of a significant differences is marked with the same letter, and significant differences are marked with a different letter.

values for oxidative stress (urinary 8-epi-PGF$_{2\alpha}$ and MDA) were higher in the 45–54 y and 55–79 y groups than in the 19–34 y and 35–44 y groups (**Table 1**).

BaPWV, hs-CRP, LDL Particle Size and Oxidative Stress According to Age, and MS

We examined samples from obtained subjects who were aged 19 to 79 years old to determine the impact of age and MS on baPWV, hs-CRP, LDL particle size, and oxidative stress (**Table 2**). The baPWV values were higher in MS subjects than in non-MS subjects in all of the age groups. In the non-MS subjects, baPWV progressively and significantly increased with age. Similarly, the highest baPWV values in the MS subjects were in the oldest group (55–79 y), and the mean value for the 45–54 y group was higher than the mean values for the 19–34 y and 35–44 y groups. MS subjects had higher hs-CRP than non-MS subjects except for the 55–79 y group. In non-MS subjects, the level of hs-CRP was highest in the oldest group, and the mean value for the 45–54 y group was higher than the mean value in the 19–34 y group. However, in the MS group, there was no significant difference in hs-CRP across age groups.

MS subjects had smaller LDL particle sizes than non-MS subjects in all age groups. In the non-MS subjects, the 45–79 y group had smaller LDL particle sizes than were observed in the 19–44 y group. Plasma oxidized LDL, urinary 8-epi-PGF$_{2\alpha}$, and plasma MDA levels were higher in the MS subjects than in the non-MS subjects in all age groups. In the non-MS subjects, plasma oxidized LDL, urinary 8-epi-PGF$_{2\alpha}$, and plasma MDA levels were higher in the 45–79 y group than in the 19–44 y group. However, there was no significant difference in LDL particle size or plasma oxidized LDL levels among the MS groups according to age. In the MS subjects, urinary 8-epi-PGF$_{2\alpha}$ levels were higher in the 35–79 y group than in the 19–34 y group, MDA levels were the highest in the oldest group, and the mean MDA level was higher in the 45–79 y group than in the 19–34 y group.

Age-specific Multiple Regression Analysis of baPWV

The Pearson's correlation analysis across all subjects showed that baPWV was positively correlated with age, MS components (waist, SBP, DBP, TGs, and glucose), inflammatory markers (hs-CRP), and oxidative stress (oxidized LDL, 8-epi-PGF$_{2\alpha}$, and MDA) and negatively correlated with LDL particle size (data not shown).

A multiple regression analysis showed that among all the included subjects, baPWV was significantly associated with age, sex, BMI, elevated BP, elevated TGs, elevated fasting glucose, hs-CRP, and oxidized LDL but was not associated with smoking,

Table 3. Age-specific multiple regression analysis of baPWV

Variables	19-34 (n=687)		35-44 (n=1,413)		45-54 (n=1,384)		55-79 (n=834)		Total (n=4,318)	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Age (year)	0.007	0.930	0.155	<0.001	0.156	<0.001	0.359	<0.001	0.409	<0.001
Sex	−0.346	0.001	−0.23	<0.001	−0.105	0.041	−0.004	0.945	−0.131	<0.001
Smoking	−0.018	0.819	0.043	0.336	−0.002	0.962	−0.075	0.144	0.001	0.979
Drinking	−0.085	0.277	0.005	0.899	0.005	0.896	0.083	0.118	0.011	0.626
BMI (kg/m^2)	0.133	0.207	0.162	0.003	0.052	0.255	0.212	0.001	0.116	<0.001
Elevated waist circumference	−0.003	0.975	0.008	0.871	0.062	0.171	0.010	0.882	0.036	0.158
Elevated blood pressure	0.179	0.018	0.309	<0.001	0.382	<0.001	0.300	<0.001	0.293	<0.001
Elevated triglycerides	0.092	0.272	0.111	0.019	0.018	0.662	0.029	0.607	0.051	0.027
Reduced HDL cholesterol	−0.117	0.122	−0.048	0.240	0.032	0.390	0.112	0.035	0.015	0.483
Elevated fasting glucose	−0.001	0.991	−0.006	0.889	0.132	0.001	0.160	0.003	0.077	<0.001
hs-CRP (mg/L)§	0.143	0.063	0.061	0.156	0.091	0.017	0.075	0.132	0.072	0.001
LDL particle size (nm)§	−0.122	0.157	−0.035	0.457	−0.039	0.358	−0.036	0.506	−0.040	0.090
Oxidized LDL (U/L)§	0.143	0.065	0.058	0.153	0.076	0.039	0.117	0.018	0.077	<0.001
8-epi-PGF$_{2\alpha}$ (pg/mg creatinine)§	−0.015	0.836	−0.010	0.796	0.052	0.166	−0.083	0.091	−0.005	0.795
Malondialdehyde (nmol/mL)§	−0.007	0.928	0.014	0.739	0.061	0.116	−0.015	0.766	0.019	0.368

