보건학석사학위논문

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

한 농촌지역 인구 집단에서 미세알부민뇨에 독립적으로 영향을 미치는 BaPWV 상승에 관한 연구

2016 년 2 월

서울대학교 보건대학원

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이 논문을 보건학석사학위논문으로 제출함

2015년 11월

서울대학교 보건대학원

보건학과 보건학전공

서 주 연

서주연의 석사학위논문을 인준함

2015년 12월

위 원 장 김 호 (인)

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Abstract

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

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Objectives

Microalbuminuria is used to a predictor for cardiovascular morbidity and mortality due to cardiovascular diseases. Also, microalbuminuria is a marker of generalized endothelial dysfunction resulting from arterial stiffness or insulin resistance. However, the mechanism of microalbuminuria is unclear. Therefore, it is important to evaluate the relationship between arterial stiffness or insulin resistance and microalbuminuria. Meanwhile, brachial-ankle pulse wave velocity (baPWV) is a good measure of arterial stiffness. Thus, baPWV is a useful measure for explain the relationship between arterial stiffness and microalbuminuria. This study aimed to investigate whether elevated baPWV is independently associated with microalbuminuria.

Methods

This study included 1,648 individuals aged over 40 who participated in baseline Multi-Rural Cohort Study conducted in Korean rural communities between 2005 and 2006. The participants were classified into: less than 30mg/g as normoalbuminuria or 30-300mg/g as microalbuminuria using urinary albumin creatinine ratio (UACR). BaPWV data were transformed to a normal distribution using natural logarithms to improve normality. Multivariate logistic regression analyses were performed to determine associations with baPWV and microalbuminuria and odds ratios were calculated.

Results

The median and Q1-Q3 baPWV values were significantly higher in the microalbuminuric group both in men (1538, 1370-1777 cm/s vs. 1776, 1552-2027 cm/s, $p<0.001$) and in women (1461, 1271-1687cm/s vs. 1645, 1473-1915cm/s, $p<0.001$). Five models were used to estimate the relation between baPWV and microalbuminuria. The baPWV was independently associated with microalbuminuria in both genders after adjusting for heart rate, fasting blood glucose, triglyceride, homeostatic model assessment insulin resistance and history of hypertension and diabetes. Fasting blood sugar and $HOMA_{IR}$ were judged they had nothing to do with multicolinearity (r=0.532, $p<0.001$). 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 by adjusting for all significant variables in the univariate

analyses.

Conclusion

BaPWV was the only factor examined that was independently associated with microalbuminuria in both genders and in all the models examined. Elevated baPWV is independently associated with microalbuminuria regardless of insulin resistance among rural subjects over 40 yr. However, baPWV can't be a very good indicator considering relatively low explanatory power representing for adjusted R^2 value. It means that many factors contribute to microalbuminuria except baPWV as well as other factors used this study. However, in consideration of not only the ease of the measurement of baPWV but results of this study, it may be a useful screening tool for predicting cardiovascular complications.

Keywords: albuminuria, insulin resistance, risk factor, vascular stiffness

Student number: 2010-22091

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Introduction

Background

Microalbuminuria is a well-known risk factor or predictor for cardiovascular morbidity and mortality in individuals with hypertension or diabetes mellitus (De Cosmo, Minenna et al. 2005; Afonso, Hari et al. 2010; Matsui, Ishikawa et al. 2011; Yokoyama, Sone et al. 2011) and even in a general population (Hillege, Janssen et al. 2001; Arnlov, Evans et al. 2005) 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 (Forman and Brenner 2006; Dabla 2010; Abdelhafiz, Ahmed et al. 2011; Bellasi, Ferramosca et al. 2011; Singh and Satchell 2011). In addition, insulin resistance is a risk factor of microalbuminuria, especially in patients with diabetes or dyslipidemia (Wallace and Matthews 2002; Lin, Chen et al. 2008).

Another mechanism of microalbuminuria is associated with generalized vascular dysfunction through arterial stiffness (Dabla 2010; Abdelhafiz, Ahmed et al. 2011; Bellasi, Ferramosca et al. 2011). It is not clear the cause of microalbuminuria is an independent action of arterial stiffness and insulin resistance or dependent interaction of them (Liu, Pi-Sunyer et al. 2010). 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 (Abdelhafiz, Ahmed et al. 2011; Bellasi, Ferramosca et al. 2011).

Pulse wave velocity (PWV) is an indicator of arterial stiffness and a marker of atherosclerosis (Yamashina, Tomiyama et al. 2002). Of the various PWV parameters, carotid-femoral PWV (cfPWV) is the noninvasive gold standard of arterial stiffness (Hashimoto and Ito 2011), 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 (Wallace and Matthews 2002; Yamashina, Tomiyama et al. 2002; Lin, Chen et al. 2008). In addition, baPWV is useful as a means of estimating the atherosclerotic disease of arteries (Horinaka, Yabe et al. 2009).

Literature Review and Necessity of this study

Several studies have shown that arterial stiffness is a risk factor for microalbuminuria (Kohara, Tabara et al. 2004; Munakata, Nunokawa et al. 2006; Ishikawa, Hashimoto et al. 2008; Munakata, Miura et al. 2009; Liu, Pi-Sunyer et al. 2010; Kim, Lee et al. 2011). As an example, the Taichung study performed in Taiwan targeting middle aged community population showed the strong association between albuminuria and arterial stiffness, especially hypertensive or diabetic subjects (Liu, Pi-Sunyer et al. 2010). However, the prevalence of the hypertension and diabetes varies depending on the population characteristics; Therefore, the result 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 (Kim, Lee et al. 2011) however, there is no study of the community general population in Korea. Besides, the result of epidemiologic evidence is easy to generalize and reconfirm, so

this study is further needed.

There are a lot of studies that insulin resistance is related to microalbuminuria. Chin-cheng Hsu et al. concluded that insulin resistance could significantly predict development of microalbuminuria in type 2 diabetic patients in Taiwan (Hsu, Chang et al. 2011). In a study performed targeting nondiabetic Native Americans by Hoehner et al. the insulin resistance syndrome was associated with increased prevalence of microalbuminuria (Hoehner, Greenlund et al. 2002). They found elevated blood pressure was independently associated risk of prevalent microalbuminuria. Their findings suggested that lowering of not only insulin resistance and obesity bur also hypertension could prevent renal and cardiovascular disease, particular in Native American population. Besides, studies by Esteghamati et al. in Iran (Esteghamati, Ashraf et al. 2009), Chien-Yu Lin et al.in Taiwan (Lin, Chen et al. 2008) suggested that insulin resistance was the major determinant of microalbuminuria. However, their studies were targeting a particular population, especially with hypertension or diabetes mellitus. In addition, a common feature of these studies was that they did not consider the relationship between pulse wave velocity and microalbuminuria. Therefore, this study is necessary in order to investigate between microalbuminuria and arterial stiffness as well as insulin resistance. Also, ethnic difference is the target to be considered.

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

Objectives

The purpose of this study mentioned above was to assess whether baPWV is an independent risk factor of microalbuminuria regardless of insulin resistance in the over-40yr. Therefore, the final objectives of this study were as follows when including other additional analyses.

To investigate the difference between normoalbuminuric and microalbuminuric groups in the middle aged and elderly population.

To investigate the influence of microalbuminuria according to baPWV in hypertension or diabetes mellitus group in the middle aged and elderly population.

To investigate the independent influence of microalbuminuria according to baPWV in general middle aged and elderly population.

