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Elevated Brachial-Ankle Pulse Wave Velocity Is Independently Associated with Microalbuminuria in a Rural Population

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Microalbuminuria is a marker of generalized endothelial dysfunction resulting from arterial stiffness or insulin resistance, and brachial-ankle pulse wave velocity (baPWV) is a good measure of arterial stiffness. We aimed to investigate whether elevated baPWV is independently associated with microalbuminuria. This study included 1,648 individuals aged over 40 who participated in the baseline Multi-Rural Cohort Study conducted in Korean rural communities between 2005 and 2006. Participants were classified into less than 30 mg/g as normoalbuminuria or 30-300 mg/g as microalbuminuriausing urinary albumin creatinine ratio (UACR). The median and Q1-Q3 baPWV values were significantly higher in the microalbuminuric group both in men (1,538, 1,370-1,777 cm/s vs. 1,776, 1,552-2,027 cm/s, $P < 0.001$) and women (1,461, 1,271-1,687 cm/s vs. 1,645, 1,473-1,915 cm/s, $P < 0.001$). BaPWV was independently associated with microalbuminuria in both genders after adjusting for pulse rate; fasting blood glucose; triglyceride; homeostatic model assessment insulin resistance ($HOMA_{IR}$) and, history of hypertension and diabetes. Fasting blood sugar and $HOMA_{IR}$ were judged as having nothing to do with multicolinearity ($r = 0.532$, $P < 0.001$). Elevated baPWV was independently associated with microalbuminuria regardless of insulin resistance among rural subjects over 40 yr.

Keywords: Albuminuria; Insulin Resistance; Risk Factors; Vascular Stiffness

INTRODUCTION

Microalbuminuria is a well-known risk factor or predictor for cardiovascular morbidity and mortality in individuals with hypertension or diabetes mellitus (3, 4) and even in the general population (1, 2) as well. The mechanism of occurrence of microalbuminuria is unclear although it is known to be a marker of generalized endothelial dysfunction triggered by metabolic processes, and insulin resistance (5-7). In addition, insulin resistance is a risk factor of microalbuminuria, especially in patients with diabetes or dyslipidemia (8, 9).

Another mechanism of microalbuminuria is associated with generalized vascular dysfunction through arterial stiffness (5-7). It is not clear whether the cause of microalbuminuria is an independent action of arterial stiffness and insulin resistance or dependent interaction of them (10). So, it is important to verify the independency between arterial stiffness and insulin resistance to understand the mechanism of microalbuminuria occurrence. Arterial stiffness is a useful marker of vascular damage and cardiovascular disease (CVD) risk (5, 7). Pulse wave velocity (PWV) is an indicator of arterial stiffness and a marker of atherosclerosis (11). Of the various PWV parameters, carotid-femoral PWV (cfPWV) is the noninvasive gold standard of arterial stiffness (12), but brachial-ankle pulse wave velocity (baPWV) is a promising new measure for screening large samples for arterial stiffness due to its technical simplicity and short sampling time (8, 9, 11). In addition, baPWV is useful as a means of estimating the atherosclerotic disease of arteries (13).

Several studies have shown that arterial stiffness is a risk factor for microalbuminuria (10, 14-17). As an example, the Taichung study performed in Taiwan targeting a middle aged community population showed the strong association between albuminuria and arterial stiffness, especially on hypertensive or diabetic subjects (10, 18). However, the prevalence of hypertension and diabetes varies depending on the population characteristics; therefore, results may be different in Korea. In addition, a study revealing the association between albuminuria and arterial stiffness existed targeting participants visiting the health promotion center for health screening (15). However, there is no study of the general population in Korea. Besides, results of epidemiologic evidence are easy to generalize, so this study is further needed.

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The purpose of this study was to assess whether baPWV is an independent risk factor of microalbuminuria regardless of insulin resistance in the elderly population (over-40 yr).

MATERIALS AND METHODS

Subjects

From February 2005 to December 2006, a total of 1,841 people aged over 40 yr, living in Yangpyeong, Gyeonggi-do, Korea, were invited to participate in the baseline Multi-Rural Cardiovascular Cohort Study conducted in Korean rural communities. Arterial stiffness has been measured in the Multi-Rural Cardiovascular Cohort since 2005 as part of the Korean Genetic Epidemiology Study. Participants responded to a questionnaire which included sociodemographic information, past medical history (defined as "diseases diagnosed by medical doctors") and lifestyle behavior, including smoking, alcohol consumption, daily physical activity and dietary patterns. Participants also underwent a complete physical examination including height, weight, waist circumference and blood pressure. Blood chemistry such as fasting blood glucose and lipid profile, urinalysis and baPWV measurement was carried out. Definitions of history of hypertension and diabetes mellitus were based upon whether they had been diagnosed by a medical doctor and included taking drugs. Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or taking antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, having diabetes mellitus history or taking antidiabetic drugs. We excluded participants who fitted the following exclusion criteria: history of cardiovascular disease, stroke or cancer (n = 149), presence of macroalbuminuria or overt proteinuria (n = 22) and incomplete data (n = 22). Finally, a total of 1,648 participants were included in the study. The study was approved by the Institutional Review Board of Hanyang University Medical Center and all participants gave their informed consents.

