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Comparison of Nonculprit Coronary Plaque Characteristics Between Patients With and Without Diabetes

A 3-Vessel Optical Coherence Tomography Study

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Objectives The aim of the present study was to compare the characteristics of nonculprit coronary plaques between diabetes mellitus (DM) and non-DM patients using 3-vessel optical coherence tomography (OCT) imaging.

Background DM patients have a higher recurrent cardiovascular event rate.

Methods Patients who had undergone 3-vessel OCT imaging were identified from the Massachusetts General Hospital OCT Registry. Characteristics of nonculprit plaques were compared between DM and non-DM patients.

Results A total of 230 nonculprit plaques were identified in 98 patients. Compared with non-DM patients, DM patients had a larger lipid index (LI) (averaged lipid arc × lipid length; 778.6 ± 596.1 vs. 1358.3 ± 939.2, $p < 0.001$) and higher prevalence of calcification (48.4% vs. 72.2%, $p = 0.034$) and thrombus (0% vs. 8.3%, $p = 0.047$). DM patients were divided into 2 groups based on glycated hemoglobin (A_{1C}) levels of ≤7.9% and ≥8.0%. LI was significantly correlated with diabetic status (778.6 ± 596.1 [non-DM] vs. 1,171.5 ± 708.1 [A_{1C} ≤7.9%] vs. 1,638.5 ± 1,173.8 [A_{1C} ≥8%], p value for linear trend = 0.005), and fibrous cap thickness was inversely correlated with the A_{1C} level (99.4 ± 46.7 μm [non-DM] vs. 91.7 ± 29.6 μm [A_{1C} ≤7.9%] vs. 72.9 ± 22.7 μm [A_{1C} ≥8%], p value for linear trend = 0.014). Patients with A_{1C} ≥8% also had the highest prevalence of thin-cap fibroatheroma (TCFA) and macrophage infiltration.

Conclusions Compared with non-DM patients, DM patients have a larger LI and a higher prevalence of calcification and thrombus. The LI was larger and TCFA and macrophage infiltration were frequent in patients with A_{1C} ≥8%. (J Am Coll Cardiol Intv 2012;5:1150–8) © 2012 by the American College of Cardiology Foundation

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Diabetes mellitus (DM) is an independent risk factor for the development of coronary heart disease (CHD) (1–3). DM patients have been reported to have a 2- to 5-fold higher incidence of myocardial infarction or death (4,5) and a 2-fold higher incidence of recurrent ischemic events during a 7-year follow-up (45.0% vs. 20.2%) (4). The risk of myocardial infarction or death in DM patients without known CHD is as high as that in non-DM patients with known CHD (4). DM patients have worse outcomes after acute coronary syndrome (ACS) (6–8), percutaneous coronary intervention (9,10), and surgical revascularization (9,11). The underlying pathophysiology for the poor outcomes and high recurrent ischemic events in DM patients has not been fully elucidated. A postmortem study showed that compared with non-DM patients, DM patients had plaques with larger necrotic cores and increased macrophage infiltration, and that the size of the necrotic core was correlated positively with the glycated hemoglobin (A_{1C}) level (12). Prospective studies have shown continuous associations of blood glucose and A_{1C} level with the risks of major vascular events (13,14). A recent large-scale observational study reported that compared with subjects with A_{1C} = 6% to 8%, patients with A_{1C} >8% had a 16% higher risk of cardiac events over 3 years (15). In vivo coronary plaque characteristics in DM patients have not been well established.

Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality that enables detailed assessment of coronary plaque morphology. The aim of the present study was to characterize the nonculprit plaques in DM patients using 3-vessel OCT imaging and compare them with those in non-DM patients.