Materials and Methods

Subjects and General characteristics variables

From February 2005 to December 2006, a total of 1,841 participants aged over 40, living in Yang Pyeong County, Gyeonggi-do, Korea, were invited to participate in 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 diseases by a medical doctor and included taking drugs. Hypertension was defined as systolic blood pressure (BP) $\geq$140mmHg or diastolic BP$\geq$90mmHg or on taking antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose $\geq$126mg/dL on taking antidiabetic drugs (Table 1). This study excluded participants who fitted the following exclusion criteria: history of coronary heart disease, stroke or cancer (149 individuals), presence of macroalbuminuria or overt proteinuria (22 individuals), and incomplete data (22 individuals). Finally, a total of 1,648 participants

were included in the study (Figure 1). The study was approved by the Institutional Review Board of Hanyang University Medical Center and all participants gave their informed consents.

Table 1.Explanation and research method of general characteristics and physical exam

Variables (unit)	Explanation	Research method
Age (year)	international age a using real birthday	questionnaire
BMI (kg/m^2)	$weight/(height)^2$	measurement using a standardized tool
Waist circumference (cm)	the middle portion between the lower rib and the pelvis	measurement using a standardized tool
History of hypertension	diseases diagnosed by medical doctors	questionnaire
History of DM	diseases diagnosed by medical doctors	questionnaire
Hypertension	systolic BP≥140mmHg or diastolic BP≥90mmHg or on taking antihypertensive drugs	measurement using a standardized tool and questionnaire
Diabetes mellitus	fasting plasma glucose ≥126mg/dL or on taking antidiabetics	measurement using a standardized tool and questionnaire
Smoking history	≥400 (20pack/whole year)	questionnaire
Alcohol consumption history	alcohol consumption including all kinds of drinking	questionnaire
Physical activity	3 times/week and ≥30min/ time	questionnaire

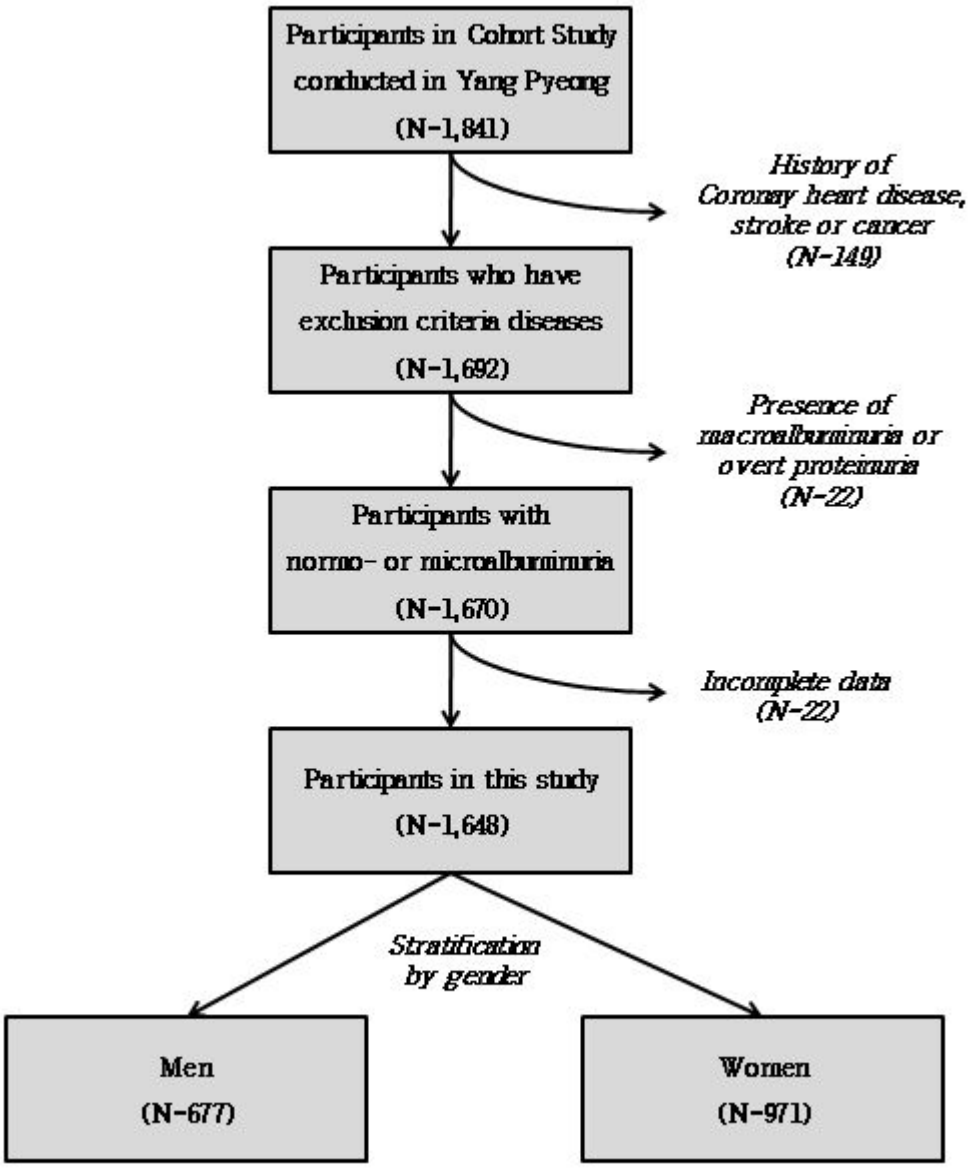

Figure 1.Study Population

Study Modeling

The mechanism of microalbuminuria occurrence is known as a generalized endothelial dysfunction triggered by metabolic inflammatory processes (chemical mechanism including insulin resistance) as well as vasomotor processes (physical mechanism including arterial stiffness). Many factors are associated with both mechanisms, for examples general characteristics as age and sex, lifestyle behaviors as smoking, alcohol consumption and physical activity, heart rate, blood pressure, blood glucose level, lipid profile, and chronic disease status (hypertension, diabetes mellitus e.g.). These factors are known to affect endothelial damage. (Forman and Brenner 2006; Abdelhafiz, Ahmed et al. 2011; Singh and Satchell 2011). Figure 2 illustrated the mechanism of microalbuminuria. As it stated in the objectives of this study, the dependent variable of this study is microalbuminuria occurrence and the independent variable is baPWV which represents a measure of arterial stiffness. Confounders affecting both are age, sex, blood pressure, and insulin resistance e.g. Model of this study was shown in Figure 3.

