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Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
CI = confidence interval
hs-CRP = high-sensitivity C-reactive protein
MI = myocardial infarction
OR = odds ratio

(14,15) concomitant with rapid progression of coronary stenosis (15–18). Thus, evaluation of coronary lesion complexity is clinically useful for the estimation of plaque instability. Although complex lesions are frequently observed in ACS patients (19), coronary angiography may also reveal these lesions in patients with stable CAD (17,18); therefore, symptomatic stability does not always reflect coronary plaque stability. Practical evaluation of coronary plaque instability, in addition to the degree of luminal stenosis, is important in assessing clinical disease activity and the risk of subsequent vascular complications in patients with CAD. Diabetes mellitus and metabolic syndrome have been shown to contribute to the development of ACS; however, the mechanisms of such metabolic disorders involving plaque vulnerability remain to be fully elucidated. In this regard, adiponectin may be involved in the pathogenesis of coronary lesions' vulnerability.

The hypothesis tested in the present study was that adiponectin is associated with the presence of complex coronary lesions, reflecting coronary vulnerability. To investigate this hypothesis, we measured plasma levels of adiponectin and evaluated angiographic coronary stenosis morphology in men with CAD.

METHODS

Study population. Those eligible for entry in this study were male patients who underwent coronary angiography at Kumamoto University Hospital from January 2000 through June 2005 because of an abnormal electrocardiogram or angina-like chest symptoms. Patients with a previous history of coronary intervention or coronary artery bypass graft surgery were excluded to avoid artificial bias from such procedures. We also excluded patients with malignant disease, infectious disease, inflammatory disease such as collagen disease, advanced liver disease, and advanced renal disease. None of the patients was taking any type of thiazolidinedione, which is an insulin-sensitizing agent known to increase plasma concentrations of adiponectin (20).

According to these criteria, this study enrolled 207 consecutive men with CAD (55 patients with ACS and 152 patients with stable CAD). Patients with ACS included 31 with acute MI (who were catheterized within 6 h from the onset of chest pain) and 24 patients with unstable angina pectoris. A diagnosis of acute MI was made if the patient had typical chest pain with ST-segment elevation on the electrocardiogram and an increase in the serum level of creatine kinase-MB isoenzyme to greater than twice the upper limit of the normal range. A diagnosis of unstable angina (Braunwald's class IIB or IIIB [21]) was made if the patient had characteristic chest symptoms at rest associated with transient ischemic ST-segment shifts and normal serum level of creatine kinase-MB isoenzyme. Stable CAD was defined as no episodes of angina at rest but angiographically documented organic stenosis of >50% in at least one of the major coronary arteries and no previous MIs. Written informed consent was obtained from each patient before study participation. The study was conducted in accordance with guidelines approved by the ethics committee of our institution.

Coronary angiography. ANGIOGRAPHIC SCORING SYSTEM (EXTENT SCORE). All patients underwent selective coronary angiography, and the extent of coronary stenosis was assessed using the scoring system previously described by Sullivan et al. (22). The length proportion of each vessel involved by angiographically detectable atheroma was evaluated and multiplied by a factor for each vessel: left main stem, 5; left anterior descending artery, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery a factor of 10. When a vessel was occluded and the distal segments were not fully visualized by collateral flow, the proportion of vessel not visualized was given the mean extent score of the remaining vessels. The scores for each vessel or branch were added to give a total score up to a maximum of 100, representing the percentage of the coronary luminal surface area involved by atheroma, as described in previous studies (22,23).

ANGIOGRAPHIC MORPHOLOGY OF CORONARY STENOSIS. Coronary stenosis was assessed morphologically according to the Ambrose classification (19,24) and was classified as either simple or complex. A simple lesion was defined as stenosis with smooth and regular borders without intraluminal filling defects, whereas a complex lesion comprised stenosis with irregular, rough borders; ulceration with or without intraluminal filling defects, suggestive of thrombus formation; and long atherosclerotic lesions with severe narrowing in series. Angiographic evaluations were performed independently by 2 cardiologists who were blinded to the clinical features of the patients and, in case of disagreement, the decision was based on the judgment of a third, more experienced observer. The interobserver reproducibility for morphologic assessment of coronary lesions was 95%.

Blood sampling and measurement of plasma adiponectin. Venous blood samples were obtained just before the emergency coronary angiography in patients with ACS and were obtained in the early morning after a 12-h fast in patients

with stable CAD. The serum profile, including fasting blood glucose, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, creatinine, and high-sensitivity C-reactive protein (hs-CRP) levels, was measured in the hospital laboratory. Plasma samples were immediately stored at −80 °C for subsequent assay for adiponectin levels by enzyme-linked immunosorbent assay as described previously (4,7).

Statistical analysis. Results of normally distributed continuous variables are expressed as the mean value ± SD, and those for continuous variables with skewed distribution are expressed as the median value (interquartile range). Comparisons of continuous variables were analyzed with the unpaired *t* test and the Mann-Whitney *U* test, as appropriate. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by the chi-square test. Associations between the presence of complex lesions and all other parameters were first analyzed by simple logistic regression analysis and then by multivariate analysis. The base-2 logarithms ($\log_2$) of the plasma levels of adiponectin, triglycerides, and hs-CRP were used in all the logistic regression analysis to account for skewed distribution of these parameters (25). Thus, odds ratios (ORs) for these variables reflect the change in odds for an increase of 1 $\log_2$ (the equivalent of a doubling of the value) in the measure. We performed polytomous logistic regression analysis to calculate the ORs and 95% confidence intervals (CIs) for single and multiple complex lesions, as compared with simple lesions, in relation to all parameters. In this analysis, factors that were associated with the dependent variable at $p < 0.20$ in the univariate analysis were entered into the multivariate model and eliminated using a backward procedure. Statistical significance was defined as $p < 0.05$. All analyses were performed using Stat View-5.0 software (SAS Institute Inc., Cary, North Carolina) and SPSS 14.0J for Windows (SPSS Inc., Tokyo, Japan).

RESULTS

Plasma levels of adiponectin in patients with stable CAD and ACS. Figure 1 shows plasma levels of adiponectin in patients with stable CAD and ACS. Patients with ACS had significantly lower plasma levels of adiponectin than those with stable CAD (3.81 [range 2.66 to 5.22] vs. 4.60 [range 3.36 to 7.36] μg/ml, p = 0.003).

Characteristics of patients with stable CAD. We assessed the association between plasma levels of adiponectin and coronary lesion complexity in patients with stable CAD. The baseline clinical characteristics of the 152 men with stable CAD are summarized in Table 1. Complex coronary lesions were angiographically identified in 60 patients (39%), and simple lesions were identified in the remaining 92 patients (61%). Coronary multi-vessel involvement was noted in 76 patients (50%), and multiple complex lesions were observed in 30 of these patients (20%).

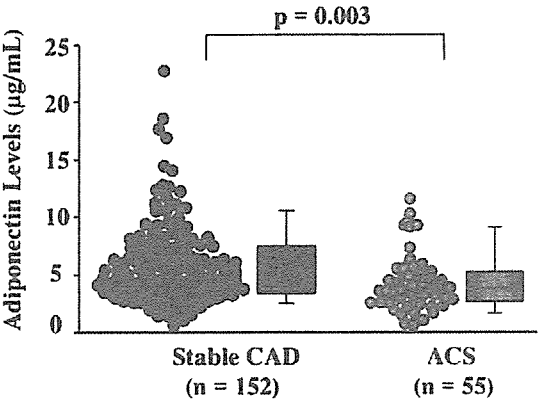

Figure 1. Plasma levels of adiponectin in patients with stable coronary artery disease (CAD) (n = 152, **blue circles**) and acute coronary syndromes (ACS) (n = 55, **yellow circles**). Box-and-whisker plot showing plasma levels of adiponectin in patients with stable CAD and ACS. In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively.

Comparison of adiponectin levels in stable CAD patients with simple and complex lesions. Stable CAD patients with complex lesions had significantly lower plasma levels of adiponectin than those with simple lesions (4.14 [range 2.95 to 6.02] vs. 5.27 [range 3.67 to 8.12] μg/ml, p = 0.006) (Table 1, Fig. 2). Low-density lipoprotein cholesterol, triglyceride levels, and the extent score were significantly higher, and left ventricular ejection fraction was significantly lower in patients with complex lesions than in those with simple lesions (Table 1).

Adiponectin and presence of complex coronary lesions in patients with stable CAD. Simple logistic regression analysis showed that low-density lipoprotein cholesterol concentrations (OR 1.010, 95% CI 1.001 to 1.020; p = 0.037), hs-CRP (OR 1.305, 95% CI 1.015 to 1.679; p = 0.038), left ventricular ejection fraction (OR 0.970, 95% CI 0.943 to 0.999; p = 0.041), extent score (OR 1.163, 95% CI 1.107 to 1.222; $p < 0.001$), and plasma adiponectin levels (OR 0.531, 95% CI 0.347 to 0.811; p = 0.003) were associated with the presence of complex coronary lesions (Table 2). Multiple logistic regression analysis revealed that the extent score was strongly associated with the presence of complex coronary lesions (OR 1.158, 95% CI 1.098 to 1.222; $p < 0.001$); however, plasma adiponectin levels remained as a significant and independent predictor of complex lesions (OR 0.514, 95% CI 0.278 to 0.951; p = 0.034) (Table 2). Furthermore, hypoadiponectinemia, which was defined by using a cutoff value for plasma adiponectin of 4.0 μg/ml (8), was a significant risk factor for the presence of complex coronary lesions in patients with stable CAD (OR 2.138, 95% CI 1.090 to 4.194; p = 0.027).

