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Adiponectin and progression of arterial stiffness in hypertensive patients

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ABSTRACT

Background: Recent studies suggest that adiposity is associated with arterial stiffness. However, it is unclear which adipokine or what adiposity related parameters are related with the progression of arterial stiffness. We hypothesized that in hypertensive patients, initial levels of adipokines such as adiponectin and resistin are related to the progression of arterial stiffness, which has been proven to be associated with increased risk of cardiovascular events.

Methods: One hundred forty one consecutive patients with treated essential hypertension (81 men, 57.7 ± 8.2 years) were enrolled. Pulse wave velocity (PWV) was measured at baseline, and after 24 months. Clinical variables and laboratory findings at the time of initial enrollment were analyzed to reveal the determinants of arterial stiffening.

Results: Mean heart to femoral PWV (hfPWV) was 992 ± 202 cm/s at baseline, and 1021 ± 263 cm/s at 24 months follow up. hfPWV progressed in seventy two patients (51.1%) during follow up period. In patients with hfPWV progression, mean plasma adiponectin level was significantly lower than patients with nonprogression (progressor: 5.18 ± 3.21 μg/ml, non-progressor: 7.02 ± 5.19 μg/ml, $p = 0.013$). Multivariate regression analysis revealed plasma adiponectin level to being an independent predictor of hfPWV changes (ß = −0.018, $p = 0.032$) when controlled for age, gender, SBP changes, BP control and HOMA.

Conclusions: Plasma adiponectin levels are associated with progression of arterial stiffness in hypertensive patients. These findings may be one explanation for the high association between adiposity and arterial stiffness in hypertensive patients.

1. Introduction

Arterial stiffening is a process of structural changes in the central arteries that are accompanied by arterial dilatation, elastin degradation, increased collagen and vascular smooth muscle cell proliferation in the intima media of the arterial wall [1,2]. Arterial stiffness is pathophysiologically linked with increased systolic blood pressure, increased pulse pressure and decreased diastolic blood pressure, predisposing the patients to increased risk of heart failure and coronary artery disease [3,4]. Studies have shown that arterial stiffness is an independent predictor of cardiovascular mortality in hypertensive subjects [3,5].

Previous studies suggest that adiposity is associated with increased risk of cardiovascular disease [6,7]. Among the adipokines that are pathophysiologically linked with adiposity, adiponectin has been demonstrated to be an important mediator between adiposity and cardiovascular disease, with hypoadiponectinemia being demonstrated to be associated with endothelial dysfunction, increased vascular inflammation, increased vascular proliferation and increased oxidative stress in the vascular system [8–11].

In cross sectional studies, adiposity has been linked to increased arterial stiffness [1,12,13]. Therefore, adiponectin could have a pathophysiological role in the progression of arterial stiffness. However, to our knowledge, there have not been any studies done regarding the relationship between adiponectin and the progression of arterial stiffness. Störk et al. have reported low level of adiponectin predict worsening of arterial morphology and function. However population of this study was confined to the postmenopausal non-diabetic women with increased carotid intima-media thickness (IMT) and arterial stiffness was measured by carotid distensibility using ultrasound [14]. Therefore we sought to determine the association of baseline plasma adiponectin level with progression of arterial stiffness in a prospective cohort of treated hypertensive patients with biannual follow-up of pulse wave velocity.

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2. Materials and methods

2.1. Study population

The study population consisted of 141 hypertensive patients diagnosed and treated at the Yonsei Cardiovascular Hospital as part of the Yonsei cardiovascular genome center cohort. The cohort consisted of 141 consecutive hypertensive patients who were enrolled in the Yonsei cardiovascular genome center cohort and consented to the baseline and follow up pulse wave velocity measurement. The average age was 57.7 ± 8.2 years (41 to 80, M:F = 81:60). For the purpose of this study, we recruited hypertensive subjects with either a documented systolic blood pressure greater than 140 mm Hg and/or a diastolic blood pressure greater than 90 mm Hg after at least 5 min rest in a sitting position, over three different visits prior to blood pressure medication. Also, patients currently taking antihypertensive medications for treatment of hypertension were enrolled. Patients with any of the following conditions were excluded from participation: prior myocardial infarction, unstable angina, congestive heart failure, valvular heart disease, peripheral vascular disease, malignant debilitating disease, severe respiratory disease, renal failure (creatinine > 1.4 mg/dL), anemia (hemoglobin < 12 g%), history of inflammatory disease and/or on anti inflammatory medications, clinically significant atrioventricular conduction disturbance, history of atrial fibrillation or other serious arrhythmia, malignant hypertension (>200/140 mm Hg).

