Original Article

Adiponectin, but Not Leptin or High-Sensitivity C-Reactive Protein, Is Associated with Blood Pressure Independently of General and Abdominal Adiposity

Shih-Hsien SUNG[1)], Shao-Yuan CHUANG[2)], Wayne Huey-Herng SHEU[3)], Wen-Jane LEE[4)], Pesus CHOU[5),6)], and Chen-Huan CHEN[1),5),7),8)]

The role of adiponectin, a marker of the metabolic syndrome, on the pathogenesis of hypertension in comparison with markers of adipose tissue mass (leptin) and inflammation (high-sensitivity C-reactive protein [hs-CRP]) remains to be clarified. The eligible study population consisted of 2,045 residents aged≥40 years who had participated in a community-based survey and had complete data for serum adiponectin, leptin, and hs-CRP, and for whom homeostasis model assessment of insulin resistance (HOMA-IR) had been calculated from insulin and plasma glucose. Among all eligible participants, as well as in the subgroup of nondiabetic normotensives (blood pressure <140/90 mmHg and without antihypertensive medication), all three markers were significantly correlated with systolic blood pressure (negative correlation for adiponectin and positive correlations for leptin and hs-CRP). Among all participants, systolic blood pressure and the presence of hypertension were determined mainly by age, sex, body mass index, and waist circumference. None of the markers further contributed to the multivariate linear regression or logistic regression models. In contrast, adiponectin, but not leptin, hs-CRP, or HOMA-IR, was significantly associated with systolic blood pressure and the presence of pre-hypertension (blood pressure within 120–139/80–89 mmHg) after adjustment for age, sex, body mass index, and waist circumference in the nondiabetic normotensive subgroup. Similarly, adiponectin was independently associated with diastolic blood pressure in the nondiabetic normotensive subgroup but not in the whole population. In conclusion, adiponectin, but not leptin or hs-CRP, was independently associated with blood pressure in a nondiabetic normotensive subgroup. (*Hypertens Res* 2008; 31: 633–640)

***Key Words*: hypertension, metabolic syndrome, inflammation, obesity**

Introduction

Hypertension is a major contributor to the current global disease burden, and the majority of diagnosed hypertensives are inadequately controlled (*1*). This lack of control may be due in part to the incomplete understanding of the pathogenesis of hypertension. Hypertension has long been defined by blood

From the [1)]Department of Internal Medicine and [7)]Department of Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [2)]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, ROC; [3)]Department of Internal Medicine and [4)]Department of Research and Education, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; and [5)]Department of Public Health, [6)]Community Medicine Research Center, and [8)]Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, ROC.

This work was supported in part by serial grants from the National Science Council (NSC 92-2320-B-010-058; NSC 93-2314-B-010-040; NSC 94-2314-B-010-058), by intramural grants from the Taipei Veterans General Hospital (Grant No.93-198C), and grants-in-aid from the Research Foundation of Cardiovascular Medicine (91-02-032, 93-02-014), Taipei, Taiwan, ROC.

Address for Reprints: Chen-Huan Chen, M.D., Department of Research and Education, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan, ROC. E-mail: chench@vghtpe.gov.tw

Received August 7, 2007; Accepted in revised form October 21, 2007.

Table 1. Characteristics of All Eligible Participants ($n=2,045$) and the Non-Diabetic Normotensive Subgroup ($n=1,512$)

Variables	All eligible participants		Non-diabetic normotensive subgroup	
	Without hypertension ($n=1,596$)	With hypertension ($n=449$)	Without pre-hypertension ($n=645$)	With pre-hypertension ($n=867$)
Age, years	55.3±10.4	59.5±11.0**	53.2±9.5	56.5±10.7**
Men, %	31.6	43.2**	25.1	34.8*
BMI, kg/m^2	23.8±3.3	25.0±3.5**	23.1±3.14	24.2±3.2**
WC, cm	84.3±9.6	89.3±10.3**	82.0±9.4	85.4±9.4**
SBP, mmHg	119.3±10.6	146±12**	110±7	126±7**
DBP, mmHg	75.5±7.7	90±9**	70±6	80±6**
Fasting plasma glucose, mg/dL	101.0±21.7	104.8±27.6*	96.3±13.0	98.7±16.1*
Fasting insulin, μU/mL	13.0±6.9	14.5±7.7**,†	11.6±4.8	13.3±6.1**,†
HOMA-IR	3.3±2.4	3.9±2.8**	2.8±1.2	3.3±1.7**
Adiponectin, μg/mL	10.0±5.0	10.3±5.7	10.7±5.0	9.7±5.1**,†
Leptin, ng/mL	6.9±5.4	7.1±5.5**,†	6.74±4.77	7.00±5.67**,†
hs-CRP, mg/dL	0.18±0.36	0.22±0.42**,†	0.15±0.32	0.19±0.36**,†