Moreover, the ORs and 95% CIs for single and multiple complex lesions as compared with simple lesions in relation to all parameters were assessed using polytomous logistic regression analysis (Table 3). Univariate analysis showed that adiponectin levels were significantly associated with

Table 1. Baseline Clinical Characteristics and Coronary Angiographic Findings of 152 Men With Stable Coronary Artery Disease

	Simple Lesion (n = 92)	Complex Lesion (n = 60)	p Value
Age (yrs)	66.8 ± 9.2	67.6 ± 8.3	0.589
BMI (kg/m^2)	23.7 ± 3.2	24.0 ± 3.0	0.616
Smoking	68 (74)	42 (70)	0.733
Systolic BP (mm Hg)	133.9 ± 18.5	138.3 ± 20.8	0.176
Diastolic BP (mm Hg)	77.9 ± 11.6	78.0 ± 10.7	0.965
Total cholesterol (mg/dl)	191.6 ± 36.7	200.5 ± 42.8	0.174
HDL cholesterol (mg/dl)	49.8 ± 16.0	45.8 ± 10.4	0.084
LDL cholesterol (mg/dl)	122.1 ± 32.3	134.7 ± 39.6	0.033
Triglycerides (mg/dl)	105.0 (73.0–159.0)	127.5 (92.5–176.5)	0.043
Diabetes mellitus	28 (30)	22 (37)	0.534
Fasting blood glucose (mg/dl)	99.2 ± 26.9	106.3 ± 29.9	0.132
Hemoglobin A1c (%)	5.9 ± 1.2	5.9 ± 1.2	0.975
Adiponectin (μg/ml)	5.27 (3.67–8.12)	4.14 (2.95–6.02)	0.006
Creatinine (mg/dl)	0.92 ± 0.21	0.97 ± 0.20	0.149
hs-CRP (mg/l)	0.80 (0.50–1.60)	1.00 (0.50–2.42)	0.208
Family history of MI	23 (25)	18 (30)	0.623
LVEF (%)	68.3 ± 12.4	63.5 ± 11.0	0.018
Number of diseased vessels			
One	69 (75)	7 (12)	
Two	19 (21)	23 (38)	<0.001
Three	4 (4)	30 (50)	
Extent score (%)	10.2 ± 7.4	28.1 ± 15.0	<0.001
Number of complex coronary lesions			
One	0	30 (50)	
Two	0	21 (35)	
Three	0	5 (8)	
Four	0	4 (7)	

Values are mean ± SD or median value (25th to 75th percentile range) or n (%).
BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

both single and multiple complex lesions, and ORs for multiple complex lesions were lower than those for single complex lesions (OR 0.565, 95% CI 0.336 to 0.948; p = 0.031 for single complex lesions, OR 0.463, 95% CI 0.273 to 0.784; p = 0.004 for multiple complex lesions). Multivariate analysis demonstrated that extent score and plasma adiponectin level were significantly and independently associated with both single and multiple complex lesions (extent score; OR 1.135, 95% CI 1.075 to 1.199; p < 0.001 for single complex lesions, OR 1.199, 95% CI 1.126 to 1.277; p < 0.001 for multiple complex lesions, adiponectin; OR 0.505, 95% CI 0.261 to 0.979; p = 0.043 for single complex lesions, OR 0.290, 95% CI 0.128 to 0.658; p = 0.003 for multiple complex lesions) (Table 3).

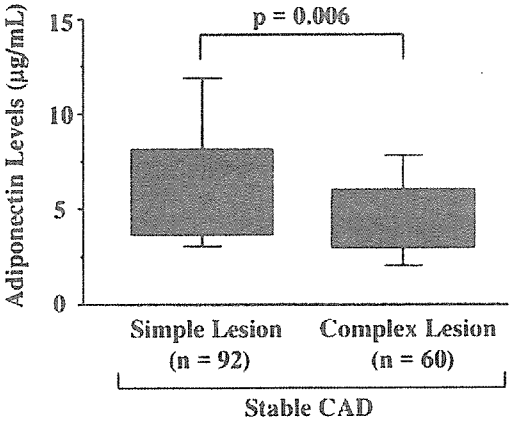

Figure 2. Box-and-whisker plot showing plasma levels of adiponectin in stable coronary artery disease patients with simple (n = 92, **blue**) and complex lesions (n = 60, **red**). In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively. Abbreviations as in Figure 1.

Comparison of adiponectin levels in ACS patients with single and multiple complex lesions. Finally, we evaluated the association between plasma levels of adiponectin and coronary lesion complexity in patients with ACS. Of the 55 ACS patients, 47 had angiographically complex lesions. Acute coronary syndrome patients with multiple complex lesions (n = 24) had significantly lower plasma levels of adiponectin than those with single complex lesions (n = 23) (3.26 [range 2.26 to 4.46] vs. 4.21 [range 3.36 to 5.41] μg/ml, p = 0.032) (Fig. 3).

DISCUSSION

In the present study, we demonstrated that men with stable CAD and complex coronary lesions had significantly lower plasma adiponectin levels than those with simple lesions, and that the plasma level of adiponectin was an independent predictor of angiographically complex coronary lesions.

Table 2. Logistic Regression Analysis for the Presence of Complex Coronary Lesions in Patients With Stable Coronary Artery Disease

Factor	Simple Regression		Multiple Regression	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (per yr)	1.010 (0.973–1.049)	0.587		
BMI (per kg/m^2)	1.028 (0.925–1.142)	0.614		
Smoking (yes)	0.824 (0.400–1.696)	0.598		
Systolic BP (per mm Hg)	1.012 (0.995–1.029)	0.177		
Diastolic BP (per mm Hg)	1.001 (0.972–1.030)	0.965		
Total cholesterol (per mg/dl)	1.006 (0.997–1.014)	0.175		
HDL cholesterol (per mg/dl)	0.978 (0.953–1.003)	0.089		
LDL cholesterol (per mg/dl)	1.010 (1.001–1.020)	0.037	1.011 (0.997–1.024)	0.125
Triglycerides (per doubling)	1.362 (0.886–2.093)	0.159		
Diabetes mellitus (yes)	1.323 (0.665–2.632)	0.425		
FBG (per mg/dl)	1.009 (0.997–1.021)	0.138		
Hemoglobin A1c (per %)	1.004 (0.763–1.322)	0.975		
Adiponectin (per doubling)	0.531 (0.347–0.811)	0.003	0.514 (0.278–0.951)	0.034
Creatinine (per 0.1 mg/dl)	1.125 (0.958–1.320)	0.150		
hs-CRP (per doubling)	1.305 (1.015–1.679)	0.038	1.125 (0.788–1.608)	0.516
Family history of MI (yes)	1.286 (0.622–2.658)	0.498		
LVEF (per %)	0.970 (0.943–0.999)	0.041	0.962 (0.921–1.005)	0.081
Extent score (per %)	1.163 (1.107–1.222)	<0.001	1.158 (1.098–1.222)	<0.001

FBG = fasting blood glucose; OR = odds ratio; other abbreviations as in Table 1.

Furthermore, among patients with ACS (who had significantly lower adiponectin levels than stable CAD patients), those with multiple complex lesions had significantly lower adiponectin levels than those with single complex lesions. Thus, hypoadiponectinemia is associated with coronary lesion complexity, and our results suggest that the extent of hypoadiponectinemia may provide valuable information about coronary plaque vulnerability.

Vulnerable coronary plaques, which include rupture-prone plaques and atheromatous plaques with high likelihood of thrombotic complications and rapid progression, play crucial roles in the development of ACS (11). Inflammation and metabolic disorders are thought to be implicated in the pathogenesis of coronary plaque vulnerability (26). Previous studies demonstrated that inflammatory serologic markers, serum neopterin, and pregnancy-associated plasma protein A are associated with coronary lesion complexity (23,27). In addition to such inflammatory processes, metabolic disorders, including diabetes mellitus, may also affect coronary plaque vulnerability (26,28). Indeed, pathologic studies demonstrated that coronary plaques of diabetic patients exhibited increased infiltration of macrophages and thrombus formation (29), indicating vulnerable and activated plaque condition.

Adiponectin, an adipocyte-derived plasma protein with anti-diabetic and anti-atherogenic properties, may be a key molecule in the pathogenesis of diabetes mellitus and metabolic syndrome (3). Adiponectin suppresses macrophage-to-foam cell transformation (30,31) and increases the expression of tissue inhibitor of metalloproteinase-1 in monocyte-derived macrophages through induction of interleukin-10 (32), suggesting that adiponectin may be a positive contributor to the stabilization of atherosclerotic plaques.

To our knowledge, the present study represents the first report demonstrating that low adiponectin levels are significantly associated with coronary lesion complexity, reflecting plaque vulnerability, in men with CAD. This finding may in part help explain the missing link between metabolic disorders and cardiovascular complications resulting from the disruption of vulnerable plaques.

Several lines of evidence point to the role of adiponectin in atherogenesis, and it is conceivable that the low adiponectin levels in patients with complex coronary lesions in the present study can be the cause and consequence of active atherosclerosis. Adiponectin could reduce atherosclerosis by inhibiting endothelial expression of adhesion molecules (6), modulation of macrophage functions (30,31), and suppression of vascular smooth muscle cell proliferation (33). Plasma levels of adiponectin are reduced in patients with CAD (6), and a previous study (9) reported significantly lower adiponectin levels in patients with ACS than those with stable CAD. A recent report found that low levels of plasma adiponectin were associated with future development of MI in men without cardiovascular disease (10), suggesting that low adiponectin may contribute to the development of ACS. We have recently reported (34) the reduction of plasma adiponectin in the early phase of acute MI, and accumulation of adiponectin has been demonstrated in the walls of injured vessels, but not in intact vessels (30,35). Therefore, increased consumption of circulating adiponectin in active atheroma might lower the plasma levels of this molecule in patients with complex lesions.

