Calcitropic Hormones and Arterial Physiology: “D”-lightful Insights

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In this issue of JASN, London et al. (11) again advance our understanding of human arterial physiology and calcitropic hormones, highlighting the importance of adequate vitamin D nutrition to maintenance of vascular structure and function in ESRD (8). As expected (10), age and hypertension strongly contribute to risk for reduced arterial compliance, evidenced by reduced brachial artery (BA) distensibility, increased aortic pulse wave velocity (PWV), and diminished flow-mediated dilation (FMD). As a sensitive index of perturbed intimal-medial signaling, reduced FMD identifies and confirms dysfunction in arterial physiology (10). The BA distensibility relationship also is important; this assessment of arterial compliance is not altered significantly by blood’s rheologic properties and, like PWV, quantifies how vascular material and geometric properties integrate to determine arterial stiffness (12,13). In ESRD, therefore, aberrancies in endothelial-medial signaling (FMD) and integrated arterial mechanical properties (PWV, BA) coexist. It is intriguing that vitamin D nutritional status, reflected by serum 25-hydroxyvitamin D (25-OHD) levels, provided substantial additional information (11). Even after accounting for the protean influences of age and BP, approximately 20% of the total variance in arterial compliance and approximately 30% of FMD response was related to the prevailing vitamin D nutritional status—positively correlated with healthy endothelial and arterial mechanical physiology (11).

What mechanisms might mediate beneficial actions of vitamin D on arterial physiology? The answer is not straightforward because of (1) the individual contributions of wall thickness, matrix composition, and neuroendocrine control of vascular smooth muscle cell (VSMC) contractility that determine net vascular compliance (13); (2) the biphasic effects of vitamin D “nutrition versus toxicity” on cardiovascular health (14–16); and (3) the differential actions—direct (endothelial, VSMC) versus indirect (endocrine, immunomodulatory)—that mediate vitamin D’s vasculotropic actions (14). In VSMC, cell-autonomous activation of the vitamin D receptor (VDR) is pro-calcific and therefore deleterious to vascular compliance (17,18). In vitro, the potent VDR agonist calcitriol (1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]) promotes VSMC calcification in part via PTH-related protein (PTHrP) signals that limit alkaline phosphatase induction (17,18) and thereby collapse the paracrine inorganic pyrophosphate mineralization defense mechanism (5) (Figure 1). Calcitriol promotes medial artery calcification in vivo (19); whether this requires suppression of
vascular PTHrP is unknown. Moreover, toxic levels of vitamin D and calcitriol elevate serum calcium and phosphate in vivo—potent stimuli for VSMC production of pro-calcific matrix vesicles (21,22).

How, then, might adequate vitamin D nutrition improve arterial physiology? From the traditional endocrine viewpoint, this might reflect amelioration of secondary hyperparathyroidism; integrated circadian production of PTH may be lower with improved vitamin D nutrition. The PTH/PTHrP receptor is functionally active on both endothelium and VSMC (23). Whereas acute PTH administration is vasodilatory (24), the chronically elevated PTH profile of primary and secondary hyperparathyroidism promotes hypertension (25,26). In patients with primary hyperparathyroidism, FMD is impaired but improves after surgical therapy (25,26). However, the few well-done studies indicate that hyperparathyroidism per se does not alter arterial PWV (again, index of material and geometric properties) (25,26). Therefore, in ESRD, the concomitant deficiencies in endothelial and integrated mechanical properties that are associated with vitamin D deficiency probably are not due simply to undetected, exaggerated hyperparathyroidism.

Could adequate vitamin D nutrition, by maintaining normal bone formation and skeletal mineralization (27,28), reduce vascular calcification and vascular stiffness? This is an attractive hypothesis, based on London’s previous study that demonstrated that low rates of bone formation are inversely related to the extent of arterial calcium load (9). In this study, however, no significant connection could be drawn between vitamin D nutritional status and clinical extent of calcific vasculopathy—even though arterial compliance was reduced significantly (11). This may relate to limitations in the available method used to quantify vascular calcium deposition. London’s method implements nonparametric scoring of the anatomic extent of arterial calcification, without quantifying mineral mass. In the slightly larger study mentioned, this method was capable of establishing inverse relationships between osteoblast-dependent bone formation and arterial calcification (9). However, other specialized methods—such as phantom-calibrated arterial mineral mass measurements using summed computed tomography (CT) numbers from thresholded multidetector CT scans—can be used to robustly quantify calcium content in any arterial segment (29,30). Mineral mass measurement has advantages in that it is less biased (29,30) and is a continuous variable (29), like measures of vascular compliance. Demer unambiguously demonstrated that arterial calcification does contribute to vessel wall stiffness on direct assessment of balloon catheter pressure-volume relationships (31). Therefore, after adjustment for age, the present study may have been inadequately powered to identify relationships between 25-OHD status and arterial calcium load with the available noninvasive metrics and appropriately conservative nonparametric statistical testing; the $P$ value for the nonsignificant trend was 0.15 (11).

