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Decrease in Plasma Adiponectin Concentrations in Patients with Vasospastic Angina

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ABSTRACT

Background and Objectives : Plasma adiponectin, which decreases the progression of atherosclerosis and insulin resistance, as well as suppressing lipid accumulation in macrophages, is decreased in patients with acute myocardial infarction and unstable angina pectoris; however, the correlation between plasma adiponectin and vasospastic angina pectoris (VAP) remains to be verified. We compared the plasma adiponectin concentration between patients with VAP and other coronary artery diseases; moreover, we investigated the association between the plasma adiponectin concentration and VAP. **Subjects and Methods :** Following coronary angiography for the evaluation of chest pain, 395 subjects (180 women and 215 men) were divided into 4 groups: acute coronary syndrome (ACS)(n=117), VAP (n=94), stable angina pectoris (SAP)(n=108) and angiographically normal coronary artery (n=76). The acetylcholine provocation test was used to confirm VAP, and plasma adiponectin concentrations were measured in all participants. **Results :** The plasma adiponectin concentrations in patients with VAP and ACS were significantly lower than that of the normal coronary artery group (6.6±5.4 vs. 5.2±4.0 vs. 9.0±6.2 μg/mL, p<0.001, respectively). A multivariate analysis indicated that plasma adiponectin [odd ratio (OR) 0.744, 95% confidence interval (CI) 0.645 to 0.858, p=0.001], smoking (OR 2.054, 95% CI 1.027 to 4.106, p=0.042) and age (OR 0.966, 95% CI 0.935 to 0.997, p=0.031) were independently correlated in patients diagnosed with VAP. **Conclusion :** Our results suggest that a decreased plasma adiponectin concentration may be associated with VAP. **(Korean Circulation J 2006;36:255-260)**

KEY WORDS : Adiponectin ; Coronary artery vasospasm ; Acetylcholine.

Introduction

The precise mechanisms of vasospastic angina pectoris (VAP) remain to be fully understood. Endothelial dysfunction, with a systemic alteration in nitric oxide production, may be a cause of VAP.[1)2)] Even though the long-term survival of patients with VAP has been acceptable, occasional cases of acute myocardial infarction and sudden cardiac death have been reported.[1)3)] Therefore, a prompt diagnosis for the proper treatment is important for patients with VAP.

Much work has been published regarding the role of adiponectin in the progression of atherosclerosis, the suppression of lipid accumulation in human monocyte-derived macrophages and decreasing in insulin resistance.[4-7)] Moreover, adiponectin inhibits macrophage to foam cell transformation.[8)] Plasma adiponectin is decreased in patients with coronary artery diseases, especially in those with acute coronary syndrome (ACS)[9)] however, the correlation between plasma adiponectin and VAP, to our knowledge, remains to be fully investigated. In this single centered observational study, we compared the plasma adiponectin concentrations between patients with VAP and other coronary artery diseases; moreover, we investigated the association between plasma adiponectin and VAP.

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Subjects and Methods

Study patients

A total of 395 subjects (180 women and 215 men)

with suspected coronary artery disease, between November 2002 and March 2004, who underwent coronary angiography (CAG) for the evaluation of chest pain were included in this study. The study was approved by the institutional review board at our institution. The potential risks were explained, after which each participant provided written informed consent before the procedures. Patients in the VAP group (n=94) with an episode of spontaneous angina at rest, associated with ST segment changes on 12-lead electrocardiogram (ECG) or ambulatory ECG underwent CAG with acetylcholine chloride (ACh) provocation. The VAP group included patients with an angiographically documented coronary spasm associated with ischemic ST segment changes after an intracoronary injection of ACh. The VAP group was compared with the following 3 groups: ACS (n=117), stable angina pectoris (SAP) (n=108) and angiographically normal coronary artery (n=76) without ischemic changes after an intracoronary injection of ACh. The ACS group (n=117) included patients with acute myocardial infarction (n=33) and unstable angina pectoris (n=84).