Brachial-ankle pulse wave velocity

BaPWV was measured with an automatic apparatus (VP-2000; Colin Corporation, Komaki, Japan). Participants rested for at least 5 min to stabilize their heart rate and were then examined in a supine position with a pneumatic cuff connected to a plethymographic sensor to determine volume pulse waveform and an oscillometric pressure sensor to measure blood pressure placed on both upper arms and ankles, and electrocardiogram electrodes placed on both wrists. The average of the left and right side baPWV values was used in the analysis. Subjects were divided into the following four quartiles with respect to baPWV values: < 1,325 cm/s, 1,325-1,515 cm/s, 1,515-1,765 cm/s, > 1,765 cm/s; males were divided into < 1,379 cm/s, 1,379-1,557 cm/s, 1,557-1,796 cm/s, > 1,796 cm/s; and females into < 1,285 cm/s, 1,285-1,489 cm/s, 1,489-1,724 cm/s, > 1,724 cm/s.

Blood pressure and blood chemistry

Blood pressure was measured twice, with a 5-min interval, after at least a 5-min rest, on the right side arm in a seated position, using a mercury sphygmomanometer. Two trained observers performed the measurements in a standardized manner according to a written protocol covering preparation of subjects, arm level, peak inflation pressure, inflation and deflation rate, reading the scale, and measurement of systolic and diastolic blood pressure by Korotkoff sound I and V, respectively. We used the mean of the two measurements in the analysis.

All blood samples were taken after overnight fasting for at least 8 hr. Fasting blood glucose, total cholesterol and triglycerides were analyzed enzymatically using an automatic analyzer (Hitachi 747 automatic analyzer, Hitachi, Tokyo, Japan). High density lipoprotein cholesterol (HDL-C) was measured directly and low density lipoprotein cholesterol (LDL-C) was estimated using the Friedwald's method (19). Serum insulin levels were analyzed with a Gamma Counter (Packard, Ramsey, Minnesota, USA) and an insulin RIA Kit (Biosource, Nivelles, Belgium) using immunoradiometric assays (IRMA). Insulin resistance was measured with thehomeostatic model assessment ($HOMA_{IR}$) using serum glucose and insulin levels. It was obtained from the following formula (20):

$$HOMA_{IR} = (\text{fasting glucose [mg/dL]} \times \text{fasting insulin [}\mu\text{IU/mL]})/405$$

Microalbuminuria

First-voided morning spot urine samples were collected from all participants and stored in a -20°C deep-freezer. Urinary albumin and creatinine were assayed by turbidimetric immunoassay and radio-immunoassay using an ADVIA Centaur Immunoassay System (Siemens Healthcare Diagnosis, Tokyo, Japan), respectively. We calculated urinary albumin to creatinine ratios (UACR) using urinary albumin and creatinine concentrations from the same samples, and categorized them in the same way for men and women (6) into 3 groups: 1) UACR less than 30 mg/g, normoalbuminuria; 2) UACR 30-300 mg/g, microalbuminuria; 3) higher than 300 mg/g, macroalbuminuria or overt proteinuria.

Statistical analysis

All analyses were gender stratified due to the different characteristics of men and women. Age adjusted comparison of general characteristics according to baPWV were conducted by the general linear model for continuous variables, and by the Cochran-Mantel-Haenszel test for categorical variables. Participants were classified into those with normoalbuminuria and those with microalbuminuria, and their general characteristics

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and clinical results were compared using Student's t-test and the chi-square or Fisher's exact test. UACR, triglyceride, $HOMA_{IR}$ and baPWV data were transformed to a normal distribution using natural logarithms to improve normality. Multivariate logistic regression analysis was performed to determine associations with baPWV by adjusting for significant variables in the univariate analysis. Odds ratios (ORs) were calculated by multivariate logistic regression analysis. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed with SAS 9.2 (SAS Inc., Cary, NC, USA).

Ethics statement

This study was reviewed and approved by the institutional review boards of Hanyang University (HYUH IRB 2010-R-38). Written informed consent was obtained from all participants in the study.

RESULTS

General characteristics of the study population

General characteristics of the study population by gender are described in Table 1. The average age of the subjects was 60.9 ± 10.5 yr; and 677 individuals (41.1%) were male. Body mass index (BMI) was 24.6 ± 3.2 (kg/m^2). Systolic blood pressure (SBP) was 123.7 ± 17.3 mmHg and diastolic blood pressure (DBP) 79.8 ± 10.7 mmHg. $HOMA_{IR}$ was 2.6 ± 1.5, UACR 12.6 ± 33.5 mg/g and baPWV 1,521.9 ± 451.1 cm/s. Prevalence of microalbuminuria in the total study population was 9.9%; 8.3% in men, and 11.0% in women. There were no statistically significant differences in the history of diabetes mellitus (DM), physical activities, or prevalence of microalbuminuria between genders. However, BMI, total cholesterol, triglyceride, fasting insulin, HDL-C, LDL-C, $HOMA_{IR}$, frequency of histories of hypertension, were all significantly higher in women than men. On the other hand, waist circumference, SBP, DBP, fasting blood glucose, triglyceride and baPWV were higher in men than women. Also, the proportion of men that smoked or drank alcohol was higher than that in women.

