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REVIEW

Role of vitamin D in cardiovascular disease

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ABSTRACT

There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. Treatment with vitamin D receptor agonists (VDRAs) is associated with reduced mortality in (pre)dialysis patients. Interestingly, these relations are independent of PTH levels and calcium x phosphorus product. This suggests the presence of biological functions of vitamin D that are independent of its interaction with the parathyroid glands. Because chronic kidney disease leads to increased cardiovascular mortality, mechanisms in which VDRAs can influence cardiovascular disease are discussed. These mechanisms comprise the potential ameliorating effects of VDRAs on atherosclerosis, arterial media calcification, cardiac hypertrophy, the renin-angiotensin system and thrombosis. Moreover, treatment strategies with VDRAs are discussed together with several recent observational studies. Treatment advice consists of correction of 25(OH) vitamin D deficiency, low-dose calcitriol in patients with secondary hyperparathyroidism, and activated vitamin D analogues may be indicated when higher doses are needed to suppress PTH secretion. New insights into biological and clinical effects of VDRAs may broaden the patient group that may benefit from VDRA treatment to patients with creatinine clearances in the 30 to 60 ml/min range.

KEYWORDS

Vitamin D receptor activation, cardiovascular disease, kidney disease

INTRODUCTION

Vitamin D is known for its primary role in calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond these classical functions. The VDR is expressed by many tissues and is present in, for instance, arteries, heart, the immune system and endocrine organs (*table 1*).[1] As kidney function deteriorates, activated vitamin D levels decline.[2] Therefore patients with renal dysfunction are a suitable population to study the effects of vitamin D treatment. Low serum 1,25$(OH)_2$D levels cause an increase in PTH secretion and the development of secondary hyperparathyroidism (SHPT). High serum PTH and hyperphosphataemia are known risk factors for increased mortality among patients on dialysis. Therefore, recent guidelines have formulated new, stricter, target ranges for serum calcium, phosphorus and PTH levels.[3,4]

In recent years, it has become clear that there is increased mortality among vitamin D deficient patients on dialysis.[5] Moreover, treatment with vitamin D receptor activators (VDRAs) is associated with reduced mortality in (pre) dialysis patients.[6-8] Interestingly, these relations are

Table 1. *Tissue distribution of the vitamin D receptor*

System	Tissue
Endocrine	Parathyroid, pancreatic B cells, thyroid C cells
Cardiovascular	Arterial smooth muscle cells, cardiac myocytes
Musculoskeletal	Osteoblasts, chondrocytes, striated muscle
Gastrointestinal	Oesophagus, stomach, intestine
Hepatic	Liver parenchymal cells
Renal	Tubules, juxtaglomerular apparatus, podocytes
Reproductive	Testis, ovary, uterus
Immune	T and B cells, bone marrow, thymus
Respiratory	Lung alveolar cells
Epidermis	Keratinocytes, hair follicles
Central nervous system	Brain neurons

independent of PTH levels and calcium x phosphorus product. This suggests the presence of biological functions of vitamin D that are independent of its interaction with the parathyroid glands. What these theoretical mechanisms comprise and what the effects are of VDRA use will be discussed.

CARDIOVASCULAR DISEASE

Below an estimated glomerular filtration rate (eGFR) of 60 ml/min, chronic kidney disease (CKD) leads to increased cardiovascular mortality in nondialysed patients.[9] In patients on dialysis this risk further increases: half of the mortality rate is caused by cardiovascular events.[10]

The two most important arterial complications leading to cardiovascular events are intimal and medial calcification. Arterial intima calcification is associated with atherosclerosis and leads to plaque formation and rupture with subsequent blood vessel occlusion. Arterial media calcification is associated with proliferation of vascular smooth muscle cells and leads to calcification and stiffening of the vessel wall.[11] The magnitude of coronary artery calcification, assessed by electron beam computed tomography and ultrasound, is correlated with clinical cardiac events.[12] Studies evaluating patients with stage 3 to 5 CKD (*table 2*) have demonstrated excessive coronary artery calcification,[13] even in young adults,[14] and suggest that coronary artery calcification is an independent predictor of death in patients on dialysis.[15] Whether this excessive calcification is primarily due to intimal or medial calcification is subject of debate. There is evidence that in patients with CKD increased arterial media calcification, more than arterial intima calcification, is responsible for the high cardiovascular mortality rate. This was demonstrated histologically through staining of inferior epigastric arteries from patients on dialysis that showed 'pure' medial calcification.[16] In another study among patients on dialysis ultrasonography of carotid arteries showed arterial intima calcification in older patients with a clinical history of atherosclerosis. Arterial media calcification was observed mainly in the younger group without conventional atherosclerotic risk factors.[11] Vitamin D can inhibit various aspects of inflammation leading to intimal and medial calcification. Further on we will explain how.

