Bone–Vascular Axis in Chronic Kidney Disease: A Reality?

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Chronic kidney disease (CKD) is characterized by changes in mineral metabolism associated with alterations of its hormonal regulation and various forms of bone disease. In the past, these associations focused attention on the kidney–bone axis. The last decade has seen renewed interest on interactions among mineral metabolism disorders and extraosseous and cardiovascular calcifications observed in CKD or end-stage renal disease (ESRD). Vascular calcification is an active process similar to bone formation that implicates a variety of proteins involved in bone and mineral metabolism (1,2) and is considered part of a systemic dysfunction defined as CKD–mineral and bone disorder (3). Growing evidence linking bone with different functional and structural characteristics of the arterial tree has contributed to developing the concept of the bone–vascular axis (4).

The first observations suggesting the existence of the bone–vascular axis were the frequent associations of osteoporosis and atherosclerotic vascular calcifications observed in postmenopausal women (5–7). Longitudinal population-based studies revealed a relationship between the progression of vascular calcifications and bone demineralization, and others were identified between bone mineral density (BMD) and aortic or central artery calcifications (6), or coronary arteries in type 2 diabetes (8). The osteopenia–osteoporosis association was also linked with arterial functional indexes, such as aortic stiffness and interactions independent of calcifications, suggesting broader biologic interplay (9,10).

Relationships between bone and vascular modifications were also observed in CKD and ESRD patients. In dialysis patients, coronary artery calcification score was found to be inversely correlated with vertebral bone mass (11,12). In addition, a high systemic arterial calcification score combined with bone histomorphometry suggestive of low bone activity was observed in hemodialysis patients (13,14). Arterial stiffening and low spine BMD or calcaneal osteopenia were significantly associated in CKD and hemodialysis patients (15–17).

In the present issue of the *Journal*, Adragao *et al.* (18) provide new evidence linking altered bone metabolism to coronary calcifications in patients with stage-5 CKD on hemodialysis. In their cross-sectional study performed on 38 hemodialyzed patients, they analyzed the relationships between bone biopsy parameters (bone volume/total volume, bone formation rate/bone surface, and activation frequency) and coronary calcifications determined by multislide computer tomography. Their principal conclusion was that low bone volume is associated with more coronary calcifications, whereas histomorphometric parameters of bone turnover were independent of coronary calcifications.

Their results complete those of Barreto *et al.* (12), who found a negative correlation between coronary calcifications and trabecular bone volume or its thickness. The absence of correlations between histomorphometric indexes of bone turnover and coronary calcifications differ from reports by London *et al.* (13,14), who found an association between systemic arterial calcifications (aorta and the main peripheral arteries) and indexes of low bone turnover, but not trabecular volume. One important difference between these publications resides in the arterial territories analyzed and the relationships of the different bone changes (bone volume, osteoblasts number, or tetracycline labeling), which do not necessarily reflect the same mechanisms. Adragao *et al.* (18) studied coronary artery calcifications, whereas London *et al.* (13,14) examined the aorta and systemic arteries.

Researchers investigating the arterial system should keep in mind the marked heterogeneity of the arterial tree (19). Blood vessel formation recruits cells of different origins whose components are derived from vascular smooth muscle cells (VSMC) and pericytes. VSMC is a tissue generated by at least seven unique and nonoverlapping sources, and different vessels or even segments of the same vessel, are composed of VSMC arising from distinct progenitors that respond in origin-specific ways to different common stimuli. The observations linking arterial calcifications to bone usually concern the aorta or large conduit arteries and coronary arteries. Whereas the coronary arteries are derived from proepicardium, the aorta's origin even more complex. The ascending aorta and aortic arch originate from neural crest, the thoracic aorta (athero-resistant) is derived from somites, and splanchnic mesoderm gives rise to the abdominal aorta (athero-susceptible). The boundaries of these different segments are sharp and are associated with quite different responses to common risk factors. Arterial bed-specific susceptibilities were documented in human studies showing that despite common risk factors, each analyzed vascular segment (coronary arteries, ascending aorta and its major arteries, thoracic aorta at the renal artery level, and terminal aorta and femoral arteries) mounted its own distinct response to atherogenesis (20).

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The eventual biologic link between vascular calcifications and bone changes is certainly part of the aging process, but in many studies, these bone–vascular associations remained significant after adjustment for age, which suggests an age-independent causal relationship (5–7). The mechanisms responsible for bone–vascular interactions are not well understood.

The results of increasing numbers of experimental studies led to the recognition of similarities between bone development and mineralization and the process of arterial calcifications. The calcification process involves VSMC differentiation into osteoblast-like cells, with subsequent mineralization. This process is induced and regulated by equilibrium between factors promoting or inhibiting calcification, involving a variety of proteins that are important for bone metabolism but are also expressed in arteries (1–3). Clinical data on humans indicate that osteoporosis and vascular calcifications are influenced by several common risk factors, such as diabetes, inflammation, dyslipidemia, oxidative stress, estrogen deficiency, vitamin D and K deficiencies, and others (21–24). The roles of dyslipidemia, oxidative stress, and inflammation seem to be of importance. Oxidized lipids can paradoxically induce atherosclerosis and the differentiation of osteoblasts, with subsequent arterial wall mineralization having the opposite effect, that is, inhibiting osteoblastic differentiation into bone osteoblasts (25). Oxidized lipids are also a substrate for peroxisome proliferator-activator receptor-γ (PPARγ), which redirects the differentiation of mesenchymal progenitors from preosteoblasts to adipocytes and Cbfa1/Runx2 expression essential for osteoblastogenesis.

