Arterial Interactions with Mineral and Bone Disorders

11

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Associated with deleterious changes in the structure and function damage to large arteries is a major risk factor contributing to the cardiovascular complications in hypertension, diabetes, chronic kidney disease, and chronic inflammatory diseases [1–3]. In many circumstances, these changes are in many aspects similar to those occurring with aging, with this age-related process accelerated and intensified in diabetes and chronic kidney disease (CKD) [4, 5]. Although atherosclerosis and plaque-associated occlusive lesions are the frequent underlying causes of these complications, the spectrum of arterial alterations is broader, including remodeling of large arteries and stiffening of arterial walls, with consequences that differ from those due to atherosclerotic plaques burden [6, 7]. Arterial stiffening is related to intrinsic changes in biophysical and geometric characteristics of arteries with increased calcium content and arterial calcifications (AC) as one of the most frequent consequences of arterial damage associated with deleterious changes in the structure and function of the arterial system [7–10]. AC are frequently associated with mineral and bone disorders which play an important pathophysiological role in the pathogenesis and progression of arterial damage [11–16]. Many studies showed that the extents of calcifications are associated with subsequent cardiovascular mortality and morbidity beyond established conventional risk factors [17–20].

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11.1 Arterial Calcifications and Mineral and Bone Disorders

AC develop in two distinct sites: the intima and media layers of the large and medium-sized arterial wall. These two forms are frequently associated. Intima plaque calcification occurs in the context of common atherosclerosis and progresses in parallel with the plaque evolution. Calcium accumulation in the media (Mönckeberg's sclerosis or mediacalcosis) of arteries is observed with high frequency with aging, diabetes, and CKD [4, 5, 10, 11]. For a long time, it was thought that these calcifications resulted from passive deposition of calcium salts as the consequence of extracellular fluid volume oversaturation with a high calcium–phosphate product. Experimental and clinical studies indicate that cardiovascular calcifications are an active process that is regulated by a variety of genes and proteins involved in mineral and bone metabolism. AC is a process akin to bone formation, regulated by an equilibrium between factors promoting or inhibiting calcification [21–23]. Emerging evidence indicates that senescence, diabetes, inflammation, dyslipidemia, oxidative stress, estrogen deficiency, and vitamin D and K deficiencies could provide stimuli for osteogenic phenotype expression process involving differentiation of contractile vascular smooth muscle cells, pericytes, and calcifying vascular cells into phenotypically distinct, "osteoblast-like" cells with secretory phenotype [24–31].

Aging is the most typical condition associated with the development of vascular calcifications. VSMC senescence is associated with the switch to a secretory phenotype (senescence-associated secretory phenotype, SASP) that initiates osteoblastic transition with calcifications and artery-wall remodeling [32, 33]. SASP is linked to low-grade arterial inflammation with production of proinflammatory cytokines (IL-1, TNF-α) and oxidative stress all factors leading to NF-κB activation [34]. NF-κB activity, inflammation, and excessive production of reactive oxygen species (ROS) are associated with several features of the progeroid syndrome, such as accumulation of prelamin A [35], low telomerase activity and telomere shortening [36], and DNA damage [37], all conditions being associated with the development of an osteogenic program by activation of BMP 2/4 and Wnt/β-catenin signals (Fig. 11.1).

Molecular imaging in vivo has demonstrated inflammation-associated osteogenesis in early stages of atherosclerosis [38], confirming the role of inflammation in triggering the metabolic cascade leading to the transformation of VSMC into an osteogenic phenotype. Macrophage activation releases proinflammatory cytokines (such as IL-6 and TNFα) and proteolytic enzymes (metalloproteinases MMP 2, MMP 9, and cathepsin S) whose release is associated with osteochondrocytic VSMC transdifferentiation [23, 38]. IL-6 and TNFα are the first steps for the activation of BMP2:BMP4 and Msx2 which promote calcification by activating paracrine Wnt signals and nuclear activation and localization of β-catenin, an indispensable coregulator of expression of Runx2, osterix, and Sox9 which are all transcription factors associated with the osteochondrogenic phenotype conversion of VSMC and pericytes [23, 38–40]. The second aspect of inflammation-related calcification is the proteolytic activation of elastolysis and degradation of extracellular matrix. The fragmentation of elastic lamellae and release of biologically active elastin-derived peptides also promote VSMC dedifferentiation and calcium deposition [41].