Table 2. *Stages of kidney disease*

Stage	GFR	Description
1	>90	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
2	60 - 89	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease
3	30 - 59	Moderately reduced kidney function
4	15 - 29	Severely reduced kidney function
5	<15 or on dialysis	Very severe, or end-stage kidney failure

GFR = glomerular filtration rate.

VDRA DIRECTED CYTOKINES: EFFECTS ON ATHEROSCLEROSIS

T lymphocytes and macrophages are known stimulators of intimal thickening and plaque formation in arteries susceptible of atherosclerosis. Th1 lymphocytes secrete interferon-gamma (IFN-γ), which is a potent macrophage activator and a Th2 lymphocyte suppressor. Th2 lymphocytes, in their turn, are antiatherogenic through production of Il-10, which inhibits macrophage activation.[17] The development of CD4+ T cells into either Th1 or Th2 cells determines the outcome of an immune response, and is primarily directed by cytokines; Th1 cells develop in response to IL-12 and IFN-γ, whereas IL-4 induces the development of Th2 cells. VDRA have potential ameliorating effects on the development of atherosclerosis by several mechanisms. Firstly, they have a direct effect on naive CD4+ T cells by enhancing the development of Th 2 lymphocytes (through Il-4 production).[18] Furthermore treatment with VDRA inhibits the transcription of IFN-γ that is either required for Th1 development or is a product of Th1 cells.[18,19] Moreover, human and mouse naive CD4+ cells differentiated into IL-10 producing T cells, after treatment with VDRAs and dexamethasone.[20] Through these mechanisms VDRAs may change the Th1/Th2 balance and influence the production of (anti) inflammatory mediators.

VASCULAR CALCIFICATION

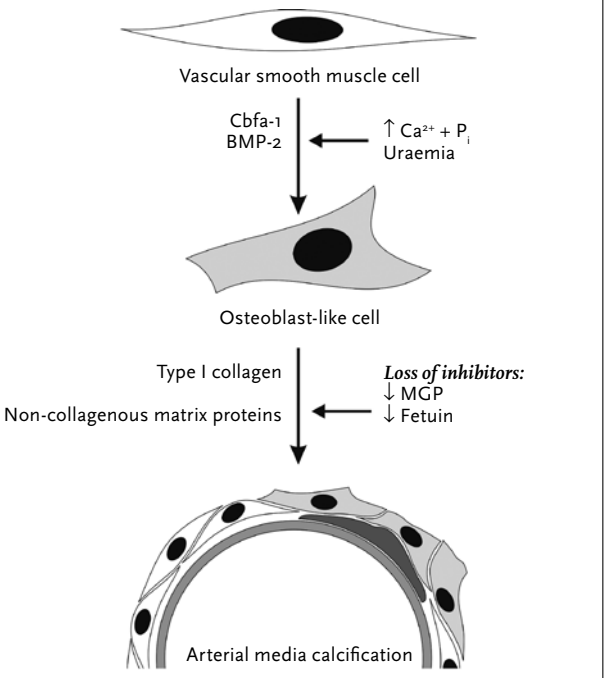
Vascular smooth muscle cells (VSMCs) and osteoblasts derive from a similar mesenchymal precursor cell. Core binding alpha-1 (Cbfa1) is thought to be the switch that turns this mesenchymal cell into an osteoblast. Moe and Chen observed expression of Cbfa1 in inferior epigastric arteries of renal transplant patients while only minimal expression was found in noncalcified arteries.[21] Uraemic toxins present in serum from dialysis patients and the expression of osteogenic markers, such as bone morphogenetic protein-2 (BMP-2), also lead to accelerated transformation of VSMCs into osteoblast-like cells.[16] These cells are capable of producing bone matrix proteins (type1 collagen, osteopontin, bone sialoprotein), which may subsequently regulate mineralisation.[22]

Once mineralisation is initiated, an increased calcium x phosphorus product, as occurs in patients with renal insufficiency, may accelerate the process of calcification which leads to stiffening of the vessel.[23] In the past accelerated calcification in patients on dialysis has been interpreted to be caused by the presence of potentiators of calcification. An alternative interpretation is that uraemic serum lacks calcification inhibitors.

