Coronary Plaque Characteristics in Hemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography

Chee Yang Chin, MD, MSc[a,b,c], Mitsuaki Matsumura, BS[a], Akiko Maehara, MD[a,b], Wenbin Zhang, MD[a,b], Cheolmin Tetsumin Lee, MD[a,b], Myong Hwa Yamamoto, MD[a,b], Lei Song, MD[a,b,d], Yasir Parviz, MD[b], Nisha B. Jhalani, MD[b], Sumit Mohan, MD[e], Lloyd E. Ratner, MD, MPH[f], David J. Cohen, MD[f], Ori Ben-Yehuda, MD[a], Gregg W. Stone, MD[a,b], Richard A. Shlofmitz, MD[g], Tsunekazu Kakuta, MD[h], Gary S. Mintz, MD[a], and Ziad A. Ali, MD, DPhil[a,b,*]

Coronary arteries in patients with chronic kidney disease (CKD) have been shown to exhibit more extensive atherosclerosis and calcium. We aimed to assess characteristics of coronary plaque in hemodialysis (HD)-dependent patients using optical coherence tomography (OCT). This was a multicenter, retrospective study of 124 patients with stable angina who underwent OCT imaging. Sixty-two HD-dependent patients who underwent pre-intervention OCT for coronary artery disease were compared 1:1 with a cohort of patients without CKD, matched for age, diabetes mellitus, gender, and culprit vessel. Baseline characteristics were comparable. Pre-intervention OCT imaging identified 62 paired culprit, 53 paired non-culprit, and 19 paired distal vessel lesions. Lesion length, minimum lumen area, and area stenosis were similar between groups. The HD-dependent group had greater mean calcium arcs in culprit (54.3° vs 26.4°, p = 0.004) and non-culprit lesions (34.3° vs 24.5°, p = 0.02) and greater maximum calcium arc in distal vessel segments (101.6° vs 0°, p = 0.03). There were no differences in lipid arcs between groups. There was a higher prevalence of thin intimal calcium, defined as an arc of calcium >30° within intima <0.5 mm thick, in patients in the HD-dependent group (41.9% vs 4.8%, p <0.001). There was a higher prevalence of calcified nodules in the HD-dependent group (24.2% vs 9.7%, p = 0.049) but no differences in medial calcification or thin-cap fibroatheroma. In conclusion, in this OCT study, HD-dependent patients, compared with matched patients without CKD, had more extensively distributed coronary calcium and uniquely, a higher prevalence of non-atherosclerotic thin intimal calcium. This thin intimal calcium may cause an overestimation of calcium burden by intravascular ultrasound and may contribute to the lack of correlation between increased coronary artery calcification scores with long-term outcomes in patients with CKD. **(Am J Cardiol 2017;119:1313−1319)**

Chronic kidney disease (CKD) is strongly associated with accelerated coronary artery disease (CAD). Accordingly, cardiovascular disease is the leading cause of morbidity and mortality in patients with hemodialysis (HD)-dependent end-stage renal disease (ESRD), with a mortality risk up to 20-fold greater than in an age- and gender-matched general population.[1−3] Autopsy and in vivo imaging studies by computed tomography and intravascular ultrasound (IVUS) have demonstrated significant associations between CKD and CAD severity and calcification.[4−8] Optical coherence tomography (OCT) provides high-resolution assessment of coronary plaque with the additional benefit over IVUS of penetration through calcium; however, its use in patients with CKD is limited by the need for additional contrast medium used for flush clearing the artery during OCT image acquisition. Consequently, understanding of coronary plaque characteristics by OCT in patients with CKD is limited. The aim of the present study was to use OCT to assess coronary plaque characteristics of patients with HD-dependent ESRD.

Methods

Patients across 3 sites (Columbia University Medical Center, New York, New York; St. Francis Hospital and Heart Center, Roslyn, New York; Tsuchiura Kyodo Hospital,

[a]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York; [b]Division of Cardiology, [e]Division of Nephrology, and [f]Department of Surgery, New York-Presbyterian Hospital/Columbia University Medical Center, New York, New York; [c]Department of Cardiology, National Heart Centre Singapore, Singapore; [d]Department of Cardiology, National Center for Cardiovascular Disease, China Peking Union Medical College, Fuwai Hospital, Beijing, China; [g]St. Francis Hospital and Heart Center, Roslyn, New York; and [h]Department of Cardiology, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan. Manuscript received October 22, 2016; revised manuscript received and accepted January 23, 2017.

