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Regulation of Calcific Vascular and Valvular Disease by Nuclear Receptors

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Abstract

Purpose of review: This review addresses recent developments in studies of lipid regulation of calcific disease of arteries and cardiac valves, including the role of nuclear receptors. The role of lipid-soluble signals and their receptors is timely given the recent evidence and concerns that lipid-lowering treatment may increase the rate of progression of coronary artery calcification, which has been long associated with increased cardiovascular risk. Understanding the mechanisms will be important for interpreting such clinical information.

Recent findings: New findings support regulation of calcific vascular and valvular disease by nuclear receptors, including the vitamin D receptor, glucocorticoid receptor, nutrient-sensing nuclear receptors (liver X receptor, farnesoid X receptor, and peroxisome proliferator-activated receptors), and sex hormone (estrogen and androgen) receptors. There were two major unexpected findings: First, vitamin D supplementation, which was previously believed to prevent or reduce vascular calcification, showed no cardiovascular benefit in large randomized, controlled trials. Second, both epidemiological studies and coronary intravascular ultrasound studies suggest that treatment with HMG-CoA reductase inhibitors increases progression of coronary artery calcification, raising a question of whether there are mechanically stable and unstable forms of coronary calcification.

Summary: For clinical practice and research, these new findings offer new fundamental mechanisms for vascular calcification and provide new cautionary insights for therapeutic avenues.

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Conflicts of interest

None

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Keywords

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Introduction

This review is focused on lipids and mineralization, specifically the contributions of nuclear receptors to calcific vascular and valvular diseases (CVVD) as well as interactions between therapies for osteoporosis and cardiovascular disease. A number of recent reviews have considered other aspects of these disorders, including the roles of oxidized lipoproteins [1], lipoprotein(a) [2], and both [3]; the unique manifestations in patients with chronic kidney disease [4], affecting primarily the medial layer of vessels [5]; the role of matrix vesicles and extracellular vesicles [6, 7]; potential inhibition by vitamin K and its relationship to clinical warfarin therapy [8]; potential artifacts in imaging [9]; and biomechanical factors [10].

Nuclear receptors

A number of landmark studies in the 1980s provided unequivocal evidence that structurally related transcription factors can directly interact with endogenous signaling molecules to specify physiologic effects [11], launching the field of nuclear receptor biology. Today, much is known about the functional domains, interacting partners, and preferential DNA binding patterns of the 48 members of this superfamily [12]. This research has provided fundamental insights into contributions of gene regulatory mechanisms in health and disease.

In general, nuclear receptors are activated inside of cells in response to hormones or lipid soluble signals such estrogen, retinoic acid or vitamin D [13]. They can exist as monomers, homodimers or heterodimers and bind specific DNA sequences to induce or repress the expression of target genes upon ligand stimulation [13]. Not surprisingly, the ability of nuclear receptors to serve as important conduits between environmental clues and gene expression is absolutely critical to the maintenance of vascular homeostasis and bone turnover. Dysregulation in nuclear receptor pathways can lead to a number of pathologic states including cardiac calcification, atherogenesis, and abnormal skeletal mineralization. We review below the contributions of specific nuclear receptors in calcific vascular disease.

Vitamin D receptor

In recent years, vitamin D has received widespread attention due to a campaign targeting physicians to measure levels and treat presumed deficiency [14]. Based on observational studies, which had unavoidable biases, it was believed that vitamin D supplementation would prevent cardiovascular disease as well as numerous other diseases including cancer. However, recent results from the VITAL [15] and J-DAVID [16] randomized, controlled trials showed that vitamin D supplementation fails to reduce risk of cardiovascular or other diseases. Thus, the campaign led to a marked increase in the number of tests for blood levels and an increased rate of clinical hypervitaminosis D from excess supplementation without demonstrable benefit [15]. The past few years have seen a global increase in 25(OH)D levels

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in the general population attributed to excess vitamin D supplementation [17], and this may increase the risk of calcific vascular and valvular disease worldwide [18].

