Plasma Adiponectin Levels and Left Ventricular Remodeling in Hypertrophic Cardiomyopathy

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SUMMARY

Adiponectin, which is an adipose-derived protein with antiatherosclerogenic activities, has been reported to be elevated in patients with heart failure. However, there are no reports on the significance of adiponectin in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to elucidate the clinical significance of plasma adiponectin levels in HCM patients.

Clinical characteristics, echocardiographic parameters, and levels of plasma B-type natriuretic peptide (BNP) and adiponectin were evaluated in 106 HCM patients. The plasma adiponectin levels were 10.8 ± 6.3 (range, 2.7-37.3) μg/mL. Plasma adiponectin levels were positively related to age and inversely related to body mass index (BMI). Among echocardiographic parameters, % fractional shortening (r = -0.20, P = 0.03) and maximum LV wall thickness (r = -0.23, P = 0.02) were inversely related to plasma adiponectin levels. A significant correlation between plasma adiponectin levels and BNP levels was also observed (r = 0.27, P = 0.005). In multivariate analysis, BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels.

Plasma adiponectin levels are associated with impaired LV systolic function in HCM patients, but not with the LV outflow gradient. Together with BNP, adiponectin can be a useful biomarker for assessing disease severity in HCM patients. (Int Heart J 2010; 51: 51-55)

Key words: Hypertrophic cardiomyopathy, Adiponectin, B-type natriuretic peptide, LV remodeling, Heart failure

Hypertrophic cardiomyopathy (HCM), a relatively prevalent genetic cardiac disease caused by mutations in genes encoding sarcomere proteins, is clinically defined as left ventricular (LV) hypertrophy with heterogeneous clinical and morphological features in the absence of other cardiovascular diseases.¹,² The clinical and morphological features are diverse and the natural history varies from an asymptomatic and benign clinical course to sudden premature death.

Biomarkers are molecules that are objectively measured by laboratory techniques, which can give us useful information in patients with cardiovascular disease, including HCM.³ Adipocytokine adiponectin is an adipose-derived protein and shows antiatherosclerogenic and insulin-sensitizing effects. The low plasma levels of adiponectin are associated with type 2 diabetes and ischemic heart disease.⁴,⁵ Moreover, the novel cardiovascular effects of adiponectin have attracted considerable attention in patients with LV hypertrophy and chronic heart failure.⁶⁻¹⁰ However, the significance of adiponectin has not yet been evaluated in patients with HCM. The purpose of this study was to elucidate the significance of plasma adiponectin levels in HCM.

METHODS

Patients and study protocol: The study group included 106 patients with HCM diagnosed based on echocardiographic demonstration of a hypertrophied left ventricle (maximum wall thickness ≥ 15 mm) in the absence of systemic hypertension or other cardiac disease that could produce the magnitude of evident hypertrophy. Clinical characteristics, and electrocardiographic, echocardiographic and laboratory findings were determined for all patients during a clinically stable period. Patients with renal failure (serum creatinine ≥ 2.0 mg/dL), myocardial infarction or malignancy were excluded from the study. The study protocol was approved by the Ethics Committee on Medical Research at our institute and written informed consent was provided by all patients.

Echocardiography: Echocardiographic studies were performed using a Sequoia 512 (Mountain View, CA, USA). The dimensions of the left ventricle and the left atrium were measured and the magnitude and distribution of LV hypertrophy were assessed from two-dimensional images. The greatest wall thickness measured at any site in the left ventricle was regarded as the maximum thickness. The LV outflow pressure gradient was also measured using a continuous-wave Doppler under basal conditions.

Based on echocardiographic findings, the morphologic
subtype of HCM was defined as 1) obstructive (LV outflow gradient of ≥ 30 mmHg), 2) nonobstructive, 3) apical (LV wall thickening confined to the most distal region at the apex below the papillary muscle level), and 4) dilated phase (LV systolic impairment defined as % fractional shortening of < 25%).

