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Effect of race and genetics on vitamin D metabolism, bone and vascular health

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Abstract

The pathophysiology of chronic kidney disease–mineral and bone disorder accounts for an inverse relationship between bone mineralization and vascular calcification in progressive nephropathy. Inverse associations between bone mineral density (BMD) and calcified atherosclerotic plaque are also observed in individuals of European and African ancestry without nephropathy, suggesting a mechanistic link between these processes that is independent of kidney disease. Despite lower dietary calcium intake and serum 25-hydroxyvitamin D (25(OH)D) concentrations, African Americans have higher BMD and develop osteoporosis less frequently than do European Americans. Moreover, despite having more risk factors for cardiovascular disease, African Americans have a lower incidence and severity of calcified atherosclerotic plaque formation than do European Americans. Strikingly, evidence is now revealing that serum 25(OH)D and/ or 1,25 dihydroxyvitamin D levels associate positively with atherosclerosis but negatively with BMD in African Americans; by contrast, vitamin D levels associate negatively with atherosclerosis and positively with BMD in individuals of European ancestry. Biologic phenomena, therefore, seem to contribute to population-specific differences in vitamin D metabolism, bone and vascular health. Genetic and mechanistic approaches used to explore these differences should further our understanding of bone–blood vessel relationships and explain how African ancestry protects from osteoporosis and calcified atherosclerotic plaque, provided that access of African Americans to health care is equivalent to individuals of European ethnic origin. Ultimately, in our opinion, a new mechanistic understanding of the relationships between bone mineralization and vascular calcification will produce novel approaches for disease prevention in aging populations.

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Author contributions

Both authors contributed to all aspects of the article.

Competing interests

The authors declare no competing interests.

Introduction

The association between metabolic bone disease and vascular calcification is widely reported in patients with advanced nephropathy. Emerging evidence supports relationships between susceptibility to osteoporosis and calcified atherosclerotic plaque in the absence of kidney disease. This Review summarizes the evidence indicating that maintenance of bone and vascular health is biologically linked and discusses the marked racial differences in susceptibility to low bone density and athero sclerosis. African Americans, despite lower dietary calcium ingestion and serum 25 hydroxyvitamin D (25(OH)D) levels, are less likely to develop osteo porosis than are European Americans. Similarly, African Americans develop lower levels of calcified atherosclerotic plaque than do European Americans, despite greater exposure to conventional cardiovascular disease risk factors (for example, hypertension and diabetes mellitus). Potential biologic mechanisms and genetic susceptibility to development of bone and vascular disease are also discussed here. Moreover, we describe the processes of calcium and vitamin D metabolism as well as novel risk factors that could mediate crosstalk between blood vessels and bone health in individuals with preserved kidney function.

CKD, bone and vascular calcium

Chronic kidney disease–mineral and bone disorder (CKD–MBD) provides a mechanistic explanation of the events that link progressive nephropathy with the development of low bone mineralization and vascular calcification.[1] A central component of CKD–MBD is phosphate retention, which leads to an elevation of fibroblast growth factor 23 (FGF-23) levels, as early as chronic kidney disease (CKD) stage 2. Hyperphosphatemia may worsen if hypocalcemia leads to parathyroid hormone (PTH)-induced increases in bone resorption, which releases calcium from bone, but also liberates additional phosphate from the bone calcium–phosphate reservoir. This model, however, remains under debate.[2] Although bone mineral density (BMD) and vascular calcification are tightly linked in patients with CKD, this process is best viewed as the response of bone and systemic vasculature to an overarching environmental insult—progressive kidney failure. Individual patients with CKD have their own inherent genetic susceptibility to osteoporosis and atherosclerosis; however, the environmental effects of CKD could be a more powerful risk factor than innate genetic risk. Ultimately, in CKD, hyperphosphatemia seems to drive osteoporosis and arterial calcification.