As background, the dihydroxy- form of vitamin D [1,25$(OH)_2$D] is the active form, which is a ligand for the vitamin D receptor (VDR), which regulates calcium and phosphate homeostasis. The level of the monohydroxy- form [25(OH)D] is an indicator of the adequacy of stores. Activation of 25(OH)D to the dihydroxy form occurs by the action of 1-alpha hydroxylase, located primarily in the kidney, but also in the vasculature and in activated immune cells [19]. Thus, chronic kidney disease requires supplementation with the active form. VDR forms a permissive heterodimer with retinoid X receptor (RXR) and, upon stimulation of its ligand-binding domain by 1,25$(OH)_2$D, it is capable of regulating a specific subset of genes that mediate calcium/phosphate transport and bone turnover, such as osteocalcin, osteopontin, transient receptor potential (TRPV6, which functions in renal calcium resorption), parathyroid hormone (PTH), and its related peptide (PTHrP), Cyp24a1 (24-hydroxylase, which limits formation of active vitamin D) and Cyp27b1 (1alpha-hydroxylase, which converts the monohydroxy- to the dihydrox- form) [19]. VDR also collaborates with other transcriptional regulators, such as RUNX2, which is considered a central factor in osteoblastic differentiation of vascular cells [20].

Excess vitamin D intake, leading to hypervitaminosis D, has been a known cause of vascular calcification for almost a century [18]. Administration of vitamin D to mice, rats, rabbits, and pigs is widely used as an experimental model for vascular, renal, and pulmonary calcification [21–24]. A recent report raises the possibility of that fibroblast growth factor 21 may mitigate vitamin D-induced vascular calcification [25], but therapies, other than discontinuing unnecessary supplementation, are not established. Thus, unmonitored, prolonged, and empirical vitamin D supplementation carries risk of widespread calcific cardiovascular disease [17].

At the same time, extremely low levels of vitamin D, hypovitaminosis D, have also been associated, to a lesser degree, with vascular calcification. Epidemiologically, the links between low vitamin D levels and poor health in human observational studies are confounded by the fact that infirm individuals typically have limited sun exposure. That is, illness causing low vitamin D may account for the associations. Recent studies in mice, though, show that low dietary vitamin D is also associated with vascular calcification in wild type, LDLR null mice [26] and apolipoprotein E null mice [27]. But the degree of vascular calcification caused by low dietary vitamin D was much less than that caused by excess vitamin D. In mice deficient in VDR, aortic calcification was reported [27], but it was only on the valve leaflets where pigmentation may be mistakenly identified as calcification by von Kossa histochemical stain. Humans with loss-of-function mutations in VDR, known as hereditary vitamin D resistant rickets [28], are not known to have vascular calcification, though possibly because of the young age of subjects. Interpretation of the findings in VDR mutants is complex, given that there are ligand-independent effects of VDR, such as alopecia and gut-adipose crosstalk [29].

These results are consistent with the notion that the relationship between vitamin D and vascular calcification is complex, and multiple redundant regulatory circuits work

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cooperatively to regulate its levels, including a negative feedback loop through 24-hydroxylase. Adding another layer of complexity is that serum vitamin D level, often used as surrogate marker of vitamin D activity in clinical practice and investigative studies, does not generally reflect VDR transcriptional output and signaling [30, 31].

It is well established that inflammation augments vascular calcification. Although VDR is abundantly expressed in immune-cells and has potent anti-inflammatory properties [32–35], these effects are likely minor compared with the pro-mineralization effects of hypervitaminosis D. Intriguingly, statins, which possess potent anti-inflammatory properties and overall favorable effects on cardiovascular outcomes, have been shown to accelerate vascular calcification [36]. Thus, it is tempting to speculate, based on these observations, that sustained immune suppression or direct effects of statins on 25(OH)D levels and VDR activity [37, 38] may contribute to vascular mineralization. With recent guidelines placing a stronger emphasis on use of calcium scans in cardiovascular risk stratification [39], a better understanding of the connections between statins, vitamin D, and vascular calcification has become essential.

