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Features of Coronary Plaque in Patients With Metabolic Syndrome and Diabetes Mellitus Assessed by 3-Vessel Optical Coherence Tomography

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Background—The pathophysiological basis for the association between metabolic syndrome (MetS) and coronary artery disease is not well understood. We sought to characterize coronary plaques in patients with MetS by using optical coherence tomography.

Methods and Results—We identified 451 coronary plaques from 171 subjects who underwent optical coherence tomographic imaging in 3 coronary arteries. Subjects were divided into 3 groups: diabetes mellitus (DM, n=77), MetS (n=35), and a control group (C group, n=59) without DM or MetS. Optical coherence tomographic analysis included the presence of lipid-rich plaque, maximum lipid arc, lipid-core length, lipid index (LI), fibrous cap thickness, and thin-cap fibroatheroma. We defined LI as mean lipid arc multiplied by lipid-core length. Lipid-core length and LI were significantly greater in DM and MetS than in C group (lipid-core length: 7.7±4.0 and 7.0±3.8 versus 5.5±2.4 mm; $P<0.001$ and $P=0.012$, and LI: 1164±716 and 1086±693 versus 796±417 mm; $P<0.001$ and $P=0.008$). Maximum lipid arc was significantly greater in DM than in C group, whereas no significant difference was observed between MetS and C group (196±45°, 187±42° versus 176±52°; $P=0.002$ and $P=0.182$). Fibrous cap thickness and thin-cap fibroatheroma showed no significant difference among the 3 groups. In multivariate analysis, DM and MetS were independently associated with LI, whereas only acute coronary syndrome was the independent predictor for thin-cap fibroatheroma.

Conclusions—Compared with control subjects, coronary plaques in MetS contain larger lipid. However, the MetS criteria used in this study could not distinguish the vulnerable features such as thin-cap fibroatheroma, suggesting the necessity of complementary information to identify patients at high risk for cardiovascular events. **(*Circ Cardiovasc Imaging*. 2013;6:665-673.)**

Key Words: diabetes mellitus ■ metabolic syndrome ■ plaque ■ tomography, optical coherence

Metabolic syndrome (MetS) is defined by a set of inter-related clinical features that includes obesity, hypertension, dyslipidemia, and hyperglycemia.[1,2] The association and clustering of these factors have been extensively studied, and previous studies have revealed an association between MetS and a higher incidence of cardiovascular events.[3,4] Despite many clinical and epidemiological studies that have reported an elevated risk for cardiovascular disease in patients with MetS, unique coronary plaque characteristics in patients with MetS have not been identified. A further understanding of the pathophysiology of coronary artery atherosclerosis in MetS may enable us to better understand and treat ischemic heart disease in this population.

Clinical Perspective on p 673

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Optical coherence tomography (OCT) is an intravascular imaging technique that allows for high resolution visualization of the coronary arteries.[5,6] OCT can provide detailed structural information on intracoronary pathology, including atherosclerotic plaques in vivo. As such, it provides a unique platform to evaluate the association between MetS and coronary artery pathology. The purpose of this study was to determine the coronary plaque characteristics of subjects with MetS in comparison with subjects who are diabetic and normoglycemic by using OCT.

Methods

Study Population

The Massachusetts General Hospital OCT Registry is an ongoing multicenter registry of patients undergoing OCT of the coronary arteries and includes 20 sites across 6 countries. Patient selection for the present study is summarized in Figure 1. In a total of 1406 subjects who were enrolled in the registry between August 2010 and May 2012, a total of 255 subjects underwent OCT imaging of all 3 major epicardial coronary arteries during the same procedure. Only patients with complete information on clinical history, laboratory data, and physical status and those with sufficient image quality for all 3 vessels were selected. Therefore, 198 subjects with complete demographic data and sufficient 3-vessel OCT images were identified. From this cohort, we selected the patients who had nonculprit or nontarget coronary plaques with area stenosis >50% as measured by OCT. Patients without any nonculprit plaques were also excluded. In-stent restenosis and lesions that required balloon angioplasty before OCT imaging were excluded. The final data set comprised 451 plaques from 171 subjects. Subjects were divided into 3 groups: those with diabetes mellitus (DM group, 206 plaques in 77 subjects), non-DM subjects with MetS (MetS group, 102 plaques in 35 subjects), and subjects without DM or MetS (control group [C] group, 143 plaques in 59 subjects; Figure 2). The registry was approved by the institutional review board in each participating site, and all subjects provided informed consent.

