Serial longitudinal changes of coronary calcified plaques with clear outer borders under intensive lipid management: insights from optical coherence tomography

（脂質強化療法下における境界明瞭な冠動脈石灰化プラークの経時的変化：光干渉断層法による検討）

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Abstract

Background: Percutaneous coronary intervention (PCI) for calcified lesions is one of the most challenging procedures related to worse clinical outcomes. To stabilize vulnerable plaques, intensive lipid management is recommended; however, the serial changes of calcified plaques under intensive lipid management are unknown.

Methods: A total of 31 patients (mean age, 63 ± 10 years; men, 29 patients) who underwent PCI with intensive lipid management were retrospectively studied. We evaluated the serial longitudinal changes of calcified plaques with clear outer borders by using optical coherence tomography (OCT) at two time points: at the time of PCI (baseline) and the chronic phase.

Results: The median interval from PCI to chronic phase was 287 (233–429) days. Twenty-eight patients (90.3%) had increased calcium volume at the chronic phase compared with those at baseline (2.6 [1.3–5.1] vs. 1.8 [0.7–4.3] mm^2, $p < 0.05$), and the median increase rate of calcium volume was 27.4% at the chronic phase. According to the median increase rate of calcium volume (27.4%), patients were divided into the following two groups: rapid progression (≥27.4%, RP group) and non-rapid progression (<27.4%, non-RP group). The RP group had more patients with diabetes, and diabetes was independently associated with rapid progression by multivariate analysis. Furthermore, patients with diabetes had significantly higher changes in calcium index and volume from the baseline to the chronic phase than those without diabetes.

Conclusions: Coronary calcification progression during relatively short intervals was observed using OCT even under intensive lipid management. Diabetes was an independent predictor for rapid coronary calcification progression.

Keywords:

Coronary artery calcification, Percutaneous coronary intervention, Rapid progression, Optical coherence tomography, Diabetes

Introduction

Coronary artery calcification is an end-stage of advanced atherosclerosis. Percutaneous coronary intervention (PCI) for these advanced calcified lesions is one of the most challenging procedures, and these lesions are related to worse clinical outcomes [1, 2]. A previous study reported that the degree and extent of coronary artery calcification evaluated by computed tomography (CT) are correlated with increased cardiovascular events [3, 4]. Moreover, some studies reported that spotty calcium is associated with plaque vulnerability [5, 6]. Conversely, lipid management with statin was reported to stabilize vulnerable plaques by promoting coronary atheroma calcification [7, 8]; however, the serial changes of coronary calcifications under intensive lipid management are not fully understood.

Although several previous studies investigated the progression of calcifications using either CT or intravascular ultrasound (IVUS) [3, 4, 7, 8], both imaging modalities are limited by a lower resolution for serial change detection of coronary calcifications compared with optical coherence tomography (OCT). Therefore, OCT is an ideal imaging device for evaluating and quantifying coronary calcifications, showing a better correlation with histological assessments [9]. However, data on the evaluation of the serial changes of coronary calcifications by OCT remains limited [10, 11]. This study aimed to evaluate the serial longitudinal changes of coronary calcifications under intensive lipid management using OCT images.

Materials and Methods

Study population

This was a single-center retrospective study to evaluate the serial changes of coronary calcifications using OCT images. Fifty-eight patients who underwent PCI with serial OCT imaging at Hirosaki University Hospital between January 2015 and September 2022 were enrolled. We evaluated the serial changes of calcifications with clear outer borders in non-culprit lesions by OCT at two time points: at the PCI procedure and the chronic phase. Among 58 patients, 13, 7, and 7 were excluded owing to the absence of calcification at the time of the PCI procedure, absence of OCT images of the equivalence segment, and calcification with vague or invisible outer borders due to strong attenuation, respectively. Finally, 31 patients were included in the final analysis. This study was conducted in accordance with the Helsinki Declaration's ethical guidelines for medical research on humans. The research protocol was approved by the Institutional Review Board (IRB) of the Hirosaki University Graduate School of Medicine (IRB number: 2023-014).

Analyses of OCT images

A frequency–domain OCT system (OPTIS™ Mobile System, Abbott Laboratories, Abbott Park, IL, USA) was used in this study. The OCT imaging catheter was advanced farther

than the lesion, and a contrast medium or dextran was injected through the guiding catheter to clear blood from the imaging field. The OCT image acquisition was obtained using an automated pull-back. Two independent investigators who were masked to the clinical and angiographic data performed the analysis. It was performed throughout the calcium lesion by frame in 0.2-mm intervals using Abbott's proprietary software (OPTIS™ Off-line Review Workstation). Previously stented coronary segments and coronary segments undergoing stent placement or balloon angioplasty during the PCI procedure at baseline were excluded from the OCT analysis. The target calcification was identified using several landmarks, including stent edges and anatomical landmarks, such as side branches, pericardium, plaque position, configuration, and lumen shape.

Calcifications were identified as heterogeneous areas of high and low reflectivity, with low signal attenuation and sharply demarcated borders [12]. We evaluated the calcifications with clear outer borders in non-culprit lesions. The following calcification parameters were evaluated using OCT (**Figure 1**): calcium area, arc, longitudinal length, depth, index, and volume. The calcium arc was measured from the gravitational center of the vessel lumen to the two lateral extremities of the calcium. The calcium depth was defined as the distance between the most superficial edge of calcification and the vessel lumen. The calcium index was the product of the mean calcification arc and longitudinal length [13]. The calcium volume was calculated on the basis of the disk summation method. In other words, the calcium area was measured by planimetry

in each frame, and the calcium volume was calculated by multiplying the calcium areas in each frame times the number of frames (0.2 mm). Spotty calcification was defined as calcium longitudinal length ≤4 mm and maximal calcium arc ≤90°. Macrocalcification was defined as maximal calcium length >4 mm or maximal calcium arc >90°.