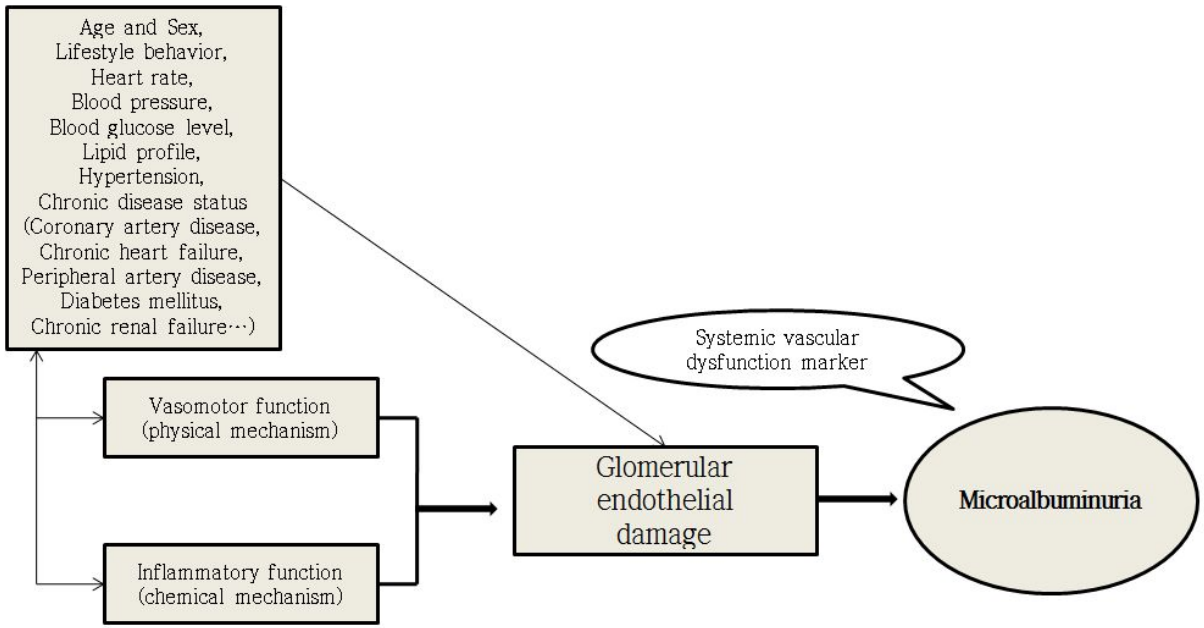

Figure 2.Mechanism of Microalbuminuria

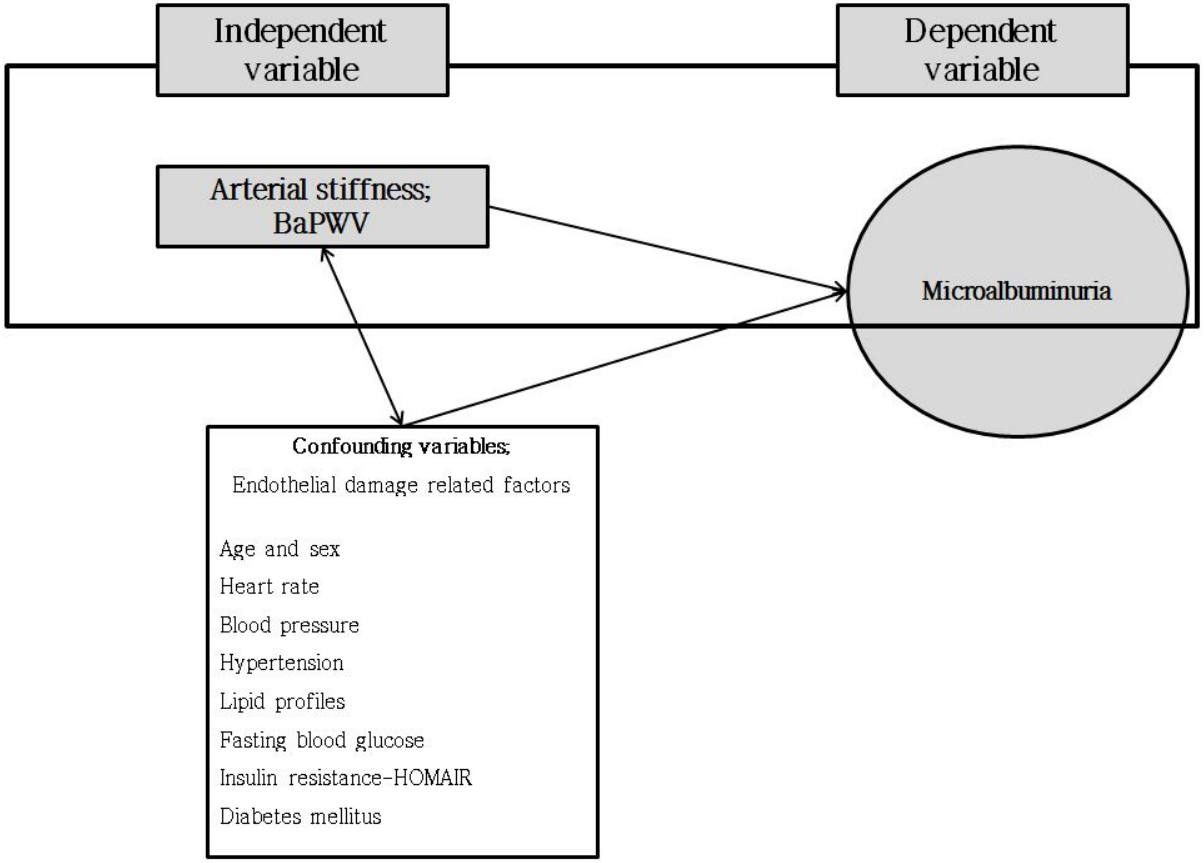

Figure 3.Study Model

Brachial-ankle pulse wave velocity

Pulse wave velocity (PWV) is the speed at which the blood pressure pulse travels from the heart to the peripheral artery after blood rushes out during contraction. It is mostly used to evaluate stiffness of arterial wall. Pulse wave velocity increases with arterial stiffness. PWV is L (distance)/ PTT (Pulse transit time). Therefore, baPWV is Distance between respective brachium and ankle/ Pulse transit time between respective brachium and ankle (Naidu, Reddy et al. 2005).

BaPWV was measured with an automatic apparatus (VP-2000; Colin Corporation, Komaki, Japan). Participants rested for at least 5 minutes 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. BaPWV data were transformed to a normal distribution using natural logarithms to improve normality. BaPWV data had a strong association with ln(baPWV)($r=0.93$, $p<0.05$). The relationship between baPWV and ln(baPWV) was described in Figure 4.

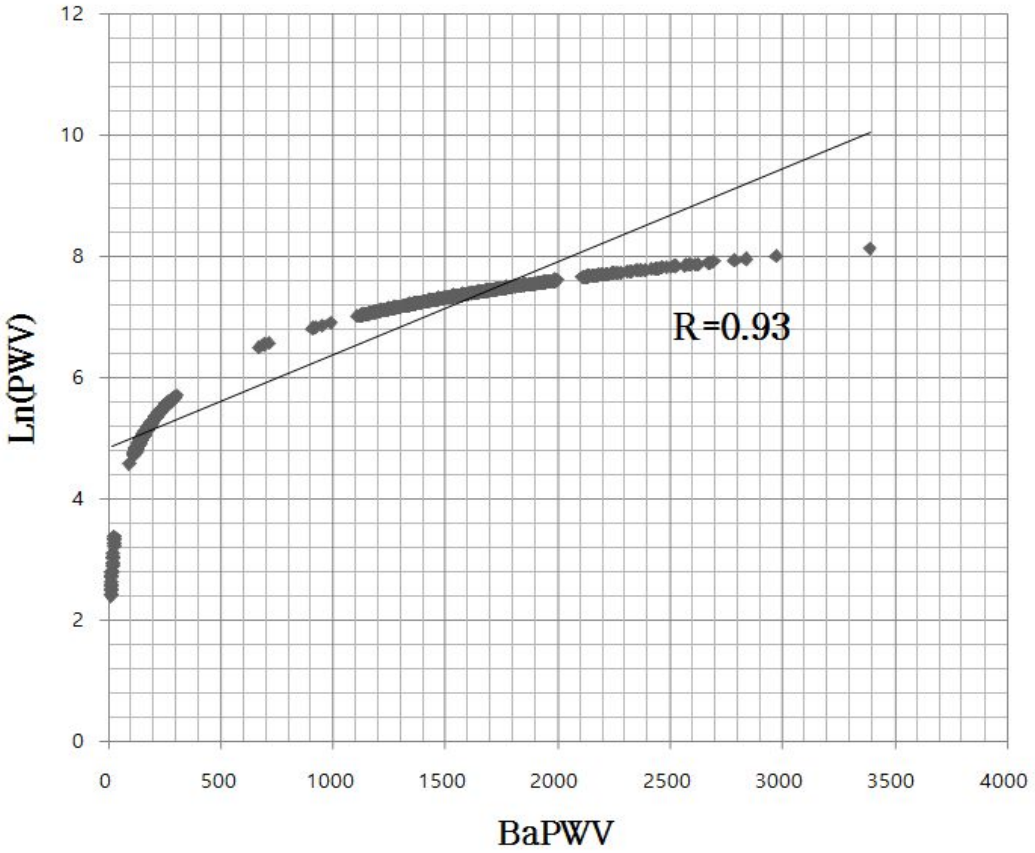

Figure 4.The relationship between baPWV and ln(baPWV)

Microalbuminuria

First-voided morning spot urine samples were collected from all participants and stored in a -20℃ 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. I 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 (Dabla 2010) 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 (Table 2.).

