Vitamin D, Shedding Light on the Development of Disease in Peripheral Arteries

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Abstract—Vitamin D is generally associated with calcium metabolism, especially in the context of uptake in the intestine and the formation and maintenance of bone. However, vitamin D influences a wide range of metabolic systems through both genomic and nongenomic pathways that have an impact on the properties of peripheral arteries. The genomic effects have wide importance for angiogenesis, elastogenesis, and immunomodulation; the nongenomic effects have mainly been observed in the presence of hypertension. Although some vitamin D is essential for cardiovascular health, excess may have detrimental effects, particularly on elastogenesis and inflammation of the arterial wall. Vitamin D is likely to have a role in the paradoxical association between arterial calcification and osteoporosis. This review explores the relationship between vitamin D and a range of physiological and pathological processes relevant to peripheral arteries. (Arterioscler Thromb Vasc Biol. 2005;25:39-46.)

Key Words: vitamin D ■ peripheral artery disease ■ aortic aneurysm ■ vascular smooth muscle cell

The primary role of vitamin D and its active metabolites is maintaining calcium homeostasis by increasing intestinal calcium absorption and, depending on circulating calcium levels, influencing the balance between bone resorption and formation. The physiological role of vitamin D in skeletal and cellular health has been reviewed elsewhere. Vitamin D also has effects on the microendocrine systems of the vasculature, some of which have only been appreciated recently. This review reflects on the possible influence of vitamin D on peripheral arterial disease, which includes diseases (both occlusive and dilating) of the abdominal aorta and the distal arteries supplying the lower limb. Atherosclerosis is a major contributor to peripheral arterial disease, but the risk factors are subtly different from those for coronary artery disease: smoking is the dominating risk factor for peripheral arterial disease. Does vitamin D have any influence on the disease process?

Vitamin D Metabolites and Analogues

Cholecalciferol is a prohormone that is synthesized in the skin by photochemical conversion of 7-dehydrocholesterol (Figure 1). It is subsequently hydroxylated to 25-hydroxycholecalciferol [25(OH)D3] in the liver and finally to the active metabolite, 1α,25 dihydroxycholecalciferol [1α,25(OH)2D3] in the kidney. Some dietary sources provide a cholecalciferol derivative, with a double carbon-carbon at position 22,23 known as vitamin D2 that also undergoes 1,25 hydroxylation. The active vitamin D metabolites are transported in the circulation by vitamin D-binding protein which has additional effects, including the binding of globular actin and fatty acids and immunomodulation. Because little vitamin D is available in most diets, photochemical synthesis of vitamin D is paramount for its homeostasis, and it is for this reason that rickets became a problem in industrialized cities.

1α,25(OH)2D3 is a steroid hormone shown to regulate >60 genes. This is accomplished by the translocation of 1α,25(OH)2D3 into cells where it binds with high affinity to the vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily. This complex then interacts with the vitamin D response elements in the promoter region of target genes thereby altering rates of gene expression (Figure 2). By this pathway, 1α,25(OH)2D3 influences a number of genes relevant to the arterial wall, including vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, and structural proteins, such as elastin and type I collagen. In addition, there is evidence of an alternative pathway for 1α,25(OH)2D3 altering gene transcription through intracellular vitamin D–binding proteins. The newly recognized use of 1α,25(OH)2D3 analogues as immunomodulatory agents is based on the ability of these...
7-dehydrocholesterol

\[ \text{photochemical conversion in skin} \]

cholecalciferol (vitamin D₃)

\[ \text{dietary sources* (includes vitamin D₃)} \]

25-hydroxylation in liver

25-hydroxycholecalciferol (25(OH)D₃)

1α-hydroxylation in kidney

1α,25-hydroxycholecalciferol (1α,25(OH)₂D₃)

Secreted into the circulation and bound to Vitamin D Binding Protein.

* Dietary vitamin D may be carried by lipoproteins. The ingestion of vitamin D is not directly correlated with serum 1α,25-dihydroxycholecalciferol concentrations because the enzymes, 25-hydroxylase and 1α-hydroxylase, are tightly regulated.

Nongenomic Effects

In common with other steroid hormones, 1α,25(OH)₂D₃ induces a range of effects which occur too rapidly to involve gene expression. These include increases in intracellular calcium and cGMP levels, activation of protein kinase C and changes in phosphoinositide metabolism (Figure 2). The effects are known to be mediated by 1 or more plasma membrane receptors, but their role is unclear in most cell types. An example relevant to the arterial wall includes the stimulation of vascular smooth muscle cell (VSMC) migration through activation of phosphatidylinositol 3-kinase.

