HHS Public Access

Author manuscript

Curr Osteoporos Rep. Author manuscript; available in PMC 2015 May 06.

Published in final edited form as:

Curr Osteoporos Rep. 2009 July ; 7(2): 42–46.

Mechanisms Linking Osteoporosis with Cardiovascular Calcification

Linda Demer[*,¶,§] and **Yin Tintut**[*]

[*]Department of Medicine, The David Geffen School of Medicine at UCLA

[§]Department of Physiology, The David Geffen School of Medicine at UCLA

[¶]Department of Biomedical Engineering, The David Geffen School of Medicine at UCLA

Abstract

Cardiovascular calcium deposition is associated with osteoporosis through a variety of potential mechanisms involving molecular regulatory factors at the nanoscale level that govern both skeletal bone and cardiovascular tissues. In this review, several possible mechanisms linking cardiovascular calcification and osteoporosis are discussed, including aging, tissue-specific responses to chronic inflammation, flow-limiting atherosclerosis of skeletal end-arteries causing ischemic abnormalities in metabolism, shared, endogenous regulatory factors that affect the two tissues in a reciprocal manner, and changes in a cysteine protease inhibitor, fetuin. Any or all of these factors and phenomena may contribute to the association.

Introduction

Cardiovascular calcification is a widespread disorder that affects the majority of individuals over 60 years of age. Surprisingly, it is more common in patients with osteoporosis. Many studies suggest that this effect is independent of age. The calcium deposits in arteries and heart valves often consist of fully formed bone tissue, including trabeculae and marrow. Thus, patients who are losing bone from their skeleton are simultaneously producing bone in their arteries. It is not known whether aortic calcification is a direct or indirect effect of bone loss or shares a common cause with it. Nevertheless, if the relationship is age independent, it raises important questions about whether dietary calcium could truly represent a limiting factor in osteoporosis and whether treatments for osteoporosis may simultaneously affect cardiovascular calcification.

Calcium deposits arise in many anatomic locations in the cardiovascular tree, and their growth is accelerated by certain metabolic conditions including atherosclerosis, diabetes, and chronic kidney disease. They are most common in the aorta, coronary arteries, cardiac valves, and peripheral arteries. The most extensive cases are in patients with renal failure, which as Dwight Towler has noted, have a combination of features creating a “perfect storm” for vascular calcification [1,2]. Most vascular calcium deposits appear amorphous,

Corresponding author: Linda L. Demer, M.D., Ph.D., Department of Medicine, BH-307 Center for Health Sciences, 10833 LeConte Avenue, Los Angeles, CA 90095-1679, FAX 310-825-4963, Phone 310-206-2677, Ldemer@mednet.ucla.edu.

but in atherosclerotic plaque and cardiac valves, they also contain fully formed bone tissue. Calcium deposits associated with atherosclerosis are located in the neointima, whereas those associated with renal failure are prominent in the medial layer. Both layers may be affected simultaneously, as often seen in diabetes.

The clinical significance of calcific vasculopathy depends on its location. In the aorta, it greatly increases stiffness, thus impairing cardiac function and hemodynamics and promoting systolic hypertension. Aortic calcification correlates with risk of myocardial infarction and stroke, even after adjusting for age, lipoproteins, triglycerides, blood pressure, smoking, renal function, health status, and baseline diagnoses of diabetes mellitus, hypertension, angina, and prior stroke [3]. In coronary and carotid arteries, it serves as a marker for subclinical atherosclerosis. In the peripheral arteries, it associates with greater ischemia, and it is a better predictor for lower extremity amputation than ankle-brachial index and traditional risk factors. In microvessels of the extremities, where it is known as calcific uremic arteriolopathy, tissues downstream of the calcified microvessels infarct, leading to necrosis and auto-amputation [4]. In the cardiac leaflets, it causes valvular stenosis and regurgitation. Overall, calcium deposition has profound impact on cardiovascular function.

Plaque vulnerability

Calcium deposits also have local effects within atherosclerotic plaque of the intimal layer. Plaque rupture is considered the initiating event in most cases of coronary thrombosis and myocardial infarction. Theoretical analyses of mechanical stress using finite element modeling indicate that calcium deposits within atherosclerotic plaque affect the vulnerability of plaque to rupture, depending on their location relative to lipid deposits [5] and their proximity to the lumen where shear stress comes into play [6]. Experimental evidence is sparse due to limited models, but Lin et al recently established a novel cell culture model for rupture of calcified plaque under shear stress [7].

