JACC: ADVANCES VOL. 2, NO. 9, 2023

EDITORIAL COMMENT

Medial Artery Calcification

Is it a Disease, a Marker, or a Prognostic Predictor?*

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Arterial calcifications can be described as intimal artery calcification (IAC), internal elastic lamina-artery calcification (IEL-AC), or medial artery calcification (MAC).[1] This "classification" relies more on pathology than on imaging (including high resolution intracoronary techniques) which often does not distinguish the different topographies also due to the common overlapping of IAC and MAC and the scarce clinical use of the distinction.

Decades of research on arterial calcifications have focused on IAC in atherosclerosis, which remains the most common substrate of arterial calcifications, predictors of cardiovascular morbidity and mortality as well as potential substrate of major acute plaque events.[2] However, increasing attention to MAC has emerged in recent years, supported by a spectrum of evidences ranging from rare monogenic diseases in newborns and children[3] to pathology, mainly in patients with chronic kidney disease (CKD) and diabetes, and by the evidence that the loss of elasticity of the media and the increase in arterial stiffness severely affect blood pressure levels especially when MAC is multidistrict, irrespective of the luminal narrowing.[4]

In CKD up to end-stage renal disease stage 5 (when dialysis and renal transplantation are needed), medial calcification is a consolidated cause of extensive arterial calcifications that can involve the media or intima, or both. All arterial vessels can be affected, including the aorta, coronary, brain, and peripheral arteries.[5] The severity as well as duration of the disease are important determinants of the arterial calcium burden and progression of the calcification.[1,4] Although aging may contribute, even children and young adults with CKD or on dialysis develop vascular calcification.[6]

In this issue of *JACC: Advances*, Kato and Coll[7] report the results of an extensive pathologic study of arterial calcifications in 77 lower extremity arteries, both above-knee (superficial femoral artery and popliteal artery) and below-knee (anterior tibial artery, posterior tibial artery, and fibula artery), from 36 patients (21 CKD in hemodialysis and 5 CKD of 15 nonhemodialysis controls) who underwent autopsy or lower limb amputation. The authors found: 1) higher prevalence and burden of intimal and medial calcification in the hemodialysis patients than the nonhemodialysis patients; 2) hemodialysis as an independent risk factor for medial calcification in below-knee lesions; 3) bone formation to be more common in the hemodialysis patients; 4) more advanced intimal atherosclerotic above-knee lesions in the hemodialysis-than the nonhemodialysis patients; and 5) calcified nodules more common in the hemodialysis patients than in nonhemodialysis patients but a similar prevalence of plaque rupture.[7] Although the findings are not new, one of the merits of the study is the distinct description of IAC from MAC, which may occur as isolated lesion even in the absence of significant intimal lesions. Whereas IAC has always been the target of clinical and diagnostic attention in vivo and in pathological studies, isolated, nonobstructive MAC has often been considered a condition without clinical relevance especially when it occurs in patent arteries.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100652

TABLE 1 Major Acquired, Genetic, and Drug-Induced Causes of Medial Artery Calcification

Acquired
Atherosclerosis
CKD (dialysis and non dialysis) → secondary hyperparathyroidism
Noninsulin-dependent diabetes mellitus
Inherited, monogenic [Gene symbol, MIM #, Inheritance, *Gene*]
Generalized arterial calcification of infancy [GACI1; #208000; AR; *ENPP1*]
Generalized arterial calcification of infancy [GACI2; #614473; AR; *ABCC6*]
Pseudoxanthoma elasticum [PXE; #264800; AR; *ABCC6*]
Calcification of joints and arteries [ACDC or CALJA; #211800; AR; *NT5E*]
Idiopathic basal ganglion calcification [IBGC1; #213600; AD; *SLC20A2*]
Idiopathic basal ganglion calcification [IBGC4; #615007; AD; *PDGFRB*]
Idiopathic basal ganglion calcification [IBGC5); #615483; AD; *PDGFB*]
Idiopathic basal ganglion calcification [IBGC6; #616413; AD; *XPR1*]
Hutchinson-Gilford progeria syndrome [HGPS; #176670; de novo; *LMNA* (premature ATS)]
Hyperphosphatemic familial tumoral calcinosis [HFTC) [#211900], AR, *GALNT3*]
Primary hydroxaluria I, II, III, [HPI; HPII, HPIII; AR; AGXT, *GRHPR, HOGA1*]
Singleton-Merten syndrome 1 [SGMRT1; #182250; AD; *IFIH1*]
Singleton-Merten syndrome 2 [SGMRT2; #616298; AD; *DDX58*]
Keutel syndrome [KTLS; #245150; AR; *MGP*]
Gaucher disease, subtype IIIC [GD3; #231005; AR; *GBA*]
Drugs
Warfarin (inhibits the carboxylation of matrix gamma-carboxyglutamic acid (Gla) protein).
Glucocorticoids
Other causes, eg, uremic tumoral calcinosis (both benign and malignant conditions)

AD = autosomal dominant; AR = autosomal recessive; CKD = chronic kidney disease.