Statistical analysis

Continuous variables were presented as means ± standard deviations or medians and interquartile ranges. Categorical variables were presented as percentages. To compare the differences between the two groups, an unpaired t-test or chi-square test was used, whereas the Mann–Whitney U test was used for nonparametric variables. To compare corresponding coronary artery calcification at baseline and chronic phase, the Wilcoxon signed-rank test was used. Predictors for rapid coronary calcification progression were assessed using a multivariable logistic regression model. An analysis of covariance (ANCOVA) was used to adjust the baseline calcification parameters and compare the serial changes in calcification parameters between the two groups. Statistical significance was defined as a p-value of <0.05. All the statistical analyses were performed using the JMP software (JMP Pro 16 for Windows, SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

The baseline characteristics of the study patients are shown in **Table 1**. The mean age of participants was 63 ± 10 years, and 29 patients (94%) were men. More than 70% of them had hypertension and dyslipidemia, and 17 patients (55%) had diabetes. Thirteen patients (42%) had a medical history of prior PCI procedures, and 4 (13%) were undergoing hemodialysis. Regarding the clinical presentation, 14 patients (45%) were complicated with acute coronary syndrome (ACS), and the others with stable angina. All patients received aspirin and statin treatments at the time of hospital discharge. The median duration between the two time points of the serial OCT was 287 (233–429) days. All patients received statin treatments until the chronic phase. Under intensive lipid-lowering therapy, 29 patients (94%) achieved low-density lipoprotein (LDL)-cholesterol levels of <100 mg/dL, and 17 (55%) achieved <70 mg/dL. The mean LDL-cholesterol level of the study patients in the chronic phase was 69 ± 20 mg/dL.

OCT analyses of coronary calcifications

Representative OCT images of the serial changes in coronary calcifications at the time of PCI and the chronic phase are shown in **Figure 2**. Spotty calcification (**Figure 2A**) and macrocalcification (**Figure 2C**) at baseline progressed at the chronic phase, respectively (**Figures 2B and 2D**). The details of OCT analysis are shown in **Table 2**. A total of 33 calcifications were identified and evaluated from 31 patients, and 18 (55%) spotty calcifications and 15 (45%)

macrocalcifications were noted at baseline. Significantly increased mean calcium arc (56° [41°–69°] vs. 47° [31°–70°], $p < 0.05$) and mean calcium area (0.8 [0.5–1.3] vs. 0.6 [0.4–1.1] mm^2, $p < 0.05$) were observed at the chronic phase compared with those at baseline as well as maximal calcium arc and area. Furthermore, significant increases in the calcium longitudinal length (3.0 [2.5–4.3] vs. 3.0 [1.8–4.0] mm, $p < 0.05$) and calcium index (198 [90–304] vs. 159 [62–267] mm, $p < 0.05$) at the chronic phase were observed. Moreover, the calcium volume was significantly increased at the chronic phase compared with that at baseline (2.6 [1.3–5.1] vs. 1.8 [0.7–4.3] mm^3, $p < 0.05$). The calcium volume was increased in 28 patients (90.3%) during the median follow-up period of 287 (233–429) days. Calcium volumes at baseline and the chronic phase were not significantly different between patients with ACS and those with SAP (patients with ACS, 1.8 [0.5–3.8] mm^3 vs. patients with SAP, 1.8 [0.9–4.7] mm^3 at baseline, $p = 0.59$; patients with ACS, 2.5 [1.2–5.2] mm^3 vs. patients with SAP, 2.6 [1.2–5.1] mm^3 at the chronic phase, $p = 0.77$), respectively.

Predictors for rapid coronary calcification progression

The median increase rate of the calcium volume was 27.4% at the chronic phase in all study patients. According to the median increase rate of the calcium volume, we divided the study patients into the following two groups to determine clinical predictors for the rapid progression of the calcium volume: patients with rapid calcification progression who have increased rate of

the calcium volume with the median or more (≥27.4%) (RP group, n = 16) and those with less than the median (<27.4%) (non-RP group, n = 15). The baseline characteristics of the two groups are shown in **Table 1**. No significant differences in mean age, sex, and past medical histories, including dialysis and clinical presentations, were noted between the two groups. The RP group had significantly higher diabetes prevalence and longer follow-up duration than the non-RP group. The RP group had significantly higher triglyceride and lower high-density lipoprotein-cholesterol levels than the non-RP group. No differences in antiplatelet medications were observed between the two groups. All study patients were under lipid-lowering therapy with statin, and LDL-cholesterol levels at the chronic phase were equivalent between the two groups. Multivariate analyses are presented in **Table 3**. The variables that showed significant differences between the RP and non-RP groups were used as Model 1. Diabetes was independently associated with rapid coronary calcification progression (odds ratio [OR], 11.19; 95% confidence interval [CI], 1.02–123.19; $p < 0.05$). Moreover, diabetes remained an independent predictor following adjusting for age in addition to Model 1 (OR, 21.2; 95% CI, 1.09–414.89; $p < 0.05$, Model 2).