MetS Factors

DM was diagnosed in the participating site based on the American Diabetes Association definition if the patient had ≥1 of the following criteria: fasting glucose ≥126 mg/dL, 2-hour plasma glucose level ≥200 mg/dL in the oral glucose tolerance test, classic symptom with casual plasma glucose level ≥200 mg/dL or A1c ≥6.5%.[7] Patients who were taking hypoglycemic agents were also diagnosed as DM in the present study. MetS was based on the definition established in the Joint Scientific Statement as a subject with ≥3 of the following: waist circumference ≥102 cm for men or ≥88 cm for women; triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol ≤40 mg/dL; blood pressure ≥135/85 mm Hg; and fasting blood glucose level ≥100 mg/dL.[1] In the present study, we used body mass index (BMI) as a substitute for waist circumference because data on waist circumference were not obtained in our registry. We used a BMI cut-off of 29.4 kg/m^2 for men and 26.7 kg/m^2 for women as previously reported.[8,9] In addition, history of hypertension was used as an alternative for the presence of documented blood pressure ≥135/85 mm Hg because the majority of subjects had been treated with antihypertensive agents. Therefore, MetS was defined by the presence of 3 or more MetS factors of the following: (1) BMI ≥29.4 kg/m^2 for men and 26.7 kg/m^2 for women; (2) triglycerides ≥150 mg/dL; (3) high-density lipoprotein cholesterol ≤40 mg/dL; (4) history of hypertension; and (5) fasting blood glucose level ≥100 mg/dL, as shown in Figure 2.

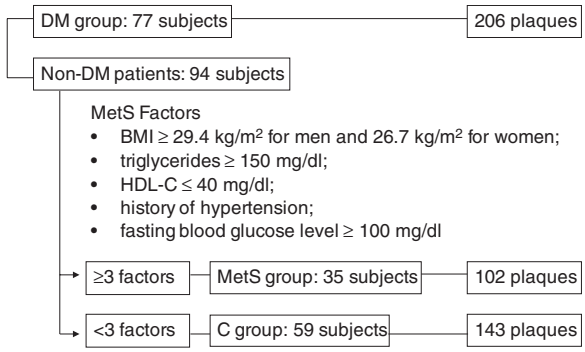

Figure 2. Categorization of subjects. Subjects were divided into 3 groups: subjects with diabetes mellitus (DM group), nondiabetic subjects with metabolic syndrome (MetS group), and subjects without DM or MetS (control group [C group]). Subjects with ≥3 MetS factors were diagnosed as MetS. BMI indicates body mass index; and HDL-C, high-density lipoprotein cholesterol.

Coronary Angiography

Coronary angiograms were analyzed by offline quantitative coronary angiography (CAAS version 5.10.1, Pie Medical Imaging BV. Maastricht, The Netherlands). Reference diameter, minimum lumen diameter, diameter stenosis, and lesion length were measured.

OCT Image Acquisition

Either the time-domain (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc, Westford, MA) or frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN) was used in the study. The intracoronary OCT imaging technique has been previously described.[10] In brief, with the M2/M3 system, an occlusion balloon (Helios, LightLab Imaging Inc,

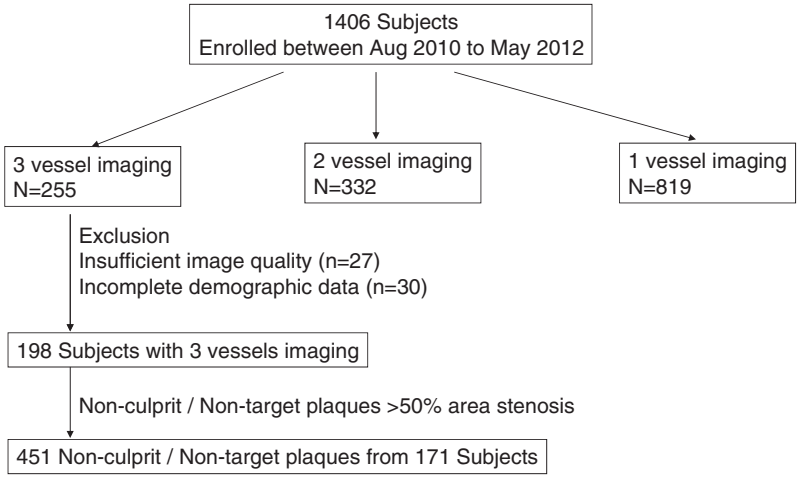

Figure 1. Study population. From the subjects who were enrolled in the Massachusetts General Hospital optical coherence tomography (OCT) registry, we selected those who underwent OCT investigations for 3 coronary vessels in the same procedure. After exclusion of the subjects who had insufficient image quality and incomplete demographic data, a total of 198 subjects were analyzed, and 451 plaques from 171 subjects were identified in the final data set.

Westford, MA) is advanced proximal to the lesion and inflated ≤0.4 to 0.6 atm during image acquisition. The imaging wire is automatically pulled back from distal to proximal at 1.0 to 3.0 mm/s, and saline is continuously infused from the tip of occlusion balloon. With the C7 system, a 2.7 F OCT imaging catheter (Dragonfly, LightLab Imaging Inc, Westford, MA) is advanced distal to the lesion, and automatic pullback is started as soon as the blood is cleared. All images were digitally stored, deidentified, and submitted to the Massachusetts General Hospital (Boston, MA) for analysis.