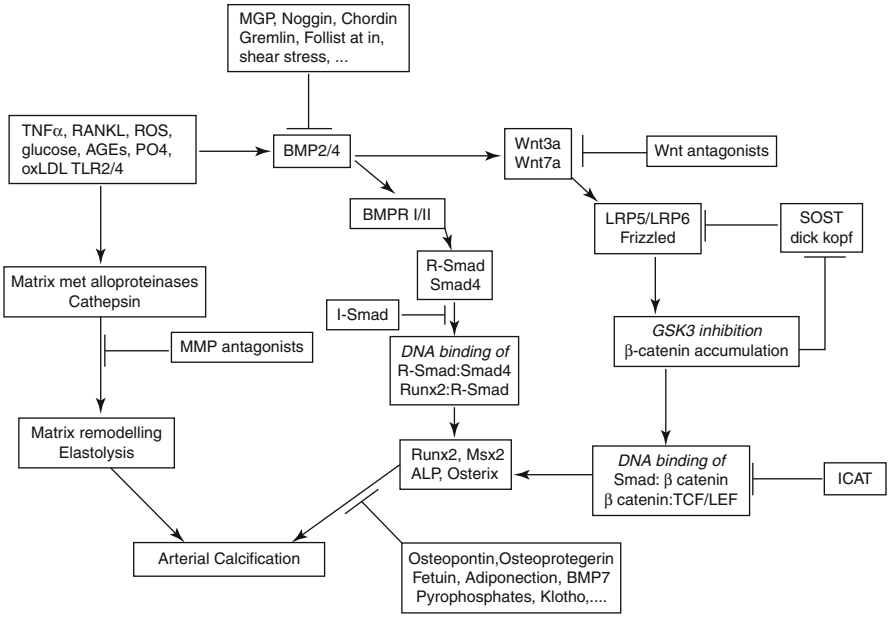

Fig. 11.1 Osteochondrogenic BMP- Msx2-Wnt signaling in arterial calcifications

In the presence of normal serum, VSMC do not calcify. Serum inhibits spontaneous calcium and phosphate precipitation in solution [42], indicating that systemic calcification inhibitors are present in the serum. VSMC which constitutively express potent local or systemic inhibitors of calcification [21], such as matrix GLA protein [43], may limit AC by binding to bone morphogenic proteins [44]. Osteopontin and osteoprotegerin are potent inhibitors of AC in vivo, and inactivation of their genes enhances the calcification process [45, 46]. Fetuin-A (AHSG or α_2-HS glycoprotein) is a potent circulating AC inhibitor that is abundant in the plasma [47]. Pyrophosphate is another potent inhibitor. In vitro, phosphate-stimulated apatite production can be completely prevented by adding pyrophosphates that antagonize the cellular sodium–phosphate cotransport system [48].

While in the general populations the presence of cardiovascular calcifications could be observed in the absence of overt mineral metabolism disorders in several clinical conditions such as CKD/ESRD, the associations between vascular calcifications are associated with deterioration of mineral and bone metabolism caused by changes in serum phosphorus and calcium and disruption of endocrine and humoral pathways including parathyroid hormone (PTH), calcitriol, FGF-23/Klotho, and vitamin D. In vitro, calcium and phosphate promote both synergistically and independently VSMC calcification [28, 49]. Recent findings indicate that hyperphosphatemia, through activation of mitochondrial respiration, stimulates the production of ROS with final activation of NF-κB, enhancing Runx2 (Cbfa1) activation [50].

Hyperphosphatemia is tightly related to disruption of Klothe-FGF23 axis [51, 52]. Several experimental models and clinical conditions such as CKD are characterized by increased FGF23 and decreased Klotho activity [53, 54]. In animal models, Klotho and FGF23 knockout animals are characterized by short life span, accelerated aging phenotype, extensive arterial calcifications, osteoporosis, and hyperphosphatemia [52, 55, 56]. Suppression of phosphate from the diet or knockout of gene for Pit1 and sodium-dependent phosphate uptake restores normal life span and phenotype [52, 55]. Klotho deficiency increases expression of Pit1 and expression of Runx2 associated with secretory osteogenic phenotype of VSMC [53]. In animal models, FGF23 is not directly associated with vascular calcifications since neutralization of FGF23 with specific antibodies results in extensive arterial calcifications and premature death of animals [57].