Table 2.UACR category

UACR category	
Normal	0-29 mg/g
Microalbuminuria	30-299 mg/g
Macroalbuminuria or overt proteinuria	300 mg/g ≤

Blood pressure and blood chemistry

Blood pressure was measured twice, with a 5 minute interval, after at least 5 minutes' 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. I used the mean of the two measurements in the analysis.

All blood samples were taken after overnight fasting for at least 8 hours. 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 by Friedwald's method (Friedewald, Levy et al. 1972). Serum insulin levels were analyzed with a Gamma Counter (Packard, USA) and an insulin RIA Kit (Biosource, Belgium) using immunoradiometric assays (IRMA). Insulin resistance was measured with the homeostatic model assessment insulin resistance ($HOMA_{IR}$) using serum glucose and insulin levels. It was obtained from the following formula (Matthews, Hosker et al. 1985):

$HOMA_{IR}$ = [fasting glucose (mg/dL) × fasting insulin (uIU/mL)] / 405

The explanation and research method of these variables are described in Table 3.

Table 3.Explanation and research method of laboratory exam

Variables (unit)	Explanation	Research method
BaPWV (cm/s)	distance between respective brachium and ankle/ Pulse transit time between respective brachium and ankle	automatic apparatus
UACR (mg/g)	urinary albumin to creatinine ratios	first-voided morning spot urine sampling
Heart rate (/min)	the number of heart beats that occur within a minutes	standardized manner
Blood pressure (mmHg)	mean of the two measurements	standardized manner using a mercury sphygmomanometer
Fasting blood glucose (mg/dL)	blood glucose level analyzed enzymatically using an automatic analyzer	blood sampling after overnight fasting for at least 8 hours
Total cholesterol (mg/dL)	total cholesterol level analyzed enzymatically using an automatic analyzer	blood sampling after overnight fasting for at least 8 hours
HDL cholesterol (mg/dL)	HDL cholesterol level analyzed enzymatically using an automatic analyzer	blood sampling after overnight fasting for at least 8 hours
LDL cholesterol (mg/dL)	Friedwald's method; total cholesterol-HDL-(0.2×triglyceride)	blood sampling after overnight fasting for at least 8 hours
Triglyceride (mg/dL)	triglyceride level analyzed enzymatically using an automatic analyzer	blood sampling after overnight fasting for at least 8 hours
Fasting insulin (uIU/mL)	insulin level analyzed enzymatically using an automatic analyzer	blood sampling after overnight fasting for at least 8 hours
$HOMA_{IR}$	[fasting glucose (mg/dL)×fasting insulin (uIU/mL)] / 405	blood sampling after overnight fasting for at least 8 hours

Statistical analysis

All analyses were gender stratified due to the different characteristics of men and women. Age adjusted comparison of general characteristics according 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 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).

Results

General characteristics of the study population

General characteristics of the study population by gender are described in Table 4. The average age of the subjects was 60.9±10.5 years; 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 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 in women.

Table 4.General characteristics of the study population

	Total (N=1,648)	Men (N=677)	Women (N=971)	P †
Age (year)	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*
Heart 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 93-189	137 99-210	120 90-176	*<0.001*
Fasting insulin (uIU/mL)	10 ± 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)	1515 1325-1764	1557 1378-1796	1487 1285-1724	*0.041*
History of hypertension,n,%	440 26.7	146 21.6	294 30.3	*<0.001*
History of DM,n,%	141 8.6	58 8.6	83 8.6	*0.989*
Smoking history ‡,n,%				
Never	1070 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,n,%				
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§,n,%							
	Never/irregular	1186	72	475	70.2	711	73.2	*0.174*
	Regular	462	28	202	29.8	260	26.8	
Category of UACR,n,%							
	Normal (0-30 mg/g)	1485	90.1	621	91.7	864	89	*0.066*
	Microalbuminuria (30-300 mg/g)	163	9.9	56	8.3	107	11	

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

* 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 (20pack/whole year)

§ ≥3 times/week and ≥30min/ time

Age-adjusted characteristics according to baPWV quartiles

Table 5 and Table 6 present age-adjusted characteristics according to baPWV quartiles. Age, SBP, DBP, fasting blood glucose, triglyceride, $HOMA_{IR}$, 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

Table 5.Age-adjusted characteristics according to baPWV quartiles in Men

	BaPWV quartiles†												
	1st Q (lower) (N=169)			2nd Q (N=170)			3rd Q (N=169)			4th Q (highest) (N=169)			*P* ‡
Men													
Age (year)	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*
Heart 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		91-193	136		93-191	142		102-229	147		113-225	*<0.001*
Fasting insulin (uIU/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	2.1		1.50-3.06	*0.126*
BaPWV (cm/s) (median,Q1-Q3)	1250		1080-1330	1468		1419-1508	1674		1603-1728	2000		1886-2157	*<0.001*
History of hypertension,n,%	19		11.2	31		18.2	38		22.5	58		34.3	*0.003*
History of DM,n,%	10		5.9	11		6.5	13		7.7	24		14.2	*0.081*
Smoking history§,n,%													
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,n,%													

	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‖,n,%										
	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	

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

* Values are 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: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

‡Using a general linear model for continuous variables and the Cochran-Mantel-Haenzsel test for categorical variables adjusted for age

§ ≥400 (20pack/whole year)

‖ ≥3 times/week and ≥30min/time

Table 6.Age-adjusted characteristics according to baPWV quartiles in Women

	BaPWV quartiles†				
	1st Q (lower) (N=243)	2nd Q (N=242)	3rd Q (N=244)	4th Q (highest) (N=242)	*P* ‡
Women					
Age (year)	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*
Heart 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 78-146	115 90-165	131 94-186	142 108-197	*<0.001*
Fasting insulin (uIU/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)	1185 1100-1230	1384 1336-1433	1590 1544-1652	1932 1828-2114	*<0.001*
History of hypertension,n,%	30 12.4	52 21.5	90 36.9	122 50.4	*<0.001*
History of DM,n,%	5 2.1	11 4.6	26 10.7	41 16.9	*<0.001*
Smoking history§,n,%					
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,n,%					
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‖,n,%										
	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	

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

* Values are 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: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

‡Using a general linear model for continuous variables and the Cochran-Mantel-Haenzsel test for categorical variables adjusted for age

§ ≥400 (20pack/whole year)

‖ ≥3 times/week and ≥30min/time

UACR levels and distribution of microalbuminuria of study population according to baPWV quartiles

Table 7 and Table 8 show UACR levels according to baPWV quartiles stratified by gender. Because UACR data did not follow a normal distribution, after the data were transformed to a normal distribution using natural logarithms to improve normality, the means of log (UACR) were calculated according to baPWV quartiles. The number and proportion of microalbuminuria were compared to baPWV quartiles. In men, the proportion of microalbuminuria according to baPWV was significant (p=0.019). Unlike the results, in women, the both of log (UACR) means (p=0.002) and proportion of microalbuminuria (p<0.001) were increased with higher quartiles significantly.

The relationship between UACR and baPWV was described in Figure 5 and 6 by scatter plot. The correlation coefficients were 0.13 in men, 1.19 in women, respectively.

