

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

Gérard M. London

Service de Néphrologie, Centre Hospitalier Manhès, Fleury Mérogis, France; INSERM U970, Paris, France

Clin J Am Soc Nephrol 4: 254–257, 2009. doi: 10.2215/CJN.06661208

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 multislice 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).

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

Correspondence: Dr. Gérard London, Centre Hospitalier Manhès, 8, rue Roger Clavier, 91712 Fleury-Mérogis Cedex, France. Phone: 33 1 69256485; Fax: 33 1 69256525; E-mail: glondon@club-internet.fr

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 (PPAR γ), 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- κ B) 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 in 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.

References

- Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM: Exploring the biology of vascular calcification in chronic kidney disease: What's circulating? *Kidney Int* 73: 384–390, 2008
- Demer LL, Tintut Y: Vascular calcification: Pathobiology of multifaceted disease. *Circulation* 117: 2938–2948, 2008
- Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G: Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69: 1945–1953, 2006
- Hamerman D: Osteoporosis and atherosclerosis: Biological linkage and the emergence of dual-purpose therapies. *Q J Med* 98: 467–484, 2005
- Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC: Progression of aortic calcification is associated with metacarpal bone loss during menopause: A population-based longitudinal study. *Arterioscler Thromb Vasc Biol* 20: 1926–1931, 2000
- Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V: Aortic calcification and the risk of osteoporosis and fractures. *J Clin Endocrin Metab* 89: 4246–4253, 2004
- Tanko LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR: Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *J Bone Mineral Res* 20: 1912–1920, 2005
- Carr JJ, Register TC, Hsu F-Ch, Lohman K, Lenchik L, Bowden DW, Langefeld CD, Xu J, Rich SS, Wagenknecht LE, Freedman BI: Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: The diabetes heart study. *Bone* 42: 43–52, 2008
- Sumino H, Ichikawa S, Kasama S, Takahashi T, Sakamoto H, Kumakura H, Takayama Y, Kanda T, Murakami M, Kurabayashi M: Elevated arterial stiffness in postmenopausal women with osteoporosis. *Maturitas* 55: 212–218, 2006
- Sumino H, Ichikawa S, Kasama S, Takahashi T, Sakamoto H, Kumakura H, Takayama Y, Kanda T, Murakami M, Kurabayashi M: Relationship between brachial arterial endothelial function and lumbar spine bone mineral density in postmenopausal women. *Circ J* 71: 1555–1559, 2007
- Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC: Electron-beam computed tomography in the evaluation of cardiac calcifications in chronic dialysis patients. *Am J Kidney Dis* 27: 394–401, 1996
- Barreto DV, Barreto FC, Carvalho AB, Cuppari L, Cendoroglo M, Draibe SA, Moyses RM, Neves KR, Jorgetti V, Blair A, Guiberteau R, Fernandes Canziani ME: Coronary calcification in hemodialysis patients: The contribution of traditional and uremia-related risk factors. *Kidney Int* 67: 1576–1582, 2005
- London GM, Marty C, Marchais SJ, Guérin AP, Métivier F, de Vernejoul MC: Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 15: 1943–1951, 2004
- London GM, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul MC: Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 19: 1827–1835, 2008
- Joki N, Hase H, Shiratake M, Kishi N, Tochigi S, Imamura Y: Calcaneal osteopenia is a new marker for arterial stiffness in chronic hemodialysis patients. *Am J Nephrol* 25: 196–202, 2005
- Raggi P, Bellasi A, Ferramosca E, Block GA, Muntner P: Pulse wave velocity is inversely related to vertebral bone density in hemodialysis patients. *Hypertension* 49: 1278–1284, 2007
- Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG: Association between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. *Nephrol Dial Transplant* 23: 586–593, 2008
- Adragao T, Herberth J, Monier-Faugere M-C, Branscum AJ, Ferreira A, Frazao JM, Curto JD, Malluche HH: Low bone volume—a risk factor for coronary calcifications in hemodialysis patients. *Clin J Am Soc Nephrol* 4: 450–455, 2009
- Majesky MW: Developmental basis of vascular smooth muscle diversity. *Atheroscler Thromb Vasc Biol* 27: 1248–1258, 2007
- DeBackey M, Glaser D: Patterns of atherosclerosis: Effect of risk factors on recurrence and survival – Analysis of 11,890 cases with more than 25-years follow-up. *Am J Cardiol* 85: 1045–1053, 2000
- Parhami F, Garfinkel A, Demer LL: Role of lipids in osteoporosis. *Arterioscler Thromb Vasc Biol* 20: 2346–2348, 2000
- Koh JM, Khang YH, Jung CH, Bae S, Kim DJ, Chung YE, Kim GS: Higher circulating hsCRP levels are associated with lower bone mineral density in healthy pre- and postmenopausal women: Evidence for a link between systemic inflammation and osteoporosis. *Osteoporos Int* 16: 1263–1271, 2005
- Braam LA, Hoeks APG, Brouns F, Hamulyák K, Gerichhausen MJ, Vermeer C: Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: A follow-up study. *Thromb Haemost* 91: 373–380, 2004
- Gerdhem P, Obrant KJ: Effects of cigarette smoking on bone mass as assessed by dual-energy X-ray absorptiometry and ultrasound. *Osteoporos Int* 13: 932–936, 2002
- Mody N, Parhami F, Sarafian TA, Demer LL: Oxidative