Atherosclerosis and bone health

Inverse relationships between skeletal and vascular calcification are clearly present in individuals with preserved kidney function. In 1964, Anderson *et al.*[3] reported that atherosclerotic calcification of the aorta accompanied osteoporosis in individuals who were routinely assessed in bone clinics. This observation supported the hypothesis proposed by Elkeles in 1957 that a relationship existed between osteoporosis and vascular calcification, particularly in postmenopausal women.[4] These sentinel reports were verified nearly 30 years later in European, European American and African American populations.[5–13] A major issue involved determining whether these phenomena were related or simply reflected

the simultaneous effects of aging on bone and blood vessels. Two longitudinal studies strongly indicated that bone metabolism and calcified atherosclerotic plaque formation are mechanistically related.[6,11] Further support was provided by cross-sectional studies, as the observed inverse associations between BMD and calcified atherosclerotic plaque persisted after adjustment for age and conventional cardiovascular disease (CVD) risk factors such as BMI and LDL cholesterol.[12,13]

Animal models of osteoporosis also provided evidence that genetic mechanisms underlie the relationships between BMD and calcified atherosclerotic plaque. Indeed, mice in which genes that encode inhibitors of mineralization are not expressed have important vascular phenotypes.[14] For example, mice that do not express matrix Gla protein (encoded by *Mgp*), osteo pontin (*Spp1*), fetuin A (also known as α-2-HS glyco protein; encoded by *Ahsg*), klotho (*Kl*), and osteoprotegerin (also known as TNFRSF11B; encoded by *TnfrsfF11b*) demonstrate not only bone, cartilage, and skeletal abnormalities, but also arterial calcification.[15–19] These mice generally have normal kidney function, with the exception of the *Ahsg* deficient mouse, in which accelerated vascular calcification precedes development of CKD.[17] Interestingly, circulating osteoprotegerin concentrations are elevated in humans with high levels of coronary and aortic calcified atherosclerotic plaque.[20] This observation seems to contradict studies using the *TnfrsfF11b* knockout mouse, in which the mice had elevated vascular calcification. This relationship is suggestive of a U-shaped response curve, whereby an optimal level of local *TnfrsfF11b* expression has an inhibitory effect on the development of arterial calcification, but where calcification can occur below or above this level. Moreover, we predict that high levels of circulating osteoprotegerin could occur as a response to ectopic mineralization or be related to a bone metabolic problem. Nonetheless, these results strongly indicate the presence of biologic relationships between bone and blood vessel health in the absence of CKD (Figure 1).

Proposed mechanistic links

Although calcified atherosclerotic plaques have a morpho logic appearance similar to those observed in bone formation,[21] the events that contribute to the initial calcium phosphate (CaPi) precipitation and hydroxyapatite formation in the artery are poorly understood. A number of models, from passive to active, have been proposed to explain these initial events, and are described below (Figure 2).[22–25] The microenvironment of advanced atherosclerotic lesions resembles hyper trophic cartilage in the endochondral growth plate prior to mineralization during long bone development. Cell death, alkaline phosphatase, acidic CaPi complexes, and anoxia are all present in areas that will soon mineralize and form immature CaPi mineral complexes.[26–31] Thus, atherosclerotic plaque calcification might be initiated locally in the arterial wall, perhaps independently from bone metabolism.

Passive models

Simple passive models of vessel-mediated calcification involve apoptosis and/or necrosis of cells in core regions of plaques, resulting in the development of an area rich in acidic phospholipids complexed with Ca^{2+}, and/or simply an elevated local Ca*Pi ion product, perhaps from intracellular sarcoplasmic reticulum and mitochondrial Ca^{2+} stores in dead or

dying cells. Nucleated or spontaneous CaPi precipitation could then lead to the formation and growth of amorphous CaPi and, eventually, hydroxyapatite crystals in the blood vessel.[22–25]

Alternatively, or perhaps in conjunction with the above scenario, the loss of local inhibitors of mineralization, including γ-carboxyglutamic-acid-containing proteins (for example, matrix Gla protein), fetuin A, acidic proteoglycan aggregates (such as versican core protein, which act as calcium sequestrants) and pyrophosphate or other polyphosphates, which can act as crystal poisons, could remove the block to local crystal formation and growth and enable mineralization to progress. The presence of plaque mineral crystals could then cause local cells to dedifferentiate and/or become quiescent,[31] or lead to the recruitment of pluripotent circulating cells (that is, osteoprogenitor or chondroprogenitor cells) to the site of calcification, resulting in a tissue phenotype with similarities to bone by the presence of cells with osteoblastic and/or osteoclastic appearances.