Table 7.UACR levels of study population according to baPWV quartiles in Men

	BaPWV quartiles				
	1st Q (lower) (N=169)	2nd Q (N=170)	3rd Q (N=169)	4th Q (highest) (N=169)	*P*
Men					
UACR (mg/g)					
mean	6.1 ± 19.4	9 ± 30.7	11.6 ± 32.6	17.6 ± 41.1	
median	1.8	1.5	1.7	2.2	
range	0.1-169.0	0.1-284.6	0.1-250.7	0.1-277.5	
Log(UACR) mean	0.9	0.8	0.8	0.9	*0.818*
Microalbuminuria (30-299 mg/g),n,%	4 2.4	11 6.5	15 8.9	26 15.4	*0.019*

Table 8.UACR levels of study population according to baPWV quartiles in Women

	BaPWV quartiles				
	1st Q (lower) (N=243)	2nd Q (N=242)	3rd Q (N=244)	4th Q (highest) (N=242)	*P*
Women					
UACR (mg/g)					
mean	6.1 ± 14	8.0 ± 22.2	16.7 ± 41.6	24 ± 46	
median	1.4	1.9	4.6	4.6	
range	0.1-98.7	0.1-191.2	0.1-297.2	0.1-286.2	
Log(UACR) mean	0.9	0.9	1.1	1.5	*0.002*
Microalbuminuria (30-299 mg/g),n,%	12 4.9	16 6.6	30 12.3	49 20.2	*<0.001*

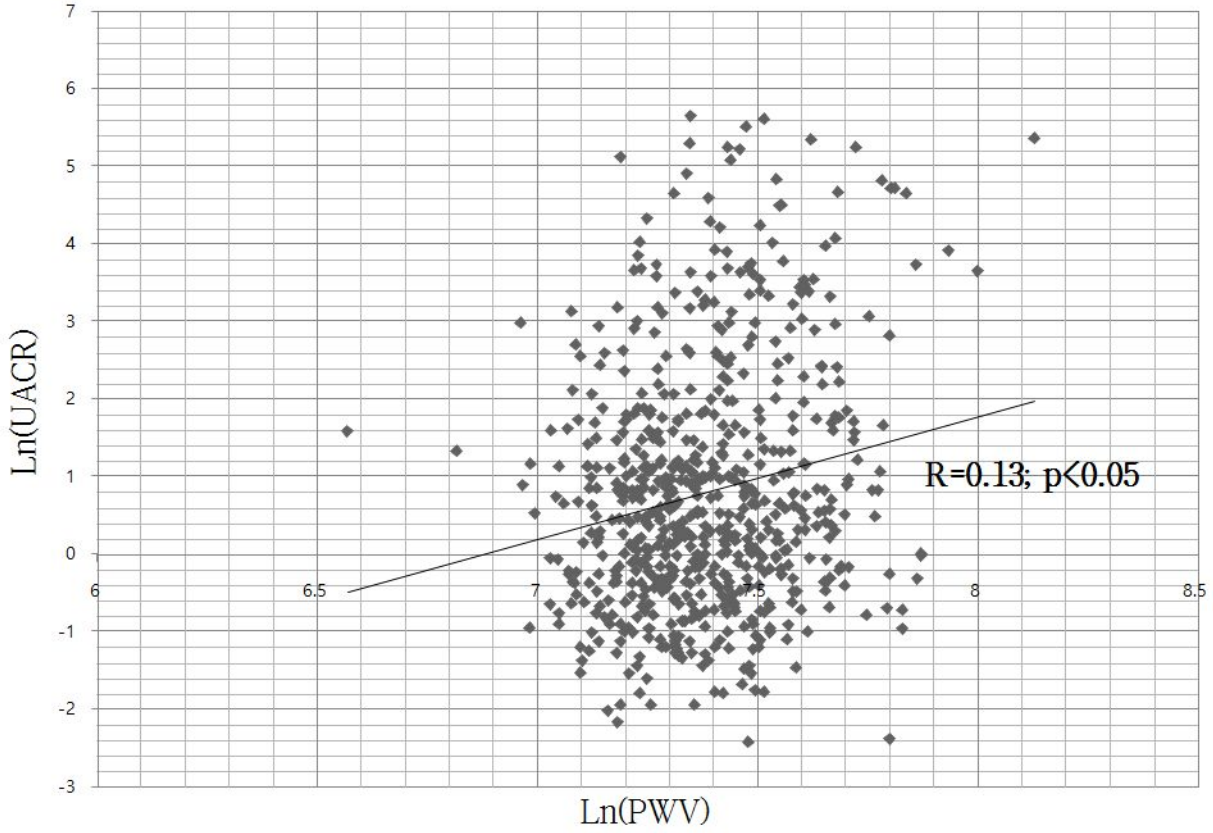

Figure 5.Correlation between baPWV and UACR in men

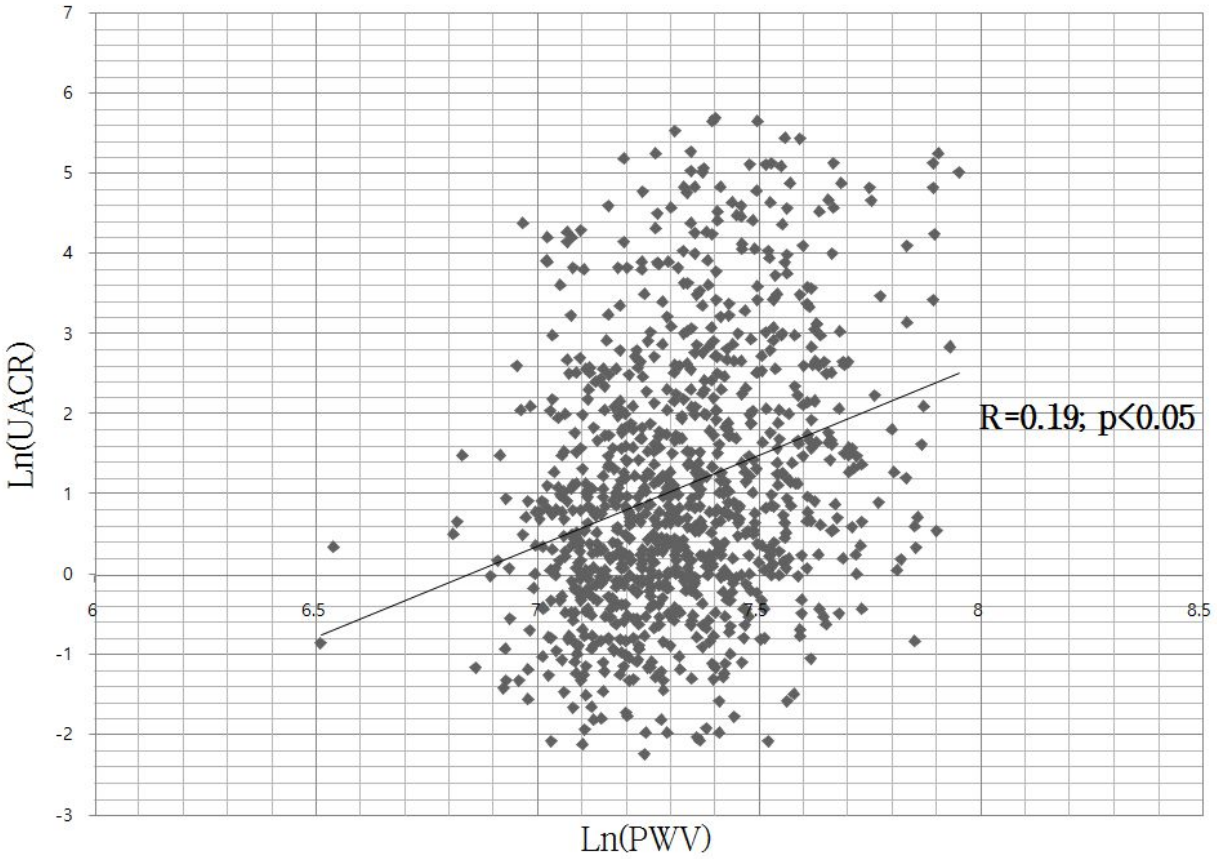

Figure 6.Correlation between baPWV and UACR in women

Comparison of the normoalbuminuric and microalbuminuric group

Table 9 and Table 10 compare characteristics of the normoalbuminuric and microalbuminuric groups. Age, fasting blood glucose, the proportion of history of hypertension and DM were significantly higher in the microalbuminuric 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, 1,473-1,915cm/s, p<0.001).