*$p<0.05$; **$p<0.001$. †Dependent variables were log transformed. BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; WC, waist circumference. Comparisons were adjusted for sex, age and both sex and age where appropriate. No statistical tests were performed for medians of adiponectin, leptin, and hs-CRP.

pressure levels (*1*), a measure of hemodynamic properties. Consequently, the control of hypertension has focused on the lowering of blood pressure by the manipulation of cardiac output, peripheral resistance, and/or arterial stiffness using lifestyle modification and/or pharmacological interventions. The recent inclusion of high blood pressure as one of five components of the clinical identification of the metabolic syndrome may provide an opportunity to re-define hypertension as a metabolic, instead of a hemodynamic, disorder (*2*).

Longitudinal epidemiological studies have confirmed the importance of general and abdominal obesity at baseline and their progression during follow-up in the development of future hypertension (*3*). Adipose tissue is a rich source of metabolically active molecules, including adiponectin and leptin (*4*). Adiponectin is considered a marker of metabolic syndrome (*5*), and leptin directly reflects the amount of adipose tissue mass (*6*). Obesity is also strongly associated with high-sensitivity C-reactive protein (hs-CRP), a marker of chronic systemic inflammation (*7*). All three markers have been associated with hypertension in either cross-sectional (*6*, *8*) or longitudinal studies (*9*–*11*). However, few studies directly compared the relative associations of the three markers with blood pressure or the presence of hypertension (*12*). It is also intriguing how the complex interplay of the metabolic syndrome, adipose tissue mass, and inflammation is involved in the pathogenesis of hypertension. In the present study, we investigated the associations between adiponectin, leptin, hs-CRP, and blood pressure in a community-based population.

Methods

Study Population

In 2000–2003, a health survey was offered to the residents ≥40 years in the town of Kinchen on the island of Quemoy, whose inhabitants are homogeneous Chinese. Some of the survey results have been published previously (*3*). The target population consisted of 6,600 individuals, based on household registration data. The survey was funded by the Bureau of Public-Health Government of Kinmen County, ROC, as a free health service for the local communities. The participants signed a consent form that permits the use of collected data for research, teaching, medical service, and health management without disclosure of personal identity. The research protocol of the present study, which involved the use of the survey data and the analysis of stocked sera to determine insulin levels and other biomarkers, was approved by the institutional review board of Taipei Veterans General Hospital.

Of the 6,600 in the target population, 2,377 subjects (36%) participated. Among the participants, 2,045 subjects, who were not taking any medications for the treatment of hypertension and/or diabetes and who had complete data for serum adiponectin, leptin, hs-CRP, insulin, and plasma glucose, were eligible for the present study.

Data Collection

The details of the data collection have been reported (*3*). In brief, the demographic data and the medical history of each