Active models

Active models of vascular calcification involve increased activity of local phosphatases which catalyze CaPi precipitation and crystal formation through increases in free inorganic phosphate generated through hydrolysis of organic phosphates such as nucleoside diphosphates and pyrophosphates, leading to a local elevation in the Ca*Pi ion product. Active programmed models in which resident vascular cells (including pericytes and vascular smooth muscle cells [VSMCs]) independently (in absence of pre-existing mineral) acquire a phenotype similar to that of mineralizing cells (that is, chondrocytes or osteoblasts) and initiate the initial precipitation of CaPi have also been suggested.[32] This phenotypic change has been postulated to occur, in part, in response to oxidized lipids, hyperglycemia, or inflammation in the vessel wall—conditions that have been shown to promote mineral formation *in vitro* in cultured VSMCs.[21,24,25,32]

Postulated mechanisms that directly link bone loss with calcification in the artery include the release of Ca^{2+} and phosphate from bone, perhaps in the form of CaPi complexes, via increased osteoclast-mediated resorptive processes.[32] The released mineral ions and/or complexes may then localize to vascular sites that are susceptible to atherosclerosis where they form a nidus for future mineralization or lead to locally elevated Ca^{2+} and/or phosphate levels, promoting spontaneous CaPi precipitation or growth of arterial CaPi precipitates. In the absence of inhibitors of vascular calcification (such as fetuin or matrix Gla protein), the growth of these precipitates is likely to occur regardless of the mechanism underlying the initial CaPi precipitate. Substantial evidence suggests that the elevation of phosphate levels is important in the initiation and propagation of plaque mineral.[33] Clearly, the inverse relationships between bone mineralization and vascular calcification indicate that a net transfer of mineral ions from bone to mineralization-prone sites occurs in arteries. Sex hormones, calciotropic hormones, calcification inhibitors, cell differentiation machinery, and inflammatory factors have been suggested as being important in these models and may underlie, in part, the observed ethnic and sex differences in bone mineralization and vascular calcification.

Ethnicity and serum vitamin D

Consistent inverse relationships are seen between bone mineralization and vascular health in diverse population groups of both African and European ethnic origin. Despite these common relationships, interesting and unique population-specific characteristics are also present, which require detailed investigation. Serum 25(OH)D concentrations are markedly lower in individuals of African ancestry than in those of European ancestry,[34–36] which might be attributable to the association of darker skin pigmentation with a low efficiency of vitamin D activation.[37] However, this hypothesis fails to account for a multitude of potentially related biologic observations. If individuals with African ancestry truly had higher frequencies of 25(OH)D deficiency, this effect should, theoretically, lead to a lower BMD and put them at higher risk of osteoporosis than individuals of European ancestry; data from epidemiologic and clinical studies conducted in the USA have, however, revealed the opposite trends.[38,39] Indeed, despite lower 25(OH)D levels and generally lower dietary calcium ingestion, African Americans have greater bone mass, higher bone density and lower rates of osteoporosis than do European Americans.[38,39] Therefore, the lower plasma 25(OH)D levels observed in African Americans might be physiologically normal. In our opinion, the normal range of 25(OH)D levels in individuals with African ancestry is likely to be lower than in individuals of European origin[35,36] and, as such, the appropriate ‘normal’ range for 25(OH)D levels needs to be determined in different population groups.[40–42] In addition, young adult African Americans have higher levels of active (intact PTH and 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) and increased renal tubular calcium reabsorption than do European Americans.[43–45] These factors are also likely to contribute to racial differences in susceptibility to bone disease.

In agreement with the recognized racial differences in the risk of developing calcified athero sclerotic plaque and osteoporosis, the association of serum vitamin D ($1,25(OH)_2D$) and vitamin D precursor or metabolite levels with these disease processes differ in different populations (Box 1). BMD and calcified athero sclerotic plaque have negative relationships in both African Americans and European Americans; however, vitamin D and/or vitamin D precursor levels are positively associated with BMD in European Americans and negatively associated in African Americans.[42,46] In addition, 25(OH)D levels were negatively associated with calcified atherosclerotic plaque in European Americans and positively associated in African Americans.[42,46] These findings strongly indicate that biologic differences exist across population groups. We believe that osteoporosis favors the development of atheromatous intimal calcification, which is associated with an increased risk of CVD events and death in the presence of increasing coronary artery calcified atherosclerotic plaque.[47,48] Medial calcification is commonly present in patients with CKD and/or diabetes; however, whether low BMD favors development of medial calcification remains unknown.