This study received prior approval from the institutional ethics committee, and the procedures followed were in accordance with the institutional guidelines. All patients gave informed consent prior to being enrolled.

2.2. Adipokine measurements

The plasma adiponectin level was measured by radioimmunoassay using Human Adiponectin RIA Kit (Millipore, Missouri, USA). The lower limit of the plasma adiponectin was 1 ng/mL; The intra- and interassay coefficients of variation (CVs) were 6.2% and 6.9% respectively. The plasma resistin level was measured by ELISA using Quantikine Human Resistin Immunoassay Kit (R&D Systems, Minneapolis, USA). The lower limit of the plasma resistin was 0.026 ng/mL; intra- and interassay coefficients of variation (CVs) were 3.8% and 7.8% respectively.

2.3. Anthropometric measurements

Body weight and height were measured without shoes and in light clothing, and body mass index (BMI) was calculated. Waist circumference, an index of total abdominal fat, was measured at the midpoint between the lower border of the rib cage and the iliac crest, at the narrowest section of waist. Hip circumference was measured at the level of maximal extension of the buttocks when viewed laterally. Mean waist circumference and hip circumference values were determined from 3 measurements using a non-stretchable measuring tape and were used to calculate waist hip ratio (WHR). Total body fat percent was quantified using TBF-105 body fat analyzer (Tanita, Tokyo, Japan).

2.4. Blood pressure and pulse wave velocity measurements

The blood pressure was measured with the dominant arm after being seated for 5 min using a mercury sphygmomanometer. The blood pressure was measured twice at 5 minute intervals and the average value used for analysis. The blood pressure was measured before the measurement of pulse wave velocity. The pulse wave velocity was determined by measuring the hfPWV and baPWV with a VP-2000 pulse wave unit (Nippon Colin Ltd, Komaki City, Japan) as described previously [15]. Briefly, after an overnight fast and 5 min rest, the PWV was measured from a supine position. Carotid and femoral artery pressure waveforms were recorded in multi-element tonometry sensors at the left carotid and the left femoral arteries. The electrocardiogram was monitored by electrodes on both wrists. The heart sounds S1 and S2 were detected by a microphone on the left edge of the sternum at the third intercostal space. The waveform analyzer measures the time intervals between S2 and the notch of the carotid pulse wave (Thc), and again between the carotid and femoral artery pulse waves (Tcf). The sum of the Thc and Tcf gives the time required for pulse waves to travel from the heart (aortic orifice) to the femoral artery (Thf). The hfPWV, a marker for central aortic stiffness, was calculated from the equation Lhf/(Thc + Tcf), where Lhf is the distance from the heart to the femoral artery. The baPWV, a marker for both central and peripheral arterial stiffness, was calculated from the equation (D1 − D2)/T, where D1 is the distance between the heart and ankle, D2 is the distance between the heart and brachium, and T is the transit time between the right brachial artery wave and right tibial artery wave. The Lhf and the distance between the sampling points are calculated from the patient height and divided by the time interval for the waveform from each measuring point.

2.5. Statistical analysis

Continuous variables were summarized as a mean ± SD. Categorical variables were summarized as a percentage of the group total. Discrete variables were compared using the chi-squared method, and independent t-tests were used for continuous variables. Pearson's correlation analysis was used for the simple correlation between continuous variables.