OCT Image Analysis

Each plaque was classified as lipid-rich or fibrous plaque. We defined lipid as a diffusely bordered signal-poor region with signal attenuation by the overlying signal-rich layer, and lipid-rich plaque as a plaque with lipid >90°.[5] For lipid-rich plaque, we determined lipid arc, lipid-core length, thinnest fibrous cap thickness (FCT), as well as the presence of thin-cap fibroatheroma (TCFA), macrophage accumulation, cholesterol crystal, and microvessels (Figure 3). Lipid arc was measured every 1 mm within a lipid-rich plaque, and mean and maximum values were recorded (Figure 3A). Lipid-core length was defined as the length of plaque with >90° of lipid and measured on the longitudinal view (Figure 3B). We also calculated the lipid index, which was defined as the mean lipid arc multiplied by lipid-core length.[10] The thinnest FCT of a lipid-rich plaque was measured at the thinnest part 3×, and the values were then averaged (Figure 3C). TCFA was defined as a lipid-rich plaque with a maximum lipid arc >90° and FCT ≤65 μm.[11] Macrophage accumulation on the OCT images was defined as increased signal intensity within the plaque, accompanied by heterogeneous backward shadows (Figure 3D).[12,13] Cholesterol crystals were characterized as thin and linear regions of high intensity existing beside lipid core.[14] Microvessels were defined as small vesicular or tubular structures with diameters 50 to 300 μm and differentiated from any other branch (Figure 3E).[15] Plaque disruption was defined as a discontinuity of the fibrous cap with communication between the vessel lumen and the cavity. Calcification was also recorded when an area with low backscatter and a sharp border was identified inside a plaque.[16] OCT images were analyzed by 2 investigators who were blinded to the subject's information. When there was discordance between the readers, a consensus reading was obtained from a third independent investigator.

Statistical Analysis

Categorical data were presented as counts and proportions and were compared using either a χ^2 test or Fisher exact test, depending on the data. Continuous measurements were presented as mean±SD and analyzed with the ANOVA and Bonferroni correction for multiple comparisons. For comparisons between groups, analysis was performed by means of the generalized estimating equations approach to take into account the within-subject correlation attributable to multiple plaques analyzed within a single subject. Multiple linear regression and logistic regression analyses were performed to assess the independent predictors for lipid index and the presence of TCFA. Multiple regression models included the parameters that showed statistical significance with the $P<0.05$ in the univariate analysis. The correlation between OCT parameters and the number of MetS factors was analyzed with Spearman rank correlation coefficients. Interobserver and intraobserver reliabilities were estimated by means of κ coefficient for binary outcomes and intraclass correlation coefficient for continuous measurements. All statistical analyses were performed with SPSS version 17.0. A $P<0.05$ was considered statistically significant.

Results

Clinical Characteristics

Patient characteristics are summarized in Table 1. As expected, there were significant differences between the 3 groups. A history of hypertension was significantly more frequent in the DM and MetS groups than in the C group. Body weight, BMI, and triglyceride level were significantly greater in the MetS group than in the C group. High-density lipoprotein cholesterol was significantly lower in MetS than in the C group. Fasting blood glucose level was significantly different among the 3 groups, and the highest in the DM group. The number

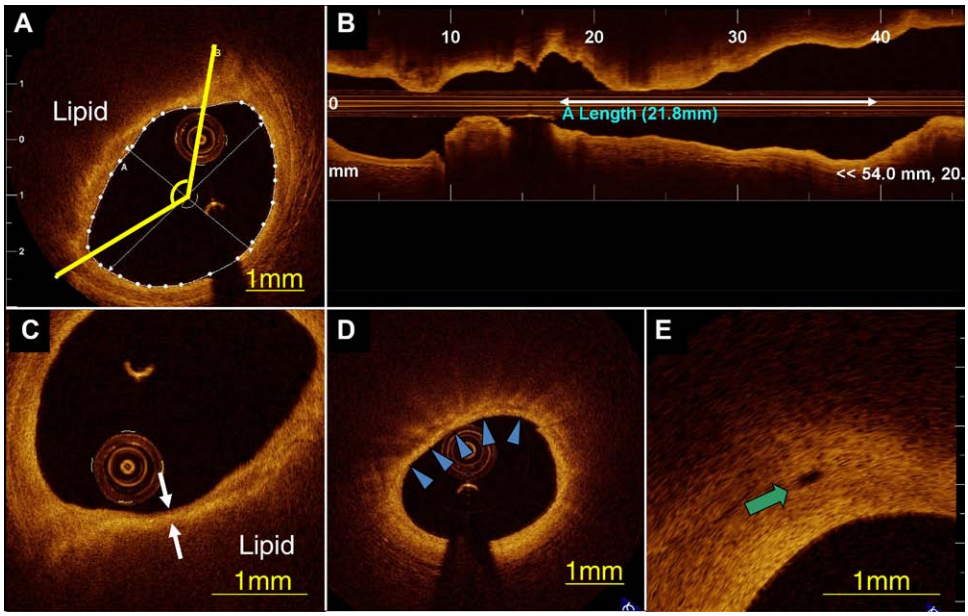

Figure 3. Representative images for optical coherence tomographic (OCT) analyses. **A**, Measurement of lipid arc for a lipid-rich plaque. Lipid arc was measured every 1 mm within a lipid-rich plaque (yellow lines). **B**, Lipid-core length, defined as the length of plaque with >90° of lipid, was measured in the longitudinal view (white arrow). **C**, Measurement of fibrous cap thickness. Fibrous cap thickness was measured at the thinnest part 3×, and the values were averaged (white arrows). **D**, Macrophage accumulation on the OCT images was defined as increased signal intensity within the fibrous cap, accompanied by heterogeneous backward shadows (arrow heads). **E**, Microvessels were defined as small vesicular or tubular structures with diameters 50 to 300 μm and differentiated from any other branch (green arrow).

