Circulating Adiponectin Levels in Patients With Atrial Fibrillation

Masayuki Shimano, MD; Rei Shibata, MD; Yukioi Tsuji, MD*; Hiromi Kamiya, MD; Tomohiro Uchikawa, MD; Shuji Harata, MD; Masahiro Muto, MD; Noriyuki Ouchi, MD**; Yasuya Inden, MD; Toyoaki Murohara, MD

Background Atrial fibrillation (AF) characterized by atrial remodeling occurs with obesity-related conditions. Adiponectin, an adipose tissue-derived hormone exerts beneficial effects on ventricular remodeling, so in the present study the potential association between circulating adiponectin levels and atrial remodeling in patients with AF was investigated.

Methods and Results The levels of plasma adiponectin, serum carboxy-terminal telopeptide of collagen type I (CITP), as a collagen type I degradation marker, and serum type III procollagen-N-peptide (PIIINP), as a collagen type III synthesis marker, were measured in 304 consecutive patients (162 paroxysmal AF, 46 persistent AF, 96 paroxysmal supra-ventricular tachycardia [controls]). Plasma adiponectin levels were significantly higher in patients with persistent AF than in those with paroxysmal AF or the control patients (p<0.05). Serum CITP levels, but not serum PIIINP levels, were higher in patients with persistent AF compared with the paroxysmal AF and control patients (p<0.05). In addition, there was a positive correlation between adiponectin levels and CITP levels in patients with persistent AF (r=0.39, p<0.005).

Conclusions High plasma adiponectin levels are associated with the presence of persistent AF, which is accompanied by increased CITP levels. Thus, measurement of plasma adiponectin could be useful for assessment of AF.

Key Words: Adiponectin; Atrial fibrillation; Biomarkers; Fibrosis; Remodeling

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. In most cases, it progresses from a paroxysmal to sustained arrhythmia. The occurrence and development of AF are associated with changes in the electrical properties and structure of the atria, known as electrical and structural remodeling. Adiponectin is an adipocyte-derived plasma protein with antidiabetic, antiatherogenic and antiinflammatory properties. We and other groups have shown that adiponectin has a protective action on the heart in various pathological conditions. Adiponectin-deficient (APN-KO) mice exhibit severe left ventricular (LV) hypertrophy after pressure-overload and develop larger infarcts following ischemia–reperfusion injury. In the absence of adiponectin subjects also developed exacerbated LV dilation, myocardial hypertrophy, interstitial fibrosis and contractile dysfunction after myocardial infarction. These findings indicate that adiponectin influences the extent of LV remodeling.

A number of clinical studies show that adiponectin is associated with the prevalence of various obesity-related complications. Plasma adiponectin levels are decreased in obese subjects and in patients with type 2 diabetes coronary artery disease and hypertension. In contrast, high adiponectin levels are observed in established heart failure patients and in dialysis patients when compared with healthy controls. Obesity-linked disorders are also an important, potentially modifiable risk factor for AF. These observations led us to speculate that adiponectin levels affect the development and prevalence of AF, so in the present study we examined the potential association of plasma adiponectin levels with the presence of AF and the markers of atrial remodeling.

Methods

Study Population

We recruited 304 consecutive patients with paroxysmal, persistent AF and paroxysmal supra-ventricular tachycardia (PSVT) without AF history, admitted for scheduled radiofrequency catheter ablation (RFCA) with coronary angiography at Nagoya University Hospital between April 2005 and March 2007. We excluded patients with dilated or hypertrophic cardiomyopathy, congenital heart disease, congestive heart failure or valvular heart diseases and those on hemodialysis. All patients were on appropriate therapy with antiarrhythmic drugs, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, spironolactone and statins at the time of undergoing RFCA. Each patient’s pattern of AF (paroxysmal or persistent) was determined on the episode of AF as follows. (1) Paroxysmal AF was defined as a history of 1 or more episodes of AF that was medically- or self-terminated within 7 days. (II)
Persistent AF was defined as a history of 1 or more episodes of AF over 7 days which required pharmacological cardioversion or electrical cardioversion to establish normal sinus rhythm. The etiologies were paroxysmal AF in 162 and persistent AF in 46 patients. None of the patients in this study had permanent AF. In addition, we assessed 96 patients with PSVT and no previous document of AF, who were considered to represent the control group. This study was approved by the Ethics Committee of the Nagoya University School of Medicine, and all patients enrolled in this study gave written informed consent.

**Biomarker Analysis**

Blood samples were obtained from every patient while in a fasting state. After 10 min resting supine, vital signs were recorded and 35 ml blood was collected from the antecubital vein. Plasma adiponectin levels were determined with adiponectin ELISA kits (Otsuka Pharmaceutical Co Ltd, Tokyo, Japan). Serum levels of carboxy-terminal telopeptide of collagen type I (CITP) and type III procollagen-N-peptide (PIINP) were measured by Mitsubishi Chemical Medience Corp (Tokyo, Japan) and Bio Medical Laboratories Inc (Tokyo, Japan), respectively.