Effects of diabetes on calcification parameters

Calcification parameters were evaluated between patients with and without diabetes (n = 17 and 14, respectively). All values for calcification parameters at baseline except the minimal calcium depth were similar between patients with and without diabetes (**Supplementary Figure**

1). Furthermore, no differences in all calcification parameters at the chronic phase were noted between the two groups (**Supplementary Figure 2**). Notably, patients with diabetes had significantly higher changes in maximal and mean calcium areas, as well as changes in the calcium index and volume, from the baseline to the chronic phase than those without (**Figure 3**). Even after adjusting for baseline calcium parameters, similar results were obtained (**Figure 3**, ANCOVA). Additionally, higher changes in maximal and mean calcium arc were observed in patients with diabetes compared with those without.

Discussion

Major findings

In the present study, we demonstrated that the calcium volume evaluated using OCT images increased in 90.3% of study patients following PCI even under intensive lipid management. Moreover, diabetes was an independent predictor for rapid coronary calcification progression. Indeed, patients with diabetes developed coronary calcifications more rapidly than those without diabetes. These findings indicate that diabetes is associated with rapid coronary calcification progression even under intensive lipid management.

Serial changes of coronary calcification evaluated using OCT images

Several previous studies evaluated the serial changes in coronary calcium lesions using

IVUS images [7, 8, 14, 15]. The main advantage of IVUS images is their deep penetration ability; therefore, deep calcifications and the cross-section of the entire vessel wall can be evaluated. The main disadvantages of IVUS include its limited resolution and the strong reflection of ultrasound waves by endoluminal calcium, making it challenging to evaluate the extent and depth of calcification [16, 17]. Conversely, owing to its high resolution of 10–20 μm, OCT enables us to evaluate the details of near-lumen plaque characteristics. OCT allows us to visualize the real extent of the calcification in the relatively superficial layer of the vessel wall without being excessively reflected and attenuated, which can evaluate calcifications more accurately [9, 12]. Therefore, OCT can be useful for evaluating the calcium arc, area, longitudinal length, and volume more precisely than IVUS [18].

Okutsu et al. reported that OCT estimates the calcium thickness more accurately compared to coronary computed tomography angiography [19]. However, some of the calcifications show strong attenuation, making the outer border invisible. A previous report showed that when lipid-rich components such as lipid pool and necrotic core exist, OCT might underestimate the volume of atheromatous plaques due to the attenuation of light by transmissions through plaque tissues [12]. In addition, Ijichi et al. demonstrated a higher frequency of lipid contents in calcified plaques with vague or invisible outer borders compared to those with clear outer borders observed using OCT [20]. Thus, visualization of calcification is influenced not only

by the whole thickness of calcification but also by lipid contents. Therefore, in the present study, we focused on calcified plaques that have clear outer borders and can be measured, in order to evaluate the serial longitudinal change in coronary calcification accurately.

Few studies focus on the serial changes of coronary calcifications using OCT images. Zeng et al. evaluated calcium progression by fusing IVUS and OCT images in bioresorbable vascular scaffold-treated patients from baseline to 5-year follow-up [10]. They reported that the calcium volume in 13 calcifications detectable on OCT was significantly increased from baseline to follow-up. However, this study was limited to bioresorbable vascular scaffold-treated segments. Therefore, the serial changes of calcifications in non-culprit lesions could not be evaluated. Another study by Nakajima et al. showed rapid coronary calcification progression evaluated using OCT images in patients who underwent PCI [11]. They showed that the maximal calcification arc, mean arc, and length were significantly increased from baseline following 6 months of PCI. Moreover, the calcium index increased in 95.3% of the study patients from 132 to 178 (median) after 6 months, and the median change was 40.6 during the follow-up period. Consistent with this, we also showed that the calcium index increased in 90.3% of the study patients from 159 to 198 (median) during a median follow-up period of 287 days. These results indicate that coronary calcification in non-culprit lesions evaluated using OCT progresses in most patients who underwent PCI.

Serial changes of the calcium volume under intensive lipid management

Recent studies reported that statins are associated with a progression in calcified plaque components of atherosclerotic lesions over time [7, 8, 21]. The PARADIGM study prospectively analyzed atherosclerotic plaques, which included calcifications in patients who underwent serial coronary CT angiography. The study showed that statins are associated with slower progression of overall coronary atherosclerosis volume with increased calcification and reduction of vulnerable plaque features [21]. In the present study, all patients were prescribed statin at hospital discharge and continued intensive lipid management until the chronic phase following PCI. No significant difference in LDL-cholesterol levels at the chronic phase was noted between the two groups. In our study, despite intensive lipid management, 90.3% of patients increased coronary calcifications, which is consistent with several previous studies [7, 8, 21].

Although the calcifications remained heterogeneous areas with clear outer borders in the chronic phase, the high-intensity signal reflections appeared to be somewhat noticeable inside the calcification. As a healing response to intense inflammation within the necrotic core in atherosclerosis, facilitation of macrophage to osteogenic differentiation and maturation of vascular smooth muscle cells (VSMCs) proceed to stabilized calcification. Statins may also facilitate the healing process against plaque inflammation, resulting in increased calcification [22]. Therefore, changes in characteristics of calcification under lipid management in the OCT analysis

may reflect the healing and stabilizing process of arteriosclerosis.

