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Familial hypercholesterolemia and vulnerability of coronary plaque in patients with coronary artery disease

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ABSTRACT

Objectives: Patients with familial hypercholesterolemia (FH) are at a very high risk of coronary artery diseases. The aim of the present study was to clarify the characteristics of coronary plaque in patients with FH.

Design: and Methods: A total of 569 patients who underwent optical coherence tomography (OCT) imaging of culprit plaque were included. The characteristics of culprit plaque were compared between patients with and without FH.

Results: A total of 38 patients (6.7%) were clinically diagnosed with FH. The location of the culprit plaque was significantly different ($p < 0.001$) with a trend toward higher frequency of left main lesion in the FH group than in the group with no FH (7.9 vs. 0%). Culprit plaque was significantly shorter in patients with FH than those without FH (28.1 vs. 33.2 mm, $p = 0.016$). A trend toward higher prevalence of plaque with macrophage accumulation in patients with FH than those without FH (50.0 vs. 34.7%, $p = 0.056$) was observed, although the prevalence of other vulnerable characteristics including thin-cap fibroatheroma (TCFA) was comparable between patients with and without FH. Among patients with FH, significant increases in the prevalence of lipid-rich plaque ($p = 0.028$) and TCFA ($p = 0.003$) were observed according to the increase in low-density lipoprotein cholesterol (LDL-C) levels.

Conclusions: Patients with FH had shorter culprit plaque without significant difference in the prevalence of vulnerable plaque components compared with patients without FH. A higher LDL-C level was associated with higher prevalence of vulnerable plaque in patients with FH.

1. Introduction

Patients with familial hypercholesterolemia (FH) are at a very high risk of coronary artery diseases. Because they are exposed to high LDL cholesterol (LDL-C) levels from birth [1], the onset of acute coronary syndrome in patients with FH is at a younger age than in patients without FH [2]. These distinct characteristics may cause the difference in the characteristics of coronary atherosclerosis between patients with and without FH. Previous studies using coronary angiography and coronary computed tomography have reported more multivessel disease and left main disease in patients with FH than those without FH [3,4]. In addition, several reports using intra-coronary imaging have suggested the larger number of high-risk plaques in patients with FH [5,6]. However, the detailed characteristics of coronary plaque in patients with FH remain unclear. The purpose of our present study was to clarify the morphological

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characteristics of coronary plaque in patients with FH using optical coherence tomography (OCT), which has the highest spatial resolution among clinically available intra-coronary imaging modalities.

2. Methods

2.1. Study population

A total of 1137 consecutive patients underwent percutaneous coronary intervention (PCI) at our institution between June 2016 and March 2019. Among them, we identified 672 consecutive patients who underwent OCT assessment of culprit lesions before stenting. Of those, a total of 569 patients were enrolled in the present study after excluding cases of restenosis (n = 84) and poor OCT images (n = 19; Fig. 1). The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committees of our institution.

2.2. Definitions

FH was diagnosed using the 2017 Japan Atherosclerosis Society guidelines [2] (Fig. 2). The LDL-C levels before the prescription of lipid-lowering drugs were collected from the hospital record to diagnose FH. If the LDL-C levels before treatment were not available, we used serum LDL-C levels obtained from the patients 1 day before PCI. Achilles tendon thickness was measured on soft x-ray radiogram according to a recommended method (Supplementary Fig. 1) [7]. According to a report demonstrating a 1-mm gap between local measurement by institutional investigators and central measurement by experts [8], we defined Achilles tendon thickening as the adjusted Achilles tendon thickness of 9 mm or more, which was calculated by the measured Achilles tendon thickness minus 1 mm. A family history was defined as positive for FH and/or premature CAD (<55 years in men and <65 years in women) within first- and second-degree relatives [2]. Acute coronary syndrome (ACS) consisted of ST-segment elevation myocardial infarction and non-ST-segment elevation ACS. Other cases were categorized as stable coronary disease. Dyslipidemia was defined as LDL-C levels over 140 mg/dL and/or the prescription of lipid-lowering drugs. Multivessel disease was defined as 70% or greater stenosis and/or PCI history in at least one other epicardial coronary artery in addition to the culprit artery.

