Original Article

Insulin Resistance Is Associated with Arterial Stiffness in Nondiabetic Hypertensives Independent of Metabolic Status

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We sought to determine whether insulin resistance (IR) is related to arterial stiffness in nondiabetic hypertensive patients, independent of metabolic status and gender. IR has been associated with increased arterial stiffness in patients with diabetes. In nondiabetic hypertensive patients, the correlation between IR and arterial stiffness has yet to be investigated. We enrolled 284 nondiabetic patients who were being treated for hypertension. At the time of enrollment, the patients underwent a baseline laboratory assessment including homeostatic model assessment (HOMA) IR index and pulse wave velocity (PWV). The HOMA IR index is used as a marker of IR, and brachial to ankle PWV (baPWV) was used as a marker of arterial stiffness. Of the 284 study subjects, 121 were classified as having metabolic syndrome. The patients with metabolic syndrome were older than the non-metabolic syndrome patients (55.4±10.7 *vs.* 52.1±11.6 years, $p=0.013$), but there was no gender difference between the two groups. The average baPWV was significantly higher in the patients with metabolic syndrome (1,506±235 *vs.* 1,435±211 cm/s, $p=0.009$). The HOMA index was independently associated with an increase in arterial stiffness ($r=0.548$, $p<0.001$) after controlling for age, systolic blood pressure (SBP), heart rate, medication and gender. The independent association of HOMA with arterial stiffness was demonstrated in subgroup analysis, regardless of the metabolic status and gender. In conclusion, increased IR was associated with arterial stiffness, independent of age, baseline SBP, gender and heart rate. This independent association of IR was demonstrated regardless of gender and metabolic status. (*Hypertens Res* 2005; 28: 945–951)

***Key Words*: insulin resistance, arteriosclerosis, hypertension**

Introduction

Many epidemiological studies have demonstrated that increasing arterial stiffness is associated with an increased risk of stroke and ischemic heart disease, resulting in increased risk of cardiovascular mortality (*1–4*). Increasing age, microcirculatory rarefaction, and a high sodium diet are known to cause increases in arterial stiffness (*4–6*). Also, increased blood pressure (BP) and pulse pressure are known to be associated with increased insulin resistance (IR) in hypertensives (*7–9*).

IR increases BP through multiple mechanisms, such as increased sympathetic stimulation, increased renal sodium absorption, decreased insulin-mediated vasodilation due to endothelial dysfunction, and increased activation of the renin-

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Table 1. Baseline Characteristics

	Metabolic syndrome (n=121)	Non-metabolic syndrome (n=163)	p-value*
Age (years)	55.4±10.7	52.1±11.6	0.013
Sex (M:F)	53:68	74:89	0.789
Official BP (mmHg)			
SBP	127.8±18.6	121.2±16.8	0.002
DBP	80.1±12.3	78.6±10.9	0.294
Smoking (%)	23 (19.0%)	35 (21.5%)	0.610
BMI (kg/m^2)	26.2±2.7	23.9±2.6	<0.001
Total cholesterol (mg/dl)	187.7±36.4	184.7±34.2	0.489
TG (mg/dl)	185.6±84.7	109.1±41.7	<0.001
HDL cholesterol (mg/dl)	40.8±7.9	49.6±12.3	<0.001
LDL cholesterol(mg/dl)	113.4±33.8	114.7±31.7	0.740
FBG (mg/dl)	95.8±14.3	87.6±9.9	<0.001
Serum insulin (mU/l)	9.97±6.19	7.76±3.66	<0.001
HOMA index	2.37±1.44	1.68±0.82	<0.001
Average baPWV (cm/s)	1,506±235	1,435±211	0.009

Values are n (%) or mean±SD. M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; HOMA, homeostatic model assessment; baPWV, brachial-ankle pulse wave velocity.

