Postprandial Hyperchylomicronemia and Thin-Cap Fibroatheroma in Nonculprit Lesions

A Multivessel Optical Coherence Tomography Study

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Objective—Although postprandial hypertriglyceridemia can be a risk factor for coronary artery disease, the extent of its significance remains unknown. This study aimed to investigate the correlation between the postprandial lipid profiles rigorously estimated with the meal tolerance test and the presence of lipid-rich plaque, such as thin-cap fibroatheroma (TCFA), in the nonculprit lesion.

Approach and Results—A total of 30 patients with stable coronary artery disease who underwent a multivessel examination using optical coherence tomography during catheter intervention for the culprit lesion were enrolled. Patients were divided into 2 groups: patients with TCFA (fibrous cap thickness ≤65 μm) in the nonculprit lesion and those without TCFA. Serum remnant-like particle-cholesterol and ApoB-48 (apolipoprotein B-48) levels were measured during the meal tolerance test. The value of remnant-like particle-cholesterol was significantly greater in the TCFA group than in the non-TCFA group (P=0.045). Although the baseline ApoB-48 level was similar, the increase in the ApoB-48 level was significantly higher in the TCFA group than in the non-TCFA group (P=0.028). In addition, the baseline apolipoprotein C-III levels was significantly greater in the TCFA group (P=0.003). These indexes were independent predictors of the presence of TCFA (ΔApoB-48: odds ratio, 1.608; 95% confidence interval, 1.040–2.486; P=0.032; apolipoprotein C-III: odds ratio, 2.581; 95% confidence interval, 1.177–5.661; P=0.018).

Conclusions—Postprandial hyperchylomicronemia correlates with the presence of TCFA in the nonculprit lesion and may be a residual risk factor for coronary artery disease. **(*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.118.311245.)**

Key Words: apolipoprotein B-48 ■ cholesterol ■ coronary artery disease ■ remnant-like particle cholesterol ■ tomography, optical coherence

Although the elevation of nonfasting serum triglyceride level has been established as a risk factor for coronary artery disease (CAD),[1] the correlation between the levels of postprandial lipid profiles rigorously estimated with the meal tolerance test (MTT) and CAD has not yet been fully validated. Postprandial hypertriglyceridemia is characterized by the accumulation of triglyceride-rich lipoprotein (TGRL) particles.[2–4] Recently, it has become possible to measure the number of chylomicron particles based on the intestinally derived lipoprotein, ApoB-48 (apolipoprotein B-48). ApoB-48 is a TGRL that acts as the primary structural component of chylomicrons.[5] Previous clinical studies have suggested that ApoB-48 can be identified in human atherosclerotic plaque,[6] and an elevated fasting serum ApoB-48 level has a close independent correlation with CAD.[7,8] However, no reports were found concerning the association between postprandial ApoB-48 levels and the vulnerability of coronary atherosclerosis leading to acute coronary syndrome in patients with CAD.

The principal pathogenesis of acute coronary syndrome is disruption of culprit plaques composed of a large lipid core under a thin fibrous cap, the so-called thin-cap fibroatheroma (TCFA), which is considered vulnerable.[9,10] The intracoronary imaging system optical coherence tomography (OCT) enables a detailed characterization of coronary plaques; this technique is a novel modality that can measure fibrous cap thickness because of its high-resolution images.[11] Prospective OCT studies showed that OCT-detected TCFA cause plaque

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Nonstandard Abbreviations and Acronyms

ApoB-48	apolipoprotein B-48
ApoC	apolipoprotein C
CAD	coronary artery disease
CM-R	chylomicron remnant
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
MTT	meal tolerance test
OCT	optical coherence tomography
RLP-C	remnant-like particle-cholesterol
TCFA	thin-cap fibroatheroma
TGRL	triglyceride-rich lipoprotein
VLDL	very-low-density lipoprotein
VLDL-R	very-low-density lipoprotein remnant

stenotic progression on angiography and adverse clinical outcomes.[12,13]

The aim of this study was to evaluate whether the presence of TCFA correlates with changes in lipoprotein profiles after MTT.

Materials and Methods

OCT Analysis

A total of 30 patients with stable CAD who consented to participate after a full explanation of the study purpose and underwent percutaneous coronary intervention for the culprit lesion and OCT observation for multivessels between March 2014 and October 2015 were enrolled. Patients with left main disease (n=24), chronic total occlusion (n=68), bypass graft disease (n=17), and on regular hemodialysis (n=23) were excluded from the study.