Target Cells and Tissues for 1α,25(OH)₂D₃

Classically, the action of 1α,25(OH)₂D₃ is to maintain calcium and phosphate homeostasis, with the intestine and bone being key targets. It also acts on a wide range of nonclassical target tissues, including the heart and arterial wall. The influence of 1α,25(OH)₂D₃ on these tissues could have important implications for vascular function and disease. 1α,25(OH)₂D₃ appears to cause cell cycle arrest and inhibit
proliferation of most cell types, including lymphocytes. VDRs are present in VSMCs. There is controversy concerning the action of vitamin D on VSMCs, with some studies reporting stimulation of proliferation and others reporting inhibition of proliferation and a synthetic phenotype being induced by 1α,25(OH)2D3. The direction of the effect may depend on the culture conditions, with effects in vivo being uncertain. VDRs have been identified in dermal capillaries, and cultured endothelial cells appear to express a 1α-hydroxylase enzyme, indicating the possibility of a vitamin D microendocrine system in endothelial cells. 1α,25(OH)2D3 causes apoptosis in tumor endothelial cells, interferes with vascular endothelial growth factor signaling, and suppresses angiogenesis. Macrophages and lymphocytes are other important target cells for vitamin D in the diseased artery wall. The vitamin D microendocrine systems of the diseased arterial wall are shown in Figure 3.

**Dietary Requirements and Human Consumption of Vitamin D**

After the discovery that cod liver oil prevented rickets in 1919, overall consumption of vitamin D in Europe and North America was probably excessive during the first half of the 20th century. It was not unusual for infants to consume 100 μg per day and an “epidemic” of infantile hypercalcemia and supravalvular aortic stenosis coincided with the increased vitamin D supplementation of milk in the 1940s. It was not until 1963 that infant food supplementation was reduced in the United States. Sensitivity to vitamin D appears to vary until 1963 that infant food supplementation was reduced in the United States. Sensitivity to vitamin D appears to vary because not all infants developed hypercalcemia, and a reduced susceptibility to rickets may be associated with an increased susceptibility to vitamin D toxicity. Cod liver oil may have disappeared from infant food supplements, but a significant proportion of adults in Western countries continue to use fish oil supplements. A recent dietary study in southwest England indicated that about 20% of healthy adults were using fish oil supplements.

Dietary recommendations for vitamin D consumption vary among advisory bodies, reflecting uncertainty about vitamin D status and health (particularly osteoporosis). Recommended daily intake ranges from 0 in those at low risk of osteoporosis to 15 μg per day for those at high risk (≥65 years, dark skin, restricted exposure to sunlight). Some authorities feel that fear of toxicity has tended to keep the recommended daily intake at “woefully inadequate” levels.

**Epidemiological Studies of Vitamin D and Arterial Disease**

Despite a number of articles over the last 50 years or more arguing that vitamin D is a risk factor in atherosclerosis, the published data, at least with respect to ischemic heart disease, remain conflicting. Linden initially reported that patients with myocardial infarction appeared to have a higher intake of vitamin D than controls. This has been followed by reports that serum levels of 25(OH)D3 were not elevated in patients with myocardial infarction, and the mortality from ischemic heart disease (in postmenopausal women) was not associated with intake of vitamin D. Scragg et al even reported an inverse relationship between levels of 25(OH)D3 and myocardial infarction. Ironically, vitamin D deficiency [serum levels of 25(OH)D3 <9 ng/mL] because of immobility causing lack of sunlight exposure has been reported in patients with peripheral arterial disease.

Similar uncertainty surrounds the relevance of vitamin D in hypertension (an established risk factor for peripheral arterial disease). Despite evidence from various animal models that vitamin D may be important in blood pressure control and hypertension, its clinical importance remains unclear. There is an inverse relationship between exposure to sunlight (needed to synthesize cholecalciferol) and both blood pressure and prevalence of hypertension. Some studies have found a similar inverse relationship between levels of 1α,25(OH)2D3 and blood pressure and plasma renin activity, although others report a positive association. Recent results from a large population-based study failed to find any convincing association between serum vitamin D concentrations and blood pressure. Vitamin D supplementation appears to lower blood pressure in those with preexisting hypertension. Li et al have recently shown this to be mediated through the direct actions of 1α,25(OH)2D3 in suppressing renin expression. Critical assessment of the role of vitamin D in blood pressure control is beyond the scope of this review. However, in the context of blood pressure control, vitamin D...
D may provide some protection against peripheral arterial disease.