Decreased Klotho expression and increased FGF23 precede the elevation of parathormone (PTH) secretion also responsible for mineral and bone homeostasis [58]. Chronic elevation of PTH upregulates RANKL and downregulates OPG gene expression and enhances the RANKL–OPG ratio, RANK–RANKL–OPG (receptor activator of nuclear factor (NF)-κB–receptor activator of NF-κB ligand–osteoprotegerin) signaling pathway, and the RANKL–OPG ratio [59–61]. Once bound to RANK, RANKL activates the alternative NF-κB pathway and initiates production of inflammatory cytokines and activates MSx2/Runx2 pathway. Results of a recent study demonstrated that RANKL increased VSMC calcification directly through BMP4 upregulation, providing autocrine stimulus and activation of Wnt signaling [62]. The arterial calcifications observed with increased PTH secretion are attributed to RANKL-mediated bone resorption by osteoclast-associated excessive calcium and phosphate releases.

11.2 Bone–Vascular Cross-Talk

There is growing clinical and experimental evidence linking bone pathology and different functional and structural characteristics of cardiovascular system. Several population-based longitudinal studies demonstrated associations between osteoporosis and AC or arterial stiffness, as well as an association between the progression of aortic calcifications and decreased bone mineral density [14–17, 63–65]. The mechanisms accounting for these associations are not well understood. Several possibilities should be considered: (1) common risk factors for osteoporosis or bone remodeling and vascular calcifications, (2) role of primary vascular pathologies on bone function and remodeling, and/or (3) the participation of bone cells in vascular remodeling.

11.2.1 Common Factors

Clinical data show that osteoporosis and vascular calcifications are influenced by several common risk factors, such as age, menopausal status, diabetes, dyslipidemia with inflammation, and oxidative stress as the final common mechanisms [27, 66–69].

Aging is associated with bone loss and with development of vascular calcifications especially in postmenopausal women [66, 67]. Nevertheless, this bone–vascular association remained significant after adjustment for age suggesting a biologically linked phenomenon [14, 16, 65]. Aging is the most typical condition associated with the development of vascular calcifications. VSMC senescence is associated with the switch to a secretory phenotype (senescence-associated secretory phenotype, SASP) linked to low-grade arterial inflammation with production of proinflammatory cytokines associated with AC by activation of BMP 2/4 and Wnt/β-catenin signals [32, 33]. Direct evidence that inflammation was the factor linking bone remodeling and arterial calcifications was recently provided by Hjortnaes et al. who, using near-infrared fluorescence molecular imaging, showed that arterial and aortic valve calcifications inversely were correlated with osteoporotic bone remodeling [69]. Chronic inflammation is also associated with unbalanced bone formation and bone resorption [70].

Normal bone remodeling is characterized by a balance between osteoclast bone resorption and osteoblast bone matrix deposition. This balance is disrupted in osteoporosis and is influenced by the RANKL–OPG equilibrium. The discovery that OPG-deficient mice develop severe arterial calcifications concomitantly with severe osteoporosis, cortical and trabecular bone porosity, and their high fracture rate provided robust evidence pointing to the RANKL–OPG disequilibrium as a possible common factor linking osteoporosis and arterial calcifications [71]. RANKL activates the alternative NF-κB pathway and initiates production of inflammatory cytokines and arterial calcifications in parallel with RANKL-mediated bone resorption by osteoclasts whose apoptosis is suppressed osteoclast apoptosis. The association between arterial calcification and osteoporosis is most typically observed in postmenopausal women. It could largely reflect estrogen deficiency since estrogen inhibits RANKL-signaling and induces osteoblast OPG expression [72].