2.3. Optical coherence tomography image acquisition and analysis

OCT images of culprit lesions were acquired before stent implantation after 100–200 μg i.c. nitroglycerin using frequency-domain OCT (ILUMIEN OCT Intravascular Imaging Systems; Abbott, Santa Clara, CA, USA) (Fig. 3). All the images were analyzed using offline proprietary software at the cardiovascular laboratory at the Kitasato University School of Medicine. The images were qualitatively and quantitatively analyzed at 0.2-mm intervals. Plaque morphologies were assessed using previously established criteria [9,10]. Fibrous cap thickness was measured at its thinnest part on three times, and the average was calculated. Thin-cap fibroatheroma (TCFA) was defined as a plaque with a lipid arc >90° and the thickness of the fibrous cap <65 μm. Bright spots within the fibrous cap with backward shadowing were considered as macrophage accumulation [10]. Microchannels were defined as black holes or tubular structures of 50–100 μm in diameter, which were present within a plaque on at least 3 consecutive cross-sectional frames [11]. Cholesterol crystals were defined as linear and thin regions with high light intensity without signal attenuation [12]. Calcifications were defined as heterogeneous or signal-poor areas delimited by sharp borders. Spotty calcification was defined as calcification with an arc <90° [13].

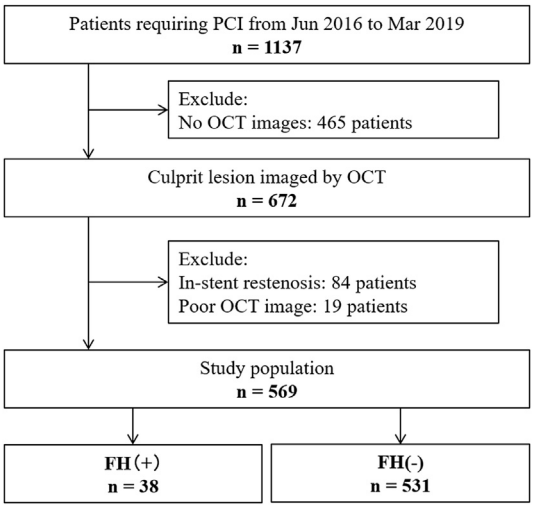

Fig. 1. Study flow chart
FH, familial hypercholesterolemia; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