Glucocorticoid Receptor

One of the most widely studied nuclear receptors, the glucocorticoid receptor (GR), has an established role in potently inhibiting inflammation. GR is ubiquitously expressed, and insights into the contributions of GR to vascular mineralization stem from well-known side effects of glucocorticoids (GC) on bone, including increased turnover. Activation of GR is known to modulate osteoblast and osteoclast differentiation and function, resulting in reduced bone mass. It also leads to induction of receptor activator of nuclear factor-kappa b ligand (RANKL), which promotes osteoclast differentiation, and it also suppresses osteoblast-derived cytokines such as IL-11 [40]. In vascular pericytes, which may be the origin of at least some resident vascular pre-osteoblastic cells [41], GC treatment leads to enhanced osteogenic differentiation, effects that were abolished with GR antagonist treatment [42]. In addition, GR signaling in macrophages may contribute to vascular calcification. Deletion of the GR in macrophages showed no effect on atherosclerosis burden, but it attenuated vascular calcification and expression of osteogenic factors RANKL, BMP2, and Msx2 [43]. More recent evidence has linked GR activation with cancer metastasis, a feature that may lead to eventual arteriolar calcification [44]. In addition to activating GR, the effects of steroids on vascular calcification are thought to be, at least in part, mediated by the closely related mineralocorticoid receptor [45], whose activation leads to osteoblastic differentiation and mineralization of vascular smooth muscle cells [46]. The structurally related growth hormone-releasing hormone (GHRH) has been recently shown to inhibit vascular calcification through regulation of inflammation-mediated osteogenesis [47]. Thus, multiple lines of evidence support the notion that GR plays an important role in VC, but whether the observed effects are due to direct transcriptional activities of GR remains unclear.

Nutrient-sensing nuclear receptors (LXR, FXR, and PPARs)

Liver X receptors (LXRs) are sterol-sensing nuclear receptors with critical roles in regulating lipid metabolism. Like other nuclear receptors, LXRs are activated upon

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stimulation of their ligand-binding domain. In response to accumulation of oxysterols, they exchange transcriptional corepressors with coactivators to potently inhibit inflammation and to induce the expression of genes involved in cholesterol efflux, triglyceride synthesis, lipid uptake, phospholipid composition, and cholesterol feedback [48]. LXR activation *in vitro* has been shown to augment vascular cell calcification induced by PKA signaling [49], while loss of LXR function attenuates this effect [50]. The mechanism may be related to LXR-mediated increases in lipogenesis [50]. Similar in some respect to LXRs, farnesoid X receptors (FXRs) are bile-acid sensors that play important roles in cholesterol and bile acid regulation. Activation of FXR in calcifying vascular cells reduces triglyceride accumulation and inhibits mineralization [51]. In addition, activation of FXR *in vivo* reduces vascular calcification without impacting atherosclerosis development, possibly via JNK phosphorylation [51]. In contrast, in bone marrow stromal cells, FXR activation increases calcification [52], suggesting context-dependence. Finally, activation of the peroxisome proliferator-activated receptors (PPARs), the targets of thiazolidinedione drugs, inhibits vascular calcification through favorable metabolic effects that lead to upregulation of Klotho or modulation of WNT signaling [53–55]. In general, precise mechanisms as to how nutrient-sensing nuclear receptors may regulate vascular calcification remain undefined. Direct transcriptional control of canonical regulators of bone mineralization has not been shown. A common thread, however, to the activity of the above nuclear receptors is regulation of inflammatory activation as well as modulation of intracellular stearate and lipid content with downstream ossification [50]. Development of selective modulators of LXR and FXR has been of immense interest owing to the favorable effects of these receptors on atherosclerosis (LXR), cancer (LXR) and fatty liver diseases (FXR). A number of compounds are currently in various stages of clinical development, which should provide more insights into the contributions of these receptors to human vascular calcification.

Sex hormone receptors (ER and AR)

The role of estrogen in cardiovascular health and disease has been a controversial topic, both with respect to hormone replacement therapy in patients and with respect to effects on vascular calcification. Estrogen activates two subtypes of estrogen receptor (ER), ER-alpha and ER-beta. While some in vitro studies had shown 17beta-estradiol (E2) inhibited vascular cell calcification [56, 57], one showed E2 stimulated vascular cell calcification [58]. A more definitive study showed not only stimulation of osteogenic calcification in vascular cells by E2, but also in vivo stimulation of osteogenic calcification in aged (atherosclerotic) ApoE null mice of both sexes [59]. In a seeming paradox, they also found that direct antagonism of either alpha or beta subtypes of ER also promoted vascular calcification, but it was consistent with their finding that E2 suppressed expression of ER-beta [59], suggesting an inhibitory feedback mechanism, non-genomic effects of E2, or cross-talk with other co-activators or nuclear receptors in the presence of excess E2.