Osteopenia, poor fracture healing, arterial calcifications, and higher risk of hip fractures are frequently found simultaneously in patients with diabetes mellitus [73]. Increased AGE accumulation could be the common factor linking bone and arterial pathologies in diabetes. Endogenous ligands for AGE receptors (RAGE) trigger activation of transcription factor NF-κB and ROS signaling, leading to the production of proinflammatory cytokines and activation of VSMC osteogenic BMP/Wnt signaling through Runx2 upregulation inducing AC [74]. In vitro, through their accumulation in diabetes, AGEs stimulate osteoblast apoptosis and modify osteoclast activity by delaying bone regeneration and contributing to defective bone formation [75, 76].

11.2.2 Arterial Disorders and Bone Alterations

Atherosclerosis also affects bone circulation and impaired bone perfusion. With aging, bone arteries and arterioles are subjected to arteriosclerosis, with reduced bone marrow blood supply that renders the marrow ischemic and diminishes the cortex blood supply, which is replaced by the periosteal circulation [77]. That a

link between compromised intraosseous circulation and consequent osteoporosis might exist is also suggested by the observation associating decreased bone mineral density and peripheral artery disease [78]. Intraosseous angiogenesis and bone remodeling are regulated by similar cytokines and growth factors, and bone formation–resorption and blood supply are tightly associated [79]. Some results showed that, in healthy women, bone perfusion indices were lower in subjects with osteoporosis than those with osteopenia or normal bone–mineral density [79, 80].

11.2.3 Bone Functions and Arterial Alterations

Several experimental findings support that bone and osteoblast physiology are involved in the control of fat-tissue metabolism and adipokine release, energy expenditure, and insulin secretion and sensitivity, all factors directly affecting cardiovascular function and health. Lee et al. [81] showed that osteoblasts exert endocrine regulation on energy metabolism, with osteocalcin (OCN) playing an important role. Uncarboxylated osteocalcin can regulate the expression of insulin genes and β-cell proliferation and adiponectin (ADPN) release and expression by adipocytes [81, 82]. In CKD patients, serum OCN was positively associated with serum ADPN [83]. ADPN is anti-inflammatory, suppresses atherosclerosis, increases insulin secretion and sensitivity, and activates osteoblastogenesis [84]. Moreover, ADPN regulates arterial calcifications [85], and an inverse relationship was observed between ADPN and the progression of coronary calcifications [86]. In ESRD patients, cardiovascular calcifications are frequently observed in the presence of low bone volume and adynamic bone disease, characterized by decreased osteoblast numbers/activity [15, 87] suggesting that bone cells could influence vascular function and calcification. In a recent study in ESRD patients, it has been shown that peripheral artery disease with extensive calcifications is associated with low osteoblastic activity characterized by pronounced osteoblast resistance to PTH [87].

In conclusion, the results of cross-sectional studies on general populations and several clinical conditions showed an association between atherosclerosis/arteriosclerosis and arterial calcifications. The two types of calcifications, i.e., intimal and medial, have a different impact on arterial functions. The intimal calcification as a part of advanced atherosclerosis results in the development of plaques and arterial lumen decrease or occlusion and ischemic lesions downstream. Medial calcifications result in the stiffening of arterial walls with increased systolic and decreased diastolic pressures. Arterial changes occur in relation with mineral and bone disorders, including osteoporosis, low bone volume, and high or low bone activity. The pathophysiology and biological links between bone and arterial abnormalities suggest the existence of bone-vascular cross-talk and common regulatory factors shared by vascular and bone systems.

This leads to cardiac pressure overload, left ventricular hypertrophy, and decreased myocardial perfusion. The two types of calcifications are associated with increased mortality.