Moreover, 79 patients with preserved LV systolic function were studied by tissue Doppler imaging (TDI) to evaluate the relationship between plasma adiponectin levels and diastolic function. The peak velocity of early (E) and late (A) waves and the E/A ratio were determined from transmitral flow velocity using an apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets during diastole. Tissue Doppler velocity was measured during early diastole (Ea) at the septal and lateral corners of the mitral annulus from the apical 4-chamber view by positioning the sample volume at the lateral margin of the mitral annulus. Finally, the septal and lateral E/Ea ratio was also calculated.

**Laboratory measurements:** Peripheral venous blood samples were collected from the antecubital vein after the patients had remained supine for at least 15 minutes without discontinuing drugs. The plasma adiponectin level was measured using a sandwich enzyme-linked immunosorbent assay system (adiponectin ELISA kit, Otsuka Pharmaceutical Co., Japan). In addition, the plasma BNP level was also measured using an enzyme immunoassay (TOSOH II(BNP), TOSOH Co., Japan).

**Statistical analysis:** Data are presented as the mean ± SD. The nonparametric Wilcoxon rank-sum test was used to compare plasma adiponectin levels between two groups. Variables with non-normal distribution were transformed logarithmically. Correlations between plasma adiponectin levels and other variables were evaluated using univariate linear regression analysis. By forward stepwise multiple regression analysis, parameters that were associated with plasma adiponectin at the level of P < 0.10 on univariate analysis were analyzed. Analysis of variance (ANOVA) was used for comparison between groups and the significances of individual differences were evaluated by Tukey’s HSD procedure if ANOVA was significant. A level of P < 0.05 was considered to indicate statistical significance.

**RESULTS**

**Patient characteristics:** The patients were aged 63 ± 13 years and 69 (65%) were male. Body mass index (BMI) was 24.2 ± 2.8 kg/m² and 43 patients (41%) had a BMI of > 25 kg/m². Most of the patients had no or mild symptoms and 7 (7%) had symptoms of severe heart failure (New York Heart Association functional class III). Thirty-six patients (34%) had a family history of HCM. Patients had the following HCM subtypes: obstructive (n = 10), nonobstructive (non-apical) (n = 67), apical (n = 24), and dilated phase (n = 5). Of these 106 patients, 47 were administered beta-blockers and 35 were taking calcium antagonists. In addition, 30 patients were taking either angiotensin converting enzyme inhibitors or angiotensin receptor blockers for mild systemic hypertension or heart failure due to LV systolic impairment. None had been prescribed PPAR-γ agonists.

**Adiponectin levels and clinical characteristics:** The mean plasma adiponectin level of the patients was 10.8 ± 6.3 (range, 2.7-37.7) μg/mL. The mean adiponectin level in females was higher than that in males (13.1 ± 6.9 μg/mL versus 9.6 ± 5.6 μg/mL, P = 0.002). Plasma adiponectin levels were positively related to age (r = 0.22, P = 0.02) and inversely related to BMI (r = -0.27, P = 0.004). Nine patients with atrial fibrillation showed higher plasma adiponectin levels compared to those with sinus rhythm (14.6 ± 9.2 μg/mL versus 10.0 ± 5.2 μg/mL, P = 0.03). The

<table>
<thead>
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<th>Variable</th>
<th>Mean ± SD</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>46 ± 6</td>
<td>0.07</td>
<td>0.47</td>
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<tr>
<td>LV end-systolic dimension (mm)</td>
<td>27 ± 7</td>
<td>0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>% fractional shortening (%)</td>
<td>41 ± 8</td>
<td>-0.20</td>
<td>0.03</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>45 ± 7</td>
<td>0.10</td>
<td>0.28</td>
</tr>
<tr>
<td>Maximum LV wall thickness (mm)</td>
<td>20 ± 4</td>
<td>-0.23</td>
<td>0.02</td>
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</table>

SD indicates standard deviation; and LV, left ventricular.

