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Decrease in Plasma Adiponectin Concentrations in Patients With Variant Angina Pectoris

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Background Plasma adiponectin is decreased in patients with coronary artery diseases, especially in patients with acute coronary syndrome (ACS). However, the correlation between plasma adiponectin and variant angina pectoris (VAP) has not been verified. Plasma adiponectin concentrations between VAP and other coronary artery diseases was compared in the present study. The association between plasma adiponectin concentration and VAP was also investigated.

Methods and Results Plasma adiponectin concentrations in the VAP group (n=101) were compared with those of the ACS group (n=117), the stable angina pectoris group (n=108), and the normal coronary group (n=81). Plasma adiponectin concentrations in VAP and ACS were significantly lower than that of the normal coronary group (6.6±5.4 vs 5.2±4.0 vs 9.0±6.2 μg/ml, p<0.001, respectively). Multivariate analysis indicated that plasma adiponectin (odds ratio (OR) 0.735, 95% confidence interval (CI) 0.621–0.855, p=0.011), smoking (OR 2.012, 95% CI 1.210–3.880, p=0.020), and age (OR 0.976, 95% CI 0.957–0.997, p=0.022) correlated independently with the development of VAP.

Conclusions Our results suggest that a decrease in plasma adiponectin concentration might be associated with the development of VAP. (*Circ J* 2006; **70:** 414–418)

Key Words: Acetylcholine; Acute coronary syndrome; Adiponectin; Variant angina

The precise mechanisms of variant angina pectoris (VAP) have not been fully understood. Endothelial dysfunction with a systemic alteration in nitric oxide production might be a cause of VAP[1,2] Even though long-term survival of patients with VAP has been outstanding, occasional cases of acute myocardial infarction and sudden cardiac death have been reported[1] Therefore, prompt diagnosis with proper treatment is important for patients with VAP.

Many reports related to adiponectin, a novel adipocyte derived protein, have been published. An increasing number of data support its role in decreasing the progression of atherosclerosis and in decreasing insulin resistance[3–6] Moreover, adiponectin suppresses lipid accumulation in human monocyte-derived macrophages and inhibits macrophage to form cell transformation[7] Plasma adiponectin is decreased in patients with coronary artery diseases, especially in patients with acute coronary syndrome (ACS)[8] However, the correlation between plasma adiponectin and VAP, to our knowledge, has yet to be fully investigated. In this single center observational study, we compared plasma adiponectin concentrations between VAP and other coronary artery diseases and investigated the association between plasma adiponectin and VAP.

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Methods

Study Patients

A total of 407 subjects (187 women and 220 men) with suspected coronary artery disease were included in the present study from November 2002 to March 2004, and all patients underwent coronary angiography (CAG) in evaluation of rest or effort angina. The study was approved by the institutional review board at our institution. Each participant provided written informed consent before procedures and potential risks were explained. Patients in the VAP group (n=101) 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 angiographically documented coronary spasm associated with ischemic ST segment changes after intracoronary injection of ACh. The VAP group was compared with 3 other groups: ACS (n=117), stable angina pectoris (SAP) (n=108), and angiographically normal coronary (n=81) with no ischemic changes after 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 evidences of >0.1 mV ST elevation in at least 2 leads (in cases of ST elevation myocardial infarction), and greater than a twofold increase in serum myocardial-bound creatine kinase (CK-MB) concentration from the upper limit of the normal range. CAG confirmed the occlusion of a coronary artery with thrombolysis in myocardial infarction grade flow <3. Unstable angina pectoris was diagnosed on the basis of clinical

Table 1 Baseline Patient Characteristics

	Acute coronary syndrome (n=117)	*Variant angina (n=101)*	*Stable angina (n=108)*	*Normal coronary (n=81)*	*p value*
Age (years)	*61.4±10.3*	*58.6±12.4*	*61.3±10.3*	*58.2±11.5*	*0.069*
Men	*75 (64.1%)*	*52 (51.5%)*	*54 (50.0%)*	*39 (48.1%)*	*0.041*
Diabetes mellitus	*32 (27.4%)*	*17 (16.8%)*	*29 (26.9%)*	*8 (9.9%)*	*0.039*
Hypertension	*63 (59.4%)*	*62 (61.4%)*	*57 (62.6%)*	*41 (50.6%)*	*0.404*
Cigarette smoking	*54 (46.2%)*	*61 (60.4%)*	*39 (42.9%)*	*25 (30.9%)*	*0.033*
Hypercholesterolemia	*35 (30.0%)*	*15 (14.9%)*	*17 (15.7%)*	*11 (13.6%)*	*0.025*
Family history of coronary artery disease	*14 (12.8%)*	*11 (10.9%)*	*9 (9.9%)*	*8 (9.9%)*	*0.630*
Body mass index (kg/m^2)	*24.3±2.6*	*24.2±2.2*	*24.2±2.3*	*24.0±2.3*	*0.552*

