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Plaque Characteristics in Culprit Lesions and Inflammatory Status in Diabetic Acute Coronary Syndrome Patients

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OBJECTIVES The aim of this study was to assess the plaque characteristics in culprit lesions in diabetic patients with acute coronary syndrome (ACS).

BACKGROUND Data of the relationship between diabetes mellitus and plaque characteristics in patients with ACS are lacking.

METHODS We performed grayscale intravascular ultrasound (IVUS) analysis in 422 ACS patients and virtual histology (VH)-IVUS in 310 ACS patients. By subgroup analysis, 112 patients with acute myocardial infarction (AMI) with plaque ruptures also were evaluated.

RESULTS In the diabetic subgroup, high-sensitivity C-reactive protein (hs-CRP) was significantly increased ($p = 0.008$), multivessel disease was more common (65% vs. 29%, $p < 0.001$), and plaque burden was greater (79.7 ± 9.8 mm^2 vs. 74.2 ± 8.9 mm^2, $p < 0.001$). In the subgroup analysis of 112 AMI patients with plaque ruptures, the presence of multiple plaque ruptures (60% vs. 29%, $p = 0.001$) and thrombus (72% vs. 52%, $p = 0.032$) were more common in diabetic group. Diabetes mellitus was the independent predictor of hs-CRP elevation (odds ratio [OR]: 3.030, 95% confidence interval [CI]: 1.204 to 7.623, $p = 0.019$), and multiple plaque ruptures (OR: 2.984, 95% CI: 1.311 to 6.792, $p = 0.009$) by multivariable analysis. In 310 VH-IVUS subsets, the absolute and percent necrotic core volumes were significantly greater (16.9 ± 15.1 mm^3 vs. 11.5 ± 11.4 mm^3, $p < 0.001$, and 17.3 ± 9.4% vs. 13.7 ± 7.5%, $p < 0.001$, respectively), and the presence of at least one thin-cap fibroatheroma (TCFA) (60% vs. 42%, $p = 0.003$) and multiple TCFAs (28% vs. 11%, $p < 0.001$) were more common in the diabetic group. Diabetes mellitus was the only independent predictor of TCFA by multivariable analysis (OR: 2.139, 95% CI: 1.266 to 3.613, $p = 0.004$).

CONCLUSIONS Diabetic patients with ACS have more plaques with characteristics of plaque vulnerability, different composition of plaques, and have increased inflammatory status compared with nondiabetic patients with ACS. (J Am Coll Cardiol Img 2009;2:339–49) © 2009 by the American College of Cardiology Foundation

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Autopsy studies have shown that acute myocardial infarction (AMI) results from spontaneous plaque rupture or erosion and subsequent thrombosis (1,2). Intravascular ultrasound (IVUS) studies have reported culprit-lesion ruptured plaques in a varying percentage of patients with acute coronary syndrome (ACS) (3–7). There is a strong inflammatory response to the tissue injury that occurs during an AMI, and plaque rupture and the degree of the inflammatory response might be an important determinant of the clinical outcome (8). Several studies have demonstrated an association between elevated C-reactive protein (CRP) levels and culprit lesion ruptured plaques in patients with AMI (5,7,9). C-reactive protein has emerged as a simple tool for detecting systemic inflammation in patients with subsequent coronary events (10,11). Recently, several virtual histology (VH)-IVUS studies have demonstrated the coronary plaque components in patients with ACS (12–14).

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AMI = acute myocardial infarction
CRP = C-reactive protein
CSA = cross-sectional area
DC = dense calcium
EEM = external elastic membrane
FF = fibro-fatty
FT = fibrotic
hs-CRP = high-sensitivity C-reactive protein
IVUS = intravascular ultrasound
MI = myocardial infarction
NC = necrotic core
OR = odds ratio
P&M = plaque plus media
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
TCFA = thin-cap fibroatheroma
VH = virtual histology

In a study of sudden death due to coronary thrombosis, Davies (15) reported that rupture accounted for 84% of thrombi in 134 men without diabetes and that rupture was found in 59% in 27 women without diabetes, whereas only 34% of thrombi were due to rupture in 41 patients with diabetes mellitus (men and women). However, another pathological study showed diabetic patients had a greater amount of macrophage-infiltrated lipid-rich plaques compared with nondiabetic patients (16). This means specific IVUS and VH-IVUS findings could be identified in diabetic patients. However, no studies have demonstrated a relationship between diabetes mellitus and inflammatory response indicated by CRP versus plaque characteristics, including plaque composition and the incidence of thin-cap fibroatheroma (TCFA) in patients with ACS. Therefore, the aim of this study was to assess the plaque characteristics using IVUS and VH-IVUS and inflammatory response in diabetic patients with ACS.

METHODS

Patient population. We assessed the impact of diabetes mellitus on IVUS findings in AMI patients with plaque ruptures. A total of 3,895 patients with a first AMI were admitted to our institute from January 2001 to July 2007. We performed pre-percutaneous coronary intervention (PCI) IVUS within 24 h from symptom onset in 380 patients. Of these, we identified a total of 112 patients with plaque ruptures for the analysis: 47 were diabetics and 65 were nondiabetic. In addition, we evaluated the impact of diabetes mellitus on plaque composition and the incidence of TCFA by using VH-IVUS in patients with ACS. A total of 2,250 patients with ACS were admitted to our institute from July 2006 to March 2008. Of these, we identified 310 patients with ACS who underwent pre-PCI VH-IVUS of native, de novo coronary lesion: 100 were diabetic and 210 were nondiabetic.