Table 9.Comparisons of the normoalbuminuric and microalbuminuric group in Men

	Men				
	Normal	(N=621)	MAU†	(N=56)	P ‡
Age (year)	61.1 ±	10.3	66.2 ±	10.6	*<0.001*
BMI (kg/m^2)	24.2 ±	3.1	24 ±	3	*0.61*
Waist circumference (cm)	87.9 ±	8	89.3 ±	7.9	*0.216*
Heart rate (/min)	68.8 ±	9.9	72.6 ±	13	*0.038*
SBP (mmHg)	125 ±	15.6	131 ±	26.7	*0.102*
DBP (mmHg)	81.4 ±	10.4	82 ±	17.5	*0.809*
Fasting blood glucose (mg/dL)	102.8 ±	21.7	117.8 ±	32.5	*0.001*
Total cholesterol (mg/dL)	189.4 ±	35.2	196.2 ±	32.9	*0.166*
HDL cholesterol (mg/dL)	45.3 ±	11.6	45 ±	11.6	*0.858*
LDL cholesterol (mg/dL)	112.9 ±	31	114.2 ±	27.5	*0.772*
Triglyceride (mg/dL) (median,Q1-Q3)	136	98-204	158	113-239	*0.065*
Fasting insulin (uIU/mL)	10.9 ±	5.7	10.5 ±	6.5	*0.138*
$HOMA_{IR}$ (median,Q1-Q3)	2.04	1.51-2.95	2.64	1.69-3.59	*0.013*
UACR (mg/g) (median,Q1-Q3)	1.56	0.70-3.45	67.14	40.00-125.05	*<0.001*
BaPWV (cm/s) (median,Q1-Q3)	1538	1370-1777	1776	1552-2027	*<0.001*
History of hypertension,n,%	128	20.6	18	32.1	*0.045*
History of DM,n,%	45	7.3	13	23.2	*<0.001*
Smoking history§ n,%					
Never	138	22.2	11	19.6	*0.579*
Past	271	43.6	22	39.3	
Current	212	34.1	23	41.1	
Alcohol consumption history,n,%					

	Never	116	18.7	6	10.7	*0.297*
	Past	69	11.1	8	14.3	
	Current	436	70.2	42	75	
Physical activity‖ n,%						
	Never/irregular	433	69.7	42	75	*0.409*
	Regular	188	30.3	14	25	
BaPWV quartiles¶ n,%						
	1st Q (lower)	165	26.6	4	7.1	*<0.001*
	2nd Q	159	25.6	11	19.6	
	3rd Q	154	24.8	15	26.8	
	4th Q (highest)	143	23	26	46.4	

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

*Values expressed 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 (20pack/whole year)

‖ ≥3 times/week and ≥30min/1 time

¶ baPWV values were divided into4 quartiles: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

Table 10.Comparisons of the normoalbuminuric and microalbuminuric group in Women

	Women						
	Normal	(N=864)		MAU†	(N=107)		*P* ‡
Age (year)	60.1	±	10.6	62.9	±	9.9	*0.01*
BMI (kg/m^2)	24.9	±	3.3	25	±	3.4	*0.779*
Waist circumference (cm)	87.1	±	8.3	87.6	±	9	*0.562*
Heart rate (/min)	69.7	±	9.9	70.4	±	11	*0.531*
SBP (mmHg)	121.5	±	16.9	130.7	±	20.3	*<0.001*
DBP (mmHg)	78.2	±	9.8	82.5	±	12	*0.001*
Fasting blood glucose (mg/dL)	100.1	±	21.4	110.1	±	36.8	*0.007*
Total cholesterol (mg/dL)	201.3	±	37.4	209.9	±	35.1	*0.024*
HDL cholesterol (mg/dL)	47	±	10.6	46.7	±	10	*0.774*
LDL cholesterol (mg/dL)	126.6	±	32.1	132.2	±	32.7	*0.091*
Triglyceride (mg/dL) (median,Q1-Q3)	118		90-173	139		97-198	*0.034*
Fasting insulin (uIU/mL)	10.5	±	4.7	9.2	±	4.4	*0.46*
$HOMA_{IR}$ (median,Q1-Q3)	2.3		1.78-3.08	2.54		1.75-3.45	*0.055*
UACR (mg/g) (median,Q1-Q3)	1.93		0.87-4.81	71.01		45.81-124.56	*<0.001*
BaPWV (cm/s) (median,Q1-Q3)	1461		1271-1687	1645		1473-1915	*<0.001*
History of hypertension,n,%	250		28.9	44		41.1	*0.01*
History of DM,n,%	68		7.9	15		14	*0.032*
Smoking history§ n,%							
Never	818		94.7	103		96.3	*0.925*
Past	12		1.4	1		0.9	
Current	34		3.9	3		2.8	
Alcohol consumption history,n,%							

	Never	551	63.8	80	74.8	*0.0798*
	Past	23	2.7	2	1.9	
	Current	290	33.6	25	23.4	
Physical activity‖ n,%						
	Never/irregular	629	72.8	82	76.6	*0.398*
	Regular	235	27.2	25	23.4	
BaPWV quartiles¶ n,%						
	1st Q (lower)	231	26.7	12	11.2	*<0.001*
	2nd Q	226	26.1	16	15	
	3rd Q	214	24.8	30	28	
	4th Q (highest)	193	22.3	49	45.8	

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

*Values expressed as mean±SD or median and 25% percentile-75% percentile or number and percent

† UACR 30-300 mg/g

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§ ≥400 (20pack/whole year)

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¶ baPWV values were divided into4 quartiles: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

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

Table 11 and Table 12 show adjusted ORs and 95% CIs of microalbuminuria according to baPWV qaurtiles stratified by hypertension and diabetes status adjusted for age, heart rate, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerige, and $HOMA_{IR}$. Especially, the OR of microalbuminuria was 4.46 (95% CI, 1.27-15.63) according to baPWV 4^{th} quartiles (Q4) in women without hypertension.

Table 11.Odds ratios and 95% Confidence intervals* of microalbuminuria stratified by diseases status (hypertension and diabetes) adjusted for baPWV quartiles, age, heart rate, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride and HOMAIR in Men

Men		Microalbuminuria vs. normal							
		Hypertension†				Diabetes Mellitus‡			
		Yes	(n=251)	No	(n=426)	Yes	(n=92)	No	(n=585)
BaPWV quartiles §	1st Q (lower)	1	ref	1	ref	1	ref	1	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

BaPWV, brachial-ankle pulse wave velocity; HOMAIR, homeostasis model for insulin resistance; HDL, high density lipoprotein

*Using multiple logistic regression

†Systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg 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: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

Table 12.Odds ratios and 95% Confidence intervals* of microalbuminuria stratified by diseases status (hypertension and diabetes) adjusted for baPWV quartiles, age, heart rate, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride and HOMAIR in Women

Women		Microalbuminuria vs. normal							
		Hypertension†				Diabetes Mellitus‡			
		Yes	(n=304)	No	(n=610)	Yes	(n=110)	No	(n=864)
BaPWV quartiles§	1st Q (lower)	1	ref	1	ref	1	ref	1	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

BaPWV, brachial-ankle pulse wave velocity; HOMAIR, homeostasis model for insulin resistance; HDL, high density lipoprotein

*Using multiple logistic regression

†Systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg 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: <1379, 1379-1557, 1557-1796, >1796 cm/s in men, <1285, 1285-1489, 1489-1724, >1724 cm/s in women

The relation between baPWV and microalbuminuria

The multivariate logistic regression analyses were performed. Five models were used to estimate the relation between baPWV and microalbuminuria as Table 13. Results of multivariate logistic regression analyses are described in Table 14 and Table 15. BaPWV, triglyceride and $HOMA_{IR}$ data were transformed and used were for analysis. In model Ⅰ, which 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 factors in women. In model Ⅲ, in case of men, which adjusted also for fasting blood glucose, log (baPWV) (OR,15.830; 95%CI,2.687-93.248) 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; $p<0.0001$). 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, 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 the 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. Adjusted R^2 values were higher in men than women.