Patients were divided into 2 groups according to the presence or absence of TCFA in the nonculprit lesion (TCFA group or non-TCFA group, respectively). Nonculprit lesions were defined as plaques that had not been treated during the session of coronary angiography or percutaneous coronary intervention based on the results of a stress test or electrocardiographic changes during spontaneous ischemic attacks. OCT images were obtained using TERUMO optical frequency domain imaging system (LUNAWAVE, FastView; Terumo, Tokyo, Japan). With the assistance of a 6F or 7F guiding catheter, images were obtained using a continuous flush of contrast media or low molecular weight dextran-L at a rate of 4 to 5 mL/s through the guiding catheter, and the imaging wire was pulled back at a rate of 20 to 40 mm/s. Each plaque was separated at least 5 mm from the edge of another plaque or from an implanted stent edge as seen on the longitudinal OCT pullback. Any plaque continuous to an implanted stent was excluded. TCFA was defined as a plaque with fibrous cap thickness <65 mm overlying a lipid-rich plaque (maximum lipid arc >90°) as detected on cross-sectional imaging(Figure 1).[14] Calcifications were defined as signal-poor or heterogeneous areas delimited by sharp borders. Calcified lesions subtending an arc <90° and extending in length for 1 to 4 mm were classified as spotty calcium.[15] The presence of bright spots within the fibrous cap with backward shadowing was considered indicative of macrophage accumulation.[14]

Study Protocol

All patients in our study were scheduled for coronary angiography or percutaneous coronary intervention, and data on the patients' sex, history of myocardial infarction, and coronary risk factors, such as hyperlipidemia, diabetes mellitus, and hypertension, were collected from medical records. Blood samples were obtained from the antecubital vein in the fasting state before the procedure. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dL,

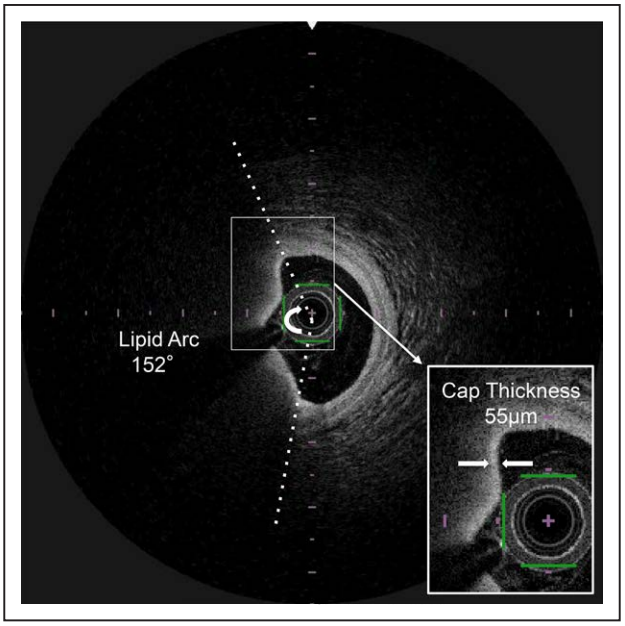

Figure 1. Representative case of thin-cap fibroatheroma (TCFA). The angle of the lipid tissue was measured as 152° from edge to edge, and the minimum fibrous thickness of this lesion was 55 μm.

self-reported clinician-diagnosed diabetes mellitus, or a hemoglobin A1c level ≥6.5%.[16] Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or patients already taking antihypertensive drugs.[17] Hyperlipidemia was defined as medication-dependent or previously known hyperlipidemia, fasting serum LDL-C (low-density lipoprotein cholesterol) level ≥140 mg/dL, or fasting serum total cholesterol level ≥220 mg/dL.[18]

After an overnight fast for 12 hours, MTT was performed by loading test meal A, which is a standard test meal authorized by the Japan Diabetes Association,[19] and 35 g of oral fat tolerance test cream (Jomo Shokuhin, Takasaki, Japan)[20] to each patient. Blood samples were drawn before and 1, 2, 4, 5, and 6 hours after MTT; concentrations of triglyceride, remnant-like particle-cholesterol (RLP-C), and ApoB-48 were measured. We defined the Δ value as the increment in serum levels of triglyceride, RLP-C, and ApoB-48 from fasting to peak value and the peak time as the arrival time to peak value from fasting within an individual patient.

