Role of Vitamin D in Vascular calcification

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**Abstract**

The role of vitamin D and its derivatives in vascular calcification is complex. It has long been known that in humans, hypervitaminosis D may be associated with extensive arterial calcium phosphate deposits, mostly in the form of apatite crystals.

**Keywords:** Vitamin D; Vascular Calcification; Hypervitaminosis D

**Introduction**

In experimental animals, the administration of pharmacological doses of vitamin D sterols can lead to widespread arterial calcification, especially in association with favorable conditions such as atherosclerosis, diabetes and chronic kidney disease (CKD) [1-5].

The mechanisms by which high doses of vitamin D or its derivatives induce vascular calcification include an increase in serum calcium and phosphate, the formation of fetuin-A mineral complexes in association with a decrease in free serum levels of fetuin-A [6] and the local induction of osteochondrogenic programs with transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells [7].

In adult patients with CKD, both before [8] and after the initiation of dialysis therapy [9], the severity and progression of vascular calcification have been found by two groups to correlate with circulating 25-hydroxyvitamin D (25(OH)D) levels. However, another group failed to identify an independent association of arterial calcification with serum 25(OH)D and 1,25-dihydroxyvitamin D [1,25(diOH)D] concentrations although both of them were negatively correlated with pulse wave velocity and positively with brachial artery distensibility and flow-mediated dilatation [10]. Barreto et al. [11] also did not find an association between serum 25(OH)D levels and aortic calcification or stiffness in patients with different stages of CKD [11].

The long-term administration of vitamin D sterols to children and young adults with CKD was found to induce vascular calcification [12,13]. The prevalence of calcinosis was higher in the children treated with calcitriol than in those treated with vitamin D2 or vitamin D3 [13]. Of note, different types of active vitamin D derivatives, when given in high amounts to animals with CKD, are not endowed with the same calcification-inducing capacity.

Available data indicate that vitamin D exerts a biphasic ‘dose response’ curve on vascular calcification with deleterious consequences not only of vitamin D excess but also of vitamin D deficiency [14]. Karol E. Watson et al. [15] undertook the current investigation to determine the role of systemic osteoregulatory factors on development of vascular calcification. The surprising finding of these studies is that lower serum 1,25-vitamin D levels, which have been shown by other investigators to be associated with lower levels of bone calcification, [15] are associated with higher levels of vascular calcification [16].

Mizobuchi et al. [17] suggest that experimental and clinical researches have revealed that both vitamin D excess and vitamin D deficiency have been shown to be associated with vascular calcification in uremic milieu. On the other hand, although there are some biases, recent large observational studies have demonstrated that vitamin D has beneficial effects on the mortality of patients with CKD independent of serum Ca, P, and parathyroid hormone levels, likely due to its activation of the vitamin D receptor in vasculature and cardiac myocytes [17].

The relationships of vitamin D with atherosclerotic calcification and with aortic medial calcification are strong and most likely involve multiple mechanisms within the complex, bone-vascular-renal endocrine axis. Nevertheless, clinical studies also indicate that there is a narrow range of vitamin D levels within which vascular function is optimized and levels above or below this range seem to confer increased risk for cardiovascular disease [18].
At dosage sufficient to correct secondary hyperparathyroidism, calcitriol and paricalcitol were protective against aortic calcification, but higher dosages stimulated aortic calcification. They concluded that low, clinically relevant dosages of calcitriol and paricalcitol may protect against CKD-stimulated vascular calcification [19].

Harvey et al. [20] concluded that (1) calcium and vitamin D supplementation leads to a modest reduction in fracture rate, although population-level intervention has not shown to be an effective public health strategy; (2) supplementation with calcium alone for fracture reduction is not supported by the literature; (3) side effects of calcium supplementation include renal stones and gastrointestinal symptoms; (4) vitamin D supplementation, rather than calcium supplementation, may reduce falls risk; and (5) assertions of increased cardiovascular risk consequent to calcium supplementation are not convincingly supported by current evidence. In conclusion, they recommend, on the basis of the current evidence, that calcium supplementation, with concomitant vitamin D supplementation, is supported for patients at high risk of calcium and vitamin D insufficiency, and in those who are receiving treatment for osteoporosis [20].

Palermo et al. [21] Vitamin K is in fact required for osteocalcin carboxylation that in turn regulates bone mineral accretion; it seems to promote the transition of osteoblasts to osteocytes and also limits the process of osteoclastogenesis. Several observational and interventional studies have examined the relationship between vitamin K and bone metabolism, but findings are conflicting and unclear [21].

It has been suggested that vitamin D and vitamin K may have a synergistic action, but it is not currently known if it occurs in an independent manner.

Conclusion
Deficient calcitriol concentrations probably contribute to the massive vascular calcification seen in chronic kidney disease. In patients with end-stage renal disease and end-stage heart failure, very low-circulating calcitriol levels or nonuse of active vitamin D or both are independently associated with high mortality rates. The effects of vitamin D on vascular calcification are complex and highly dependent upon the dose being administered. Whether the effects of vitamin D are beneficial or toxic falls within a narrow range of vitamin D levels.

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