symptoms (class IB, IIB, IIIB in the Braunwald classification)[9], CAG finding of >70% stenosis in ≥1 coronary artery, and no significant elevation in serum CK-MB concentration. SAP was diagnosed on the basis of typical chest pain during the exercise test and CAG findings of >70% stenosis in ≥1 coronary artery. The normal coronary group included patients with normal CAG findings with negative provocation test. We excluded patients with malignancies, renal insufficiency, and chronic inflammatory disease at study entry.

Diabetes mellitus was defined as a history of diabetes, a fasting plasma glucose concentration of ≥126 mg/dl, or the use of hypoglycemic medications. Systemic hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic pressure of ≥90 mmHg, and/or the use of antihypertensive medication. Smokers were defined as current or recent history of smoking within the past 1 year. Hypercholesterolemia was defined as a total cholesterol level of ≥200 mg/dl, a low-density lipoprotein (LDL) cholesterol level of ≥130 mg/dl, or treatment with a lipid-lowering agent. Family history of premature coronary artery disease was defined as coronary artery disease in a male first-degree relative <55 years and female first-degree relatives <65 years. Body mass index (BMI) was the weight in kilograms dividing the square of the height in meters.

Provocation Test for VAP

Except for nitroglycerin medications, all vasodilator drugs were discontinued 72 h prior to CAG. No study patient had taken nitroglycerin within 12 h of the study. After control coronary angiographic images 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 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 40 s at incremental doses of 20, 50, and 100 μg. The interval between each injection was at least 5 min, and left CAG was performed in cases of chest pain development, ST segment changes, or 1 min after the termination of each injection. If no changes were detected at left coronary artery, incremental doses of 20 and 50 μg of ACh were injected into the right coronary artery in the same way. In cases of coronary spasm induction, nitroglycerin (Millisrol, Kayaku, Tokyo, Japan) at 200 to 400 μg was injected into the induced 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 diagnosis of VAP.

Laboratory Analysis

The blood samples were obtained from all patients on admission to the hospital. Plasma adiponectin concentration was assessed by radioimmunoassay (Linco Research, St. Charles, Missouri, USA). The sensitivity of this assay was 0.78 ng/ml. The coefficients of variation for intra- and interassay were 9.3% and 15.3%, respectively. All lipid profiles including lipoprotein(a) [Lp(a)] were collected following overnight fasting. Blood samples were obtained by venipuncture into EDTA-containing tubes. Blood samples were centrifuged to obtain plasma, and the plasma was stored at –70°C. Total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were determined by enzymatic methods using standard biochemical procedures on a B.M. Hitachi automated clinical chemistry analyzer (Hitachi, Tokyo, Japan). Moreover, LDL cholesterol was calculated using the Friedewald's formula in patients without dysbetalipoproteinemia or those with triglyceride levels <400 mg/dl. Lp(a) concentration was measured by particle enhanced immunoturbidimetric method using commercial kits (Roche Diagnostics, IN, USA). C-reactive protein (CRP) was measured by using commercially available high-sensitive CRP assays (Dade Behring, Newark, DE, USA). Fasting plasma glucose was measured by the glucose oxidase method.

Statistical Analysis

Data for the categorical variables are expressed as the number and the percentage of patients. For continuous variables, data are expressed as mean ± SD. We used one-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA on ranks to compare variables in 4 different groups. Post hoc comparisons between different groups were made using the Tukey multiple comparison procedures. Fisher's exact test or a chi-square test was used for categoric variables. Pearson's or Spearman's correlation coefficient analysis was used to assess association between 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 (OR) are shown with 95% confidence intervals (CI). Differences were considered significant at $p<0.05$.