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*Corresponding author: Tel: (212) 305-7060; fax: (212) 342-3660.
E-mail address: zaa2112@columbia.edu (Z.A. Ali).

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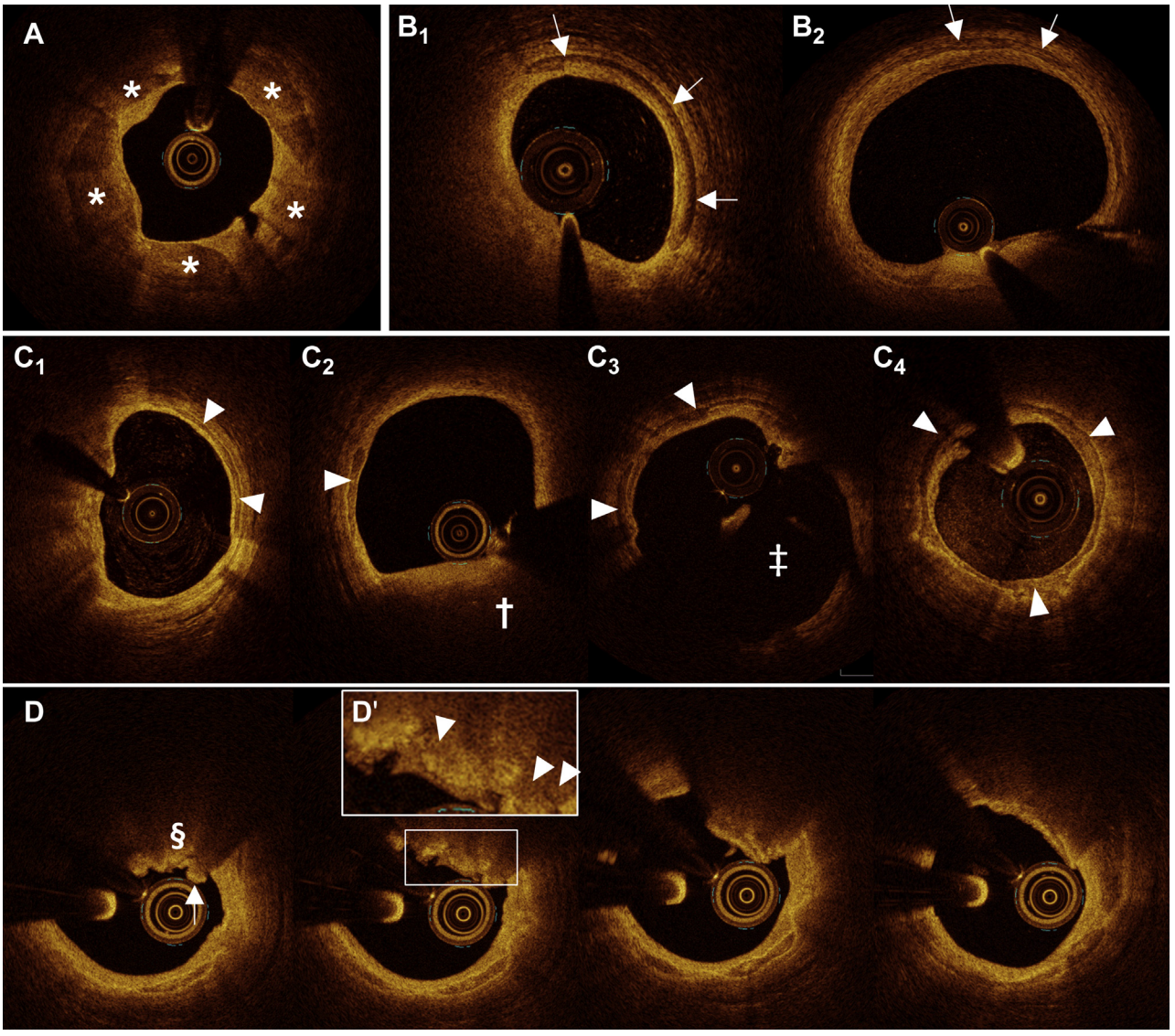