Acute myocardial infarction was diagnosed on the basis of clinical symptoms, ECG evidence of a greater than 0.1 mV ST elevation in at least 2 leads (in cases of ST elevation myocardial infarction), and a greater than two-fold increase in the level of serum CK-MB from the upper limit of the normal range. CAG confirmed the occlusion of a coronary artery with a TIMI grade flow of less than 3 for acute myocardial infarction. Unstable angina pectoris was diagnosed on the basis of the clinical symptoms (class IB, IIB, IIIB in the Braunwald classification),[10] the CAG finding of greater than 70% stenosis in at least one coronary artery, and no significant elevation in the level of serum CK-MB. Stable angina pectoris was diagnosed on the basis of typical chest pain during an exercise test and the CAG finding of greater than 70% stenosis in at least one coronary artery. The normal coronary group included patients with normal CAG findings and a negative ACh provocation test. Patients with malignancies, renal insufficiency and chronic inflammatory disease were excluded from entry into the study.

Diabetes mellitus was defined as a history of diabetes, a fasting plasma glucose concentration greater than or equal to 126 mg/dL, or the use of hypoglycemic medications. Systemic hypertension was defined as a systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic pressure greater than or equal to 90 mmHg and/or the use of antihypertensive medication. Smokers were defined as those with a current or recent history of smoking within the past 1 year. Hyperlipidemia was defined as a total cholesterol level greater than or equal to 200 mg/dL, a LDL cholesterol level greater than or equal to 130 mg/dL, or treatment with a lipid-lowering agent. A family history of premature coronary artery disease was defined as coronary artery disease in a male first-degree relative less than 55 years of age and a female first-degree relatives less than 65 years of age. The body mass index (BMI) was calculated from the body weight in kilograms divided by the square of the height in meters.

Provocation test for VAP

With the exception of sublingual nitroglycerin medications, all vasodilator drugs were discontinued 72 hours prior to the CAG. No study patient had taken nitroglycerin within 12 hours of the study. After the baseline coronary angiogram in multiple projections in patients with an episode of spontaneous angina at rest, associated with ST segment changes on 12-lead ECG or ambulatory ECG, an electrode catheter was inserted into the right ventricular apex through the right femoral vein. A temporary pacemaker was connected to the electrode catheter, at a pacing rate of 40 beats/min. Acetylcholine chloride (Ovisot, Daiichi Pharmaceutical, Tokyo, Japan), dissolved in 0.9% saline, was injected into the left coronary artery over a 40 second period, at incremental doses of 20, 50 and 100 μg. The interval between each injection was at least 5 minutes, and left coronary angiography was performed in cases of chest pain development, ST segment changes or 1 minute after the termination of each injection. If no changes were detected at the left coronary artery, incremental doses of 20 and 50 μg of ACh were similarly injected into the right coronary artery. In cases of coronary artery spasm, 200 to 400 μg nitroglycerin (Millisrol, Kayaku Co., Tokyo, Japan) was injected into the provoked coronary artery. VAP was confirmed when total or near total occlusion occurred, with chest pain or ST segment changes on the ECG, or both. Calcium channel antagonists and/or long acting nitrates were administered in patients with confirmed VAP.

Laboratory analysis

Blood samples were obtained from all patients on admission to the hospital by venipuncture into EDTA-containing tubes, which were centrifuged to obtain plasma, with the plasma stored at -70℃. The plasma adiponectin concentration was assessed using a radioimmunoassay (Linco Research, Inc. St. Charles, Missouri, USA). The sensitivity of this assay was 0.78 ng/mL. The coefficients for intra- and interassay variations were 9.3 and 15.3%, respectively. Samples for all lipid profiles, including lipoprotein (a) [Lp(a)], were collected following overnight fasting. Total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol were determined by enzymatic methods, employing standard biochemical procedures, using a B.M. Hitachi automated clinical chemistry analyzer (Hitachi, Tokyo, Japan).