Nanoscale factors

Skeletal and vascular biomineralization share features not only at the cellular level, but also at the nanoscale. Matrix vesicles are nanovesicles generated by osteoblasts that appear to provide a nidus for hydroxyapatite crystal initiation in cartilage matrix mineralization. They are also enriched in certain active enzymes including alkaline phosphatase and NPP1, and are found in human atherosclerotic plaque and in cultured human and bovine vascular smooth muscle cells (VSMC). Chen and colleagues recently showed that when VSMC are treated with osteogenic medium (containing inorganic phosphate or beta-glycerophosphate), their matrix vesicles have greater alkaline phosphatase activity but less fetuin, and they mineralize when plated on type I collagen but not on type II collagen [8].

Additional nanoscale similarities were recently observed by Duer and colleagues [9]. Using solid-state nuclear magnetic resonance (NMR) technique, they found that in both tissues, the mineral-organic interface is a bonded nanocomposite rather than a simple mixture, and that it is enriched in glycosaminoglycans, a major component of cartilage matrix.

Epidemiological association between cardiovascular calcification and osteoporosis

Several reports show an inverse relationship between vascular calcification and bone mineral density [10]. In many, but not all, studies, this relationship is independent of age. In a study of approximately 3000 healthy postmenopausal women, aortic calcification, measured by conventional lateral x-ray, was associated with diminished bone density in the proximal femur. Importantly, the severity of aortic calcification was an independent predictor of hip fractures, low bone density, and accelerated bone loss in the femur [11]. In postmenopausal women, increased bone density was associated with significantly lower odds of having coronary artery calcification, independent of age, fat-free mass, high-density lipoprotein cholesterol, current smoking, and use of cholesterol-lowering medications. To determine whether coronary artery disease (CAD) itself, as opposed to coronary calcification, correlates with low bone density, Tekin and colleagues measured BMD in patients undergoing coronary angiography. Their results showed that coronary stenotic narrowing, irrespective of calcification, was significantly more prevalent among women with low bone density [12].

In some studies, the inverse relationship with BMD was not age-independent for all types of vascular calcification. In healthy, middle-aged women, the inverse association between aortic calcification and vertebral BMD was found to be age-independent, but the inverse association of coronary artery calcification with BMD was not [13]. To control for genetic confounders, Shen et al. studied Amish men and women and found that coronary artery calcification or aortic calcification were not associated with lower femoral BMD, though a history of cardiovascular disease was correlated with low BMD [14]. In a study of approximately 300 postmenopausal women, Sinnott and colleagues also found a significant inverse association between coronary calcification score and lumbar vertebral bone density, but it was not independent of age [15].

In dialysis patients, low femoral, but not lumbar spine, bone density was associated with greater aortic stiffness measured by higher pulse wave velocity, as well as more extensive vascular calcification and peripheral artery disease [16]. Even in pre-dialysis renal patients, vascular calcification increases rapidly with age, hypertriglyceridemia, and reduced renal function. In these patients, femoral bone density is significantly, inversely associated with vascular calcification [10].

Potential mechanisms linking coronary calcification with osteoporosis

One possible mechanism for a relationship between coronary calcification and osteoporosis is that both processes are tissue-specific responses to chronic inflammation. It is clinically well known that osteolysis and lytic changes accompany inflammation, osteomyelitis and arthritides. Towler and colleagues have provided compelling evidence that the inflammatory cytokine, tumor necrosis factor alpha, potently regulates osteochondrogenic differentiation in both osteoblastic and vascular cells through Msx2 and Wnt signaling pathways, based on both in vitro and in vivo models [17, 18]. These investigators also demonstrated the

importance of these signaling pathways in mediating effects of osteopontin, oxidant stress, and bone morphogenetic protein on biomineralization [19].