Based on the mechanisms of acute coronary events, we have recognized the clinical importance of evaluating not only the degree of coronary luminal stenosis but also plaque vulnerability in determining disease activity and the risk of

Table 3. Polytomous Logistic Regression Analysis of Factors Associated With Single and Multiple Complex Lesions in Patients With Stable Coronary Artery Disease

Factor	Single Complex Lesion				Multiple Complex Lesions			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (per yr)	0.980 (0.937–1.025)	0.368			1.052 (0.996–1.112)	0.072		
BMI (per kg/m^2)	1.025 (0.897–1.172)	0.715			1.030 (0.901–1.177)	0.666		
Smoking (yes)	1.111 (0.400–3.089)	0.840			0.648 (0.257–1.634)	0.358		
Systolic BP (per mm Hg)	1.014 (0.993–1.036)	0.200			1.010 (0.988–1.031)	0.381		
Diastolic BP (per mm Hg)	1.011 (0.975–1.048)	0.566			0.990 (0.953–1.028)	0.607		
Total cholesterol (per mg/dl)	1.010 (1.000–1.021)	0.057			1.001 (0.990–1.012)	0.822		
HDL cholesterol (per mg/dl)	0.973 (0.939–1.007)	0.119			0.982 (0.951–1.015)	0.279		
LDL cholesterol (per mg/dl)	1.016 (1.004–1.028)	0.010	1.014 (1.000–1.029)	0.049	1.004 (0.992–1.017)	0.471	1.006 (0.989–1.022)	0.499
Triglycerides (per doubling)	1.213 (0.704–2.089)	0.486			1.523 (0.896–2.590)	0.120		
Diabetes mellitus (yes)	1.323 (0.557–3.144)	0.526			1.524 (0.648–3.582)	0.334		
FBG (per mg/dl)	1.006 (0.992–1.021)	0.391			1.011 (0.997–1.025)	0.116		
Hemoglobin A1c (per %)	1.007 (0.716–1.416)	0.970			1.002 (0.701–1.431)	0.992		
Adiponectin (per doubling)	0.565 (0.336–0.948)	0.031	0.505 (0.261–0.979)	0.043	0.463 (0.273–0.784)	0.004	0.290 (0.128–0.658)	0.003
Creatinine (per 0.1 mg/dl)	1.007 (0.815–1.245)	0.948			1.241 (1.021–1.509)	0.030		
hs-CRP (per doubling)	1.252 (0.915–1.712)	0.159			1.361 (0.995–1.862)	0.054		
Family history (yes)	1.091 (0.428–2.784)	0.856			1.500 (0.614–3.667)	0.374		
LVEF (per %)	0.965 (0.932–1.000)	0.049	0.962 (0.922–1.004)	0.077	0.976 (0.941–1.012)	0.184	0.992 (0.938–1.048)	0.766
Extent score (per %)	1.140 (1.083–1.201)	<0.001	1.135 (1.075–1.199)	<0.001	1.199 (1.131–1.270)	<0.001	1.199 (1.126–1.277)	<0.001

Abbreviations as in Tables 1 and 2.

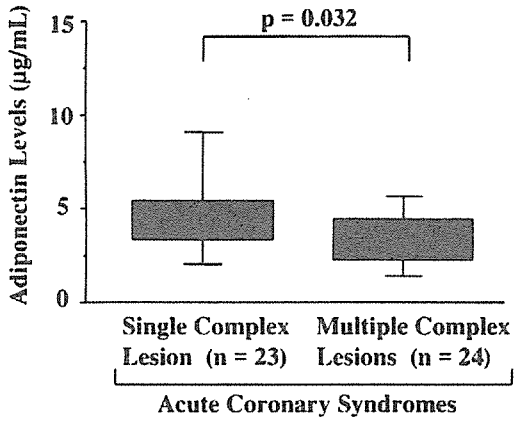

Figure 3. Box-and-whisker plot showing plasma levels of adiponectin in acute coronary syndrome patients with single (n = 23, **blue**) and multiple complex lesions (n = 24, **red**). In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively. Abbreviations as in Figure 1.

subsequent vascular complications (11). Angiographically, the presence of complex coronary lesions correlates with pathologic plaque rupture and thrombus formation (13). Clinical observations demonstrated that complex lesions were associated with accelerated progression of plaque stenosis (15–18), and they were also predictive of future cardiac events (14,15). Angiographic assessment of the morphology of coronary stenosis is well established and considered to be clinically useful for risk stratification of CAD patients (15). In the present study, we showed that adiponectin is significantly associated with coronary lesion complexity in men with CAD. Our results may indicate that low plasma adiponectin could perhaps be used to predict the occurrence of future cardiovascular events; however, further prospective studies are required to clarify this issue because we did not assess clinical outcomes in the present study.

It is widely accepted that inflammation plays an important role in the pathogenesis of atheromatous plaque vulnerability (36). In our present study, hs-CRP levels in patients with stable CAD were significantly associated with the presence of complex coronary lesions in simple logistic regression analysis. Furthermore, hs-CRP levels in patients with complex lesions were higher than those with simple lesions, though the difference was not statistically significant. Previous studies have demonstrated that hs-CRP levels correlate with coronary lesion complexity in patients with unstable angina (37,38), whereas such associations cannot be observed consistently in patients with stable CAD (27,39,40). In part, our results were in line with the previous observations; however, the rather weak association between hs-CRP and coronary lesion complexity in patients with stable CAD is intriguing.

This study was limited by the relatively small number of patients studied. We demonstrated that plasma adiponectin level is an independent predictor of complex lesions in men with stable CAD in multiple logistic regression analysis, though it was barely statistically significant. Further studies in a large number of patients should confirm our results. There was some overlap of distribution in adiponectin levels between patients with complex and simple lesions, however, hypoadiponectinemia (<4.0 μg/ml) (8) was a significant risk factor for the presence of complex coronary lesions in the present study. Thus, our finding regarding lower adiponectin levels in patients with complex lesions may support the concept that hypoadiponectinemia could be implicated in the development of coronary plaque instability and may suggest that hypoadiponectinemia could be helpful for the evaluation of coronary plaque instability as well as the presence of CAD. Moreover, therapeutic utility of increasing adiponectin levels remains to be elucidated, and our results may in part suggest that thiazolidinedione, a peroxisome proliferator-activated receptor-gamma agonist known to increase adiponectin (20), could be an agent to stabilize the atheromatous plaques and prevent atherothrombosis. However, further studies are needed to clarify the issue because we did not evaluate the effect of such agents in the present study.

In conclusion, plasma adiponectin levels in men with stable CAD and complex coronary lesions were significantly lower than in those with simple lesions, and ACS patients with multiple complex lesions had significantly lower adiponectin levels than those with single complex lesions. Thus, hypoadiponectinemia is associated with coronary lesion complexity in patients with CAD. Our results suggest that low levels of adiponectin may contribute to coronary plaque vulnerability, and plasma adiponectin levels may provide valuable information regarding coronary plaque vulnerability.

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別紙５

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Plasma Adiponectin Levels Are Associated With Coronary Lesion Complexity in Men With Coronary Artery Disease

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OBJECTIVES We sought to assess whether plasma adiponectin levels correlate with angiographic coronary lesion complexity in patients with coronary artery disease (CAD).

BACKGROUND Metabolic disorders, including diabetes mellitus and metabolic syndrome, are important risk factors for acute cardiovascular events, and adiponectin is a key molecule of metabolic disorders, with anti-atherogenic properties. Low plasma adiponectin levels are associated with CAD and future incidence of myocardial infarction. The involvement of adiponectin in coronary plaque vulnerability, which may be reflected by angiographic complex lesions, remains to be elucidated.

METHODS We measured plasma adiponectin levels in 207 men (152 with stable CAD and 55 with acute coronary syndromes [ACS]). Coronary lesions were classified as of simple or complex appearance.

RESULTS Plasma adiponectin levels were significantly lower in stable CAD patients with complex coronary lesions (n = 60) than in those with simple lesions (n = 92) (4.14 [range 2.95 to 6.02] vs. 5.27 [range 3.67 to 8.12] μg/ml, p = 0.006). Multiple logistic regression analysis demonstrated that adiponectin level was independently associated with complex lesions (odds ratio 0.514, 95% confidence interval 0.278 to 0.951; p = 0.034). Polytomous logistic regression revealed that adiponectin correlated independently with both single and multiple complex lesions. Among patients with ACS, who had lower adiponectin levels than stable CAD patients, those with multiple complex lesions had significantly lower adiponectin than those with a single complex lesion (3.26 [range 2.26 to 4.46] vs. 4.21 [range 3.36 to 5.41] μg/ml, p = 0.032).

CONCLUSIONS Plasma adiponectin levels are significantly associated with coronary lesion complexity in men with CAD. Low adiponectin levels may contribute to coronary plaque vulnerability. (J Am Coll Cardiol 2006;48:1155–62) © 2006 by the American College of Cardiology Foundation

The incidence of diabetes mellitus, a major and important risk factor for cardiovascular events including acute coronary syndromes (ACS), is increasing worldwide (1). Similarly, the metabolic syndrome, a clustering of cardiovascular disease risk factors characterized by abdominal obesity, insulin resistance, dyslipidemia, and hypertension, is associated with increased cardiovascular morbidity and mortality (2). There is increasing evidence that adiponectin, an adipocyte-derived plasma protein, plays an important role in the development of diabetes mellitus and metabolic syndrome, with anti-diabetic and anti-atherogenic properties (3). Plasma levels of adiponectin are significantly decreased in obesity (4), in type 2 diabetes (5), and in patients with coronary artery disease (CAD) (6). In addition, we recently reported a significant association between plasma adiponectin levels and atherosclerotic burden (7).