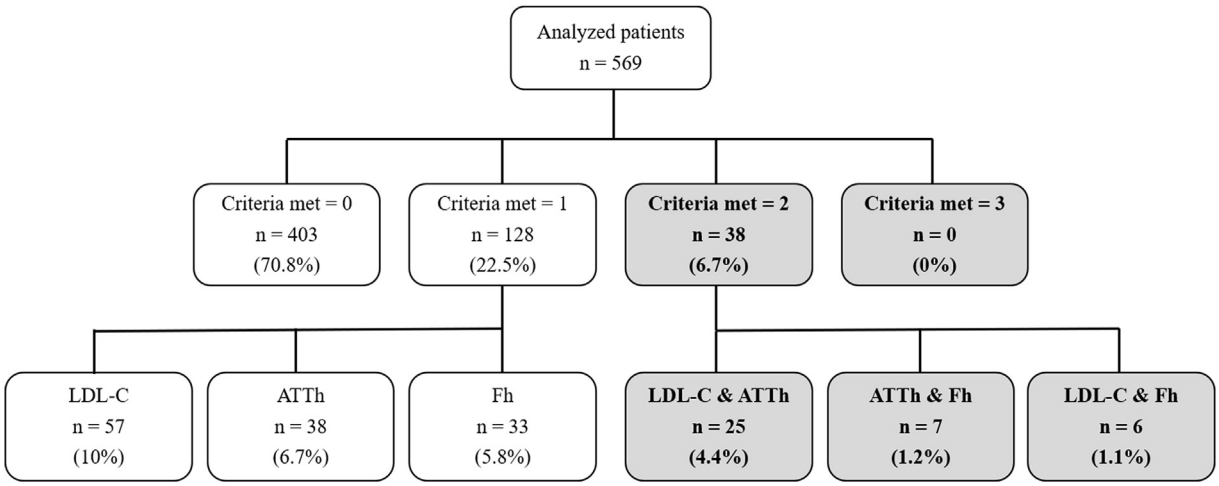

Fig. 2. Diagnosis of familial hypercholesterolemia
ATTh, Achilles tendon thickening; FH, familial hypercholesterolemia; Fh, family history; LDL-C, low-density lipoprotein cholesterol.

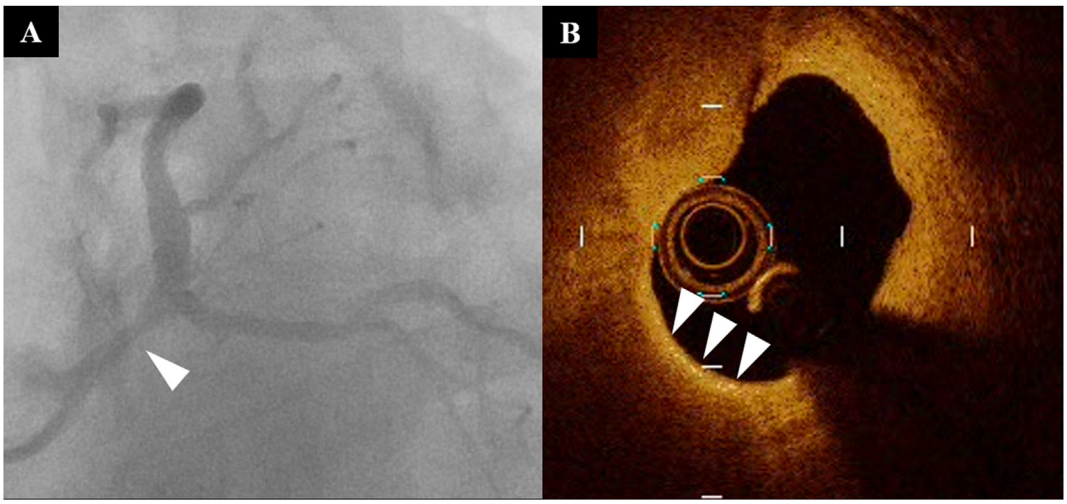

Fig. 3. Representative coronary angiogram and optical coherence tomography image in a patient with familial hypercholesterolemia
A, Angiogram showing a significant stenosis (arrowhead) at the body of left main trunk. B, A cross-sectional optical coherence tomography image of the corresponding site of a stenosis in Panel A. Arrowheads represent macrophage accumulation.

Large calcification was defined as calcification with an arc $\geq 180^{\circ}$ [14]. Thrombus was defined as a mass >250 μm protruding from the luminal surface or floating within the lumen [9,15].

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation and compared using the unpaired *t*-test or the Wilcoxon rank-sum test. Categorical variables are presented as numbers and frequencies and compared using the Chi-square test. The Cochran–Armitage trend test and the Jonckheere-Terpstra trend test were used to examine the frequency of OCT findings of the culprit lesion according to the LDL-C levels and Achilles tendon thickness among patients with FH. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using JMP version 13 software (SAS Institute, Cary, NC, USA) and SPSS version 24 software (IBM SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

A total of 38 patients (6.7%) were diagnosed with FH in the present cohort. Clinical characteristics according to the presence of FH are shown in Table 1 and Supplementary Table 1. The location of the culprit was significantly different ($p < 0.001$) with a trend toward higher frequency of the left main lesion in the FH group than in the group with no FH (7.9 vs. 0%). The left ventricular ejection fraction on echocardiogram was significantly lower in the FH group than in the group with no FH (52.2 ± 13.2 vs. 57.1 ± 12.4%, $p = 0.028$). Laboratory findings obtained from the patients 1 day before PCI are shown in Table 2 and Supplementary Table 1. The LDL-C levels (119.9 ± 45.9 vs. 97.0 ± 35.2, $p = 0.003$) were significantly higher in the FH group than in the group with no FH.