The medical ethics committee at Nippon Medical School Chiba Hokusoh Hospital approved this study protocol (no. 312), and written informed consent was obtained from all patients before the catheterization procedures. This study conformed to the Declaration of Helsinki.

Biochemical Measurements

Plasma glucose was measured using the glucose oxidase method, and hemoglobin A1c was measured using high-performance liquid chromatography. Serum total cholesterol, LDL-C (Choletest-LDL, Sekisui Medical, Tokyo, Japan), high-density lipoprotein cholesterol (Choletest-HDL, Sekisui Medical), and triglyceride were measured using enzymatic methods. Serum apolipoproteins were measured using immunoturbidimetric methods (Sekisui Medical). The serum ApoB-48 levels were measured using chemiluminescence enzyme immunoassay (Fujirebio, Inc, Tokyo, Japan).[5] The RLP-C level was measured using a homogenous assay (MetaboLead, Kyowa Medex, Tokyo, Japan).[21]

Statistical Analysis

Continuous variables are presented as means±SD and were compared using Student *t* test. Because apolipoprotein A-II and ApoC (apolipoprotein C)-III levels did not distribute normally, these

values are presented as medians and the interquartile ranges and were compared by the Mann-Whitney *U* test. Categorical variables are presented as frequencies and were compared using the Pearson χ^2 test. Repeated measures ANOVA, post hoc analysis using Tukey-Kramer test, and Student *t* tests were used to analyze the results of MTT in terms of serum triglyceride, RLP-C, and ApoB-48. The correlation between ΔApoB-48 and Apo C-III was evaluated by linear regression analysis. Univariate logistic regression analysis was used to determine the lipid profiles associated with the existence of TCFA. The values achieved significant levels ($P<0.05$) in univariate logistic regression analysis; they were adjusted for age and sex in the multivariate logistic regression model. All differences were evaluated at the 95% level of significance ($P<0.05$). All statistical analyses were performed using IBM SPSS version 21 (IBM Japan, Tokyo, Japan).

Results

Our study population consisted of select patients who consented to participate after a full explanation of the study purpose, nature, and risks. The baseline characteristics, including age and coronary risk factors, were similar between the whole patient cohort undergoing scheduled percutaneous coronary intervention during the study period (n=422) and the select patients in this study (age, 66.3 versus 69.4 years, $P=0.094$; hypertension, 67% versus 75%, $P=0.335$; hyperlipidemia, 73% versus 66%, $P=0.390$; diabetes mellitus, 47% versus 51%, $P=0.615$, respectively).

A total of 72 lipid plaques were identified in 84 coronary arteries. Among them, 10 plaques were categorized as TCFA in 10 patients. The clinical characteristics of the patients and OCT findings are summarized in Table 1. There were 20 patients (67%) in the non-TCFA group and 10 patients (33%) in the TCFA group. Baseline characteristics, distributions of the observed coronary arteries, and the number of lipid plaques per patient were similar between the 2 groups. The prevalence of macrophage accumulation was significantly higher in the TCFA group than in the non-TCFA group ($P=0.032$), and the prevalence of calcification and spotty calcium was similar between the 2 groups. Statins were prescribed almost equally in the TCFA and non-TCFA groups, and no patients were being treated with fibrate or ezetimibe.

Table 2 shows the fasting lipid profile, including apolipoprotein. Fasting serum levels of total cholesterol, non–high-density lipoprotein cholesterol, RLP-C, ApoC-II, and ApoC-III were significantly higher in the TCFA group than in the non-TCFA group. Table 3 and Figure 2 show the postprandial changes in lipid profiles during MTT. As shown in Table 3, although the fasting, peak, and area under the curve RLP-C levels were significantly different ($P=0.045$, $P=0.031$, and $P=0.027$, respectively), the levels of ApoB-48 and triglyceride were not found to be different.