The inflammatory nature of vascular mineralization was dramatically demonstrated by Aikawa and colleagues using innovative imaging technologies in mice [20]. In atherosclerosis, inflammation results from deposition and oxidation of lipids in the subendothelial space. Lipid deposits are also found in osteoporotic bone tissue, in the subendothelial spaces within the Haversian canals [21]. Brodeur and colleagues have shown adverse effects of oxidized lipids on osteoblasts as well as evidence that osteoblasts mediate lipid oxidation, strongly suggesting increased local concentrations of oxidized lipids in bone tissue [22]. In genetically hyperlipidemic (*Apoe*$^{-/-}$) mice, volume, thickness and formation rate of cortical bone are significantly reduced by a high-fat diet compared with wild-type C57BL/6 mice [23]. The lipids not only inhibit spontaneous osteoblast mineralization, they also attenuate osteoblastic differentiation induced by osteogenic agents such as PTH and BMP-2 [24]. In vivo findings suggest that oxidized lipids interfere with anabolic effects of PTH [25], raising the question of whether osteoporosis treatment would be beneficial in chronically hyperlipidemic patients. Interestingly, intermittent PTH treatment was found to ameliorate aortic calcification in an experimental model of renal failure [26,27].

An alternative mechanism for the association between calcific atherosclerosis and osteoporosis, suggested by Bagger and colleagues, is flow-limiting atherosclerosis of skeletal end-arteries, causing metabolic abnormalities due to hypoperfusion. These investigators studied over 1000 elderly women, and found that coronary calcification severity was significantly inversely associated with veterbral BMD, but that lipid profile parameters did not correlate with bone parameters, including spine and hip BMD. Although some of the subjects were taking lipid-lowering drugs, which could mask an association, the study raises the important possibility that the correlation may not be attributable to lipid metabolic abnormalities affecting both tissues, but rather atherosclerotic disease of arteries supplying bone tissue [28].

Another potential mechanism for the inverse relationship between coronary calcification and osteoporosis is a shared, endogenous regulatory factor that affects in the two tissues in a reciprocal manner. Skeletal bone and vascular tissue have many osteogenic regulatory molecules in common. One such factor, transglutaminase 2 (TG2), was previously known to mediate differentiation of osteoblasts [29]. Recently, Johnson and colleagues demonstrated that it has an important role in vascular calcification. TG2 modulates tissue repair by transamidation-catalyzed covalent crosslinking of extracellular matrix proteins. This investigative group showed that its release is critical for chondro-osseous differentiation and matrix mineralization in smooth muscle cells whether induced by inorganic phosphate supplementation or bone morphogenetic protein-2 [30].

Other bone regulatory factors also associate with cardiovascular calcification. Some soluble factors produced by bone cells may be released into the circulation; and some may be produced directly by vascular cells. For example, in patients, levels of osteoprotegerin (OPG), an inhibitor of bone resorption, positively associates with clinical coronary calcification [31] and aortic stiffness [32], suggesting an adverse effect of OPG on the

vasculature. However, in mice, OPG deficiency is associated with aortic calcification[33], suggesting a protective role. Similarly, in hyperlipidemic mice, OPG deficiency worsens atherosclerosis progression and calcification [34], and recombinant OPG treatment of hyperlipidemic mice reduces aortic calcification without affecting atherosclerosis severity [35]. Using a different mouse model of OPG deficiency developed in mice of a different background strain, Orita et al found that aortic calcification requires a high phosphate diet and vitamin D treatment, conditions similar to those in patients with renal insufficiency [36]. As further evidence of complexity, OPG production in cultured vascular cells has a biphasic response during osteogenic differentiation induced by exposure to cytokines such as IL-4, showing an increase in OPG with short-term exposure and a decrease in OPG with long-term exposure [37]. While it is an attractive possibility that OPG and its ligand RANKL mediate the association between coronary calcification and BMD, at least in one study of postmenopausal women using estrogen, neither OPG nor RANKL serum levels were significant effect modifiers of the vascular-bone relationship after adjustment for age and other risk factors [38]. Altogether, these findings indicate a complex relationship between serum OPG regulation and cardiovascular calcification.

Another serum factor that may link vascular with bone metabolism is the cysteine protease inhibitor, fetuin. Serum fetuin levels correlate with intimal-media thickness, a measure of atherosclerosis, but correlate inversely with the osteogenic differentiation marker, alkaline phosphatase, and vertebral and femoral bone mass [39].

Osteophytes and aortic calcification

Soft-tissue calcification also comes in the interesting form of osteophytes, outgrowths of bone into neighboring soft tissue such as the ligament anterior to the lumbar vertebrae. Karasik and colleagues showed that lumbar osteophytes are significantly associated with abdominal aortic calcification independently of age, sex, body mass index, smoking, alcohol consumption, physical activity, systolic blood pressure, total cholesterol level, diabetes, and estrogen replacement therapy [40]. In this location, osteophytes and abdominal aortic calcification may confound BMD measurements based on DXA, because these structures overlie the path of the x-ray path beam traversing the lumbar vertebrae. Such an effect may yield false-positive benefits in therapeutic trials, if the agents promote soft tissue calcium deposition.