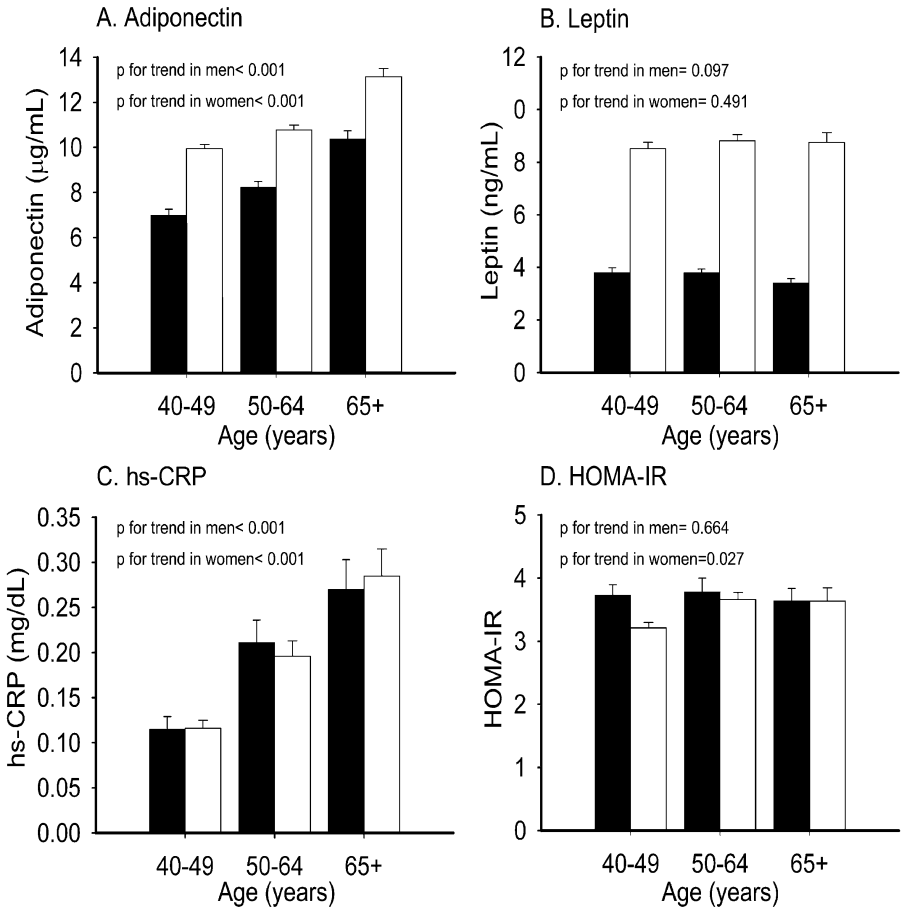

Fig. 1. *Levels of adiponectin (A), leptin (B), hs-CRP (C), and HOMA-IR (D) stratified by sex and age. Error bars are SEM of estimate. Solid bars are for men and hollow bars are for women.*

individual were obtained during face-to-face interviews in which a structured questionnaire was used. Anthropometric parameters including weight, height, and waist circumference (WC) were acquired. Seated systolic and diastolic blood pressure (SBP and DBP) were the average of three measurements taken manually at 5-min intervals using a mercury sphygmomanometer and a standard-sized cuff (13 cm × 50 cm).

Overnight fasting serum and plasma samples were acquired for glucose, insulin, lipid, and other biochemical measurements. Fasting plasma glucose was determined by the hexokinase-glucose-6-phosphate dehydrogenase method with a glucose (HK) reagent kit (Gilford, Oberlin, USA). Fasting serum insulin was measured by radioimmunoassay (Incstar, Stillwater, USA). Serum hs-CRP was determined by particle-enhanced immunoturbidimetry using latex microparticles sensitized with duck anti-CRP IgY (Good Biotech, Taichung, Taiwan). The intra-assay and inter-assay coefficients of variance for hs-CRP were 1.4% and 1.42%, respectively. Serum concentrations of leptin and adiponectin were measured by an enzyme-linked immunosorbent assay microtiter plate (Linco Research, Billerica, USA). For adiponectin, the intra-assay and inter-assay coefficients of variance were 6.2% and 0.05%, respectively; for leptin, the corresponding values were 5.9% and 0.24%.

Definitions

Subjects with a fasting glucose ≥6.99 mmol/L (126 mg/dL) were defined as having diabetes (*3*). Subjects with SBP≥140 mmHg or DBP≥90 mmHg were defined as having hypertension (*1*). Subjects with blood pressure within the ranges of 140>SBP≥120 mmHg or 90>DBP≥80 mmHg were defined as having pre-hypertension (*1*). We used the homeostasis model assessment of insulin resistance (HOMA-IR) to estimate the levels of insulin resistance by the equation: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (*3*).

Statistical Methods

Student's *t*-test or the χ^2 test was used to compare the differences of means or percentages between groups. Pearson cor-

Table 2. Age- and Sex-Adjusted Correlation Coefficients of Adiponectin, Leptin, and hs-CRP with Other Risk Variables

Variables	Correlation coefficients, *r*					
	All eligible participants			Non-diabetic normotensive subgroup		
	log adiponectin	log leptin	log hs-CRP	log adiponectin	log leptin	log hs-CRP
BMI, kg/m^2	−0.26**	0.59**	0.27**	−0.28**	0.58**	0.25**
WC, cm	−0.24**	0.47**	0.22**	−0.28**	0.46**	0.21**
SBP, mmHg	−0.08**	0.12**	0.05*	−0.13**	0.08*	0.06*
DBP, mmHg	−0.11**	0.16**	0.07*	−0.16**	0.11**	0.05*
Fasting plasma glucose, mg/dL	−0.10**	0.12**	0.078	−0.11**	0.14**	0.004
log insulin, μU/mL	−0.28**	0.45**	0.14**	−0.27**	0.44**	0.06*
HOMA-IR	−0.22**	0.34**	0.15**	−0.26**	0.44**	0.07*
log adiponectin, μg/mL	1.00	−0.20**	−0.18**	1.00	−0.23**	−0.18**
log leptin, ng/mL	−0.20**	1.00	0.28**	−0.23**	1.00	0.25**
log hs-CRP, mg/dL	−0.18**	0.28**	1.00	−0.18**	0.25**	1.00