Current 25(OH)D target ranges are based largely on reference ranges set in populations of European origin. As mentioned above, this ‘normal’ range is likely to differ in African Americans. The African American–Diabetes Heart Study reported that higher ambient 25(OH)D serum levels were associated with higher levels of vascular calcified atherosclerotic plaque in a cross-sectional analysis; the opposite trend is observed in

populations of European ancestry.[46] This observation may cause concern regarding the safety of providing vitamin D supplements for presumed low vitamin D levels observed in African Americans. Aloia *et al.*[49] supplemented 25(OH)D in calcium-replete postmenopausal African American women with osteopenia and found no changes in BMD even after 2 years, suggesting that replacing 25(OH)D to the desired levels in European American women was ineffective in African Americans. Additional evidence for population specific ranges for optimal circulating vitamin D levels is provided by our paradoxical observation that higher vitamin D levels were associated with lower BMD in African Americans.[46] This initially surprising finding is supported by observations of higher fracture rates with higher 25(OH)D levels in African American participants in the Women's Health Initiative (WHI), an observation directly opposing that seen in European American WHI participants.[50] In concert with the racially variable relationships between 25(OH)D, bone and vascular health, the 2011 Institute of Medicine Report recommends vitamin D supplements only for maintaining bone health; benefits on cardiovascular health and cancer risk remain unproven.[42] We feel that the optimal 25(OH)D levels in African Americans are likely to be lower than those in European Americans.[35] At present, supplemental 25(OH)D in African Americans with levels <30 ng/ml does not seem to be indicated in those without osteopenia or osteoporosis.[42]

Vitamin D has been associated with both inhibition and progression of vascular calcification.[51] Levels of $1,25(OH)_2D$ in African Americans are typically equal or higher than those in European Americans. These increased levels could be a protective factor against calcified atherosclerotic plaque and osteoporosis in African-derived populations, although no evidence for such a relationship was found in our studies. Some evidence exists to suggest that higher administered doses of active vitamin D may underlie improved survival rates in African Americans with end-stage renal disease (ESRD), relative to European Americans.[52,53] Clearly, the mechanisms underlying racial differences in vitamin D handling and tissue-specific responses require additional study.

Ethnicity and calcium metabolism

The existing literature provides evidence that systemic calcium, vascular, and bone metabolism are differentially regulated between populations of African and European origin (Table 1). Observations of racial differences in susceptibility to osteoporosis and vascular calcification date back to 1968.[54] In addition to markedly lower 25(OH)D levels, African Americans also ingest less dietary calcium than European Americans,[55] perhaps in part, owing to lactase deficiency resulting in reduced ingestion of dairy products.[56] Lactase deficiency in African Americans often relates to variation in genes regulating lactose metabolism.[57] Despite this reduced calcium intake, however, African Americans have lower rates of osteoporosis than do European Americans and show skeletal resistance to the effects of PTH, potentially contributing to lower rates of bone resorption.[58] Lower rates of calcium-containing kidney stone formation are also seen in African Americans when compared with European Americans.[59] In a small study of healthy individuals and patients with CKD, postprandial phosphorus and calcium excretion were lower in African Americans than in European Americans with and without CKD, whereas FGF-23 and PTH levels were similar in both populations.[60] Polymorphisms in *VDR*, the gene that

encodes the vitamin D_3 receptor, affect PTH levels in patients with nephropathy;[61] genetic variation in *VDR* could therefore be responsible for the observed differences between African Americans and European Americans.[45] As discussed above, ethnic differences are present in the circulating levels of factors and/or hormones regulating bone and blood vessel mineralization. Moreover, differences in the tissue response to such factors and hormones might also exist. Indeed, Shao *et al.*[62] revealed that the bone and vascular tissue in mice with diabetes and deficient in the LDL receptor responded differently to exogenous PTH administration—PTH reduced vascular calcification but enhanced bone mineralization in these knockout mice. Thus, bone tissue and blood vessels could also respond differently to regulatory factors in African Americans and European Americans; relationships between PTH and BMD or calcified atherosclerotic plaque, however, were not observed in our prior report.[13]

Numerous unique metabolic characteristics related to calcium and phosphate handling distinguish African Americans from European Americans; these characteristics may have a genetic basis. A genome-wide association study performed in Icelandic and Dutch Europeans revealed that variants in *CLDN14*, which encodes Claudin-14, were associated with susceptibility to calcium nephrolithiasis and increased urinary calcium excretion (with lower serum bicarbonate concentrations), as well as lower BMD in the hip and spine. These observations thereby link genes that encode proteins involved in renal calcium metabolism and those involved in bone health.[63]

The variable risk of developing calcified atherosclerotic plaque between African Americans and European Americans is considered to be one of the most striking biologic effects related to differences in calcium metabolism between populations.[64–68] It is widely reported that African Americans in the general population are at higher risk of myocardial infarction and CVD events than are European Americans.[69] This increased risk likely reflects higher rates of conventional CVD risk factors in African Americans, including higher rates of hypertension and diabetes (with associated poorer regulation of blood pressure and diabetes), higher rates of albuminuria and subclinical nephropathy, and generally more restricted access to health care and lower socioeconomic status.

