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Hypoadiponectinemia in Patients With Paroxysmal Atrial Fibrillation

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Background and Objectives: Adiponectin is an adipose tissue-derived hormone that has beneficial effects on cardiac function and has been reported to be associated with lipid metabolism, glucose metabolism, and insulin resistance. Serum levels of adiponectin are reduced in obese individuals compared with non-obese individuals. Obesity is associated with an increased incidence of atrial fibrillation (AF); however, the role of adiponectin in AF is unclear. The aim of this study is to evaluate the relationship between the plasma adiponectin level and AF. **Subjects and Methods:** Sixty-one consecutive patients were prospectively enrolled for this study. Subjects were divided into two groups: patients with AF (n=30) and controls (n=31). Laboratory evaluation, including levels of plasma adiponectin, was performed and echocardiographic parameters were measured. **Results:** The baseline characteristics were not different between the two groups. The plasma adiponectin level of patients in the AF group was significantly lower than in the control group (14.9±7.2 vs. 19.±8.9 μg/mL, p<0.05). In addition, when we divided the AF patients into paroxysmal and chronic AF, the plasma adiponectin level was significantly lower in patients with paroxysmal AF, compared with the control group. In multiple binary logistic regression analysis to evaluate the independent predictors for AF, adiponectin and left atrial diameter were strong independent predictors of AF. **Conclusion:** In this study a lower plasma adiponectin concentration was significantly associated with that of paroxysmal AF. Hypoadiponectinemia can potentially be an important risk factor for AF. **(Korean Circ J 2012;42:668–673)**

KEY WORDS: Adiponectin; Atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia, associated with an adverse prognosis. AF has been associated with hypertension, ischemic heart disease (IHD), heart failure (HF), and valvular heart disease, and with different metabolic disturbances. Furthermore, AF is also a major risk factor for stroke.[1]

Multiple factors are involved in the etiology of AF, including st-retching, autonomic imbalance, hyperthyroidism, and inflammation.[2-4] Among these, obesity and metabolic syndrome are associated with AF: patients with metabolic syndrome have a larger left atrial (LA) size than those without metabolic syndrome.[5] Obesity is also a strong risk factor for the occurrence of post-operative AF in patients older than 50 years.[6]

Adiponectin is a protein, secreted by adipose cells that may couple the regulation of insulin sensitivity with energy metabolism, and serve to link obesity with insulin resistance through its anti-diabetic, anti-atherogenic, and anti-inflammatory properties. Adiponectin itself is controlled in conditions of metabolic stress by a number of hormones and factors involved in the regulation of metabolic function. Most factors with a significant impact on adiponectin regulation have inhibitory effects, including catecholamines, glucocorticoids, cytokines (interleukin-6, tumor necrosis factor-α), prolactin, growth hormones, and androgen.[7]

Many clinical studies have shown that adiponectin is associated with various obesity-related complications. Plasma adiponectin levels are decreased in obese subjects, and in those with type 2 diabetes, coronary artery disease, and hypertension. However, the role

of adiponectin in AF has not been extensively evaluated. In the present study, we examined the correlation of plasma adiponectin levels and AF in various type of AF.

Subjects and Methods

Study population

We prospectively enrolled 30 consecutive AF patients (mean age 57±12 years), who visited Kosin University Gospel Hospital. The presence of AF was determined by a serial electrocardiogram and ambulatory monitoring. Thirty-one patients with normal sinus rhythm (NSR) were enrolled as controls. Control patients were matched on the basis of age and sex.

Subjects were excluded before enrollment if they had a history of coronary artery disease, rheumatic heart disease, cardiomyopathy, congestive HF, or significant valvular disease. Type of AF was determined, based on the episodes of AF, as follows:[8)9)] 1) Paroxysmal AF was defined as a history of 1 or more episodes of AF that was medically or self-terminated within 7 days; 2) Persistent and chronic 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 a NSR or continuous AF of more than 1 year in duration.

The study protocols were reviewed and approved by the institutional committee. All patients agreed to participate in the study, and informed consent was obtained from all participating subjects.