We excluded patients with subacute or late stent thrombosis, totally occluded lesions, restenosis after stenting, coronary artery bypass graft failure, factors associated with increased risk of bleeding, severe heart failure or cardiogenic shock, important systemic disease, or serum creatinine ≥2.5 mg/dl, and patients in whom adequate IVUS images could not be obtained.

Diabetes mellitus was defined as receiving oral hypoglycemic agents or insulin to lower blood glucose levels or known fasting blood glucose values of ≥126 mg/dl or post-prandial 2-h blood glucose values of ≥200 mg/dl. The presence of unstable angina was determined by chest pain within the preceding 72 h with or without ST–T-wave changes or positive cardiac biochemical markers (creatine kinase-myocardial band or cardiac specific troponin-I). The presence of ST-segment elevation myocardial infarction (MI) was determined by >30 min of continuous chest pain, a new ST-segment elevation ≥2 mm on at least 2 contiguous electrocardiographic leads, and creatine kinase-myocardial band >3 × normal. The presence of non–ST-segment elevation MI was diagnosed by chest pain and a positive cardiac biochemical markers (creatine kinase-myocardial band or cardiac specific troponin-I) without new ST-segment elevation. The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

Laboratory analysis. Peripheral blood samples were obtained before IVUS study. The blood samples were centrifuged, and serum was removed and stored at −70°C until the assay could be performed. High-sensitivity (hs)-CRP was analyzed turbidimetrically with sheep antibodies against human CRP; this has been validated against the Dade-Behring method (17). We defined elevated hs-CRP as ≥0.3 mg/dl in accordance with the definition adopted elsewhere (5). Absolute creatine kinase-

myocardial band levels were determined by radioimmunoassay (Dade Behring Inc., Miami, Florida). Cardiac-specific troponin I levels were measured with the use of paramagnetic particles and a chemiluminescent immunoenzymatic assay (Beckman Coulter Inc., Fullerton, California). The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by the use of standard enzymatic methods.

Quantitative coronary angiography (QCA) analysis. The location of the target coronary lesion was designated as ostial, proximal, middle, and distal. We performed offline QCA analysis. Coronary angiogram was analyzed with validated QCA system (Phillips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, the Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and reference diameter were measured in diastolic frames from orthogonal projections.

Imaging and analysis using IVUS. All IVUS examinations were performed before PCI after intracoronary administration of 300 μg of nitroglycerin using a commercially available IVUS system (Boston Scientific Corporation/SCIMed, Minneapolis, Minnesota). Pre-PCI VH-IVUS examinations were performed with the use of a 20-MHz, 2.9-F IVUS imaging catheter (Eagle Eye, Volcano Corp., Rancho Cordova, California). The IVUS catheter was advanced >10 mm beyond the lesion; and automated pullback was performed to a point >10 mm proximal to the lesion at a speed of 0.5 mm/s.

Grayscale IVUS and VH-IVUS data were analyzed by 2 independent observers (H.Y.J and C.Y.H). The levels of reproducibility for external elastic membrane (EEM), lumen, and plaque plus media (P&M) cross-sectional areas (CSAs) using the Spearman rank-order correlation coefficients were 0.95, 0.97, and 0.97, respectively. Similarly, for plaque components by VH-IVUS, reproducibility for the fibrous, fibro-fatty, dense calcium, and necrotic core volume measurements using the Spearman rank-order correlation coefficients were 0.95, 0.92, 0.93, and 0.93, respectively.

Grayscale IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (18). At the reference and minimum lumen sites, we measured EEM and lumen CSA. We calculated P&M CSA as EEM CSA minus lumen CSA, and plaque burden was calculated as P&M CSA divided by EEM CSA. Coronary artery remodeling was assessed by comparing the lesion site to the reference EEM CSA. Remodeling index was the minimum lumen site EEM CSA divided by the average of the proximal and distal reference EEM CSA. Positive remodeling was defined as a remodeling index >1.05, intermediate remodeling as a remodeling index between 0.95 and 1.05, and negative remodeling as a remodeling index <0.95 (19).

Hypoechoic plaque was less bright compared with the reference adventitia. Hyperechoic, noncalcified plaque was as bright as or brighter than the reference adventitia without acoustic shadowing. Hyperechoic, calcified plaque was hyperechoic with acoustic shadowing. A calcified lesion contained >90° of circumferential lesion calcium. When there was no dominant plaque composition, the plaque was classified as mixed. A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. A fragmented and loosely adherent plaque without a distinct cavity and without a fibrous cap fragment was not considered a plaque rupture. Rupture sites separated by a length of artery containing smooth lumen contours without cavities were considered to represent different plaque ruptures (multiple plaque ruptures) (20,21). Plaque cavity was measured and extrapolated to the ruptured capsule area. Thrombus was an intraluminal mass having a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation (Fig. 1) (21,22).

We performed VH-IVUS analyses across the entire lesion segment (volumetric analysis), and cross-sectional analysis was performed at the minimum lumen sites, at the largest necrotic core (NC) sites, and at the reference sites. With VH-IVUS analysis, we classified the color-coded tissue into 4 major components: green (fibrotic, FT); yellow-green (fibro-fatty, FF); white (dense calcium, DC); and red (NC) (12,23). We reported VH-IVUS analysis in absolute amounts and as a percentage of plaque area or volume. We defined TCFA as a NC ≥10% of plaque area in at least 3 consecutive frames without overlying fibrous tissue in the presence of ≥40% plaque burden (Fig. 2) (12).

No-reflow and stent thrombosis. We evaluated the incidences of post-stenting no-reflow (post-PCI Thrombolysis In Myocardial Infarction [TIMI] flow grade 0, 1, and 2) and acute (<24 h after stent implantation) and subacute stent thromboses (between 1 day and 30 days after stent implantation).