Figure 1. Qualitative OCT analyses. *(A)* Intimal calcific plaque, seen as bulky signal-poor regions (*) with sharply delineated borders. *(B_1, B_2)* Medial calcification, seen as a segment of well-defined media with borders more sharply delineated *(arrows)* than adjacent noncalcific media. *(C)* Thin intimal calcification, seen as a calcium arc >30° *(arrowheads)* within nonlipidic intima <0.5 mm thick, separated from the media, and located opposite classic intimal calcific plaque *(C_1)*, opposite a lipid pool *(C_2, †)*, opposite a ruptured plaque *(C_3, ‡)*, or circumferentially in a distal vessel segment *(C_4)*. *(D)* Calcified nodule (§) seen as an accumulation of small nodular calcifications *(D′, arrowheads)* above a calcium plate, with attenuation because of platelet-rich thrombus *(D, arrow)* and fibrin.

Tsuchiura, Japan) who underwent OCT to guide CAD management from November 2008 to January 2016 were identified. From this pooled cohort, all HD-dependent patients were included in this study. These patients were compared 1:1 with a propensity score−matched cohort of patients without CKD, defined by an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease study equation[9] and without clinical, imaging, tissue, or laboratory evidence of kidney damage. Matching criteria were (in order) age, diabetes mellitus, gender, and culprit vessel. The study was approved by the institutional review board at each center, and all patients provided signed written, informed consent.

OCT was performed using a commercially available frequency domain OCT system (ILUMIEN OPTIS or C7-XR FD-OCT System; St. Jude Medical, St. Paul, Minnesota; or Lunawave optical frequency domain imaging system; Terumo Corporation, Tokyo, Japan) or time domain OCT system (M2/M3 Cardiology Imaging System; Lightlab Imaging, Westford, Massachusetts). After diagnostic angiography, patients received 100 μg intracoronary nitroglycerin. For frequency domain OCT imaging, a 2.7Fr (Dragonfly Duo or Dragonfly OPTIS; St. Jude Medical) or 2.6Fr catheter (Fastview; Terumo Corporation) was advanced distal to the target lesion. Automated pullback was triggered using intracoronary contrast injection (3 to 4 ml/s, 12 to 14 ml total) with a motorized pullback speed of up to 25 mm/s (Dragonfly) or 40 mm/s (Fastview), a frame rate of 100 per second (Dragonfly) or 160 per second (Fastview), and a maximum scan length of 75 mm (Dragonfly) or

150 mm (Fastview). For time domain OCT imaging, a low-pressure occlusion balloon (Helios; Goodman, Nagoya, Japan) with distal flush ports was inflated proximal to the lesion, and the imaging wire was automatically pulled back at 1.0 to 3.0 mm/s during continuous saline infusion. All OCT images were de-identified and digitally stored. Only previously untreated segments were included. OCT images were analyzed by 2 independent investigators (CYC and MM) using St. Jude Medical Offline Review Workstation software (version E.0.2). In case of a disagreement, consensus was achieved with a third investigator (AM).

A culprit lesion was defined as the segment that was stented by comparing pre- and post-PCI OCT images. When post-PCI OCT was not performed, the stented segment was determined by co-registering the pre-PCI OCT pullback with the final coronary angiogram. When PCI was not performed, the culprit lesion was determined as the segment most likely to be causing ischemia, most commonly the segment containing the minimum lumen area (MLA). Nonculprit lesions were defined as any ≥10-mm-long segment adjacent to the culprit lesion.

Calibration was performed for each segment, and every frame was evaluated. Structures were classified according to established OCT reporting standards, and all arcs were measured relative to the center of mass of the lumen.[10] Area stenosis was calculated using the formula (1 − [MLA/mean reference lumen cross-sectional area]) and expressed as a percentage. The maximum calcium and lipid arcs for each culprit and nonculprit lesion were measured. Where superficial calcium was identified, this was classified as calcific plaque regardless of whether lipid was present deep to the calcium; as such, analyzed calcium and lipid arcs never overlapped. In addition, calcium and lipid arcs were measured at 1-mm intervals over the entire length of each lesion and were summed and divided by the number of 1-mm-interval frames analyzed to obtain the mean calcium and lipid arcs. Where the distal coronary artery segment, as defined angiographically,[11] was imaged by OCT, the maximum calcium arc was measured.