One mechanism by which estrogen may influence vascular calcification is through upregulation of BMP-2 [60, 61]. The involvement of other sex hormones, such as the androgen receptor (AR), in vascular calcification remains unclear with studies showing opposing effects of AR activation on vascular calcification [62, 63]. With respect to human calcific disease, recent evidence from the large, NIH-funded Multi-ethnic Studies of

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Atherosclerosis (MESA) indicates that baseline sex hormone levels are not associated with coronary calcium score, but that higher free testosterone levels associate with greater CAC progression at up to 10-years in post-menopausal women [64]. Overall, potential therapeutic directions based on associations need to take into consideration potential confounding due to effects of patient compliance and its correlation with health lifestyle [65].

Relations to skeletal calcification

Calcific atherosclerosis and osteoporosis often co-exist in patients [66], as do coronary artery disease and osteoporosis [67–70]. One possible mechanism for this reciprocal relationship between artery and bone mineral deposition is that proatherogenic lipid oxidation products, increased by high-fat diets, promote osteoblastic differentiation of vascular smooth muscle cells while they inhibit differentiation and mineralization in skeletal osteoblasts [71]. Hyperlipidemia, whether due to genetic modification or a high-fat diet, reduces bone mineral density in mouse models [72–75].

Effects of cardiovascular therapies on osteoporosis

The effects of lowering serum lipids on osteoporosis remain unclear. When lipid-oxidation products were neutralized in mice, high-fat-diet-induced bone loss was reversed [76]. However, effects of lipid-lowering, and statin treatment in particular, on bone have been controversial. Recent observational studies report improvement in bone health [77–79], however, randomized controlled trials, which are far more reliable, fail to confirm those findings, likely because patients adhering to one healthy regimen adhere to other healthy regimens as well [65].

Effects of osteoporosis therapies on cardiovascular disease

Two types of osteoporosis treatments, teriparatide, a bone anabolic agent, and bisphosphonate, an anti-resorptive agent, impact the cardiovascular system. Effects of teriparatide are of particular concern, because of its pro-mineralization functions. One earlier study showed that teriparatide actually inhibits initiation of cardiovascular calcification [80]. In a recent study in hyperlipidemic mice with basal cardiovascular calcification, teriparatide did not appear to affect the progression of aortic calcification, at least in terms of content [81]. However, it did appear to reduce surface area of vascular calcium deposits, based on histologic analysis, which could affect plaque stability [81]. For about three decades, bisphosphonates have been proposed as treatments for atherosclerotic calcification, given their similarity to the potent endogenous inhibitor, pyrophosphate. The concern has been that the doses required are toxic, and the clinical use of bisphosphonates is limited in duration due to adverse effects. However, this may be open to reconsideration based on a recent report of a novel bisphosphonate that shows 10-fold greater potency than etidronate, in inhibiting aortic calcification induced by vitamin D in rats [82].

Lastly, cardiovascular therapy may actually influence the efficacy of osteoporosis therapy, based on results of a small, retrospective study of 52 patients treated with teriparatide for severe osteoporosis. The degree of improvement in bone density depended on baseline lipid

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profiles: bone density improved more in patients with favorable baseline lipid profiles (low LDL-cholesterol and high HDL-cholesterol) and less in patients with unfavorable baseline lipid profiles [83].

Conclusion

Growing evidence links lipids and lipid oxidation products to regulation of calcium mineralization, in arteries and cardiac valves as well as in skeletal bone. Nuclear receptors and their ligands contribute in a variety of ways. Both excess and deficiency of vitamin D promote vascular calcification. Activation of liver X receptor promotes vascular calcification whereas activation of farnesoid X receptor or PPAR inhibit it. 17beta-estradiol appears to promote vascular calcification. Lipid-lowering therapies for cardiovascular disease may affect osteoporosis, whereas bone anabolic therapies for osteoporosis may affect cardiovascular disease. Moreover, lipid-lowering therapy may impact efficacy of bone anabolic treatment. Observational studies of effects of lipid-lowering on bone are subject to confounding because adherence to treatments, even placebos, correlates with healthier outcomes. Randomized controlled trials are needed to test the potential value of lipid-lowering for osteoporosis.

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Key points

- Nuclear receptors and their ligands have important and varying effects on vascular calcification.
- Vitamin D in excess promotes vascular calcification; deficiency has similar, though lesser, effects.
- While observational studies suggest that statins benefit bone health, the finding has not been detected in randomized controlled trials.
- Poor lipid profiles may reduce efficacy of bone anabolic therapy for osteoporosis.