Laboratory analysis

Venous blood sampling from all subjects was performed after overnight fasting. Height and body weight were measured, and a body mass index (BMI) was calculated by weight (kg)/height (m)^2. Blood samples were obtained in ethylenediaminetetraacetic acid-containing tubes, which were centrifuged to extract the plasma. The extracted plasma was stored at -70°C. The plasma adiponectin concentration was assessed using a radioimmunoassay (Linco Research, Inc., St. Charles, MO, USA). All assays were performed in duplicate. This assay is both sensitive (detection limit <1.5 μg/L) and precise (within-assay coefficient of variation of standards and unknown samples averaged 5%). Finally, the assay yielded an average adiponectin level of 14 mg/L (range 6 to 27 mg/L).

We also measured a lipid concentration, fasting glucose, fasting insulin, and high sensitivity C-reactive protein (hs-CRP), and performed an echocardiography. Total cholesterol, triglyceride (TG), and high density lipoprotein-cholesterol were determined by enzymatic methods, employing standard biochemical procedures and using a BM Hitachi automated clinical chemistry analyzer (Hitachi, Tokyo, Japan). C-reactive protein (CRP) was measured using commercially available

hs-CRP assays (Dade Behring Inc. Newark, DE, USA). Fasting plasma glucose was measured by the glucose oxidase method.

Echocardiography

Two-dimensional and Doppler echocardiography was performed by an experienced sonographer, using an Acuson-Sequoia 512 (Siemens Medical Solutions, Mountain View, CA, USA) with patients in the left lateral decubitus position. Transthoracic echocardiography studies were carried out according to the recommendations of the American Society of Echocardiography.[10] M-mode LA dimension, right ventricular dimension, and interventricular septal dimension were measured in the parasternal long-axis view at the end-diastole. Left ventricular (LV) end diastolic dimension, LV end-systolic dimension, and ejection fraction were measured in the parasternal long-axis view.

The images were recorded digitally, and were analyzed by offline software. LV end-diastolic diameter and LA dimensions were determined by standard M-mode measurements. LV ejection fraction was calculated, using the modified Simpson's rule.

Statistical analysis

Characteristics of the study population are given as the mean± standard deviation. Correlation analysis was performed for adiponectin plasma level and risk factors for cardiac disease.

Mann-Whitney U test was used to analyze the difference in adiponectin serum level between AF patients and sinus rhythm patients. Spearman's correlation method was applied for the correlation between adiponectin and other factors. Entered multiple binary logistic regression was performed to determine the most influential factor on AF. A $p<0.05$ was considered significant. Data were analyzed with Statistical Package for the Social Sciences (SPSS) software (version 16.0, SPSS, Inc., Chicago, IL, USA).

Results

Baseline patient characteristics

A total of 61 consecutive subjects (male : female=34 : 27; average age 57.5±14.5 years, range 18-73 years; BMI 19.9-33.5 kg/m^2) were prospectively enrolled in this study. Subjects were divided into two groups: AF patients (n=30) and NSR controls (n=31). Table 1 shows the baseline characteristics for both groups. There were no significant differences in sex, BMI, blood pressure, age, or prevalence of diabetes mellitus (DM), hypertension, and smoking.

In the AF group, 73% of patients were treated with a β-blocker, 56.7% were treated with angiotensin converting enzyme (ACE) inhibitor or an angiotensin II antagonist, and 13.3% were treated with a calcium-channel blocker. In the control group, 19.4% of patients were treated with a calcium channel blockers, 6.5% were treated

with ACE inhibitor or an angiotensin II antagonist, and 6.5% were treated with a β-blocker.

Echocardiographic findings

The mean LA size was significantly increased in the AF group, compared with that in the control group (4.2±0.6 vs. 3.7±0.8 cm, p= 0.008) (Table 2). The mean value of other echocardiographic parameters, including EF, LV wall thickness, and E/E´, were not different between the two groups.

If we divided the AF patients into paroxysmal and chronic AF, LA size was significantly increased in the chronic AF group (3.8±0.4 vs. 4.5±0.6 cm, p=0.028).