A different clinical pattern emerged when access of African Americans and European Americans to health care was equalized: African Americans with diabetes had approximately 50% lower rates of myocardial infarction compared with European Americans with diabetes in the Veteran's Administration and Kaiser Permanente Healthcare Systems.[70,71] These landmark studies recruited nearly 500,000 patients with diabetes and the results were consistent between reports. Although significantly higher rates of subclinical nephropathy were detected in African Americans in both of these healthcare system reports, CVD rates were significantly lower in African Americans. These results parallel those in patients receiving Medicare-supported renal replacement therapy.[72] African Americans undergoing dialysis (who tend to receive equivalent access to medical care as European Americans) have markedly lower rates of myocardial infarction and longer survival rates than do European Americans.[72–74] However, one report found poorer survival of young African American men (aged 18–30 years) than of European men at this age.[75]

Racial differences in susceptibility to CVD are likely to contribute to the lower mortality rates observed in African Americans with ESRD.[76]

Shared risk of CVD and low BMD

Equivalent access to health care might enable detection of biologic differences favoring lower rates of athero sclerosis (improved vascular health) in African Americans. Nearly all published reports reveal that African Americans have substantially lower rates of calcified atherosclerotic plaque than do European Americans. This phenomenon is not unique to patients with diabetes; populations with and without diabetes mellitus clearly reveal this effect.[64–68] Even the large population-based Dallas Heart Study, one of the few reports that failed to observe lower levels of calcified atherosclerotic plaque in African Americans relative to European Americans, reported similar levels of calcified atherosclerotic plaque in African and European Americans despite excessive frequencies of conventional CVD risk factors in African Americans.[77] Conventional CVD risk factors including hypertension, diabetes mellitus, smoking, and LDL-cholesterol levels fail to explain racially variable patterns of calcified atherosclerotic plaque.[78] Novel CVD risk factors, including genetic polymorphisms, albuminuria, and pericardial adipose tissue, however, do seem to have a role.[79–81] A landmark report by the Multi-Ethnic Study of Atherosclerosis (MESA) investigators demonstrated that African Americans with higher levels of calcified atherosclerotic plaque had significantly higher degrees of European ancestry than those with lower levels of calcified atherosclerotic plaque.[79] These findings reverse the long-held belief that African Americans face a higher biologic risk of calcified atherosclerosis than do European Americans; these individuals are actually at lower biologic (inherited) risk, although the effect may be overcome by adverse environmental exposures. Similar results have been observed in the African American-Diabetes Heart Study (B. I. Freedman, unpublished work).

Two studies have provided proof-of-concept that circulating 25(OH)D, as well as susceptibility to calcified atherosclerotic plaque, may have a genetic basis. A genome-wide association study of serum 25(OH)D levels identified polymorphisms in the enzyme 1,25-dihydroxy vitamin D_3 24-hydroxylase (encoded by the mitochondrial gene *CYP24A1* on chromosome 20) as being significantly associated with 25(OH)D deficiency.[82] *CYP24A1* is involved in the degradation of 1,25-dihydroxyvitamin D_3. In the same year, variation in *CYP24A1* was associated with levels of coronary artery calcified atherosclerotic plaque.[83] Hence, genes regulating vitamin D metabolism are associated with calcified atherosclerotic plaque. We investigated the potential role of three genes involved in bone formation in BMD and calcified atherosclerotic plaque. Several polymorphisms in the bone morphogenetic protein 7 gene (*BMP7*), but not in *BMP2* or *BMP4*, were associated with an inverse relationship between BMD and calcified atherosclerotic plaque in European Americans with type 2 diabetes.[84] Together, these studies suggest that an inverse association between BMD and calcified atherosclerotic plaque is biologically mediated and is not solely attributable to the effects of aging or shared environmental exposures.

Admixture mapping

African Americans are an admixed population group— their genomes are composed of approximately 80% African and 20% European ancestry. When continental isolation ended with forced migration during the slave trade, mixing of the African genome with European, Caribbean and other genomes ensued. This phenomenon led to the currently observed admixture in African Americans. The novel genetic mapping methodology admixture mapping (also called Mapping by Admixture Linkage Disequilibrium, MALD) can be useful in the setting of an admixed population group with differential disease risk in parental populations.[85,86] MALD employs carefully selected genetic markers with markedly different frequencies between ancestral populations. The frequencies of these ancestry informative markers are compared across the genome in admixed cases with disease versus admixed controls without disease. Case-only studies can also be performed. Frequency differences in markers are compared between cases and controls to detect regions with excess (or reduced) frequencies of ancestral markers in given chromosomal regions. Associated disease genes likely reside under MALD peaks.