Statistical analysis. The statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (SPSS, Chicago, Illinois) was used for all analyses. Continuous variables were presented as the mean value ± 1 SD; comparisons were conducted by Student *t* test or nonparametric Wilcoxon test for violations of assumptions of normality or heterogeneity. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by chi-square statistics or the Fisher exact test as appropriate. Multivariable logistic regression analyses were performed to identify independent predictors of hs-CRP elevation, multiple plaque ruptures, and TCFA. Univariable analyses were first conducted to identify potential risk factors for hs-CRP elevation, multiple plaque ruptures, and TCFA. The likelihood ratio test was used, and the variables with a p value of <0.2 were included in the multivariable model. Finally, a stepwise logistic regression was performed. The least significant variable was dropped at each step until only covariates with $p < 0.05$ remained; $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics. The baseline characteristics are summarized in Table 1. There was a female predominance in diabetic group. Diabetic patients had more hypertension and more family history of coronary artery disease compared with nondiabetic patients. Diabetic patients had lower ejection fraction and hemoglobin levels, and higher triglyceride and hs-CRP levels compared with nondiabetic patients.

Angiographic and procedural results. Angiographic findings are summarized in Table 2. There were no significant differences in culprit lesion distribution, lesion location, TIMI flow grade, reference diameter, minimal lumen diameter, and percent diameter stenosis. However, multivessel disease was observed

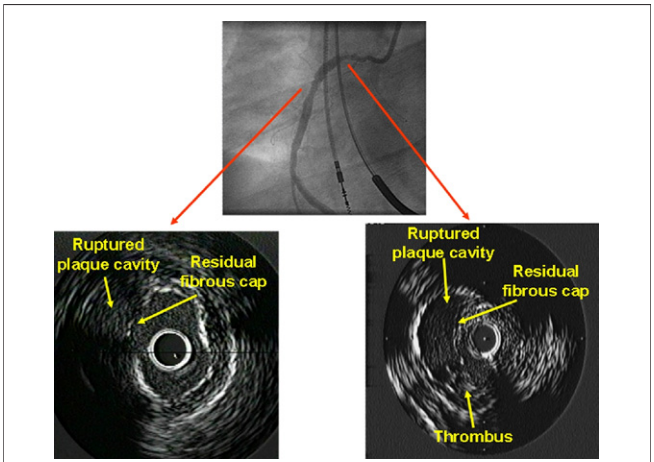

Figure 1. Ruptured Plaque Cavity, Residual Fibrous Cap, and Surrounding Thrombus

An example of ruptured plaque cavity, residual fibrous cap, and surrounding thrombus in 71-year-old diabetic patient presented with non–ST-segment elevation myocardial infarction. A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. Rupture sites separated by a length of artery containing smooth lumen contours without cavities were considered to represent different plaque ruptures (multiple plaque ruptures). Thrombus was an intraluminal mass having a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation.

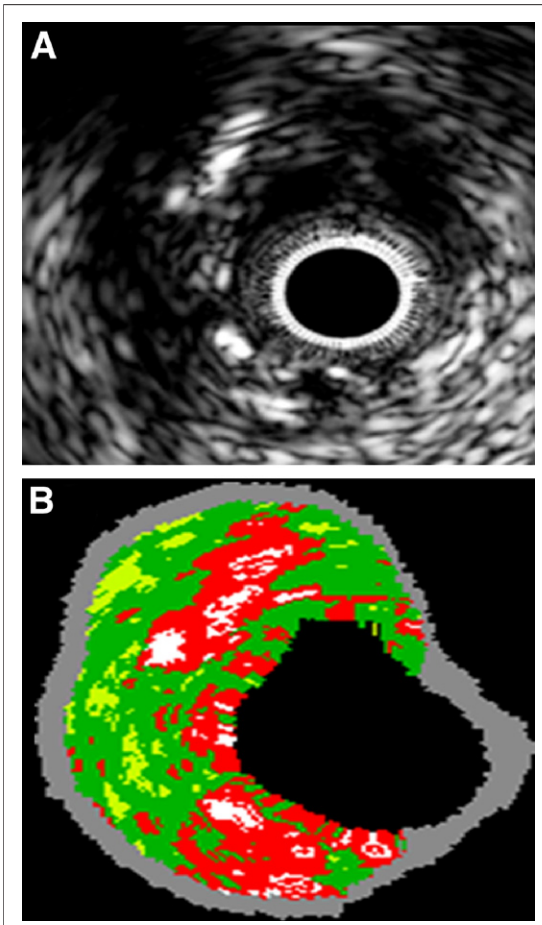

Figure 2. Images of TCFA

Grayscale intravascular ultrasound (IVUS) **(A)** and virtual histology (VH)-IVUS **(B)** images of thin-cap fibroatheroma (TCFA). We used VH-IVUS to classify the color-coded tissue into 4 major components: **green** (fibrotic); **yellow-green** (fibro-fatty); **white** (dense calcium); and **red** (necrotic core). We defined TCFA as a necrotic core ≥10% of plaque area in at least 3 consecutive frames without overlying fibrous tissue in the presence of ≥40% plaque burden. Grayscale IVUS showed the large amount of heterogeneous plaque **(A)**, VH-IVUS showed a necrotic core-rich plaque without evidence of fibrous cap (TCFA) **(B)**.