**Vitamin D and Peripheral Arterial Calcification**

Arterial calcification is important because it has been shown to be a forerunner of cardiovascular events. The molecular biology of arterial calcification will not be described in detail as it has been the subject of recent reviews.\(^42\) However, the possible role of vitamin D in arterial calcification will be discussed.

There are 2 distinct patterns of arterial calcification: calcification of the media (Monckeberg’s sclerosis, seen in aging, chronic renal failure, and diabetes) and calcification of the intima (seen in atherosclerosis). Intimal calcification has attracted considerable attention, particularly in the context of the prognostic significance of coronary artery and aortic arch calcification.\(^5,44\) However, most of the increase in arterial calcium with age is concentrated in the medial layer.\(^6\) This medial calcification is not usually occultive or associated with atherosclerotic plaque but is nevertheless a predictor of lower limb amputation and cardiovascular mortality.\(^47,48\) Medial calcification also results in incompressible arteries and difficulty in measuring true ankle pressures, which can complicate the noninvasive diagnosis of peripheral arterial disease. An inverse relationship between serum \(\alpha,25(\text{OH})_2\text{D}_3\) levels and total (intimal and medial) coronary artery calcification has been reported.\(^40,50\) This association may depend on medial calcification, whereas another study failed to demonstrate an association between intimal calcification and serum \(\alpha,25(\text{OH})_2\text{D}_3\) levels.\(^51\) The significance of an inverse relationship between levels of \(\alpha,25(\text{OH})_2\text{D}_3\) and coronary calcification is uncertain, particularly as levels of \(25(\text{OH})_2\text{D}_3\) are a better indicator of vitamin D status.\(^24\)

There is increasing evidence of a paradoxical association between osteoporosis and vascular calcification.\(^52–54\) The mechanisms underlying this association are beginning to be unraveled\(^52,55–57\) and may account for the inverse association between coronary artery calcification and serum levels of \(\alpha,25(\text{OH})_2\text{D}_3\).\(^49\) Various inhibitors of bone resorption, including bisphosphonates (alendronate and ibandronate), osteoprotegrin, and an inhibitor of osteoclastic \(\text{V}-\text{H}^+\text{-ATPase}\) (SB 242784) have been shown to inhibit calcification of the arterial media in animal models.\(^55,56,58\) Because none of these agents are known to act directly on the arterial smooth muscle cells, it has been proposed that arterial calcification is directly linked to bone resorption in this model.\(^56\) \(\alpha,25(\text{OH})_2\text{D}_3\) may, however, act directly on smooth muscle cells or osteoclast-like cells within the arterial wall.\(^59,60\)

Medial calcification is common in diabetes and end-stage renal failure, both conditions being associated with peripheral arterial disease. In renal failure, \(\alpha,25(\text{OH})_2\text{D}_3\) analogues are used to prevent secondary and tertiary hyperparathyroidism, and treatment with vitamin D has been implicated in calcification of soft tissues, including the arterial wall.\(^61\) Recently a large observational study has indicated that a selective VDR antagonist (paricalcitol) improves survival for renal failure patients, by 16% to 25%, in comparison to traditional calcitriol therapy.\(^62\) In support of this finding, in vitro experiments show that VSMCs undergo calcification when treated with \(1\alpha,25(\text{OH})_2\text{D}_3\) through a mechanism dependent on suppression of an endogenous inhibitor of calcification (PTH-related peptide) and PTH receptor signaling.\(^59,63\) Hence, vitamin D exposure may downregulate the paracrine mechanisms that, under normal circumstances, protect the vasculature from calcification. This has led to recent speculation that inflammation of the vascular adventitia with local synthesis of \(1\alpha,25(\text{OH})_2\text{D}_3\) by macrophages could lead to medial calcification.\(^64\)

\(\alpha,25(\text{OH})_2\text{D}_3\), through its interaction with VDR, can induce the calcification of cultured arterial smooth muscle cells.\(^59\) Apoptosis, which is well-documented in atherosclerosis and after arterial injury, may provide an initial stimulus for calcification within the arterial wall.\(^65,66\) \(\alpha,25(\text{OH})_2\text{D}_3\) can induce cell cycle arrest and apoptosis in some normal and malignant cell types.\(^18,67\) Although \(\alpha,25(\text{OH})_2\text{D}_3\) has been shown to inhibit angiogenesis by induction of apoptosis, there is no direct evidence linking vitamin D to peripheral arterial calcification through this mechanism.