References

1. Briet M, Boutouyrie P, Laurent S, London GM (2012) Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int 82:383–400
2. Hayden MR, Tyagi SC, Kolb L et al (2005) Vascular ossification – calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis – calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. Cardiovasc Diabetol 4:1–22
3. London GM, Drüeke TB (1997) Atherosclerosis and arteriosclerosis in chronic renal failure. Kidney Int 51:1678–1695
4. Lindner A, Charra B, Sherrard D, Scribner BM (1974) Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 290:697–702
5. Longenecker JC, Coresh J, Powe NR et al (2002) Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 13:1918–1927
6. O'Rourke MF (1995) Mechanical principles in arterial disease. Hypertension 26:2–9
7. Guérin AP, London GM, Marchais SJ, Métivier F (2000) Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 15:1014–1021
8. Braun J, Oldendorf M, Moshage W et al (1996) Electron beam computed tomography in the evaluation of cardiac calcifications in chronic dialysis patients. Am J Kidney Dis 27:394–401
9. Goodman WG, Goldin J, Kuizon BD et al (2000) Coronary artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342:1478–1483
10. Ibels LS, Alfrey AL, Huffer WE et al (1979) Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med 66:790–796
11. Block GA, Klassen PS, Lazarus JM et al (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15:2208–2218
12. Jono S, McKee MD, Murry CE et al (2000) Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 87:E10–E17
13. Yang H, Curinga G, Giachelli CM (2004) Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int 66:2293–2299
14. Hak AE, Pols HA, van Hemert AM et al (2000) Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol 20:1926–1931
15. London GM, Marty C, Marchais SJ et al (2004) Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol 15:1943–1951
16. Schulz E, Arfai K, Liu X et al (2004) Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 89:4246–4253
17. Wilson PWF, Kauppila LI, O'Donnell CJ et al (2001) Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. Circulation 103:1529–1534
18. Sangiorgi G, Rumberger JA, Severson A et al (1998) Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 31:126–133
19. Detrano R, Hsiai T, Wang S et al (1996) Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 27:285–290
20. Blacher J, Guérin AP, Pannier B et al (2001) Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 38:938–942
21. Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM (2008) Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? Kidney Int 73:384–390
22. Demer LL, Tintut Y (2008) Vascular calcification: pathobiology of multifaceted disease. Circulation 117:2938–2948
23. Bostrom KI, Rajamannan NM, Towler DA (2011) The regulation of valvular and vascular sclerosis by osteogenic morphogens. Circ Res 109:564–577
24. Jono S, Nishizawa Y, Shioi A, Morii H (1998) 1,25-Dihydroxyvitamin D3 increases in vitro vascular calcification by modulating secretion of endogenous parathyroid-hormone-related peptide. Circulation 98:1302–1306

25. Steitz SA, Speer ME, Curinga G et al (2001) Smooth muscle cell phenotypic transition associated with calcification. Upregulation of Cbfa1 and downregulation of smooth muscle lineage markers. Circ Res 89:1147–1154
26. Tintut Y, Patel J, Parhami F, Demer LL (2000) Tumor necrosis factor-alpha promotes in vitro calcification of vascular cells via cAMP pathway. Circulation 102:2636–2642
27. Parhami F, Garfinkel A, Demer LL (2000) Role of lipids in osteoporosis. Arterioscler Thromb Vasc Biol 20:2346–2348
28. Reynolds JL, Joannides AJ, Skepper JN et al (2004) 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
29. Braam LA, Hoeks APG, Brouns F et al (2004) 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
30. Shao J-S, Cai J, Towler DA (2006) Molecular mechanisms of vascular calcification: lessons learned from the aorta. Arterioscler Thromb Vasc Biol 26:1423–1430
31. Shao JS, Sadhu J, Towler DA (2010) Inflammation and the osteogenic regulation of vascular calcification. A review and perspective. Hypertension 55:579–592
32. Wang M, Monticone RE, Lakatta EG (2010) Arterial aging: a journey into subclinical arterial disease. Curr Opin Nephrol Hypertens 19:201–207
33. Nakano-Kurimoto R, Ikeda K, Uraoka M et al (2009) Replicative senescence of vascular smooth muscle cells enhances the calcification through initiating the osteoblastic transition. Am J Physiol Heart Physiol 297:H1673–H1684
34. Newgard CB, Sharpless NE (2013) Coming of age: molecular drivers of aging and therapeutic opportunities. J Clin Invest 123:946–950
35. Ragnauth CD, Warren DT, Yiwen Liu Y et al (2010) Prelamin A acts to accelerate smooth muscle cell senescence and is a novel biomarker of human vascular aging. Circulation 121:2200–2210
36. Carrero JJ, Stenvinkel P, Fellstro¨m B et al (2008) Telomere attrition is associated with inflammation, low fetuin-A levels and high mortality in prevalent haemodialysis patients. J Intern Med 263:302–312
37. Tistra JS, Robinson AR, Wang L et al (2012) NF-κB inhibition delays DNA damage-induced senescence and aging in mice. J Clin Invest 122:2601–2612
38. Aikawa E, Nahrendor M, Figueiredo J-L et al (2007) Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. Circulation 116:2841–2850
39. Shao J-S, Cheng S-L, Joyce M et al (2005) Msx2 promotes cardiovascular calcification by activating paracrine Wnt signals. J Clin Invest 115:1210–1220
40. Al-Aly Z, Shao J-S, Lai C-F et al (2007) Aortic Msx2-Wnt calcification cascade is regulated by TNF-α-dependent signals in diabetic ldlr –/– mice. Arterioscler Thromb Vasc Biol 27:2589–2596
41. Aikawa E, Aikawa M, Libby P et al (2009) Arterial and aortic valve calcification abolished by elastolytic cathepsin deficiency in chronic renal disease. Circulation 119:1785–1794
42. Moe SM, Duan D, Doehle BP et al (2003) Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. Kidney Int 63:1003–1011
43. Luo G, Ducy P, McKee MD et al (1997) Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 386:78–81
44. Sweatt A, Sane DC, Hutson SM et al (2003) Matrix Gla protein (MGP) and bone morphogenetic protein-2 in aortic calcified lesions of aging rats. J Thromb Haemost 1:178–185
45. Speer MY, McKee MD, Guldberg RE et al (2002) Inactivation of osteopontin gene enhances vascular calcification of matrix Gla protein-deficient mice : evidence for osteopontin as an inducible inhibitor of vascular calcification in vivo. J Exp Med 196:1047–1055
46. Price PA, June HH, Buckley JR et al (2001) Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol 21:1610–1616

