Original Article

Associations between Metabolic Factors and Coronary Plaque Growth or Arterial Remodeling as Assessed by Intravascular Ultrasound in Patients with Stable Angina

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Although many clinical studies have evaluated plaque growth in response to positive or negative remodeling in coronary arteries using intravascular ultrasound (IVUS), little is known about the associations between metabolic factors and coronary plaque growth or remodeling. In this cross-sectional study, we analyzed 100 consecutive patients with stable angina who had undergone preinterventional IVUS. The characteristics of coronary plaque (plaque area [PA] and volume [PV]) and remodeling patterns were analyzed by IVUS. Patients were divided into two groups: a positive remodeling (P) group (remodeling index [RI] > 1.0, *n* = 37) and a non–positive remodeling (NP) group (RI ≤ 1.0, *n* = 63). Patient characteristics, including age, gender, body mass index and angiographic variables, were similar between the two groups. Interestingly, plasma adiponectin levels in the P group were significantly lower than those in the NP group. The remodeling classification was most closely associated with plasma adiponectin levels (*p* = 0.006) among the metabolic factors. Although there were no significant correlations between RI and %PA or %PV, and although %PA but not %PV in the P group was significantly higher than that in the NP group, %PV was significantly associated with plasma low-density lipoprotein cholesterol (LDL-C) and diastolic blood pressure, but not adiponectin, in all patients. In addition, higher %PV was most closely correlated with higher plasma LDL-C (*p* = 0.009) among metabolic factors. In conclusion, among the metabolic factors examined, plasma adiponectin levels may be critical for arterial remodeling, while higher levels of LDL-C may be most useful for predicting PV. (*Hypertens Res* 2008; 31: 1879–1886)

***Key Words*: intravascular ultrasound, plaque volume, arterial remodeling, adiponectin, low-density lipoprotein cholesterol**

Introduction

Atherosclerosis is the underlying disorder in most patients with coronary artery disease (CAD). Remodeling of the vessel wall at the site of coronary atherosclerotic plaque was originally described in a necropsy study by Glagov *et al*. (*1*) and later confirmed *in vivo* with intravascular ultrasound (IVUS) (*2*). Positive remodeling is defined as a compensatory increase in local vessel size in response to an increase in plaque burden (*3*). In addition, positive remodeling is reported to be more common in patients with unstable angina than in those with stable angina, and there is a higher risk for no-reflow phenomenon after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (*4*). Negative remodeling is defined as the local shrinkage of ves-

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sel size and has been implicated in the development of native atherosclerosis (*5*, *6*) and restenosis after PCI (*7*). A recent study reported that positive remodeling had a larger plaque area and was associated with an unstable clinical presentation, whereas negative remodeling was more common in patients with a stable clinical presentation (*8*). Thus, IVUS has been used to obtain detailed insight regarding coronary atherosclerotic plaque.

Metabolic syndrome (MetS), which consists of a clustering of cardiovascular risk factors such as abdominal obesity, diabetes mellitus (DM), dyslipidemia and hypertension (HT), is associated with increased CAD morbidity and mortality (*9*, *10*). Adiponectin, a collagen-like plasma protein produced by adipose tissue, is known to play an important role in the development of MetS. A lower level of adiponectin is considered to be an independent risk factor for CAD, and is associated with patients with acute coronary syndrome (ACS) (*11*) and coronary complex lesion in stable CAD (*12*).

Although many clinical studies have evaluated the progression of plaque in response to positive or negative remodeling in coronary arteries using IVUS (*3*–*7*), little is known about the associations between metabolic factors and plaque growth or remodeling. In this cross-sectional study, we investigated the association between parameters of IVUS and metabolic factors in patients with stable CAD.

Methods

Study Population

A total of 100 consecutive patients with stable angina who underwent PCI under IVUS guidance from January 2005 to August 2006 were enrolled in this retrospective study. Stable angina was defined as no change in frequency, duration, or intensity of symptoms for 4 weeks. Patients with unstable angina or myocardial infarction within the previous 4 weeks, ejection fraction $<40\%$, secondary causes of hypercholesterolemia, and severe hypertriglyceridemia (>400 mg/dL) were excluded. We also excluded patients with obvious heart failure (NYHA$\geq$III). The ethics committee of Fukuoka University Hospital approved this study, and written informed consent was obtained from each patient.