- stress modulates osteoblastic differentiation of vascular and bone cells. *Free Radic Biol Med* 31: 509–519, 2001
26. Hofbauer LC, Schoppet M: Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. *JAMA* 292: 490–495, 2004
 27. Collin-Osdoby P: Regulation of vascular calcification by osteoclast regulatory factors RANKL and osteoprotegerin. *Circ Res* 95: 1046–1057, 2004
 28. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Caparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS: Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev* 12: 1260–1268, 1998
 29. Flore CE, Pennisi P, Ferro G, Ximenes B, Privitelli L, Mangiafico RA, Santoro F, Parisi N, Lombardo T: Altered osteoprotegerin/RANKL ratio and low bone mineral density in celiac patients on long-term treatment with gluten-free diet. *Horm Metab Res* 38: 417–422, 2006
 30. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM: Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: A potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol* 15: 2857–2867, 2004
 31. Scatena M, Liaw L, Ghiachelli CM: Osteopontin: A multifunctional molecule regulating chronic inflammation and vascular disease. *Arterioscler Thromb Vasc Biol* 27: 2304–2309, 2007
 32. Lomashvili KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC: Phosphate-induced vascular calcification: Role of pyrophosphate and osteopontin. *J Am Soc Nephrol* 15: 1392–1401, 2004
 33. Hermans MM, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Gladziwa U, Rensma PL, Bartelet K, Konings CJ, Hoeks AP, Floege J, Leunissen KM: Study on the relationship of serum fetuin-A concentration with aortic stiffness in patients on dialysis. *Nephrol Dial Transplant* 21: 1293–1299, 2006
 34. Huang JC, Sakata T, Pflieger LL, Bencsik M, Halloran BP, Bikle DD, Nissenson RA: PTH differentially regulates expression of RANKL and OPG. *J Bone Miner Res* 19: 234–244, 2004
 35. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G: Endocrine regulation of energy metabolism by the skeleton. *Cell* 130: 456–469, 2007
 36. Ferron M, Hinoi E, Karsenty G, Ducy P: Osteocalcin differentially regulates β -cells and adipocyte gene expression and affects the development of metabolic disease in wild-type mice. *Proc Natl Acad Sci U S A* 105: 5266–5270, 2008
 37. Richards JB, Valdes AM, Burling K, Perks UC, Spector TD: Serum adiponectin and bone mineral density in women. *J Clin Endocrin Metab* 92: 1517–1523, 2007
 38. Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Kurioka S, Yano S, Sugimoto T: Serum osteocalcin is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. *J Clin Endocrin Metab* 2008; (ahead of print)
 39. Oshima K, Nampei A, Matsuda M, Iwaki M, Fukuhara A, Hashimoto J, Yoshikawa H, Shimomura I: Adiponectin increases bone mass by suppressing osteoclasts and activating osteoblasts. *Biochem Biophys Res Commun* 331: 520–526, 2005
 40. Luo XH, Guo LJ, Yuan LQ, Xie H, Zhou HD, Wu XP, Liao EY: Adiponectin stimulates human osteoblast proliferation and differentiation via the MAPK signaling pathway. *Exp Cell Res* 309: 99–109, 2005
 41. Elefteriou F, Takeda S, Ebihara K, Magre J, Patano N, Kim CA, Ogawa Y, Liu X, Ware SM, Craigen WJ, Robert JJ, Vinson C, Nakao K, Capeau J, Karsenty G: Serum leptin level is a regulator of bone mass. *PNAS* 101: 3258–3263, 2004
 42. Parhami F, Tintut Y, Ballard A, Fogelman AM, Demer LL: Leptin enhances the calcification of vascular cells: Artery wall as a target of leptin. *Circ Res* 88: 954–960, 2001
 43. Coen G, Ballanti P, Fischer MS, Balducci A, Calabria S, Colamarco L, Di Zazzo G, Lifrieri F, Manni M, Sardella D, Nofroni I, Bonucci E: Serum leptin in dialysis renal osteodystrophy. *Am J Kidney Dis* 42: 1036–1042, 2003
 44. Laroche M: Intraosseous circulation from physiology to disease. *Joint Bone Spine* 69: 262–269, 2002
 45. Alagiakrishnan K, Juby A, Hanley D, Tymchak W, Sclater A: Role of vascular factors in osteoporosis. *J Gerontol* 4: 362–366, 2008
 46. Griffith JF, Yeung DK, Tsang PH, Choi KC, Kwok TC, Ahuja AT, Leung KS, Leung PC: Compromised bone marrow perfusion in osteoporosis. *J Bone Miner Res* 23: 1068–1075, 2008

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