Results

Baseline Patient Characteristics

Clinical characteristics of patients in different groups are

Table 2 Comparison of Metabolic Parameters Among Patients With Acute Coronary Syndrome, Variant Angina, Stable Angina and Normal Coronary

	Acute coronary syndrome (n=117)	*Variant angina (n=101)*	*Stable angina (n=108)*	*Normal coronary (n=81)*	*p value*
Adiponectin (μg/ml)	*5.2±4.0*	*6.6±5.4*	*8.3±5.9*	*9.0±6.2*	*<0.001*
Fasting blood sugar (mg/dl)	*135.1±72.1*	*105.4±39.0*	*108.3±42.7*	*99.5±32.4*	*<0.001*
HbA1c (%)	*6.8±1.1*	*5.3±1.2*	*5.4±0.9*	*5.1±1.1*	*<0.001*
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*

Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

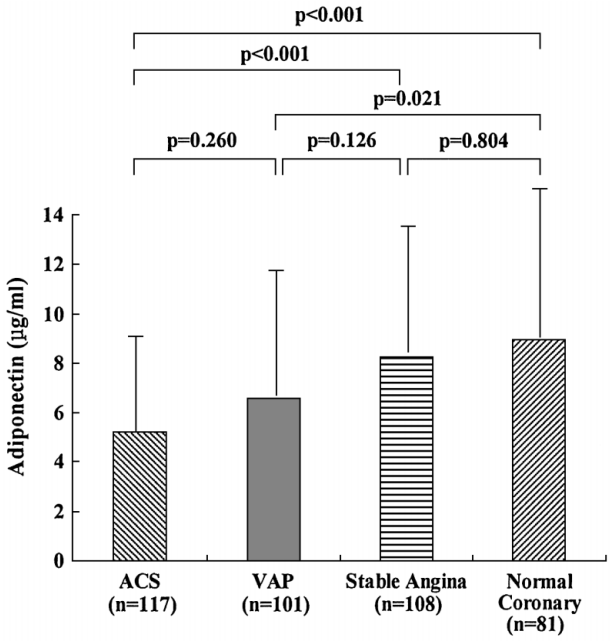

Fig 1. Plasma adiponectin concentration is significantly lower in patients with variant angina pectoris and acute coronary syndrome compared with those of normal coronary (p=0.021 and p<0.001, respectively). ACS, acute coronary syndrome; VAP, variant angina pectoris.

shown in Table 1. Patients in VAP were younger compared with those of SAP and ACS (58.6±12.4 vs 61.3±10.3 years, p=0.288 and 56.6±10.5 vs 61.4±10.3 years, p=0.243, respectively), and showed significantly higher rates of current smoking (p=0.033 by ANOVA). Rates of diabetes and hypercholesterolemia were highest in patients with ACS (p=0.039 and p=0.025 by ANOVA, respectively). There were no significant differences in rates of hypertension, family history of coronary artery disease, and BMI.

Laboratory Findings

Plasma adiponectin concentration in VAP showed significant difference only with that of the normal coronary group (6.6±5.4 vs 9.0±6.2 μg/ml, p=0.021) (Table 2, Fig 1). Fasting blood sugar, hemoglobin A1c, and CRP were only significantly higher in ACS group (all 3 variables p<0.001 by ANOVA). As shown in Table 3, a positive correlation between plasma adiponectin concentration and HDL cholesterol (r=0.243, p<0.001) and a negative correlation between plasma adiponectin concentration and triglyceride (r=–0.224, p<0.001) were noted. Furthermore, CRP (r=–0.241, p<0.001) and fasting blood sugar (r=–0.188, p=0.006) showed significant negative correlations with plasma adiponectin concentration.

Table 3 Correlation of Plasma Adiponectin Concentration With Other Various Parameters

	Pearson correlation coefficient	*p value*
Age (years)	*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; Hb, hemoglobin.

Logistic Regression Analysis

Table 4 shows simple logistic regression analysis and the rates of VAP significantly correlated with age, plasma adiponectin concentration, smoking, and fasting blood sugar. Variables in simple logistic regression analysis with p<0.20 were entered into the multivariate logistic model. Only plasma adiponectin concentration, smoking, and age showed independent correlation with the development of VAP (OR 0.735, 95% CI 0.621–0.855, p=0.011; OR 2.012, 95% CI 1.210–3.880, p=0.020; and OR 0.976, 95% CI 0.957–0.997, p=0.022, respectively).

Discussion

In the present study, patients with VAP showed low plasma adiponectin concentration comparable to the level of ACS (6.6±5.4 vs 5.2±4.0 μg/ml, p=0.26). Multivariate logistic regression analysis showed that plasma adiponectin concentration, smoking, and age correlated independently with the development of VAP. Our study also showed that plasma adiponectin concentration correlated independently with the development of ACS (OR 0.849, 95% CI 0.787–0.911, p<0.001) similar to the previous report[8] This is the