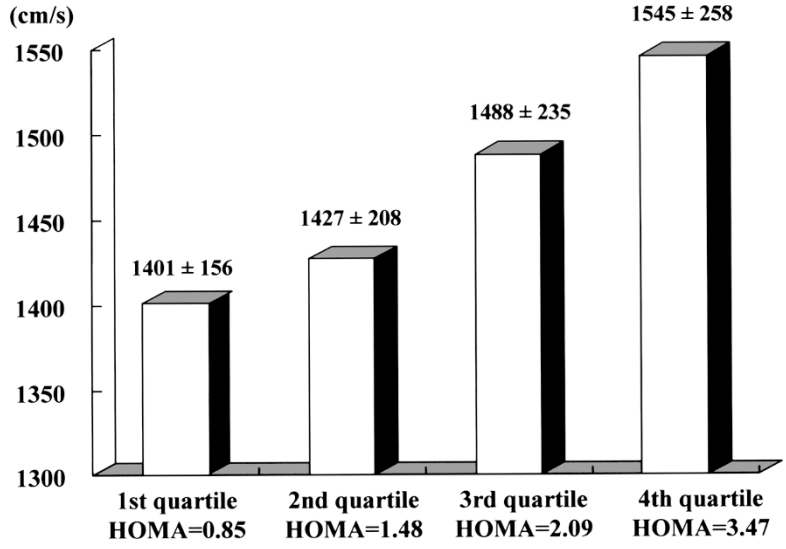

Fig. 1. *Correlation between baPWV and quartiles according to the HOMA index. The baPWV showed increasing values with increasing quartiles, and the association was statistically significant (*$p < 0.001$*).*

angiotensin-aldosterone system, resulting in adverse vascular remodeling (*10–12*). In the Atherosclerosis Risk in Communities Study, the fasting insulin concentration in diabetics was positively correlated with several indices of arterial stiffness, and this relationship was independent of age, cigarette-years, and cholesterol, suggesting that IR may contribute to the stiffening of large arteries (*13*). Also, IR has been shown to be associated with arterial stiffness in patients with metabolic syndrome (*14*) and in healthy, nondiabetic, middle-aged women (*15*). However, in regard to nondiabetic hypertensive patients, it is unclear whether IR is independently associated with arterial stiffness or if it is associated with arterial stiffness due to the clustering of coronary artery disease risk factors of the metabolic syndrome (*15*, *16*). Therefore, the purpose of this study was to determine whether IR is related to arterial stiffness, as determined by brachial-ankle pulse

Table 2. Antihypertensive Medication History

	Metabolic syndrome (n=121)	Non-metabolic syndrome (n=163)	p-value
ACE inhibitors (%)	21 (17.4%)	28 (17.2%)	0.981
Angiotensin receptor blockers (%)	52 (42.9%)	68 (41.7%)	0.854
β-Blockers (%)	71 (58.7%)	83 (50.9%)	0.205
Calcium channel blockers (%)	77 (63.6%)	83 (50.9%)	0.035
Diuretics (%)	42 (34.7%)	39 (23.9%)	0.049
Statins (%)	40 (33.1%)	49 (30.1%)	0.607

ACE, angiotensin-converting enzyme.

wave velocity (baPWV), in nondiabetic hypertensive patients, and whether this relationship is dependent on metabolic status and gender.

Methods

Study Population

The study subjects were 284 nondiabetic hypertensive patients treated at Yonsei Cardiovascular Hospital between January 2004 and April 2005. Patients were selected according to the following criteria: Hypertension was defined as a systolic BP (SBP) of more than 140 mmHg and/or a diastolic BP (DBP) of more than 90 mmHg at the time of examination, a current history of taking BP medications and/or a history of hypertension. Diabetes mellitus was considered to be present in patients who satisfied at least one of three criteria: current use of antidiabetic medications, a fasting blood glucose level of more than 126 mg/dl, and/or a random blood glucose level of more than 200 mg/dl. The patients were enrolled after providing their informed consent. Patients with any of the following conditions were excluded from participation: valvular heart disease; peripheral vascular disease; significant systemic disease; a history of inflammatory disease; a clinically significant atrioventricular conduction disturbance; a history of atrial fibrillation or other serious arrhythmia; a history of congestive heart failure; severe hypertension (>210/130 mmHg); a urine albumin creatinine ratio of more than 300 mg/g; serum creatinine greater than 1.4 mg/dl; or a history of diabetes mellitus.

At the time of initial enrollment, patients underwent a complete physical examination, a baseline electrocardiogram, and a laboratory assessment. After at least 5 min of rest in a sitting position, office BP was measured using a sphygmomanometer with the appropriate cuff size. Two BPs were measured at least 5 min apart, and the mean BP was used for analysis. The laboratory parameters assessed were blood chemistry (glucose, blood urea nitrogen [BUN], uric acid, total cholesterol, total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine, Na, K, triglyceride, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]) and fasting serum insulin. The fasting serum insulin level was determined by immunoradiometric assay using a γ counter (Hewlett Packard, Andover, USA). IR was determined by calculating the homeostatic model assessment (HOMA) IR index, which is defined as [fasting blood glucose (mg/dl) × serum fasting insulin (mIU/ml)]/405. We defined metabolic syndrome according to the modified Asian Pacific NCEP guidelines, as described below (*17*, *18*).

NCEP Criteria for Metabolic Syndrome and Modified NCEP Criteria for Asians

The NCEP ATP III guidelines (*2*) classify individuals as having metabolic syndrome if they meet three or more of the following criteria:

High BP: BPs greater than 130/85 mmHg, or current use of BP-lowering drugs.