In osteoporosis, it is osteoprotegerin (OPG), the receptor activator of the nuclear factor-kappa B (NF-κB) ligand (RANKL) system, that has attracted the most attention (26,27). OPG-deficient mice develop osteoporosis with severe cortical and trabecular bone porosity and high fractures rates. In parallel with these bone lesions, these mice develop medial calcification of the aorta and large arteries (28). By binding RANKL, OPG inhibits osteoclastogenesis and bone resorption. OPG and RANKL are also involved in immune-induced inflammatory responses. OPG can limit local inflammatory responses, and *in vitro* OPG, produced by smooth muscle and endothelial cells, acts as an antiapoptotic factor prolonging endothelial cell survival (27). Changes of the RANKL/OPG ratio are critical to the evaluation of clinical impact, and high OPG-associated cardiovascular risk probably represents an inadequate response of OPG to increased RANKL activity (29).

Although osteoporosis–arterial calcification interactions could be observed in general populations in the absence of overt mineral metabolism disorders, in CKD/ESRD patients, the associations between vascular calcifications and bone disorders are linked to deterioration of mineral and bone metabolism caused by serum phosphate and calcium changes, and disruption of endocrine and humoral pathways, including parathyroid hormone (PTH), calcitriol, fibroblast growth factor-23 (FGF-23)/Klotho, and others (1–3). Experimental and clinical data indicate that hyperphosphatemia plays a direct role in the osteoblast-like transformation of VSMC by upregulating Cbfa1/Runx2 and osterix transcription factors (1,2,30,31). The calcification could be enhanced by the imbalance between inducers and local or systemic inhibitors of calcification, such as low fetuin-A, pyrophosphate, or osteopontin (31–33). In CKD and ESRD patients, the relationship between bone and vascular calcifications concerns several aspects of bone disorders, such as high bone turnover (secondary hyperparathyroidism), and low bone activity (adynamic bone disease), and low bone volume. In secondary hyperparathyroidism, the increased bone resorption associated with the endogenous release of phosphate and calcium could play a critical role in the induction of vascular calcification. Chronic PTH elevation upregulates RANKL, downregulates *OPG* gene expression, and raises the RANKL/OPG ratio (34). The high prevalence and extent of arterial calcification is also observed in ESRD patients with bone demineralization or low bone activity (11–14,18), a clinical situation closer to the osteoporosis–vascular calcification association seen in general populations.

In general populations and ESRD patients, relationships between bone disorders and vascular dysfunction were observed independently of calcifications, age, BP, and other confounding factors, thereby suggesting direct bone–vascular cross-talk. Bone is an active "endocrine" organ, as demonstrated by fibroblast growth factor 23 (FGF-23) regulation of the phosphate balance. FGF-23 is synthesized and released by osteocytes, which are terminally differentiated osteoblasts. Osteoblast function could be an important player in the bone–vascular axis. Lee *et al.* (35) showed that osteoblasts exert endocrine regulation of energy metabolism, with osteocalcin (OCN) playing an important role. OCN can regulate the expression of insulin genes, β-cell proliferation, and adiponectin (ADPN) release and its expression adipocytes (36). In general populations, serum OCN was positively associated with ADPN (37,38). ADPN protects arteries against hypertension, slows atherosclerosis, and activates osteoblastogenesis (39,40). An inverse relationship was found between ADPN and OCN and arterial stiffness (38). Plasma ADPN levels are low in metabolic syndrome and type 2 diabetes patients. Whether this low ADPN could account for decreased osteoblastogenesis and frequently observed adynamic bone disease in diabetic patients remains a hypothesis.

Multiple hormones involved in the endocrine regulation of adipose tissue and energy metabolism could affect bone structure, including leptin. Leptin is a powerful inhibitor of *in vivo* bone formation (41) and facilitates vascular calcification (42). In ESRD, serum leptin is elevated and is associated with low PTH (43), suggesting that leptin might diminish bone activity and promote arterial calcifications in this setting.

Bone loss may also occur as a secondary consequence of ischemia related to vascular disease. Arteries and arterioles within the bone are also subject to arteriosclerosis, and a link between compromised intraosseous circulation and consequent osteoporosis may exist (44). Intraosseous angiogenesis and bone remodeling are regulated by similar cytokines and growth factors, and interactions between bone formation–resorption and blood supply are known to occur (45). A recent study showed that in otherwise healthy women, bone-perfusion indices were lower in women with osteoporosis compared with women with osteopenia or normal BMD (46).

In conclusion, increasing numbers of articles on general populations and CKD and ESRD patients have reported significant associations among arterial pathology (atherosclerosis and arterial calcifications) and bone disorders, including osteoporosis, and high or low bone activity. The pathophysiology and biologic links between bone and arterial abnormalities suggest the existence of bone–vascular cross-talk. The nature of this communication is not well understood. It could be a consequence of (*1*) the action of common factors on bone remodeling and atherosclerosis/calcification, (*2*) the direct action of bone cells (osteoblasts and/or osteocytes) on vascular biology and structure, and/or (*3*) the compromised bone blood supply resulting from arteriosclerosis of bone vessels and reduced perfusion.

Disclosures

None.

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See related article, "Low Bone Volume—A Risk Factor for Coronary Calcifications in Hemodialysis Patients," on pages 450–455.