![Figure 1. Relationship between plasma adiponectin levels and echocardiographic parameters such as % fractional shortening and maximum left ventricular (LV) wall thickness. The dotted lines represent the 95% confidence limit for the fitted line.](image)
plasma adiponectin levels in 7 patients with severe heart failure symptoms were slightly higher than those in patients with no or mild symptoms (13.8 ± 8.6 μg/mL versus 10.6 ± 6.1 μg/mL, P = NS). The plasma adiponectin levels did not differ according to the drug administered, including beta-blockers, calcium antagonists, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

**Adiponectin levels and echocardiographic findings:** Table I shows the relationship between the plasma adiponectin levels and echocardiographic parameters in all patients. The plasma adiponectin levels were positively related to LV end-systolic dimension, and inversely related to % fractional shortening and maximum LV wall thickness (Figure 1). The plasma adiponectin levels in obstructive HCM did not differ from that in other subtypes of HCM (10.9 ± 6.3 μg/mL versus 10.0 ± 5.2 μg/mL, P = NS). As a consequence, plasma adiponectin levels in patients with dilated HCM were significantly higher than those in patients with other HCM subtypes (Figure 2).

**Relation between plasma levels of adiponectin and BNP:**

The mean plasma BNP level was 211 ± 187 (range, 4-861) pg/mL. Plasma BNP levels were positively related to plasma adiponectin levels (Figure 3).

**Multivariate analysis:** Forward stepwise multiple regression analysis showed that BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels (Table II).

**Diastolic dysfunction and plasma adiponectin levels in patients with preserved LV systolic function:** There were no significant correlations between plasma adiponectin levels and conventional echocardiographic parameters in patients with preserved LV systolic function. Plasma adiponectin levels were significantly related to septal E/Ea ratio (r = 0.24, P = 0.03) and plasma BNP levels (r = 0.25, P = 0.01). However, by multivariate analysis, septal E/Ea was not an independent predictor of plasma adiponectin levels (Table III).

**DISCUSSION**

To the best of our knowledge, this is the first report to describe the significance of plasma adiponectin in patients with HCM. The main finding of this study is that the levels of plasma adiponectin were related to LV systolic impairment due to LV remodeling in patients with HCM.

**Adiponectin and LV systolic impairment:** Measurement of biomarkers such as neurohormones, inflammatory biomarkers, and metabolic biomarkers can help in understanding the pathophysiology of cardiovascular disease. For example, circulating levels of BNP constitute an established predictor of outcome in patients with chronic heart failure.

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**Table II. Stepwise Multiple Regression Analysis in All Patients**

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<tbody>
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<td>Age</td>
<td>1.39</td>
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</tr>
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<td>Gender (male 1)</td>
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<tr>
<td>BMI</td>
<td>8.95</td>
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<tr>
<td>% Fractional shortening</td>
<td>6.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum LV wall thickness</td>
<td>3.27</td>
<td>0.07</td>
</tr>
<tr>
<td>Plasma BNP levels</td>
<td>8.14</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and BNP, B-type natriuretic peptide.

**Table III. Stepwise Multiple Regression Analysis in Patients With Preserved LV Systolic Function**

<table>
<thead>
<tr>
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<th>F</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.04</td>
<td>0.16</td>
</tr>
<tr>
<td>Gender (male 1)</td>
<td>2.98</td>
<td>0.08</td>
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<tr>
<td>BMI</td>
<td>3.23</td>
<td>0.07</td>
</tr>
<tr>
<td>Septal E/Ea</td>
<td>1.14</td>
<td>0.29</td>
</tr>
<tr>
<td>Plasma BNP levels</td>
<td>3.26</td>
<td>0.08</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; BMI, body mass index; E, peak velocity of early (E) waves determined from transmural flow velocity; Ea, early diastole velocity at the corners of the mitral annulus by tissue Doppler imaging; and BNP, B-type natriuretic peptide.

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**Figure 2.** Comparison of plasma adiponectin levels in subtypes of hypertrophic cardiomyopathy. Adiponectin levels were higher in dilated HCM than in other subtypes of HCM.