Table 1. Baseline Characteristics

	Diabetic Patients (n = 147)	Nondiabetic Patients (n = 275)	p Value
Age (yrs)	65 ± 10	64 ± 13	0.4
Male sex	68 (46)	168 (61)	0.003
Clinical presentation			0.8
Unstable angina	80 (54)	154 (56)	
Non–ST-segment elevation MI	37 (25)	61 (22)	
ST-segment elevation MI	30 (20)	60 (22)	
Hypertension	121 (82)	162 (59)	<0.001
Smoking	51 (35)	105 (38)	0.5
Family history of coronary artery disease	39 (27)	40 (15)	0.003
Chest pain to coronary angiogram (h)	12.5 ± 7.6	13.5 ± 8.6	0.3
Ejection fraction (%)	54 ± 11	59 ± 13	<0.001
White blood cells (/mm^3)	8,420 ± 3,459	7,912 ± 2,704	0.15
Hemoglobin (g/dl)	12.2 ± 2.2	13.4 ± 1.6	<0.001
Platelet count (10^3/mm^3)	228 ± 75	239 ± 119	0.5
Creatinine (mg/dl)	1.7 ± 1.7	1.1 ± 0.7	<0.001
Glucose (mg/dl)	177 ± 71	120 ± 35	<0.001
Creatine kinase-myocardial band (U/l)	15.8 ± 42.7	14.9 ± 28.8	0.8
Cardiac troponin-I (ng/ml)	7.8 ± 28.1	7.8 ± 28.4	1.0
Total cholesterol (mg/dl)	174 ± 58	173 ± 43	0.8
Triglyceride (mg/dl)	124 ± 64	103 ± 51	0.002
LDL cholesterol (mg/dl)	108 ± 50	108 ± 40	0.9
HDL cholesterol (mg/dl)	47 ± 15	44 ± 10	0.096
hs-CRP (mg/dl)	2.6 ± 3.8	0.6 ± 1.4	0.008

Data are presented as the n (%) of patients or mean ± SD.
HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction.

more frequently in diabetic patients compared with nondiabetic patients (65% vs. 29%, $p < 0.001$).

In subgroup analysis of 112 patients with AMI with plaque ruptures, the presence of angiographic plaque rupture (35 of 47 [75%] vs. 36 of 65 [55%], $p = 0.039$), and thrombus appearances (21 of 47 [45%] vs. 17 of 65 [26%], $p = 0.041$) were more common in diabetic patients compared with nondiabetic patients. No-reflow was observed in 17% (8 of 47) in diabetic patients and 8% (5 of 65) in nondiabetic patients ($p = 0.13$). The incidences of acute stent thrombosis (1 of 47 [2%] vs. 0 of 65 [0%], $p = 0.2$) and subacute stent thrombosis (3 of 47 [6%] vs. 2 of 65 [3%], $p = 0.4$) were not significantly different between diabetic patients and nondiabetic patients.

Results of IVUS and VH-IVUS. Grayscale IVUS findings are summarized in Table 3. Proximal and distal reference segment lumen areas were significantly smaller in diabetic patients compared with nondiabetic patients. At the minimum lumen sites, lumen area was significantly smaller and plaque burden was significantly greater in diabetic patients compared with nondiabetic patients. There were no significant differences in IVUS lesion length, plaque morphology, and remodeling pattern between the 2 groups.

In a subgroup analysis of 112 patients with AMI and plaque ruptures, multiple plaque ruptures and thrombus were observed more frequently in diabetic patients compared with nondiabetic patients (Fig. 3). Plaque cavity area was significantly greater and ruptured plaque length was significantly longer in diabetic patients compared with nondiabetic patients (Fig. 4). There were no significant differences in the incidences of multiple plaque ruptures (43% vs. 41%, $p = 0.9$) and thrombus (64% vs. 57%, $p = 0.5$) between patients with ST-segment elevation MI and patients with non–ST-segment elevation MI. We found that hs-CRP levels were significantly greater in patients with multiple plaque ruptures compared with patients without multiple plaque ruptures (5.9 ± 4.9 mg/dl vs. 1.8 ± 3.2 mg/dl, $p = 0.002$) and also was significantly greater

Table 2. Coronary Angiographic Findings

	Diabetic Patients (n = 147)	Nondiabetic Patients (n = 275)	p Value
Culprit lesion			0.5
LAD	63 (43)	132 (48)	
LCX	31 (21)	59 (22)	
RCA	53 (36)	84 (31)	
Lesion location			0.13
Ostium	10 (7)	17 (6)	
Proximal	45 (31)	108 (39)	
Middle	74 (50)	107 (39)	
Distal	18 (12)	43 (16)	
Diseased vessel number			<0.001
1	51 (35)	197 (72)	
2	52 (35)	52 (19)	
3	44 (30)	26 (10)	
TIMI flow grade			0.4
0	0 (0)	0 (0)	
1	21 (14)	30 (11)	
2	34 (23)	56 (20)	
3	92 (63)	189 (69)	
Reference diameter (mm)	3.17 ± 0.79	3.23 ± 0.78	0.2
MLD (mm)	0.62 ± 0.30	0.68 ± 0.52	0.3
Percent diameter stenosis (%)	80.4 ± 14.2	78.9 ± 16.3	0.8

Data are presented as the n (%) of patients or mean ± SD.
LAD = left anterior descending artery; LCX = left circumflex artery; MLD = minimal lumen diameter; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Table 3. Intravascular Ultrasound Findings