**Echocardiography**

Two-dimensional and Doppler echocardiography was performed by an experienced sonographer using a Vivid4 System (GE Healthcare Bio-Sciences, Tokyo, Japan). The images were recorded on videotape and analyzed offline. LV end-diastolic diameter (LVEDD) and left atrial (LA) dimensions were standard M-mode measurements, as recommended by the American Society of Echocardiography. LV ejection fraction (LVEF) was calculated using the modified Simpson’s rule.

**Statistical Analysis**

All data are expressed as mean ± standard deviation. Statistical significance was assessed by 1-way ANOVA with Bonferroni’s correction. The correlations between adiponectin and CITP levels were examined by univariate analysis. A p-value <0.05 indicated statistical significance. All analyses were performed using Stat View-J (version 5.0; SAS Institute Inc, Cary, NC, USA).

### Results

#### Baseline Characteristics

Baseline characteristics of the patients are shown in Table 1. Mean age, percentage of males, mean body mass index and the comorbidities of diabetes and hyperlipidemia were significantly higher in the paroxysmal AF and persistent AF patients than in the control patients. However, there

<table>
<thead>
<tr>
<th>Table 1 Patients’ Characteristics</th>
<th>Control (n=96)</th>
<th>Paroxysmal AF (n=162)</th>
<th>Persistent AF (n=46)</th>
<th>ANOVA</th>
<th>Paroxysmal vs persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.1±17.0</td>
<td>58.8±11.6***</td>
<td>61.1±12.2**</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>47 (49.0%)</td>
<td>118 (72.8%)**</td>
<td>34 (73.9%)**</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2±3.3</td>
<td>23.3±2.2*</td>
<td>24.1±3.7**</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (6.3%)</td>
<td>11 (6.8%)</td>
<td>3 (6.5%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (14.5%)</td>
<td>38 (23.5%)</td>
<td>14 (30.4%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Accompanying diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (4.2%)</td>
<td>25 (15.4%)*</td>
<td>6 (13.0%)*</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15 (15.6%)</td>
<td>47 (29.0%)*</td>
<td>16 (34.8%)*</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>0 (0%)</td>
<td>3 (1.9%)</td>
<td>1 (2.2%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ARB</td>
<td>7 (7.3%)</td>
<td>33 (20.3%)*</td>
<td>13 (28.3%)*</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>0 (0%)</td>
<td>6 (3.7%)</td>
<td>2 (4.3%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Digitals</td>
<td>2 (2.1%)</td>
<td>16 (10.0%)</td>
<td>4 (8.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ß-blocker</td>
<td>5 (5.2%)</td>
<td>27 (16.7%)</td>
<td>5 (10.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>16 (16.7%)</td>
<td>40 (24.7%)</td>
<td>11 (23.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
<td>4 (4.2%)</td>
<td>17 (10.5%)</td>
<td>4 (8.9%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>0 (0%)</td>
<td>162 (100%)**</td>
<td>46 (100%)**</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>32.5±6.3</td>
<td>26.9±5.5**</td>
<td>41.8±7.0**</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>46.5±4.8</td>
<td>48.7±4.9**</td>
<td>49.4±6.3**</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67.8±7.4</td>
<td>66.5±6.7</td>
<td>64.3±8.2*</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>96.8±19.3</td>
<td>98.0±24.7</td>
<td>98.1±25.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.2±1.5</td>
<td>5.4±0.9</td>
<td>5.4±0.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>106.9±34.4</td>
<td>93.2±50.9**</td>
<td>89.4±31.8**</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>36.6±69.3</td>
<td>62.8±82.2*</td>
<td>108.2±45.0**</td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>113.3±28.3</td>
<td>119.5±30.0</td>
<td>119.1±37.5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>56.6±14.0</td>
<td>53.6±14.9</td>
<td>54.0±10.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>123.8±125.5</td>
<td>132.3±84.2</td>
<td>122.8±64.1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Free fatty acids (mmol/L)</td>
<td>0.42±0.29</td>
<td>0.53±0.77</td>
<td>0.50±0.31</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>High-sensitivity CRP (mg/dl)</td>
<td>0.13±0.20</td>
<td>0.14±0.13</td>
<td>0.17±0.18</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p<0.05, **p<0.01 vs Control; †p<0.05, ††p<0.01 vs Paroxysmal AF.

AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.
were no significant differences in these parameters between paroxysmal AF and persistent AF patients. Medications taken by the paroxysmal AF and persistent AF groups were almost similar, whereas medications such as antiarrhythmic agents, angiotensin-receptor blockers and anticoagulants differed between the control group and the 2 types of AF groups.

In the echocardiographic analysis, LA dimensions and LVEDD in the 2 types of AF patients, and LVEF in patients with persistent AF, were significantly greater than in the control patients. The LA in patients with persistent AF was also larger than that of patients with paroxysmal AF (p<0.001). There were no significant differences between persistent AF and paroxysmal AF patients in the LVEDD and LVEF values.