Age-adjusted characteristics according to baPWV quartiles

Table 2 presents age-adjusted characteristics according to baPWV quartiles. Age, SBP, DBP, fasting blood glucose, triglyceride,

Table 1. General characteristics of the study population*

Parameters	Total (n = 1,648)	Men (n = 677)	Women (n = 971)	P†
Age (yr)	60.9 ± 10.5	61.5 ± 10.4	60.4 ± 10.6	0.033
BMI (kg/m^2)	24.6 ± 3.2	24.2 ± 3.1	25 ± 3.3	< 0.001
Waist circumference (cm)	87.5 ± 8.2	88 ± 8	87.1 ± 8.4	0.044
Pulse rate (/min)	69.5 ± 10.1	69.1 ± 10.1	69.8 ± 10	0.2
SBP (mmHg)	123.7 ± 17.3	125.5 ± 16.9	122.5 ± 17.5	0.001
DBP (mmHg)	79.8 ± 10.7	81.5 ± 11.2	78.7 ± 10.2	< 0.001
Fasting blood glucose (mg/dL)	102.4 ± 23.6	104.1 ± 23.1	101.2 ± 23.8	0.017
Total cholesterol (mg/dL)	197.2 ± 36.8	190 ± 35	202.3 ± 37.2	< 0.001
HDL cholesterol (mg/dL)	46.2 ± 11	45.2 ± 11.6	47 ± 10.5	0.002
LDL cholesterol (mg/dL)	121.4 ± 32.3	113 ± 30.7	127.2 ± 32.2	< 0.001
Triglyceride (mg/dL) (median,Q1-Q3)	127.0 (93-189)	137.0 (99-210)	120.0 (90-176)	< 0.001
Fasting insulin (μIU/mL)	10.0 ± 4.8	9.3 ± 4.7	10.5 ± 4.8	< 0.001
$HOMA_{IR}$ (median,Q1-Q3)	2.24 (1.66-3.06)	2.08 (1.52-2.97)	2.31 (1.78-3.10)	0.002
BaPWV (cm/s) (median,Q1-Q3)	1,515 (1,325-1,764)	1,557 (1,378-1,796)	1,487 (1,285-1,724)	0.041
History of hypertension (No.,%)	440 (26.7)	146 (21.6)	294 (30.3)	< 0.001
History of DM (No.,%)	141 (8.6)	58 (8.6)	83 (8.6)	0.989
Smoking history‡ (No.,%)				
Never	1,070 (64.9)	149 (22)	921 (94.9)	< 0.001
Past	306 (18.6)	293 (43.3)	13 (1.3)	
Current	272 (16.5)	235 (34.7)	37 (3.8)	
Alcohol consumption history (No.,%)				
Never	753 (45.7)	122 (18)	631 (65)	< 0.001
Past	102 (6.2)	77 (11.4)	25 (2.6)	
Current	793 (48.1)	478 (70.6)	315 (32.4)	
Physical activity§ (No.,%)				
Never/irregular	1,186 (72)	475 (70.2)	711 (73.2)	0.174
Regular	462 (28)	202 (29.8)	260 (26.8)	
Category of UACR (No.,%)				
Normal (0-30 mg/g)	1,485 (90.1)	621 (91.7)	864 (89)	0.066
Microalbuminuria (30-300 mg/g)	163 (9.9)	56 (8.3)	107 (11)	

*Values are expressed as mean ± SD or median and 25% percentile-75% percentile or number and percent; †Using the t-test or chi-square test; ‡ ≥ 400 (20 pack/whole year); § ≥ 3 times/week and ≥ 30 min/ time. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; $HOMA_{IR}$, homeostasis model for insulin resistance; UACR, urinary albumin creatinine ratio; BaPWV, brachial-ankle pulse wave velocity; DM, diabetes mellitus.