Table 1. Patient Characteristics

	DM	MetS	C	*P* Value
n	77	35	59	
Age, y	59±11	60±11	60±11	0.948
Men, n (%)	55 (71)	28 (80)	48 (81)	0.347
Hypertension, n (%)	59 (77)*	29 (83)*	30 (51)	<0.001
Smoking, n (%)	14 (18)	9 (26)	16 (27)	0.422
Weight, kg	70±10*	71±8*	66±9	0.012
Height, cm	168±7	168±6	166±8	0.505
Body mass index, kg/m^2	24.9±2.5*	25.1±2.0*	23.8±2.8	0.016
Creatinine, mg/dL	1.4±1.8	1.0±0.2	1.2±1.4	0.274
Total cholesterol, mg/dL	159±46	159±37	168±39	0.428
LDL cholesterol, mg/dL	88±36	89±28	94±34	0.545
HDL cholesterol, mg/dL	42±12	38±3*	47±13	0.001
Triglyceride, mg/dL	145±75	217±145*	119±52	<0.001
HbA1c, %	6.9±1.2*	5.6±0.5	5.5±0.4	<0.001
Fasting glucose, mg/dL	130±42*	107±14	93±11	<0.001
Antidiabetic therapy				
Exercise/diet	16 (21)	0 (0)	0 (0)	
Oral hypoglycemic agents	21 (27)	0 (0)	0 (0)	
Insulin use	46 (60)	0 (0)	0 (0)	
Statin	54 (70)	21 (60)	37 (63)	0.496
ACE-I or ARB	32 (42)	17 (49)	28 (47)	0.707
Acute coronary syndrome	26 (34)	15 (43)	15 (24)	0.155
STEMI	7 (9)	4 (11)	7 (12)	0.856
NSTEMI/UAP	19 (25)	11 (31)	8 (14)	0.103

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; C, control group; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; and UAP, unstable angina.

*P<0.05 vs C.

of factors for MetS was significantly higher in the MetS group (3.4±0.5) as compared with the DM (2.8±1.0) and C (1.5±0.6) groups (P=0.002 and P<0.001). Patient characteristics of DM group or MetS group in the study cohort (3-vessel imaging cohort) were compared with those in the subjects of the registry who underwent OCT imaging for 1 or 2 coronary vessels in Tables I and II in the online-only Data Supplement. As compared with the 1- or 2-vessel OCT imaging cohort, patients with DM in 3-vessel imaging cohort had lower hemoglobin A1c level possibly because of aggressive treatment including more frequent use of insulin.

Three-Vessel OCT Imaging and Angiographic Findings

The mean total length of coronary arteries imaged by OCT was 221±45 mm; 94±25 mm in the right coronary artery, 72±23 mm in the left anterodescending coronary artery, and 55±18 mm in the circumflex. There was no significant difference in total imaged length among the DM, MetS, and C groups (205±41, 215±42, and 215±43 mm; P=0.302). Plaque location and angiographic data are shown in Table 2. There was no significant difference in plaque location and angiographic data among the 3 groups.

OCT Findings

The OCT findings from each group are summarized in Table 3. There were no significant differences in the number of plaques per subject and the prevalence of lipid-rich plaque among the 3 groups. Maximum lipid arc, lipid-core length, and lipid index were significantly greater in the DM group than those in the C group. Subjects with MetS showed a significantly longer lipid length and a greater lipid index as compared with those in C group. No significant difference was observed between DM and MetS in maximum lipid arc, lipid-core length, and lipid index. FCT only showed a trend toward smaller value in the DM and MetS groups as compared with C group. There were no significant differences in the prevalence and number of TCFA across the 3 groups. Calcification was more frequent in plaques of subjects with DM than in those of subjects with MetS. The prevalence of other microstructures, such as macrophage accumulation, microvessels, or cholesterol crystals, was not statistically different among the 3 groups.