Table 13.Five models in this study

Model	Sex	Dependent variable	Independent variable	Confounding variables
Model Ⅰ	Men	Microalbuminuria (yes/no)	log transformation baPWV (cm/s)	age (years), heart rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR, history of hypertension (yes/no) and history of DM (yes/no)
	Women			age (years), heart rate (/min), systolic blood pressure (mmHg), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR, history of hypertension (yes/no) and history of DM (yes/no)
Model Ⅱ	Both			age (years), heart rate (/min), log transformation triglyceride (mg/dL), log transformation HOMAIR
Model Ⅲ	Both			age (years), heart rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR
Model Ⅳ	Both			age (years), heart rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR, history of hypertension (yes/no) and history of DM (yes/no)
Model Ⅴ	Men			age (years), heart rate (/min), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR, history of hypertension (yes/no) and history of DM (yes/no)
	Women			age (years), heart rate (/min), systolic blood pressure (mmHg), fasting blood glucose (mg/dL), log transformation triglyceride (mg/dL), log transformation HOMAIR, history of hypertension (yes/no) and history of DM (yes/no)

Table 14.The relation between baPWV and microalbuminuria in men

	Model Ⅰ				Model Ⅱ				Model Ⅲ				Model Ⅳ				Model Ⅴ			
	OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Men																				
Age (years)	1.063	0.061	1.03	1.098	1.033	0.032	0.998	1.069	1.036	0.035	1	1.073	1.031	0.031	0.995	1.067	1.034	0.033	0.998	1.071
Ln(BaPWV) (cm/s)*					18.784	2.933	3.245	108.741	15.83	2.762	2.687	93.248	17.539	2.864	2.969	103.626	15.813	2.761	2.629	95.119
Heart rate (/min)	1.031	0.031	1.004	1.059	1.019	0.019	0.991	1.048	1.018	0.018	0.989	1.047	1.019	0.019	0.991	1.048	1.018	0.018	0.99	1.048
Fasting blood glucose (mg/dL)	1.01	0.010	0.997	1.023					1.012	0.012	1.001	1.023	1.008	0.008	0.995	1.022	1.008	0.008	0.994	1.021
Ln(Triglyceride) (mg/dL)*	1.397	0.334	0.809	2.414	1.312	0.272	0.752	2.29	1.256	0.228	0.715	2.206					1.304	0.265	0.738	2.304
Ln($HOMA_{IR}$)*	1.428	0.356	0.754	2.705	2.153	0.767	1.194	3.882	1.56	0.445	0.794	3.063	1.624	0.485	0.835	3.16	1.525	0.422	0.773	3.01
History of hypertension	0.839	-0.176	0.442	1.591									1.034	0.033	0.525	2.037	1.059	0.057	0.536	2.091
History of DM	0.617	-0.483	0.248	1.534									0.603	-0.506	0.232	1.566	0.576	-0.552	0.222	1.497
Adjusted R^2	0.143				0.14				0.157				0.174				0.176			

*Log transformation was done to obtain a normal distribution

Table 15.The relation between baPWV and microalbuminuria in women

	Model Ⅰ				Model Ⅱ				Model Ⅲ				Model Ⅳ				Model Ⅴ			
	OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI		OR	β-value	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Women																				
Age (years)	1.011	0.011	0.99	1.034	0.991	-0.009	0.967	1.016	0.992	-0.008	0.967	1.017	0.993	-0.007	0.968	1.018	0.997	-0.003	0.971	1.023
Ln(BaPWV) (cm/s)*					15.491	2.740	4.518	53.118	13.221	2.582	3.817	45.799	13.428	2.597	3.776	47.758	5.399	1.686	1.157	25.205
Heart rate (/min)	0.998	-0.002	0.978	1.018	0.993	-0.007	0.973	1.014	0.99	-0.010	0.97	1.011	0.992	-0.008	0.972	1.013	0.995	-0.005	0.974	1.016
SBP (mmHg)	1.023	0.023	1.012	1.035													1.013	0.013	0.999	1.027
Fasting blood glucose (mg/dL)	1.011	0.011	1.002	1.02					1.011	0.011	1.003	1.019	1.011	0.011	1.002	1.02	1.011	0.011	1.002	1.02
Ln(Triglyceride) (mg/dL)*	1.467	0.383	0.949	2.268	1.4	0.336	0.905	2.165	1.453	0.374	0.936	2.255					1.423	0.353	0.915	2.212
$Ln(HOMA_{IR})$*	0.81	-0.211	0.481	1.364	1.187	0.171	0.753	1.868	0.844	-0.170	0.499	1.427	0.905	-0.100	0.538	1.521	0.814	-0.206	0.479	1.385
History of hypertension	0.83	-0.186	0.532	1.295									0.811	-0.209	0.515	1.276	0.845	-0.168	0.537	1.33
History of DM	0.957	-0.044	0.456	2.01									1.188	0.172	0.558	2.529	1.074	0.071	0.505	2.287
Adjusted R^2	0.083				0.067				0.079				0.078				0.089			

*Log transformation was done to obtain a normal distribution

Discussion

Discussion on Results

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 (Agewall and Fagerberg 1996). However, the prevalence found here is greater than in a population-based study conducted in Korea (Kim, Lee et al. 2011), which might be explained by the age and prevalence of chronic disease according to the subject' old age of the subjects in the present study (Hillege, Janssen et al. 2001). 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 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 (Liu, Pi-Sunyer et al. 2010) by about 10 mmHg in the group without

microalbuminuria and by about 20 mmHg in microalbuminuria group. The prevalence of the albuminuria was also lower than the Taiwan study; however, the fasting blood glucose levels were very similar. The mean value of the baPWV in the microalbuminuria was lower than the Taiwan study by > 100 cm/sec. The relative contribution by hypertension and the diabetes to the relationship between arterial stiffness and microalbuminuria may be affected by the level of the blood pressure in a population.

In this study, SBP, DBP, fasting blood glucose, and history of hypertension increased with increasing baPWV after adjusting for age. This is consistent with a study performed in Japan (Matsui, Eguchi et al. 2010). 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 this study, all increased with increasing baPWV (Liu, Pi-Sunyer et al. 2010).

The effects of gender, age, BMI, central obesity, and smoking on microalbuminuria are controversial (Rosa and Palatini 2000). Of these factors, none was related to the presence of microalbuminuria in this study. In fact, BMI, and central obesity were not related to microalbuminuria in several previous studies (Munakata, Nunokawa et al. 2006; Ishikawa, Hashimoto et al. 2008; Munakata, Miura et al. 2009).

There is evidence that insulin resistance plays an important role in the development of microalbuminuria (Hoehner, Greenlund et al. 2002; Satchell and Tooke 2008); and insulin resistance is also reported to be positively related to high arterial stiffness (Watanabe, Okura et al. 2002). However, in the present study, in which I attempted to incorporate arterial stiffness into the previously-known microabuminuria model explained

by insulin resistance, arterial stiffness was consistently independent of their relationship with microalbuminuria even after adjusting potential factors related to microalbuminuria. These finding suggests that arterial stiffness might be so 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, Utsnomiya et al. found that central obesity and $HOMA_{IR}$ were important factors increasing UACR in men, but that these effects were not significant in women. A gender-specific hormonal effect was suggested as a hypothetical explanation (Utsunomiya, Takamatsu et al. 2009). However, in this 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. (Jager, Kostense et al. 1998). 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 5 and Table 6.

