The clinical significance of medial arterial calcification in end-stage renal disease in women

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Medial arterial calcification is common in advanced kidney disease but its impact on cardiovascular disease is uncertain because imaging techniques used to date cannot reliably distinguish it from atherosclerotic calcification. We have previously shown that breast arterial calcification (BAC) is exclusively medial and is a marker of generalized medial calcification in end-stage renal disease (ESRD). Therefore, the presence of BAC on mammograms in 202 women with ESRD (mean duration 4.1 years) was correlated with cardiovascular events to determine the clinical significance of medial arterial calcification. BAC was found in 58% of the study participants and was significantly associated with age, diabetes, and ESRD duration. Both coronary artery (27 vs. 15%) and peripheral arterial disease (PAD; 19 vs. 4%) were more likely in patients with BAC but only the latter persisted after accounting for other factors (odds ratio 4.6; 95% confidence interval 1.2–15). In 142 women without clinical events before mammography, BAC was associated with a greater incidence of new PAD events (13 vs. 3%) but not coronary artery disease events (11 vs. 11%). Thus, BAC is strongly and independently associated with PAD in women with ESRD and may be predictive of clinical events. This suggests that medial arterial calcification is a clinically significant lesion that may contribute to the accelerated PAD in ESRD.

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KEYWORDS: cardiovascular disease; coronary artery disease; mammography; peripheral arterial disease; vascular calcification

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Calcification of the medial layer of arteries, also known as Monckeberg's arteriosclerosis, is commonly observed in patients with end-stage renal disease (ESRD). This lesion, which occurs almost exclusively in subjects with chronic kidney disease, diabetes, or advanced age,[1–5] is thought to be detrimental due to arterial stiffening.[6] However, its clinical significance is uncertain because imaging techniques currently used to detect vascular calcification in humans cannot reliably distinguish medial calcification from the distinctly different neointimal calcification associated with atherosclerosis,[7] which is also exacerbated in ESRD[8] and frequently coexists in the arterial beds that are examined. Although calcification of the coronary arteries, the aorta, or other large arteries correlates with cardiovascular outcomes in the general population and in ESRD patients,[6,9,10] this may merely be a manifestation of the atherosclerotic burden rather than a direct effect of calcification on outcomes.

We have previously shown that calcification of breast arteries is exclusively medial and is fourfold more prevalent on mammograms from women with ESRD compared with age- and diabetes-matched women without renal insufficiency.[11,12] This calcification correlates with calcification in peripheral arteries and can serve as a specific marker of generalized medial arterial calcification. Thus, breast arterial calcification (BAC) provides an opportunity to examine specifically the association of medial calcification with cardiovascular outcomes. We therefore correlated BAC on screening mammograms with coronary artery disease (CAD) and peripheral arterial disease (PAD) in women with ESRD in order to determine the clinical significance of medial arterial calcification.

RESULTS

A total of 202 women with mammograms after the onset of ESRD and adequate clinical follow-up were identified. The patients were almost entirely African American (95%). BAC was present in 58% of the patients and comparison of patients with and without BAC is shown in Table 1. Patients with BAC were older, more likely to be diabetic, and had a longer duration of ESRD. Smoking history did not differ between the groups. Serum parathyroid hormone was greater in patients with BAC but this did not quite reach statistical significance. Other parameters of mineral or lipid metabolism did not differ between the two groups. Medications

Table 1 | Characteristics of patients with and without BAC

	BAC	No BAC	P
n	118	84	
Age (years)	61.5 ± 11.4	53.9 ± 12.3	<0.001
ESRD duration (years)	4.6 ± 4.1	3.4 ± 3.9	0.016
Diabetes (%)	69	40	0.001
Smoking (%)	25	21	0.62
Adjusted serum Ca (mg/dl)	9.52 ± 0.81	9.58 ± 0.64 (83)	0.56
Serum phosphorus (mg/dl)	4.82 ± 1.47 (117)	4.78 ± 1.42 (83)	0.85
Serum PTH (pg/ml)	495 ± 556 (103)	362 ± 271 (71)	0.24
Serum LDL cholesterol (mg/dl)	82 ± 37 (105)	94 ± 39 (71)	0.04
Serum HDL cholesterol (mg/dl)	52 ± 18 (105)	48 ± 16 (71)	0.11
Serum triglycerides (mg/dl)	126 ± 69 (105)	150 ± 110 (71)	0.08

Abbreviations: BAC, breast arterial calcification; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone.
Parentheses indicate the number of samples when fewer than the entire cohort. Errors are s.d.