Similarly, as shown in Figure 2, although the serum RLP-C levels in MTT were significantly different ($P=0.026$), ApoB-48 and triglyceride levels were not different between the 2 groups ($P=0.326$ and $P=0.128$, respectively). Post hoc analysis showed that triglyceride levels were similar, but RLP-C levels significantly differ at each point. ApoB-48 levels were not different between the TCFA and the non-TCFA groups except for 6 hours (6 hours, $P=0.007$). However, ΔApoB-48 was significantly higher in the TCFA group than in the non-TCFA group ($P=0.028$). Conversely, the values of triglyceride and RLP-C were not significantly different between the 2 groups. Figure 3 shows the relationship between ΔApoB-48 and ApoC-III. In the simple linear regression analysis, these values were significantly positively correlated ($R=0.448$; $P=0.013$).

Table 4 shows the results of logistic regression analysis. Univariate logistic regression analysis showed that fasting levels of ApoC-II, ApoC-III, and ΔApoB-48 were significantly associated with the presence of TCFA. Regardless of sex and

Table 1. Clinical Baseline Characteristics

	TCFA (–)	TCFA (+)	*P* Value
Patients, n	20	10	
Age, y	67.3±10.0	64.3±10.2	0.456
Sex, male	14 (70%)	9 (90%)	0.222
Hypertension, n	12 (60%)	9 (90%)	0.091
Hyperlipidemia, n	16 (80%)	6 (60%)	0.243
Diabetes mellitus	9 (45%)	5 (50%)	0.796
Hyperuricemia, n	3 (15%)	4 (40%)	0.127
Current smoking, n	8 (40%)	4 (40%)	1.000
Prior MI	9 (45%)	3 (30%)	0.429
Medication			
Statin, n	19 (95%)	9 (90%)	0.605
ACE inhibitor, n	9 (45%)	3 (30%)	0.429
ARB, n	4 (20%)	4 (40%)	0.384
β-Blockers, n	9 (45%)	5 (50%)	0.796
Calcium channel blocker, n	5 (25%)	4 (40%)	0.398
Dual antiplatelet therapy, n	20 (100%)	10 (100%)	…
Laboratory data			
Hs-CRP, mg/dL	0.08±0.10	0.07±0.07	0.757
FPG, mg/dL	105.9±15.4	106.8±22.4	0.892
HbA1c (%)	6.3±0.6	6.3±0.4	0.981
eGFR, mL/min per 1.73 meter^2	65.7±13.9	57.7±14.0	0.152
OCT findings			
Observed vessel			
LAD	20 (100%)	10 (100%)	…
LCx	18 (90%)	10 (100%)	0.301
RCA	17 (85%)	9 (90%)	0.704
No. of lipid plaques	45	27	
No. of lipid plaques per patient	2.4±0.8	2.7±1.3	0.399
Macrophage accumulation	10 (50%)	9 (90%)	0.032
Calcification	16 (80%)	7 (70%)	0.542
Spotty calcium	7 (35%)	3 (30%)	0.784

Values are presented as a number (%) or mean±SD.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; OCT, optical coherence tomography; RCA, right coronary artery; and TCFA, thin-cap fibroatheroma.

Table 2. Fasting Lipid Profile

	TCFA (–)	TCFA (+)	*P* Value
Patients, n	20	10	
T-cho, mg/dL	147.7±26.8	173.8±40.5	0.043
LDL-C, mg/dL	85.9±26.7	106.1±39.3	0.107
HDL-C, mg/dL	44.2±12.7	45.2±13.1	0.842
Non-HDL-C, mg/dL	103.5±25.7	128.6±33.1	0.029
TG, mg/dL	119.0±44.7	147.1±48.3	0.125
RLP-C, mg/dL	5.7±3.2	8.9±5.1	0.045
Apolipoprotein A-I, mg/dL	117.0±20.2	122.0±30.1	0.593
Apolipoprotein A-II, mg/dL	24.0 (21.6–25.9)	26.2 (22.9–30.8)	0.143
Apolipoprotein B, mg/dL	74.8±19.0	88.7±24.2	0.095
Apolipoprotein C-II, mg/dL	3.7±1.0	4.9±1.2	0.007
Apolipoprotein C-III, mg/dL	7.7 (6.5–8.9)	9.9 (8.6–13.3)	0.003
Apolipoprotein E, mg/dL	3.7±0.6	4.1±0.9	0.214

Values are presented as mean±SD or median (interquartile range).