Table 2. Age-adjusted characteristics according to baPWV quartiles*

Characteristics	BaPWV quartiles†				
	1st Q (lower)	2nd Q	3rd Q	4th Q (highest)	*P*‡
Men					
Age (yr)	56.7 ± 10.2	59.2 ± 10.1	62.2 ± 9.5	68 ± 8.1	< 0.001
BMI (kg/m^2)	24.7 ± 0.2	25.1 ± 0.2	25.1 ± 0.2	24.9 ± 0.2	0.64
Waist circumference (cm)	87.5 ± 0.6	88.3 ± 0.6	88.1 ± 0.6	88 ± 0.6	0.818
Pulse rate (/min)	66 ± 0.8	68.3 ± 0.8	70.4 ± 0.8	72.1 ± 0.8	< 0.001
SBP (mmHg)	116.1 ± 1.2	119 ± 1.1	128.4 ± 1.1	138.5 ± 1.2	< 0.001
DBP (mmHg)	76.2 ± 0.8	78.8 ± 0.8	82.7 ± 0.8	88.2 ± 0.8	< 0.001
Fasting blood glucose (mg/dL)	99.8 ± 1.8	100.4 ± 1.8	106.8 ± 1.8	109.3 ± 1.9	< 0.001
Total cholesterol (mg/dL)	185 ± 2.8	188.4 ± 2.7	194 ± 2.7	192.6 ± 2.8	0.105
HDL cholesterol (mg/dL)	44.7 ± 0.9	43.8 ± 0.9	45.8 ± 0.9	46.6 ± 0.9	0.167
LDL cholesterol (mg/dL)	112.3 ± 2.5	114.8 ± 2.4	114 ± 2.4	110.8 ± 2.6	0.666
Triglyceride (mg/dL) (median,Q1-Q3)	122.0 (91-193)	136.0 (93-191)	142.0 (102-229)	147.0 (113-225)	< 0.001
Fasting insulin (μIU/mL)	8.8 ± 0.4	10 ± 0.4	9.3 ± 0.4	9.2 ± 0.4	0.11
$HOMA_{IR}$ (median,Q1-Q3)	1.98 (1.44-2.57)	2.13 (1.58-3.04)	2.22 (1.50-3.14)	2.10 (1.50-3.06)	0.126
BaPWV (cm/s) (median,Q1-Q3)	1,250 (1,080-1,330)	1,468 (1,419-1,508)	1,674 (1,603-1,728)	2,000 (1,886-2,157)	< 0.001
History of hypertension (No.,%)	19 (11.2)	31 (18.2)	38 (22.5)	58 (34.3)	0.003
History of DM (No.,%)	10 (5.9)	11 (6.5)	13 (7.7)	24 (14.2)	0.081
Smoking history§ (No.,%)					
Never	35 (20.7)	48 (28.2)	35 (21.3)	30 (17.7)	0.344
Past	61 (36.1)	70 (41.2)	73 (43.2)	89 (52.7)	
Current	73 (43.2)	52 (30.6)	60 (35.5)	50 (29.6)	
Alcohol consumption history (No.,%)					
Never	32 (18.9)	36 (21.2)	35 (20.7)	19 (11.2)	0.006
Past	17 (10.1)	24 (14.1)	18 (10.7)	18 (10.7)	
Current	120 (71)	110 (64.7)	116 (68.6)	132 (78.1)	
Physical activity‖ (No.,%)					
Never/irregular	126 (74.6)	106 (62.4)	116 (68.6)	127 (75.2)	0.144
Regular	43 (25.4)	64 (37.6)	53 (31.4)	42 (24.8)	
Women					
Age (yr)	53.2 ± 9.7	56.6 ± 9.3	63.3 ± 8.6	68.4 ± 7.4	< 0.001
BMI (kg/m^2)	24 ± 0.2	24.5 ± 0.2	24.2 ± 0.2	24 ± 0.2	0.384
Waist circumference (cm)	86.4 ± 0.6	87.4 ± 0.5	87.5 ± 0.5	87.3 ± 0.6	0.508
Pulse rate (/min)	67.3 ± 0.7	68 ± 0.6	71.2 ± 0.6	72.7 ± 0.7	< 0.001
SBP (mmHg)	109 ± 1	116.6 ± 0.9	126.6 ± 0.9	137.8 ± 1	< 0.001
DBP (mmHg)	71.6 ± 0.6	76.5 ± 0.5	81.5 ± 0.6	85.1 ± 0.6	< 0.001
Fasting blood glucose (mg/dL)	94.3 ± 1.6	98.8 ± 1.5	105.1 ± 1.5	106.9 ± 1.6	< 0.001
Total cholesterol (mg/dL)	197 ± 2.5	203.7 ± 2.4	202.6 ± 2.4	205.9 ± 2.6	0.102
HDL cholesterol (mg/dL)	47.6 ± 0.7	46.8 ± 0.7	46.8 ± 0.7	46.6 ± 0.7	0.776
LDL cholesterol (mg/dL)	123.5 ± 2.2	130.4 ± 2.1	126.4 ± 2.1	128.5 ± 2.3	0.113
Triglyceride (mg/dL) (median,Q1-Q3)	105.0 78-146	115.0 (90-165)	131.0 (94-186)	142.0 (108-197)	< 0.001
Fasting insulin (μIU/mL)	9.9 ± 0.3	10.4 ± 0.3	11.4 ± 0.3	10.5 ± 0.3	0.016
$HOMA_{IR}$ (median,Q1-Q3)	2.05 (1.53-2.69)	2.27 (1.77-3.04)	2.59 (1.93-3.46)	2.49 (1.90-3.35)	< 0.001
BaPWV (cm/s) (median,Q1-Q3)	1,185 (1,100-1,230)	1,384 (1,336-1,433)	1,590 (1,544-1,652)	1,932 (1,828-2,114)	< 0.001
History of hypertension (No.,%)	30 (12.4)	52 (21.5)	90 (36.9)	122 (50.4)	< 0.001
History of DM (No.,%)	5 (2.1)	11 (4.6)	26 (10.7)	41 (16.9)	< 0.001
Smoking history§ (No.,%)					
Never	228 (93.8)	233 (96.3)	235 (96.3)	225 (93.2)	0.273
Past	3 (1.2)	3 (1.2)	4 (1.6)	3 (1.2)	
Current	12 (5)	6 (2.5)	5 (2.1)	14 (5.8)	
Alcohol consumption history (No.,%)					
Never	163 (67.1)	146 (60.3)	162 (66.4)	160 (66.1)	0.076
Past	1 (0.4)	9 (3.7)	4 (1.6)	11 (4.6)	
Current	79 (32.5)	87 (36)	78 (32)	71 (29.3)	
Physical activity‖ (No.,%)					
Never/irregular	157 (64.6)	177 (73.1)	185 (75.8)	192 (79.3)	0.061
Regular	86 (35.4)	65 (26.9)	59 (24.2)	50 (20.7)	

*Valuesare expressed as mean ± SD for age or mean ± SE or median and 25% percentile-75% percentile except age or number and percent; †baPWV values were divided into4 quartiles: < 1,379, 1,379-1,557, 1,557-1,796, > 1,796 cm/s in men, < 1,285, 1,285-1,489, 1,489-1,724, > 1,724 cm/s in women; ‡Using a generalized linear model for continuous variables and the Cochran-Mantel-Haenzsel test for categorical variables adjusted for age; § ≥ 400 (20 pack/whole year); ‖ ≥ 3 times/week and ≥ 30 min/time. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; $HOMA_{IR}$, homeostasis model for insulin resistance; UACR, urinary albumin creatinine ratio; BaPWV, brachial-ankle pulse wave velocity; DM, diabetes mellitus.