Although adequate vitamin D nutrition is essential for optimal vascular function,\(^68\) both exogenous and endogenous \(\alpha,25(\text{OH})_2\text{D}_3\) are possible axes for the association. In contrast to endogenous vitamin D, which is carried by circulating vitamin D–binding protein, exogenous vitamin D may be carried by lipoproteins.\(^69\) This may facilitate accumulation of vitamin D within atherosclerotic plaque and alter macrophage gene expression.\(^19,70,71\)

**Arterial Disease and the Genomic Effects of Vitamin D: Clinical Studies**

The relationship between common polymorphisms of the VDR gene and osteoporosis has attracted considerable research (and controversy) over the last decade.\(^72,73\) The link between osteoporosis and arterial calcification has led to the hypothesis that functional polymorphisms in the VDR gene are associated with the prevalence and severity of coronary artery disease. This has been tested in clinical populations, and although a possible association between the VDR BB genotype (resulting in decreased levels of vitamin D) and severity of coronary artery stenosis has been reported, the relationship was not statistically significant.\(^74\) The importance of such studies depends on whether they are large enough to determine effects of the magnitude attributed to the polymorphism(s) or haplotypes in vitro. There are contradictory results reported as to whether the BsmI polymorphism in intron 8 or the FokI polymorphism in the 5′ regulatory region of the VDR gene has functional effects in vitro. Therefore, even the results of large studies focusing on a single polymorphism must be treated with skepticism. Although Ortlepp et al.\(^75\) report that the BsmI polymorphism has no influence on the incidence of coronary artery disease in 3441 patients, such evidence does not refute the possibility that genetic variation in response to vitamin D has an impact on the development of arterial disease. There have been no studies of the role of the genomic effects of \(1\alpha,25(\text{OH})_2\text{D}_3\) in the development of peripheral arterial disease. Genomic associations with the more relevant clinical phenotype of arterial calcification have not been evaluated.
Nongenomic Effects of Vitamin D on Peripheral Vascular Resistance

Although the evidence concerning vitamin D exposure and hypertension is controversial, it is possible that vitamin D influences vascular tone. The single study that has investigated the short-term effect of vitamin D on cardiovascular hemodynamics showed that vitamin D caused rapid changes in patients with essential hypertension but not in controls.76 In patients with essential hypertension, the cardiac output decreased by \( \approx 15\% \) within 2 hours of intravenous administration of \( \alpha,25(\text{OH})_2\text{D}_3 \) (0.2 \( \mu \text{g/kg} \)). This was associated with transient smaller increases in pulse rate and mean blood pressure, suggesting that \( \alpha,25(\text{OH})_2\text{D}_3 \) had a nongenomic effect to increase peripheral resistance. This would be supported by an earlier report that indicated a correlation between calf vascular resistance, both before and during reactive hyperemia, with serum concentrations of \( 25(\text{OH})_3\text{D} \).77 The ability of \( \alpha,25(\text{OH})_2\text{D}_3 \) to increase vascular resistance is supported by animal studies.78 \( \alpha,25(\text{OH})_2\text{D}_3 \) increases the sensitivity of resistance arteries to norepinephrine in hypertensive but not normotensive rats79 and rapidly enhances arterial force generation by modulation of intracellular calcium concentration.34,80 Taken together these studies suggest that hypertension induces or sensitizes putative plasma membrane VDRs which modulate intracellular calcium concentrations and hence resistance artery force generation. The identity of these plasma membrane receptors is obscure, as are the downstream kinase signaling cascades. In the absence of hypertension, these fast nongenomic responses have not been observed.