The most impressive discovery of a disease-associated gene using MALD was identification of the association between the genes that encode myosin-9 (*MYH9*) and apolipoprotein L1 (*APOL1*) with nondiabetic forms of nephropathy in African Americans.[87–89] African Americans have higher rates of nondiabetic nephropathy including focal segmental glomerulosclerosis (FSGS), HIV-associated collapsing glomerulopathy, and hypertension-attributed nephropathy than do European Americans.[90] Socioeconomic factors, conventional risk factors for renal disease (including prevalence and severity of hypertension and HIV infection) failed to account for this higher frequency of nephropathy in African Americans. Marked familial aggregation of nondiabetic ESRD is observed in African Americans.[91,92] As such, MALD identified a region on chromosome 22q with a significant 10% excess frequency of African ancestry among African American cases with FSGS compared with African American non-nephropathy controls. Fine mapping under this peak subsequently identified the major *APOL1* association with nondiabetic ESRD in African Americans, with odds ratios of 7.3, 17, and 29, for hypertension-attributed ESRD, idiopathic FSGS, and HIV-associated nephropathy; these genetic associations are among the most powerful in complex human disease.[89,93]

These findings provide a strong rationale for using this genetic methodology to detect genes simultaneously regulating bone and vascular health in African Americans. Candidate gene approaches are limited by the need to test several hundred genes that are potentially involved in disease progression, as well as by our limited understanding of the pathophysiology of these syndromes.[94] Not only could genes such as *MGP*, *SPP1*, *AHSG*, *KL* and *TNFRSF11B* have a role in human disease as they do in animal models, but their receptors and signaling pathways could also be involved. It is far more appropriate to perform unbiased genome-wide mapping for these disorders. We believe that applying MALD mapping to the complex and related phenotypes of BMD and calcified atherosclerotic plaque in the admixed African American population has great potential in this regard.

As African Americans have biologically lower rates of calcified atherosclerotic plaque and osteoporosis than do European Americans, both of these related disorders seem to originate from European ancestry.[79] As such, we expect MALD to detect higher frequencies of European ancestry markers in chromosomal regions harboring disease-associated genes in African Americans who have low BMD or high levels of calcified atherosclerotic plaque. Indeed, MESA identified an excess frequency of European ancestry in African Americans with high levels of calcified atherosclerotic plaque.[79] Based on the results of animal and human studies, it seems likely that polymorphisms in genes that regulate bone mineralization, calcium, phosphate, and vitamin D metabolism are involved in susceptibility to both calcified atherosclerotic plaque and osteoporosis in individuals without advanced nephropathy.

Conclusions

Recognition of population-specific differences in susceptibility to osteoporosis and calcified atherosclerotic plaque among individuals without advanced nephropathy is an important first step towards designing studies that will enable identification of mechanisms linking bone mineralization and vascular calcification, particularly in African Americans. This research provides insights into potential pathways, which may be targeted to improve health outcomes in many ethnic groups. This work is particularly important with respect to our increasingly aging populations who are at high risk of developing these debilitating conditions.

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Key points

- Inverse relationships exist between bone mineral density (BMD) and calcified atherosclerotic plaque in individuals of European and African ancestry without nephropathy
- African Americans have higher BMD and develop osteoporosis less often than do European Americans, despite lower serum 25-hydroxyvitamin D levels and dietary calcium intake
- European Americans have higher incidence rates and severity of calcified atherosclerotic plaque relative to African Americans despite fewer cardiovascular disease risk factors
- Inherited phenomena are likely to contribute to population-specific differences in vitamin D metabolism, vascular calcification, and bone mineralization
- Molecular genetic approaches will enhance our understanding of bone and vascular health

Box 1 |

Relationship between vitamin D, BMD and atherosclerosis by ethnicity

BMD and calcified atherosclerotic plaque are inversely related in patients without nephropathy

- Serum vitamin D levels are positively associated with calcified atherosclerotic plaque in African Americans and negatively associated in European Americans
- Serum vitamin D levels are negatively associated with BMD in African Americans and positively associated in European Americans

Abbreviation: BMD, bone mineral density.