*$p<0.05$; **$p<0.001$. BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; WC, waist circumference.

relation coefficients were calculated to estimate the association between the three biochemical markers and parameters of anthropometric measurements, blood pressure, and insulin resistance, with adjustment for age and sex. Because of the skewed distribution, log transformations were performed for adiponectin, leptin, and hs-CRP prior to statistical analysis. Correlates of SBP or DBP were analyzed by multivariate linear regression. Predictors of the presence of hypertension were analyzed by multivariate logistic regression. To investigate the roles of the biochemical markers in the early stage of hypertension, similar analyses were performed in a subgroup of subjects without the presence of either diabetes or hypertension. All statistical procedures were carried out by SAS statistical package 8.0 (SAS Institute, Cary, USA). Statistical significance was set at $p<0.05$.

Results

Characteristics of the study population and of the nondiabetic normotensive subgroup are shown in Table 1. In the study population of 2,045 men and women who were not taking any antihypertensive or anti-diabetic medications, the prevalences of hypertension and diabetes were 22.0% and 4.1%, respectively. The hypertensive participants were older, had higher body mass index and WC, and higher fasting plasma glucose, fasting insulin, and HOMA-IR than the normotensives. The hypertensives also had higher levels of leptin and hs-CRP than the normotensives. In the nondiabetic normotensive subgroup (fasting plasma glucose <126 mg/dL and SBP/DBP<140/90 mmHg), similar differences between subjects with and without pre-hypertension were observed, except that adiponectin levels were significantly lower in the subjects with pre-hypertension (Table 1).

Characteristics of Adiponectin, Leptin, and hs-CRP

In the whole study population, the correlation coefficients of adiponectin, leptin, and hs-CRP with age were 0.35 ($p<0.0001$), −0.11 ($p=0.005$), and 0.18 ($p<0.0001$), respectively, in men; and 0.25 ($p<0.0001$), −0.00095 ($p=0.9725$), and 0.23 ($p<0.0001$), respectively, in women. Age- and sex-stratified levels of adiponectin, leptin, and hs-CRP with reference to the characteristic of HOMR-IR are displayed in Fig. 1. Women had significantly higher levels of adiponectin and leptin than men across the three age groups. On the other hand, the levels of hs-CRP and HOMA-IR were similar between men and women. Levels of adiponectin and hs-CRP, but not of leptin, increased with age in men and women (all $p<0.001$, for trend) (Fig. 1). In contrast, levels of HOMA-IR increased with age in women ($p=0.027$, for trend) but not in men.

The age- and sex-adjusted correlation coefficients between the biomarkers and the metabolic risk factors are shown in Table 2. Significant correlations existed between the biomarkers and the metabolic risk factors, as well as within the biomarkers. Body mass index and WC were major correlates for adiponectin, leptin, and hs-CRP, especially for leptin. Specifically, adiponectin was negatively associated with body mass index, WC, SBP, DBP, plasma glucose, insulin, HOMA-IR, leptin, and hs-CRP. In contrast, both leptin and hs-CRP had positive associations with the metabolic risk factors. Among the three biomarkers, leptin had the highest correlations with all metabolic risk factors. Similar associations were observed in the nondiabetic normotensive subgroup, except that the correlations with SBP and DBP were markedly enhanced for adiponectin but diminished for leptin. Therefore, adiponectin was the strongest correlate for blood pressure among the three biomarkers in the nondiabetic normotensive subgroup (Table 2).