3.2. OCT findings of culprit plaque

The results of OCT analyses of culprit plaques are shown in Table 3. A trend toward higher prevalence of plaque with macrophage accumulation in the FH group than in the group with no FH (50.0 vs. 34.7%, $p = 0.056$) was observed. On the other hand, a trend toward lower prevalence of calcification in the FH group than in the group with no FH (71.1 vs. 82.1%, $p = 0.091$) was observed. The prevalence of other plaque characteristics including lipid-rich plaque, TCFA, microchannel, thrombus, and cholesterol crystal were comparable in the 2 groups. The lesion was significantly shorter in the FH group than in the group with no FH (28.1 vs. 33.2 mm, $p = 0.016$). The results according to clinical presentation are described in Supplementary Tables 2 and 3. Among patients with stable coronary disease, the prevalence of plaque with macrophage accumulation was significantly higher in the FH group than in the group with no FH (51.7 vs. 32.2%, $p = 0.032$).

3.3. OCT findings of culprit plaque according to the LDL-C levels among patients with FH

The characteristics of culprit plaque in patients with FH were compared among subgroups classified by tertiles of the LDL-C levels (Fig. 4 and Supplementary Table 4). The incremental frequency of lipid-rich plaque ($p = 0.028$) and TCFA ($p = 0.003$) according to the increase in LDL-C levels was observed. The results in patients with no FH are shown in Supplementary Fig. 2.

Table 1
Clinical characteristics.

Variables	FH (+) n = 38	FH (−) n = 531	*p* value
Age, year	66.1 ± 12.1	69.0 ± 10.5	0.213
Male, n (%)	32 (84.2)	418 (78.7)	0.421
BMI, kg/m^2	24.8 ± 3.27	24.5 ± 8.56	0.233
Culprit vessel, n (%)			<0.001
LAD	17 (44.7)	306 (57.6)	
LCX	6 (15.8)	74 (13.9)	
RCA	12 (31.6)	149 (28.1)	
LM	3 (7.9)	2 (0)	
Acute coronary syndrome, n (%)	9 (23.7)	134 (25.2)	0.831
Multivessel disease, n (%)	27 (71.1)	307 (57.8)	0.109
Risk factors, n (%)			
Hypertension	22 (57.9)	383 (72.1)	0.061
Dyslipidemia	28 (73.7)	313 (58.9)	0.073
Diabetes mellitus	19 (50.0)	241 (45.4)	0.581
Current smoker	8 (21.1)	104 (19.6)	0.880
CKD (eGFR < 60)	22 (57.9)	261 (49.2)	0.298
MI history	14 (36.8)	148 (27.9)	0.243
PCI history	21 (55.3)	216 (40.7)	0.082
CABG history	0 (0)	11 (2.1)	0.369
Echo LVEF, %	52.2 ± 13.2	57.1 ± 12.4	0.028
Medication, n (%)			
ACE inhibitor/ARB	29 (76.3)	337 (63.5)	0.113
Beta blocker	24 (63.2)	247 (46.5)	0.048
Insulin	3 (7.9)	47 (8.9)	0.835
Statin	32 (84.2)	389 (73.3)	0.142
Ezetimibe	10 (26.3)	31 (5.8)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 2
Laboratory findings.

