Arteriosclerosis, Bone Biology, and Calcitropic Hormone Signaling: Learning the ABCs of Disease in the Bone-Vascular Axis

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Cardiovascular disease and musculoskeletal frailty are prominent in our patients with CKD,1 synergistically enhanced by concurrent diabetes that drives ESRD in approximately 40% of patients receiving RRT.2 As London et al. first demonstrated,3 the presence and extent of arterial calcium accrual in patients undergoing dialysis, be it in atherosclerotic intimal disease or medial artery calcification, convey significant morbidity and mortality risk.3 Importantly, these researchers established that individuals with low-turnover bone disease were at greatest risk for extensive vascular calcium load.4 Conversely, in community-dwelling older men, the presence of peripheral arterial disease (PAD), routinely defined as an ankle-brachial blood pressure ratio index (ABx) of <0.9 or >1.3, conveys increased risk of hip fracture.5 While atherosclerotic calcification lowers ABx with vessel occlusion, the medial arterial calcification of diabetes and CKD results in elevated ABx values and equally significant clinical consequences, including limb ischemia via vascular stiffening,6–8 thus, vascular calcium metabolism and musculoskeletal health have emerged as being physiologically linked.8,9 Consistent with this, women with lower bone mineral density have greater coronary artery calcification scores,10 and this portends greater probability of future coronary events.11,12 Guzman applied tibial artery calcification scoring to diabetic and non–diabetic patients with PAD.13 Intriguingly, the tibial artery calcification score receiver-operating characteristics outperformed the current clinical standard of the ABx in predicting future progression to critical limb ischemia and lower-extremity amputation.13 Thus, the appellation CKD–mineral and bone disorder was established1 to emphasize the endocrinology, integrative physiology, and therapeutic implications of disordered bone-vascular interactions that cause cardiovascular and musculoskeletal disease in CKD. However, a better understanding of these interactions is clearly needed in all clinical contexts.

In the present issue of JASN,14 London and colleagues once again blaze the trail by illuminating the physiologic relationships between osteoblast bone anabolic function, parathyroid hormone (PTH) levels, and clinically relevant PAD. In this cohort of 65 well phenotype patients receiving RRT, approximately one third had elevated ABx values as consistent with prevalent medial artery calcification, 17% had reduced ABx values indicating atherosclerotic calcification, and half possessed normal indices.14 The authors then analyzed the relationship between intact PTH levels and direct measure of osteoblast anabolic function by dynamic bone histomorphometry, comparing individuals with and without PAD. They reasoned that the slope of the regression relationship between PTH—the prototypic bone anabolic hormone—to direct histologic measures of osteoblast anabolic function (dLS/BS) would provide an index of PTH sensitivity.14 Via this enlightened analysis, the authors demonstrated that patients with PAD exhibited a significantly shallower slope in the bone formation–PTH relationship; this indicates a reduced bone anabolic response at prevailing PTH tone in those individuals with PAD (Figure 1). Because PTH exerts important bone anabolic actions in part via the inhibition of osteoprogenitor apoptosis,15 independent assessment of the PTH–osteoblast surface relationship also revealed a distinctly shallower slope in patients with PAD.14 These relationships persisted after adjustment for C-reactive protein as an index of inflammation. Most important, in stepwise regression dLS/BS—the direct histologic measure of osteoblast anabolic function—continued to significantly contribute, along with inflammation and RRT duration, to the risk for PAD
resistant to the arterial calcification, fibrosis, and vascular stiffness arising from diabetes. Thus, the relationships elucidated by London and colleagues between skeletal PTH resistance and PAD probably also reflect the global insufficiency in PTH1R signaling that arises in uremia, wherein reduced VSMC PTH1R signal transduction directly predisposes to arteriosclerotic disease.9 On the basis of the recent data of Raison et al, paracrine PTH1R activation by PTHrP in conduit arteries is likely to be significantly perturbed in CKD in ways that impair vasodilatation, vascular structure, and tissue blood flow. Unfortunately, no direct measure currently exists to quantify or establish normal vascular PTH1R signaling tone or sensitivity. Once such a measure is identified, however, it will be possible to assay vascular PTH1R pharmacokinetic-pharmacodynamic relationships, similar to London’s skeletal anabolic–PTH “modulus” (Figure 1), and thus optimize vascular PTH1R signaling tone to maintain arterial structure and function with diabetes, aging, and uremia.

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**DISCLOSURES**

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**REFERENCES**


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**Figure 1.** PAD in CKD is associated with reductions in the skeletal anabolic–PTH “modulus.” In the current issue of JASN, London and colleagues establish that compared with those without PAD, patients with PAD diagnosed by ABIx exhibit a regression relationship between osteoblast anabolic function and intact PTH that characterizes reduced PTH sensitivity.14 This elegant analysis frames for the first time the functional endocrine relationships between PTH and the bone-vascular axis in humans. PAD emerges as a PTH-regulated cause, consequence, or concomitant of the reduced anabolic state of the skeleton.9 See text for details. ABI, ankle-brachial index; dLS/BS, doubled labeled surface to bone surface ratio; Ob.S/BS, osteoblast surface to bone surface ratio.


See related article, “Ankle-Brachial Index and Bone Turnover in Patients on Dialysis,” on pages 476–483.