Table 3. Associations of Adiponectin, Leptin, and hs-CRP with Systolic Blood Pressure

	Standardized regression parameter				
	Model 1	Model 2	Model 3	Model 4	Model 5
All participants, $n=2,045$					
	$r^2=0.14$	$r^2=0.16$	$r^2=0.14$	$r^2=0.15$	$r^2=0.15$
Age, years	0.28**	0.28**	0.27**	0.27*	0.27**
Sex†	−0.06**	−0.06**	−0.06**	−0.04	−0.06*
BMI, kg/m^2	0.14**	0.15**	0.14**	0.16**	0.13**
WC, cm	0.11**	0.10**	0.11**	0.11**	0.11**
HOMA-IR		0.02			
Adiponectin, μg/mL			0.03		
Leptin, ng/mL				−0.04	
hs-CRP, mg/dL					0.02
Non-diabetic normotensive subgroup, $n=1,512$					
	$r^2=0.10$	$r^2=0.12$	$r^2=0.11$	$r^2=0.11$	$r^2=0.11$
Age, years	0.25**	0.25**	0.26**	0.24**	0.24**
Sex†	−0.06*	−0.06*	−0.05*	−0.04*	−0.06*
BMI, kg/m^2	0.20**	0.21**	0.19**	0.22**	0.20**
WC, cm	−0.00	−0.04	−0.01	−0.00	−0.00
HOMA-IR		0.06			
Adiponectin, μg/mL			−0.06*		
Leptin, ng/mL				−0.05	
hs-CRP, mg/dL					0.03

*$p<0.05$; **$p<0.001$. †1 = men; 2 = women. BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; WC, waist circumference. Age, sex, BMI, and WC are established predictors for systolic blood pressure and the independent relationships are summarized as Model 1. Other parameters were examined in Models 2–5 by adding one parameter to Model 1 at a time sequentially.

Adiponectin, Leptin, hs-CRP, and Blood Pressure

In multiple linear regression analysis, age, sex, body mass index, and WC were all independently correlated with SBP (Table 3, Model 1). Neither HOMA-IR (Table 3, Model 2), adiponectin (Table 3, Model 3), leptin (Table 3, Model 4), nor hs-CRP (Table 3, Model 5) was associated with SBP after adjusting for age, sex, body mass index, and WC in the whole study population. In contrast, in the nondiabetic normotensive subgroup, age, sex, and body mass index, but not WC, remained independently correlated with SBP. After adjustment for age, sex, body mass index, and WC, only adiponectin (Table 3, Model 3, lower panel) was independently associated with SBP ($p=0.023$). When HOMA-IR was added to Model 3, neither HOMA-IR (standardized regression parameter $=0.05$, $p=0.084$) nor adiponectin (-0.04, $p=0.217$) was significantly associated with SBP. Similarly, only adiponectin was independently associated with DBP when age, sex, body mass index, and WC were accounted for (data not shown).

In multiple logistic regression analysis (Table 4), age, sex, body mass index, and WC were independent predictors of the presence of hypertension. Neither HOMA-IR, adiponectin, leptin, nor hs-CRP could predict the presence of hypertension when age, sex, body mass index, and WC were accounted for. In contrast, in the nondiabetic normotensive subgroup, HOMA-IR and adiponectin, but not leptin or hs-CRP, predicted the presence of pre-hypertension independently of age, sex, body mass index, and WC (Table 4, lower panel).

In the nondiabetic normotensive subgroup, the subjects with high HOMA-IR (above median, 2.9 for men and 2.8 for women) and low serum adiponectin (below median, 7.3 μg/mL for men and 9.8 μg/mL for women) had significantly higher systolic blood pressure than those with low HOMA-IR and high serum adiponectin (119.8 ± 10.7 mmHg *vs.* 117.8 ± 10.7 mmHg, $p=0.014$). The presence of both high HOMA-IR and low serum levels of adiponectin presented the highest odds ratio (OR) for the prediction of prehypertension (OR = 2.03, 95% confidence interval [CI] = 1.46–2.84) with reference to the subgroup with low HOMA-IR and high adiponectin, after adjusting for age, sex, body mass index, and WC.

Discussion

The present study demonstrated high correlations of body mass index and WC with adiponectin, leptin, and hs-CRP. None of the markers for the metabolic syndrome, adipose tissue mass, and inflammation were associated with blood pressure or the presence of hypertension, independently of age, sex, body mass index, and WC. However, in the nondiabetic

Table 4. Associations of Adiponectin, Leptin, and hs-CRP with the Presence or Absence of Hypertension or Pre-Hypertension