Variables	FH (+) n = 38	FH (−) n = 531	*p* value
HbA1c, %	6.62 ± 1.15	6.49 ± 1.12	0.378
LDL-C, mg/dL	119.9 ± 45.9	97.0 ± 35.2	0.003
HDL-C, mg/dL	53.6 ± 16.3	51.8 ± 15.8	0.478
Triglyceride, mg/dL	144.5 [99.0, 203.3]	124 [85, 179]	0.117
Serum creatinine, mg/dL	0.98 [0.82, 1.13]	0.95 [0.8, 1.13]	0.757
eGFR, ml/min/1.73 m^2	56.0 [50.5, 69.3]	59.0 [47.0, 70.0]	0.925
hs-CRP, mg/dL	0.16 [0.05, 0.67]	0.11 [0.05, 0.33]	0.174
BNP, pg/mL	102.5 [50.8, 234.9]	88.2 [31.2, 228.9]	0.447

BNP, b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Table 3
OCT findings of culprit lesion according to the presence of FH.

Variables	FH (+) n = 38	FH (−) n = 531	*p* value
Qualitative assessment, n (%)			
Lipid-rich plaque	19 (50.0)	208 (39.2)	0.188
TCFA	7 (18.4)	115 (21.7)	0.639
Macrophage	19 (50.0)	184 (34.7)	0.056
Microchannel	10 (26.3)	121 (22.8)	0.622
Calcification	27 (71.1)	436 (82.1)	0.091
Large calcification	13 (34.2)	247 (46.5)	0.141
Spotty calcification	26 (68.4)	421 (79.3)	0.115
Thrombus	4 (10.5)	69 (13.0)	0.657
Cholesterol crystal	7 (18.4)	95 (17.9)	0.947
Quantitative assessment			
Max arc, °	257.1 ± 75.1	281.4 ± 74.9	0.238
Thinnest FCT, μm	104.2 ± 61.1	85.3 ± 54.8	0.081
Distal reference vessel area, mm^2	4.78 ± 2.53	4.82 ± 2.94	0.842
Distal reference vessel diameter, mm	2.38 ± 0.64	2.38 ± 0.67	0.818
Proximal reference vessel area, mm^2	6.97 ± 2.66	7.07 ± 2.88	0.951
Proximal reference vessel diameter, mm	2.92 ± 0.56	2.93 ± 0.59	0.985
Minimal lumen area, mm^2	1.43 ± 0.66	1.44 ± 0.73	0.904
Minimal lumen diameter, mm	1.31 ± 0.28	1.30 ± 0.30	0.820
Percent area stenosis, %	74.9 ± 7.12	74.1 ± 10.8	0.964
Lesion length, mm	28.1 ± 16.0	33.2 ± 14.0	0.016

FCT, fibrous cap thickness; FH, familial hypercholesterolemia; TCFA, thin cap fibroatheroma.

3.4. OCT findings of the culprit plaque according to Achilles tendon thickness among patients with FH

The characteristics of the culprit plaque in patients with FH were compared among subgroups classified by tertiles of maximum Achilles tendon thickness (Fig. 5 and Supplementary Table 5). No significant difference was observed in the frequency of plaque characteristics according to Achilles tendon thickness.

4. Discussion

The main findings of the present study are as follows: (1) Patients with FH had shorter culprit plaque than those without FH. (2) There was a trend toward higher prevalence of culprit plaque with macrophage accumulation in patients with FH than in those without FH. (3) A higher level of LDL-C was associated with higher prevalence of lipid-rich plaque and TCFA among patients with FH.