Hyperglycemia: Fasting plasma glucose greater than 6.1 mmol/l (110 mg/dl), or current use of glucose-lowering drugs.

Hypertriglyceridemia: Fasting plasma triglycerides greater than 1.69 mmol/l (150 mg/dl).

Low HDL-C: Fasting HDL-C less than 1.04 or 1.29 mmol/l (40 or 50 mg/dl) in males and females, respectively.

Central obesity: Waist circumference greater than 88 or 102 cm in females and males, respectively. However, the WHO has recognized the disproportionate contribution of obesity to the development of cardiovascular risk factors in Asians and has provisionally lowered the classification of central obesity to >80 or >90 cm in females and males, respectively.

This study was approved beforehand by the institutional ethics committee, and the procedures followed were in accordance with the institutional guidelines.

Pulse Wave Velocity (PWV) Measurement

The PWV was determined by measuring baPWV using a VP-2000 pulse wave unit (Nippon Colin Ltd., Komaki, Japan) as previously described (*19*, *20*). Briefly, this device determines the oscillometric measurement of volume pulse wave forms of the four extremities. The distances between the sampling points of the brachial and ankle pulse wave forms, automatically calculated according to the heights of the patients, were

Table 3. Multiple Linear Regression Analysis for Independent Determinants of Increased baPWV (r=0.548)

	t	Standardized coefficient	p-value
Age	5.533	0.320	<0.001
HOMA index	3.623	0.195	<0.001
Baseline SBP	4.913	0.263	<0.001
Heart rate	2.547	0.146	0.011
Male gender	−1.535	−0.084	0.126
ACEI	0.213	0.012	0.831
ARB	−0.430	−0.026	0.668
CCB	−0.043	−0.002	0.966
Diuretics	−1.172	−0.064	0.242
β-Blocker	−0.321	−0.018	0.749
Statin	−0.276	−0.015	0.783

baPWV, brachial-ankle pulse wave velocity; HOMA, homeostatic model assessment; SBP, systolic blood pressure; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

Table 4. Multiple Linear Regression Analysis for Independent Determinants of Increased baPWV According to Metabolic Status

	t	Standardized coefficient	p-value
Non-metabolic syndrome (r=0.556)			
Age	5.345	0.432	<0.001
Sex	−0.079	−0.006	0.937
SBP	2.314	0.166	0.022
Heart rate	1.826	0.140	0.070
HOMA index	2.638	0.192	0.009
Statin	−0.415	−0.031	0.679
ACEI	−0.210	−0.016	0.834
ARB	−0.897	−0.074	0.371
β-Blocker	−0.406	−0.033	0.685
CCB	−0.720	−0.056	0.472
Diuretics	−0.079	−0.006	0.937
Metabolic syndrome (r=0.554)			
Age	2.370	0.211	0.020
Sex	−2.070	−0.175	0.041
SBP	4.198	0.355	<0.001
Heart rate	1.285	0.120	0.201
HOMA index	2.017	0.175	0.046
Statin	−0.715	−0.059	0.476
ACEI	0.228	0.022	0.820
ARB	0.080	0.008	0.937
β-Blocker	−0.563	−0.051	0.574
CCB	0.579	0.051	0.564
Diuretics	−0.481	−0.042	0.632

baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; HOMA, homeostatic model assessment; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

divided by the time interval between the brachial and ankle wave forms (*19*, *20*). The baPWV is widely used as a marker of arterial stiffness due to its ease of measurement, reproducibility, and validity in previous studies (*21*, *22*).

Statistical Analysis

Values were expressed as the mean±SD. Comparisons of the discrete variables were performed using the χ^2 method. Comparisons of continuous variables between the two study groups were performed using Student's t-test. Independent

Table 5. Multiple Linear Regression Analysis for Independent Determinants of Increased baPWV According to Gender

	t	Standardized Coefficient	*p*-value
Male (r=0.529)			
Age	2.635	0.228	0.010
SBP	3.351	0.296	0.001
Heart rate	1.147	0.104	0.254
HOMA index	2.221	0.189	0.028
Statin	−0.737	−0.062	0.463
ACEI	−0.337	−0.032	0.737
ARB	0.507	0.048	0.613
β-Blocker	−0.786	−0.074	0.434
CCB	−0.202	−0.018	0.840
Diuretics	−0.184	−0.016	0.855
Female (r=0.550)			
Age	4.582	0.345	<0.001
SBP	3.134	0.228	0.002
Heart rate	2.115	0.167	0.036
HOMA index	3.049	0.227	0.003
Statin	0.233	0.017	0.816
ACEI	0.605	0.047	0.546
ARB	−1.031	−0.088	0.304
β-Blocker	0.345	0.026	0.731
CCB	0.053	0.004	0.958
Diuretics	−1.086	−0.079	0.279

baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; HOMA, homeostatic model assessment; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

predictors of baPWV were determined using multiple linear regression analysis. Statistical analysis was performed with SPSS 11.0 (SPSS Inc., Chicago, USA).