It remains probable, however, that effects of vitamin D insufficiency/deficiency on vascular stiffness are partially independent of vascular calcium load. It is intriguing to speculate that 25-OHD–dependent changes in the renin-angiotensin-al-

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**Figure 1.** Working model outlining of biphasic actions of vitamin D on vascular compliance. Nutritional vitamin D plays an important role in limiting renin-angiotensin-aldosterone axis– and cytokine-dependent mural inflammation. Vitamin D toxicity exerts both direct and indirect actions that enhance arterial calcification. ALP, alkaline phosphatase; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; PTHrP, parathyroid hormone–related protein; VSMC, vascular smooth muscle cell.
dosterone axis (32) may mediate these effects, independent of changes in BP (Figure 1). Although many patients studied were treated with angiotensin receptor blockade (ARB), these drugs were discontinued 10 d before arterial measurements. In addition to exhibiting pressor actions, angiotensin II (AngII) drives adventitial oxidative stress, cardiovascular fibrosis, and outward arterial remodeling. As robustly demonstrated by Rey and Pagano (33), AngII circumferentially activates Nox2-based arterial superoxide production in adventitial myofibroblasts. Along with medial thickening and fibrosis, an AngII-dependent adventitial-to-medial superoxide gradient antagonizes vasodilatory intimal-to-medial nitric oxide signals via chemical nullification that forms peroxynitrite (33). Adventitial inflammation also may be enhanced with vitamin D insufficiency. Vitamin D is immunomodulatory by enhancing the anti-inflammatory IL-10–to–IL-12 ratio (34). Inflammatory cytokine profiles are improved significantly in patients who have heart failure and receive supplementation with vitamin D (35). Moreover, in patients without ESRD, atherosclerotic peripheral vascular disease is associated with vitamin D deficiency (36). Therefore, vascular insult that arises from vitamin D insufficiency/deficiency may reflect exaggerated arterial oxidative stress and mural inflammation.

At this point, I caution against drawing too many conclusions on the basis of serum calcitriol levels and the full acceptance 1,25(OH)₂D₃ levels as an index of "hormonal" status (11). In the absence of ESRD, serum 1,25(OH)₂D₃ levels most often reflect responses to PTH (14) (notable exceptions exist in granulomatous disease, lymphoma, and calcitriol intoxication). In the presence of documented vitamin D deficiency with intact renal parenchyma, serum 1,25(OH)₂D₃ levels are related inversely with serum 25-OHD (37); 1,25(OH)₂D₃ levels are elevated as a result of secondary hyperparathyroidism that drives renal 1-α hydroxylation of the measurably reduced but marginally available serum 25-OHD (37). In immobilized patients with intact renal function, uncoupling of bone resorption from bone formation elevates serum calcium levels, with suppression of PTH production and secondary decreases in 1,25(OH)₂D₃ levels (38). However, as shown (11), in the presence of ESRD—the absence of intact renal parenchyma—serum 1,25(OH)₂D₃ levels directly correlate with serum 25-OHD via nonrenal 1-α hydroxylation. In London’s study (11), patients were naïve to treatment with vitamin D agonists; some contribution from calcitriol treatment of secondary hyperparathyroidism is anticipated in many patient populations. An emerging endocrine concept emphasizes that 25-OH-D is a bioactive precursor for more potent VDR agonist production within the parenchyma of multiple, nonrenal target tissues, including bone (39). This is akin to testosterone as the bioactive precursor for dihydrotestosterone and estradiol in target tissues. For 25-OHD, the inflamed endothelium (40) and activated cells of the monocyte/macrophage lineage (41) are the most studied nonrenal targets for 1,25(OH)₂D₃ synthesis (39). The regulated contributions of these nonrenal sources to serum 1,25(OH)₂D₃ levels and vitamin D signaling in vascular health are not known.

Much work remains to be done. Preclinical models should be studied for consequences of vitamin D deficiency on vascular inflammation, matrix remodeling, and arterial oxidative stress—and the contributions of the renin-angiotensin-aldosterone axis to the beneficial vascular effects of adequate vitamin D nutrition. Histomorphometric and biochemical techniques that spatially resolve arterial tunic inflammation and oxidative stress (42) should be used to assess vascular effects of vitamin D insufficiency. Moreover, Cre-Lox technology (43) could be applied to evaluate how cell-autonomous VDR signaling in VSMC, macrophages, T cells, and endothelial cells contributes to vascular physiology and pathobiology in murine models. As done with selective estrogen receptor modulators, novel VDR ligands should be evaluated for “modulator” activity—the ability to function as agonists in some tissues but antagonists in others—and encompass the arterial vasculature as a relevant target tissue. In humans, the ability of ergocalciferol or cholecalciferol to improve arterial compliance should be tested—stratified for the presence or absence of vitamin D analog therapy for secondary hyperparathyroidism. Ultrasound assessment of intimal-medial wall thickness should be assessed concomitantly; this geometric property also worsens vascular stiffness independent of vessel material properties (13). These longitudinal studies could be enhanced significantly by quantitative measures of arterial calcium mass using multidetector CT; such a method would quantify better the extent to which changes in vascular calcium metabolism may contribute to vitamin D nutritional regulation of arterial compliance. All in all, this important article significantly extends London’s elegant studies (see reference [8] for review)—the seminal body of work that establishes how calciotropic hormones are intimately related to impaired arterial physiology and cardiovascular mortality of ESRD. Assiduous attention and implementation of these lessons in vascular endocrinology will be of tremendous benefit to our patients.

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See the related article, “Mineral Metabolism and Arterial Functions in End-Stage Renal Disease: Potential Role of 25-Hydroxyvitamin D Deficiency,” on pages 613–620.