Methods

Study population. From a total of 912 subjects who were enrolled in the Massachusetts General Hospital (MGH) OCT Registry between August 2010 and September 2011, we identified 108 subjects (81 subjects from Harbin Medical University, Harbin, China, and 27 subjects from Nara Medical University, Nara, Japan) with 3-vessel OCT imaging. The MGH OCT Registry is a multicenter registry of consecutive patients who have undergone OCT, and includes 20 sites across 6 countries. Poor image quality or lack of A_{1C} information resulted in the exclusion of 10 subjects; therefore, 98 subjects (90.7%) were included in the final analysis. Eighty-eight subjects (89.8%) were studied by the M3 system (M3 Cardiology Imaging System, LightLab Imaging/St. Jude Medical, Westford, Massachusetts) and 10 subjects (10.2%) by the C7 OCT system (C7-XR OCT Intravascular Imaging System, LightLab Imaging/St. Jude Medical, Westford, Massachusetts). A subject was assigned to the DM group if the subject was receiving an oral hypoglycemic agent or insulin, or if the subject had a known fasting blood glucose value of ≥126 mg/dl or post-prandial 2-h blood glucose value of ≥200 mg/dl. Nonculprit lesions were defined as plaques viewed on an angiogram that had not been treated. Within the nonculprit lesions, only plaques with more than 30% diameter stenosis as compared with the reference diameter as measured by OCT were included in our study. Plaque characteristics were compared between DM subjects and non-DM subjects. Moreover, DM subjects were divided into 2 groups based on A_{1C} level of ≤7.9% or ≥8%, and plaque characteristics were compared. Each plaque was separated at least 5 mm from the edge of another plaque or an implanted stent edge. The Registry was approved by each site's institutional review board, and all patients provided informed consent.

Acquisition of OCT images. Images were acquired using commercially available, time-domain (M3 Cardiology Imaging System) or frequency-domain (C7-XR OCT Intravascular Imaging System) OCT systems. The intracoronary OCT imaging technique has been described previously (16–18). In brief, the M3 system uses an occlusion balloon (Helios, LightLab Imaging) that is inflated proximal to the lesion at 0.4 to 0.6 atm during image acquisition. The imaging wire is automatically pulled back from a distal to a proximal position at a rate of 1.0 to 3.0 mm/s, and saline is continuously infused from the tip of the occlusion balloon. In the C7 system, a 2.7-F OCT imaging catheter (Dragonfly, LightLab Imaging) is advanced distal to the lesion, and automated pullback is initiated in concordance with blood clearance by the injection of contrast media or dextran. All images were de-identified and digitally stored.

Abbreviations and Acronyms

A_{1C} = glycated hemoglobin
ACS = acute coronary syndrome
CHD = coronary heart disease
DM = diabetes mellitus
HDL = high-density lipoprotein
LI = lipid index
MGH = Massachusetts General Hospital
OCT = optical coherence tomography
TCFA = thin-cap fibroatheroma
VH-IVUS = virtual histology–intravascular ultrasound

OCT data analysis. Plaques were classified into 2 categories (16,19–22): 1) fibrous (homogeneous, highly backscattering region) or 2) lipid (low signal region with diffuse border). When lipid was present ≥90° in any of the cross-sectional images within the plaque, it was considered as a lipid-rich plaque. In lipid-rich plaque, the lipid arc was measured at every 1-mm interval throughout the length of each lesion, and the values were averaged. Lipid length was also measured on longitudinal view. Lipid index (LI) was defined as the mean lipid arc multiplied by lipid length. The fibrous cap thickness of a lipid-rich plaque was measured 3 times at its thinnest part, and the average value was calculated. Thin-cap fibroatheroma (TCFA)

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was defined as the thinnest fibrous cap thickness of ≤65 μm in a lipid-rich plaque on a cross-sectional image. Macrophage infiltration was defined as signal-rich, distinct or confluent punctuate regions that exceed the intensity of background speckle noise (23–25). Microchannels were defined as signal-poor voids that were sharply delineated in multiple contiguous frames (25,26). Plaque disruption was identified by the presence of fibrous cap discontinuity with a clear cavity formation inside the plaque (19). Intracoronary thrombus was defined as a mass (diameter ≥250 μm) attached to the luminal surface or floating within the lumen, including red (red blood cell–rich) thrombus, which showed high backscattering with high attenuation (resembling blood), and white (platelet-rich) thrombus, which showed less backscattering, was homogeneous, and had low attenuation (19,25,27). Calcification was also recorded when an area consisted of a signal-poor or heterogeneous region with a sharply delineated border (25). Macrophage infiltration, microchannel, plaque disruption, thrombus, and calcification were recorded only for their presence. The OCT data were analyzed at an independent MGH OCT core laboratory by 2 experienced investigators who were blinded to the angiographic and clinical findings, using proprietary software (LightLab Imaging). When there was discordance between the investigators, a consensus reading was obtained from a third independent reviewer. Intraclass correlation coefficient for inter- and intraobserver reliabilities of the lipid arc were 0.844 and 0.903, respectively.