Quantitative Coronary Angiography Analysis and IVUS Procedure

The angiographic laboratory at Fukuoka University Hospital performed all quantitative coronary angiography (QCA) analysis by a computer-assisted automated edge-detection algorithm (CMS; Medis, Leesburg, USA) using standard protocols (*13*). The angiographic laboratory was unaware of the clinical data. The target lesion was defined as the area occupied by the stent and 5 mm proximal and distal to the edge of the stent. All coronary angiogram and IVUS examinations were performed before any intervention and after the intracoronary administration of 100 to 200 μg of nitroglycerin. The IVUS procedure was performed using a commercially available IVUS system that incorporated a 40-MHz transducer within a short monorail imaging sheath (Boston Scientific Corporation/SciMed, CA, USA). The IVUS catheter was advanced distal to the target lesion (>10 mm distal), and imaging was performed before intervention in a retrograde manner back to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s.

IVUS Quantitative Analysis

In the conventional IVUS analysis, cross-sectional images were quantified for the vessel area (VA), lumen area (LA), and plaque area (PA), using planimetry software (TapeMeasure; INDEC Systems Inc.). Reference segments were the most normal-looking cross sections within 5 mm proximal and distal to the lesion, but before any side branch. The remodeling index was defined as the ratio of the VA at the lesion site to the VA at the proximal reference site. If external elastic membrane could not be detected (because of extensive calcification with acoustic shadowing), the patient was excluded from the study. Positive remodeling was defined as a remodeling index (RI)>1.0 ($n=37$, P group), and non-positive remodeling was RI≤ 1.0 ($n=63$, NP group).

Conventional 3-dimensional (3D) IVUS image analysis was conducted using commercially available software (EchoPlaque; Indec System, Mountain View, USA). After IVUS, recordings were digitized at a frame rate of 30 images/s; longitudinal views of the studied segments were automatically processed by the system. The VA and LA were manually traced at 16-frame intervals, and interpolated measurements of the remaining frames were generated automatically. Vessel volume (VV), lumen volume (LV), and total plaque volume (PV) were calculated. Percent PA ($=100 \times$ PA/VA) and %PV ($=100 \times$ PV/VV) were also calculated.

Blood Sampling and Measurement of Plasma Adipocytokines

Venous blood was drawn from all patients just before coronary angiography. The serum profile, including fasting blood sugar (FBS), hemoglobin A1c (HbA1c), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), creatinine, and high-sensitivity C-reactive protein (hs-CRP) levels, was determined in the hospital laboratory. Plasma samples were immediately stored at -80°C for subsequent assay for adiponectin and tumor necrotic factor (TNF)-α levels by enzyme-linked immunosorbent assay (ELISA) as described previously (*14*, *15*). The concentration of plasma adiponectin or TNF-α showed a coefficient of variation $<5\%$.

Patients with LDL-C greater than 140 mg/dL or TG greater than 150 mg/dL were diagnosed with hyperlipidemia. Patients with systolic (diastolic) blood pressure (SBP [DBP])

Table 1. Patients Characteristics

	All subjects (n=100)	P group (n=37)	NP group (n=63)	p value (P *vs*. NP)
Age, years	64±10	64±11	62±9	n.s.
Man, % (n)	84 (84)	91 (34)	79 (50)	n.s.
BMI, kg/m^2	24.4±3.6	24.3±3.7	24.4±3.7	n.s.
Hypertension, % (n)	66 (66)	63 (23)	68 (43)	n.s.
SBP, mmHg	147±21	142±20	148±21	n.s.
DBP, mmHg	75±12	75±12	75±13	n.s.
Diabetes mellitus, % (n)	49 (49)	51 (19)	48 (30)	n.s.
HbA1c, %	6.1±1.1	6.3±1.3	6.0±0.9	n.s.
Fasting glucose, mg/dL	94±18	97±22	93±15	n.s.
Hyperlipidemia, % (n)	71 (71)	71 (26)	71 (37)	n.s.
LDL-C, mg/dL	107±30	109±25	105±33	n.s.
TG, mg/dL	145±121	132±56	152±146	n.s.
HDL-C, mg/dL	47±14	46±13	48±15	n.s.
Smoking, % (n)	70 (70)	80 (30)	65 (40)	n.s.
Uric acid, mg/dL	5.8±1.3	5.7±1.0	5.8±1.4	n.s.
Medication, % (n)				
ARB	40 (40)	37 (14)	45 (26)	n.s.
ACEI	14 (14)	9 (3)	18 (11)	n.s.
CCB	42 (42)	27 (10)	56 (32)	n.s.
β-Blocker	6 (6)	11 (4)	3 (2)	n.s.
Diuretics	13 (13)	9 (3)	16 (10)	n.s.
ISDN	37 (37)	26 (10)	44 (27)	n.s.
Nicorandil	16 (16)	23 (9)	11 (7)	n.s.
Statin	53 (53)	50 (19)	55 (34)	n.s.
Antidiabetic	36 (36)	37 (14)	35 (22)	n.s.
Previous PCI, %	24 (24)	28 (10)	21 (14)	n.s.
Previous CABG, %	1 (1)	0 (0)	2 (1)	n.d.
Previous MI, %	5 (5)	14 (5)	0 (0)	n.d.