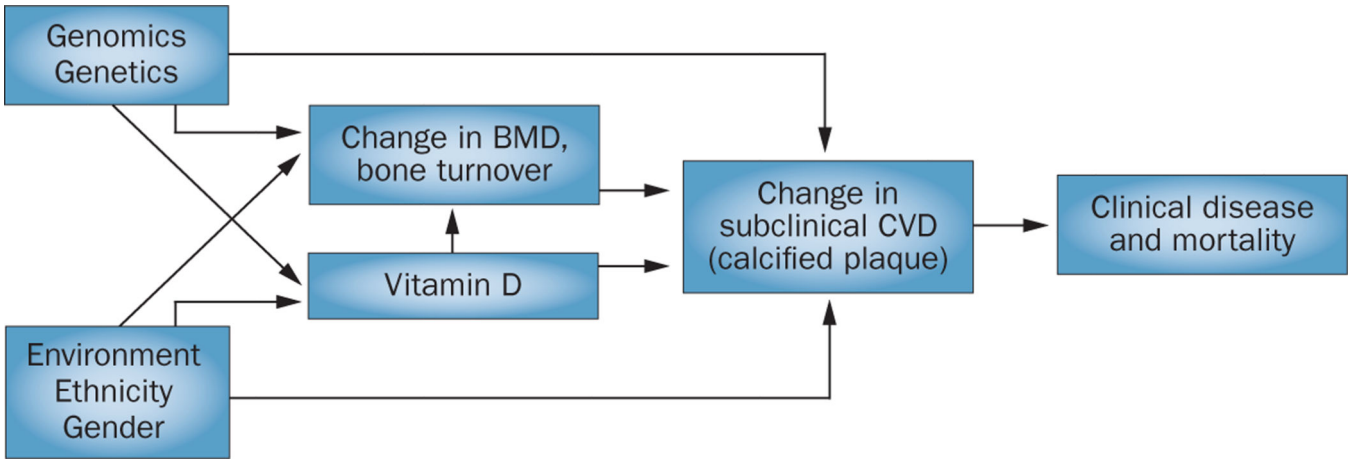

Figure 1 |.

Relationships between bone and vascular calcium and phosphate deposition and dependence upon the environment, ethnicity, sex, and genetic factors. Abbreviations: BMD, bone mineral density; CVD, cardiovascular disease.