Calcific plaque had a low-backscatter signal with sharply delineated borders (Figure 1). Calcium present in the medial layer was classified as medial calcification (Figure 1). Calcium of arc >30° within a non-atherosclerotic intima <0.5 mm thick (lumen to internal elastic lamina) was classified as thin intimal calcium (Figure 1). A calcified nodule was an accumulation of multiple small nodular calcifications with superficial thrombus or fibrin above an underlying calcium plate, with or without significant luminal protrusion (Figure 1). Lipidic plaque had a signal-poor region with diffuse borders and high attenuation, consistently over at least 5 adjacent slices. OCT thin-cap fibroatheroma (OCT-TCFA) was a lipidic plaque with an overlying fibrous cap with a minimum thickness ≤65 μm. Side branches were assessed for the presence of ostial calcium. The intra- and interobserver κ-coefficients for thin intimal calcium were both 0.833 and for medial calcification were 0.833 and 0.667, respectively.

Only propensity score−matched pairs were included for statistical analysis. In patients with both a proximal and a distal nonculprit lesion analyzable, only the proximal lesion was used for quantitative analyses, whereas both proximal and distal lesions were included in qualitative analyses.

Table 1
Baseline characteristics

Variable	HD Group (n=62)	Non-CKD Group (n=62)	*P*-value
Age (years)	63.3±10.6	65.2±11.5	0.07
Female	20 (32%)	13 (21%)	0.19
Diabetes mellitus	38 (61%)	38 (61%)	1.00
Hypertension	58 (94%)	50 (81%)	0.08
Hyperlipidemia	41 (66%)	42 (68%)	1.00
Prior smoker	24 (39%)	37 (60%)	0.03
Statin use on admission	44 (71%)	49 (79%)	0.63
Total cholesterol (mg/dL)	148.8±35.2	156.6±38.7	0.14
Low-density lipoprotein cholesterol (mg/dL)	81.5±30.6	89.5±33.6	0.20
HD duration (months)	18.7 (10.5-37.2)	—	—
eGFR, mL/min/1.73m^2	—	78.5±15.4	—
Left ventricular ejection fraction (%)	57.5 (48.1-60)	55 (53-62)	0.86
OCT system used			
Time domain OCT	10 (16%)	4 (7%)	0.11
Frequency domain OCT	47 (76%)	50 (81%)	0.51
Optical frequency domain imaging	5 (8%)	8 (13%)	0.58

Values are mean ± standard deviation, n (%), or median (interquartile range).

eGFR = estimated glomerular filtration rate; HD = hemodialysis; LDL-C = low density lipoprotein; OCT = optical coherence tomography.

Categorical variables were compared by the McNemar test or the exact McNemar test for <25 discordant pairs. Continuous variables were compared by Student's *t* test (if normally distributed) or the Wilcoxon signed rank test (if not normally distributed). p Value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 18.0 (SPSS Inc.; IBM, Armonk, New York).

Results

A total of 124 patients were included in the study; 62 HD-dependent patients with analyzable pre-PCI OCT pullbacks were matched with 62 patients with eGFR >60 ml/min/1.73 m^2. Baseline characteristics were comparable between groups (Table 1). The median duration of HD in the HD group was 18.7 months (interquartile range 10.5 to 37.2 months). The mean eGFR in the non-CKD group was 78.5 ± 15.4 ml/min/1.73 m^2.

The culprit vessel location was similar between groups. Thirty-seven patients (59.7%) in the HD group and 29 patients (46.8%) in the non-CKD group had an analyzable distal vessel, of which 19 in each group were matched pairs (Table 2). Culprit lesion length, MLA, and area stenosis were similar between groups (124 matched culprits). Mean calcium arc (54.3° vs 26.4°, p = 0.004) and maximum calcium arc (179° vs 122°, p = 0.02) were greater in the HD group. There were no differences in mean and maximum lipid arcs between groups.

Among 106 matched nonculprit lesions, lesion length, MLA, and area stenosis were similar between groups. Mean calcium arc (34.3° vs 24.5°, p = 0.02) and maximum calcium arc (133° vs 90°, p = 0.02) were greater in the HD group. There were no differences in mean and maximum