P, positive remodeling; NP, non-positive remodeling; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ISDN, isosorbide dinitrate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; n.s., not significant; n.d., not determined.

greater than 140 mmHg (90 mmHg), or those who were under antihypertensive treatment, were considered to have HT. Patients who were being treated for DM or who had a fasting glucose concentration greater than 126 mg/dL were considered to have DM. Otherwise, the results of a 75 g oral glucose tolerance test were used to diagnose DM.

Statistical Analysis

All of the data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.1; SAS Institute Inc., Cary, USA) at Fukuoka University (Fukuoka, Japan). Categorical and continuous variables were compared between the P and NP groups by a χ^2 analysis and unpaired t-test, respectively. Multivariate logistic regression analysis was performed for independent variables (metabolic factors) that were related to the coronary arterial remodeling classification. The Spearman correlation was used to examine the relation between continuous variables. Multiple regression analysis was used to quantify the correlation of metabolic factors to %PV. Data are presented as the mean±SD. Significance was defined by a p value <0.05 unless indicated otherwise.

Results

Patient Characteristics and Angiographic Variables

Patient characteristics in the overall subjects and in the P and NP groups are shown in Table 1. There were no differences in age, gender, body mass index, or medication (calcium channel blocker [CCB], α-blocker, nitroglycerin, diuretics, nicorandil, angiotensin II type 1 receptor blocker [ARB] and

Table 2. Angiographic Characteristics

	All subjects (n=100)	P group (n=37)	NP group (n=63)	p value (P *vs*. NP)
Number of vessels, % (n)				
1	44 (44)	52 (16)	40 (28)	n.s.
2	45 (45)	37 (14)	49 (31)	n.s.
3	11 (11)	11 (4)	11 (7)	n.s.
Target vessel				
RCA/LCx/LAD, % (n)	32/24/44 (32/24/44)	41/24/35 (15/9/13)	27/24/49 (17/15/31)	n.s.
AHA/ACC lesion class				
Lesion type B2/C, % (n)	78 (78)	76 (28)	80 (50)	n.s.
Referense diameter, mm	2.73±0.49	2.78±0.59	2.70±0.43	n.s.
MLD, mm	0.93±0.38	0.87±0.45	0.96±0.34	n.s.
%DS, %	65.9±12.6	68.5±14.7	64.5±11.4	n.s.
Lesion length, mm	19.2±10.6	19.3±11.3	19.0±9.9	n.s.

P, positive remodeling; NP, non-positive remodeling; RCA, right coronary artery; LCx, left circumflex; LAD, left anterior descending; AHA, American Heart Association; ACC, American College Cardiology; MLD, minimum lumen diameter; DS, diameter stenosis; n.s., not significant.

Table 3. IVUS Variables

	All subjects (n=100)	P group (n=37)	NP group (n=63)	p value (P *vs*. NP)
Proximal referense				
VA, mm^2	14.1±4.3	13.1±3.6	14.6±4.6	n.s.
LA, mm^2	6.2±2.5	5.7±2.2	6.5±2.7	n.s.
PA, mm^2	7.9±3.2	7.4±2.9	8.1±3.4	n.s.
Distal referense				
VA, mm^2	11.5±5.1	10.8±5.2	11.9±5.0	n.s.
LA, mm^2	5.6±2.9	5.2±2.7	5.8±3.0	n.s.
PA, mm^2	5.9±3.3	5.6±3.2	6.2±3.3	n.s.
Lesion				
VA, mm^2	12.3±4.2	13.6±4.2	11.4±4.0	0.0139
LA, mm^2	3.0±1.2	3.2±1.5	3.0±1.1	n.s.
PA, mm^2	9.2±3.8	10.4±3.5	8.5±3.8	0.0149
%PA (PA/VA), %	73.5±11.4	76.4±9.1	71.7±12.2	0.0488
Remodeling index	0.97±0.20	1.15±0.18	0.86±0.09	<0.0001
Volumetric analysis				
VV, mm^3	241±164	251±174	234±161	n.s.
LV, mm^3	76±49	74±52	76±49	n.s.
PV, mm^3	165±121	176±129	158±118	n.s.
%PV (PV/VV), %	67.6	68.9	66.8	n.s.
PVI, mm^3/mm	8.9±3.3	9.5±3.2	8.6±3.4	n.s.

