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

Dwight A. Towler
Sanford-Burnham Medical Research Institute Diabetes & Obesity Research Center, Florida Hospital, Translational Research Institute for Metabolism and Diabetes, Division of Endocrinology, Diabetes and Metabolism at University of Florida, Orlando, Florida

Published online ahead of print. Publication date available at www.jasn.org.

Cardiovascular disease and musculoskeletal frailty are prominent in our patients with CKD, synergistically enhanced by concurrent diabetes that drives ESRD in approximately 40% of patients receiving RRT. As London et al. first demonstrated, 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. Importantly, these researchers established that individuals with low-turnover bone disease were at greatest risk for extensive vascular calcium load. Conversely, in community-dwelling older men, the presence of peripheral arterial disease (PAD), routinely defined as an ankle-brachial blood pressure index ratio (ABIx) of <0.9 or >1.3, conveys increased risk of hip fracture. While atherosclerotic calcification lowers ABIx with vessel occlusion, the medial arterial calcification of diabetes and CKD results in elevated ABIx values and equally significant clinical consequences, including limb ischemia via vascular stiffening; thus, vascular calcium metabolism and musculoskeletal health have emerged as being physiologically linked. Consistent with this, women with lower bone mineral density have greater coronary artery calcification scores, and this portends greater probability of future coronary events. Guzman applied tibial artery calcification scoring to diabetic and non-diabetic patients with PAD, Intriguingly, the tibial artery calcification score receiver-operating characteristics outperformed the current clinical standard of the ABIx in predicting future progression to critical limb ischemia and lower-extremity amputation. Thus, the appellation CKD–mineral and bone disorder was established 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, 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 ABIx values as consistent with prevalent medial artery calcification, 17% had reduced ABIx values indicating atherosclerotic calcification, and half possessed normal indices. 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. 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, independent assessment of the PTH–osteoblast surface relationship also revealed a distinctly shallower slope in patients with PAD. 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 diagnosis. Thus, the authors conclude that in non-diabetic patients on RRT, PAD is associated with lower turnover bone disease and significant reductions in the skeletal anabolic response.

Why is this report so important? This elegant analysis frames for the first time the functional endocrine relationships between PTH and the bone-vascular axis in humans. PAD in this setting emerges as a PTH-regulated cause, consequence, or concomitant of the reduced anabolic state of the skeleton. As Fadini et al. highlight, the skeleton elaborates multiple cell types that circulate and affect vascular structure and function, including calcification. Thus, skeletal resistance to PTH may give rise to altered bone-derived cellular...
or endocrine\textsuperscript{18} cues that affect cardiovascular function. Given that osteoblast PTH/PTHrP receptor (PTH1R) signaling directly controls the size of the hematopoietic niche,\textsuperscript{19} this mechanism of bone-vascular interaction is no doubt an important contributor to arteriosclerotic disease. Resistance to PTH may also limit vascular remodeling, realignment, and perfusion necessary for bone health.\textsuperscript{20–22} However, the vascular smooth muscle cell (VSMC) also expresses the PTH1R and is a direct target of both PTHrP and PTH activation and tachyphylaxis.\textsuperscript{23} In vitro\textsuperscript{24} and in vivo,\textsuperscript{25,26} activation of the PTH1R reduces VSMC-directed arterial calcification. Indeed, we demonstrated that a transgenic mouse expressing the constitutively active Janssen PTH1R variant in VSMC is resistant to the arterial calcification, fibrosis, and vascular stiffness arising from diabetes.\textsuperscript{25} 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,\textsuperscript{27} wherein reduced VSMC PTH1R signal transduction directly predisposes to arteriosclerotic disease.\textsuperscript{9} On the basis of the recent data of Raison et al,\textsuperscript{28} 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.

ACKNOWLEDGMENTS

D.A.T. is supported by HL069229, HL081138, and HL114806 from the National Institutes of Health, the Sanford-Burnham Medical Research Institute, and the Florida Hospital Translational Research Institute for Metabolism and Diabetes.

REFERENCES


DISCLOSURES

D.A.T. serves as a consultant for Merck & Co., Daiichi-Sankyo, and Eli Lilly.


