Adiponectin and progression of arterial stiffness in hypertensive patients

Jong-Chan Youn a, Changsoo Kim c, Sungha Park a,b,*, Sang-Hak Lee a, Seok-Min Kang a, Donghoon Choi a, Nak Hoon Son b, Dong-Jik Shin b, Yangsoo Jang a,b

a Division of Cardiology, Yonsei Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea
b Cardiovascular Genome Center, Yonsei Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea
c Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 5 February 2011
Received in revised form 18 May 2011
Accepted 9 June 2011
Available online 2 July 2011

Keywords:
Adiponectin
Arterial stiffening
Vascular aging

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 progress, 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 (β = −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.

© 2011 Elsevier Ireland Ltd. All rights reserved.

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.
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. 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 mmHg and/or a diastolic blood pressure greater than 90 mmHg 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, malignancy, debilitating disease, severe respiratory disease, renal failure (creatinine >1.4 mg/dL), anemia (hemoglobin <12 g/dL), history of inflammatory disease and/or on anti-inflammatory medications, clinically significant ativoventricular conduction disturbance, history of atrial fibrillation or other serious arrhythmia, malignant hypertension (~200/140 mmHg).

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 6.9% and 8.9%, respectively. The plasma adiponectin 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; the 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 min intervals and the average value used for analysis. 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 min intervals and the average value used for analysis. 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 min intervals and the average value used for analysis.

The pulse wave velocity was determined by the method of PWV, and baPWV with a VP-2000 pulse wave unit (Nipppon 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 notches 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 PWV, 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 two groups 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,
plasma resistin level and other adiposity related parameters, such as BMI, waist circumference, WHR, total body fat percent did not show any significant differences between progressor and non-progressor.

There were no significant differences in the proportion of patients taking ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, or statins (Table 2).

3.2. Determinants of arterial stiffening

Initial adiponectin levels showed significant inverse correlation with hfPWV progression (p = 0.02). However, there was no significant correlation between adiponectin level and baPWV changes. Overall blood pressure control status during follow-up period, which was designated as 'BP control' was a significant factor (r = −0.389, p < 0.001 for ΔhfPWV progression; r = −0.341, p < 0.001 for ΔbaPWV progression) for arterial stiffening. Adiponectin level showed significant correlation with age (p = 0.028), gender (p < 0.001), and HOMA (p = 0.008).

Multiple linear regression analysis revealed plasma adiponectin level to being an independent predictor of hfPWV changes (β = −0.018, p = 0.032) when controlled for age, gender, SBP changes, BP control (blood pressure controlled below target blood pressure) and HOMA (Table 3). Adiponectin was associated with progression of arterial stiffness even after adjusting both acute blood pressure changes (SBP changes) and overall blood pressure control status (BP control).

The plasma level of adiponectin was followed up in 141 all patient. Initial level of adiponectin was shown to be well correlated with 2-year follow up level (r = 0.001, r² = 0.5505). High association between initial and follow up adiponectin level revealed that initial adiponectin level, as itself, could be used as a predictor for arterial stiffening in hypertensive patients. There were no significant relationships between adiponectin changes and PWV changes (either hfPWV changes or baPWV changes) in our study.

4. Discussion

The present study is, to our knowledge, the first to demonstrate the association of adiponectin with progression of arterial stiffness in hypertensive subjects. Adiponectin, which is a good marker of adiposity, was revealed to predict the progression of arterial stiffness after adjusting for age, gender, blood pressure and metabolic parameters. Acute hemodynamic changes in blood pressure could be a strong confounding factor in measuring pulse wave velocity. Adiponectin was associated with arterial stiffness progression despite controlling for both the changes in blood pressure between baseline and follow-up and for overall blood pressure control status. These findings may be one explanation for the high association between adiposity and arterial stiffness in hypertensive patients.

4.1. Adiponectin and hypertension

The association between adiposity and hypertension has been recognized for decades. Recent studies indicate that hypoadiponectinemia, which is a good marker of visceral adiposity, has also shown to be an independent risk factor for hypertension development, both in a cross-sectional study [16] and in a prospective study [8]. Chow et al. demonstrated a significant, inverse relationship between plasma adiponectin level and the future development of hypertension in 5-year prospective study of a normotensive non-diabetic population [8]. The association between low adiponectin and future hypertension was independent from the effect of insulin resistance or hsCRP, an index of low-grade systemic inflammation. Since increased arterial stiffness is associated with increased systolic blood pressure and pulse pressure, our findings may partially explain the pathogenic role of adiponectin in human hypertension. The association between adiponectin and arterial stiffening may be explained by several possible mechanisms. Firstly, adiponectin is known to have a direct vasculoprotective effect and may stimulate the activity of endothelial nitric oxide synthase via the serine phosphorylation activity of AMP activated protein kinase [8,17]. Secondly, hypoadiponectinemia is associated with heightened VSMC (vascular smooth muscle cell) proliferation in response to arterial injury. In a study by Matsuda et al., neointimal thickening and VSMC proliferation was exaggerated in adiponectin deficient mouse. Transfection of adiponectin producing adenovirus into the same mice resulted in attenuated neointimal proliferation similar to control [11]. The heightened VSMC proliferative response to injury may explain one possible mechanism for the association of hypoadiponectinemia with arterial stiffening.