IVUS, intravascular ultrasound; P, positive remodeling; NP, non-positive remodeling; VA, vessel area; LA, lumen area; PA, plaque area; VV, vessel volume; LV, lumen volume; PV, plaque volume; PVI, plaque volume index; n.s., not significant.

statin) between the groups. In addition, there were no differences in angiographic parameters or stent implantation procedure characteristics between the groups (Table 2).

IVUS Variables

Table 3 shows the results of 2D IVUS and 3D IVUS analysis of the culprit lesions. Reference vessel parameters were similar between the P and NP groups. Although group P had a larger VA, PA and %PA, there were no significant differences in 3D IVUS variables between the groups.

Relation between IVUS Variables and Clinical Parameters

Plasma levels of adiponectin in the P group were significantly

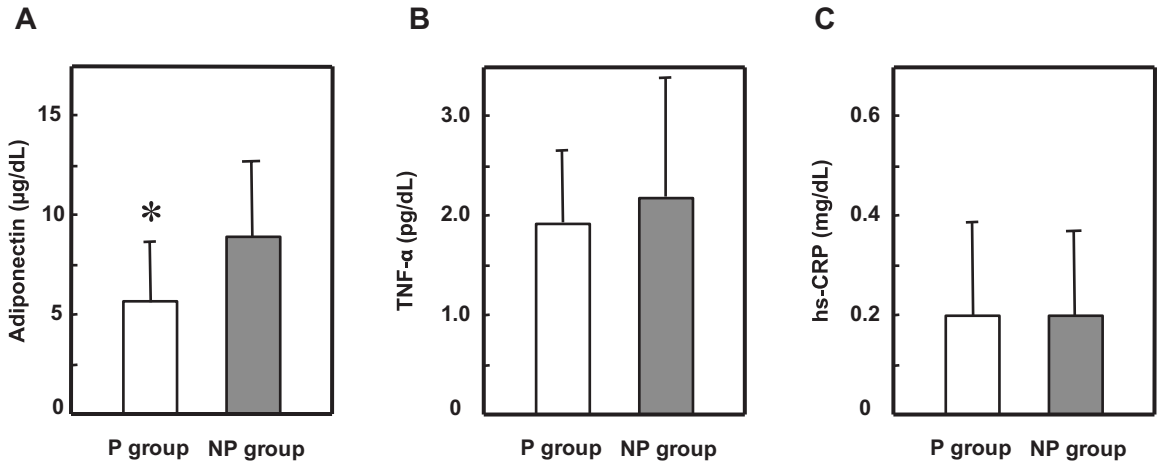

Fig. 1. *Levels of A: plasma adiponectin, B: TNF-α and C: hs-CRP in the P and NP groups. *p < 0.05 vs. NP group.*

Table 4. Multivariate Logistic Regression Analysis of Metabolic Factors Associated with Coronary Arterial Remodeling Classification

Factors	OR (95% CI)	*p* value
Age, years	1.015 (0.954–1.080)	0.63
Male, %	6.227 (0.538–72.09)	0.09
BMI, kg/m^2	0.935 (0.775–1.127)	0.48
SBP, mmHg	0.997 (0.962–1.033)	0.87
DBP, mmHg	1.031 (0.965–1.101)	0.37
HbA1c, %	1.121 (0.685–1.833)	0.65
Fasting glucose, mg/dL	1.108 (0.979–1.058)	0.36
LDL-C, mg/dL	0.995 (0.975–1.014)	0.59
TG, mg/dL	0.995 (0.986–1.003)	0.08
HDL-C, mg/dL	0.981 (0.940–1.023)	0.36
hsCRP, mg/dL	0.752 (0.058–9.801)	0.83
Adiponectin, μg/mL	0.811 (0.687–0.957)	0.006
TNF-α, pg/dL	0.651 (0.317–1.339)	0.23

OR, odds ratio; CI, confidence interval; hsCRP, high-sensitive C-reactive protein; TNF, tumor necrosis factor. Other abbreviations as in Table 1.