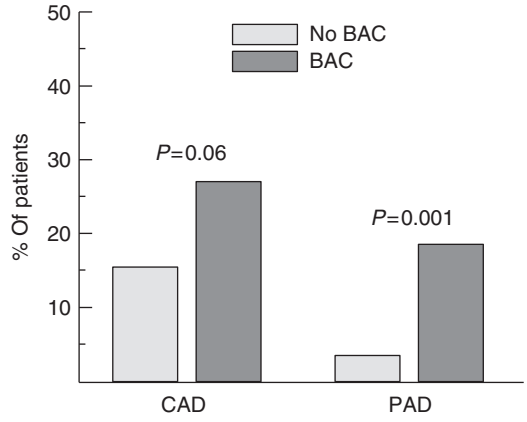

Figure 1 | Presence of coronary artery disease (CAD) or peripheral arterial disease (PAD) before and after mammography in end-stage renal disease women with or without breast arterial calcification (BAC).

Table 2 | Characteristics of patients with and without CAD

	CAD	No CAD	P
n	45	157	
Age	62.5 ± 12.0	57.2 + 12.2	0.013
Diabetes (%)	80	50	<0.001
BAC (%)	71	55	0.06
ESRD duration (years)	7.7 ± 5.0	6.3 + 5.0	0.024
Smoking (%)	31	21	0.17
Adjusted serum Ca (mg/dl)	9.69 ± 0.53	9.50 ± 0.79 (156)	0.12
Serum phosphorus (mg/dl)	4.88 ± 1.43	4.78 ± 1.50 (155)	0.69
Serum PTH (pg/ml)	446 ± 611 (39)	439 ± 416 (135)	0.93
Serum LDL cholesterol (mg/dl)	82 ± 43 (43)	88 ± 36 (133)	0.37
Serum HDL cholesterol (mg/dl)	51 ± 18 (43)	50 ± 17 (133)	0.82
Serum triglycerides (mg/dl)	130 ± 105 (43)	137 ± 83 (133)	0.65

Abbreviations: BAC, breast arterial calcification; CAD, coronary artery disease; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone.
Parentheses indicate the number of samples when fewer than the entire cohort. Errors are s.d..

Table 3 | Characteristics of patients with and without PAD

	PAD	No PAD	P
n	25	177	
Age	60.0 ± 11.6	58.1 + 12.4	0.46
ESRD duration (years)	7.7 ± 4.9	6.5 + 5.0	0.14
Diabetes (%)	92	52	<0.001
Smoking (%)	25	12	0.21
BAC (%)	88	54	0.001
Adjusted serum Ca (mg/dl)	9.73 ± 0.63	9.52 ± 0.76 (176)	0.21
Serum phosphorus (mg/dl)	4.77 ± 1.59	4.81 ± 1.43 (175)	0.90
Serum PTH (pg/ml)	455 ± 596 (24)	439 ± 443 (175)	0.73
Serum LDL cholesterol (mg/dl)	86 ± 40 (24)	87 ± 38 (152)	0.91
Serum HDL cholesterol (mg/dl)	50 ± 16 (24)	50 ± 18 (152)	0.94
Serum triglycerides (mg/dl)	125 ± 67 (24)	137 ± 91 (152)	0.54

Abbreviations: BAC, breast arterial calcification; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral arterial disease; PTH, parathyroid hormone.
Parentheses indicate the number of samples when fewer than the entire cohort. Errors are s.d.

related to mineral metabolism were not included as they changed frequently and the exposure could not be accurately quantified.

Owing to the difficulty in determining the temporal relationship between BAC and CAD or PAD, two different analyses of clinical events were performed. The primary analysis included events at any time before or after the mammogram, while the secondary analysis was limited to clinical events after the mammogram in women who did not have clinical events before the mammogram and who had at least 1 year of clinical follow-up in the medical record.

In the primary analysis (Figure 1), CAD events were less than twofold more likely to occur in women with BAC than in patients without BAC but this was of borderline significance. However, there was a significant fivefold higher occurrence of PAD events in patients with BAC. Comparisons of women with and without clinical events are shown in Tables 2 and 3, with logistic regression models presented in Table 4. Age, ESRD duration, and diabetes were significantly associated with CAD events, with borderline significance for BAC. In a logistic regression that included BAC, diabetes, smoking, ESRD duration, and age, only diabetes and ESRD duration were significant determinants of CAD events, and there was no association with BAC. In the case of PAD events

Table 4 | Multivariate logistic regressions for CAD and PAD

	CAD		PAD	
	OR	95% CI	OR	95% CI
Age	1.03	0.99–1.06	0.97	0.93–1.02
ESRD duration (years)	1.10	1.02–1.19	1.04	0.95–1.15
Diabetes	3.86	1.58–9.45	11.6	2.40–55.7
Smoking	2.24	0.99–5.08	0.37	0.10–1.39
BAC	1.06	0.48–2.38	4.56	1.20–17.3

Abbreviations: BAC, breast arterial calcification; CAD, coronary artery disease; CI, confidence interval; ESRD, end-stage renal disease; OR, odds ratio; PAD, peripheral arterial disease.
The overall χ^2-square was 24.1 for CAD ($P<0.0002$) and 29.2 for PAD ($P<0.00001$).