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RLP-C, remnant-like particle-cholesterol; T-cho, total cholesterol; TCFA, thin-cap fibroatheroma; and TG, triglyceride.

age adjustment, these variables were significantly correlated with the presence of TCFA (ApoC-II: odds ratio, 3.802; 95% confidence interval, 1.193–12.12; *P*=0.024; ApoC-III: odds ratio, 2.581; 95% confidence interval, 1.177–5.661; *P*=0.018; and ΔApoB-48: odds ratio, 1.608; 95% confidence interval, 1.040–2.486; *P*=0.032).

Table 3. Postprandial Changes

	TCFA (–)	TCFA (+)	*P* Value
Patients, n	20	10	
Fasting TG, mg/dL	119.0±44.7	147.1±48.3	0.125
Peak TG, mg/dL	191.0±65.3	239.4±80.5	0.087
AUC TG, (mg/dL)×h	946.8±352.3	1161.8±396.7	0.455
ΔTG, mg/dL	72.0±29.4	92.3±37.3	0.114
Peak time TG, h	4.1±1.1	4.2±1.3	0.737
Fasting RLP-C, mg/dL	5.7±3.2	8.9±5.1	0.045
Peak RLP-C, mg/dL	8.7±4.0	13.0±6.4	0.031
AUC RLP-C, (mg/dL)×h	43.2±20.8	66.8±34.9	0.027
ΔRLP-C, mg/dL	3.0±1.7	4.1±2.1	0.142
Peak time RLP-C, h	4.4±1.2	4.7±1.2	0.448
Fasting ApoB-48, μg/dL	3.5±1.9	3.4±1.1	0.870
Peak ApoB-48, μg/dL	8.1±3.6	10.4±3.9	0.121
AUC ApoB-48, (μg/dL)×h	38.3±16.8	43.2±15.6	0.455
ΔapoB-48, μg/dL	4.6±2.3	7.0±3.4	0.028
Peak time ApoB-48, h	4.1±1.4	5.0±1.2	0.074

Values are presented as mean±SD.

ApoB-48 indicates apolipoprotein B-48; AUC, area under the curve; RLP-C, remnant-like particle-cholesterol; TCFA, thin-cap fibroatheroma; and TG, triglyceride.

Discussion

Our results showed that ΔApoB-48, but not fasting levels of LDL-C and ApoB-48, correlated with the presence of TCFA in the nonculprit lesion. Moreover, RLP-C, ApoC-II, and ApoC-III levels were important factors associated with the presence of TCFA.

Many clinical trials have reported that the level of LDL-C is the strongest factor associated with CAD,[22,23] and lipid-lowering statin therapy clearly decreases the incidence of CAD.[24,25] Although most patients with preexisting CAD have already received statin therapy, some patients subsequently experience a cardiovascular event. These phenomena suggest that residual risks remain and are not well controlled. In our study, all patients had a history of CAD, statins were prescribed in 28 (93%), and median LDL-C levels were 89.0 mg/dL; there were no significant differences among these values between the 2 groups.

Recently, elevations of nonfasting triglyceride and RLP-C levels have been considered to be important predictors of cardiovascular events,[1,26] and postprandial hypertriglyceridemia may be a residual risk factor. After the ingestion of a meal, chylomicron and VLDL (very-low-density lipoprotein) are produced by the intestine and the liver, respectively. After secretion, triglyceride contained in the particle of TGRLs is hydrolyzed by lipoprotein lipase (LPL), and the particles of chylomicron and VLDL become smaller TGRLs, which are called remnants. Chylomicron remnant (CM-R) and a portion of the VLDL remnant (VLDL-R) are removed from the circulation by the liver, and the remaining VLDL-R is transformed into LDL by hepatic triglyceride lipase–induced hydrolyzation. The metabolic pathways of chylomicron and VLDL are termed exogenous pathway and endogenous pathway, respectively. Although postprandial hypertriglyceridemia is mainly because of the overproduction and decreased catabolism of TGRLs containing chylomicron, CM-R, VLDL, and VLDL-R,[27] there has been controversy as to whether postprandial hypertriglyceridemia is because of an increase in TGRLs derived from the exogenous or endogenous pathways.[28] ApoB-48 exists on the surface of chylomicron and CM-R, and the serum level of ApoB-48 reflects the number of chylomicron and CM-R particles.[5]