**Figure 3.** Relationship between plasma adiponectin levels and BNP levels. The dotted lines represent the 95% confidence limit for the fitted line.
associated with acquired cardiac disease. Recently, metabolic biomarkers have gained attention in various cardiovascular diseases. Adiponectin is an antiatherosclerotic and insulin-sensitizing protein comprising 247 amino acids produced by white adipose tissue. It is abundant in circulating plasma, with concentrations between 5-10 μg/mL in humans. Adiponectin is related to type 2 diabetes, essential hypertension, and ischemic heart disease. Interestingly, several investigators have recently found elevated plasma adiponectin levels in patients with heart failure, and have suggested that it might be a prognostic predictor. Although the precise mechanism of elevation of adiponectin is unclear in patients with heart failure, the following explanations can be considered. Firstly, progression to severe heart failure is often associated with weight loss, which results in an increase in the plasma adiponectin level. Secondly, mRNA and protein expression of the adiponectin receptor adiponectin-1 is increased in the left ventricle of the infarcted, compared with the normal mouse heart. Moreover, adiponectin-knockout mice develop exacerbated LV dilatation, myocyte hypertrophy, and contractile dysfunction after myocardial infarction compared with wild-type mice. Therefore, adiponectin might protect the heart from LV remodeling, although it is unclear whether or not high adiponectin levels are a compensatory mechanism.

The clinical and pathological characteristics of HCM involve a number of diverse mechanisms. Therefore, measurement of biomarkers may be useful to assess the pathophysiology, disease severity, and prognosis in HCM. For example, it has been reported that plasma BNP and N-terminal proBNP levels are related to heart failure symptoms and might be related to prognosis in patients with HCM. Plasma BNP levels are affected by several factors such as LV outflow tract gradient, LV wall thickness, LV diastolic function, and LV systolic impairment. However, there are no reports on the significance of adiponectin in HCM. We found here that the plasma adiponectin levels were not affected by the LV outflow gradient and were independently related to LV systolic impairment due to LV remodeling. A significant proportion (5-10%) of patients with HCM progress to LV systolic impairment due to LV remodeling (so-called dilated HCM). To recognize this clinical entity is important because this subgroup of patients develops refractory heart failure and has a poor prognosis. A precise explanation for the relationship between LV systolic impairment and high plasma adiponectin levels in HCM is difficult in our study. However, a recent report showed the natriuretic peptides (atrial natriuretic peptide and BNP) enhance adiponectin production by human adipocytes both in vitro and in patients with heart failure. As we have shown, plasma adiponectin levels were related to plasma BNP levels in this study. Therefore, plasma adiponectin levels might be partially regulated by plasma BNP levels also in patients with HCM.

In conclusion, plasma adiponectin levels can be a useful marker, particularly with other biomarkers such as BNP, for assessing disease severity such as a decline in LV systolic function in patients with HCM.

**Study limitations:** Several limitations are associated with this study. Firstly, the adiponectin level was measured only at one point. Secondly, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were prescribed for some patients due to mild systemic hypertension or LV systolic dysfunction. Previous studies have shown that angiotensin converting enzyme inhibitors or angiotensin receptor blockers increased the plasma adiponectin levels and the effect of beta-blockers is controversial. Therefore, it could not be ruled out that plasma adiponectin levels were influenced by the medication, although we did not identify any statistically significant relationship between them.

Adiponectin has been reported to modulate hypertrophic signals and be related to diastolic function in patients with hypertension. Therefore, it would be interesting to determine whether plasma adiponectin levels affect the degree of LV hypertrophy, LV mass, and LV diastolic function in patients with HCM. In this study using echocardiography, plasma adiponectin levels were inversely related to maximum LV thickness in all patients, but were not related to LV wall thickness in patients with preserved LV systolic function. Moreover, plasma adiponectin levels were not related to diastolic dysfunction assessed by TDI by multivariate analysis, although it was weakly related to septal E/A ratio by univariate analysis. However, echocardiography including TDI is limited to assess LV mass and LV diastolic function in HCM. Cardiac magnetic resonance is a useful tool with which to assess LV mass and myocardial fibrosis in HCM. Therefore, further investigations are warranted to elucidate the significance and mechanisms of adiponectin for LV hypertrophy and diastolic dysfunction in patients with HCM.

**References**