4.1. Focal plaque vulnerability of the culprit lesion in patients with FH

The characteristics of coronary plaque in patients with FH have been reported in several studies. Sugrue et al. investigated the angiographical characteristics of coronary atherosclerosis in patients with FH [4]. The authors found that patients with FH had a higher prevalence of left main disease than those without FH. Pang et al. also reported the higher prevalence of coronary plaque in the left coronary system including left main trunk in patients with genetically confirmed FH than age-matched controls in a study using cardiac computed tomography angiography [3]. These findings are consistent with our findings showing a difference in the location of the culprit lesion between patients with and without FH with a trend toward higher prevalence of the left main disease in patients with FH. Because the left main is short but usually widest among coronary arteries, patients with FH may be susceptible to focal large plaque rather than diffuse long plaque. In fact, we demonstrated that the culprit lesions were significantly shorter in patients with FH than those without FH. Because a trend toward lower prevalence of calcification in patients with FH than in those without FH was observed in the

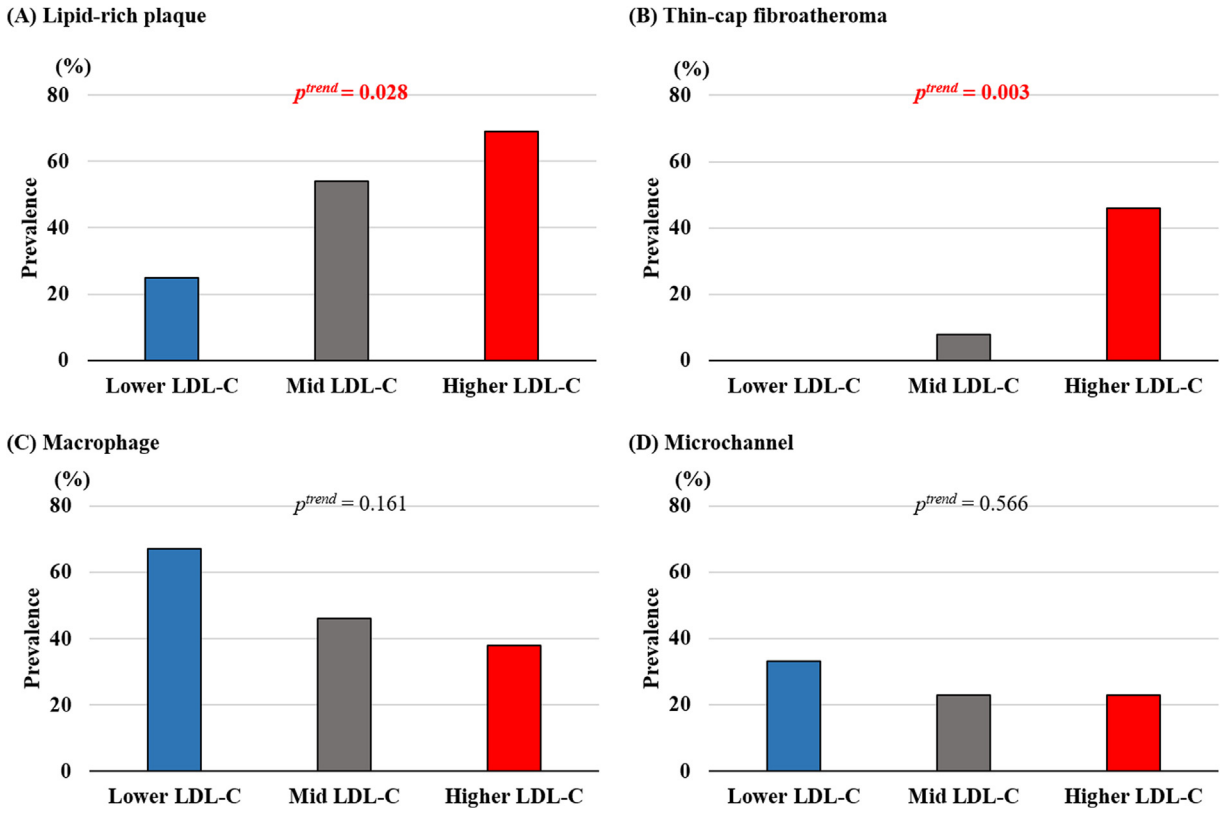

Fig. 4. OCT findings of culprit lesion according to LDL-C levels among patients with FH
FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; OCT, optical coherence tomography.