Table 2
Quantitative optical coherence tomography findings

Variable	HD Group	Non-CKD Group	*P*-value
Culprit vessel location			
Left anterior descending	33 (53%)	41 (66%)	0.13
Left circumflex	11 (18%)	8 (13%)	0.55
Right coronary	18 (29%)	13 (21%)	0.38
Culprit lesion			
Matched lesions	62	62	—
Length (mm)	21.3 (15.5-30.8)	19.8 (13.9-33.8)	0.79
Minimum lumen area (mm^2)	1.68 (1.07-2.39)	1.66 (1.16-2.36)	0.46
Average reference lumen area (mm^2)	5.6 (4.67-7.54)	5.66 (4.63-7.17)	0.80
Minimum lumen diameter (mm)	1.27 (0.97-1.44)	1.24 (1.02-1.49)	0.26
Area stenosis (%)	73.1 (59.0-80.5)	70.9 (60.3-79.4)	0.67
Mean calcium arc (°)	54.3 (15.3-145.0)	26.4 (8.0-59.7)	0.004
Maximum calcium arc (°)	179 (104-344)	122 (71-213)	0.02
Mean lipid arc (°)	20.3 (6.1-43.3)	21.9 (9.8-52.4)	0.83
Maximum lipid arc (°)	113 (71-196)	105 (67-169)	0.40
Non-culprit lesion			
Matched lesions	53	53	—
Length (mm)	17.8 (12.8-24.4)	18.4 (13.6-26.8)	0.19
Minimum lumen area (mm^2)	4.43 (3.31-5.33)	4.60 (3.68-6.14)	0.41
Average reference lumen area (mm^2)	6.84 (5.36-9.16)	6.9 (5.37-9.17)	0.14
Minimum lumen diameter (mm)	2.07 (1.80-2.43)	2.78 (2.26-3.29)	0.48
Area stenosis (%)	29.6 (20.9-38.2)	30.3 (21.2-43.1)	0.73
Mean calcium arc (°)	34.3 (10.3-109.4)	24.5 (3.8-53.2)	0.02
Maximum calcium arc (°)	133 (63-240)	90 (33-142)	0.02
Mean lipid arc (°)	10.1 (0-39.1)	8.8 (0-31.0)	0.61
Maximum lipid arc (°)	86 (0-138)	77 (0-122)	0.27
Distal vessel segment			
Analyzable by optical coherence tomography	37 (60%)	29 (47%)	—
Matched segments	19	19	—
Maximum calcium arc (°)	101 (76-313)	0 (0-78)	0.03

Values are n (%) or median (interquartile range).
HD = hemodialysis.

Table 3
Qualitative optical coherence tomography findings

Variable	HD Group	Non-CKD Group	*P*-value
Entire vessel			
Thin intimal calcification	26 (42%)	3 (5%)	<0.001
Medial calcification	11 (18%)	4 (7%)	0.12
Calcified nodule	15 (24%)	6 (10%)	0.049
Thin-cap fibroatheroma	3 (5%)	1 (2%)	0.63
Sidebranch ostial calcium	11 (18%)	5 (8%)	0.21
Culprit lesion			
Thin intimal calcification	19 (31%)	2 (3%)	<0.001
Medial calcification	8 (13%)	2 (3%)	0.11
Calcified nodule	10 (16%)	3 (5%)	0.09
Non-culprit lesion			
Thin intimal calcification	13 (25%)	1 (2%)	<0.001
Medial calcification	5 (9%)	3 (6%)	0.73
Calcified nodule	7 (13%)	4 (8%)	0.51

Values are n (%).
HD = hemodialysis.

lipid arcs between groups. The maximum calcium arc was greater in the distal segment of the coronary artery in the HD group (101.6° vs 0°, p = 0.03).

There was a significantly higher prevalence of thin intimal calcium in culprit vessels in the HD group (41.9% vs 4.8%, p <0.001) in both culprit (30.7% vs 3.2%, p <0.001) and nonculprit lesions (24.5% vs 1.9%, p <0.001) (Table 3). There was a higher prevalence of calcified nodules in the HD group (24.2% vs 9.7%, p = 0.049). There was a trend toward more medial calcification in culprit lesions in the HD group (p = 0.11), but no difference in TCFA or side branch ostial calcium between groups.

The quantitative and qualitative findings among patients in the HD group divided by tertiles of HD duration have been summarized in Table 4. The median HD duration in the first, second, and third tertiles were 5.3, 18.6, and 60.0 months, respectively. The mean calcium arc increased with increasing HD duration in both culprit (23.6° vs 30.8° vs 115.2°, p = 0.005) and non-culprit lesions (10.3° vs 24.5° vs 94.5°, p = 0.01). The prevalence of thin intimal calcium was significantly higher in patients in the highest HD duration tertile (35.0% vs 14.3% vs 76.2%, p <0.001).