lower than those in the NP group, but there were no significant differences in TNF-α and hs-CRP (Fig. 1). The plasma levels of adiponectin did not significantly depend on the patients' use of statin, ARB and CCB, or the presence of HT, DM and dyslipidemia (data not shown). To further analyze the significance of plasma levels of adiponectin, a multivariate logistic regression analysis was performed for the independent variables (metabolic factors including plasma levels of adiponectin, TNF-α, hs-CRP, LDL-C, HDL-C, TG, FBS and HbA1c, SBP, DBP, age, sex and BMI) that were related to the remodeling classification (P and NP groups) (Table 4). The remodeling classification was most closely associated with levels of plasma adiponectin ($p=0.006$).

There were no differences in %PV between patients with and without medications, such as statin, ARB and CCB, or presence of HT, DM and dyslipidemia (data not shown). This finding led us to analyze the association between %PV and metabolic factors. Figure 2 shows the correlations between %PV and LDL-C or DBP in all patients. Although there were no significant correlations between RI and %PA or %PV, and although %PA, but not %PV, in the P group was significantly higher than that in the NP group, %PV was significantly and positively associated with plasma LDL-C ($y=0.076x + 59.4$, $r=0.306$, $p=0.0022$) and DBP ($y=0.13x + 57.8$, $r=0.213$, $p=0.0354$) but not with plasma adiponectin levels ($r=0.036$, $p=0.728$). Multiple regression analysis was performed to analyze the relationship between %PV and metabolic factors indicated above (Table 5). Percent PV was most closely correlated with LDL-C ($p=0.009$), which suggests that a higher LDL-C is the best contributor to a higher %PV.

Discussion

In this cross-sectional study, we assessed the association between parameters of IVUS and metabolic factors in patients with stable CAD. To our knowledge, the present study represents the first report demonstrating that the coronary arterial remodeling classification was most closely associated with the plasma adiponectin concentration. Furthermore, we found that higher levels of LDL-C but not plasma adiponectin levels may be most useful for predicting PV.

Adiponectin has both anti-atherogenic and anti-inflammatory properties. There is increasing evidence that adiponectin plays an important role in the development of CAD (*16*). In addition, a recent study reported a significant association between plasma adiponectin levels and atherosclerotic burden (*15*). Culprit plaques in patients with ACS have more markers of instability (thrombus, positive remodeling, and large plaque mass), whereas negative remodeling is more common

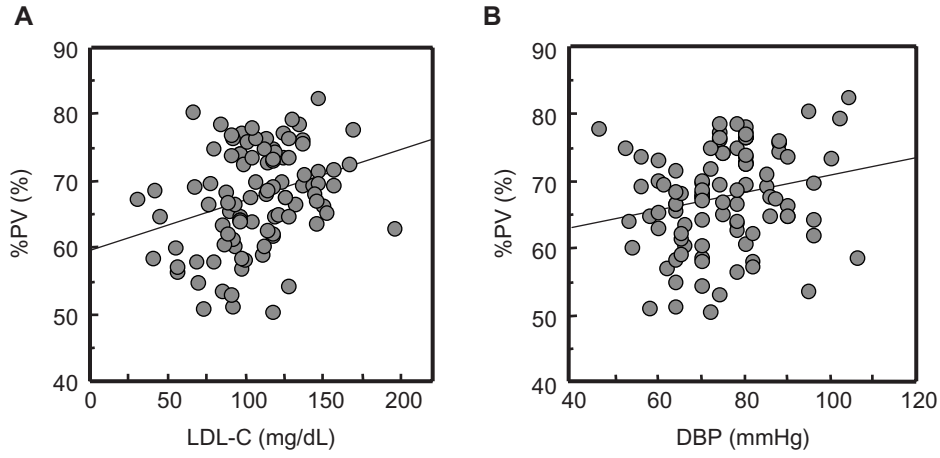

Fig. 2. *Correlations between %PV and A: LDL-C (n = 100, y = 0.076x + 59.4, r = 0.306, p = 0.0022) or B: DBP (n = 100, y = 0.13x + 57.8, r = 0.213, p = 0.0354).*

Table 5. Multiple Regression Analysis of the Relationship between %PV and Metabolic Factors