Moreover, low-density lipoprotein (LDL) cholesterol in patients without dysbetalipoproteinemia or those with triglyceride levels less than 400 mg/dL was calculated using the Friedewald's formula. The Lp(a) concentration was measured by a particle enhanced immunoturbidimetric method using commercial kits (Roche Diagnostics, IN, USA). C-reactive protein (CRP) was measured using commercially available high-sensitive CRP assays (Dade Behring Inc., Newark, DE, USA). Fasting plasma glucose was measured using the glucose oxidase method.

Statistical analysis

Data for the categorical variables are expressed as both the number and the percentage of patients. For continuous variables, data are expressed as the mean±SDs. A one way analysis of variance (ANOVA) was used to compare variables between the four different groups. Post hoc comparisons between different groups were made using the Tukey multiple comparison procedures and the chi-squared test for categorical variables. Pearson's correlation coefficient analysis was used to assess for an association between the measured parameters. To identify the predictors of VAP, multivariate logistic regression analyses were used. Univariate variables, with $p<0.20$, were entered into the multivariate logistic models. Multivariate adjusted odds ratios are shown with a 95% confidence intervals (CI). Differences were considered significant at $p<0.05$. All statistical analyses were performed using commercially available software (SPSS 11.0 for windows, SPSS Inc., Chicago, Illinois).

Results

Baseline patient characteristics

The clinical characteristics of patients for the different groups are shown in Table 1. Patients with VAP were younger compared to those with SAP and ACS (56.6±10.5 vs. 61.3±10.3 years, $p=0.008$ and 56.6±10.5 vs.

Table 1. Baseline patient characteristics

	ACS (n=117)	VAP (n=94)	SAP (n=108)	NC (n=76)	p
Age (yrs)	61.4±10.3	56.6±10.5	61.3±10.3	57.1±11.0	<0.001*
Post hoc†	a‡	b	a‡	b	
Men	75 (64.1%)	49 (52.1%)	54 (50.0%)	37 (48.7%)	0.023§
Diabetes mellitus	32 (27.4%)	14 (14.9%)	29 (26.9%)	6 (8.7%)	0.040§
Hypertension	63 (59.4%)	55 (67.9%)	57 (62.6%)	36 (52.2%)	0.385§
Cigarette smoking	54 (46.2%)	58 (61.7%)	39 (42.9%)	23 (33.3%)	0.042§
Hypercholesterolemia	35 (30.0%)	12 (12.8%)	17 (15.7%)	9 (11.8%)	0.002§
Family history of coronary artery disease	14 (12.8%)	8 (9.9%)	9 (9.9%)	6 (8.8%)	0.390§
Body mass index (kg/m^2)	24.3±2.6	24.0±2.4	24.2±2.3	23.7±2.6	0.464*

*: statistical significances were tested by a one way analysis of variances between the groups, †: the same letters indicate no significant difference between groups, based on the Tukey's multiple comparison test, ‡: difference in $p<0.05$ compared with the normal coronary artery group, §: two by four chi-squared test with linear by linear association. ACS: acute coronary syndrome, VAP: vasospastic angina pectoris, SAP: stable angina pectoris, NC: normal coronary

Table 2. Comparison of metabolic parameters between acute coronary syndrome, vasospastic angina, stable angina and normal coronary patients