Discussion

We report comprehensive atherosclerotic plaque characteristics in HD-dependent patients by OCT. (1) Compared with patients without CKD, HD-dependent patients had CAD that contained greater mean and maximum calcium arcs in both culprit and nonculprit segments and greater distal vessel calcium arcs, consistent with overall increased calcium burden (Figure 2). (2) Among patients with ESRD, higher mean and maximum calcium arcs were associated with increasing duration on HD. (3) Compared with patients without CKD, patients with HD-dependent ESRD had a higher prevalence of calcium within non-atherosclerotic thin intima.

Pathology studies clearly illustrate a link between renal dysfunction and accelerated coronary atherosclerosis, calcification, and medial thickness.[4,5] By computed tomography, coronary calcification was identified in as many as 40% of asymptomatic patients with CKD, with a 2-year doubling of the calcification score in young patients with ESRD.[12,13] IVUS studies have further demonstrated correlations between renal dysfunction and coronary calcification across all ranges of CKD.[14–16] As opposed to IVUS, OCT uses light waves, which have superior calcium penetration. In patients with a large calcium burden, this allows for better assessment of calcified plaque thickness and structures deep to calcium; however, the use of OCT in patients with CKD is problematic for the risk of contrast-induced nephropathy. Although non−contrast-based media (e.g., dextran) are available, contrast remains the most widely available, used, and only approved flushing medium for OCT. As such, OCT studies of patients with CKD are rare. Kato et al[6] examined characteristics of non-culprit plaques in 37 patients with mild-to-moderate CKD and found a higher prevalence of calcium and a greater lipid burden compared with those without CKD; however, calcium was recorded only for its presence and was not quantified.

Table 4
Hemodialysis subgroup analysis by hemodialysis duration

Variable	Hemodialysis Duration			*P*-value
	Tertile 1 (n=20)	Tertile 2 (n=21)	Tertile 3 (n = 21)	
Hemodialysis duration (months)	5.3 (1.1-9.4)	18.6 (16-23)	60.0 (37.6-75.9)	—
Culprit				
Area stenosis (%)	74.1 (63.0-82.2)	77.1 (61.1-81.9)	72.8 (58.9-74.7)	0.83
Mean calcium arc (°)	23.6 (5.3-90.3)	30.8 (15.8-137.6)	115.2 (56.1-169.2)	0.005
Max calcium arc (°)	143 (87-220)	135 (91-315)	321 (198-360)	0.003
Mean lipid arc (°)	22.0 (10.7-37.4)	20.0 (2.0-44.8)	19.6 (9.0-36.4)	0.90
Max lipid arc (°)	104 (70-178)	111 (46-200)	117 (93-196)	0.88
Thin intimal calcification	4 (20%)	1 (5%)	14 (67%)	<0.001
Medial calcification	2 (10%)	2 (10%)	4 (19%)	0.60
Calcified nodule	4 (20%)	2 (10%)	4 (19%)	0.57
Non-Culprit				
Analyzable lesions	17	20	21	
Area stenosis (%)	34.0 (27.5-44.0)	25.7 (23.6-37.5)	30.1 (15.7-37.0)	0.53
Mean calcium arc (°)	10.3 (0-56.4)	24.5 (3.6-75.6)	94.5 (30.2-133.6)	0.01
Max calcium arc (°)	95 (0-188)	92 (45-213)	194 (115-242)	0.11
Mean lipid arc (°)	10.6 (0-36.4)	28.2 (0-58.6)	3.7 (0-20.3)	0.16
Max lipid arc (°)	70 (0-124)	123 (37-184)	74 (0-123)	0.21
Thin intimal calcification	4 (24%)	2 (10%)	8 (38%)	0.10
Medial calcification	1 (6%)	2 (10%)	3 (14%)	0.69
Calcified nodule	1 (6%)	2 (10%)	4 (19%)	0.44
Entire vessel				
Thin intimal calcification	7 (35%)	3 (14%)	16 (76%)	<0.001
Medial calcification	3 (15%)	2 (10%)	6 (296%)	0.26
Calcified nodule	5 (25%)	3 (14%)	7 (33%)	0.34
Thin-cap fibroatheroma	1 (5%)	2 (10%)	0 (0%)	0.24

Values are n (%), or median (interquartile range).