§tested by logarithmic transformation. β; standardized regression coefficient.

drinking, elevated waist circumference, reduced HDL cholesterol, LDL particle size, 8-epi-PGF$_{2\alpha}$, or MDA (the far-right column in **Table 3**).

The age-specific multiple regression analysis of baPWV showed that baPWV had a significantly different relationship with each of these parameters across the age groups. For example, in the 19–34 y group, baPWV was significantly associated with sex and elevated BP, whereas in the 35–44 y group, baPWV was significantly associated with age, sex, BMI, elevated BP, and elevated TGs. Additionally, the multiple regression analysis revealed that in the 45–54 y group, baPWV was independently associated with age, sex, elevated BP, elevated fasting glucose, hs-CRP, and oxidized LDL, and in the 55–79 y group, baPWV was independently associated with age, BMI, elevated BP, reduced HDL cholesterol, elevated fasting glucose, and oxidized LDL (**Table 3**).

Sex-specific Multiple Regression Analysis of baPWV

When we separated the male and female subjects, the multiple regression analysis of baPWV indicated that baPWV was associated with age, BMI, elevated BP, elevated fasting glucose, hs-CRP, and oxidized LDL in both males and females (**Table 4**). In the female group, menopause status was significantly associated with baPWV. Among the post-menopausal female subjects (n=686), 17 subjects were in 35–44 y group, 289 subjects were in 45–54 y group, and 380 subjects were in 55–79 y group. The mean age at menopause was 49 years old.

Discussion

In the present study, we investigated how aging and MS influence inflammatory markers (hs-CRP), oxidative stress markers (oxidized LDL, 8-epi-PGF$_{2\alpha}$ and MDA) and arterial stiffness (baPWV). Our results demonstrate that age-related increases in baPWV are associated with age-related changes in MS components, inflammatory markers, and oxidative stress. However, each of these factors had an age-specific and different impact on arterial stiffness. For example, the multiple regression analysis revealed that in the 45–54 y and 55–79 y groups, baPWV was independently and positively associated with elevated fasting glucose and oxidized LDL, whereas in the 19–34 y and 35–44 y groups, these associations were not observed.

The present results indicate an independent association between baPWV and oxidized LDL, which is consistent with the previous findings of Brinkley *et al.*[6], who showed that elevated levels of plasma oxidized LDL, a key player in the pathogenesis of atherosclerosis, was associated with increased arterial stiffness, independent of demographics, and traditional cardiovascular disease risk factors. Oxidized LDL is recognized as a key step during the initiation and progression of atherosclerosis[15], which is also associated with elevated levels of known cardiovascular disease risk factors, including BP and fasting glucose[16]. In the 44–54 y and 55–79 y groups in this study, elevated fasting glucose and elevated BP were also independently associated with baPWV. A limited amount of

Table 4. Sex-specific multiple regression analysis of baPWV

Variables	Male (n = 2,165)		Female (n = 2,153)	
	β	p-value	β	p-value
Age (year)	0.395	< 0.001	0.508	< 0.001
Menopause status	-	-	0.100	0.023
Smoking	0.004	0.878	− 0.044	0.147
Drinking	0.041	0.140	0.003	0.922
BMI (kg/m^2)	0.152	< 0.001	0.107	0.008
Elevated waist circumference	0.014	0.674	0.058	0.121
Elevated blood pressure	0.290	< 0.001	0.316	< 0.001
Elevated triglycerides	0.058	0.060	0.053	0.128
Reduced HDL cholesterol	0.017	0.546	0.006	0.861
Elevated fasting glucose	0.089	0.002	0.070	0.030
hs-CRP (mg/L)§	0.072	0.011	0.075	0.021
LDL particle size (nm)§	− 0.032	0.296	− 0.027	0.437
Oxidized LDL (U/L)§	0.073	0.009	0.087	0.007
8-epi-PGF$_{2\alpha}$ (pg/mg creatinine)§	− 0.020	0.465	0.017	0.560
Malondialdehyde (nmol/mL)§	− 0.009	0.741	0.060	0.060