Correlation Between the Number of MetS Factors and Lipid-Rich Plaque

Maximum lipid arc, lipid-core length, and lipid index increased linearly as the number of MetS factors increased. Although the linear trends with positive slopes were statistically significant, their magnitudes of the explained variations by the number of MetS factors were not large (maximum lipid arc: ρ=0.182; P=0.005, lipid-core length: ρ=0.202; P=0.002,

Table 2. Angiographic Data

	DM	MetS	C	*P* Value
Plaque location				
RCA, n (%)	82 (39.8)	35 (34.3)	58 (40.5)	
LAD, n (%)	74 (35.9)	36 (35.3)	54 (37.8)	0.612
Cx, n (%)	50 (24.3)	31 (30.4)	31 (21.7)	
Minimum lumen diameter, mm	1.87±0.55	1.88±0.47	1.92±0.54	0.797
Reference diameter, mm	2.87±0.66	2.87±0.55	2.96±0.64	0.474
Lesion length, mm	9.1±3.9	9.8±4.3	9.3±4.6	0.518
Diameter stenosis, %	34.5±13.4	33.3±11.9	35.1±12.1	0.687

C indicates control group; Cx, circumflex; DM, diabetes mellitus; LAD, left anterodescending artery; MetS, metabolic syndrome; and RCA, right coronary artery.

Table 3. OCT Analysis

				P Value			
	DM	MetS	C	Overall	DM vs C	MetS vs C	DM vs MetS
No. of subjects	77	35	59				
No. of plaques	206	102	143				
Plaques/subjects	2.7±1.5	2.9±1.4	2.4±1.4	0.275	…	…	…
Lipid-rich plaques	100 (52.1)	56 (54.9)	81 (56.6)	0.701	…	…	…
Maximum lipid arc	196±45*	187±42	176±52	0.016	0.002	0.184	0.173
Lipid length	7.7±4.0*	7.0±3.8*	5.5±2.4	0.001	<0.001	0.012	0.317
Lipid index	1164±716*	1086±693*	796±417	0.001	<0.001	0.018	0.475
FCT	105±46	117±62	123±60	0.088	…	…	…
TCFA	25 (12.1)	14 (13.7)	11 (7.7)	0.270	…	…	…
No. of TCFA/subject	0.32±0.68	0.40±0.70	0.19±0.51	0.236	…	…	…
Disruption	11 (5.3)	10 (9.8)	8 (5.6)	0.340	…	…	…
Calcification	90 (43.7)	30 (29.4)	59 (41.3)	0.048	0.462	0.123	0.028
Macrophage accumulation	64 (31.1)	32 (31.4)	40 (28.0)	0.788	…	…	…
Microvessels	74 (35.9)	46 (45.1)	45 (31.5)	0.089	…	…	…
Cholesterol crystal	40 (19.4)	18 (17.6)	20 (19.6)	0.416	…	…	…

C indicates control group; DM, diabetes mellitus; FCT, fibrous cap thickness; MetS, metabolic syndrome; OCT, optical coherence tomography; and TCFA, thin-cap fibroatheroma.

*<0.05 vs C.

and lipid index: ρ=0.225; *P*<0.001). No significant correlation was observed for FCT (ρ=−0.116; *P*=0.075; Figure 4).

Multiple Regression Analyses for Lipid Index and TCFA

Multiple linear regression and logistic regression analyses were performed to assess the determinants of lipid index and the presence of TCFA. As shown in Table 4, DM and MetS were independently associated with greater lipid index. However, only ACS presentation was independently associated with TCFA although DM and MetS did not show significant trend.

Observer Variabilities

The estimated interobserver and intraobserver κ coefficients were 0.90 and 0.93 for the presence of lipid-rich plaque and 0.84 and 0.84 for the presence of microvessels. Intraclass correlations were 0.87 and 0.97 for mean lipid arc and 0.86 and 0.90 for lipid-core length, respectively.

Discussion

To our knowledge, this is the first OCT study investigating in detail the plaque characteristics of patients with MetS in comparison with patients with DM and those without DM or MetS. Our OCT data demonstrated that (1) subjects with MetS had larger lipid burden compared with those without MetS, (2) frequency of TCFA did not differ among subjects with DM, those with MetS, and those without DM or MetS, (3) the prevalence of microstructure, such as macrophage accumulation, microvessels, and cholesterol crystals, did not show any significant differences among the 3 groups.

Lipid-Rich Plaque

One of the important components of rupture-prone plaque is a large necrotic core, which may physically increase the tension of fibrous cap covering the lipid core and lead to disruption.[17] Several pathological and virtual histology-intravascular ultrasound studies have shown that coronary plaques in nonculprit lesions of patients with DM had larger plaque burdens and a larger necrotic core than in those of the patients without DM,[11,18,19] which is consistent with our data. However, a recent OCT study by Niccoli et al[20] demonstrated smaller lipid arc, larger calcium, and comparable FCT in the culprit lesions of DM at the first ACS manifestations as compared with non-DM patients. Their results suggest that even small amount of lipid may be able to cause an acute coronary syndrome in patients with DM, which supports the importance of aggressive lipid-lowering therapy in patients with DM for primary or secondary prevention. Although the pathophysiological features of atherosclerosis in DM have been substantially explored, those in MetS have not been elucidated. The present study demonstrates a greater amount of lipid in nonculprit/nontarget plaques in subjects with MetS as compared with plaques in subjects without MetS or DM. These results support the previous virtual histology-intravascular ultrasound studies reporting a greater percentage of necrotic core in patients with MetS than in those without MetS.[19,21]