Relationship between diabetes and coronary calcification

Diabetes is a well-known risk factor for coronary atherosclerosis and subsequent cardiovascular events. Moreover, it is associated with coronary artery calcification, which is related to worse clinical outcomes [23, 24]. In patients with diabetes, free radical accumulation could activate an array of cellular pathways, including advanced glycation end products (AGEs). AGE simulation for VSMCs promotes calcification through multiple mechanisms, including increasing levels of alkaline phosphatase, a bone matrix protein, and increased runt-related transcription factor-2 expression [24]. The interaction of AGEs with receptors for advanced glycation end products also exacerbates oxidative stress, which promotes VSMC calcification. Moreover, hyperglycemia increases oxidative stress in the citric acid cycle [24, 25]. Furthermore, hyperglycemia can activate the protein kinase C pathway, which promotes ingestion by inflammatory macrophages of basic calcium phosphate crystals deposited in atherosclerotic lesions. Macrophages trigger inflammatory cytokine secretion, which may produce a vicious cycle that promotes VSMC calcification [26]. Therefore, in diabetic patients undergoing intensive lipid management therapy, coronary calcification may be attributed to the increased oxidative stress and inflammation caused by diabetes, in addition to the stabilization of arteriosclerosis by statins.

Milzi A et al. reported that type 2 diabetes has no impact on the localization, size, shape, or extent of the calcification evaluated using OCT images [27]. They evaluated culprit lesions at only one time point before PCI. Moreover, patients with ACS were excluded, and the rate of lipid management with statins was only 60% in their study. In contrast, we evaluated the serial changes of coronary calcifications in patients with intensive lipid management, including patients with ACS, and these differences may lead to adverse consequences. Moreover, our results showed that diabetes was an independent predictor for rapid coronary calcification progression, whereas CCr was not different between the RP and non-RP groups. Nakajima et al. reported that diabetes and chronic kidney disease are independent clinical predictors for rapid coronary calcification progression [11]. Calcium and phosphate metabolism dysregulation is common in CKD, which is recognized as a risk factor driving vascular calcification [24, 28]. Coronary artery calcification was frequently detected by OCT in coronary artery disease patients with end-stage renal disease on dialysis [29]. The reason why CCr was not the predictor for rapid coronary calcification progression in our study remains unclear but may refer to the different study populations; our study included several patients who had preserved renal function except for four patients undergoing dialysis.

Study limitations

This study had several limitations. First, this was a single-center retrospective study with

a relatively small number of patients. Consecutive patients who underwent serial OCT examination were not enrolled in this study. Second, owing to the need for contrast media injection, patients who underwent OCT examination frequently had preserved renal function and no symptoms of heart failure. Moreover, half of the patients were complicated with acute coronary syndrome, and the others with stable angina. Therefore, selection bias cannot be excluded. Third, we did not have detailed information on medications, such as the type and dose of oral hypoglycemic drugs and statins. Additionally, the diabetes duration was unknown. Fourth, serum calcium and phosphorus might affect coronary calcification progression; however, we could not collect data on them. Finally, the RP group had a longer follow-up duration than the non-RP group. However, multivariate analysis after adjusting the follow-up period also supported our results. Our findings should be confirmed by further large-scale studies in the future.

Conclusions

We demonstrated that the calcium volume evaluated using OCT following PCI increased in almost all patients even under intensive lipid management. Diabetes was an independent clinical predictor for rapid coronary calcification progression.

Acknowledgment

None.

Declarations

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Conflict of interest: Dr. Hirofumi Tomita has received research grant support from Abbott Medical Japan LCC. The other authors have nothing to disclose.

Data availability: The data in this study are available from the corresponding author upon reasonable request.

Ethics approval: This study was conducted in accordance with the ethical guidelines for medical research on humans in the Helsinki Declaration. The research protocol was approved by the Institutional Review Board of the Hirosaki University Graduate School of Medicine (IRB number: 2023-014).

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Figure legends

Figure 1. Representative images and measurement of coronary calcification using optical coherence tomography (OCT). Calcifications are shown as areas surrounded by white lines (A and B). The calcium arc and minimal calcium depth are measured as in blue and purple lines, respectively (B). The longitudinal length of calcification is shown as a white arrow (C).

Figure 2. Representative serial images of coronary calcifications evaluated using OCT at the baseline (A and C) and the chronic phase (B and D). White arrows indicate calcifications. A and B: spotty calcification. C and D: macrocalcification. Both calcification areas increased from the baseline to the chronic phase.

Figure 3. Comparison of changes in calcification parameters between patients with and without diabetes mellitus (DM). The lines within the boxes represent median values, and the top and bottom borders of the boxes represent interquartile ranges, respectively. The whiskers above and below the boxes indicate the 10th and 90th percentiles. An analysis of covariance (ANCOVA) was used to adjust the baseline calcification parameters and p-values are shown.