	ACS (n=117)	VAP (n=94)	SAP (n=108)	NC (n=76)	p*
Adiponectin (μg/mL)	5.2±4.0	6.6±5.4	8.3±5.9	9.0±6.2	<0.001
Post hoc†	a§	a,b‡	b,c	c	
Fasting blood sugar (mg/dL)	135.1±72.1	105.4±39.0	108.3±42.7	99.5±32.4	<0.001
Post hoc†	a§	b	b	b	
HbA1c (%)	6.8±1.1	5.3±1.2	5.4±0.9	5.1±1.1	<0.001
Post hoc†	a§	b	b	b	
Total cholesterol (mg/dL)	179.0±49.2	179.5±36.7	181.0±43.3	173.0±27.1	0.657
HDL-cholesterol (mg/dL)	43.2±13.2	46.5±12.5	45.4±12.2	45.0±11.3	0.356
Triglyceride (mg/dL)	144.0±87.4	130.8±88.3	130.1±80.2	117.9±49.5	0.254
LDL-cholesterol (mg/dL)	108.7±46.0	106.1±30.0	109.2±37.2	106.1±26.0	0.917
Lipoprotein (a) (mg/dL)	29.0±28.9	28.7±48.5	30.7±28.3	25.8±22.5	0.882
Uric acid (mg/dL)	5.1±1.4	5.1±1.4	4.7±1.4	5.0±1.7	0.167
CRP (mg/L)	6.66±7.06	2.20±4.31	0.90±1.12	0.76±1.17	<0.001
Post hoc†	a§	b	b	b	

*: statistical significances were tested by a one way analysis of variances between the groups, †: the same letters indicate no significant difference between groups, based on the Tukey's multiple comparison test, ‡: difference in $p<0.05$ compared with the normal coronary artery group, §: difference in $p<0.01$ compared with the normal coronary artery group, ACS: acute coronary syndrome, VAP: vasospastic angina pectoris, SAP: stable angina pectoris, NC: normal coronary, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C-reactive protein

61.4±10.3 years, p=0.005, respectively), with significantly higher rates of current smoking (Table 1). The prevalence of diabetes and hyperlipidemia were highest in patients with ACS (Table 1). There were no significant differences in the prevalence of hypertension, family history of coronary artery disease or the body mass index.

Laboratory findings

The plasma adiponectin concentration in VAP was only significantly different from that of the normal coronary group after the Post hoc analysis (6.6±5.4 vs. 9.0±6.2 μg/mL, p=0.021) (Table 2) (Fig. 1). Fasting blood sugar, HbA1c and CRP were significantly higher only in the ACS group (all three variables p<0.001 by ANOVA). As shown in Table 3, there was a positive correlation between the plasma adiponectin concentration and HDL cholesterol (r=0.243, p<0.001) and a negative correlation between the plasma adiponectin concentration and triglyceride (r=-0.224, p<0.001). Moreover, CRP (r=-0.241, p<0.001) and fasting blood sugar (r=-0.188, p=0.006) showed significant negative correlations with the plasma adiponectin concentration.

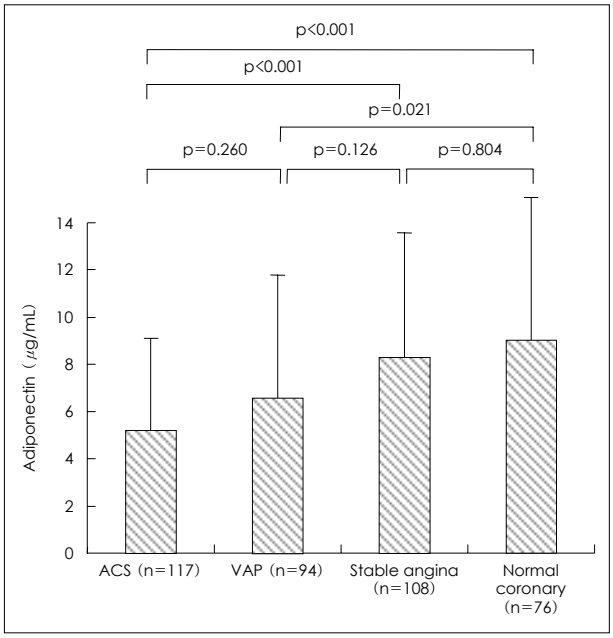

Fig. 1. The plasma adiponectin concentration is significantly lower in patients with vasospastic angina pectoris and acute coronary syndrome compared with normal coronary patients (p=0.021 and p<0.001, respectively). ACS: acute coronary syndrome, VAP: vasospastic angina pectoris.