Factors	Standardized regression coefficient	*p* value
Age, years	0.03	0.84
Male, %	−0.09	0.45
BMI, kg/m^2	−0.08	0.93
SBP, mmHg	0.04	0.81
DBP, mmHg	0.39	0.02
HbA1c, %	0.26	0.03
Fasting glucose, mg/dL	0.08	0.47
LDL-C, mg/dL	0.31	0.009
TG, mg/dL	−0.08	0.49
HDL-C, mg/dL	0.08	0.52
hsCRP, mg/dL	−0.08	0.48
Adiponectin, μg/mL	−0.02	0.85
TNF-α, pg/dL	−0.02	0.15

hsCRP, high-sensitive C-reactive protein; TNF, tumor necrosis factor. Other abbreviations as in Table 1.

in patients with a stable clinical presentation (*9*, *17–20*). Thus, positive remodeling observed predominantly in ACS may be caused by rapid expansion of the vessel either inward or outward due to thrombus formation in the ruptured atherosclerotic plaque. In addition, a high prevalence of soft plaque, greater eccentricity and lower degree of calcium were observed in the culprit lesion of ACS. In this way, coronary atherosclerosis with these characteristics as determined by IVUS may be vulnerable to ACS. In the present study, plasma adiponectin levels in patients with positive remodeling were significantly lower than those in patients with non-positive remodeling, and the remodeling classification was most closely associated with plasma adiponectin levels. These findings suggest that adiponectin may positively contribute to the stabilization of atherosclerotic plaques because adiponectin suppresses the macrophage-to-foam cell transformation (*21*, *22*) and increases the expression of tissue inhibitor of metalloproteinase-1 in monocyte-derived macrophages through the induction of interleukin-10 (*23*). Moreover, Kojima *et al*. suggested that strong inflammatory activity in vulnerable coronary plaque may induce a reduction of plasma adiponectin for up to 72 h after the onset of acute myocardial infarction (*24*). Although there was no difference in hs-CRP between the P and NP groups because we analyzed patients with stable angina, the decrease in the plasma adiponectin concentration in patients with positive remodeling might accelerate the inflammatory process. On the other hand, the consumption of circulating adiponectin may be needed to prevent coronary restenosis after stent implantation to induce a reduction in adhesion molecule expression because these molecules have been shown to be related to the post-angioplasty restenosis (*25*). Although we analyzed the initial stenosis of vessels but not the restenosis of vessels, the role of plasma adiponectin in initial stenosis might differ from that in restenosis.

Adiponectin has three major oligomeric forms: trimers, hexamers, and a high–molecular-weight form. Although each may have different biologic effects, the ELISA we used in this study did not distinguish between the forms. A new ELISA for measurement of the high–molecular-weight fraction was recently proposed (*26*). Future studies using novel assays that enable the various forms to be distinguished should help determine whether there are specific associations between particular forms of adiponectin, remodeling, and plaque accumulation. Plasma adiponectin concentration is regulated by many metabolic factors, such as obesity, as well as by the presence of DM, HT and dyslipidemia. Although medications such as statins (*27*) and ARBs (*28*) have been

shown to significantly increase plasma adiponectin concentration, in this study there were no differences in patient characteristics between the P and NP groups.

We also found that %PV was most closely correlated with LDL-C independent of current medications. The relation between serum lipids and coronary events has been established in patients with overt CAD (*3*, *29*). The value of lowering LDL-C levels in preventing major cardiovascular events (*30*) has been well documented. In addition, lipid-lowering therapy with a statin is associated with significant plaque regression in coronary arteries as assessed by IVUS (*31*, *32*), and a recent study demonstrated a positive linear relation between LDL-C and annual changes in coronary artery plaque size (*33*). Although we and others have suggested that a lower level of LDL-C is the most critical factor in preventing coronary restenosis (*34*), the lower LDL-C level regardless of medication may be the most important factor in preventing plaque growth. Finally, we do not know why plasma adiponectin levels were associated with arterial remodeling but not plaque volume. Further studies are warranted to evaluate the potential mechanism of these observations.

Study Limitations

This study was a retrospective analysis of a limited number of patients who underwent IVUS-guided angioplasty, and the indications for IVUS may not have been uniform. Thus, the results represent only a selected group of patients and the sample size was relatively small, which limited our ability to determine the significance of associations. To confirm the results of this study, a larger population needs to be examined.

Conclusion

Our study provides the first insight into the association of plasma adiponectin levels and coronary arterial remodeling. Plasma adiponectin levels may be critical for predicting arterial remodeling, while a higher level of LDL-C may be more useful for predicting a higher PV than other metabolic markers.

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