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Hypoadiponectinemia is considered an independent risk factor for CAD (8), and a recent study demonstrated that plasma adiponectin levels in patients with ACS were significantly lower than those in patients with stable CAD (9). Moreover, it has been shown (10) that lower levels of plasma adiponectin are associated with increased risk of future myocardial infarction (MI). Thus, low adiponectin may contribute to the development of atherosclerosis and acute vascular complications including ACS.

The vulnerability of coronary plaques is implicated in the pathogenesis of ACS (11). Vulnerable atheromatous plaques lead to coronary plaque disruption with superimposed thrombosis (12), which is often manifested as angiographically complex lesions (13). The presence of complex coronary lesions is associated with acute coronary events

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
CI = confidence interval
hs-CRP = high-sensitivity C-reactive protein
MI = myocardial infarction
OR = odds ratio

(14,15) concomitant with rapid progression of coronary stenosis (15–18). Thus, evaluation of coronary lesion complexity is clinically useful for the estimation of plaque instability. Although complex lesions are frequently observed in ACS patients (19), coronary angiography may also reveal these lesions in patients with stable CAD (17,18); therefore, symptomatic stability does not always reflect coronary plaque stability. Practical evaluation of coronary plaque instability, in addition to the degree of luminal stenosis, is important in assessing clinical disease activity and the risk of subsequent vascular complications in patients with CAD. Diabetes mellitus and metabolic syndrome have been shown to contribute to the development of ACS; however, the mechanisms of such metabolic disorders involving plaque vulnerability remain to be fully elucidated. In this regard, adiponectin may be involved in the pathogenesis of coronary lesions' vulnerability.

The hypothesis tested in the present study was that adiponectin is associated with the presence of complex coronary lesions, reflecting coronary vulnerability. To investigate this hypothesis, we measured plasma levels of adiponectin and evaluated angiographic coronary stenosis morphology in men with CAD.

METHODS

Study population. Those eligible for entry in this study were male patients who underwent coronary angiography at Kumamoto University Hospital from January 2000 through June 2005 because of an abnormal electrocardiogram or angina-like chest symptoms. Patients with a previous history of coronary intervention or coronary artery bypass graft surgery were excluded to avoid artificial bias from such procedures. We also excluded patients with malignant disease, infectious disease, inflammatory disease such as collagen disease, advanced liver disease, and advanced renal disease. None of the patients was taking any type of thiazolidinedione, which is an insulin-sensitizing agent known to increase plasma concentrations of adiponectin (20).

According to these criteria, this study enrolled 207 consecutive men with CAD (55 patients with ACS and 152 patients with stable CAD). Patients with ACS included 31 with acute MI (who were catheterized within 6 h from the onset of chest pain) and 24 patients with unstable angina pectoris. A diagnosis of acute MI was made if the patient had typical chest pain with ST-segment elevation on the electrocardiogram and an increase in the serum level of creatine kinase-MB isoenzyme to greater than twice the upper limit of the normal range. A diagnosis of unstable angina (Braunwald's class IIB or IIIB [21]) was made if the patient had characteristic chest symptoms at rest associated with transient ischemic ST-segment shifts and normal serum level of creatine kinase-MB isoenzyme. Stable CAD was defined as no episodes of angina at rest but angiographically documented organic stenosis of >50% in at least one of the major coronary arteries and no previous MIs. Written informed consent was obtained from each patient before study participation. The study was conducted in accordance with guidelines approved by the ethics committee of our institution.

Coronary angiography. ANGIOGRAPHIC SCORING SYSTEM (EXTENT SCORE). All patients underwent selective coronary angiography, and the extent of coronary stenosis was assessed using the scoring system previously described by Sullivan et al. (22). The length proportion of each vessel involved by angiographically detectable atheroma was evaluated and multiplied by a factor for each vessel: left main stem, 5; left anterior descending artery, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery a factor of 10. When a vessel was occluded and the distal segments were not fully visualized by collateral flow, the proportion of vessel not visualized was given the mean extent score of the remaining vessels. The scores for each vessel or branch were added to give a total score up to a maximum of 100, representing the percentage of the coronary luminal surface area involved by atheroma, as described in previous studies (22,23).

ANGIOGRAPHIC MORPHOLOGY OF CORONARY STENOSIS. Coronary stenosis was assessed morphologically according to the Ambrose classification (19,24) and was classified as either simple or complex. A simple lesion was defined as stenosis with smooth and regular borders without intraluminal filling defects, whereas a complex lesion comprised stenosis with irregular, rough borders; ulceration with or without intraluminal filling defects, suggestive of thrombus formation; and long atherosclerotic lesions with severe narrowing in series. Angiographic evaluations were performed independently by 2 cardiologists who were blinded to the clinical features of the patients and, in case of disagreement, the decision was based on the judgment of a third, more experienced observer. The interobserver reproducibility for morphologic assessment of coronary lesions was 95%.

Blood sampling and measurement of plasma adiponectin. Venous blood samples were obtained just before the emergency coronary angiography in patients with ACS and were obtained in the early morning after a 12-h fast in patients

with stable CAD. The serum profile, including fasting blood glucose, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, creatinine, and high-sensitivity C-reactive protein (hs-CRP) levels, was measured in the hospital laboratory. Plasma samples were immediately stored at −80 °C for subsequent assay for adiponectin levels by enzyme-linked immunosorbent assay as described previously (4,7).

Statistical analysis. Results of normally distributed continuous variables are expressed as the mean value ± SD, and those for continuous variables with skewed distribution are expressed as the median value (interquartile range). Comparisons of continuous variables were analyzed with the unpaired *t* test and the Mann-Whitney *U* test, as appropriate. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by the chi-square test. Associations between the presence of complex lesions and all other parameters were first analyzed by simple logistic regression analysis and then by multivariate analysis. The base-2 logarithms ($\log_2$) of the plasma levels of adiponectin, triglycerides, and hs-CRP were used in all the logistic regression analysis to account for skewed distribution of these parameters (25). Thus, odds ratios (ORs) for these variables reflect the change in odds for an increase of 1 $\log_2$ (the equivalent of a doubling of the value) in the measure. We performed polytomous logistic regression analysis to calculate the ORs and 95% confidence intervals (CIs) for single and multiple complex lesions, as compared with simple lesions, in relation to all parameters. In this analysis, factors that were associated with the dependent variable at $p < 0.20$ in the univariate analysis were entered into the multivariate model and eliminated using a backward procedure. Statistical significance was defined as $p < 0.05$. All analyses were performed using Stat View-5.0 software (SAS Institute Inc., Cary, North Carolina) and SPSS 14.0J for Windows (SPSS Inc., Tokyo, Japan).

RESULTS

Plasma levels of adiponectin in patients with stable CAD and ACS. Figure 1 shows plasma levels of adiponectin in patients with stable CAD and ACS. Patients with ACS had significantly lower plasma levels of adiponectin than those with stable CAD (3.81 [range 2.66 to 5.22] vs. 4.60 [range 3.36 to 7.36] μg/ml, p = 0.003).

Characteristics of patients with stable CAD. We assessed the association between plasma levels of adiponectin and coronary lesion complexity in patients with stable CAD. The baseline clinical characteristics of the 152 men with stable CAD are summarized in Table 1. Complex coronary lesions were angiographically identified in 60 patients (39%), and simple lesions were identified in the remaining 92 patients (61%). Coronary multi-vessel involvement was noted in 76 patients (50%), and multiple complex lesions were observed in 30 of these patients (20%).

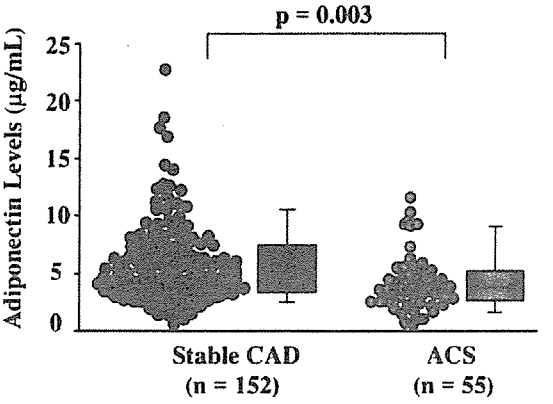

Figure 1. Plasma levels of adiponectin in patients with stable coronary artery disease (CAD) (n = 152, **blue circles**) and acute coronary syndromes (ACS) (n = 55, **yellow circles**). Box-and-whisker plot showing plasma levels of adiponectin in patients with stable CAD and ACS. In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively.

Comparison of adiponectin levels in stable CAD patients with simple and complex lesions. Stable CAD patients with complex lesions had significantly lower plasma levels of adiponectin than those with simple lesions (4.14 [range 2.95 to 6.02] vs. 5.27 [range 3.67 to 8.12] μg/ml, p = 0.006) (Table 1, Fig. 2). Low-density lipoprotein cholesterol, triglyceride levels, and the extent score were significantly higher, and left ventricular ejection fraction was significantly lower in patients with complex lesions than in those with simple lesions (Table 1).

Adiponectin and presence of complex coronary lesions in patients with stable CAD. Simple logistic regression analysis showed that low-density lipoprotein cholesterol concentrations (OR 1.010, 95% CI 1.001 to 1.020; p = 0.037), hs-CRP (OR 1.305, 95% CI 1.015 to 1.679; p = 0.038), left ventricular ejection fraction (OR 0.970, 95% CI 0.943 to 0.999; p = 0.041), extent score (OR 1.163, 95% CI 1.107 to 1.222; p < 0.001), and plasma adiponectin levels (OR 0.531, 95% CI 0.347 to 0.811; p = 0.003) were associated with the presence of complex coronary lesions (Table 2). Multiple logistic regression analysis revealed that the extent score was strongly associated with the presence of complex coronary lesions (OR 1.158, 95% CI 1.098 to 1.222; p < 0.001); however, plasma adiponectin levels remained as a significant and independent predictor of complex lesions (OR 0.514, 95% CI 0.278 to 0.951; p = 0.034) (Table 2). Furthermore, hypoadiponectinemia, which was defined by using a cutoff value for plasma adiponectin of 4.0 μg/ml (8), was a significant risk factor for the presence of complex coronary lesions in patients with stable CAD (OR 2.138, 95% CI 1.090 to 4.194; p = 0.027).