Microalbuminuria is caused by endothelial damage that can arise by several mechanisms (Abdelhafiz, Ahmed et al. 2011; Bellasi, Ferramosca et al. 2011). 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 (Liu, Pi-Sunyer et al. 2010; Abdelhafiz, Ahmed et al. 2011). 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 (Satchell and Tooke 2008). This result implies that microalbuminuria is a marker of endothelial damage especially in hypertension. 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 (Satchell and Tooke 2008). Several previous studies found that higher $HOMA_{IR}$ was associated with microalbuminuria (De Cosmo, Minenna et al. 2005; Lin, Chen et al. 2008; Utsunomiya, Takamatsu et al. 2009). Recently, evidence has emerged that high pulse pressure may have an important effect on albuminuria. High pulse pressure leads to arterial stiffness (Baumann, Pan et al. 2010); and kidney cells are passively perfused by pulsatile flow and high pulsatile stress which can cause endothelial damage by disrupting small arterial vessels (O'Rourke and Safar 2005). 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 (Satchell and Tooke 2008; Liu, Pi-Sunyer et al. 2010). Furthermore, an association between arterial stiffness and insulin resistance has been reported (Sengstock, Vaitkevicius et al. 2005; Seo, Kang et al. 2005). This relationship was also seen in women in the present study.

The results of this 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 as a risk factor of microalbuminuria. 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 presence and severity of peripheral artery disease (PAD) (Watson, Sutton-Tyrrell et al. 2011). Therefore, the consideration of ankle-brachial index (ABI) reflecting PAD might be needed in this study. I did a multiple logistic regression except for participants with low ABI (<0.9, men 21, women 32) and high ABI (>1.2, men 35, women 16) (Oksala, Viljamaa et al. 2010), however the results were similar to that in Table 14 and Table 15. The reason for that is the subjects are general population, the number of individuals with abnormal ABI is few.

Limitations and Strengths

This study has several limitations. First, it had a cross-sectional design. Therefore, it is unable to establish any causal relationship between arterial stiffness and microalbuminuria. Second, this study used a single measurement of first morning spot urine to calculate urinary albumin to creatinine ratios. Urinary albumin excretion can be affected by transitory factors such as oral fluid intake (Ravikovich, Messersmith et al. 2002), so a more accurate measure such as using 24-hour urine collections would be desirable. However, single void urine samples give good estimates of 24-hour urine albumin excretion (Chang, Chen et al. 2000). In addition, it has been reported that spot urine protein-creatinine ratio reflects the amount of 24-hour urinary protein excretion with high accuracy (Biradar, Kallaganad et al. 2011). Besides, spot urine protein creatinine ratio has strong correlation ($r=0.9$, $p<0.05$) as well as high positive likelihood

ratio with 24-hour urine protein creatinine ratio (Patil, Shah et al. 2014). Spot urine protein excretion estimates are equivalent to 24-hour urine assessment for predicting clinical outcome especially (Teo, Loh et al. 2015). Third, this study 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 (Rehman, Rahman et al. 2002; Matsui, Eguchi et al. 2010), because I 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 general population, especially elderly from rural communities. This study was able to reconfirm relationship between PWV and microalbuminuria has already been reported. This study provides more useful and strong epidemiologic evidence of the association between arterial stiffness and microalbuminuria in population of over 40 yr.

Conclusion

Results show that there is a strong association between microalbuminuria and arterial stiffness regardless of insulin resistance in a rural population past middle age. However, baPWV can't be a very good indicator considering relatively low explanatory power representing for adjusted R^2 value. It means that many factors contribute to microalbuminuria except baPWV as well as other factors used this study. However, in

consideration of not only the ease of the measurement of baPWV but results of this study, it may be a useful screening tool for predicting cardiovascular complications.

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국문초록

한 농촌지역 인구 집단에서 미세알부민뇨에 독립적으로 영향을 미치는 BaPWV 상승에 관한 연구

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연구 목적

미세알부민뇨는 심혈관질환으로 인한 유병률과 사망률의 지표로 사용되어 왔다. 또한 동맥 경직이나 인슐린 저항성으로 인한 전신적인 혈관 내피의 기능 장애의 지표이기도 하다. 그러나 미세알부민뇨의 기전은 아직 확실히 밝혀지지 않았다. 그러므로 동맥 경직이나 인슐린 저항성과 미세알부민뇨의 관계를 밝히는 것은 중요하다. 한편, brachial-ankle pulse wave velocity (baPWV)는 동맥 강직의 좋은 측정법이다. 따라서 baPWV 는 동맥 강직과 미세알부민뇨의 관계를 설명해 주는데 유용한 지표라 볼 수 있다. 이 연구는 baPWV 의 증가가 미세알부민뇨에 독립적으로 미치는 영향을 평가하기 위해 수행되었다.

연구 방법

본 연구는 2005년에서 2006년 사이에 한국 농촌 다기관 코호트 연구의 기반 조사로 수행된 40세 이상의 성인 1,648명을 대상으로 하였다. 대상자는 urinary albumin creatinine ratio (UACR) 수치 30mg/g 미만의 정상알부민뇨군과 30-300mg/g 의 미세알부민뇨군으로 나뉘어 분석되었다. BaPWV 수치는 정규분포성을 획득하기 위하여 자연로그 변환된 수치를 이용하였다. BaPWV 와 미세알부민뇨의 관계를 구명하기 위하여 다변량 로지스틱 회귀분석을 사용하였고 오즈비를 계산하였다.

연구 결과

미세알부민뇨군의 baPWV 수치의 중위수와 사분위수 범위는 남성(1538, 1370-1777 cm/s vs. 1776, 1552-2027 cm/s, $p<0.001$) 과 여성 (1461, 1271-1687cm/s vs. 1645, 1473-1915cm/s, $p<0.001$) 모두에서 유의하게 정상알부민뇨군보다 높았다. 미세알부민뇨과 baPWV의 관련성을 분석하기 위해 5가지 모형을 이용하여 분석하였다. 심박수, 공복혈당, 중성지방, homeostatic model assessment insulin resistance ($HOMA_{IR}$), 고혈압과 당뇨 과거력을 보정 후에도 baPWV는 미세알부민뇨와 유의한 통계적 관련성을 보였다. 공복 혈당과 $HOMA_{IR}$ 사이에서는 다중공선성 관련성을 보이지 않았다.($r=0.532$, $p<0.001$). 단변량 분석에서 유의하였던 모든 변수를 보정한 분석에서 남성에서는 Log(baPWV) (OR;15.813, 95%CI;2.629-95.119) 가 유일하게 유의한 변수였고, 반면에 여성에서는 log(baPWV) (OR;5.399, 95%CI;1.157-25.205)과 공복혈당(OR;1.011, 95%CI;1.002-1.020)이 유의한 위험 요인이었다.

결론

BaPWV 는 분석한 모든 모형에서 미세알부민뇨와 유일하게 독립적으로 관련성이 있는 변수로 조사되었다. BaPWV 의 증가는 40 세 이상의 농촌 성인에서 인슐린 저항과 관련 없이 독립적으로 미세알부민뇨와 연관이 있었다. 그러나 수정된 R 제곱 값으로 대표되는 설명력이 비교적 낮음을 감안했을 때 baPWV 는 미세알부민뇨 예측에 아주 좋은 지표는 아닐 수 있다. 이는 본 연구에서 사용된 여러 변수 이외에도 많은 요소들이 미세알부민뇨의 발생에 관여함을 시사하지만, 본 연구의 결과와 baPWV 측정의 용이성을 고려하였을 때, baPWV 는 향후 심혈관 질환의 합병증을 예측하는데 유용한 스크리닝 도구로 활용될 수 있을 것이다.

주요어: 알부민뇨, 인슐린 저항성, 위험 요인, 혈관 경직

학번: 2010-22091