Table 1. Characteristics of the study patients

	Study patients (n=31)	RP group (n = 16)	Non-RP group (n = 15)	p-value
Baseline characteristics				
Age, years	63 ± 10	60 ± 11	67 ± 8	0.09
Male, n (%)	29 (94)	14 (88)	15 (100)	0.48
BMI, kg/m^2	25.4 ± 3.7	26.3 ± 4.2	24.4 ± 3.0	0.27
Coronary risk factors, n (%)				
Hypertension	22 (71)	13 (81)	8 (53)	0.14
Dyslipidemia	26 (84)	15 (94)	11 (73)	0.18
Diabetes mellitus	17 (55)	13 (81)	4 (27)	< 0.05
Current smoker	7 (23)	5 (31)	2 (13)	0.39
Prior MI, n (%)	3 (10)	2 (13)	1 (7)	1.00
Prior PCI, n (%)	13 (42)	9 (56)	4 (27)	0.15
Prior CABG, n (%)	1 (3)	0 (0)	1 (7)	0.48
Dialysis, n (%)	4 (13)	3 (19)	1 (7)	0.60
Clinical presentation, n (%)				
STE-ACS	12 (39)	7 (44)	5 (33)	0.71
NSTE-ACS	2 (6)	1 (6)	1 (7)	1.00
SAP	17 (55)	8 (50)	9 (60)	0.72
Laboratory data at admission				
Hemoglobin, g/dL	14.2 ± 1.5	14.2 ± 1.4	14.2 ± 1.6	0.84
CCr, mL/min	81 (61-101)	88 (42-99)	80 (69-100)	0.91
Total cholesterol, mg/dL	140 ± 28	184 ± 48	176 ± 47	0.58
Triglyceride, mg/dL	169 ± 116	214 ± 129	121 ± 116	< 0.05
LDL-cholesterol, mg/dL	100 ± 41	100 ± 38	100 ± 45	0.97
HDL-cholesterol, mg/dL	46.2 ± 13.4	41.1 ± 10.3	51.7±14.4	< 0.05
hs-CRP, ng/dL	290 ± 570	205 ± 307	398 ± 756	0.91
HbA1c, %	6.2 ± 0.7	6.5 ± 0.8	5.9 ± 0.4	< 0.05
BNP, pg/mL	40 (15-79)	41 (10-84)	38 (20-73)	0.80
Medication at discharge, n (%)				
Aspirin	31 (100)	16 (100)	15 (100)	-
P2Y12 receptor inhibitors	30 (97)	15 (94)	15 (100)	1.00
Oral anticoagulant	2 (6)	2 (13)	0 (0)	0.48
Statin	31 (100)	16 (100)	15 (100)	-
ACEI/ARB	20 (65)	9 (56)	11 (73)	0.46
Beta-blocker	23 (74)	12 (75)	11 (73)	1.00
Oral hypoglycemic agents	12 (39)	10 (63)	2 (13)	< 0.05
Insulin	4 (13)	4 (25)	0 (0)	0.10
Medication at chronic phase, n (%)				
Aspirin	30 (97)	15 (94)	15 (100)	1.00

P2Y12 receptor inhibitors	29 (94)	14 (88)	15 (100)	1.00
Oral anticoagulant	2 (6)	2 (13)	0 (0)	0.48
Statin	31 (100)	16 (100)	15 (100)	-
ACEI/ARB	21 (68)	10 (63)	11 (73)	0.70
Beta-blocker	24 (78)	13 (81)	11 (73)	0.68
Oral hypoglycemic agents	12 (39)	10 (63)	2 (13)	< 0.05
Insulin	5 (16)	5 (31)	0 (0)	< 0.05
Follow-up duration, days	287 (233-429)	350 (287-1032)	274 (201-292)	< 0.05

Data are presented as mean ± standard deviation, n (%), or median values (interquartile ranges).

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CCr, creatinine clearance; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; NSTE-ACS, non-ST-segment-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RP, rapid progression in calcification; SAP, stable angina pectoris; STE-ACS, ST-segment-elevation acute coronary syndrome.

Table 2. Optical coherence tomography analysis of the coronary calcification

	Baseline	Chronic phase	Change (Chronic phase-Baseline)	p-value
Calcium classification, n (%)				
Spotty calcification	18 (55)	15 (45)		
Macrocalcification	15 (45)	18 (55)		
Maximal calcium arc, degree	65 (44-113)	74 (62-110)	9 (2-15)	< 0.05
Mean calcium arc, degree	47 (31-70)	56 (41-69)	5 (3-12)	< 0.05
Maximal calcium area, mm^2	1.0 (0.7-1.9)	1.3 (0.8-2.2)	0.2 (0.1-0.4)	< 0.05
Mean calcium area, mm^2	0.6 (0.4-1.1)	0.8 (0.5-1.3)	0.1 (0.04-0.2)	< 0.05
Calcium longitudinal length, mm	3.0 (1.8-4.0)	3.0 (2.5-4.3)	0.2 (0-0.6)	< 0.05
Minimal calcium depth, μm	80 (40-150)	60 (20-115)	-10 (-30-0)	< 0.05
Calcium index	159 (62-267)	198 (90-304)	24 (9-72)	< 0.05
Calcium volume, mm^3	1.8 (0.7-4.3)	2.6 (1.3-5.1)	0.6 (0.1-1.2)	< 0.05

Data are presented as n (%), or median values (interquartile ranges). P-value indicates difference between baseline and chronic phase.

Table 3. Predictors for rapid progression of coronary calcification

	Model 1		**Model 2**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Diabetes mellitus	11.19 (1.02-123.19)	< 0.05	21.2 (1.09-414.89)	< 0.05
Follow-up duration	1.00 (0.99-1.01)	0.24	1.00 (0.99-1.01)	0.34
Triglyceride	1.01 (0.99-1.02)	0.18	1.01 (0.99-1.03)	0.14
HDL-cholesterol	0.95 (0.85-1.07)	0.40	0.96 (0.84-1.09)	0.53
Age			0.92 (0.82-1.02)	0.11

HDL indicates high-density lipoprotein; OR, odds ratio; CI, confidence interval.