Laboratory findings

The mean adiponectin concentration was decreased in subjects with AF, compared with those in the control group (14.9±7.2 µg/mL vs. 19.9±8.9 µg/mL, p=0.021) (Table 3, Fig. 1). When we divided the AF group into paroxysmal AF and chronic AF, the adiponectin level sh-

Table 1. Baseline characteristics of subjects with AF and controls

Baseline characteristics	AF (n=30)	Controls (n=31)	p
Males (%)	21 (70.0)	17 (54.8)	0.29
Body mass index (kg/m²)	25.3±2.9	23.2±2.9	0.01
Systolic BP (mm Hg)	121.2±17.0	116.8±13.7	0.15
Diastolic BP (mm Hg)	75.5±13.9	74.5±10.3	0.73
Age (years)	57.1±12.2	58.1±15.7	0.65
DM (%)	5 (16.7)	2 (6.5)	0.22
Hypertension (%)	14 (46.7)	10 (32.3)	0.25
Smoking (%)	8 (26.7)	6 (19.4)	0.50
Medication (%)			
β-blocker	22 (73.3)	2 (6.5)	
ACE inhibitor	17 (56.7)	2 (6.5)	
Calcium channel blocker	4 (13.3)	6 (19.4)	
Digoxin	7 (23.3)		
Anti-arrhythmic agent	8 (37.5)		

All values are presented as number (percentage) or mean±SD. AF: atrial fibrillation, BP: blood pressure, DM: diabetes mellitus, ACE: angiotensin converting enzyme

Table 2. Echocardiographic characteristics of AF patients and controls

Echocardiographic parameters	AF	Control	p
Ejection fraction (%)	59.5±11.8	63.3±9.6	0.189
Left atrial size (cm)	4.2±0.6	3.7±0.8	0.008
Interventricular septal thickness (cm)	1.3±0.2	1.2±0.2	0.063
Posterior wall thickness (cm)	1.0±0.1	1.0±0.2	0.160
E/E'	8.55±2.4	9.7±3.6	0.171
E'	8.27±2.6	7.3±3.0	0.181

Values are presented as mean±SD. AF: atrial fibrillation

owed a significant difference between paroxysmal AF and controls (12.2±4.9 µg/mL vs. 19.9±8.9 µg/mL, p=0.016), but not between chronic AF and controls (17.1±8.3 µg/mL vs. 19.9±8.9 µg/mL). The fasting s-insulin level was also significantly increased in AF patients (12.7±9.4 vs. 8.4±5.9 µU/mL, p=0.04) (Table 3).

In univariate analysis, TG, and CRP were correlated with plasma adiponectin level. As shown in Table 4, there was a negative correlation between the plasma adiponectin concentration and TG (r=-0.267, p=0.037) and CRP (r=-0.392, p=0.021) levels.

Multiple logistic regression analysis was done to evaluate the independent predictors for AF. Adiponectin and LA diameter were strong independent predictors of AF in a binary logistic regression model (adjusted for clinical and echocardiographic parameters) (Table 5).

Discussion

The major findings of our study are: 1) The plasma concentration of adiponectin was significantly different between the AF and control groups, indicating that there may be some patho-physiological links between adiponectin and AF; 2) Adiponectin level was negatively correlated with the TG level and CRP level.; 3) Adiponectin level and LA diameter were significant independent predictors of AF; 4) There are significant changes in the adiponectin level between paroxysmal and chronic AF.

Adiponectin is a protein secreted specifically by adipose cells that may couple regulation of insulin sensitivity with energy metabolism, and are served to link obesity with insulin resistance.[7] Adiponectin increases fatty acid oxidation and glucose uptake and inhibits gluconeogenesis. Decreased plasma adiponectin levels are observed in patients with DM, metabolic syndrome, and IHD, and

Table 3. Comparison of metabolic parameters between AF and control groups

Metabolic parameters	AF	Controls	p
Adiponectin (µg/mL)	14.9±7.3	19.9±8.9	0.021
Fasting BS (mg/dL)	103.1±18.1	103.3±19.2	0.924
HbA1c (%)	6.8±1.3	6.3±1.5	0.048
S-insulin (pmol/L)	12.7±9.4	8.4±5.9	0.032
Total cholesterol (mg/dL)	178.7±43.7	165.4±34.4	0.185
HDL-C (mg/dL)	45.9±12.0	45.2±14.2	0.871
Triglyceride (mg/dL)	143.9±76.9	119.5±67.3	0.110
LDL-C (mg/dL)	108.3±42.4	107.1±61.1	0.889
Uric acid (mg/dL)	6.1±2.2	5.5±1.9	0.312
CRP (mg/dL)	0.6±1.4	1.4±6.2	0.435