TCFA and FCT

Although the variability and heterogeneity of FCT at the time of plaque rupture have been reported in vivo,[22,23] thin fibrous cap (<65 μm) defined by pathological study[11] has been recognized as the most critical feature of vulnerable plaque. However, there was no significant trend in the frequency of TCFA and FCT across the 3 groups in the present study, whereas the extent of lipid expressed by lipid index was greater in DM and MetS groups. A previous virtual histology-intravascular ultrasound study showed a high prevalence of TCFA in patients with DM and MetS.[19] However, a larger cohort of subanalysis

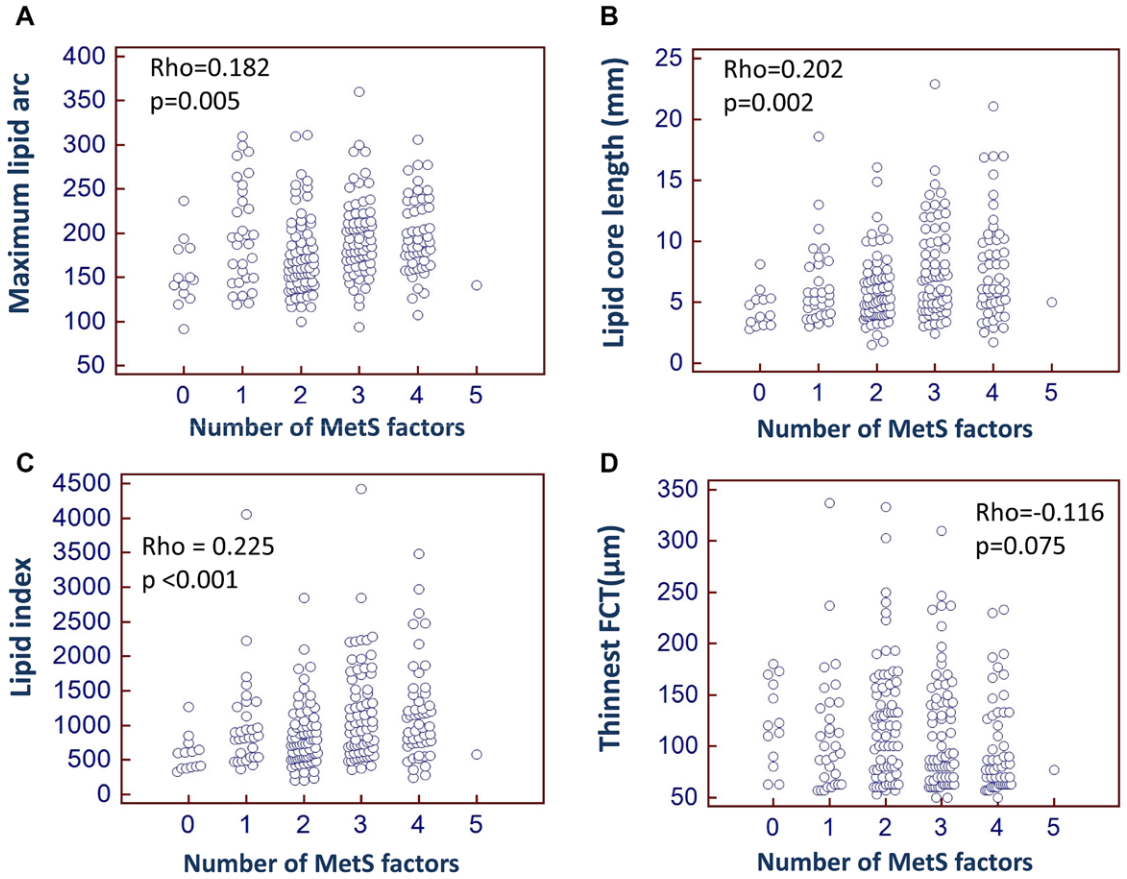

Figure 4. Correlation between the number of metabolic syndrome (MetS) factors and plaque characteristics as represented by lipid index and fibrous cap thickness. **A**, Correlation between the number of MetS factors and maximum lipid arc (ρ=0.182; *P*=0.005). **B**, Correlation between the number of MetS factors and lipid-core length (ρ=0.202; *P*=0.002). **C**, Correlation between the number of MetS factors and lipid index (ρ=0.225; *P*<0.001). **D**, Correlation between the number of factors and thinnest fibrous cap thickness (FCT; ρ=–0.116; *P*=0.075).

in PROSPECT trial showed insignificant association of MetS with the presence of virtual histology–derived TCFA.[21] These inconsistent results may reflect the ambiguous effect of MetS on plaque instability. In a previous intravascular ultrasound and OCT study, Takarada et al[24] reported that FCT was significantly correlated with high-sensitive C reactive protein rather than with lipid profiles, whereas atheroma volume showed a significant correlation only with cholesterol profiles. Their results suggested different mechanisms of regulation between lipid volume and FCT. Although several formal definitions of MetS have been proposed so far, the traditional definition that served as the basis for the present study does not include biomarkers of inflammation. These markers are likely to correlate more strongly with structural features of plaque vulnerability, including the development of thin fibrous cap. Indeed, only the independent predictor for TCFA in the present study was the clinical presentation of ACS, which is related to systemic inflammation. Previous studies demonstrated that stratification by inflammatory status indicated by high-sensitive C reactive protein adds prognostic information to the diagnosis of MetS.[8,25] The lack of a significant association between MetS and FCT or TCFA in the present study likely results from the incompleteness of traditional MetS criteria. Additional information including inflammatory markers might be helpful for better differentiation of plaque vulnerability in addition to the diagnosis of MetS and DM.