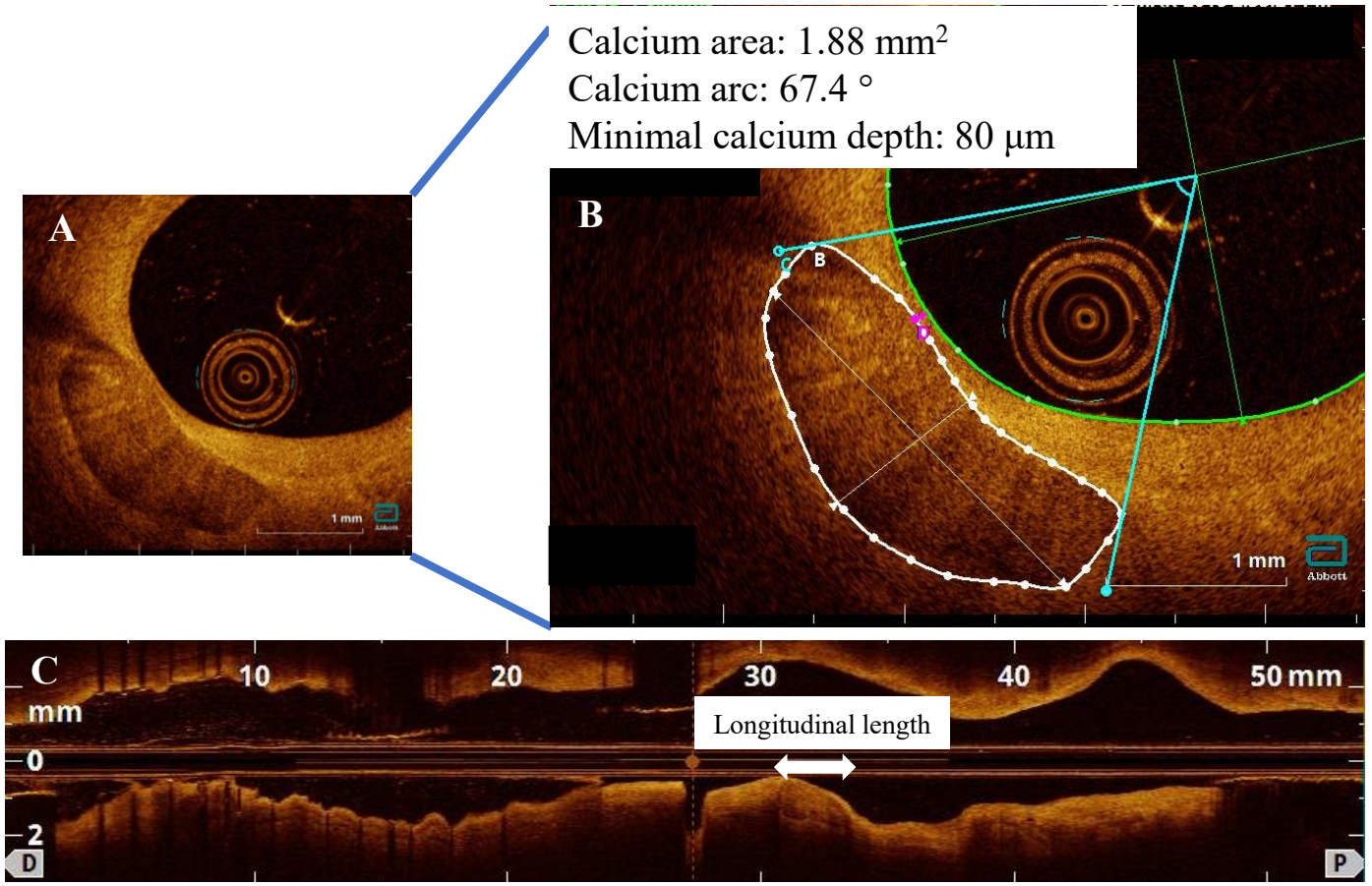

A
1 mm
Calcium area: 1.88 mm2
Calcium arc: 67.4 °
Minimal calcium depth: 80 μm
B
1 mm
Abbott
C
mm
10
20
30
40
50 mm
Longitudinal length
0
2
D
P