	Diabetic Patients (n = 147)	Nondiabetic Patients (n = 275)	p Value
Reference			
EEM CSA (mm^2)	16.2 ± 5.4	18.2 ± 5.9	0.002
Lumen CSA (mm^2)	10.0 ± 3.3	11.6 ± 4.1	<0.001
P&M CSA (mm^2)	6.2 ± 3.3	6.7 ± 3.1	0.2
Plaque burden (%)	38.3 ± 10.7	37.2 ± 11.4	0.4
Minimum lumen site			
EEM CSA (mm^2)	14.8 ± 5.1	15.1 ± 4.8	0.19
Lumen CSA (mm^2)	3.0 ± 2.2	3.9 ± 2.5	0.018
P&M CSA (mm^2)	11.8 ± 4.5	11.2 ± 3.6	0.15
Plaque burden (%)	79.7 ± 9.8	74.2 ± 8.9	<0.001
IVUS lesion length (mm)	20.6 ± 11.2	19.9 ± 11.1	0.2
Distal reference			
EEM CSA (mm^2)	13.9 ± 5.4	14.7 ± 5.5	0.2
Lumen CSA (mm^2)	8.3 ± 3.7	9.2 ± 3.3	0.021
P&M CSA (mm^2)	5.7 ± 2.6	5.6 ± 3.1	0.8
Plaque burden (%)	40.2 ± 10.6	36.6 ± 11.1	0.004
Plaque morphology			0.12
Hypoechoic	91 (62)	165 (60)	
Hyperechoic, noncalcified	22 (15)	53 (19)	
Hyperechoic, calcified	27 (18)	33 (12)	
Mixed	7 (5)	24 (9)	
Remodeling pattern			0.12
Positive remodeling	47 (32)	75 (27)	
Intermediate remodeling	40 (27)	59 (22)	
Negative remodeling	60 (41)	141 (51)	

Data are presented as the n (%) of patients or mean ± SD.
EEM = external elastic membrane; CSA = cross-sectional area; P&M = plaque plus media; IVUS = intravascular ultrasound.

in patients with IVUS-detected thrombus compared with patients without thrombus (3.9 ± 4.9 mg/dl vs. 1.9 ± 1.5 mg/dl, p = 0.022) (Fig. 5).

In subgroup analysis of 310 VH-IVUS subset, at the minimum lumen sites, the absolute and percent NC and DC areas were significantly greater in diabetic patients compared with nondiabetic patients; conversely, percent FT area was significantly smaller in diabetic patients compared with nondiabetic patients (Fig. 6). At the largest NC sites, the absolute and percent NC and DC areas were significantly greater in diabetic patients compared with nondiabetic patients (NC areas: 1.85 ± 0.92 mm^2 vs. 1.14 ± 0.83 mm^2, p < 0.001, 30.1 ± 11.0% vs. 20.4 ± 9.6%, p < 0.001, respectively; and DC areas: 0.92 ± 0.63 mm^2 vs. 0.53 ± 0.54 mm^2, p < 0.001, 14.3 ± 7.9% vs. 10.9 ± 10.4%, p = 0.037, respectively); conversely percent FT and FF areas were significantly smaller in diabetic patients compared with nondiabetic patients (47.6 ± 11.2% vs. 58.0 ± 11.5%, p < 0.001, and 7.8 ± 6.8% vs. 11.3 ± 9.2%, p = 0.007, respectively). The absolute and percent NC and DC volumes were significantly greater in diabetic patients compared with nondiabetic patients; conversely, percent FT and FF volumes were significantly smaller in diabetic patients compared with nondiabetic patients (Fig. 7). The percent NC area at the proximal reference sites (11.6 ± 11.3% vs. 8.8 ± 8.5%, p = 0.041) and the percent NC and DC areas at the distal reference sites (12.9 ± 13.4% vs. 8.5 ± 10.2%, p = 0.009, and 8.3 ± 11.7% vs. 2.6 ± 4.4%, p < 0.001, respectively) were significantly greater in diabetic patients compared with nondiabetic patients. At least one TCFA and multiple TCFAs were observed more frequently in diabetic patients compared with nondiabetic patients (Fig. 8).

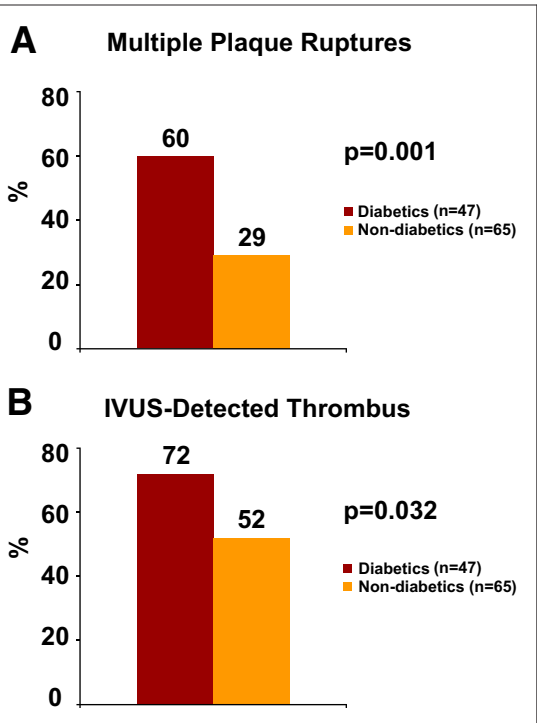

Figure 3. The Incidences of Multiple Plaque Ruptures and Thrombus

The incidences of multiple plaque ruptures **(A)** and intravascular ultrasound (IVUS)-detected thrombus **(B)** in 112 patients with acute myocardial infarction with plaque ruptures. A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. Rupture sites separated by a length of artery containing smooth lumen contours without cavities were considered to represent different plaque ruptures (multiple plaque ruptures). Thrombus was an intraluminal mass having a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation. Multiple plaque ruptures **(A)** and thrombus **(B)** were observed more frequently in diabetic patients compared with nondiabetic patients.