Values are presented as mean±SD. AF: atrial fibrillation, BS: blood sugar, HbA1c: hemoglobin A1c, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, CRP: C-reactive protein
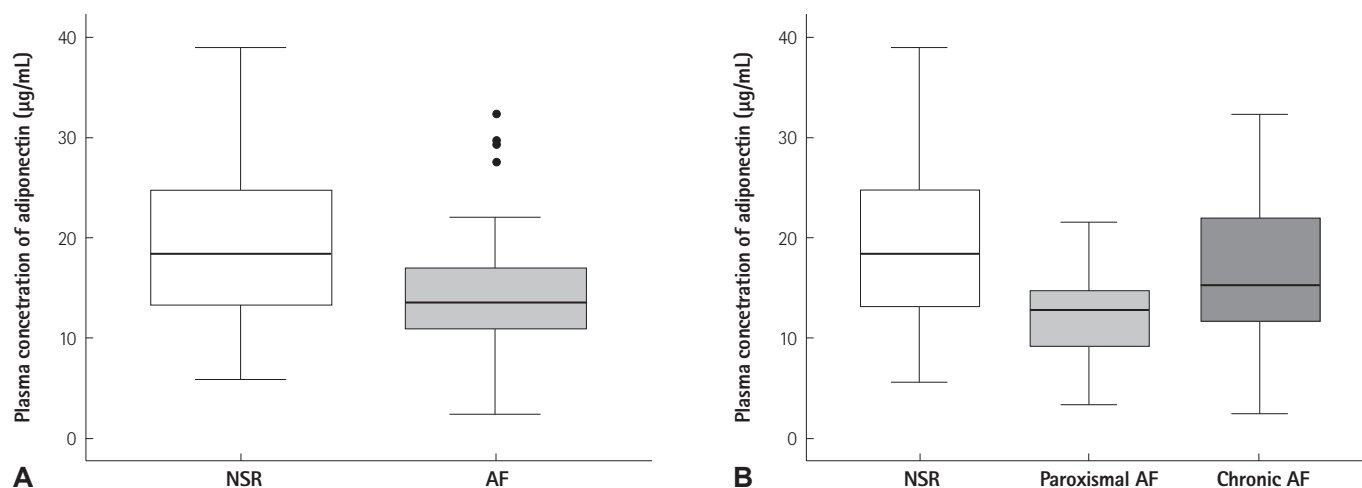
Fig. 1. Serum adiponectin level in AF and control patients. Circulating levels of adiponectin were measured in patients with AF and in patients with NSR as controls. Box plots represent median levels with 25th and 75th percentiles of observed data, whereas whiskers show the 5th and 95th percentiles in each group. A: comparison of NSR and AF patients (p=0.021). B: comparison of NSR (n=31), paroxysmal AF (n=13), and chronic AF (n=17) (p=0.016, control vs. paroxysmal AF). AF: atrial fibrillation, NSR: normal sinus rhythm.

Table 4. Correlation between plasma adiponectin concentration and other parameters

	Spearman correlation coefficient	p
Age (years)	0.091	0.488
Total cholesterol (mg/dL)	-0.188	0.146
HDL-C (mg/dL)	0.198	0.125
Triglyceride (mg/dL)	-0.267	0.037*
LDL-C (mg/dL)	-0.205	0.112
Uric acid (mg/dL)	-0.200	0.123
CRP (mg/dL)	-0.392	0.021*
Fasting blood sugar (mg/dL)	-0.222	0.085
HbA1c (%)	-0.047	0.718
Body mass index (kg/m^2)	-0.126	0.334
Serum insulin	-0.070	0.590

*$p<0.05$. HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, CRP: C-reactive protein, HbA1c: hemoglobin A1c

Table 5. Multivariate logistic regression analysis of independent predictors for AF

	HR (95% CI)	p
Adiponectin	0.831-0.993	0.035
Age	0.938-1.021	0.320
S-insulin	0.979-1.012	0.574
TG	0.994-1.011	0.609
Uric acid	0.670-1.276	0.634
CRP	0.723-1.164	0.477
LA size	1.409-9.102	0.007