47. Schafer C, Heiss A, Schwarz A et al (2003) The serum protein alpha 2-Heremans–Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 112:357–366
48. Lomashvili K, Cobbs S, Hennigar RA et al (2004) Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. J Am Soc Nephrol 15:1392–1401
49. Shanahan C, Crouthamel MH, Kapustin A et al (2011) Arterial calcification in chronic kidney disease: key role for calcium and phosphate. Circ Res 109:697–711
50. Zhao M-M, Xu M-J, Cai Y et al (2011) Mitochondrial reactive oxygen species promote p65 nuclear translocation mediating high-phosphate induced vascular calcification in vitro and in vivo. Kidney Int 79:1071–1079
51. Quarles LD (2008) Endocrine function of bone in mineral regulation. J Clin Invest 118:3820–3828
52. Stubbs JR, Liu S, Tang W et al (2007) Role of hyperphosphatemia and 1,25-dihydroxy vitamin D in vascular calcifications and mortality in fibroblast growth factor 23 null mice. J Am Soc Nephrol 18:2116–2124
53. Hu MC, Shi M, Zhang J et al (2011) Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol 22:124–136
54. Lim K, Lu T-S, Molostvov G et al (2012) Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation 125:2243–2255
55. Ohnishi M, Razzaque MS (2010) Dietary and genetic evidence for phosphate toxicity accelerating mammalian aging. FASAB J 24:3562–3571
56. Kuro-O M (2009) Klotho and aging. Biochem Biophys Acta 1790:1049–1058
57. Shalhoub V, Shatzen EM, Ward SC et al (2012) FGF23 neutralization improves chronic kidney disease-associated hyperparathyroidism yet increases mortality. J Clin Invest 122:2543–2553
58. Isakova T, Wahl P, Vargas GS et al (2011) Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 79:1370–1378
59. Huang JC, Sakata T, Pfleger LL et al (2004) PTH differentially regulates expression of RANKL and OPG. J Bone Miner Res 19:234–244
60. Hofbauer LC, Schoppet M (2004) Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 292:490–495
61. Collin-Osdoby P (2004) Regulation of vascular calcification by osteoclast regulatory factors RANKL and osteoprotegerin. Circ Res 95:1046–1057
62. Panizo S, Cardus A, Encinas M et al (2009) RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4 dependent pathway. Circ Res 104:1041–1048
63. Raggi P, Bellasi A, Ferramosca E et al (2007) Pulse wave velocity is inversely related to vertebral bone density in hemodialysis patients. Hypertension 49:1278–1284
64. Toussaint ND, Lau KK, Strauss BJ et al (2008) Association between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. Nephrol Dial Transplant 23:586–593
65. Kiel DP, Kauppila LI, Cupples LA et al (2001) Bone loss and progression of abdominal aortic calcification over a 25 year period: the Framingham Heart Study. Calcif Tissue Int 68:271–276
66. Tanko LB, Christiansen C, Cox DA et al (2005) Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res 20:1912–1920
67. Hamerman D (2005) Osteoporosis and atherosclerosis: biological linkage and the emergence of dual-purpose therapies. Q J Med 98:467–484
68. Doherty TM, Asotra K, Fitzpatrick LA et al (2003) Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proc Natl Acad Sci U S A 100:11201–11206
69. Hjortnaes J, Butcher J, Figueiredo J-L et al (2010) Arterial and aortic valve calcification inversely correlates with osteoporotic bone remodelling: a role for inflammation. Eur Heart J 31:1975–1984
70. Koh JM, Khang YH, Jung CH et al (2005) 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