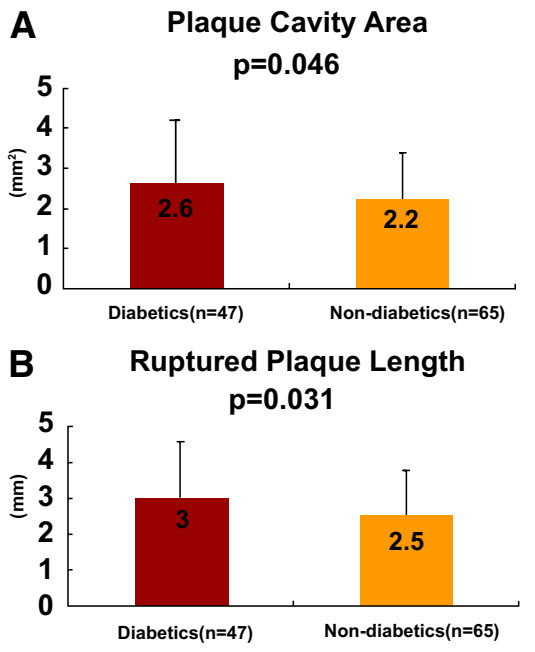

Figure 4. The Plaque Cavity Area and Ruptured Plaque Length

The plaque cavity area (**A**) and ruptured plaque length (**B**) in 112 patients with acute myocardial infarction with plaque ruptures. A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. Plaque cavity was measured and extrapolated to the ruptured capsule area. Plaque cavity area was significantly greater in diabetic patients compared with nondiabetic patients (**A**). Ruptured plaque length was significantly longer in diabetic patients compared with nondiabetic patients (**B**).

Independent predictors of hs-CRP elevation, multiple plaque ruptures, and TCFA. In a subgroup analysis of 112 patients with AMI with plaque ruptures, we performed multivariate analysis to determine independent predictors of hs-CRP elevation. The following variables were tested (all with $p < 0.2$ in univariable analysis): diabetes mellitus, smoking, ejection fraction, initial diagnosis, positive remodeling, soft plaque, minimum lumen site plaque burden, IVUS-detected thrombus, and IVUS-detected multiple plaque ruptures. Diabetes mellitus (odds ratio [OR]: 3.030, 95% confidence interval [CI]: 1.204 to 7.623, $p = 0.019$), IVUS-detected multiple plaque ruptures (OR: 6.305, 95% CI: 2.612 to 15.220, $p < 0.001$), and IVUS-detected thrombus (OR: 3.178, 95% CI: 1.134 to 8.911, $p = 0.028$) were the independent predictors of hs-CRP elevation. Multivariable analysis determined independent predictors of multiple plaque ruptures to be diabetes mellitus, age, smoking, initial diagnosis, positive remodeling, soft plaque, hs-CRP, and minimum lumen site plaque burden (all with $p < 0.2$ in univariable analysis). Diabetes mellitus was the only independent predictor of multiple plaque ruptures (OR: 2.984, 95% CI: 1.311 to 6.792, $p = 0.009$), and hs-CRP approached significance (OR: 1.013, 95% CI: 0.999 to 1.026, $p = 0.061$).

In VH-IVUS subset, multivariable analysis determined independent predictors of TCFA to be age, male sex, diabetes mellitus, hypertension, smoking, ejection fraction, hs-CRP, and minimum lumen site plaque burden (all with $p < 0.2$ in univariable analysis). Diabetes mellitus was the only independent predictor of TCFA (OR: 2.139, 95% CI: 1.266 to 3.613, $p = 0.004$).

DISCUSSION

Diabetic patients had more plaques, which appeared to have characteristics of plaque vulnerability

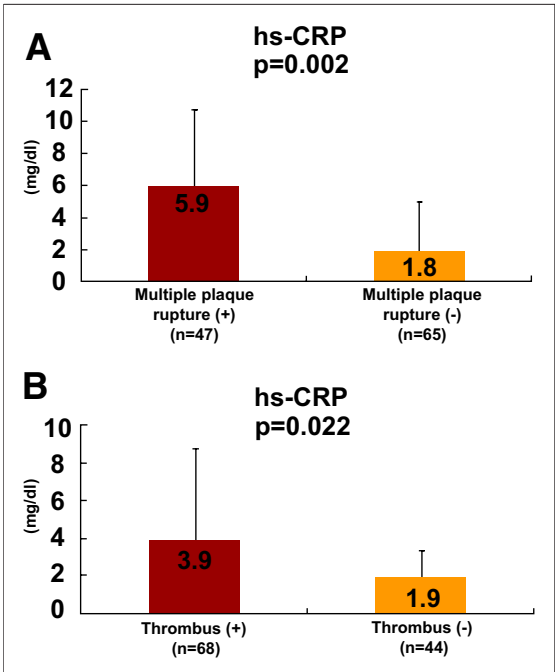

Figure 5. The hsCRP Levels

The high-sensitivity C-reactive protein (hs-CRP) levels according to the presence/absence of multiple plaque ruptures (**A**) and according to the presence/absence of intravascular ultrasound-detected thrombus (**B**) in 112 patients with acute myocardial infarction with plaque ruptures. We analyzed hs-CRP turbidimetrically with sheep antibodies against human CRP; this has been validated against the Dade-Behring method. We found that hs-CRP levels were significantly greater in patients with multiple plaque ruptures compared with patients without multiple plaque ruptures (**A**) and also were significantly greater in patients with intravascular ultrasound-detected thrombus compared with patients without intravascular ultrasound-detected thrombus (**B**).