Moreover, the ORs and 95% CIs for single and multiple complex lesions as compared with simple lesions in relation to all parameters were assessed using polytomous logistic regression analysis (Table 3). Univariate analysis showed that adiponectin levels were significantly associated with

Table 1. Baseline Clinical Characteristics and Coronary Angiographic Findings of 152 Men With Stable Coronary Artery Disease

	Simple Lesion (n = 92)	Complex Lesion (n = 60)	p Value
Age (yrs)	66.8 ± 9.2	67.6 ± 8.3	0.589
BMI (kg/m^2)	23.7 ± 3.2	24.0 ± 3.0	0.616
Smoking	68 (74)	42 (70)	0.733
Systolic BP (mm Hg)	133.9 ± 18.5	138.3 ± 20.8	0.176
Diastolic BP (mm Hg)	77.9 ± 11.6	78.0 ± 10.7	0.965
Total cholesterol (mg/dl)	191.6 ± 36.7	200.5 ± 42.8	0.174
HDL cholesterol (mg/dl)	49.8 ± 16.0	45.8 ± 10.4	0.084
LDL cholesterol (mg/dl)	122.1 ± 32.3	134.7 ± 39.6	0.033
Triglycerides (mg/dl)	105.0 (73.0–159.0)	127.5 (92.5–176.5)	0.043
Diabetes mellitus	28 (30)	22 (37)	0.534
Fasting blood glucose (mg/dl)	99.2 ± 26.9	106.3 ± 29.9	0.132
Hemoglobin A1c (%)	5.9 ± 1.2	5.9 ± 1.2	0.975
Adiponectin (μg/ml)	5.27 (3.67–8.12)	4.14 (2.95–6.02)	0.006
Creatinine (mg/dl)	0.92 ± 0.21	0.97 ± 0.20	0.149
hs-CRP (mg/l)	0.80 (0.50–1.60)	1.00 (0.50–2.42)	0.208
Family history of MI	23 (25)	18 (30)	0.623
LVEF (%)	68.3 ± 12.4	63.5 ± 11.0	0.018
Number of diseased vessels			
One	69 (75)	7 (12)	
Two	19 (21)	23 (38)	<0.001
Three	4 (4)	30 (50)	
Extent score (%)	10.2 ± 7.4	28.1 ± 15.0	<0.001
Number of complex coronary lesions			
One	0	30 (50)	
Two	0	21 (35)	
Three	0	5 (8)	
Four	0	4 (7)	

Values are mean ± SD or median value (25th to 75th percentile range) or n (%).
BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

both single and multiple complex lesions, and ORs for multiple complex lesions were lower than those for single complex lesions (OR 0.565, 95% CI 0.336 to 0.948; p = 0.031 for single complex lesions, OR 0.463, 95% CI 0.273 to 0.784; p = 0.004 for multiple complex lesions). Multivariate analysis demonstrated that extent score and plasma adiponectin level were significantly and independently associated with both single and multiple complex lesions (extent score; OR 1.135, 95% CI 1.075 to 1.199; p < 0.001 for single complex lesions, OR 1.199, 95% CI 1.126 to 1.277; p < 0.001 for multiple complex lesions, adiponectin; OR 0.505, 95% CI 0.261 to 0.979; p = 0.043 for single complex lesions, OR 0.290, 95% CI 0.128 to 0.658; p = 0.003 for multiple complex lesions) (Table 3).

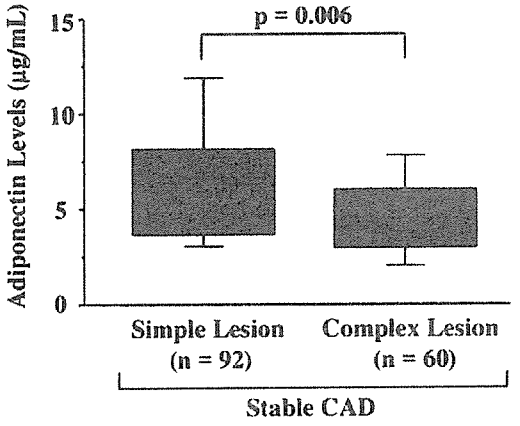

Figure 2. Box-and-whisker plot showing plasma levels of adiponectin in stable coronary artery disease patients with simple (n = 92, **blue**) and complex lesions (n = 60, **red**). In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively. Abbreviations as in Figure 1.

Comparison of adiponectin levels in ACS patients with single and multiple complex lesions. Finally, we evaluated the association between plasma levels of adiponectin and coronary lesion complexity in patients with ACS. Of the 55 ACS patients, 47 had angiographically complex lesions. Acute coronary syndrome patients with multiple complex lesions (n = 24) had significantly lower plasma levels of adiponectin than those with single complex lesions (n = 23) (3.26 [range 2.26 to 4.46] vs. 4.21 [range 3.36 to 5.41] μg/ml, p = 0.032) (Fig. 3).

DISCUSSION

In the present study, we demonstrated that men with stable CAD and complex coronary lesions had significantly lower plasma adiponectin levels than those with simple lesions, and that the plasma level of adiponectin was an independent predictor of angiographically complex coronary lesions.

Table 2. Logistic Regression Analysis for the Presence of Complex Coronary Lesions in Patients With Stable Coronary Artery Disease

Factor	Simple Regression		Multiple Regression	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (per yr)	1.010 (0.973–1.049)	0.587		
BMI (per kg/m^2)	1.028 (0.925–1.142)	0.614		
Smoking (yes)	0.824 (0.400–1.696)	0.598		
Systolic BP (per mm Hg)	1.012 (0.995–1.029)	0.177		
Diastolic BP (per mm Hg)	1.001 (0.972–1.030)	0.965		
Total cholesterol (per mg/dl)	1.006 (0.997–1.014)	0.175		
HDL cholesterol (per mg/dl)	0.978 (0.953–1.003)	0.089		
LDL cholesterol (per mg/dl)	1.010 (1.001–1.020)	0.037	1.011 (0.997–1.024)	0.125
Triglycerides (per doubling)	1.362 (0.886–2.093)	0.159		
Diabetes mellitus (yes)	1.323 (0.665–2.632)	0.425		
FBG (per mg/dl)	1.009 (0.997–1.021)	0.138		
Hemoglobin A1c (per %)	1.004 (0.763–1.322)	0.975		
Adiponectin (per doubling)	0.531 (0.347–0.811)	0.003	0.514 (0.278–0.951)	0.034
Creatinine (per 0.1 mg/dl)	1.125 (0.958–1.320)	0.150		
hs-CRP (per doubling)	1.305 (1.015–1.679)	0.038	1.125 (0.788–1.608)	0.516
Family history of MI (yes)	1.286 (0.622–2.658)	0.498		
LVEF (per %)	0.970 (0.943–0.999)	0.041	0.962 (0.921–1.005)	0.081
Extent score (per %)	1.163 (1.107–1.222)	<0.001	1.158 (1.098–1.222)	<0.001

FBG = fasting blood glucose; OR = odds ratio; other abbreviations as in Table 1.

Furthermore, among patients with ACS (who had significantly lower adiponectin levels than stable CAD patients), those with multiple complex lesions had significantly lower adiponectin levels than those with single complex lesions. Thus, hypoadiponectinemia is associated with coronary lesion complexity, and our results suggest that the extent of hypoadiponectinemia may provide valuable information about coronary plaque vulnerability.

Vulnerable coronary plaques, which include rupture-prone plaques and atheromatous plaques with high likelihood of thrombotic complications and rapid progression, play crucial roles in the development of ACS (11). Inflammation and metabolic disorders are thought to be implicated in the pathogenesis of coronary plaque vulnerability (26). Previous studies demonstrated that inflammatory serologic markers, serum neopterin, and pregnancy-associated plasma protein A are associated with coronary lesion complexity (23,27). In addition to such inflammatory processes, metabolic disorders, including diabetes mellitus, may also affect coronary plaque vulnerability (26,28). Indeed, pathologic studies demonstrated that coronary plaques of diabetic patients exhibited increased infiltration of macrophages and thrombus formation (29), indicating vulnerable and activated plaque condition.

Adiponectin, an adipocyte-derived plasma protein with anti-diabetic and anti-atherogenic properties, may be a key molecule in the pathogenesis of diabetes mellitus and metabolic syndrome (3). Adiponectin suppresses macrophage-to-foam cell transformation (30,31) and increases the expression of tissue inhibitor of metalloproteinase-1 in monocyte-derived macrophages through induction of interleukin-10 (32), suggesting that adiponectin may be a positive contributor to the stabilization of atherosclerotic plaques.

To our knowledge, the present study represents the first report demonstrating that low adiponectin levels are significantly associated with coronary lesion complexity, reflecting plaque vulnerability, in men with CAD. This finding may in part help explain the missing link between metabolic disorders and cardiovascular complications resulting from the disruption of vulnerable plaques.