71. Bucay N, Sarosi I, Dunstan CR et al (1998) Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 12:1260–1268
72. Osako MK, Nakagami H, Koibuchi N et al (2010) Estrogen inhibits vascular calcification via vascular RANKL system: common mechanism of osteoporosis and vascular calcification. Circ Res 107:466–475
73. Hofbauer LC, Bueck CC, Singh SK, Dobnig H (2007) Osteoporosis in patients with diabetes mellitus. J Bone Miner Res 22:1317–1328
74. Tanikawa T, Okaya Y, Tanikawa R, Tanaka Y (2009) Advanced glycation end products induce calcification of vascular smooth muscle cells through RAGE/p38 MAPK and upregulation of Runx2. J Vasc Res 46:572–580
75. Alikhani M, Alikhani Z, Boyd C et al (2007) Advanced glycation end-products stimulate osteoblast apoptosis via MAP kinase and cytosolic apoptotic pathway. Bone 40:345–353
76. Valcourt U, Merle B, Gineyts E et al (2007) Non-enzymatic glycation of bone collagen modifies osteoclastic activity and differentiation. J Biol Chem 282:5691–5703
77. Bridgeman G, Brookes M (1996) Blood supply to the human femoral diaphysis in youth and senescence. J Anat 188:611–621
78. Laroche M (2002) Intraosseous circulation from physiology to disease. Joint Bone Spine 69:262–269
79. Alagiakrishnan K, Juby A, Hanley D et al (2008) Role of vascular factors in osteoporosis. J Gerontol 4:362–366
80. Griffith JF, Yeung DK, Tsang PH et al (2008) Compromised bone marrow perfusion in osteoporosis. J Bone Miner Res 23:1068–1075
81. Lee NK, Sowa H, Hinoi E et al (2007) Endocrine regulation of energy metabolism by the skeleton. Cell 130:456–469
82. Ferron M, Wei J, Yoshizawa T et al (2010) Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell 142:296–308
83. Bacchetta J, Boutroy S, Guebre-Egziabher F et al (2009) The relationship between adipokines, osteocalcin and bone quality in chronic kidney disease. Nephrol Dial Transplant 24:3120–3125
84. Oshima K, Nampei A, Matsuda M et al (2005) Adiponectin increases bone mass by suppressing osteoclasts and activating osteoblasts. Biochem Biophys Res Commun 331:520–526
85. Luo XH, Zhao LL, Yuan LQ et al (2009) Development of arterial calcification in adiponectin-deficient mice: adiponectin regulates arterial calcification. J Bone Miner Res 24:1461–1468
86. Maahs DM, Ogden LG, Kinney GL et al (2005) Low plasma adiponectin levels predict progression of coronary artery calcification. Circulation 111:747–753
87. London GM, Marchais SJ, Guérin AP, de Vernejoul MCh (2015) Ankle–brachial index and bone turnover in patients on dialysis. J Am Soc Nephrol 26:476–483