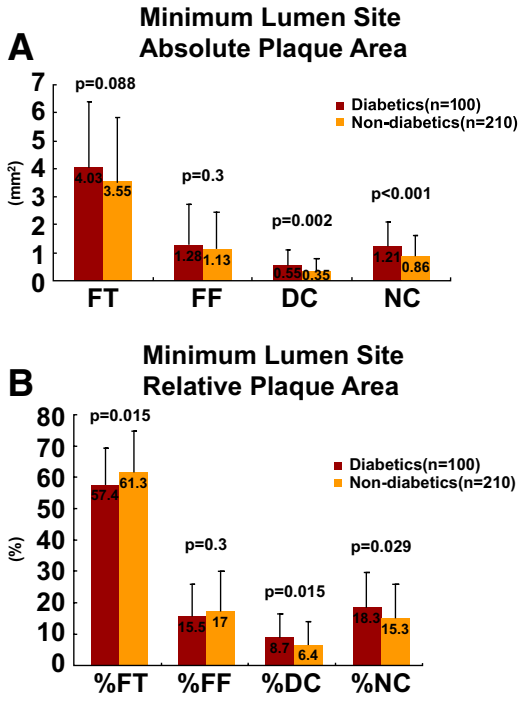

Figure 6. The Absolute and Relative Plaque Areas at the Minimum Lumen Sites

The absolute (**A**) and relative (**B**) plaque areas at the minimum lumen sites in 310 virtual histology-intravascular ultrasound (VH-IVUS) subset. We used VH-IVUS to classify the color-coded tissue into 4 major components: green (fibrotic, FT); yellow-green (fibro-fatty, FF); white (dense calcium, DC); and red (necrotic core, NC). The absolute NC and DC areas and percent NC and DC areas were significantly greater in diabetic patients compared with nondiabetic patients; conversely, percent FT area was significantly smaller in diabetic patients compared with nondiabetic patients.

and a different composition of plaques than nondiabetic patients for those presenting with ACS. We found that hs-CRP levels were significantly higher in diabetic ACS patients compared with nondiabetic ACS patients. In AMI patients with plaque rupture, multiple plaque ruptures and thrombus were observed more frequently in diabetic patients compared with nondiabetic patients, and diabetes mellitus was an independent predictor of hs-CRP elevation and multiple plaque ruptures. In VH-IVUS subset, the NC-containing plaque was significantly greater, TCFAs were observed more frequently in diabetic patients compared with nondiabetic patients, and diabetes mellitus was an independent predictor of TCFA.

Pathological studies have demonstrated that plaque rupture and subsequent thrombosis is the most important mechanism leading to an ACS (1,2). Previous grayscale IVUS studies have reported varying frequencies of infarct-related artery plaque rupture in patients with AMI (3–7). Several VH-IVUS studies have reported that ACS patients had more TCFAs compared with stable angina patients (12,13). Morbidity and mortality in diabetic patients is markedly greater compared with nondiabetic patients (24,25). This greater event rate in diabetic patients may be associated with abnormalities in endothelial and vascular smooth muscle cell function, as well as a propensity to thrombosis, which contribute to atherosclerosis and its complications (26–28).

Plaque composition may play a role in the plaque disruption and thrombosis that leads to acute coronary events (29–32). Lesions with a large lipid core may have a greater risk for disruption than sclerotic plaques (32–34). In the study by Moreno et al. (16), the incidence of coronary thrombosis was greater in atherectomy specimens from patients

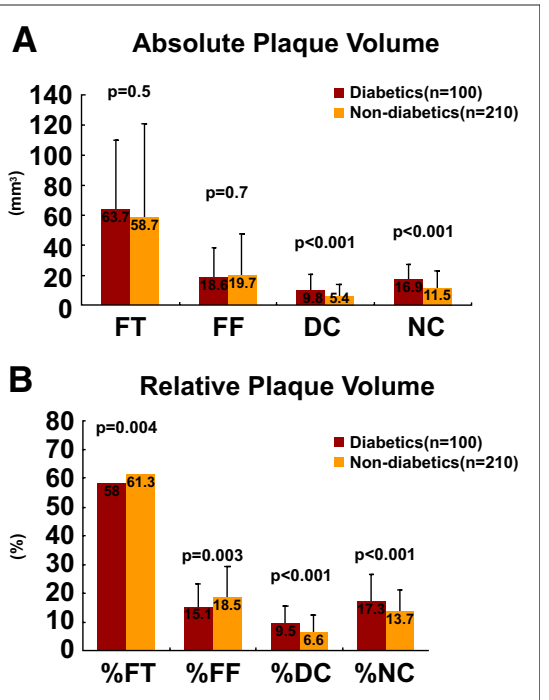

Figure 7. The Volumetric Absolute and Relative Plaque Components

The volumetric absolute (**A**) and relative (**B**) plaque components in 310 virtual histology-intravascular ultrasound (VH-IVUS) subset. We used VH-IVUS to classify the color-coded tissue into 4 major components: green (fibrotic, FT); yellow-green (fibro-fatty, FF); white (dense calcium, DC); and red (necrotic core, NC). The absolute NC and DC volumes and percent NC and DC volumes were significantly greater in diabetic patients compared with nondiabetic patients; conversely, percent FT and FF volumes were significantly smaller in diabetic patients compared with nondiabetic patients.