Several lines of evidence point to the role of adiponectin in atherogenesis, and it is conceivable that the low adiponectin levels in patients with complex coronary lesions in the present study can be the cause and consequence of active atherosclerosis. Adiponectin could reduce atherosclerosis by inhibiting endothelial expression of adhesion molecules (6), modulation of macrophage functions (30,31), and suppression of vascular smooth muscle cell proliferation (33). Plasma levels of adiponectin are reduced in patients with CAD (6), and a previous study (9) reported significantly lower adiponectin levels in patients with ACS than those with stable CAD. A recent report found that low levels of plasma adiponectin were associated with future development of MI in men without cardiovascular disease (10), suggesting that low adiponectin may contribute to the development of ACS. We have recently reported (34) the reduction of plasma adiponectin in the early phase of acute MI, and accumulation of adiponectin has been demonstrated in the walls of injured vessels, but not in intact vessels (30,35). Therefore, increased consumption of circulating adiponectin in active atheroma might lower the plasma levels of this molecule in patients with complex lesions.

Based on the mechanisms of acute coronary events, we have recognized the clinical importance of evaluating not only the degree of coronary luminal stenosis but also plaque vulnerability in determining disease activity and the risk of

Table 3. Polytomous Logistic Regression Analysis of Factors Associated With Single and Multiple Complex Lesions in Patients With Stable Coronary Artery Disease

	Single Complex Lesion				Multiple Complex Lesions			
	Univariate		Multivariate		Univariate		Multivariate	
Factor	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (per yr)	0.980 (0.937–1.025)	0.368			1.052 (0.996–1.112)	0.072		
BMI (per kg/m^2)	1.025 (0.897–1.172)	0.715			1.030 (0.901–1.177)	0.666		
Smoking (yes)	1.111 (0.400–3.089)	0.840			0.648 (0.257–1.634)	0.358		
Systolic BP (per mm Hg)	1.014 (0.993–1.036)	0.200			1.010 (0.988–1.031)	0.381		
Diastolic BP (per mm Hg)	1.011 (0.975–1.048)	0.566			0.990 (0.953–1.028)	0.607		
Total cholesterol (per mg/dl)	1.010 (1.000–1.021)	0.057			1.001 (0.990–1.012)	0.822		
HDL cholesterol (per mg/dl)	0.973 (0.939–1.007)	0.119			0.982 (0.951–1.015)	0.279		
LDL cholesterol (per mg/dl)	1.016 (1.004–1.028)	0.010	1.014 (1.000–1.029)	0.049	1.004 (0.992–1.017)	0.471	1.006 (0.989–1.022)	0.499
Triglycerides (per doubling)	1.213 (0.704–2.089)	0.486			1.523 (0.896–2.590)	0.120		
Diabetes mellitus (yes)	1.323 (0.557–3.144)	0.526			1.524 (0.648–3.582)	0.334		
FBG (per mg/dl)	1.006 (0.992–1.021)	0.391			1.011 (0.997–1.025)	0.116		
Hemoglobin A1c (per %)	1.007 (0.716–1.416)	0.970			1.002 (0.701–1.431)	0.992		
Adiponectin (per doubling)	0.565 (0.336–0.948)	0.031	0.505 (0.261–0.979)	0.043	0.463 (0.273–0.784)	0.004	0.290 (0.128–0.658)	0.003
Creatinine (per 0.1 mg/dl)	1.007 (0.815–1.245)	0.948			1.241 (1.021–1.509)	0.030		
hs-CRP (per doubling)	1.252 (0.915–1.712)	0.159			1.361 (0.995–1.862)	0.054		
Family history (yes)	1.091 (0.428–2.784)	0.856			1.500 (0.614–3.667)	0.374		
LVEF (per %)	0.965 (0.932–1.000)	0.049	0.962 (0.922–1.004)	0.077	0.976 (0.941–1.012)	0.184	0.992 (0.938–1.048)	0.766
Extent score (per %)	1.140 (1.083–1.201)	<0.001	1.135 (1.075–1.199)	<0.001	1.199 (1.131–1.270)	<0.001	1.199 (1.126–1.277)	<0.001

Abbreviations as in Tables 1 and 2.

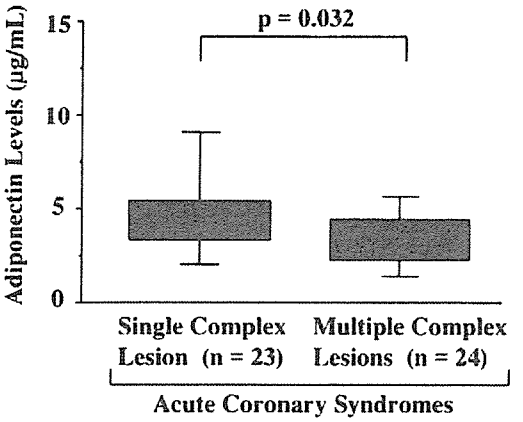

Figure 3. Box-and-whisker plot showing plasma levels of adiponectin in acute coronary syndrome patients with single (n = 23, **blue**) and multiple complex lesions (n = 24, **red**). In these plots, **lines within boxes** represent median values; the **upper and lower lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively. Abbreviations as in Figure 1.

subsequent vascular complications (11). Angiographically, the presence of complex coronary lesions correlates with pathologic plaque rupture and thrombus formation (13). Clinical observations demonstrated that complex lesions were associated with accelerated progression of plaque stenosis (15–18), and they were also predictive of future cardiac events (14,15). Angiographic assessment of the morphology of coronary stenosis is well established and considered to be clinically useful for risk stratification of CAD patients (15). In the present study, we showed that adiponectin is significantly associated with coronary lesion complexity in men with CAD. Our results may indicate that low plasma adiponectin could perhaps be used to predict the occurrence of future cardiovascular events; however, further prospective studies are required to clarify this issue because we did not assess clinical outcomes in the present study.

It is widely accepted that inflammation plays an important role in the pathogenesis of atheromatous plaque vulnerability (36). In our present study, hs-CRP levels in patients with stable CAD were significantly associated with the presence of complex coronary lesions in simple logistic regression analysis. Furthermore, hs-CRP levels in patients with complex lesions were higher than those with simple lesions, though the difference was not statistically significant. Previous studies have demonstrated that hs-CRP levels correlate with coronary lesion complexity in patients with unstable angina (37,38), whereas such associations cannot be observed consistently in patients with stable CAD (27,39,40). In part, our results were in line with the previous observations; however, the rather weak association between hs-CRP and coronary lesion complexity in patients with stable CAD is intriguing.

This study was limited by the relatively small number of patients studied. We demonstrated that plasma adiponectin level is an independent predictor of complex lesions in men with stable CAD in multiple logistic regression analysis, though it was barely statistically significant. Further studies in a large number of patients should confirm our results. There was some overlap of distribution in adiponectin levels between patients with complex and simple lesions, however, hypoadiponectinemia (<4.0 μg/ml) (8) was a significant risk factor for the presence of complex coronary lesions in the present study. Thus, our finding regarding lower adiponectin levels in patients with complex lesions may support the concept that hypoadiponectinemia could be implicated in the development of coronary plaque instability and may suggest that hypoadiponectinemia could be helpful for the evaluation of coronary plaque instability as well as the presence of CAD. Moreover, therapeutic utility of increasing adiponectin levels remains to be elucidated, and our results may in part suggest that thiazolidinedione, a peroxisome proliferator-activated receptor-gamma agonist known to increase adiponectin (20), could be an agent to stabilize the atheromatous plaques and prevent atherothrombosis. However, further studies are needed to clarify the issue because we did not evaluate the effect of such agents in the present study.

In conclusion, plasma adiponectin levels in men with stable CAD and complex coronary lesions were significantly lower than in those with simple lesions, and ACS patients with multiple complex lesions had significantly lower adiponectin levels than those with single complex lesions. Thus, hypoadiponectinemia is associated with coronary lesion complexity in patients with CAD. Our results suggest that low levels of adiponectin may contribute to coronary plaque vulnerability, and plasma adiponectin levels may provide valuable information regarding coronary plaque vulnerability.

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Adiponectin Concentration in Umbilical Cord Serum Is Positively Associated with the Weight Ratio of Fetus to Placenta

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Context: Adiponectin (APN) concentration in umbilical cord serum is higher than that in adult serum. Except for the positive association between birth weight and cord APN concentration, little is known about the pathophysiological function of APN in fetal development.

Objective: The objective of this study was to evaluate the relationship of cord serum APN and IGF-I concentrations with the development of the fetoplacental unit.

Design and Methods: Umbilical cord serum APN and IGF-I concentrations were measured in term singleton deliveries (n = 94). The association of cord APN and IGF-I concentrations was evaluated in relation to fetal weight, placental weight, and fetoplacental (F/P) weight ratio.

Results: Mean concentrations and SD of APN and IGF-I were 36.1 ± 14.0 μg/ml and 58.6 ± 27.0 ng/ml, respectively. Cord APN concentration was positively associated with F/P weight ratio ($r = 0.375$, $P < 0.001$) as well as fetal weight ($r = 0.389$, $P < 0.001$) but not placental weight. Cord IGF-I concentration was positively associated with fetal weight ($r = 0.405$, $P < 0.001$) and placental weight ($r = 0.400$, $P < 0.001$) but not F/P weight ratio. In multiregression analysis, only APN concentration resulted in a significant determinant of F/P weight ratio among variables ($\beta = 0.376$, $P < 0.001$).

Conclusions: In cord hyperadiponectinemia, fetuses tend to be disproportionately larger for their placental weight and vice versa in cord hypoadiponectinemia. APN is shown to be the first biomarker positively associated with F/P weight ratio. (***J Clin Endocrinol Metab* 91: 5090–5094, 2006**)

ADIPONECTIN WAS ORIGINALLY purified and identified from human adipose tissue (1) and was characterized as one of the major cytokines exerting pivotal protective effects against metabolic diseases such as diabetes and atherosclerosis (2–6). The mouse counterparts of adiponectin, Acrp30 or AdipoQ, were also independently cloned by two groups (7, 8). Hypoadiponectinemia is observed in patients with obesity (9), diabetes mellitus (10, 11), or coronary artery disease (12). Animal studies have shown that plasma glucose levels were lowered by injection of adiponectin (13). Elevated fatty acid levels were also decreased by injection of the globular domain of adiponectin (14).