Isolated MAC is a distinct pathological entity including monogenic, acquired (multifactorial or oligofactorial) diseases and pharmacological causes. The nosology setting of MAC is well illustrated by the spectrum of diseases ranging from monogenic arterial ectopic calcification syndromes in children (**Table 1**) to end-stage renal disease in both adults and children and non insulin-dependent diabetes mellitus[8] in adult/old patients. In these latter forms, imaging commonly used in vivo such as angio-computed tomography may not distinguish between MAC and IAC. Vice versa, in newborns, when the reactive intimal disease is still absent, calcifications can be exclusively assigned to IEL and media (eg, GACI1, GACI2, ACDC/CALJA, and PXE). These monogenic models show different calcific phenotypes and the involvement of arteries in different districts. PXE, affecting skin, eyes, and arteries, is characterized by fragmentation and calcification along the length of the IEL, followed by extensive medial and intimal calcification.[9] ACDC (or CALJA) causes arterial dilation, tortuosity, and vascular calcification in lower extremity arteries; the substrate is elastic fiber fragmentation followed by calcifications.[10] In GACI, the extensive deposition of hydroxyapatite starts in the inner elastic lamina of medium- and large-sized arteries.[11]

In acquired arterial calcifications, typically in adult/old patients with CKD or diabetes, MAC may coexist with IAC. MAC is very common in old patients with critical limb ischemia: medial calcification was present in 170 of 239 (71.1%) large arteries investigated by Narula and Coll.[12] However, also children on dialysis who are unlikely to have intimal disease, rapidly develop medial vascular calcification[13]; these human models offer the possibility of differentiating the structural substrates and pathogenic mechanisms underlying MAC and IEL-AC from those of IAC, a diagnostic goal to be pursued now that the distinct conditions can be precisely assigned to different causes. The implications are important for developing treatments targeting ectopic arterial calcification, which may require the identification of individual patient causes and risk factors in individual patients.

The evidence that IAC and MAC may coexist but may also stand alone suggests that their pathogenesis can occur independently and on different substrates. It is therefore potentially useful to understand the domains in which IAC and MAC are placed as markers of arterial disease. IAC is certainly an essential marker of clinical and subclinical atherosclerosis, at the level of all arterial districts (coronary, carotid, and cerebral). If Monckeberg medial calcification (MAC of small- and medium-sized arteries) is also included in the overall MAC spectrum, the clinical warning about cardiovascular risk deriving from medial calcifications expands. Irrespective of the mechanisms ad extension, MAC seems to carry a worse prognosis and is supported by a different pathogenesis and different risk factors from those associated with IAC.[5] MAC is also a strong marker of cardiovascular events in non-insulin-dependent diabetes unrelated to other cardiovascular risk factors, supporting the hypothesis that reduced arterial elasticity may contribute to clinical manifestations of diabetic macroangiopathy.[1,4,8]

Most imaging studies attempting to distinguish IAC and MAC are in CKD patients with arteriopathy of the lower extremities and are based on noncontrast computed tomography scanning. Ex vivo pathology-intravascular imaging studies strongly contribute to expanding the characterization of MAC and IAC whose distinction remains especially difficult when the calcification borders between media and intima overlap.[14] The addition of noninvasive arterial testing parameters can improve sensitivity and provide

detailed profiles of the anatomy of the calcific arterial lesions.[15] Multiparametric in vivo characterization could better support novel treatment strategies for peripheral artery disease such as endovascular lithotripsy[16] whose applications can go beyond luminal gain and support the feasibility of other cardiovascular procedures such as transcatheter aortic valve implantation.[17] The question is whether imaging in vivo should be asked to distinguish MAC from IAC, especially when IAC is extensive and expands to the tunica media that is often thinned or lost in severely remodeled atherosclerotic plaques.

Overall, the spectrum of knowledge on ectopic mineralization disorders affecting arteries is expanding due to advanced diagnostics, both imaging and molecular, and deep phenotyping of calcific arterial lesions. In this context, peripheral artery disease in dialysis patients remains one of the clinical areas deserving more efforts to offer treatment alternatives to amputations. While waiting for future medication-based strategies eventually benefiting from ongoing studies in monogenic diseases, the goal of distinguishing in vivo IAC and MAC is a novel challenge with diagnostic, prognostic, and management implications in an expanding clinical setting.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Imaging-pathology correlation research of atherosclerotic plaques is supported by INERSTRAT-CAD FRRB of Regione Lombardia, Italy, RCR-2022-23682288 (to Dr Arbustini) from the Italian Ministry of Health (to Dr Arbustini), and CLI Foundation (Rome), Italy (to Dr Prati). Dr Bozzani has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS artery, calcification, tunica media