present study, the majority of plaques might be focal lipid plaque rather than diffuse calcified plaque in patients with FH. Another important OCT finding in our study was a trend toward higher prevalence of plaque with macrophage accumulation in patients with FH than in those without FH. Among several plaque components, macrophage plays central roles for the deterioration of the integrity of the fibrous cap overlying the lipid core and subsequent incidence of acute coronary syndrome [16,17]. Although the significant difference in hsCRP levels between patients with and without FH was not demonstrated in the present study, the higher prevalence of plaque with macrophage accumulation may suggest the enhanced inflammatory cell infiltration at the culprit lesion in patients with FH. In fact, a recent report using OCT images demonstrated the presence of lipid-rich plaque along with macrophage accumulation in a left main lesion in patients with FH presenting as acute coronary syndrome [5]. Because a pre-clinical study demonstrated a significant correlation between the longer high-fat exposure and the larger plaque area with macrophage [18], the long duration of high LDL-C exposure in patients with FH might partly cause the trend toward higher prevalence of plaque with macrophage accumulation shown in the present study. Further studies targeting focal and systemic status of inflammation in patients with FH may explore other therapeutic options which could complement current pharmacological regimens for patients with FH.

4.2. Elevated LDL-C levels and vulnerability of culprit plaque in patients with FH

The impact of LDL-C levels on the incidence of cardiovascular events among patients with FH has been reported in several studies [19,20]. Silva et al. prospectively investigated the incidence of cardiovascular events for one year in patients with FH. The authors demonstrated that the baseline LDL-C level was 29% higher in patients with subsequent cardiovascular events than in those without cardiovascular events [19]. The reason for the higher incidence of cardiovascular events in patients with higher LDL-C levels can be explained by the advanced status of coronary artery disease. Neefjes et al. investigated the coronary plaques in cardiac asymptomatic patients with FH using computed tomography. The authors demonstrated the significant association between the treated LDL-C levels and the extent of coronary artery disease [21]. In the present study, we further showed the significant correlation between higher LDL-C levels and higher prevalence of lipid-rich plaque and TCFA at the culprit coronary lesion among patients with FH. Because the presence of TCFA has been demonstrated as the most critical morphological discriminator for plaque rupture among plaque characteristics, the present results suggested the presence of rupture-prone plaque in patients with FH concomitant with higher LDL-C levels [22]. In conjunction with the findings in the present study and previous studies, patients with FH and higher LDL-C levels should be considered at extremely high risk for cardiovascular events caused by vulnerable coronary plaque, although all patients with FH are at a higher risk for cardiovascular disease than those without FH. Studies incorporating life-long accumulated LDL-C levels in addition to the