Recently several inhibitors of vascular calcification have been identified. Matrix gla protein (MGP) inhibits vascular calcification in several possible ways. Muscle phenotype transition was tested *in vivo* using MGP -/- mice that spontaneously develop calcification in all major arteries. The calcified arteries showed an upregulation of osteopontin and induction of Cbfa1 protein expression.[24] Furthermore MGP is an inhibitor of BMP-2.[25] A number of circulating proteins may inhibit the vascular calcification process, including fetuin-A,[26] PTH-related-peptide and C-natriuretic protein.[27]

These mechanisms demonstrate that vascular calcification is a highly regulated process resulting from an imbalance between the loss of inhibitory factors and the increase of inducing factors present both in vessels and in the circulation (*figure 1*). Knowledge of the role of VDRAs in this new paradigm is evolving.

Figure 1. *Development of vascular calcification*



Cbfa-1 = core binding alpha-1; BMP-2 = bone morphogenetic protein-2; MGP = Matrix gla protein.

ROLE OF VDRAS IN VASCULAR CALCIFICATION

The survival benefit of the use of VDRAs seems contradictory to the perception that VDRAs, due to their potential impact of increasing serum phosphorus and calcium, may cause vascular calcification.[28] Yet there is evidence for an inhibitory role of VDRAs in vascular calcification. For a start, VDRs are present in VSMCs and treatment with VDRAs inhibits the synthesis of type 1 collagen.[22] More importantly, VDRA treatment reduces cbfa-1 synthesis,[29] stimulates the synthesis of MGP and inhibits BMP-2 production in cultured osteoblastic cells.[30,31]

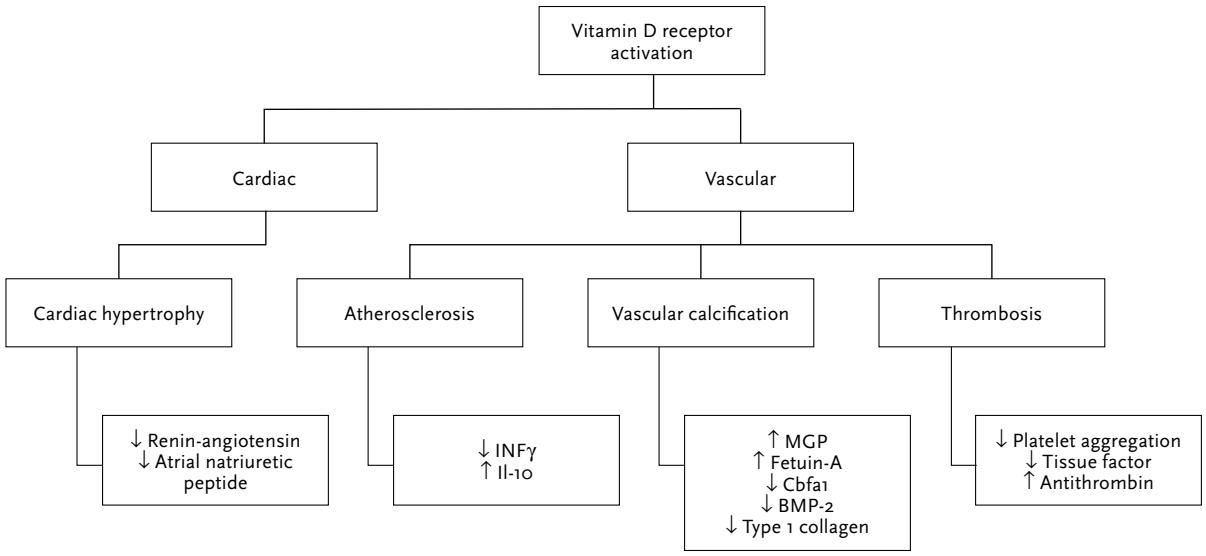
OTHER MECHANISMS

Decreased vitamin D activity increases renin expression, renin levels, atrial natriuretic peptide and angiotensin II levels and causes hypertension and cardiac myocyte hypertrophy in mouse models.[32-34] Recently it was found that VDR activation has ameliorating effects on cardiac hypertrophy and inhibits several renin-angiotensin system (RAS) components. Intravenous treatment with calcitriol in patients on haemodialysis has been demonstrated to be strongly associated with regression of myocardial hypertrophy.[35] Treatment of nephrectomised rats with paricalcitol was associated with suppression of renin, renin receptor, angiotensinogen and angiotensin II type 1 receptor. Hypertension and the deterioration of renal function were significantly improved with VDRA treatment.[34] Furthermore VDR activation probably has impact on the cardiovascular system by preventing thrombosis. In vitamin D knockout mice platelet aggregation was enhanced, tissue factor expression was upregulated and thrombomodulin/antithrombin were downregulated,[36] which are all prothrombotic conditions (*figure 2*).