Our study compared HD-dependent patients with ESRD with a matched group of patients with eGFR >60 ml/min/1.73 m^2, using matching criteria shown to be independent predictors of coronary intimal and medial calcification.[7,17,18] Although it would have been insightful to have a third group of patients with moderate CKD, the number of these patients in our cohort was too small to be able to perform effective propensity score matching, primarily because of the risk of contrast-induced nephropathy. We studied only stable angina patients. First, most HD-dependent patients who underwent OCT interrogation at our centers presented with stable angina. This may be explained by the presence of more extensive coronary calcium, which may confer plaque stability.[19] Indeed, the incidence of TCFA in our cohort was low despite a high prevalence of diabetes mellitus. Second, plaque characteristics in patients with stable symptoms are more likely to reflect the natural history of calcification. Third, coronary arteries of stable patients were unlikely to contain thrombus that may obscure vessel wall structures by OCT.

The prevalence of CAD in patients with CKD is, in part, explained by the clustering of atherosclerotic risk factors in these patients.[20] Additionally, increased duration of HD, oxidative stress, inflammation, and metabolic imbalances, such as homocysteinemia, hyperphosphatemia, and hypercalcemia, are also postulated risk factors for atherosclerosis and calcification.[13,21–23]

The mechanism of classic intimal calcification is imperfectly understood but is currently considered to be an active process that may begin within lipid pools and involve apoptosis of smooth muscle cells and macrophages and the release of matrix vesicles that calcify in the extracellular environment.[24] The presence of bone proteins and cartilage in the vessel wall, and cells that display osteoblastic differentiation, supports the notion that vascular calcification shares processes similar to bone formation.[25] A uremic environment stresses inhibitory mechanisms of calcification, promoting further calcium deposition.[18,26] Calcified areas are mostly located around and proximal, rather than distal to a necrotic core.[27] As they progress, they enlarge to form calcified plates that are the hallmark of stable and fibrocalcific plaque. These plates may fracture and form nodular calcification, observed as small, rounded calcified fragments separated by fibrin that were also more common in the present study. Calcified nodules can cause discontinuity of overlying collagen and endothelium predisposing to acute thrombosis[24] and may be one reason for increased cardiovascular mortality in patients with ESRD.

Medial calcification occurs independently of intimal calcification and is strongly linked with CKD, age, and diabetes mellitus.[17,18,28] It is not associated with lipid deposition or inflammation and starts within elastic fibers and smooth muscle cells of the media.[24] These smooth muscle cells lose their contractile properties and gain osteochondrogenic markers, forming bands of calcium-rich deposits that extend deep into the inner layer of the media and may involve the circumference of the vessel.[17] At advanced stages, calcification progresses to form solid plates or sheaths, increasingly distorting the medial architecture and intruding on the intima. Studies show increased medial