Statistical analysis. All statistical analyses were performed by an independent statistician. For analysis of patient characteristics, categorical data were compared using the chi-square test or Fisher exact test, depending on which test was most suitable; these data are presented as frequencies (percent). Continuous measurements are presented as mean ± SD and median (25th to 75th percentile). The means of the continuous measurements in the 2 groups were compared using the Student's *t* test. Thrombus analysis was carried out using the Fisher exact test because of the infrequency of the events. Linear regression analysis was used to analyze the relationship between the OCT plaque measurement and A_{1C} level. For comparisons of plaque characteristics between the groups, the analysis was carried out using the generalized estimating equations approach to account for the within-subject correlation due to the analysis of multiple plaques within a single patient. Intra-observer and interobserver reliabilities were estimated by the intraclass correlation coefficient for continuous measurement. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina). Values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics. Baseline patient characteristics are shown in Table 1. The non-DM group consisted of 62 subjects, and the DM group 36 subjects. No significant differences were observed in the baseline characteristics between the 2 groups, except for a higher frequency of smoking and a higher level of high-density lipoprotein (HDL) cholesterol in the non-DM group. In the total population, 85.7% patients underwent percutaneous coronary intervention at index procedure (85.5% of non-DM patients, 86.1% of DM patients, p = 0.999). Procedure-related complications with respect to 3-vessel imaging were not reported from any institution. The DM patients consisted of 23 subjects with A_{1C} ≤7.9% and 13 subjects with A_{1C} ≥8.0%. In the A_{1C} ≤7.9% group, 13 subjects (56.5%) were receiving insulin therapy, 4 subjects (17.4%) were on oral agents, and 6 subjects (26.0%) were on no medicine. In the A_{1C} ≥8.0% group, 11 subjects (84.6%) were receiving insulin therapy, and 2 subjects (15.9%) were on no medical therapy.

Angiographic findings. A total of 230 nonculprit plaques were detected in 98 subjects: 145 plaques in 62 non-DM subjects (2.3 ± 1.0 plaques/patient) and 85 plaques in 36 DM subjects (2.4 ± 1.3 plaques/patient) (Table 2). The distribution of plaques in the 3 coronary arteries was as follows: 43.5% of plaques were located in the right coronary artery, 34.3% in the left anterior descending artery, and 22.2% in the left circum-

Table 1. Baseline Patient Characteristics

	Non-DM (n = 62)	DM (n = 36)	p Value
Age, yrs	59.6 ± 9.5	58.0 ± 11.3	0.465
Male	47 (75.8%)	24 (66.7%)	0.356
Hypertension	34 (54.8%)	27 (75.0%)	0.054
Hyperlipidemia	51 (82.3%)	29 (80.6%)	0.999
Smoking	41 (66.1%)	15 (41.7%)	0.021*
Current	15 (24.2%)	9 (25.0%)	0.999
Former (quit >3 months)	26 (41.9%)	6 (16.7%)	0.014*
ACS	10 (16.1%)	6 (16.7%)	0.999
STEMI	3 (4.8%)	4 (11.1%)	0.450
Non-STEMI/UA	7 (11.3%)	2 (5.6%)	0.559
Prior myocardial infarction	22 (35.5%)	12 (33.3%)	0.999
Peripheral artery disease	3 (4.8%)	1 (2.8%)	0.999
Chronic kidney disease	6 (9.7%)	4 (11.1%)	0.999
Fasting glucose	100.3 ± 14.2	145.2 ± 62.0	<0.001*
A_{1C}, %	5.5 ± 0.8	7.4 ± 1.3	<0.001*
LDL-C, mg/dl	84.7 ± 25.2	83.9 ± 30.8	0.886
HDL-C, mg/dl	44.1 ± 12.7	39.6 ± 5.0	0.017*
Triglyceride, mg/dl	145.7 ± 111.8	138.4 ± 56.5	0.719
hs-CRP, mg/dl	0.21 ± 0.40	0.25 ± 0.18	0.570

Values are mean ± SD or n (%). *p < 0.05.