TREATMENT STRATEGIES

Recently it has become clear that very low levels of 25(OH) vitamin D (<17.8 ng/ml or 44.5 nmol/l) are associated with increased all-cause mortality in patients with and without kidney disease.[37,38] Studies examining replacement of 25(OH) vitamin D in patients without kidney disease support a small but beneficial effect on survival.[39] Moreover, treatment with 25(OH) vitamin D results in significant reduction in PTH levels in patients with 25(OH) vitamin D levels <75 nmol/l, irrespective of their kidney function.[40,41] Therefore patients with 25(OH) vitamin D levels below 75 nmol/l should receive replacement therapy with native vitamin D/ergocalciferol.

Figure 2. *Inhibitors of cardiac hypertrophy and vascular damage through vitamin D receptor activation*



Usually this treatment is not sufficient to achieve suppression of SHPT in advanced chronic kidney disease and VDRAs are needed. VDRA therapy in patients with CKD has been associated with improved survival. Intravenous calcitriol or paracalcitriol treatment of patients on haemodialysis offered a significant survival advantage of 20 to 25% over patients who did not receive parental vitamin D.[6] This has prompted some other observational studies examining outcomes associated with the use of VDRAs by patients on dialysis and predialysis patients.[7,8] These studies consistently showed that patients treated with any kind of VDRA experienced significantly lower all-cause and cardiovascular mortality rates compared with patients not receiving any treatment. Subgroup analyses indicated that virtually all patients benefited from VDRA therapy, including patients with lower PTH or higher calcium or phosphorus levels. These findings emphasise a physiological effect of VDRAs that is PTH independent. Despite these convincing data we have to be cautious in using observational data as a final proof of a beneficial effect and randomised trials are warranted.

WHICH VDRA, DOES IT MATTER?

Several studies using oral calcitriol in predialysis and dialysis patients have shown a reduced overall mortality risk ranging from -26 to -45%.[8,42,43] The advantage included patients with the highest levels of serum calcium, phosphorus and PTH. In predialysis patients high pharmacological doses of calcitriol may hasten loss of kidney function,[44] but this effect is not seen with lower doses of calcitriol. On the contrary: low-dose calcitriol (<0.25 µg/day) has been associated with a trend towards slower progression of kidney disease and lower mortality risk.[8] For reasons of convenience, in haemodialysis patients active vitamin D is often administered parenterally after dialysis. Oral treatment with calcitriol is presumably equally effective in reducing SHPT and mortality risk and is far less expensive.

Clinical guidelines suggest stringent control of PTH, calcium and phosphate in an attempt to lower the risk of vascular calcification and bone disease.[3] Very recently KDIGO (Kidney Disease: Improving Global Outcome) guidelines stated that in patients with CKD stage 3 to 5 not on dialysis, in whom serum PTH is rising above the upper limit of normal, despite modifiable factors, VDRAs are warranted.[4] Implicit in these recommendations is the avoidance of the native VDR activator calcitriol if the calcium and phosphate levels exceed their upper limits. This has advocated the use of several VDRAs that can suppress PTH production with less induction of concomitant hypercalcaemic and hyperphosphataemic effects.[45] One could question the importance of this favourable side-effect profile since the benefit of calcitriol extends to patient groups with high calcium and phosphorus levels. On the other hand long-term positive calcium balance may contribute to vascular calcification. Moreover, observational data suggest a decreased rate of progression of established vascular calcification with non-calcium containing phosphate binders.[46]

Examples of activated vitamin D analogues with this favourable side-effect profile are doxercalciferol, paricalcitol, and alfacalcidol. Animal models show a potential advantage for paricalcitol; it induces less vascular calcification compared with calcitriol.[47] Earlier we mentioned the historical cohort study by Teng *et al.*, where 67,339 patients on haemodialysis were examined. In this

study paricalcitol was associated with a 16% lower all-cause mortality compared with treatment with calcitriol.[6] In another study these findings were not confirmed. Tentori *et al*. compared outcomes in patients receiving calcitriol, paricalcitol and doxercalciferol and found lower mortality in patients on paricalcitol and doxercalciferol in unadjusted models. But in adjusted models this difference was not statistically significant.[7] Obviously, more studies are needed to prove the benefit of activated vitamin D analogues on survival.

TREATMENT ADVICE

Treatment of SHPT is the generally accepted and approved indication for treatment with vitamin D. It seems reasonable to correct 25(OH) vitamin D deficiency as a first step in the treatment of SHPT. New insights into biological and clinical effects of VDR activation may broaden the patient group that may benefit from VDRA treatment to patients with creatinine clearances in the 30 to 60 ml/min range. Low-dose calcitriol is indicated for patients with early SHPT. A switch to activated vitamin D analogues is indicated when higher doses are needed to suppress PTH secretion and treatment goals concerning calcium x phosphorus levels have to be met.

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