Figure. 1

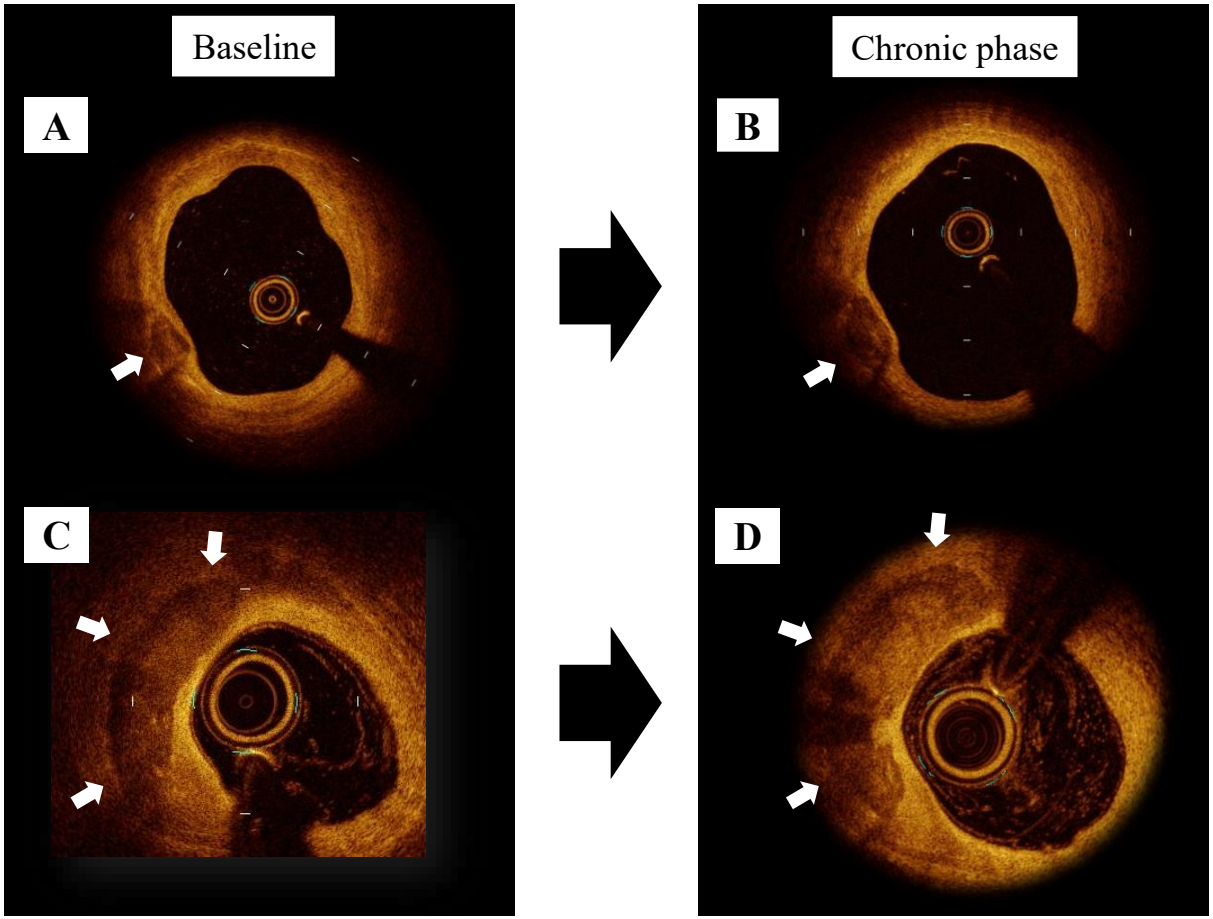


Figure. 2

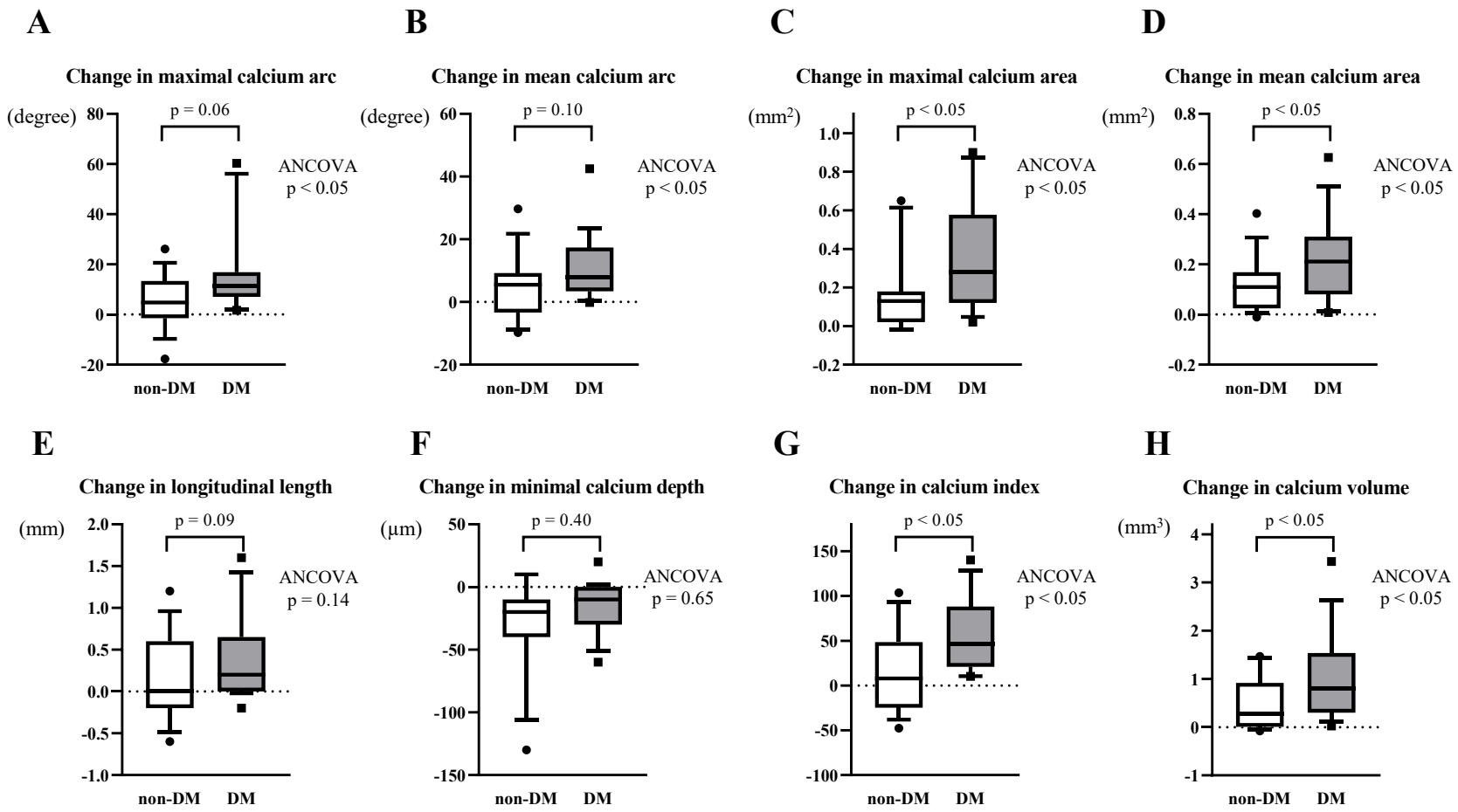
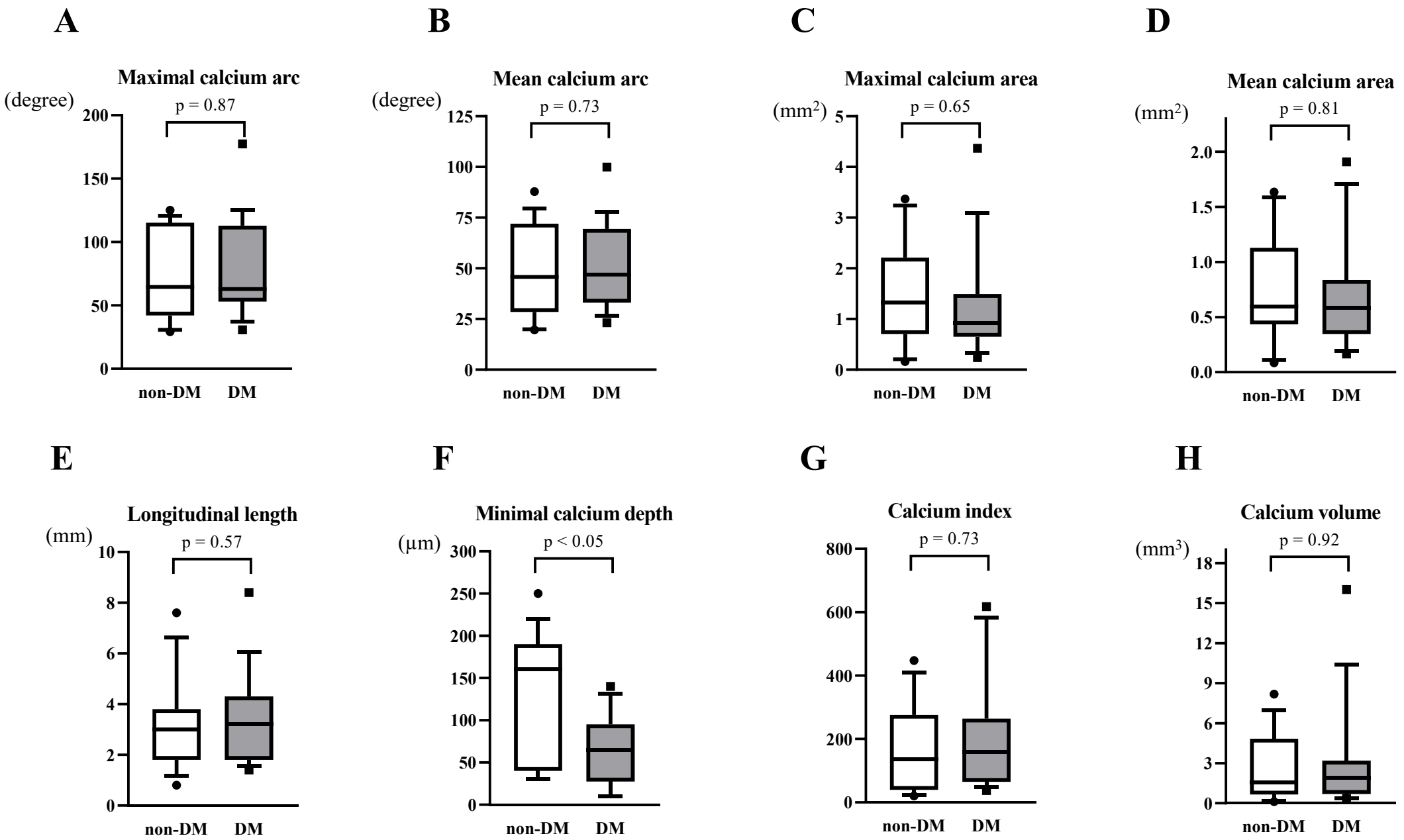

A
Change in maximal calcium arc
(degree)
p = 0.06
ANCOVA
p < 0.05
non-DM
DM
B
Change in mean calcium arc
(degree)
p = 0.10
ANCOVA
p < 0.05
non-DM
DM
C
Change in maximal calcium area
(mm²)
p < 0.05
ANCOVA
p < 0.05
non-DM
DM
D
Change in mean calcium area
(mm²)
p < 0.05
ANCOVA
p < 0.05
non-DM
DM
E
Change in longitudinal length
(mm)
p = 0.09
ANCOVA
p = 0.14
non-DM
DM
F
Change in minimal calcium depth
(μm)
p = 0.40
ANCOVA
p = 0.65
non-DM
DM
G
Change in calcium index
p < 0.05
ANCOVA
p < 0.05
non-DM
DM
H
Change in calcium volume
(mm³)
p < 0.05
ANCOVA
p < 0.05
non-DM
DM

Figure. 3

Supplementary Figure 1



Supplementary Figure 2