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$HOMA_{IR}$ and history of hypertension were significantly different among the quartiles in both men and women. History of alcohol consumption was significantly different among the quartiles in men only. DM history was significantly different among the quartiles in women.

Comparison of the normoalbuminuria and microalbuminuria groups

Table 3 compares characteristics of the normoalbuminuria and microalbuminuria groups. Age, fasting blood glucose, the proportion of history of hypertension and DM were significantly higher in the microalbuminuria group in both sexes. SBP, DBP and total cholesterol were significantly higher only in women of the microalbuminuria group, while $HOMA_{IR}$ was significant higher only in men ($P = 0.013$ in men vs. $P = 0.055$ in women).

BaPWV values were higher in the microalbuminuria group than the normoalbuminuria group in both men (1,538, 1,370-1,777 cm/s vs. 1,776, 1,552-2,027 cm/s, $P < 0.001$) and women (1,461, 1,271-1,687 cm/s vs. 1,645, 1,473-1,915 cm/s, $P < 0.001$).

Odds ratios and 95% Confidence intervals (CI) of microalbuminuria stratified by diseases status

Table 4 shows adjusted ORs and 95% CIs of microalbuminuria according to baPWV quartiles stratified by hypertension and diabetes status adjusted for age, pulse rate, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride and $HOMA_{IR}$. Especially, the OR of microalbuminuria was 4.46 (95% CI, 1.27–15.63) according to baPWV 4th quartiles (Q4) in women without hypertension.

Relationship between baPWV and microalbuminuria

Results of multivariate logistic regression analyses are described

Table 3. Comparisons of the normoalbuminuria and microalbuminuria group*

Parameters	Men			Women		
	Normal (N = 621)	MAU† (N = 56)	P‡	Normal (N = 864)	MAU† (N = 107)	P‡
Age (yr)	61.1 ± 10.3	66.2 ± 10.6	< 0.001	60.1 ± 10.6	62.9 ± 9.9	0.01
BMI (kg/m^2)	24.2 ± 3.1	24 ± 3	0.61	24.9 ± 3.3	25 ± 3.4	0.779
Waist circumference (cm)	87.9 ± 8	89.3 ± 7.9	0.216	87.1 ± 8.3	87.6 ± 9	0.562
Pulse rate (/min)	68.8 ± 9.9	72.6 ± 13	0.038	69.7 ± 9.9	70.4 ± 11	0.531
SBP (mmHg)	125 ± 15.6	131 ± 26.7	0.102	121.5 ± 16.9	130.7 ± 20.3	< 0.001
DBP (mmHg)	81.4 ± 10.4	82 ± 17.5	0.809	78.2 ± 9.8	82.5 ± 12	0.001
Fasting blood glucose (mg/dL)	102.8 ± 21.7	117.8 ± 32.5	0.001	100.1 ± 21.4	110.1 ± 36.8	0.007
Total cholesterol (mg/dL)	189.4 ± 35.2	196.2 ± 32.9	0.166	201.3 ± 37.4	209.9 ± 35.1	0.024
HDL cholesterol (mg/dL)	45.3 ± 11.6	45 ± 11.6	0.858	47 ± 10.6	46.7 ± 10	0.774
LDL cholesterol (mg/dL)	112.9 ± 31	114.2 ± 27.5	0.772	126.6 ± 32.1	132.2 ± 32.7	0.091
Triglyceride (mg/dL) (median,Q1-Q3)	136 (98-204)	158 (113-239)	0.065	118 (90-173)	139 (97-198)	0.034
Fasting insulin (μIU/mL)	10.9 ± 5.7	10.5 ± 6.5	0.138	10.5 ± 4.7	9.2 ± 4.4	0.46
$HOMA_{IR}$ (median,Q1-Q3)	2.04 (1.51-2.95)	2.64 (1.69-3.59)	0.013	2.30 (1.78-3.08)	2.54 (1.75-3.45)	0.055
UACR (mg/g) (median,Q1-Q3)	1.56 (0.70-3.45)	67.14 (40.00-125.05)	< 0.001	1.93 (0.87-4.81)	71.01 (45.81-124.56)	< 0.001
BaPWV (cm/s) (median,Q1-Q3)	1,538 (1,370-1,777)	1,776 (1,552-2,027)	< 0.001	1,461 (1,271-1,687)	1,645 (1,473-1,915)	< 0.001
History of hypertension (No.,%)	128 (20.6)	18 (32.1)	0.045	250 (28.9)	44 (41.1)	0.01
History of DM (No.,%)	45 (7.3)	13 (23.2)	< 0.001	68 (7.9)	15 (14)	0.032
Smoking history§ (No.,%)						
Never	138 (22.2)	11 (19.6)	0.579	818 (94.7)	103 (96.3)	0.925
Past	271 (43.6)	22 (39.3)		12 (1.4)	1 (0.9)	
Current	212 (34.1)	23 (41.1)		34 (3.9)	3 (2.8)	
Alcohol consumption history (No.,%)						
Never	116 (18.7)	6 (10.7)	0.297	551 (63.8)	80 (74.8)	0.0798
Past	69 (11.1)	8 (14.3)		23 (2.7)	2 (1.9)	
Current	436 (70.2)	42 (75)		290 (33.6)	25 (23.4)	
Physical activity‖ (No.,%)						
Never/irregular	433 (69.7)	42 (75)	0.409	629 (72.8)	82 (76.6)	0.398
Regular	188 (30.3)	14 (25)		235 (27.2)	25 (23.4)	
BaPWV quartiles¶ (No,%)						
1st Q (lower)	165 (26.6)	4 (7.1)	< 0.001	231 (26.7)	12 (11.2)	< 0.001
2nd Q	159 (25.6)	11 (19.6)		226 (26.1)	16 (15)	
3rd Q	154 (24.8)	15 (26.8)		214 (24.8)	30 (28)	
4th Q (highest)	143 (23)	26 (46.4)		193 (22.3)	49 (45.8)	