ACS = acute coronary syndrome; A_{1C} = glycated hemoglobin; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

Table 2. Plaque Characteristics in Nonculprit Lesions per Patient and per Plaque

	Patients (n = 98)			Plaques (n = 230)		
	Non-DM (n = 62)	DM (n = 36)	p Value	Non-DM (n = 145)	DM (n = 85)	p Value
Plaques (per patient), n	145 (2.3 ± 1.0)	85 (2.4 ± 1.3)	0.925			
Lipid-rich plaques	42 (67.7%)	23 (63.9%)	0.825	74 (51.0%)	45 (52.9%)	0.826
Lipid-rich plaques/patient	1.2 ± 1.1	1.3 ± 1.4	0.825			
TCFA	12 (19.4%)	10 (27.8%)	0.277	16 (11.0%)	16 (18.8%)	0.218
Macrophage infiltration	26 (41.9%)	17 (47.2%)	0.675	41 (28.3%)	26 (30.6%)	0.759
Disruption	9 (14.5%)	6 (16.7%)	0.778	13 (9.0%)	6 (7.1%)	0.620
Microchannel	35 (56.5%)	19 (52.8%)	0.834	49 (33.8%)	28 (32.9%)	0.902
Calcification	30 (48.4%)	26 (72.2%)	0.034*	48 (33.1%)	39 (45.9%)	0.111
Thrombus	0 (0.0%)	3 (8.3%)	0.047*	0 (0.0%)	3 (3.5%)	0.049*
Plaque location						
RCA						0.922
Proximal				20 (13.8%)	16 (18.9%)	
Mid				21 (14.5%)	14 (16.5%)	
Distal				20 (13.8%)	9 (10.6%)	
LAD						
Proximal				15 (10.3%)	10 (11.8%)	
Mid				22 (15.2%)	9 (10.6%)	
Distal				15 (10.3%)	8 (9.4%)	
LCX						
Proximal				22 (15.2%)	14 (16.5%)	
Distal				10 (6.9%)	5 (5.9%)	

Values are n (mean ± SD), n (%), or mean ± SD. *$p < 0.05$.
DM = diabetes mellitus; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; TCFA = thin-cap fibroatheroma.

flex; 42.2% of plaques were located in proximal lesions and 57.8% of plaques were in mid to distal lesions. This distribution was not different between the 2 groups.

OCT findings. The prevalence of OCT plaque characteristics per patient and per plaque are shown in Table 2. The prevalence of lipid-rich plaques was similar between non-DM and DM subjects (67.7% vs. 63.9%, p = 0.825), and the number of lipid-rich plaques per patient was also similar between the groups (1.2 ± 1.1/patient vs. 1.3 ± 1.4/patient, p = 0.825). The prevalence of TCFA (19.4% [non-DM] vs. 27.8% [DM], p = 0.277), macrophage infiltration (41.9% [non-DM] vs. 47.2% [DM], p = 0.675), disruption (14.5% [non-DM] vs. 16.7% [DM], p = 0.778), and microchannels (56.5% [non-DM] vs. 52.8% [DM], p = 0.834) were not different between the groups. DM subjects had higher frequencies of calcification (48.4% [non-DM] vs. 72.2% [DM], p = 0.034) and thrombus (0.0% [non-DM] vs. 8.3% [DM], p = 0.047).

Comparisons of quantitative OCT findings between non-DM and DM plaques are shown in Figure 1. Compared with plaques of non-DM subjects, those of DM subjects had a wider lipid arc (114.5° ± 35.5°, 106.2 [87.5 to 133.9] vs. 136.3° ± 32.3°, 140.1 [111.1 to 162.3], p = 0.001), a longer lipid length (6.7 ± 3.8 mm, 5.6 [4.1 to 8.1] vs. 9.5 ± 5.1 mm, 8.9 [5.4 to 11.9], p = 0.001), and a greater LI (778.6 ± 596.1, 629.1 [381.3 to 1,089.2] vs. 1,358.3 ± 939.2, 1,225.7 [650.5 to 1,627.5], p <0.001). However, although the fibrous cap thickness tended to be thinner in plaques of DM subjects, this difference was not significant (99.4 ± 46.7 μm, 80.0 [70.0 to 117.8] [non-DM] vs. 84.2 ± 28.3 μm, 70.0 [61.5 to 105.0] [DM], p = 0.076).