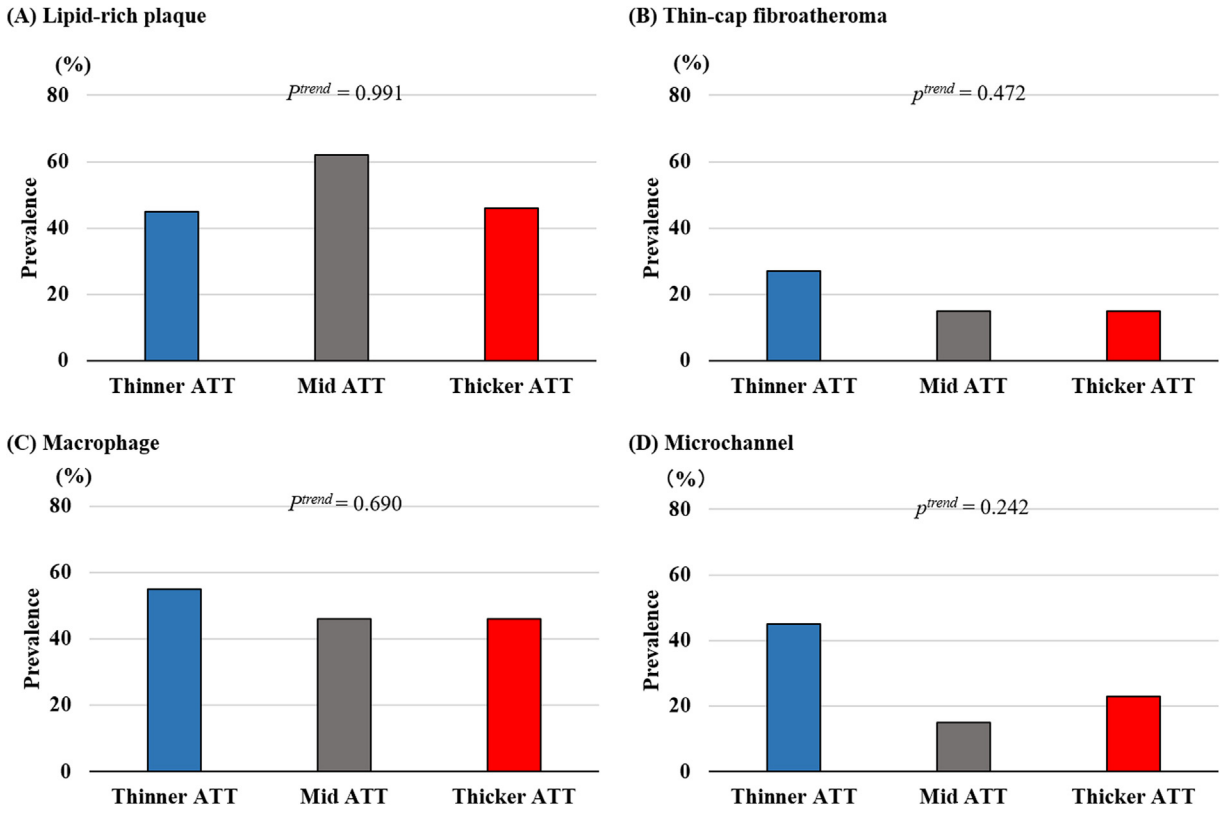

Fig. 5. OCT findings of culprit lesion according to measured Achilles tendon thickness among patients with FH
ATT, measured Achilles tendon thickness; FH, familial hypercholesterolemia; OCT, optical coherence tomography.

cross-sectional assessment of LDL-C may give further insight into the correlation between LDL-C and the development and deterioration of coronary plaques.

4.3. Limitations

Our study had several limitations. First, this was a retrospective study conducted in a single center. Patients with OCT imaging of culprit lesions were exclusively included in the present study, thus causing possible selection bias. We did not exclusively include patients at their first chance of revascularization. This might also cause selection bias. Second, we did not perform genetic molecular analysis to diagnose FH. Third, Achilles tendon thickness was evaluated only by radiography. Although the thickness was adjusted according to a pivotal report [8], the prevalence of FH in the present study was still higher than that evaluated on physical examination in other studies [23,24]. Fourth, we did not collect the data regarding the details of statin, including the type, intensity and treatment duration. The differences in these factors might affect the results. Finally, we could not identify the FH-specific plaque component with statistical significance. Although the reason is unclear, we might miss the FH-specific plaque features caused by the limited performance of OCT. Thus, further studies using other intravascular modalities are still required to clarify the FH-specific plaque characteristics.

5. Conclusions

Patients with FH had shorter culprit plaque without significant difference in the prevalence of vulnerable plaque components compared with patients without FH. A higher LDL-C level was associated with higher prevalence of vulnerable plaque in patients with FH. The results of our study further highlight the importance of intensive lipid-lowering therapy for patients with FH, particularly in patients with high LDL-C levels.

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CRediT authorship contribution statement

Masahiro Katamine: Data curation, Formal analysis, Writing - original draft. **Yoshiyasu Minami:** Project administration, Conceptualization, Writing - review & editing. **Takuya Hashimoto:** Formal analysis, Writing - review & editing. **Junya Ako:** Supervision, Writing - review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2021.e00202.

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