It is interesting to note that adiponectin was significantly associated with hfPWV, an index of central arterial stiffness, but not with baPWV, which is an index of both central and peripheral arterial stiffness index [15]. Perhaps this may be explained by the fact that central artery remodeling involves VSMC hypertrophy, vascular inflammation, and accumulation of extracellular matrix components such as collagen and fibronectin [18,19], pathophysiological processes that are known to be associated with hypoadiponectinemia. In contrast, because small arterial remodeling is characterized predominantly inward eutrophic remodeling with an increase in the media cross sectional area having minor contribution to the remodeling process, adiponectin may have minimal influence on the remodeling process of peripheral arteries [18,20–23].

Resistin, which was known to be a systemic marker of vascular inflammation [24], was revealed not to be associated with the progression of arterial stiffness in this study. High plasma resistin level is known to be associated with enhanced hsCRP [25] and both resistin and hsCRP are good markers of low grade systemic inflammation. However, they might not have a causal role in the

Table 3

<table>
<thead>
<tr>
<th>β</th>
<th>Standard error</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log ΔhfPWV (R² = 0.333)</td>
<td>Age</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.009</td>
<td>0.011</td>
</tr>
<tr>
<td>SBP changes</td>
<td>0.002</td>
<td>−0.001</td>
</tr>
<tr>
<td>BP control</td>
<td>−0.038</td>
<td>0.013</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.006</td>
<td>0.005</td>
</tr>
<tr>
<td>Log adiponectin</td>
<td>−0.018</td>
<td>0.008</td>
</tr>
</tbody>
</table>

| Log ΔbaPWV (R² = 0.426) | Age | 0.001 | 0.001 | 0.238 |
| Male gender | 0.002 | 0.019 | 0.919 |
| SBP changes | 0.005 | 0.001 | <0.001 |
| BP control | −0.026 | 0.022 | 0.254 |
| HOMA | 0.020 | 0.008 | 0.010 |
| Log adiponectin | −0.004 | 0.014 | 0.762 |

β, unstandardized coefficient; hfPWV, heart to femoral pulse wave velocity; baPWV, brachial to ankle pulse wave velocity; SBP changes, systolic blood pressure changes during follow up period; BP control, the patients had their blood pressure controlled below the target blood pressure.

* P < 0.05 is considered significant.

Table 2

<table>
<thead>
<tr>
<th>Antihypertensive medication at the time of initial enrollment.</th>
<th>Progressor (N = 72)</th>
<th>Non-progressor (N = 69)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors (%)</td>
<td>8 (11.1%)</td>
<td>9 (13.0%)</td>
<td>0.799</td>
</tr>
<tr>
<td>ARB (%)</td>
<td>31 (43.1%)</td>
<td>27 (39.1%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>33 (45.8%)</td>
<td>25 (36.2%)</td>
<td>0.305</td>
</tr>
<tr>
<td>CCB (%)</td>
<td>38 (52.8%)</td>
<td>44 (63.8%)</td>
<td>0.232</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>11 (15.3%)</td>
<td>13 (18.8%)</td>
<td>0.656</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>31 (43.1%)</td>
<td>29 (42.0%)</td>
<td>0.519</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin-converting enzyme receptor blocker; CCB, calcium channel blocker.
development of arterial stiffening. Rather they may simply act as a marker of vascular damage (i.e., reverse causality) [26,27].

Recently, there were several reports which cover important issues regarding the relationship between adiponectin and arterial stiffness [28–30]. Sung SH et al. reported that adiponectin, but not hs-CRP, is independently associated with both baPWV and NT-proBNP in the general population [28]. However, this study is cross-sectional design and does not explore the longitudinal changes of arterial stiffness. Öz O et al. revealed that in type II diabetic patients, treatment with thiazolidinediones (TZDs) was associated with a significant improvement in adiponectin levels, but no significant effects were seen on arterial compliance [29]. However, the limitation of the above mentioned study was the short follow up period of 12 weeks, which may be too short to observe any significant changes in arterial stiffness. Miyoshi et al. reported that treatment with olmesartan for 6 months significantly reduced arterial stiffness and the serum levels of adipocyte fatty acid binding protein (A-FABP) in hypertensive patients [30]. Also, the ameliorating effects of ARB on arterial stiffening are relatively well documented. However, there was no significant difference in the proportion of patients taking angiotensin receptor blockers between progressors and nonprogressors in our study.

4.2. Study limitations

The present study has several potential limitations. First, our study population was relatively small. There were difficulties recruiting a large number of patients due to the relatively long follow-up period of over 2 years and the strict exclusion criteria of our study. Secondly, the study was performed in treated hypertensive patients, which may confound both the measurement of arterial stiffness and the plasma level of adiponectin. However, there was no significant difference between the progressors and the nonprogressors for the types of anti-hypertensive medication, which should minimize the confounding effect of medications on the results of this study.

5. Conclusion

Hypertension is highly prevalent in obese patients. The pathogenesis of hypertension in obese patient is explained by multiple mechanisms such as insulin resistance, endothelial dysfunction, low grade systemic inflammation and vascular smooth muscle cell proliferation. However the causal relationship between adiposity, adipocytokines and hypertension has not been well defined. This study demonstrated that in hypertensive patients, adiponectin level independently predicts the progression of arterial stiffness. These dynamic relationship between adiponectin and arterial stiffening may give a meaningful contribution to the understanding the pathogenesis of human hypertension. Prospective studies in large population would be needed to reveal more clear relationship among adiponectin, arterial stiffening and subsequent major adverse cardiovascular event.

Acknowledgments

This study was supported by a grant A000385 from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea, and by a grant 2010-0020766 from the Public Welfare & Safety research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, Republic of Korea. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具