§ tested by logarithmic transformation. β; standardized regression coefficient.

evidence suggests that oxidized LDL is associated with the development of arterial stiffness. Oxidized LDL stimulates collagen synthesis in arterial smooth muscle cells[17] and promotes intimal thickening[18]. Additionally, oxidized LDL also induces endothelial dysfunction by impairing endothelium-dependent vasodilation, inhibiting nitric oxide bioavailability, and reducing the expression and activity of endothelial nitric oxide synthase[19]. All of these roles of oxidized LDL may contribute to the observed increase in arterial stiffness. Furthermore, arterial stiffness may be either directly or indirectly explained by oxidative stress-mediated cellular injury[20].

The differences that were observed in arterial stiffness according to age could be partly explained by the involvement of estradiol in nitric oxide stimulation[21, 22]. In the present study, menopause status was independently associated with baPWV in the female group. Considering that the mean age at menopause was 49 years old in this study, the different modality in multiple regression analysis between the age groups under 45 y and over 45 y could be convincible. Indeed, there was no significant association of sex with baPWV in the subjects aged ≥ 55 years old in this study, suggesting that the differences that were observed in baPWV between males and females disappeared after menopause.

Age and BP have long been considered to be two important factors that affect baPWV[8]. In this study, elevated BP was a positive independent factor for baPWV in all of the age groups. The effect of elevated BP on progressive baPWV may be the result of a direct effect on arterial walls. Elevated BP may accelerate arterial stiffening, because it forces endothelial cells and arterial smooth muscle cells to be chronically exposed to the increased arterial wall dispensability, which reflects arterial stiffening[8]. Additionally, arterial stiffness can increase SBP, and because of the rapid PWV, the reflected wave returns during systole rather than diastole, thereby amplifying SBP even further and imposing an additional workload on the heart[23, 24].

Hyperglycemia induces a large number of alterations at the cellular level in vascular tissues that can potentially accelerate the atherosclerotic process. Animal and human studies have revealed several major mechanisms that underlie most of the pathological alterations that have been observed in diabetic vasculature[25]. These include a hyperglycemia-mediated increase in oxidative stress that involves several pathways, the major mechanism of which appears to include the overproduction of the superoxide anion by the mitochondrial electron transport chain and the promotion of inflammation by hyperglycemia. In this study, elevated fasting glucose and oxidized LDL were positively and independently associated with baPWV in the 45–54 y and 55–79 y groups.

Several limitations of the present study should be considered. First, because this study was cross-sectional in design, we could not determine whether arterial stiffening was caused by an increase in oxidative stress or was simply a by-product of other disease processes. Second, although there is strong *in vitro* evi-

dence supporting a role for oxidative stress in the development of the vascular changes that promote arterial stiffness, we could not determine how or where the oxidation occurred, nor could we identify the mechanisms by which plasma oxidative stress markers might have been related to arterial stiffness.

Despite these limitations, our results show that age-related increases in baPWV are associated with age-related changes in MS components, inflammatory markers, and oxidative stress. However, each of these factors has an age-specific and different impact on arterial stiffness. In particular, our data suggest that oxidative stress may be independently associated with arterial stiffness in subjects older than 45 y old. Hence, reducing oxidative stress is an attractive therapeutic target for preventing age-related changes in arterial structure and function and subsequent disease.

Acknowledgments

This study was funded by the Bio-Synergy Research Project (NRF-2012 M3A9C4048762) and the Mid-career Researcher Program (NRF-2016R1A2B4011662) of the Ministry of Science, ICT and Future Planning through the National Research Foundation of the Republic of Korea.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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