*Valuesexpressed as mean ± SD or median and 25% percentile-75% percentile or number and percent; †UACR 30-300 mg/g; ‡Using t-test or chi-square test; § ≥ 400 (20 pack/whole year); ‖ ≥ 3 times/week and ≥ 30 min/1 time; ¶baPWV values were divided into4 quartiles: < 1,379, 1,379-1,557, 1,557-1,796, > 1,796 cm/s in men, < 1,285, 1,285-1,489, 1,489-1,724, > 1,724 cm/s in women. MAU, microalbuminuria; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; $HOMA_{IR}$, homeostasis model for insulin resistance; UACR, urinary albumin creatinine ratio; BaPWV, brachial-ankle pulse wave velocity; DM, diabetes mellitus.

Table 4. Odds ratio and 95% confidence intervals* of microalbuminuria stratified by disease status (hypertension and diabetes) adjusted for baPWV quartiles, age, pulse rate, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride and $HOMA_{IR}$

BaPWV by sex		Microalbuminuria vs. normal							
		Hypertension†				Diabetes mellitus‡			
Men		Yes	(n = 251)	No	(n = 426)	Yes	(n = 92)	No	(n = 585)
BaPWV quartiles§	1st Q (lower)	1.00	ref	1.00	ref	1.00	ref	1.00	ref
	2nd Q	1.05	0.36-3.08	1.51	0.49-4.68	2.28	0.49-1.07	0.94	0.37-2.38
	3rd Q	0.71	0.17-2.95	1.61	0.48-5.42	0.35	0.06-2.11	1.51	0.46-4.96
	4th Q (highest)	2.18	0.37-12.69	3.18	0.63-16.04	-	-	1.31	0.39-4.35
Women		Yes	(n = 304)	No	(n = 610)	Yes	(n = 110)	No	(n = 864)
BaPWV quartiles§	1st Q (lower)	1.00	ref	1.00	ref	1.00	ref	1.00	ref
	2nd Q	1.66	0.78-3.53	1.51	0.61-3.76	0.71	0.20-2.53	2.26	1.17-4.34
	3rd Q	3.25	0.96-10.86	2.81	0.94-8.39	6.89	0.51-93.95	2.64	1.18-5.89
	4th Q (highest)	1.98	0.49-7.97	4.46	1.27-15.63	-	-	2.88	1.15-7.19

*Using multiple logistic regression; †Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or medication of antihypertensive drugs; ‡Fasting blood glucose ≥ 126 mg/dL or history of diabetes mellitus or medication for diabetes mellitus; §BaPWV values were divided into4 quartiles: < 1,379, 1,379-1,557, 1,557-1,796, > 1,796 cm/s in men, < 1,285, 1,285-1,489, 1,489-1,724, > 1,724 cm/s in women. BaPWV, brachial-ankle pulse wave velocity; $HOMA_{IR}$, homeostasis model for insulin resistance; HDL, high density lipoprotein.

Table 5. The relation between baPWV and microalbuminuria

Parameters	Model I			Model II			Model III			Model IV			Model V		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Men															
Age (yr)	1.063	1.030	1.098	1.033	0.998	1.069	1.036	1.000	1.073	1.031	0.995	1.067	1.034	0.998	1.071
Ln (BaPWV) (cm/s)*				18.784	3.245	108.741	15.830	2.687	93.248	17.539	2.969	103.626	15.813	2.629	95.119
Pulse rate (/min)	1.031	1.004	1.059	1.019	0.991	1.048	1.018	0.989	1.047	1.019	0.991	1.048	1.018	0.990	1.048
Fasting blood glucose (mg/dL)	1.010	0.997	1.023				1.012	1.001	1.023	1.008	0.995	1.022	1.008	0.994	1.021
Ln (Triglyceride) (mg/dL)*	1.397	0.809	2.414	1.312	0.752	2.290	1.256	0.715	2.206				1.304	0.738	2.304
Ln ($HOMA_{IR}$)*	1.428	0.754	2.705	2.153	1.194	3.882	1.560	0.794	3.063	1.624	0.835	3.160	1.525	0.773	3.010
History of hypertension	0.839	0.442	1.591							1.034	0.525	2.037	1.059	0.536	2.091
History of DM	0.617	0.248	1.534							0.603	0.232	1.566	0.576	0.222	1.497
Women															
Age (yr)	1.011	0.990	1.034	0.991	0.967	1.016	0.992	0.967	1.017	0.993	0.968	1.018	0.997	0.971	1.023
Ln (BaPWV) (cm/s)*				15.491	4.518	53.118	13.221	3.817	45.799	13.428	3.776	47.758	5.399	1.157	25.205
Pulse rate (/min)	0.998	0.978	1.018	0.993	0.973	1.014	0.990	0.970	1.011	0.992	0.972	1.013	0.995	0.974	1.016
SBP (mmHg)	1.023	1.012	1.035										1.013	0.999	1.027
Fasting blood glucose (mg/dL)	1.011	1.002	1.020				1.011	1.003	1.019	1.011	1.002	1.020	1.011	1.002	1.020
Ln (Triglyceride) (mg/dL)*	1.467	0.949	2.268	1.400	0.905	2.165	1.453	0.936	2.255				1.423	0.915	2.212
Ln ($HOMA_{IR}$)*	0.810	0.481	1.364	1.187	0.753	1.868	0.844	0.499	1.427	0.905	0.538	1.521	0.814	0.479	1.385
History of hypertension	0.830	0.532	1.295							0.811	0.515	1.276	0.845	0.537	1.330
History of DM	0.957	0.456	2.010							1.188	0.558	2.529	1.074	0.505	2.287