Number of Factors and Lipid

Although each factor of MetS is known separately to be a cardiovascular risk factor, it is generally accepted that the combination of those components and their inter-relationship lead to the progression of atherosclerosis.[26] However, some studies have cast doubt on the association between MetS and cardiovascular events.[27,28] In the present study, multiple linear regression analysis demonstrated that MetS is an independent predictor for large amount of lipid. However, caution should be exercised when interpreting these data. As shown in Figure 4, correlations between the number of MetS factors and OCT findings including lipid index and FCT were mild, and significant overlaps were found across the number of MetS factors (Figure 4). In other words, MetS does not provide additive predictive values beyond its individual components. Furthermore, these OCT parameters are just surrogates of the extent of lipid, which may not be necessarily associated with the risk of future cardiovascular events.

Microstructures Observed in OCT

OCT is a unique in vivo intravascular imaging modality that allows for visualization of microstructures such as macrophage accumulation, microvessels, and cholesterol crystals.[12,13,29,30] These microscopic changes are affected by multiple factors such as systemic inflammation, hypoxia, oxidative stress, and statin therapy.[31,32] Although DM and MetS were expected to

have impacts on these factors, our data showed only a weak trend toward more frequent microvessels in DM and MetS groups (P=0.091). The statin use and low-density lipoprotein cholesterol levels were not different among the groups at the time of OCT imaging (P=0.496 and P=0.545, respectively). Unfortunately, we do not have information on the previous low-density lipoprotein cholesterol levels and duration of statin therapy. A prospective systemic study may elucidate this relationship.

Calcification in DM and MetS

The present study showed higher prevalence of calcification in plaques of subjects with DM as compared with those of subjects with MetS in nonculprit or nontarget lesions. Our data are consistent with a previous computed tomographic study that revealed an intermediate association between MetS and Agatston score by multidetector computed tomography, whereas patients with DM showed remarkable association with greater calcium scores regardless of MetS.[33] A recent OCT study also demonstrated more frequent superficial calcium and larger calcium amount in the culprit vessels of ACS in patients with DM as compared with non-DM patients,[20] which is also consistent with our data. One of the advantages of OCT imaging for the evaluation of calcium is the potential to detect a small calcification in the plaque and to determine the morphological characteristics of calcium such as nodular calcium. As of now, the nature and process of coronary calcification have not been well studied in vivo. Further study with use of serial OCT imaging would be warranted to understand the pathophysiology of coronary calcification.

Limitations

The present study has several limitations. First, this study is a retrospective observational study from a registry database; therefore, selection bias may have influenced the results. In addition, we selected the patients who underwent 3-vessel OCT investigation to diminish the bias from the studied vessel. However, there still might have been a selection bias as shown in Tables I and II in the online-only Data Supplement. Second, our OCT registry data did not include information on waist circumference, so we used BMI as a substitute for the determination of obesity. Moreover, the presence of high blood pressure was substituted with the history of hypertension. Our modified definition of MetS may have affected the results. Third, we included only plaques with area stenosis >50% as indicated by OCT. Although this criterion is accepted in the consensus documents,[34] it is the criteria for a stenosis rather than the definition of a plaque. Early stages of atherosclerosis

Table 4. Multiple Linear and Logistic Regression Models for Lipid Index and Fibrous Cap Thickness

	Univariate Models										
			95% CI					95% CI			
	B	SE	Lower	Upper	*P* Value	B	SE	Lower	Upper	VIF	*P* Value
Lipid index											
Age	−4.5	4.0	−12.3	3.4	0.266						
Men	131.7	104.5	−73.1	336.5	0.208						
Hypertension	75.6	103.7	−127.5	278.9	0.466						
Hyperlipidemia	209.8	85.5	42.2	377.4	0.014	61.2	109.6	−154.9	277.3	1.164	0.577
Diabetes mellitus	239.0	90.4	61.8	416.2	0.008	179.6	85.1	11.9	347.4	1.084	0.036
Current smoker	127.5	113.5	−95.0	349.9	0.261						
Metabolic syndrome	317.8	90.2	141.0	494.5	<0.001	211.1	93.1	27.6	394.6	1.332	0.024
Statin use	−100.9	95.9	−288.8	87.0	0.293						
ACE-I/ARB use	−74.5	93.4	−257.6	108.5	0.425						
Acute coronary syndrome	218.6	87.4	47.3	389.9	0.012	90.5	86.5	−80.0	261.0	1.133	0.297
TCFA											
Age	0.00	0.02	−0.05	0.04	0.874						
Men	0.34	0.50	−0.65	1.33	0.502						
Hypertension	−0.33	0.38	−1.08	0.43	0.396						
Hyperlipidemia	0.00	0.45	−0.87	0.88	0.992						
Diabetes mellitus	0.19	0.36	−0.52	0.89	0.605						
Current smoker	0.87	0.39	0.11	1.63	0.024	0.53	0.35	−0.17	1.22	1.080	0.136
Metabolic syndrome	0.53	0.37	−0.19	1.25	0.147						
Statin use	−0.82	0.35	−1.51	−0.13	0.020	−0.49	0.35	−1.17	0.19	1.144	0.155
ACE-I/ARB use	−0.09	0.37	−0.81	0.63	0.811						
Acute coronary syndrome	1.23	0.37	0.50	1.96	0.001	0.89	0.36	0.18	1.60	1.085	0.014