	OR (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Model 5
All participants (hypertension as dependent variable), $n=2,045$					
	$C=0.67$	$C=0.69$	$C=0.68$	$C=0.70$	$C=0.67$
Age, years	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.03 (1.02–1.04)	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Sex†	0.73 (0.58–0.92)	0.70 (0.55–0.91)	0.69 (0.54–0.88)	0.77 (0.58–1.003)	0.74 (0.59–0.93)
BMI, kg/m^2	1.04 (1.00–1.09)	1.05 (1.00–1.10)	1.05 (1.01–1.10)	1.05 (1.002–1.05)	1.04 (0.996–1.09)
WC, cm	1.04 (1.02–1.05)	1.04 (1.02–1.05)	1.04 (1.02–1.05)	1.04 (1.02–1.05)	1.04 (1.02–1.05)
HOMA-IR		1.02 (0.97–1.07)			
Adiponectin, μg/mL			1.02 (0.999–1.05)		
Leptin, ng/mL				0.99 (0.96–1.02)	
hs-CRP, mg/dL					1.01 (0.76–1.35)
Non-diabetic normotensive subgroup (pre-hypertension as dependent variable), $n=1,512$					
	$C=0.65$	$C=0.67$	$C=0.66$	$C=0.37$	$C=0.65$
Age, years	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.04 (1.02–1.05)	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Sex†	0.71 (0.56–0.91)	0.67 (0.52–0.88)	0.78 (0.60–0.997)	0.73 (0.55–0.97)	0.71 (0.55–0.90)
BMI, kg/m^2	1.11 (1.06–1.17)	1.11 (1.06–1.17)	1.10 (1.05–1.15)	1.12 (1.06–1.18)	1.11 (1.06–1.16)
WC, cm	1.01 (0.99–1.03)	1.00 (0.99–1.02)	1.01 (0.99–1.02)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
HOMA-IR		1.02 (1.09–1.32)			
Adiponectin, μg/mL			0.96 (0.94–0.99)		
Leptin, ng/mL				0.99 (0.97–1.02)	
hs-CRP, mg/dL					1.12 (0.81–1.55)

†1 = men; 2 = women. BMI, body mass index; *C*, *C* statistics for logistic regression analysis; CI, confidence interval; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; WC, waist circumference. Age, sex, BMI, and WC are established predictors for hypertension and the independent relationships are summarized as Model 1. Other parameters were examined in Models 2–5 by adding one parameter to Model 1 at a time sequentially.

normotensive subgroup, associations with blood pressure and the presence of pre-hypertension independently of body mass index and WC were established for adiponectin but not for leptin or hs-CRP.

Adiponectin in the Early Stage of Hypertension

Adiponectin has insulin-sensitizing, anti-atherosclerotic, and anti-inflammatory effects, and hypoadiponectinemia predicts the development of metabolic syndrome, new diabetes, and atherosclerotic cardiovascular events (*5*, *13–15*). Hypothetical pathways leading from hypoadiponectinemia to hypertension have been proposed (*16*). Hypoadiponectinemia may cause insulin resistance, endothelial dysfunction, activation of the inflammatory cascade, and vascular hypertrophy and stiffness, all of which are involved in the pathogenesis of hypertension (*16*, *17*). Furthermore, a direct role of adiponectin on blood pressure regulation has been investigated in adiponectin-knockout mice: a high-salt diet induced hypertension even in the absence of insulin resistance, and adiponectin therapy lowered the elevated blood pressure (*18*).

On the other hand, the epidemiological association between adiponectin and blood pressure has not been fully established. The inverse associations between adiponectin and SBP and/or DBP independently of body mass index were shown in Japanese men and women not taking any medication for metabolic disease (*19*), and in healthy Taiwanese female adolescents (*20*). In contrast, no associations between adiponectin levels and blood pressure were found, with or without adjustment for age and body mass index, in Japanese men and women (*19*), in overweight/obese Taiwanese subjects, in newly diagnosed and formerly untreated hypertensive young Turkish males (*21*), and in nondiabetic high-risk Caucasian patients undergoing coronary angiography (*22*). More recently, the relationship between serum adiponectin and the development of hypertension was investigated in a nested case-control study (*9*). Baseline serum adiponectin was a significant independent predictor of incident hypertension at year 5 (*9*). Although the results suggest that hypoadiponectinemia may be involved in the pathogenesis of hypertension in humans, the causal relationship remains to be examined in future cohort studies (*16*).

In the present study, independent associations between low serum adiponectin levels and both SBP and prehypertension were shown only in the nondiabetic normotensive subgroup. The absence of an independent association between serum adiponectin and blood pressure in the whole study population may be attributable in part to the fact that interactions among various metabolic factors, sympathetic activation, and renin-angiotensin stimulation commonly observed in established

hypertension could interfere with serum adiponectin levels and/or mask the influence of adiponectin on blood pressure (*23*, *24*). On the other hand, the independent association observed in the nondiabetic normotensive subgroup was consistent with observations in other studies involving normotensives (*25*), subjects with high-normal blood pressure (*26*), and young adults with a family history of essential hypertension (*27*, *28*). These positive studies, including the present one, support a role of adiponectin in the early stage of hypertension.