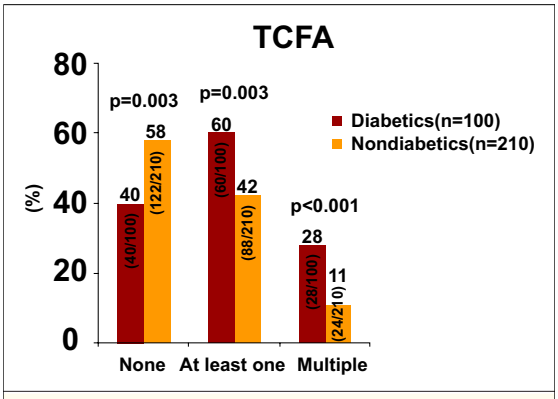

Figure 8. The Incidence of Culprit Lesion TCFA

The incidence of culprit lesion TCFA in 310 VH-IVUS subset. We used VH-IVUS to classify the color-coded tissue into 4 major components: green (fibrotic); yellow-green (fibro-fatty); white (dense calcium); and red (necrotic core). We defined TCFA as a necrotic core ≥10% of plaque area in at least 3 consecutive frames without overlying fibrous tissue in the presence of ≥40% plaque burden. The presence of at least one TCFA and multiple TCFAs within culprit lesions were observed more frequently in diabetic patients **(brown bars)** compared with nondiabetic patients **(orange bars)**. Abbreviations as in Figure 2.

with diabetes mellitus compared with patients without diabetes mellitus. This finding is in agreement with the study of Silva et al. (31), who found an increased incidence of coronary thrombosis documented by angioscopy in diabetic patients with unstable angina. In the present study which included AMI patients with plaque rupture, the incidences of multiple plaque ruptures and thrombus were 60% and 72% in diabetic patients, respectively, which were greater than those of nondiabetic patients (29% and 52%, respectively).

Thin-cap fibroatheroma is the precursor of plaque rupture, which accounts for a majority of coronary thrombi and coronary death (29,35,36). Previous pathological study showed diabetic patients had a larger content of lipid-rich plaque compared with nondiabetic patients (16). One autopsy study reported inflammation and NC size play a greater role in the progression of atherosclerosis in diabetic subjects in sudden coronary death (37). This result suggests that diabetic patients have a greater probability of vulnerable plaque (TCFA, plaque rupture, and thrombus), which can lead to acute coronary events. Nasu et al. (38) reported that the prevalence of TCFA in target vessels of diabetic stable angina patients was significantly greater than in nondiabetic stable angina patients. In their VH-IVUS study for nonculprit vessel, Valgimigli et al. (39) reported that distance from the ostium to the plaque was an independent predictor of relative lipid content, as well as older age, unstable presentation, no use of statin, and presence of diabetes mellitus.

Unlike the study by Nasu et al. (38) and Valgimigli et al. (39), we assessed the plaque components and the incidence of TCFA in diabetic ACS patients. The present study showed that diabetic ACS patients had more NC-containing lesions at the reference sites as well as at the culprit lesion sites and had more TCFAs compared with nondiabetic ACS patients. Thus, diabetic patients may have a high risk of plaque rupture and thrombus formation, which can lead to MI and cardiac death, because of the disruption of TCFA, and more post-intervention problems such as edge stenoses and dissections. Therefore, the recognition of NC burden and the presence of TCFA by VH-IVUS may be important in regard to improve the prognosis of diabetic ACS patients.

Several IVUS studies have demonstrated an association between increased CRP levels and culprit lesion plaque ruptures in AMI patients (5,7,10). Sano et al. (5) reported that more plaque ruptures were observed in AMI patients with increased CRP levels than in AMI patients with a normal CRP levels. Hong et al. (7) reported that the only independent predictor of plaque rupture in AMI patients was an elevated CRP level in their 3-vessel IVUS study. Tanaka et al. (10) reported that AMI patients with culprit lesion plaque ruptures presented with greater CRP levels as compared with AMI patients without plaque rupture. In the present study, hs-CRP levels were significantly greater in diabetic AMI patients with plaque rupture compared with nondiabetic AMI patients with plaque rupture (4.6 ± 3.2 mg/dl vs. 2.4 ± 2.1 mg/dl, $p = 0.005$), and hs-CRP levels were significantly greater in patients with multiple plaque ruptures or IVUS-detected thrombus compared with patients without multiple plaque ruptures or thrombus. The results of the present study are consistent with those of previous studies.

Study limitations. First, the study population was relatively small. Second, IVUS and VH-IVUS imaging were performed at the discretion of the individual operators, leading to potential selection bias. Third, the analyses were retrospective and are subject to limitations inherent in this type of clinical investigation. Fourth, we did not perform 3-vessel IVUS and VH-IVUS. Therefore, we did not assess the frequency of noninfarct-related artery plaque ruptures or thrombus and nonculprit site TCFAs, and we did not demonstrate the relationship be-

tween multivessel plaque ruptures or thrombus and multivessel TCFAs vs. clinical events. Fifth, we did not attempt to differentiate between atherosclerotic plaque and thrombus because VH-IVUS could not determine the presence of thrombus, a finding that may obscure the identification of TCFA. Sixth, because the CRP level was not measured serially after AMI, it cannot be ascertained whether the CRP elevations were the result or the cause of the plaque rupture or thrombus. Seventh, heavily calcified plaques may induce an artifact regarding the codification of plaques by VH-IVUS resulting in an increase in NC content. This remains a potential limitation of the present VH study. Eighth, because we excluded the patients with serious conditions like totally occluded coronary lesions, increased risk of bleeding, severe heart failure, cardiogenic shock, important systemic disease, or renal dysfunction, the present study might not reflect the true spectrum of plaque ruptures, thrombus, TCFA, and the percentage of NC in untested ACS populations. Ninth, this report was exploratory and that direct associations cannot be inferred from the analysis.

CONCLUSIONS

Diabetic patients with ACS have more plaques and have characteristics of plaque vulnerability and a different composition of plaques and greater inflammatory status compared with nondiabetic ACS patients. The IVUS features of vascular disease consistent with plaque vulnerability and rupture are more prevalent in diabetics likely due to the type of vascular involvement in this diffuse disease.

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Key Words: acute coronary syndrome ■ diabetes mellitus ■ plaque ■ intravascular ultrasound ■ inflammation.