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CI, confidence interval; TCFA, thin-cap fibroatheroma; and VIF, variance inflation factor.

with expansive remodeling may have been excluded. Fourth, no inflammatory markers such as high-sensitive C reactive protein were assessed in this study. Fifth, the duration and type of DM were not available in the registry, which might have influenced plaque characteristics. Sixth, we used lipid index calculated from OCT parameters. However, this value is a surrogate of the necrotic core burden. Finally, a lack of longitudinal follow-up data did not allow for the assessment of the clinical impact of OCT findings on the future events.

Conclusions

Plaques in subjects with MetS contain larger lipid content than those in subjects without MetS, whereas FCT was not significantly associated with the diagnosis of MetS.

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CLINICAL PERSPECTIVE

Previous studies have reported an association between metabolic syndrome (MetS) and cardiovascular disease. However, the underlying pathophysiology has not been fully explored. Moreover, some reports have raised questions about the strength of the association between MetS and cardiovascular events. In the present study, we evaluated the plaque characteristics of MetS in comparison with patients with diabetes mellitus and control group without MetS or diabetes mellitus by using 3-vessel optical coherence tomographic investigation. Our data demonstrated larger amount of lipid in nonculprit/nontarget lesions of MetS and diabetes mellitus groups as compared with control group. However, fibrous cap thickness and presence of thin-cap fibroatheroma, which are recognized as hallmarks of plaque vulnerability, were not different among the 3 groups. Our results suggest additional information is needed to identify patients with MetS who are at higher risk for cardiovascular events.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Patient characteristics of DM group in subjects who underwent 1 or 2 vessel optical coherence tomography and those with 3 vessel imaging.

	1 or 2 vessel OCT	3 vessel OCT	p value
N	232	77	
Age	62±13	59±11	0.070
Male, n(%)	160 (69)	55 (71)	0.830
Hypertension, n(%)	170 (73)	59 (77)	0.667
Current smoking, n(%)	38 (16)	14 (18)	0.849
Weight, kg	71±12	70±10	0.511
Height, cm	165±8	168±7	0.004*
Body mass index, kg/m^2	26.0±3.6	24.9±2.5	0.013*
Creatinine, mg/dl	1.0±0.8	1.4±1.8	0.011*
Total cholesterol, mg/dl	160±43	159±46	0.862
LDL cholesterol, mg/dl	90±37	88±36	0.680
HDL cholesterol, mg/dl	45±13	42±12	0.075
Triglyceride, mg/dl	150±100	145±75	0.688
HbA1c, %	7.4±1.6	6.9±1.2	0.012*
Fasting glucose, mg/dl	150±59	130±42	0.006*
Insulin, n(%)	101 (44)	46 (60)	0.020*
OHA, n(%)	119 (51)	21 (27)	<0.001*
Statin, n(%)	168 (72)	54 (70)	0.810
ACS, n(%)	91 (39)	26 (34)	0.472

* $p<0.05$ OHA indicates oral hypoglycemic agent; ACS, acute coronary syndrome.

Supplemental Table 2. Patient characteristics of MetS group in subjects who underwent 1 or 2 vessel optical coherence tomography and those with 3 vessel imaging.

	1 or 2 vessel OCT	3 vessel OCT	p value
N	181	35	
Age	60±11	60±11	0.885
Male, n(%)	133 (73)	28 (80)	0.550
Hypertension, n(%)	147 (81)	29 (83)	0.993
Current smoking, n(%)	53 (29)	9 (26)	0.824
Weight, kg	77±15	71±8	0.022*
Height, cm	168±8	168±6	1.000
Body mass index, kg/m^2	27.3±4.3	25.1±2.0	0.003*
Creatinine, mg/dl	1.0±0.3	1.0±0.2	0.852
Total cholesterol, mg/dl	173±43	159±37	0.073
LDL cholesterol, mg/dl	97±37	89±28	0.227
HDL cholesterol, mg/dl	40±11	38±3	0.288
Triglyceride, mg/dl	200±110	217±145	0.429
HbA1c, %	6.0±0.7	5.6±0.5	0.002*
Fasting glucose, mg/dl	110±16	107±14	0.302
Statin, n(%)	111 (61)	21 (60)	0.966
ACS, n(%)	109 (60)	15 (43)	0.086

*$p<0.05$ ACS indicates acute coronary syndrome.