Model I was adjusted for age (yr), pulse rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$, history of hypertension (yes/no) and history of DM (yes/no) in men; Model I was adjusted for age (yr), pulse rate (/min), systolic blood pressure (mmHg), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$, history of hypertension (yes/no) and history of DM (yes/no) in women; Model II was adjusted for age (yr), log transformation baPWV (cm/s), pulse rate (/min), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$; Model III was adjusted for age (yr), log transformation baPWV (cm/s), pulse rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$; Model IV (yes/no) was adjusted for age (years), pulse rate (/min), log transformation baPWV (cm/s), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$, history of hypertension (yes/no) and history of DM (yes/no); Model V was adjusted for age (yr), log transformation baPWV (cm/s), pulse rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$, history of hypertension (yes/no) and history of DM (yes/no) in men; Model V was adjusted for age (yr), log transformation baPWV (cm/s), pulse rate (/min), systolic blood pressure (mmHg), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation $HOMA_{IR}$, history of hypertension (yes/no) and history of DM (yes/no) in women. *Log transformation was done to obtain a normal distribution. BaPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; $HOMA_{IR}$, homeostasis model for insulin resistance; DM, diabetes mellitus.

in Table 5. Five models were used to estimate the relationship between baPWV and microalbuminuria. BaPWV, triglyceride and $HOMA_{IR}$ data were log-transformed and used for analysis. In model I, which was adjusted for age, no variables were independently associated with microalbuminuria in both men and women. In model II, $HOMA_{IR}$ was also included. Log (baPWV) (OR, 18.784; 95% CI, 3.245-108.741) and log ($HOMA_{IR}$) (OR, 2.153; 95% CI, 1.194-3.882) were both independent risk factors of microalbuminuria in men, but log ($HOMA_{IR}$) (OR, 1.187; 95% CI, 0.753-1.868) was not an independent risk factor in women. In model III, in case of men, which was also adjusted for fasting blood glucose, log (baPWV) (OR, 15.830; 95% CI, 2.687-93.248)

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was an independent risk factor; however, ($HOMA_{IR}$) (OR, 1.560; 95% CI, 0.794-3.063) was not. Fasting blood glucose was a significant risk factor in both men (OR, 1.012; 95% CI, 1.001-1.023) and women (OR, 1.011; 95% CI, 1.003-1.019). Fasting blood glucose and $HOMA_{IR}$ were included in same model, because there were judged not to have multicolinearity between them (r, 0.532; $P < 0.001$). In model IV, which included additional variables such as history of hypertension or diabetes, only log (baPWV) (OR, 17.539; 95% CI, 2.969-103.626) was significant in men, and log (baPWV) (OR, 13.428; 95% CI, 3.776-47.758) and fasting blood glucose (OR, 1.011; 95% CI, 1.002-1.020) in women. Finally, in model V, also adjusted for clinical parameters such as SBP (women), log (triglyceride), log (baPWV) (OR, 15.813; 95% CI, 2.629-95.119) was the only independent risk factor in men, while log (baPWV) (OR, 5.399; 95% CI, 1.157-25.205) and fasting blood glucose (OR, 1.011; 95% CI, 1.002-1.020) were significant in women, just as model IV.

In summary, baPWV was the only factor examined that was independently associated with microalbuminuria in both genders and in all the models studied here.

DISCUSSION

The present study showed that elevated baPWV was an independent risk factor of microalbuminuria in both genders regardless of potential confounders. Fasting blood glucose was an additional independent risk factor of microalbuminuria in women. On the other hand, the effect of $HOMA_{IR}$ was not statistically significant after adjusting for various confounding factors.

In this study, the prevalence of microalbuminuria was 9.9% (163/1,648) overall; and 8.3% (56/677) in men and 11.0% (107/971) in women. This result is similar to a previous study performed in Sweden (21). However, the prevalence found here is bigger than in a population-based study conducted in Korea (15), which might be explained by age and prevalence of chronic disease according to the subjects' old age in the present study (2). In addition, the prevalence of microalbuminuria was different according to gender. The prevalence of microalbuminuria was higher in women. However, the prevalence of women might be higher within an insignificant range ($P = 0.066$). Afterward, further study is needed in association with the difference of prevalence according to gender.

Blood pressure in the present study was lower than the previous study performed in Taiwan by about 10 mmHg in the group without microalbuminuria and by about 20 mmHg in the microalbuminuria group (10). The prevalence of albuminuria was also lower than the Taiwan study; however, fasting blood glucose levels were very similar. The mean value of baPWV in microalbuminuria was lower than the Taiwan study by > 100 cm/sec. The relative contribution of hypertension and diabetes to the relationship between arterial stiffness and microalbuminuria may be affected by the blood pressure level in the population (22).