Independent predictors of baPWV and hfPWV progression were determined using a multiple linear regression analysis. For the multiple linear regression model, variables that were significant at the $p<0.05$ level based on a simple linear regression analysis, and/or those known to be significantly associated with adiponectin, were entered in the linear regression analysis. All statistical analyses were performed with SPSS 13.0. (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics and laboratory findings

Mean heart to femoral PWV (hfPWV) was 992 ± 202 cm/s at baseline, and 1021 ± 263 cm/s at 24 months follow up. hfPWV progressed in seventy two patients (51.1%) during follow up period. Overall blood pressure control status was acceptable in this cohort, both at the initial enrollment (SBP controlled 80.1%, DBP controlled 88.7%; SBP < 140 mm Hg, DBP < 90 mm Hg in non-diabetic patients and SBP < 130 mm Hg, DBP < 80 mm Hg in diabetic patients) and at the 2-year follow up (SBP controlled 79.4%, DBP controlled 88.7%; same criteria as above). The clinical characteristics and laboratory findings of the study population between patients with progression of arterial stiffness (progressor) and nonprogression of arterial stiffness (non-progressor) are shown in Table 1. Blood pressure changes at follow up, both changes in systolic blood pressure at follow up (7.0 ± 15.6 vs. −6.7 ± 14.0, $p<0.001$) and changes in diastolic blood pressure at follow up (3.6 ± 10.5 vs. −4.2 ± 9.1, $p<0.001$) were significantly different between two groups. Also, the percentage of patients who had their blood pressure controlled below the target blood pressure was significantly different between progressors and non-progressors (Table 1). In patients with hfPWV progression, mean plasma adiponectin level was significantly lower than patients with non-progression (progressor: 5.18 ± 3.21 μg/ml, non-progressor: 7.02 ± 5.19 μg/ml, $p = 0.013$). However,

Table 1
Clinical characteristics and laboratory findings between progressors and non-progressors.

	Progressor (N = 72)	Non-progressor (N = 69)	*P*-value*
Age (years)	57.9 ± 8.8	57.5 ± 7.5	0.807
Male (%)	44 (61.1%)	37 (53.6%)	0.398
SBP changes (mm Hg)	7.0 ± 15.6	−6.7 ± 14.0	<0.001
DBP changes (mm Hg)	3.6 ± 10.5	−4.2 ± 9.1	<0.001
SBP control	50 (69.4%)	62 (89.9%)	0.003
DBP control	58 (80.6%)	67 (97.1%)	0.003
Smoking (%)	8 (11.1%)	6 (8.7%)	0.442
DM (%)	6 (8.3%)	6 (8.7%)	0.588
CAD (%)	24 (33.3%)	21 (30.4%)	0.426
Hyperlipidemia (%)	29 (40.3%)	22 (31.9%)	0.381
Body Weight (kg)	67.7 ± 10.3	65.1 ± 10.6	0.143
BMI (kg/m^2)	25.2 ± 2.7	24.8 ± 2.8	0.391
WC (cm)	89.3 ± 8.3	87.9 ± 8.6	0.321
WHR	0.905 ± 0.055	0.890 ± 0.051	0.107
Total body fat (%)	28.2 ± 6.8	27.8 ± 6.9	0.741
T. chol (mg/dL)	181.3 ± 42.7	175.2 ± 37.7	0.374
TG (mg/dL)	156.6 ± 99.7	141.1 ± 92.1	0.338
HDL (mg/dL)	48.4 ± 11.9	52.5 ± 15.0	0.078
LDL (mg/dL)	102.0 ± 38.6	97.0 ± 34.4	0.435
FBS (mg/dL)	99.0 ± 33.8	93.0 ± 17.5	0.194
HOMA	2.48 ± 1.13	2.18 ± 1.13	0.122
BUN (mg/dL)	15.8 ± 5.3	15.9 ± 5.6	0.909
Creatinine (mg/dL)	0.82 ± 0.26	0.84 ± 0.46	0.640
Uric acid (mg/dL)	5.37 ± 1.48	5.02 ± 1.15	0.121
Adiponectin (μg/mL)	5.18 ± 3.21	7.02 ± 5.19	0.013
Resistin (ng/mL)	6.48 ± 3.79	5.93 ± 4.16	0.414

Values are presented as n (%) or mean ± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; SBP control, SBP <140 mm Hg for non-diabetic patients and SBP <130 mm Hg for diabetic patients; DBP control, DBP <90 mm Hg for non-diabetic patients and DBP <80 mm Hg for diabetic patients; DM, diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; WC, waist circumference; WHR, waist hip ratio; T. chol, Total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBS, fasting blood sugar. *p-value<0.05 is considered significant.