Ex vivo and in vivo models

A variety of models are available to investigate associations between vascular calcification and osteoporosis, especially in the context of hypervitaminosis and renal insufficiency. Price and colleagues have provided both ex vivo and rodent models providing evidence for a direct role of osteoporosis in artery wall calcification [41,42]. In a rat model of renal failure induced by an adenine diet, severe abnormalities of calcium metabolism develop rapidly. As in human patients with chronic kidney disease and uremia, cortical bone density was reduced, and coronary and aortic calcification was increased [43].

Exercise

Fitness and activity appear to benefit both coronary and bone metabolism. Cardiovascular fitness, measured by VO_2 max, showed a significant inverse correlation with coronary calcification in men [44]. In a 15-year follow up of over 2000 young adults, physically fit individuals had a lower risk of developing coronary calcification than individuals in poor condition [45]. Similarly, in the BONTURNO study, physical activity was significantly associated with bone formation markers in cross-sectional and longitudinal aspects of the study, including adjustment for age and body weight [46].

Conclusion

Overall, recent findings suggest that coronary calcification is associated with osteoporosis through a variety of potential mechanisms involving molecular regulatory factors that govern both skeletal bone and cardiovascular tissues.

Acknowledgments

The authors were supported in part by NIH grants HL069261 and DK076009.

References

1. Towler DA. Vascular calcification in ESRD: Another cloud appears in the perfect storm--but highlights a silver lining? Kidney Int. 2004; 66:2467–2468. [PubMed: 15569340]
2. Vattikuti R, Towler DA. Osteogenic regulation of vascular calcification: an early perspective. Am J Physiol Endocrinol Metab. 2004; 286:E686–696. [PubMed: 15102615]
3. Schousboe JT, Taylor BC, Kiel DP, Ensrud KE, Wilson KE, et al. Abdominal aortic calcification detected on lateral spine images from a bone densitometer predicts incident myocardial infarction or stroke in older women. J Bone Miner Res. 2008; 23:409–416. [PubMed: 17956153]
4. Guzman RJ. Clinical, cellular, and molecular aspects of arterial calcification. J Vasc Surg. 2007; 45:A57–63. [PubMed: 17544025]
5. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, et al. The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation. 2001; 103:1051–1056. [PubMed: 11222465]
6. Bluestein D, Alemu Y, Avrahami I, Gharib M, Dumont K, et al. Influence of microcalcifications on vulnerable plaque mechanics using FSI modeling. J Biomech. 2008; 41:1111–1118. [PubMed: 18258240]
7. Lin TC, Tintut Y, Lyman A, Mack W, Demer LL, et al. Mechanical response of a calcified plaque model to fluid shear force. Ann Biomed Eng. 2006; 34:1535–1541. [PubMed: 17006755]
8. Chen NX, O'Neill KD, Chen X, Moe SM. Annexin-mediated matrix vesicle calcification in vascular smooth muscle cells. J Bone Miner Res. 2008; 23:1798–1805. [PubMed: 18597635]
9•. Duer MJ, Friscic T, Proudfoot D, Reid DG, Schoppet M, et al. Mineral surface in calcified plaque is like that of bone: further evidence for regulated mineralization. Arterioscler Thromb Vasc Biol. 2008; 28:2030–2034. This report links vascular calcification to bone mineralization at the nanoscale. [PubMed: 18703777]
10. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. Nephrol Dial Transplant. 2008; 23:586–593. [PubMed: 17933842]
11. Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C. Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med. 2006; 259:598–605. [PubMed: 16704561]

12. Tekin GO, Kekilli E, Yagmur J, Uckan A, Yagmur C, et al. Evaluation of cardiovascular risk factors and bone mineral density in post menopausal women undergoing coronary angiography. Int J Cardiol. 2008

13. Farhat GN, Cauley JA, Matthews KA, Newman AB, Johnston J, et al. Volumetric BMD and vascular calcification in middle-aged women: the Study of Women's Health Across the Nation. J Bone Miner Res. 2006; 21:1839–1846. [PubMed: 17002567]

14. Shen H, Bielak LF, Streeten EA, Ryan KA, Rumberger JA, et al. Relationship between vascular calcification and bone mineral density in the Old-order Amish. Calcif Tissue Int. 2007; 80:244–250. [PubMed: 17431532]