The correlations between the quantitative OCT findings and A_{1C} level are shown in Figure 2. The lipid arc (114.4 ± 35.5°, 106.2 [87.5 to 133.9] [non-DM] vs. 127.3 ± 32.5°, 129.9 [94.9 to 147.7] [A_{1C} ≤7.9%] vs. 149.9 ± 27.5°, 146.1 [123.6 to 174.7] [A_{1C} ≥8%], p value for linear trend ≤0.001), lipid length (6.7 ± 3.8 mm, 5.6 [4.1 to 8.1] [non-DM] vs. 8.9 ± 4.4 mm, 8.9 [4.9 to 11.1] [A_{1C} ≤7.9%] vs. 10.4 ± 6.0 mm, 9.0 [5.6 to 13.8] [A_{1C} ≥8%], p value for linear trend = 0.011), and LI (778.6 ± 596.1, 629.1 [381.3 to 1,089.2] [non-DM] vs. 1,171.5 ± 708.1, 1,210.4 [619.6 to 1,522.9] [A_{1C} ≤7.9%] vs. 1,638.5 ± 1,173.8, 1,368.2 [670.0 to 2,202.6] [A_{1C} ≥8%], p value for linear trend = 0.005) were significantly correlated with A_{1C} level. The fibrous cap thickness was inversely correlated with A_{1C} level (99.4 ± 46.7 μm, 80.0 [70.0 to 117.8] [non-DM] vs. 91.7 ± 29.6 μm, 80.0 [70.0 to 120.0] [A_{1C} ≤7.9%],

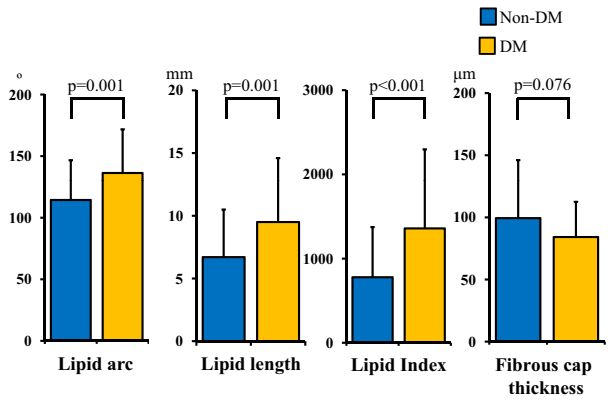

Figure 1. Comparison of OCT Quantitative Findings Between Non-DM and DM Plaques

Nonculprit plaques of diabetes mellitus (DM) patients had a wider lipid arc ($p = 0.001$), a longer lipid length ($p = 0.001$), and a greater lipid index ($p < 0.001$). Fibrous cap thickness tended to be thinner in plaques of DM patients; however, this difference was not significant ($p = 0.076$). OCT = optical coherence tomography.

72.9 ± 22.7 μm, 61.5 [60.0 to 81.8] [A_{1C} ≥8%], p value for linear trend = 0.014).

Comparison of plaque characteristics among non-DM patients, patients with A_{1C} ≤7.9%, and those with A_{1C} ≥8% are shown in Table 3. Compared with plaques of non-DM subjects and those with A_{1C} ≤7.9%, those with A_{1C} ≥8% had higher prevalence of TCFA (11.0% [non-DM] and 8.9% [A_{1C} ≤7.9%] vs. 37.9% [A_{1C} ≥8%]; p = 0.043 vs. A_{1C} ≤7.9%, and p = 0.037 vs. non-DM) and macrophage infiltration (28.3% [non-DM] and 21.4% [A_{1C} ≤7.9%] vs. 48.3% [A_{1C} ≥8%], p = 0.024 vs. A_{1C} ≤7.9%, and p = 0.042 vs. non-DM), and thinner fibrous cap thickness (p = 0.035 vs. A_{1C} ≤7.9%, p = 0.004 vs. non-DM).

When all subjects were divided into a normal-HDL group or low-HDL group based on a cutoff HDL cholesterol level of 40 mg/dl for men and 50 mg/dl for women (28), there was no significant difference in the plaque characteristics between the 2 groups (lipid arc: 117.4 ± 3.7°, 103 [92 to 138.5] [normal-HDL] vs. 123.6 ± 36.2°, 115.3 [95.1 to 150.2] [low-HDL], p = 0.495; lipid length: 6.6 ± 4.3 mm, 5.1 [3.7 to 8.4] [normal-HDL] vs. 8.0 ± 4.5 mm, 6.9 [4.3 to 10.8] [low-HDL], p = 0.233; LI: 845.4 ± 709.9, 573.1 [366.8 to 1,245.6] [normal-HDL] vs. 1,020.2 ± 804.0, 794.7 [473.3 to 1,355.9] [low-HDL], p = 0.389; fibrous cap thickness: 94.5 ± 43.4, 80.0 [77.5 to 92.5] [normal-HDL] vs. 88.9 ± 26.1, 80.0 [63.0 to 110.0] [low-HDL], p = 0.598).