Several studies have shown possible involvement of adiponectin in fetal development (15, 16). As early as 24 wk of gestation, adiponectin is detectable in cord serum, and its level increases dramatically during gestation, reaching near plateau at term (17). The adiponectin level in term pregnancy is higher than that in adult serum (15, 16). In fetal tissue, adiponectin is expressed in not only adipocytes but also other organs including muscle cells and intestinal wall (18).

Adiponectin receptors have been purified and shown to increase AMP kinase and peroxisomal proliferator-activated receptor-α ligand activities as well as glucose uptake by adiponectin (19). More recently the gene expression of adiponectin and its receptor in placental tissue has been reported (20).

In human species, both the placenta and fetus grow as the gestational weeks advance. However, their growth curves differ from each other, and hence, the weight ratio of the fetus to the placenta or fetoplacental weight ratio (F/P weight ratio) shows a linear increase during gestation and then reaches near a plateau level at term (21). The weight ratio is approximately one sixth in term pregnancy and one seventh when the umbilical cord and membrane are removed (22, 23). However, the placenta tends to be larger in a adverse environment including maternal anemia (24, 25), diabetes mellitus (26), and living at higher altitudes (27). Evidence has shown that fetuses with larger placenta disproportionate to their body size have higher incidences of developing hypertension later in adult life (28).

Currently there is little known about the mechanism of regulating both fetal and placental size or about the interrelationship between the two.

In this paper, we evaluated the association of umbilical cord adiponectin concentration with fetoplacental development. The findings showed that fetal umbilical cord adiponectin concentration is positively associated with the birth weight of the fetus and, interestingly, with the weight ratio of the fetus to placenta as well. This finding shows that adiponectin is the first bioactive molecule associated with the F/P weight ratio and that adiponectin might facilitate fetal development with a lower increase in placental size.

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Abbreviations: BMI, Body mass index; F/P, fetoplacental.

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Patients and Methods

Patients complicated with thyroid disease, diabetes mellitus, or collagen diseases were not recruited. All participants gave informed consent for the study. An oral glucose tolerance test was carried out in all participants during the second trimester, and one patient diagnosed as having gestational diabetes mellitus was excluded. Accordingly, 94 patients with term singleton delivery were included in the analysis. None of the newborns were complicated with any anomaly.

Identification of gestational age

Gestational age was determined basically according to the first-trimester crown-rump length scan or based on the ovulation date on basal body temperature when available.

Anthropometric measurements of fetus and placenta

After delivery, the umbilical cord was clamped, and blood was drawn from the umbilical vein. The umbilical cord was cut, and the placenta was collected. Blood and clots on the surface were removed, and placental weight was measured with a calibrated scale and recorded. Birth weight was measured soon after delivery, and birth length was measured with the use of a wooden measuring board. F/P weight ratio [birth weight (grams) divided by placental weight (grams)] was calculated in each delivery. Fetal body mass index (BMI) was defined as birth weight in kilograms divided by birth length in meters squared.

Assay of umbilical cord serum adiponectin and IGF-I

Plasma samples were kept at −80 C for subsequent assay. The concentration of adiponectin was measured by a sandwich ELISA system (adiponectin ELISA kit; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), as described previously (9). IGF-I was measured by a ELISA system (human IGF-I immunoassay kit; R&D systems, Minneapolis, MN). The intra- and interassay coefficiencies of variations were 3.3 and 7.4% for adiponectin and 4.0 and 8.0% for IGF-I. The limits of detection for adiponectin and IGF-I were 120 and 2.6 ng/ml, respectively.

Evaluation of the relationships of adiponectin and IGF-I concentrations with anthropometric measures of mother, fetus, and placenta

The relationship between cord adiponectin and IGF-I concentrations with birth weight, placental weight, F/P weight ratio, and other anthropometric measurements were evaluated with univariate regression analysis. Scatterplots for F/P weight ratio against adiponectin and IGF-I concentrations were shown, and a regression line was inserted.

To evaluate the dependency of birth weight, placental weight, and F/P weight ratio on umbilical adiponectin concentration, we stratified the subjects into four groups according to adiponectin concentration. Because mean value and SD of adiponectin concentrations were 36 and 14 μg/ml, respectively, cases were stratified as follows, *i.e.* less than 22 μg/ml (mean −1.0 SD) in adiponectin concentration was considered the low adiponectin group, and adiponectin concentration more than 50 μg/ml (mean +1.0 SD) was considered the high adiponectin group. The group with a middle level concentration (22 μg/ml < adiponectin ≤ 50 μg/ml) was subdivided into two groups. The clinical and laboratory background of the groups are also shown.

Multivariate regression analysis with F/P weight ratio as an independent variable

Multiple regression analysis was carried out to estimate independent contributions of selected variables (adiponectin, IGF-I, maternal BMI at booking, gestational week, and fetal sex) on F/P weight ratio.

Statistical analysis

The differences in F/P weight ratio among the groups were assessed with Student *t* test. Statistics, including insertion of regression line, and multivariate regression analysis were all processed with SPSS 12.0 for Windows (SPSS Japan Inc., Tokyo, Japan).

Results

Relationships of cord serum adiponectin and IGF-I concentrations with birth weight, placental weight, F/P weight ratio, and other anthropometric measurements of fetus and mother

Both adiponectin and IGF-I concentrations were positively associated with fetal anthropometric measurements including birth weight, birth length, and BMI. Whereas IGF-I was positively associated with placental weight, adiponectin did not show any association (Table 1). When association with F/P weight ratio was examined, the positive association was found in adiponectin concentration, whereas IGF-I concentration was not correlated with the F/P weight ratio (Table 1 and Fig. 1). Neither adiponectin nor IGF-I in umbilical cord was associated with anthropometric measurements of the mother.

Evaluation of fetoplacental development and the clinical and laboratory background of the groups categorized according to umbilical cord adiponectin concentration

As shown in Fig. 2, F/P weight ratio demonstrated significant differences among the groups. There were no significant differences in maternal BMI at booking, fetal BMI, or gestational week among the groups. There was also no significant difference in IGF-I concentrations (Table 2). Although fetal BMI and birth length are positively associated with APN concentration on univariate regression analysis, the trends were attenuated in evaluation among the groups (Table 2). In the high adiponectin group, birth weights tended to be larger without a significant increase in placental weight; whereas in the low adiponectin group, birth weight was lower without significant change in placental weight (Fig. 2).

Multivariate regression analysis with F/P weight ratio as independent variable

At univariate regression analysis, F/P weight ratio significantly correlated with both adiponectin concentration and gestational week (Table 3). When the independent contribution of physical and metabolic variables on F/P weight ratio was tested, only adiponectin resulted in a significant deter-

TABLE 1. Relationships between umbilical cord serum adiponectin and IGF-I concentrations with birth weight, placental weight, F/P weight ratio, and other clinical background data

Variables	Adiponectin		IGF-I	
	r	*P*	r	*P*
Fetus and placenta				
Birth weight	0.389	<0.001	0.405	<0.001
Placental weight	−0.020	0.845	0.400	<0.001
F/P weight ratio	0.375	<0.001	−0.083	0.425
Birth length	0.346	<0.001	0.222	<0.05
BMI	0.316	<0.01	0.427	<0.001
Sex (1, female; 0, male)	−0.050	0.637	0.130	0.228
Mother				
Body weight at booking	0.087	0.407	0.045	0.663
Body weight at term	0.094	0.369	0.104	0.319
Weight gain	0.037	0.726	0.150	0.148
Height	−0.022	0.835	0.075	0.472
BMI at booking	0.114	0.273	0.013	0.900
BMI at term	0.131	0.207	0.077	0.458
Gestational week	0.118	0.259	−0.038	0.715

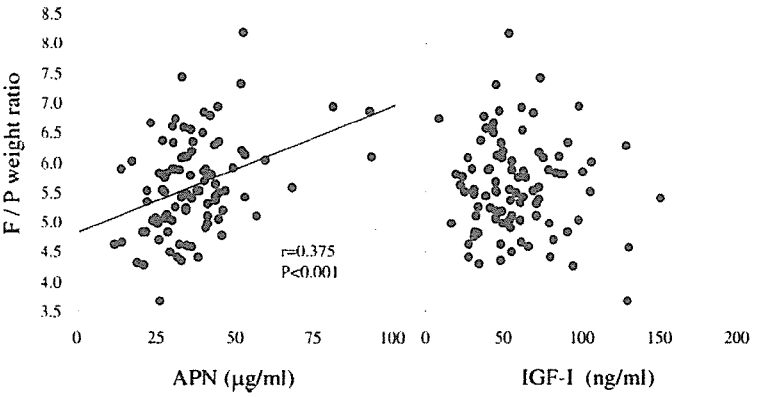

FIG. 1. Relationship between umbilical cord serum adiponectin (APN) and IGF-I concentrations with F/P weight ratio. Adiponectin concentration is positively associated with F/P weight ratio. IGF-I concentration is not associated with F/P weight ratio. The regression line and Pearson correlation coefficient are shown.