15. Sinnott B, Syed I, Sevrukov A, Barengolts E. Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. Calcif Tissue Int. 2006; 78:195–202. [PubMed: 16604285]

16. Adragao T, Branco P, Birne R, Curto JD, de Almeida E, et al. Bone mineral density, vascular calcifications, and arterial stiffness in peritoneal dialysis patients. Perit Dial Int. 2008; 28:668–672. [PubMed: 18981400]

17••. Al-Aly Z, Shao JS, Lai CF, Huang E, Cai J, et al. Aortic Msx2-Wnt calcification cascade is regulated by TNF-alpha-dependent signals in diabetic Ldlr-/- mice. Arterioscler Thromb Vasc Biol. 2007; 27:2589–96. This report identifies molecular signaling mechanisms between inflammation and mineralization. [PubMed: 17932314]

18••. Cheng SL, Shao JS, Cai J, Sierra OL, Towler DA. Msx2 exerts bone anabolism via canonical Wnt signaling. J Biol Chem. 2008; 283:20505–22. This report ties the signaling mechanisms from reference 17 to bone anabolism. [PubMed: 18487199]

19•. Lai CF, Seshadri V, Huang K, Shao JS, Cai J, et al. An osteopontin-NADPH oxidase signaling cascade promotes pro-matrix metalloproteinase 9 activation in aortic mesenchymal cells. Circ Res. 2006; 98:1479–89. [PubMed: 16709900]

20. Aikawa E, Nahrendorf M, Figueiredo JL, Swirski FK, Shtatland T, et al. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. Circulation. 2007; 116:2841–2850. [PubMed: 18040026]

21. Tintut Y, Morony S, Demer LL. Hyperlipidemia promotes osteoclastic potential of bone marrow cells ex vivo. Arterioscler Thromb Vasc Biol. 2004; 24:e6–10. [PubMed: 14670933]

22. Brodeur MR, Brissette L, Falstrault L, Ouellet P, Moreau R. Influence of oxidized low-density lipoproteins (LDL) on the viability of osteoblastic cells. Free Radic Biol Med. 2008; 44:506–517. [PubMed: 18241787]

23. Hirasawa H, Tanaka S, Sakai A, Tsutsui M, Shimokawa H, et al. ApoE gene deficiency enhances the reduction of bone formation induced by a high-fat diet through the stimulation of p53-mediated apoptosis in osteoblastic cells. J Bone Miner Res. 2007; 22:1020–1030. [PubMed: 17388726]

24. Huang MS, Morony S, Lu J, Zhang Z, Bezouglaia O, et al. Atherogenic phospholipids attenuate osteogenic signaling by BMP-2 and parathyroid hormone in osteoblasts. J Biol Chem. 2007; 282:21237–21243. [PubMed: 17522049]

25•. Huang MS, Lu J, Ivanov Y, Sage AP, Tseng W, et al. Hyperlipidemia impairs osteoanabolic effects of PTH. J Bone Miner Res. 2008; 23:1672–1679. This report links hyperlipidemia with potential osteoporotic effects, with important therapeutic implications. [PubMed: 18505371]

26. Sebastian EM, Suva LJ, Friedman PA. Differential effects of intermittent PTH(1-34) and PTH(7-34) on bone microarchitecture and aortic calcification in experimental renal failure. Bone. 2008; 43:1022–1030. [PubMed: 18761112]

27. Shao JS, Cheng SL, Charlton-Kachigian N, Loewy AP, Towler DA. Teriparatide (human parathyroid hormone (1-34)) inhibits osteogenic vascular calcification in diabetic low density lipoprotein receptor-deficient mice. J Biol Chem. 2003; 278:50195–50202. [PubMed: 14504275]

28. Bagger YZ, Rasmussen HB, Alexandersen P, Werge T, Christiansen C, et al. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? Osteoporos Int. 2007; 18:505–512. [PubMed: 17109061]

29. Al-Jallad HF, Nakano Y, Chen JL, McMillan E, Lefebvre C, et al. Transglutaminase activity regulates osteoblast differentiation and matrix mineralization in MC3T3-E1 osteoblast cultures. Matrix Biol. 2006; 25:135–148. [PubMed: 16469487]

30•. Johnson KA, Polewski M, Terkeltaub RA. Transglutaminase 2 is central to induction of the arterial calcification program by smooth muscle cells. Circ Res. 2008; 102:529–537. This report identifies a new regulatory factor shared between bone and vascular mineralization. [PubMed: 18202319]