Discussion

The present study demonstrated that nonculprit plaques in patients with DM had a wider lipid arc, a longer lipid length, a larger LI, and a higher prevalence of calcification and thrombus. When DM patients were further divided into 2 groups based on A_{1C} level, the nonculprit plaques in patients with an A_{1C} ≥8% had a higher prevalence of TCFA and macrophage infiltration, and thinner fibrous cap.

Plaque characteristics in DM and non-DM patients. In a postmortem study, coronary plaques in DM patients were associated with larger necrotic core size and more diffuse atherosclerosis with inflammatory cell infiltrates, such as macrophage and T lymphocytes (12). Moreover, a positive correlation was found between mean percent necrotic core size and the A_{1C} level (12). A directional coronary atherectomy study by Moreno et al. (29) also showed that coronary tissue from DM patients exhibited a larger content of lipid-rich atheroma, macrophage infiltration, and thrombus than did coronary tissue from non-DM patients. In the present study, nonculprit plaques of DM patients had a wider lipid arc, a longer lipid length, and a larger LI than those of non-DM patients, and this feature was correlated with DM status. It has been reported that nonculprit lesions that lead to major adverse cardiovascular events are frequently observed as mild stenotic lesions on angiogram; however, the majority of events arose from plaques characterized by a large plaque burden, a small luminal area, or both, on gray-scale intravascular ultrasound (30). The prevalence of lipid-rich plaque was not different between the non-DM and DM groups (67.7% vs. 63.9%, respectively, p = 0.825). The subanalysis of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study demonstrated the presence of any fibroatheroma detected by virtual histology–intravascular ultrasound (VH-IVUS) was not different between non-DM and DM groups; however, average necrotic core cross-sectional area was significantly greater in the nonculprit lesions of DM patients with a future major adverse cardiac event (31).

Macrophage infiltration and TCFA. Previous pathological studies have reported that the level of inflammatory cell infiltration is higher in DM patients than in non-DM patients (12,29). Moreover, an increased number of macrophages was related to necrotic core expansion, fibrous cap thinning, and plaque instability (12). In the present study, although the prevalence of macrophage infiltration did not differ between DM and non-DM patients, the patients with an A_{1C} ≥8% had a higher prevalence of macrophage infiltration compared with non-DM and A_{1C} ≤7.9% patients. This finding suggests that poorly controlled DM patients had a higher level of vulnerability in their coronary plaques compared with non-DM patients or relatively well-controlled DM patients.

TCFA is the precursor to plaque rupture, which accounts for the majority of ACS and sudden cardiac death (32). In a VH-IVUS study, Hong et al. (33) demonstrated that