Table 3. Correlation of the plasma adiponectin concentration with various other parameters

	Pearson correlation coefficient	p
Age (yrs)	0.069	0.169
Total cholesterol (mg/dL)	-0.008	0.879
HDL-cholesterol (mg/dL)	0.243	<0.001
Triglyceride (mg/dL)	-0.224	<0.001
LDL-cholesterol (mg/dL)	-0.016	0.770
Lipoprotein (a) (mg/dL)	0.026	0.664
Uric acid (mg/dL)	-0.208	<0.001
CRP (mg/L)	-0.241	<0.001
Fasting blood sugar (mg/dL)	-0.188	0.006
HbA1c (%)	-0.181	0.011
Body mass index (kg/m^2)	-0.070	0.194

HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C-reactive protein

Logistic regression analysis

As shown in Table 4, the univariate logistic regression analysis indicated the rates of VAP were significantly correlated with age, the plasma adiponectin concentration and smoking. The variables in the univariate regression analysis with p<0.20 were entered into the multivariate logistic model. The plasma adiponectin concentration (odd ratios [OR] 0.744, 95% CI 0.645 to 0.858, p=0.001), smoking (OR 2.054, 95% CI 1.027 to 4.106, p=0.042) and age (OR 0.966, 95% CI 0.935 to 0.997, p=0.031) were independently correlated in patients diagnosed with VAP.

Discussion

Adiponectin is the most abundant gene product in adipose tissue,[11] but accounts for approximately 0.01% of the total plasma protein, with concentrations ranging from 5 to 30 μg/mL.[12] The plasma adiponectin concentration is decreased in patients with hypertension, visceral obesity, diabetes mellitus and coronary artery disease.[4][12-14] These findings suggest that adiponectin is intimately involved in various metabolism, endothelial dysfunction and atherogenesis processes. The precise mechanisms of how low plasma adiponectin concentrations contribute to the development of VAP remain to be elucidated. Endothelial dysfunction may initiate and contribute to the development of VAP,[15-17] with vascular smooth muscle hypersensitivity also considered to play a role in the process of VAP.[15][18] Increased sympathetic activity and decreased vagal control, in addition to the vasoactive mediators, may also facilitate the progression of VAP.[19] The anti-atherogenic properties of adiponectin may delay the progression of endothelial dysfunction.[4][5] Adiponectin has a potent inhibitory effect on the expression of adhesion molecules in endothelial cells and macrophages that protect against cardiovascular disease.[8][20] By reducing the expression of adhesion molecules in the endothelium, adiponectin prevents the endothelium from early atherosclerotic vascular change. Adiponectin reduced the atherogenic transformation of macrophages to foam cells by suppressing the expression of scavenger receptors and by decreasing the cytokine production of macrophages.[8] Adiponectin also interferes with the tumor necrosis factor-α induced expres-