The postprandial levels of triglyceride, RLP-C, and ApoB-48 significantly increase after the intake of a meal.[29] In our series, the results of MTT analyzed with repeated multivariate ANOVA showed that the triglyceride levels were not different, but those of serum RLP-C levels were significantly higher in the TCFA group than in the non-TCFA group. The reason for the divergence between triglyceride and RLP-C in MTT is that although triglyceride is unlikely to cause cardiovascular disease directly,[30,31] RLP-C is more likely to be the causal CAD factor.[26] Although RLP-C includes CM-R and VLDL-R in the fasting state, increased lipoproteins in the postprandial state as measured by RLP-C represent VLDL-R, but not CM-R,[32,33] that is, ΔRLP-C in MTT represents VLDL-R. In our series, because ΔRLP-C in MTT was similar between the 2 groups, the incrementing of VLDL in the postprandial state might have no correlation with the presence of TCFA. In contrast, fasting total cholesterol and non-HDL levels were significantly higher in the TCFA group

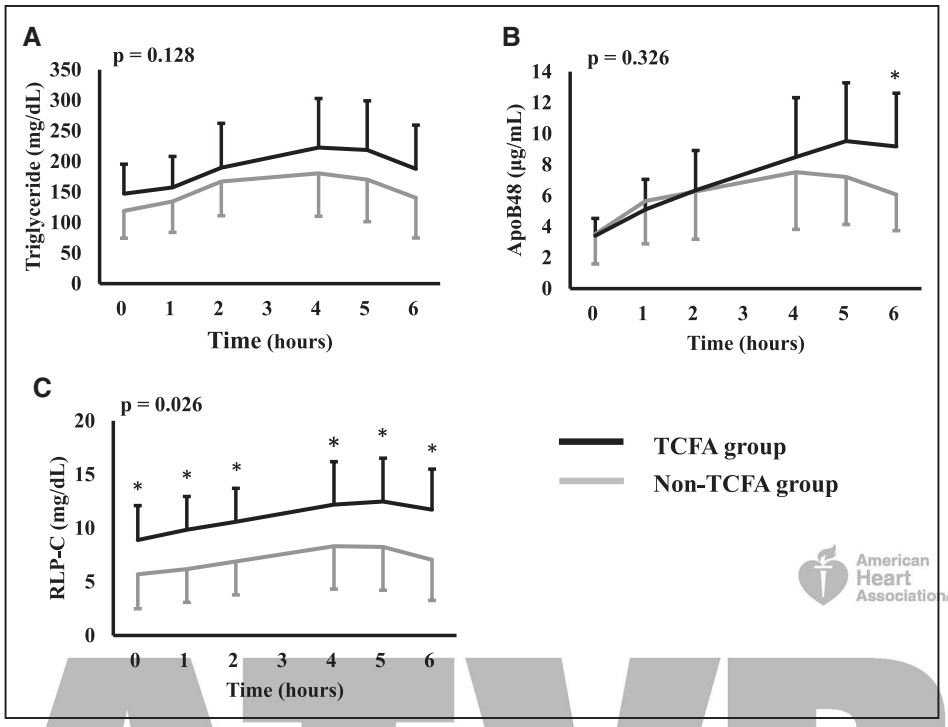

Figure 2. Plasma levels of each lipoprotein after the meal tolerance test. The black line indicates the presence of thin-cap fibroatheroma (TCFA); the gray line indicates the absence of TCFA. Blood samples were drawn during fasting and 1, 2, 4, 5, and 6 h after test meal A and oral fat tolerance test cream loading. **A**, Triglyceride; (**C**) remnant-like particle-cholesterol (RLP-C); (**B**) ApoB-48 (apolipoprotein B-48). Repeated ANOVA showed that the value of serum RLP-C level was significantly different (P=0.026) while those of ApoB-48 and triglyceride were not significantly different between the 2 groups (P=0.326, P=0.128). *P<0.05 as calculated using Tukey-Kramer test.

than in the non-TCFA group. Similarly, the fasting RLP-C levels were significantly higher in the TCFA group than in the non-TCFA group, but the fasting ApoB-48 levels were similar between the 2 groups.

Current data suggested the following 2 possibilities: (1) the particle size of CM-R is larger, and (2) VLDL-R is increased in the TCFA group compared with the non-TCFA group in the fasting state. In other words, the enlargement of CM-R and elevation of VLDL-R in the fasting state might correlate with the presence of TCFA.