The findings that leptin and hs-CRP were not independently associated with blood pressure or pre-hypertension in the nondiabetic normotensive subgroup suggest that adiponectin is more important than leptin and hs-CRP in the pathogenesis of hypertension. These findings may also be useful in elucidating the roles of total adipose tissue mass and subclinical chronic inflammation in the pathogenesis of hypertension. The relationship between hyperleptinemia and hypertension remains controversial, and leptin may mainly be involved in the sympathetic activation commonly found in obese hypertensive patients (*29*). In the present study, leptin had apparently greater correlations with body mass index, WC, and HOMA-IR than did adiponectin and hs-CRP, indicating that leptin is strongly dependent on general or abdominal obesity. It may be reasonable to speculate that the association between leptin and blood pressure or hypertension is mainly due to the strong relationship between blood leptin levels and the extent of obesity.

High hs-CRP levels have been associated with prevalent (*30*, *31*) and incident hypertension (*10*, *11*). However, the role of inflammation in the development of hypertension cannot be considered established without more longitudinal studies involving more diverse ethnicities (*31*). Hypertension prevalence varies considerably across countries and ethnic groups. It has been shown in a multi-ethnic cohort of men and women that the difference in hs-CRP by hypertension status was largest in Chinese participants, followed by Caucasians and African-Americans, whereas Hispanics had no significant difference in hs-CRP by hypertension status (*31*). It has been shown that obesity is characterized by a state of chronic low-grade inflammation and that hs-CRP is associated with total body fat in adults and adolescents (*32*). Therefore, our results may suggest that the association between hs-CRP and blood pressure or hypertension is partly due to the relationship between hs-CRP levels and the extent of obesity.

Insulin Resistance and Adiponectin

Insulin resistance has been a hallmark of the metabolic syndrome until recently, when the importance of abdominal obesity and adiponectin in the syndrome's pathogenesis was recognized (*33*). Substantial ethnic differences exist in the association between insulin resistance and hypertension (*34*), and insulin resistance may be significant to the pathogenesis of hypertension mainly in the early stage of hypertension or in subjects without diabetes (*3*, *34*). There were complex interactions between insulin resistance and adiponectin, and recent studies indicated that insulin resistance may be the downstream result of hypoadiponectinemia (*16*, *35*). In the present study, the level of adiponectin, but not that of HOMA-IR, was associated with blood pressure, and both levels were predictors of prehypertension, independently of age, sex, body mass index, and WC in the nondiabetic normotensive subgroup. Although the interaction between adiponectin and insulin resistance in the cardiovascular system is complex and remains to be clarified (*13*), our results may suggest that low levels of adiponectin and high HOMA-IR synergistically predict the presence of pre-hypertension.

Limitations of the Present Study

The present study was a cross-sectional design that precluded the establishment of a causal relationship between the biomarkers and the development of hypertension.

In conclusion, adiponectin, but not leptin or hs-CRP, was independently associated with blood pressure and pre-hypertension in a nondiabetic normotensive subgroup. This may support the hypothesis that metabolic syndrome, but not the amount of adipose tissues or chronic inflammation, is involved in the early stage of hypertension.

References

1. Chobanian AV, Bakris GL, Black HR, *et al*: The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
2. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome—a new worldwide definition. *Lancet* 2005; **366**: 1059–1062.
3. Chuang SY, Chou P, Hsu PF, *et al*: Presence and progression of abdominal obesity are predictors of future high blood pressure and hypertension. *Am J Hypertens* 2006; **19**: 788–795.
4. Jazet IM, Pijl H, Meinders AE: Adipose tissue as an endocrine organ: impact on insulin resistance. *Neth J Med* 2003; **61**: 194–212.
5. Brooks NL, Moore KS, Clark RD, *et al*: Do low levels of circulating adiponectin represent a biomarker or just another risk factor for the metabolic syndrome? *Diabetes Obes Metab* 2007; **9**: 246–258.
6. Beltowski J: Role of leptin in blood pressure regulation and arterial hypertension. *J Hypertens* 2006; **24**: 789–801.
7. Hak AE, Stehouwer CD, Bots ML, *et al*: Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol* 1999; **19**: 1986–1991.
8. Barba G, Russo O, Siani A, *et al*: Plasma leptin and blood pressure in men: graded association independent of body mass and fat pattern. *Obes Res* 2003; **11**: 160–166.
9. Chow WS, Cheung BM, Tso AW, *et al*: Hypoadiponectine-