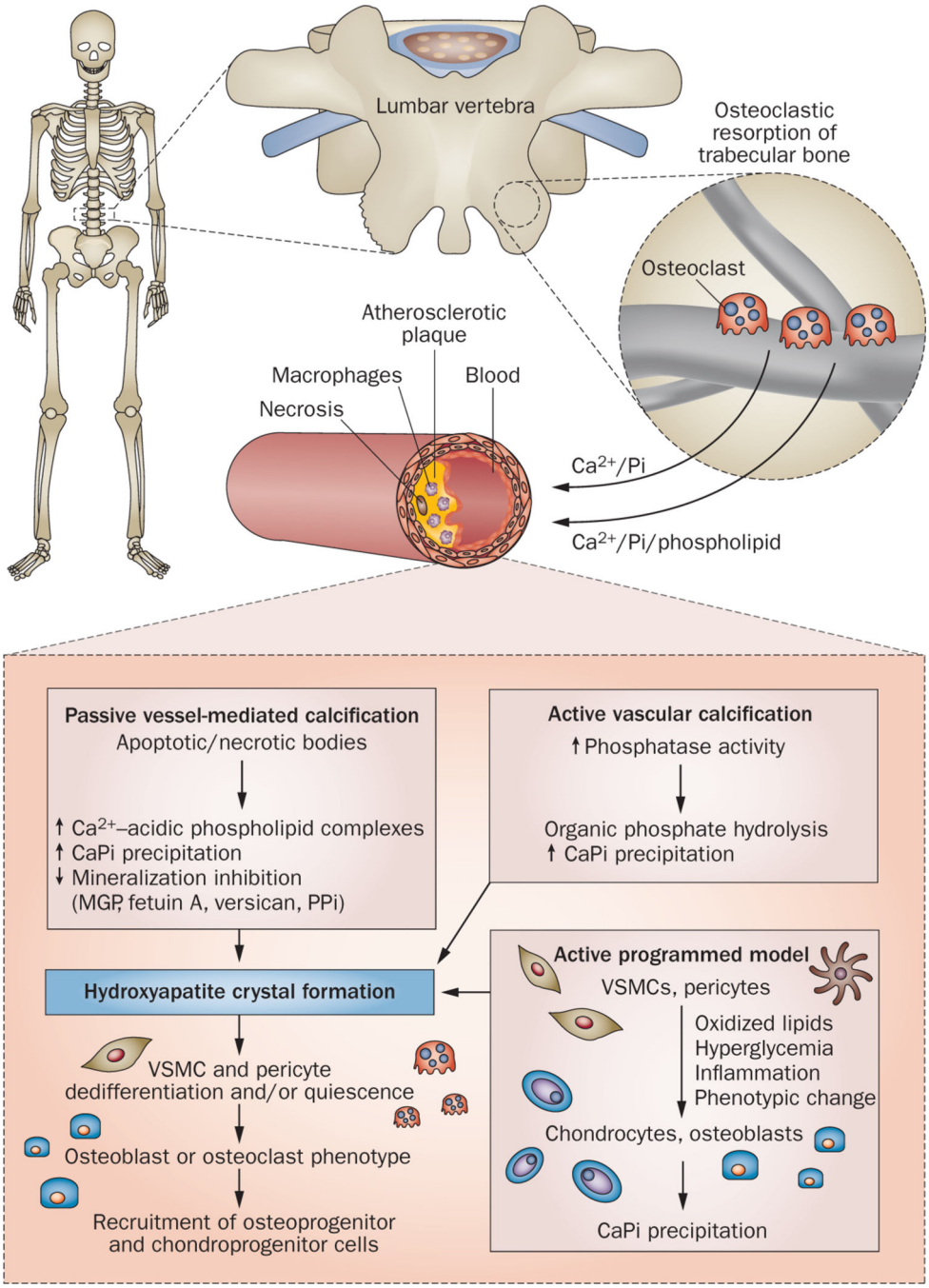

Figure 2 |.

Proposed mechanistic links between metabolic bone disease, atherosclerosis, and vascular calcification. Passive, vessel-mediated calcification in an advanced atherosclerotic lesion may involve apoptosis and/or necrosis of cells in core regions of plaques, which results in the development of an area rich in acidic phospholipids complexed with Ca^{2+}, and/or an elevated local CaPi ion product. CaPi precipitation could then lead to the formation and growth of amorphous CaPi and eventually to hydroxyapatite crystals in the vessel. The loss of local inhibitors of mineralization could remove the block to local crystal formation

and growth and allow mineralization to progress. The presence of plaque mineral crystals could then facilitate a process whereby local cells dedifferentiate and/or become quiescent and assume a phenotype consistent with the bone remodeling process (that is, osteoblasts and/or osteoclasts), or lead to recruitment of pluripotent circulating cells (osteoprogenitor or chondroprogenitor cells) to the site. More active models of vascular calcification involve increased activity of local enzymes (phosphatases), which catalyze amorphous CaPi precipitation and crystal formation through increases in free inorganic phosphate generated through hydrolysis of organic phosphates. Active programmed models in which resident vascular cells independently assume a phenotype consistent with mineralizing cells (chondrocytes or osteoblasts) and initiate the initial precipitation of CaPi have also been suggested. This phenotypic change might occur, in part, in response to oxidized lipids, hyperglycemia, or inflammation in the vessel wall. Postulated mechanisms linking bone loss directly to mineralization in the artery include the release of Ca^{2+} and Pi from bone, perhaps in the form of CaPi complexes, which then localize to atherosclerosis-prone vascular sites where they form a nidus for future mineralization or lead to locally elevated Ca^{2+} and/or Pi levels. These increased levels would then promote spontaneous CaPi precipitation or growth of arterial CaPi precipitates or hydroxyapatite. Abbreviations: CaPi, calcium phosphate; MGP, matrix Gla protein; PPi, pyrophosphate; VSMC, vascular smooth muscle cell.

Table 1 |

Factors that potentially affect racial variation in bone and vascular disease

Parameter	African Americans	European Americans
Calcified atherosclerotic plaque	↓	↑
Osteoporosis	↓	↑
Serum 25 hydroxyvitamin D	↓	↑
Serum 1,25 dihydroxyvitamin D	↑	↓
Serum intact parathyroid hormone	↑	↓
Dietary calcium ingestion	↓	↑
Renal tubular calcium reabsorption	↑	↓
Calcium containing kidney stones	↓	↑

Abbreviations: ↑, increased risk of the specified parameter; ↓, decreased risk of the specified parameter.