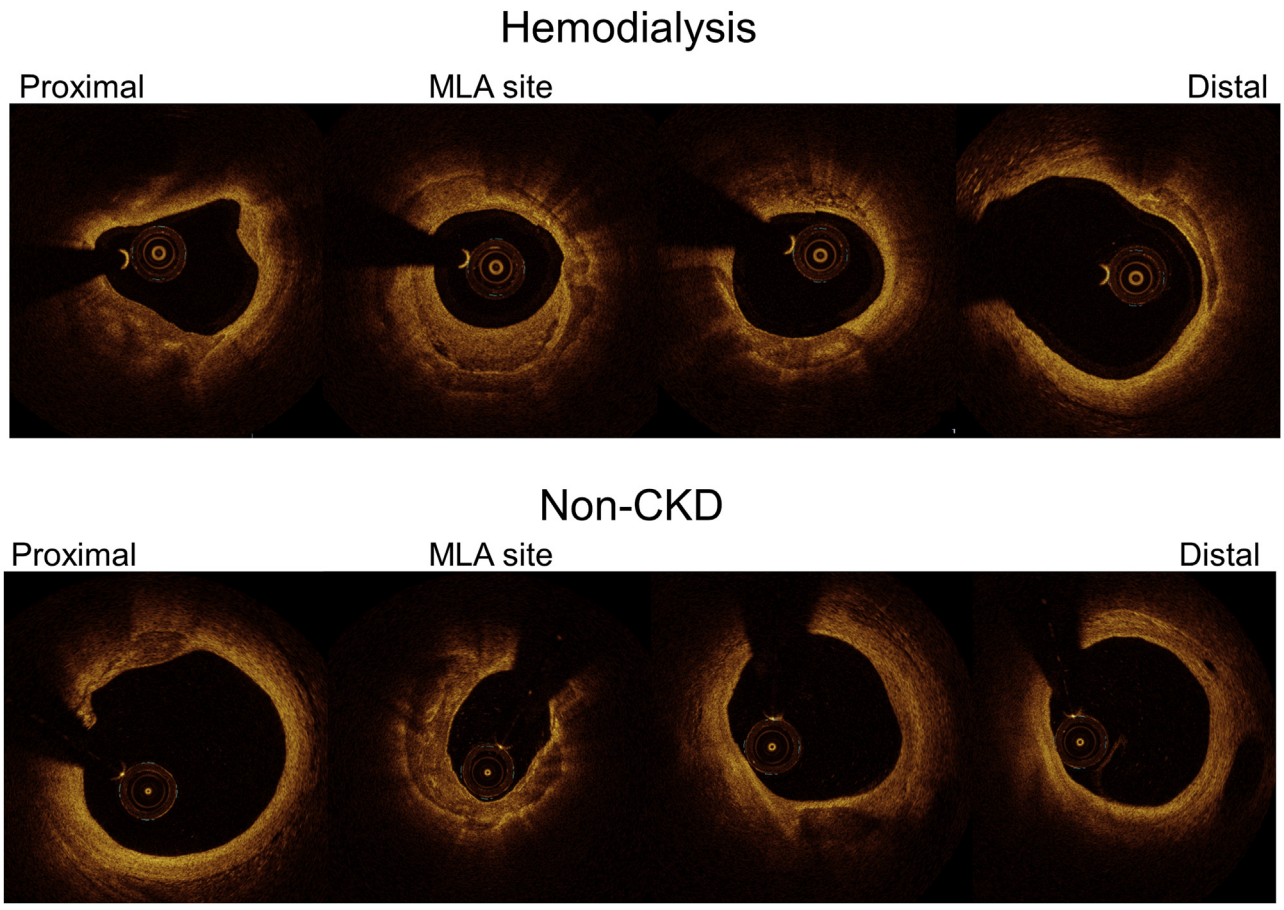

Figure 2. Distribution of calcification in representative cases. OCT frames of representative cases from the HD *(top panel)* and non-CKD *(bottom panel)* groups are compared. Both were left anterior descending arteries and contained effectively circumferential calcium at the MLA site. The main difference in calcium distribution between the 2 vessels was seen away from the MLA site where the vessel in the HD-dependent patient continued to contain greater calcification proximally and distally compared with the patient without CKD.

calcification in patients with CKD, with evidence of functional and prognostic relevance because of increased arterial stiffness.[29] The present study only showed a trend toward more medial calcification in culprit lesions in HD-dependent patients, likely owing to an overall underestimation of medial calcification because of the limited penetration of OCT through large calcific and lipidic plaques that were more common in the HD group.

A unique finding of the present study, especially in patients with HD, was the observation of an arc of calcium within thin intima. We postulate this pattern of thin intimal calcification to be distinct from classic atherosclerotic intimal calcification that commonly occurs as patchy clusters near lipid pools. The significantly higher prevalence in patients with HD suggests a mechanism linked either to chronic renal impairment or to the hemodynamic effects of HD. A potential clinical implication of thin intimal calcium is an overestimation of calcium burden when assessed by IVUS. Thin intimal calcium may contribute to the lack of correlation between increased coronary artery calcification scores with obstructive CAD and long-term outcomes in patients with CKD. Coronary artery calcification scores, as derived by computed tomography, has been shown to be an unreliable marker of the degree of coronary stenosis in uremic patients, with a sensitivity and specificity significantly lower than in the general population.[30]

Our study has a number of limitations. This study was observational with discretionary use of OCT. In addition, because of the avoidance of contrast media in patients with non−HD-dependent CKD, we could not perform comparison with non-CKD or ESRD patients. Also, our use of lipid arc may have underestimated the amount of lipidic plaque. Importantly, OCT imaging did not include the entire coronary artery length and included only a single vessel. Finally, the study population comprised patients with stable angina warranting invasive coronary angiography; therefore, these data cannot be extrapolated to asymptomatic patients or those presenting with acute coronary syndromes.

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