In our study, SBP, DBP, fasting blood glucose and hypertension history increased with increasing baPWV after adjusting for age. This is consistent with a study performed in Japan (23). However, in the Taichung community health study in Taiwan, BMI, waist circumference, total cholesterol and $HOMA_{IR}$, as well as the variables which were significant in our study, all increased with increasing baPWV (10).

The effects of gender, age, BMI, central obesity and smoking on microalbuminuria are controversial (24). Of these factors, none was related to the presence of microalbuminuria in our study. In fact, BMI and central obesity were not related to microalbuminuria in several previous studies (14, 16, 17).

There is evidence that insulin resistance plays an important role in the development of microalbuminuria (25); and insulin resistance is also reported to be positively related to high arterial stiffness (26). However, in the present study, we attempted to incorporate arterial stiffness into the previously-known microalbuminuria model explained by insulin resistance. Insulin resistance was consistently independent of their relationship with microalbuminuria even after adjusting for potential factors related to microalbuminuria. These findings suggest that arterial stiffness might be important in the development of microalbuminuria. So that independent action of arterial stiffness needs to be included in the microalbuminuria model for future study.

In the present study, considering only women, not $HOMA_{IR}$ but fasting blood glucose was an independent factor in addition to arterial stiffness. Regarding gender differences, Utsunomiya et al. (27) found that central obesity and $HOMA_{IR}$ were important factors increasing UACR in men, but not in women. A gender-specific hormonal effect was suggested as a possible factor. However, in our study $HOMA_{IR}$ was not related to microalbuminuria in the general population or in subjects with hypertension or diabetes. This outcome was similar to the results of a Dutch study performed by Jager et al. (28). In the model including baPWV or arterial stiffness for predicting microalbuminuria, fasting blood glucose suggests that the effect of $HOMA_{IR}$ is partly mediated by increased arterial stiffness on women, as shown in Table 2.

Microalbuminuria is caused by endothelial damage that can arise by several mechanisms (7, 29), but the precise mechanism is not clear. Generally, microalbuminuria is seen as a pathological event related to microvascular abnormalities resulting from hemodynamic or metabolic processes (7, 10). Thus, hypertension is an important risk factor for microalbuminuria. Even if hypertension is not a direct cause of microalbuminuria, the prevalence of microalbuminuria is greatly elevated in individuals who have essential hypertension (25). This result implies that microalbuminuria is a marker of endothelial damage especially in hypertension (22). Another possible mechanism is related to

insulin resistance. Metabolic changes caused by hyperglycemia, for example, chronic inflammation triggered by reactive oxygen species, inflammatory cytokines and growth factors, are associated with generalized and glomerular endothelial dysfunction (25). Several previous studies found that higher $HOMA_{IR}$ was associated with microalbuminuria (4, 8, 27). Recently, evidence has emerged that high pulse pressure may have an important effect on albuminuria. High pulse pressure leads to arterial stiffness (30); and kidney cells are passively perfused by pulsatile flow which can cause endothelial damage by disrupting small arteriolar vessels (31). It is not yet clear whether the two mechanisms i.e. the metabolic process-associated level of blood pressure and the pulsatile character of the arterial pulse, work independently (10, 25). Furthermore, an association between arterial stiffness and insulin resistance has been reported (32, 33). This relationship was also seen in women in the present study.

The results of our study do not support an independent role of $HOMA_{IR}$ as a parameter of insulin resistance related to microalbuminuria when arterial stiffness is adjusted for. Fasting glucose level may be an independent risk factor of microalbuminuria, but only in women with their more adverse metabolic and lipid profiles.

It is well known that baPWV is affected by the presence and severity of peripheral artery disease (PAD) (34). Therefore, the consideration of the ankle-brachial index (ABI) reflecting PAD might be needed in this study. We did a multiple logistic regression analysis except for participants with low ABI (< 0.9, men n = 21, women n = 32) and high ABI (> 1.2, men n = 35, women n = 16) (35); however, results were similar to that in Table 5. The reason for that is the subjects of this study are from the general population; therefore, the number of individuals with abnormal ABI is few.

This study has several limitations. First, it had a cross-sectional design. Therefore, it was unable to establish any causal relationship between arterial stiffness and microalbuminuria. Second, we used a single measurement of first morning spot urine to calculate urinary albumin to creatinine ratios. Urinary albumin excretion can be affected by several factors such as oral fluid intake (36), so a more accurate measure such as using 24-hr urine collections would be desirable. However, single void urine samples give good estimates of 24-hr urine albumin excretion (37). In addition, it has been reported that spot urine protein-creatinine ratio reflects the amount of 24-hr urinary protein excretion with high accuracy (38). Third, we did not consider the influence of drug treatment such as angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, which are known to be able to reduce arterial stiffness (23, 39) because we had no information about medications taken by the patients.

Nevertheless, the strengths of this study are its relatively large sample size and the fact that it was not based on patients who visited hospitals but on a rural population. Therefore, this study can reflect the characteristics of the general population, especially elderly from rural communities. We were able to confirm a relationship between PWV and microalbuminuria. This study provides more useful and strong epidemiologic evidence of association between arterial stiffness and microalbuminuria in population of over 40 yr. Results show that there is a strong association between microalbuminuria and arterial stiffness regardless of insulin resistance in rural population groups past middle age. Also, high baPWV measurements may be a good indicator of microalbuminuria. In other words, baPWV may be a useful screening tool for predicting cardiovascular complications.

DISCLOSURE

There are no conflicts of interest to report.

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