Table 4. Logistical regression analysis for vasospastic angina pectoris

Parameters	Univariate			Multivariate		
	p	OR	95% CI	p	OR	95% CI
Age (yrs)	0.004	0.969	0.948-0.990	0.031	0.966	0.935-0.997
Women	0.608	1.129	0.710-1.796	-	-	-
Adiponectin (μg/mL)	0.001	0.796	0.719-0.883	0.001	0.744	0.645-0.858
Diabetes mellitus	0.104	0.593	0.316-1.113	0.078	2.814	0.892-8.880
Hypertension	0.137	1.492	0.881-2.525	0.248	1.511	0.750-3.046
Smoking	0.001	2.236	1.384-3.612	0.042	2.054	1.027-4.106
Hyperlipidemia	0.105	0.576	0.295-1.123	0.919	0.942	0.298-2.978
CRP (mg/L)	0.191	0.960	0.903-1.021	0.301	0.961	0.891-1.036
FBS (mg/dL)	0.086	0.995	0.989-1.001	0.063	0.991	0.982-1.000
Total cholesterol (mg/dL)	0.801	0.998	0.992-1.003	-	-	-
HDL cholesterol (mg/dL)	0.189	1.013	0.994-1.033	0.164	1.022	0.991-1.053
Triglyceride (mg/dL)	0.881	1.000	0.997-1.003	-	-	-
LDL cholesterol (mg/dL)	0.637	0.998	0.992-1.005	-	-	-
Lipoprotein (a) (mg/dL)	0.975	1.000	0.992-1.008	-	-	-
Uric acid (mg/mL)	0.337	1.086	0.917-1.286	-	-	-
Body mass index (kg/m^2)	0.819	0.988	0.893-1.094	-	-	-

CI: confidence interval, CRP: C-reactive protein, FBS: fasting blood sugar, HDL: high-density lipoprotein, LDL: low-density lipoprotein, OR: odds ratio

sion of endothelial adhesion molecules in endothelial cells.[4] Therefore, hypoadiponectinemia may be associated with endothelial dysfunction, leading to VAP and other coronary artery diseases. Adiponectin might protect directly or indirectly against endothelial damage and interferes with the progression of vascular atherosclerosis, thereby reducing the rate of VAP.

The patients with VAP in this study showed lower plasma adiponectin concentrations, comparable with the levels found with ACS (6.6±5.4 vs. 5.2±4.0 μg/mL, p=0.26). A multivariate logistic regression analysis showed the plasma adiponectin concentration, smoking and age to be independently correlated with the presence of VAP. Our study also showed the plasma adiponectin concentration to be independently correlated with the presence of ACS (OR 0.849, 95% CI 0.787 to 0.911, p< 0.001), which was similar to a previous report.[9] To our knowledge, this is the first report to illustrate an independent correlation between the plasma adiponectin concentration and VAP, and to infer that plasma adiponectin may be utilized in the presence of VAP, in addition to other risk factors, such as smoking, age, mental stress and oral contraceptive use.[21][22]

The incidence of VAP is known to be higher in Asian than Western countries,[23] and has probably been underestimated due to the widespread use of calcium antagonists in hypertensive patients. We evaluated the possibilities of VAP in all cases of spontaneous angina at rest, associated with ST segment changes on 12-lead ECG or ambulatory ECG, and attempted to discontinue the use of oral nitrate and calcium antagonist at least 72 hours before the procedure where appropriate, with the exception of intermittent sublingual nitroglycerine medications. In this study, an intracoronary injection of ACh in patients with VAP induced either focal or diffuse coronary artery spasms, which suggested endothelial dysfunction with a hypercontractile response of the vascular smooth muscle. A relatively low plasma adiponectin concentration was noted in patients with VAP, which presumably contributed to the endothelial dysfunction in patients with VAP. Endothelial dysfunction may lead to the decreased production of nitric oxide in the pathogenesis of VAP, which may accelerate atherosclerotic coronary artery diseases.[15] Although the physiological function of adiponectin in humans is not fully understood, our cross-sectional data undoubtedly showed a trend for an inverse correlation between the plasma adiponectin concentration and the incidence of VAP. A long-term clinical follow-up with a larger group of participants will be needed to establish the cutoff value for differentiating the VAP from normal coronary groups.

Study limitations

The patients in our normal coronary artery group were angiographically normal; positive vascular remodeling cases could also have been included in the normal coronary artery group since intravascular ultrasound (IVUS) was not used in all cases. Moreover, hypoadiponectinemia, leading to VAP and ACS, will require further molecular studies to determine the exact cause-and-effect of this link.

Conclusion

Our results suggest that a decreased plasma adiponectin concentration may be associated with VAP.

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