Model was adjusted for clinical and echocardiographic characteristics. AF: atrial fibrillation, HR: hazard ratio, CI: confidence interval, TG: triglyceride, CRP: C-reactive protein, LA: left atrial

may play a key role in the development of insulin resistance.[11] In contrast, high adiponectin levels are observed in HF patients[12-15] and in dialysis patients.[16][17] In our study, low adiponectin levels were observed in paroxysmal AF, but not in chronic AF, indicating that the role of adiponectin is different in terms of AF disease progression.[18] Our report is not fully in line with other studies. Rienstra et al.[19] reported that in a community-based longitudinal study, no statistically significant association between adiponectin and incident of AF was found. These differences may be partially related with the disease progression state of AF. Shimano et al.[18] reported that it is possible for the elevated adiponectin level to reflect a disconnection between adiponectin and the adiponectin receptors in AF, with a resulting increase in adiponectin secretion. Further study is needed to confirm the role of adiponectin in the disease progres-

sion of AF.

Multiple factors are involved in the etiology of AF. Among these, stretching and inflammation increase the angiotensin II level, thereby, inducing calcium overload and ectopic focal activities that initiate AF.[20][21] Structural changes in the atria, in association with inflammation, might promote AF persistence. Our study showed that LA size is also a determinant of AF, together with adiponectin level. This implies that anatomical changes reflected by LA size and pathophysiological changes reflected by adiponectin may act together to promote the progress of AF. An inflammatory contribution, to at least some forms of AF, was initially suggested by the high incidence (25-40%) of AF after a cardiac surgery. Although the underlying mechanisms are not well understood, adiponectin clearly has anti-inflammatory properties that may be related to decreased adiponectin levels in AF patients in this study.

Another important mechanism related to adiponectin is the renin-angiotensin-aldosterone system (RAS). Human preadipocytes

possess a functional RAS, and both undifferentiated preadipocytes and immature adipocytes secrete Angiotensin II. Expression of the RAS components seems to be related to the body weight because obese women are reported to have higher circulating levels of angiotensinogen, renin, aldosterone, and ACE than lean women. On the other hand, weight reduction reduced angiotensinogen, renin, and aldosterone levels and decreased ACE expression.[22]

Thus, an upregulated adipose RAS may have deleterious local and systemic effects in obese individuals and might contribute to insulin resistance and hypertension. RAS blocking agent increased adiponectin levels with an accompanying improvements in the insulin sensitivity, but did not affect the degree of adiposity.[21] Previously, Guo et al.[23] reported that the treatment of losartan are accompanied by decreased adiponectin levels, which might offer potential protection in humans. Yenisecu et al.[24] also reported that ramipril corrects proteinuria and increases the low adiponectin levels in patients with diabetic nephropathy. Further study is needed to confirm the role of adiponectin and ARB system.

There are several limitations of this study. First, the sample size is limited. As such, this study is underpowered to make a firm conclusion concerning the relation with adiponectin and AF. Second, although there was no statistically significant difference in the prevalence of DM, diabetes was more common in the AF group, as compared to the control patients. These differences may influence the adiponectin level. Third, some of the subjects were taking drugs, such as ACE inhibitor. However, in AF patients, with a decreased adiponectin level, the influence of ACE inhibitor on adiponectin level was not significant. In addition, several important determinants of plasma adiponectin level, such as body fat content and waist circumference, were not measured in our study.

Despite these limitations, our data implicate adiponectin as a target in reducing AF and the morbidity and mortality of atherosclerotic disease. In the healthy state, such as the control group in this study, plasma adiponectin levels may play a protective role through anti-inflammatory, anti-atherogenic, and anti-AF properties. The plasma adiponectin level was reported to be decreased in patients with risk factors for HF,[12]25-29] and was decreased in AF patients in this study, compared with that of the controls. However, the plasma adiponectin level was increased in chronic AF, compared with paroxysmal AF. This is probably because the serum levels of atrial natriuretic peptide are increased in disease states, such as congestive HF and chronic AF,[30] leading to increased secretion of adiponectin.[25]

In conclusion, in this study, hypoadiponectinemia was significantly associated with the paroxysmal AF, but this hypoadiponectinemia cannot be shown in Chronic AF. Further investigation is needed to confirm the potential role for AF.

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