In addition, although the fasting serum ApoB-48 level is reportedly an independent risk factor for CAD,[7,8] the mean values of fasting ApoB-48 were similar between the 2 groups because all patients had CAD at baseline. In contrast, ΔApoB-48 was significantly higher, and peak time ApoB-48 was slightly delayed in the TCFA group compared with those in the non-TCFA group in this study. As the gradient of the mean ApoB-48 level within the first 2 hours of MTT is the same, the increase in ΔApoB-48 level and the delay in peak time ApoB-48 seemed to be caused by a disturbance of hepatic chylomicron clearance. Our result showed that fasting levels of ApoC-II and ApoC-III were significantly associated with the presence of TCFA. ApoC-II and ApoC-III have opposing effects on plasma triglyceride levels. ApoC-II is known as an

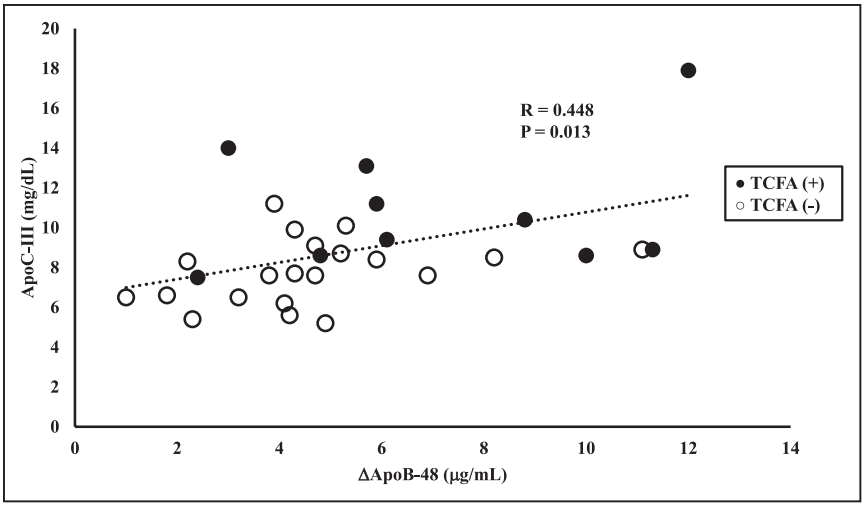

Figure 3. Simple linear regression analysis. Correlation with Δ ApoB-48 (apolipoprotein B-48) with Apo C-III (apolipoprotein C-III). R=0.448; P=0.013. TCFA indicates thin-cap fibroatheroma.

Table 4. Logistic Regression Analysis for the Predictors of Thin-Cap Fibroatheroma

	Unadjusted Analysis			Adjusted Analysis		
Explanatory Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Clinical characteristics						
Age (per 1-y increment)	0.970	0.898–1.048	0.442			
Sex (male)	3.857	0.396–37.582	0.245			
Fasting value						
T-cho (per 1 mg increment)	1.028	0.997–1.060	0.075			
LDL (per 1 mg increment)	1.022	0.994–1.069	0.131			
HDL (per 1 mg increment)	1.006	0.947–1.03	0.835			
TG (per 1 mg increment)	1.014	0.996–1.033	0.129			
RLP-C (per 1 mg increment)	1.231	0.995–1.523	0.056			
Apolipoprotein A-I (per 1 mg/dL increment)	1.009	0.977–1.042	0.580			
Apolipoprotein A-II (per 1 mg/dL increment)	1.201	0.964–1.496	0.102			
Apolipoprotein B (per 1 mg/dL increment)	1.034	0.992–1.077	0.111			
Apolipoprotein C-II (per 1 mg/dL increment)	2.846	1.194–6.786	0.018	3.802	1.193–12.12	0.024
Apolipoprotein C-III (per 1 mg/dL increment)	2.087	1.132–3.847	0.018	2.581	1.177–5.661	0.018
Apolipoprotein E (per 1 mg/dL increment)	2.012	0.658–6.151	0.220			
Peak value						
TG (per 1 mg increment)	1.010	0.998–1.022	0.097			
RLP-C (per 1 mg increment)	1.198	0.997–1.439	0.054			
ApoB-48 (per 0.1 μg increment)	1.180	0.954–1.460	0.126			
AUC						
TG (per 1 mg increment)	1.002	0.999–1.004	0.146			
RLP-C (per 1 mg increment)	1.036	1.000–1.074	0.053			
ApoB-48 (per 0.1 μg increment)	1.019	0.972–1.068	0.442			
Δ (increment from fasting to peak)						
TG (per 1 mg increment)	1.021	0.995–1.047	0.121			
RLP-C (per 1 mg increment)	1.376	0.897–2.111	0.143			
ApoB-48 (per 0.1 μg increment)	1.375	1.009–1.873	0.044	1.608	1.040–2.486	0.032
Peak time						
TG (per 1 mg increment)	1.133	0.562–2.284	0.727			
RLP-C (per 1 mg increment)	1.334	0.645–2.758	0.437			
ApoB-48 (per 0.1 μg increment)	1.967	0.895–4.324	0.092			