mia as a predictor for the development of hypertension: a 5-year prospective study. *Hypertension* 2007; **49**: 1455–1461.
10. Engstrom G, Janzon L, Berglund G, *et al*: Blood pressure increase and incidence of hypertension in relation to inflammation-sensitive plasma proteins. *Arterioscler Thromb Vasc Biol* 2002; **22**: 2054–2058.
11. Sesso HD, Buring JE, Rifai N, *et al*: C-reactive protein and the risk of developing hypertension. *JAMA* 2003; **290**: 2945–2951.
12. Wasim H, Al Daghri NM, Chetty R, *et al*: Relationship of serum adiponectin and resistin to glucose intolerance and fat topography in South-Asians. *Cardiovasc Diabetol* 2006; **5**: 10.
13. Hopkins TA, Ouchi N, Shibata R, *et al*: Adiponectin actions in the cardiovascular system. *Cardiovasc Res* 2007; **74**: 11–18.
14. Duncan BB, Schmidt MI, Pankow JS, *et al*: Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes* 2004; **53**: 2473–2478.
15. Pischon T, Girman CJ, Hotamisligil GS, *et al*: Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; **291**: 1730–1737.
16. Schillaci G, Pirro M: Hypoadiponectinemia: a novel link between obesity and hypertension? *Hypertension* 2007; **49**: 1217–1219.
17. Han SH, Quon MJ, Kim JA, *et al*: Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol* 2007; **49**: 531–538.
18. Ohashi K, Kihara S, Ouchi N, *et al*: Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* 2006; **47**: 1108–1116.
19. Yamamoto Y, Hirose H, Saito I, *et al*: Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin Sci* (*Lond*) 2002; **103**: 137–142.
20. Huang KC, Chen CL, Chuang LM, *et al*: Plasma adiponectin levels and blood pressures in nondiabetic adolescent females. *J Clin Endocrinol Metab* 2003; **88**: 4130–4134.
21. Dogru T, Sonmez A, Tasci I, *et al*: Plasma adiponectin and insulin resistance in new onset hypertension. *Endocrine* 2006; **29**: 405–408.
22. Cesari M, Pessina AC, Zanchetta M, *et al*: Low plasma adiponectin is associated with coronary artery disease but not with hypertension in high-risk nondiabetic patients. *J Intern Med* 2006; **260**: 474–483.
23. Imai J, Katagiri H, Yamada T, *et al*: Cold exposure suppresses serum adiponectin levels through sympathetic nerve activation in mice. *Obesity* (*Silver Spring*) 2006; **14**: 1132–1141.
24. Furuhashi M, Ura N, Higashiura K, *et al*: Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension* 2003; **42**: 76–81.
25. Iwashima Y, Katsuya T, Ishikawa K, *et al*: Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004; **43**: 1318–1323.
26. Kazumi T, Kawaguchi A, Sakai K, *et al*: Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. *Diabetes Care* 2002; **25**: 971–976.
27. Furuhashi M, Ura N, Higashiura K, *et al*: Low adiponectin level in young normotensive men with a family history of essential hypertension. *Hypertens Res* 2005; **28**: 141–146.
28. Patel DA, Srinivasan SR, Xu JH, *et al*: Adiponectin and its correlates of cardiovascular risk in young adults: the Bogalusa Heart Study. *Metabolism* 2006; **55**: 1551–1557.
29. Sharma AM, Chetty VT: Obesity, hypertension and insulin resistance. *Acta Diabetol* 2005; **42** (Suppl 1): S3–S8.
30. Bautista LE, Lopez-Jaramillo P, Vera LM, *et al*: Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens* 2001; **19**: 857–861.
31. Lakoski SG, Cushman M, Palmas W, *et al*: The relationship between blood pressure and C-reactive protein in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol* 2005; **46**: 1869–1874.
32. Warnberg J, Nova E, Moreno LA, *et al*: Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study. *Am J Clin Nutr* 2006; **84**: 505–512.
33. Carr DB, Utzschneider KM, Hull RL, *et al*: Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes* 2004; **53**: 2087–2094.
34. Saad MF, Rewers M, Selby J, *et al*: Insulin resistance and hypertension: the Insulin Resistance Atherosclerosis study. *Hypertension* 2004; **43**: 1324–1331.
35. Bonora E, Kiechl S, Willeit J, *et al*: Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. *Diabetes Care* 2007; **30**: 318–324.