Results

Clinical Characteristics

Of the 284 study subjects, 121 were classified as having metabolic syndrome and 163 as not having metabolic syndrome. The patients with metabolic syndrome were older and had a higher average triglyceride level and body mass index, as well as a lower HDL-C level. The fasting blood glucose, serum insulin level, and HOMA index were significantly higher in the metabolic syndrome group compared to the non-metabolic syndrome group. The average baPWV was significantly higher in patients with metabolic syndrome (Table 1). When the entire study group was divided into quartiles according to the HOMA index, the baPWV showed increasing values with increasing quartiles (Fig. 1). There were no significant differences between the metabolic syndrome group and the non-metabolic syndrome group in terms of the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers or β-blockers. Calcium channel blockers and diuretics were more frequently administered in the metabolic syndrome group (Table 2).

Multiple Linear Regression

Multiple linear regression of the entire study group revealed that after controlling for age, SBP, gender, heart rate and medications affecting arterial stiffness, the HOMA index was still independently associated with an increase in arterial stiffness (Table 3). The independent association of HOMA with arterial stiffness was demonstrated in subgroup analysis, regardless of the patients' metabolic status and gender (Tables 4 and 5).

Discussion

Causes of IR, such as abdominal obesity, and its consequences, such as dyslipidemia, are independent risk factors for cardiovascular disease. Increased central arterial stiffening is a hallmark of the aging process and also a marker for increased risk of cardiovascular disease (*23*, *24*). Recent studies have focused on the association of IR with increased arterial stiffness and subsequent systolic hypertension in patients with diabetes mellitus or metabolic syndrome (*14*, *16*, *25*).

However, the results from previous studies have not clearly demonstrated whether or not IR is associated with increased arterial stiffness independent of the clusters of risk factors (obesity, dyslipidemia) that are demonstrated in this group of patients (*26*). The results from this study demonstrate that IR

is independently associated with increasing arterial stiffness, and this finding was demonstrated regardless of the metabolic status of the patients. The mechanism behind this finding may be multifactorial. Insulin has been shown to act directly to decrease arterial stiffness in non-obese patients, but this effect is markedly blunted in patients with obesity and IR (*27*). Other studies have shown decreased IRS-1 protein expression in nondiabetic males with increased arterial stiffness (*28*). The systemic effects of IR, such as increased sympathetic tone, renin-angiotensin-aldosterone system activation, and increased vascular inflammation, are some of the other mechanisms that may be involved with increased arterial stiffness. It is interesting to note that even in patients without the metabolic syndrome, the HOMA index was significantly correlated with increasing arterial stiffness. Even in patients who do not satisfy the current diagnostic criteria for metabolic syndrome, an increasing degree of IR may be one of the important mechanisms in the development of hypertension. Active lifestyle modification and drug treatment to reduce IR may help in reducing arterial stiffness and subsequent cardiovascular events in these patients, since clinical trials have demonstrated that the reduction of IR by exercise and the administration of rosiglitazone are associated with a reduction in arterial stiffness and BP (*29*).

Data regarding the gender-specific association of IR with arterial stiffness are limited. While there are no known gender-specific differences in arterial stiffness, some features of the metabolic syndrome are reported to be more strongly associated with women than with men (*19*, *30*). However, the results from this study demonstrate that IR modulates arterial stiffness regardless of gender in nondiabetic hypertensive patients.

Because the study population consisted of treated hypertensive patients, BP medication may have influenced the measured baPWV. However, the proportion of patients taking each class of drugs did not differ according to the presence or absence of metabolic syndrome (Table 2). In fact, the proportion of patients taking calcium channel blockers and diuretics, two drugs that may lower arterial stiffness, were significantly higher in the metabolic syndrome group. Also, the proportions of the medications given were not different according to the quartiles of the HOMA index (not included in Table 2). Therefore, we believe that BP medications did not confound the analysis of data in this study.

In conclusion, increased IR was associated with arterial stiffness independent of age, sex, heart rate, or risk factors associated with metabolic syndrome in nondiabetic hypertensive patients. This independent association of IR with arterial stiffness was demonstrated to be unaffected by gender and metabolic status.

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