Variables that achieved significant levels ($P<0.05$) in the univariate logistic regression analysis were selected for testing with the use of a multivariate logistic regression model. ApoB-48 indicates apolipoprotein B-48; AUC, area under the curve; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; RLP-C, remnant-like particle-cholesterol; T-cho, total cholesterol; and TG, triglyceride.

obligate activator of LPL.[34] The deficiency in ApoC-II causes marked accumulation of chylomicron and VLDL, resulting in familiar chylomicronemia syndrome with massive hypertriglyceridemia, such as LPL deficiency.[35] In contrast, ApoC-III promotes the elevation of plasma triglyceride levels with the inhibition of ApoC-II–induced activation of LPL.[34] A recent clinical study showed that lowering plasma ApoC-III levels with ApoC-III-specific antisense oligonucleotide could reduce the serum triglyceride levels in patients with familiar chylomicronemia syndrome who have genetic defects in LPL activity.[36] The experimental data with rodent models showed that ApoC-III inhibited the hepatic clearance of TGRLs via LDL receptor and LDL receptor–related protein 1 pathway.[37] These investigations suggest that ApoC-III is a crucial regulator of TGRL metabolism through LPL-dependent and LPL-independent pathways.[34,37,38] In the current study, fasting ApoC-III and ΔApoB-48 levels were significantly correlated with TCFA and each other. The elevation of ApoC-III levels is thought to delay and elevate the postprandial chylomicron metabolism.

Moreover, recent studies showed that enhanced absorption of cholesterol is related to coronary plaque vulnerability and

plaque progression.[39,40] In the current study, we did not measure the markers of cholesterol absorption, such as sitosterol or campesterol. Although the relationship between cholesterol absorption and chylomicron metabolism is not well-known, it was reported that the inhibition of cholesterol absorption with ezetimibe lowered the peak levels of postprandial ApoB-48.[41] These previous findings might support our current data.

As the postprandial ApoB-48 and fasting ApoC-III levels were decreased by medications, such as ezetimibe and fibrate,[42–46] which improve cardiovascular outcomes,[47,48] lowering ApoB-48 and ApoC-III levels might reduce the risk of cardiovascular events. Further studies focusing on postprandial hypertriglyceridemia and hyperchylomicronemia are recommended to evaluate the effects of antiatherosclerotic drugs.

The present study has several limitations. First, the findings are from a single center and are derived from a relatively small number of patients. Second, some patients were excluded because of the difficulty in understanding the full explanation of the study purpose, nature, and risks, particularly repeated blood sampling after MTT. Third, imaging of the culprit lesion was not evaluated in all patients. Therefore, some selection bias is inevitable. Last, the circulating factors affecting lipolysis such as LPL, angiopoietin-like protein families, and apolipoprotein A-V, excluding ApoC-II and C-III, were not measured.

In conclusion, postprandial hyperchylomicronemia may be a residual risk factor for acute coronary syndrome. Thus, further investigation with a larger number of patients is needed.

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Disclosures

None.

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Highlights

- Postprandial hyperchylomicronemia correlates with the presence of thin-cap fibroatheroma in the nonculprit lesion and may be a residual risk factor for coronary artery disease.
- Although the baseline ApoB-48 (apolipoprotein B-48) level was similar, the increase in the ApoB-48 level was significantly higher in the thin-cap fibroatheroma group than in the non–thin-cap fibroatheroma group.
- The increase in the ApoB-48 and the fasting apolipoprotein C-III levels were significantly positively correlated and were important predictors of the presence of thin-cap fibroatheroma.

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Postprandial Hyperchylomicronemia and Thin-Cap Fibroatheroma in Nonculprit Lesions: A Multivessel Optical Coherence Tomography Study

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