No significant differences were observed among the 3 groups for the levels of blood glucose, high-sensitive C-reactive protein, and lipids such as low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides and free fatty acids. Creatinine clearance and the levels of BNP and hemoglobin A1c were significantly higher in the paroxysmal AF and persistent AF patients than in the control patients. BNP levels in patients with persistent AF were also higher than those in patients with paroxysmal AF (p<0.05).

Influence of AF on Adiponectin Levels

Plasma adiponectin levels were significantly higher (p<0.05) in persistent AF patients (9.86±6.52 μg/ml) when compared with paroxysmal AF patients (6.94±4.06 μg/ml) and the controls (7.76±5.04 μg/ml) (Fig 1). No statistically significant differences in adiponectin levels were found between paroxysmal AF and control patients (p=0.19). There were also no correlations between adiponectin level and the frequency of AF (data not shown).

Influence of AF on Collagen Metabolism Markers

Circulating levels of CITP, a marker of collagen type I degradation, were significantly higher in patients with persistent AF (4.64±1.28 μg/L) than in either paroxysmal AF (3.92±1.64 μg/L) or control patients (3.72±1.49 μg/L) (p<0.05). There were no significant differences between the paroxysmal AF and control groups (p=0.33) in CITP levels (Fig 2a). We did not find differences in the circulating levels of PIIINP, a marker of collagen type III synthesis, among the 3 groups (control: 0.54±0.17 μg/L; paroxysmal AF: 0.53±0.15 μg/L; persistent AF: 0.54±0.13 μg/L) (Fig 2b).

Correlation Between Adiponectin and CITP Levels in Patients With Persistent AF

We examined the association between plasma adiponectin level and CITP level and LA dimension in the persistent AF population, because among the 3 groups these parameters were markedly higher in persistent AF patients. In this cohort plasma adiponectin levels significantly correlated with serum CITP levels (r=0.39, p<0.005, Fig 3), but not with LA dimension (r=−0.20, p=0.16).
Discussion

To the best of our knowledge, we are the first to examine the association between adiponectin level and any form of cardiac arrhythmia. In this study, plasma adiponectin levels were markedly increased in patients with persistent AF compared with those with paroxysmal AF. In addition, adiponectin levels positively correlated with CITP levels, but not with PIIINP levels, in patients with persistent AF. These observations suggest that adiponectin is a useful marker of atrial remodeling; that is, a high adiponectin level in a patient with AF could indicate the need for electrical cardioversion or RFCA.

Hypoadiponectinemia is seen in obesity, type 2 diabetes, hypertension, and coronary artery disease. Because obesity-related disorders are linked to the risk of AF, we expected that plasma adiponectin levels would be lower in patients with AF compared with control patients; however, we found higher adiponectin levels in patients with persistent AF. Similarly, high plasma adiponectin levels have been recorded in patients with chronic heart failure, including dilated cardiomyopathy, and associated with an increased risk of mortality. An elevated adiponectin level may reflect a disconnect between adiponectin and the adiponectin receptors in AF, with a resulting increase in adiponectin secretion. Future studies are necessary to elucidate the prognostic value of adiponectin for AF.

Activation of fibroblasts with formation of fibrosis contributes to atrial structural remodeling, resulting in heterogeneity of the cardiac conduction tissue. Excessive deposition of extracellular matrix (ECM) promotes atrial fibrosis, leading to the development of AF. Of the ECM proteins, collagen types I and III are the major components of the atrial interstitium and it was been reported that collagen type I, but not type III, is upregulated in the atrium of patients with sustained AF. In this regard, the collagen type I degradation marker, CITP, has been found to be associated with the occurrence and maintenance of AF. Consistent with this finding, the present study demonstrated that CITP, but not PIIINP, was elevated in patients with persistent AF. In addition, the circulating CITP level positively correlated with the adiponectin level in patients with persistent AF. Recently, we showed that adiponectin supplementation diminished myocardial fibrosis after myocardial infarction. Adiponectin deficiency contributes to exacerbated fibrosis in the kidney following subtotal renal resection and adiponectin administration attenuates liver fibrosis caused by carbon tetrachloride. Thus, adiponectin may act as a general repressor of fibrosis in various tissues, suggesting that it also affects atrial fibrosis.

Study Limitations

First, we did not assess whether adiponectin levels predict AF outcomes because clinical outcomes in this study depended on whether the RFCA procedure was successful or not. Second, we also did not evaluate the change in adiponectin level before and after ablation therapy. Third, the sample size was relatively small. Finally, we did not assess adiponectin levels in patients with permanent AF, which can be related to atrial structural remodeling.

Conclusion

Our observations show that circulating adiponectin levels are closely linked to the presence of persistent AF and increased levels of the collagen type I degradation marker. Therefore, measurement of the plasma adiponectin level could provide useful information for the evaluation of atrial remodeling in patients with AF.

Acknowledgments

We gratefully acknowledge the technical assistance of Megumi Kondo and Rie Miura.

This work was supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology, the Nakashima foundation and the Aichi D.R.G foundation to R. Shibata. N. Ouchi was supported from an American Heart Association Scientist Development Grant, Northeast Affiliate.

References