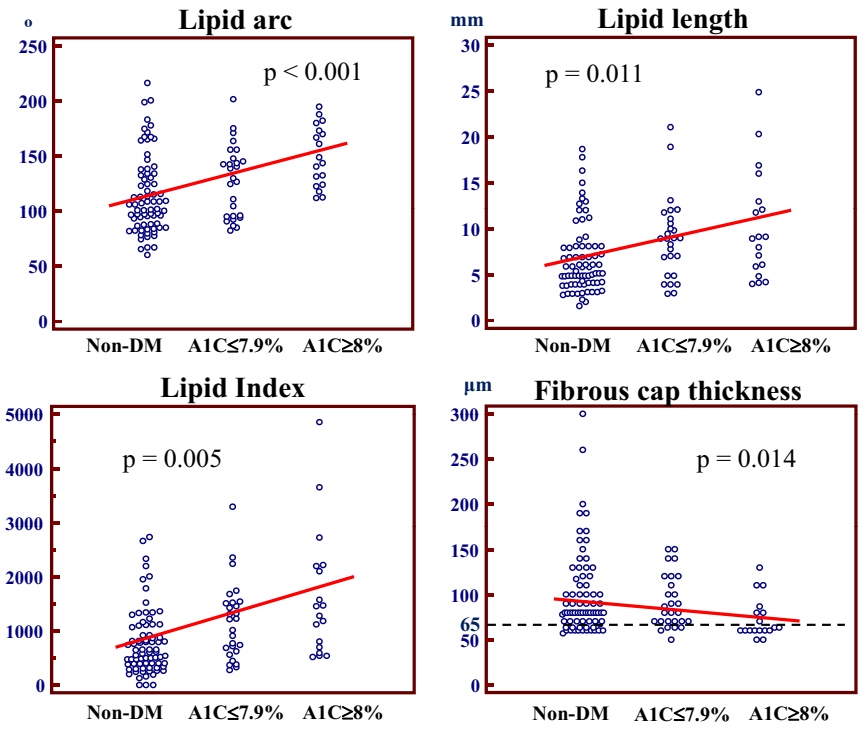

Figure 2. Correlation Between Quantitative Findings of OCT and A_{1C} Level

The lipid arc ($p < 0.001$), lipid length ($p = 0.011$), and LI ($p = 0.005$) were significantly correlated with the A_{1C} level. The fibrous cap thickness was inversely correlated with the A_{1C} level ($p = 0.014$). A_{1C} = glycated hemoglobin; other abbreviations as in Figure 1.

compared with non-DM patients, DM patients with ACS had culprit lesions with a greater necrotic core volume and higher prevalence of TCFA. A 3-vessel VH-IVUS study by Zheng et al. (34) also showed that DM patients had a larger necrotic core volume and more frequent TCFA than those of non-DM patients. In the present study, the prevalence of TCFA was not significantly different between non-DM and DM patients; however, compared with non-DM patients and patients with $A_{1C} \leq 7.9\%$, those with $A_{1C} \geq 8\%$ had a higher prevalence of TCFA.

Plaque characteristics in the poorly controlled DM group ($A_{1C} \geq 8\%$). Prospective studies have shown continuous associations of blood glucose and A_{1C} levels with the risk of major vascular events (13,14). A recent large-scale observational study reported that compared with patients with A_{1C} of 6% to 8%, patients with $A_{1C} > 8\%$ had a 16% higher risk of cardiac events over 3 years (15). In the present study, patients with $A_{1C} \geq 8\%$ had a wider lipid arc, a longer lipid length, a larger LI, thinner fibrous caps, and higher prevalence of TCFA and macrophage infiltration, all of which coincide with the typical pathological features of vulnerable plaque (32). Therefore, our data suggest that the patients with poorly controlled DM had more vulnerable plaques in the nonculprit coronary lesions.

Calcification. Calcification is another characteristic of DM patients. VH-IVUS studies have shown that DM patients have a greater amount of dense calcium than those of non-DM patients in both culprit and nonculprit lesions (35,36). Furthermore, an OCT study demonstrated that the incidence of calcification is higher in DM patients (37). The use of electron beam computed tomography for the detection of coronary artery calcium demonstrated that the extent of coronary artery calcium strongly correlates with the severity of coronary stenosis (38) and the development of subsequent coronary events (39). Moreover, the presence of coronary artery calcium in DM patients indicates a higher risk for all-cause mortality than that in non-DM patients (40). A postmortem study also showed that the mean percent calcified area was greater in DM patients than in non-DM patients (12). Our finding that DM patients have a higher prevalence of calcification is in accordance with previous findings reported by studies using VH-IVUS, electron beam computed tomography, and pathological examination.

Diabetes is not a local, but rather a systemic, disease. Physiological studies reported that hyperglycemia, excess free fatty acid, and insulin resistance in diabetes cause metabolic disarray within the endothelial cell, and the

Table 3. Comparison of Plaque Characteristics Among Non-DM Patients, Patients With A_{1C} ≤7.9% and Those With A_{1C} ≥8%

	Non-DM (n = 62)	A_{1C} ≤7.9% (n = 23)	A_{1C} ≥8% (n = 13)	Non-DM vs. A_{1C} ≤7.9%	A_{1C} ≤7.9% vs. A_{1C} ≥8%	Non-DM vs. A_{1C} ≥8%
Total number of plaques	145	56	29			
Lipid-rich plaques	74 (51.0%)	27 (48.2%)	18 (62.1%)	0.783	0.326	0.351
TCFA	16 (11.0%)	5 (8.9%)	11 (37.9%)	0.770	0.043*	0.037*
Macrophage infiltration	41 (28.3%)	12 (21.4%)	14 (48.3%)	0.436	0.024*	0.042*
Disruption	13 (9.0%)	5 (8.9%)	1 (3.4%)	0.994	0.347	0.326
Microchannel	49 (33.8%)	17 (30.4%)	11 (37.9%)	0.658	0.495	0.687
Calcification	48 (33.1%)	25 (44.6%)	14 (48.3%)	0.210	0.767	0.157
Thrombus	0 (0.0%)	2 (3.6%)	1 (3.4%)	0.077†	1.000†	0.167†
Lipid arc°	114.4 ± 35.5	127.3 ± 32.5	149.9 ± 27.5	0.176	0.038*	<0.001*
Median (IQR)	106.2 (87.5–133.9)	129.9 (94.9–147.7)	146.1 (123.6–174.7)			
Lipid length, mm	6.7 ± 3.8	8.9 ± 4.4	10.4 ± 6.0	0.039*	0.448	0.033*
Median (IQR)	5.6 (4.1–8.1)	8.9 (4.9–11.1)	9.0 (5.6–13.8)			
Lipid index	778.6 ± 596.1	1,171.5 ± 708.1	1638.5 ± 1173.8	0.042*	0.231	0.016*
Median (IQR)	629.1 (381.3–1,089.2)	1,210.4 (619.6–1,522.9)	1,368.2 (670.0–2,202.6)			
FCT, μm	99.4 ± 46.7	91.7 ± 29.6	72.9 ± 22.7	0.415	0.035*	0.004*
Median (IQR)	80.0 (70.0–117.8)	80.0 (70.0–120.0)	61.5 (60.0–81.8)			