Table 4 Logistic Regression Analysis for Variant Angina

Parameters	Univariate			Multivariate		
	p value	OR	95%CI	p value	OR	95%CI
Age (years)	0.042	0.979	0.959–0.999	0.022	0.976	0.957–0.997
Women	0.608	1.129	0.710–1.796	–	–	–
Adiponectin (μg/ml)	0.002	0.747	0.701–0.794	0.011	0.735	0.621–0.855
Diabetes mellitus	0.104	0.593	0.316–1.113	0.196	1.776	0.901–6.947
Hypertension	0.137	1.492	0.881–2.525	0.339	1.221	0.779–3.001
Smoking	0.001	2.236	1.384–3.612	0.020	2.012	1.210–3.880
Hyperlipidemia	0.105	0.576	0.295–1.123	0.889	1.090	0.669–4.017
CRP (mg/L)	0.191	0.960	0.903–1.021	0.260	0.960	0.894–1.031
FBS (mg/dl)	0.047	0.975	0.969–0.981	–	–	–
Total cholesterol (mg/dl)	0.801	0.998	0.992–1.003	–	–	–
HDL cholesterol (mg/dl)	0.189	1.013	0.994–1.033	–	–	–
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	–	–	–

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

first paper, to our knowledge, to show independent correlation between plasma adiponectin concentration and VAP, and to infer that plasma adiponectin concentration might be used as a predictor of VAP in addition to other risk factors such as smoking, age, mental stress, and oral contraceptive use.[10]

Adiponectin is the most abundant gene product in adipose tissue.[11] However, adiponectin accounts for approximately 0.01% of total plasma protein, and its concentration ranges from 5 to 30 μg/ml.[12] Plasma adiponectin concentration is decreased in patients with hypertension, visceral obesity, diabetes mellitus, and coronary artery disease.[3,12–14] These findings indicate that adiponectin is intimately involved in various processes of metabolism, endothelial dysfunction, and atherogenesis. Precise mechanisms of how low plasma adiponectin concentrations contribute to the development of VAP have not been elucidated yet. Endothelial dysfunction might initiate and contribute to the development of VAP,[15–17] and vascular smooth muscle hypersensitivity has also been considered to play a role in the process of VAP.[15] Increased sympathetic activity and decreased vagal control in addition to the vasoactive mediators can facilitate the progression of VAP.[18] Anti-atherogenic properties of adiponectin might delay the progression of endothelial dysfunction.[3,4] Adiponectin has a potent inhibitory effect on the expression of adhesion molecules in endothelial cells and in macrophages that would protect against cardiovascular disease.[7,19] By reducing the expression of adhesion molecules in endothelium, adiponectin prevents the endothelium from early atherosclerotic vascular change. Adiponectin reduced atherogenic transformation of macrophages to foam cells by suppressing scavenger receptor expression and by decreasing cytokine production from macrophages.[7] Adiponectin also interferes with tumor necrosis factor-α induced expression of endothelial adhesion molecules in endothelial cells.[3] Therefore, hypoadiponectinemia might be associated with endothelial dysfunction leading to VAP and other coronary artery diseases. Adiponectin protects directly or indirectly against endothelial damage and interferes with the progression of vascular atherosclerosis, thereby reducing the rate of VAP.

Incidence of VAP has been known to be higher in Asian countries than in Western countries.[20] The incidence of VAP has probably been underestimated because of 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 we made an effort to discontinue oral nitrate and calcium antagonist for at least 72 h before the procedure whenever appropriate, except for intermittent sublingual nitroglycerine medications. In the current study, intracoronary injection of ACh in patients with VAP induced either focal or diffuse coronary artery spasm which suggested endothelial dysfunction with hypercontractile response of vascular smooth muscle. Relatively low plasma adiponectin concentration was noted in patients with VAP, and this low plasma adiponectin concentration presumably contributed to the endothelial dysfunction in patients with VAP. Endothelial dysfunction might lead to the decreased production of nitric oxide in the pathogenesis of VAP and can accelerate atherosclerotic coronary artery diseases.[15] Although the physiologic function of adiponectin in humans has not been fully understood, our cross-sectional data undoubtedly showed the trend of an inverse correlation between plasma adiponectin and the incidence of VAP. Long-term clinical follow-ups with a larger group of participants are needed to establish the cut-off value differentiating VAP from the normal coronary group.

Study Limitations

The patients in the normal coronary group were angiographically normal, and positive vascular remodeling cases could have been included in normal coronary group because intravascular ultrasound was not used in all cases. Furthermore, hypoadiponectinemia leading to VAP and ACS needs further molecular studies to determine the exact cause-and-effect of this link.

Conclusion

Patients with various cardiovascular risk factors with low plasma adiponectin concentration require aggressive treatment and close clinical follow-ups in early detection of VAP and other coronary artery diseases, thereby lowering potential harms of low plasma adiponectin concentration.

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