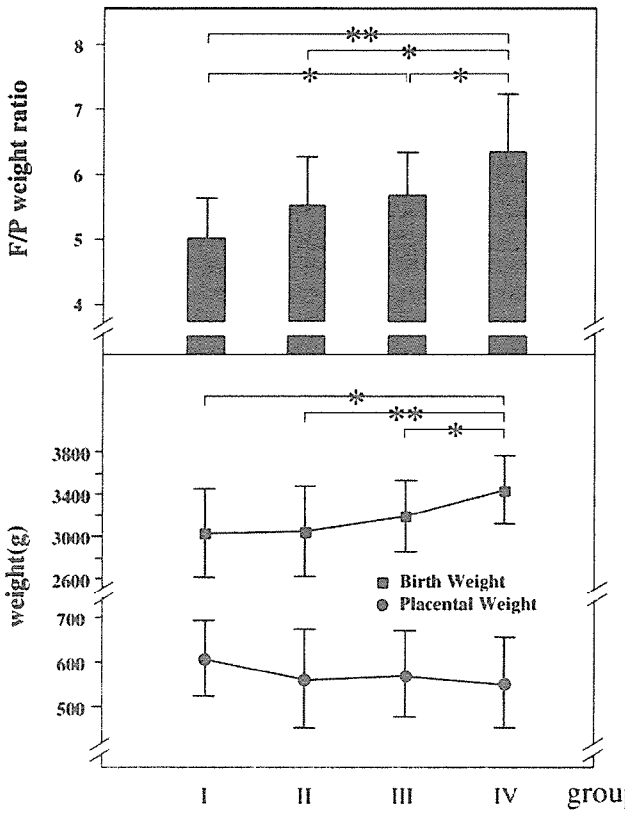

FIG. 2. Mean F/P weight ratio, placental weight, and birth weight in each group. *Error bar*, SD. *, $P < 0.05$; **, $P < 0.01$.

minant of F/P weight ratio (Table 3). Maternal BMI, fetal sex, cord IGF-I concentration, and gestational week were not correlated with F/P weight ratio.

Discussion

F/P weight ratio is dependent on gestational age, and even at the same gestational age, the ratio varies quite widely. However, a heavy fetus generally has a large placenta, whereas a small fetus has a small placenta. So when we compare the mean F/P weight ratio between two randomly selected groups, the ratio should be similar. However, when we stratify patients by umbilical cord serum adiponectin concentration, placental weight tend to be disproportionate to birth weight. In the high adiponectin group, the babies have a higher birth weight with a relatively smaller placenta; whereas in the low adiponectin group, the babies have a lower birth weight with a relatively larger placenta. Although the association of F/P weight ratio and adiponectin is significant, as shown in Fig. 1, it appears that there was a contribution of three outlying points in which APN concentrations were more than 80 μg/ml. However, even if these three points are excluded, the positive association of adiponectin and F/P weight ratio remains significant ($r = 0.311$, $P = 0.003$). Therefore, the positive association seems rather robust.

The positive association of fetal adiponectin level and fetal fat mass are suggested (16). However, because fetal BMI is high, it does not mean that the fetus has a high F/P weight ratio. On the contrary, a fetus with a high birth weight may have an even smaller F/P weight ratio as in the case of newborns from a diabetes mellitus mother. Multiple regression analysis showed

TABLE 2. Clinical and laboratory characteristics of all cases

		Group				*P* for trend
	All (n = 94; APN 11.4–92.8 μg/ml)	I (n = 10; APN ≤ 22 μg/ml)	II (n = 46; APN 22–36 μg/ml)	III (n = 27; APN 36–50 μg/ml)	IV (n = 11; APN > 50 μg/ml)	
APN (μg/ml)	36.1 ± 14.0	18.0 ± 3.9	29.9 ± 3.8	41.9 ± 3.1	64.4 ± 16.5	<0.001
IGF-I (ng/ml)	58.6 ± 27.0	63.6 ± 27.4	56.5 ± 26.5	56.0 ± 26.1	69.2 ± 32.3	0.452
Birth length (cm)	50.2 ± 1.4	50.0 ± 1.4	49.9 ± 1.3	50.4 ± 1.4	51.1 ± 1.5	0.092
BMI (fetus)	12.5 ± 1.2	12.2 ± 1.3	12.3 ± 1.3	12.6 ± 1.0	13.2 ± 0.9	0.064
BMI at booking	25.0 ± 3.2	25.9 ± 4.4	24.7 ± 3.0	25.0 ± 3.2	25.4 ± 3.2	0.374
Gestational week	39.7 ± 1.2	39.5 ± 1.4	39.6 ± 1.2	39.6 ± 1.0	40.3 ± 1.1	0.329

Groups were stratified by adiponectin concentration in umbilical cord serum. There were no significant differences in fetal and maternal BMI, birth length, umbilical cord serum IGF-I concentration, or gestational week among groups. Data are expressed as means ± SD.

neither the BMI of the newborn nor SD score of birth weight is a significant contributor to the F/P weight ratio (data not shown). We evaluated the association of F/P weight ratio with adiponectin concentration per birth weight, *i.e.* statistical analysis was performed using adiponectin per birth weight (adiponectin concentration divided by birth weight) instead of adiponectin concentration itself. The finding was almost the same. Therefore, the positive association between F/P weight ratio and adiponectin concentration is not the reflection of association of fetal body weight or adiposity with adiponectin concentration.

The regulation of adiponectin production and secretion have not been well clarified at present. In adults, the serum adiponectin level is paradoxically decreased in obesity (9). In the fetus, on the contrary, umbilical cord adiponectin level is positively associated with fetal birth weight in this study as well as others (15, 16). A recent report has shown that the adiponectin level was significantly lower in large-for-gestation newborns (29); therefore, a negative feedback mechanism between adipose tissue and adiponectin level might be exerted, even in the fetus. The expression of adiponectin in the fetus was recently reported in both white and brown adipose tissue and skeletal and smooth muscle cells (18), and gene expression of adiponectin has been demonstrated in placental tissue (20). A recent report showed that cytokines such as TNF-α, interferon-γ, IL-6, and leptin differentially modulate placental adiponectin gene expression and secretion and suggest that adiponectin controls energy metabolism at the maternofetal interface (30).

F/P weight ratio is modulated by several factors. For example, it is reported to be decreased in maternal anemia (24, 25), and ratios in diabetes mellitus mothers are also reported to be lower (31). Furthermore, the F/P weight ratio is lower in pregnant women living at high altitudes (27). These findings suggest that the placental size increases to overcome adverse intrauterine circumstances. Other factors reported to be inversely associated with F/P weight ratio are maternal BMI at booking, maternal smoking, female sex, and newborn's abdominal circumference to head circumference (32). Newborn's length to head circumference is reported to be positively associated with F/P weight ratio (32).

We do not know why a higher adiponectin level is observed in the cord blood of a large fetus with a relatively smaller placenta or why a lower adiponectin level is observed in the cord blood of a small fetus with a large placenta. We also do not know whether adiponectin is indeed a factor involved in alteration of the F/P weight ratio or the relationship of adiponectin concentration and F/P weight ratio is just an associated phenomenon in a certain intrauterine environment.

TABLE 3. Univariate and multivariate linear regression analysis for F/P weight ratio

Independent variable	Univariate analysis		Multivariate analysis	
	β	P	β	P
Maternal BMI at booking	0.010	0.922	−0.071	0.469
Sex (1, female; 0, male)	0.017	0.830	0.025	0.800
Gestational week	0.211	0.041	0.168	0.092
Adiponectin	0.375	<0.001	0.376	<0.001
IGF-I	−0.083	0.425	−0.114	0.244

Dependent variable is F/P weight ratio.

The babies of mothers with uncontrolled diabetes mellitus are often heavy for gestational age due to fetal hyperinsulinemia resulting from maternal hyperglycemia. Umbilical cord IGF-I has been shown to be positively associated with fetal growth by other studies as well as the present study (33–36). In contrast to insulin or IGF-I, adiponectin itself has no mitogenic properties. In this context, we speculate that the positive association of birth weight and adiponectin concentration might be due to augmented insulin sensitivity by adiponectin. Considering the existence of its receptor in the placenta (20), adiponectin might modulate insulin action differentially in the fetus and placenta at the level of its receptor, resulting in a positive association with F/P weight ratio. To further test these hypotheses, we need to evaluate F/P weight ratio and adiponectin concentration in various settings including gestational diabetes mellitus patients in which a low F/P weight ratio is well known (37).

The placenta is a pivotal organ supplying energy, nutrients, water, and oxygen to the fetus through the umbilical cord, and the placenta itself is also an energy-consuming organ. Just as adiponectin concentration is inversely related to the degree of adiposity in adults, adiponectin in the fetus might play a role in facilitating efficient energy consumption from limited placental energy sources by properly augmenting insulin functions.

Several studies have shown the clinical significance of F/P weight ratio. Molteni *et al.* (21) have shown that the neonate with higher F/P weight ratio has a higher incidence of low Apgar scores. Bonds *et al.* (38) also reported the association of higher F/P weight ratio and poor perinatal outcome such as low Apgar scores, fetal distress, and hyperbilirubinemia. Barker *et al.* (39) reported that adult-onset diseases such as cardiovascular diseases or diabetes mellitus originate during the fetal period, and they also have shown that small infants with a large placenta show the highest incidence of developing hypertension later in adult life (28). More recently, Hemachandra *et al.* (40) reported that the F/P weight ratio is the only anthropometric measure significantly associated with hypertension at age 7 yr in intrauterine growth retardation babies. In this context, it is interesting that adiponectin concentration is also inversely associated with blood pressure in children (41), adolescent females (42), and young men (43), independent of BMI or percent fat mass.

In this paper, we have shown that umbilical serum adiponectin is the first biomarker significantly associated with the weight ratio of the fetus and placenta. Because of its antiatherogenic and antidiabetic properties in adult, the pathophysiological function of adiponectin in fetal development remains to be elucidated.

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All authors have nothing to declare.