31. Mikami S, Hamano T, Fujii N, Nagasawa Y, Isaka Y, et al. Serum osteoprotegerin as a screening tool for coronary artery calcification score in diabetic pre-dialysis patients. Hypertens Res. 2008; 31:1163–1170. [PubMed: 18716364]

32. Frost ML, Grella R, Millasseau SC, Jiang BY, Hampson G, et al. Relationship of calcification of atherosclerotic plaque and arterial stiffness to bone mineral density and osteoprotegerin in postmenopausal women referred for osteoporosis screening. Calcif Tissue Int. 2008; 83:112–120. [PubMed: 18612580]

33. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev. 1998; 12:1260–1268. [PubMed: 9573043]

34•. Bennett BJ, Scatena M, Kirk EA, Rattazzi M, Varon RM, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE-/- mice. Arterioscler Thromb Vasc Biol. 2006; 26:2117–2124. This report links bone regulatory factors with atherosclerotic calcification in vivo. [PubMed: 16840715]

35. Morony S, Tintut Y, Zhang Z, Cattley RC, Van G, et al. Osteoprotegerin inhibits vascular calcification without affecting atherosclerosis in ldlr(-/-) mice. Circulation. 2008; 117:411–420. [PubMed: 18172035]

36. Orita Y, Yamamoto H, Kohno N, Sugihara M, Honda H, et al. Role of osteoprotegerin in arterial calcification: development of new animal model. Arterioscler Thromb Vasc Biol. 2007; 27:2058–2064. [PubMed: 17615383]

37. Hofbauer LC, Schrader J, Niebergall U, Viereck V, Burchert A, et al. Interleukin-4 differentially regulates osteoprotegerin expression and induces calcification in vascular smooth muscle cells. Thromb Haemost. 2006; 95:708–714. [PubMed: 16601843]

38. Bakhireva LN, Laughlin GA, Bettencourt R, Barrett-Connor E. Does osteoprotegerin or receptor activator of nuclear factor-kappaB ligand mediate the association between bone and coronary artery calcification? J Clin Endocrinol Metab. 2008; 93:2009–2012. [PubMed: 18319315]

39. Fiore CE, Celotta G, Politi GG, Di Pino L, Castelli Z, et al. Association of high alpha2-Heremans-Schmid glycoprotein/fetuin concentration in serum and intima-media thickness in patients with atherosclerotic vascular disease and low bone mass. Atherosclerosis. 2007; 195:110–115. [PubMed: 17010978]

40. Karasik D, Kiel DP, Kiely DK, Cupples LA, Wilson PW, et al. Abdominal aortic calcification and exostoses at the hand and lumbar spine: the Framingham Study. Calcif Tissue Int. 2006; 78:1–8. [PubMed: 16397734]

41•. Price PA, Chan WS, Jolson DM, Williamson MK. The elastic lamellae of devitalized arteries calcify when incubated in serum: evidence for a serum calcification factor. Arterioscler Thromb Vasc Biol. 2006; 26:1079–85. This report raises the possibility of a circulating factor released from bone that contributes to vascular calcification. [PubMed: 16528009]

42. Price PA, Roublick AM, Williamson MK. Artery calcification in uremic rats is increased by a low protein diet and prevented by treatment with ibandronate. Kidney Int. 2006; 70:1577–83. [PubMed: 16955099]

43. Tamagaki K, Yuan Q, Ohkawa H, Imazeki I, Moriguchi Y, et al. Severe hyperparathyroidism with bone abnormalities and metastatic calcification in rats with adenine-induced uraemia. Nephrol Dial Transplant. 2006; 21:651–659. [PubMed: 16311258]

44. Wilund KR, Tomayko EJ, Evans EM, Kim K, Ishaque MR, et al. Physical activity, coronary artery calcium, and bone mineral density in elderly men and women: a preliminary investigation. Metabolism. 2008; 57:584–591. [PubMed: 18328364]

45. Lee CD, Jacobs DR Jr, Hankinson A, Iribarren C, Sidney S. Cardiorespiratory fitness and coronary artery calcification in young adults: The CARDIA Study. Atherosclerosis. 2008

46. Adami S, Gatti D, Viapiana O, Fiore CE, Nuti R, et al. Physical activity and bone turnover markers: a cross-sectional and a longitudinal study. Calcif Tissue Int. 2008; 83:388–392. [PubMed: 18949504]