Values are n (%), mean ± SD, or median (interquartile range [IQR]). Lipid index = averaged lipid arc × lipid length. *p < 0.05. †Data were analyzed by Fisher exact test.
ACS = acute coronary syndrome; DM = diabetes mellitus; FCT = fibrous cap thickness; TCFA = thin-cap fibroatheroma.

activation of these systems impairs endothelial function, augments vasoconstriction, increases inflammation, and promotes thrombosis (41). Inflammation has been increasingly recognized as a component of atherogenesis. The levels of C-reactive protein and fibrinogen have been found to predict acute cardiovascular events in prospective studies (42); however, in the present study, the level of high-sensitivity C-reactive protein was not different between the groups. Further investigation of biochemical findings related to prediction of adverse cardiac events would be warranted.

In the present study, diabetic treatment type was not different between the A_{1C} ≤7.9% group and the A_{1C} ≥8.0% group: 56.5% of the patients in the A_{1C} ≤7.9% group and 84.6% in the A_{1C} ≥8.0% group were receiving insulin therapy. The duration of DM might affect the plaque characteristics. However, the data on duration of DM were not collected in the registry.

It has been reported in pathology (43) and OCT studies (21) that plaques are not evenly distributed along the length of the arteries. In the present study, 89.8% patients were imaged by the M3 system, which requires an occlusion balloon that is inflated proximal to the lesion. Therefore, plaques in the ostium of the coronary arteries could not be evaluated. Nevertheless, 42.2% plaques were located in proximal segments and 57.8% plaques were in mid to distal segments (Table 2).

Study limitations. First, this was a retrospective study using a registry database. Therefore, potential selection bias is unavoidable. Patients with cardiogenic shock, congestive heart failure, chronic total occlusion, left main disease, or renal failure were less likely to have 3-vessel OCT imaging performed. Second, the exact measurements of necrotic core and plaque burden by OCT were not possible because of the relatively shallow axial penetration. However, because the most important morphological determinants of plaque vulnerability are superficial, the region of greatest interest was still within the imaging range of current OCT systems. Third, disruption, microchannel, macrophage infiltration, thrombus, and calcification were not quantified or rigorously validated. Fourth, the use of 3-vessel OCT imaging resulted in a limited sample size. The number of ACS patients was small because performing 3-vessel OCT imaging in patients with hemodynamic instability is practically difficult and unethical. Fifth, although OCT imaging was performed in 3 vessels, most imaged segments did not include the distal segments or, occasionally, the very proximal segment. Sixth, although HDL cholesterol levels were higher in the non-DM group compared with the DM group, there were no differences in the plaque characteristics between the 2 groups. Seventh, the duration of DM and the time from onset of ACS to OCT were not collected in the registry. Finally, we collected data on all patients with 3-vessel imaging in our registry, rather than sampling a study sample based on a power analysis.

Conclusions

Plaques in DM patients have a wider lipid arc, a longer lipid length, a larger LI, and a higher prevalence of calcification and thrombus. Moreover, plaques of patients with poorly controlled DM contained more vulnerable features. Further studies are warranted to aid in understanding the clinical impact of the present findings and whether these are

associated with higher event rates in poorly controlled diabetic patients.

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Key Words: diabetes mellitus ■ optical coherence tomography ■ plaque.

APPENDIX

For supplementary information on the MGH OCT Registry, please see the online version of this paper.