Even in the presence of hypertension, in the longer term, the fast nongenomic responses may be counteracted by the genomic effects of \( \alpha,25(\text{OH})_2\text{D}_3 \) which may function to decrease vascular resistance. Likely mechanisms include altered expression of myosin isoforms in resistance vessels.81 This would be consistent with the reported decrease of systolic blood pressure after 8 weeks of oral calcium and vitamin D supplementation in the late winter.80

Vitamin D, Elastin, and Inflammatory Vascular Disease

Several years ago the hypothesis was elaborated that impaired synthesis of elastin in the walls of the aorta and other elastic or conduit arteries during fetal development was an initiating event in the pathogenesis of hypertension.82 Because troponin synthesis is known to be downregulated by vitamin D, through a posttranscriptional mechanism,6 excess vitamin D during fetal development could cause the impaired synthesis of elastin discussed by Martyn and Greenwald. Loss of medial elastin is a pathological hallmark of abdominal aortic aneurysm (AAA). This led to Norman elaborating a further hypothesis, that excess vitamin D consumption in early life led to the development of AAA in later life.83 The transportation of vitamin D across the placenta is specifically enhanced during the last one third of pregnancy (a period of maximal aortic elastin deposition).84,85 The neonate is dependent on stored vitamin D, because mammalian milk contains minimal vitamin D.86 This suggests that if maternal intake is excessive then fetal and neonatal exposure will also be excessive. Although there are no clinical studies to support an association between increased maternal vitamin D intake and impaired aortic elastogenesis, an experimental animal study demonstrated that exposure to increased vitamin D in early life was associated with a reduction in elastin content and elastic lamellae number in the abdominal aorta.87 The studies were not extended to investigate the possibility of aneurysm formation in aging rats.

Another pathological hallmark of AAA is inflammation.88 Interestingly, there are recent scientific observations to support an important role for vitamin D and its analogues on the immune system, particularly macrophages and T lymphocytes expressing VDR, which could have important implications for both AAA and other peripheral arterial disease. The highest expression of VDR is in CD8 lymphocytes, with less expression in CD4 lymphocytes and macrophages, whereas B cells do not express VDR. Moreover, VDR expression in CD8 cells increases in response to \( \alpha,25(\text{OH})_2\text{D}_3 \).89 Therefore, vitamin D can regulate cytokine expression in diseased arteries (Figure 3). Laboratory data suggest that \( \alpha,25(\text{OH})_2\text{D}_3 \) influences cytokine production by both CD4+ and CD8+ subsets, preferentially inhibiting cytokine production ( interleukin [IL]-2 and interferon-\( \gamma \) from Th1 cells and hence favoring Th2 responses with the production of IL-4, IL-5, and IL-10, as well as IL-6.90,91 It is these findings that might translate to a link between vitamin D and AAA, a condition where Th2 responses predominate.92

Clinical studies of the effects of vitamin D supplementation are limited. In postmenopausal women, vitamin D supplementation (2 \( \mu \text{g per day} \)) increased CD3 and CD8+ subsets of lymphocytes.93 Therefore, vitamin D may influence T cell activity and inflammation of the artery wall through several different pathways.

Wjst and Dold94 have hypothesized that deficiency of vitamin D in early life leads to allergic diseases in later life. Allergy, autoimmune deficiency, and transplant rejection are all controlled by Th1 responses, inflammatory vascular disease being important in transplant rejection. Although there is abundant experimental evidence (eg, Raisanen-Sokolowski et al95) to indicate that vitamin D supplementation increases serum levels,96,97 provide other mechanistic possibilities for a more widespread influence of vitamin D on peripheral arterial disease.

Vitamin D and Animal Models of Atherosclerotic Arterial Disease

The harmful effect of excess vitamin D on arteries has been studied in many animal models over the last 40 years or
more. Numerous dosage regimens have been described although the majority have used short courses of potentially toxic doses of vitamin D resulting in acute hypercalcemia. Chronic less toxic treatment also results in metastatic calcification and deteriorating renal function. In general, vitamin D results in arterial wall calcification and a variety of other “atherosclerotic” changes. Loss of collagen and disruption of elastic lamellae are additional features. These latter changes are usually associated with increased aortic stiffness, although one study reported a paradoxical reduction in stiffness. Vitamin D also exacerbates the intimal hyperplasia seen in balloon-injured rat carotid arteries. This is probably caused by the stimulation of migration and proliferation of smooth muscle cells. Recently, the combination of vitamin D3 and cholesterol has been used to induce both peripheral atherosclerosis and aortic valve stenosis in a rabbit model. In this model, the addition of vitamin D3 to the high cholesterol diet resulted in significantly higher levels of circulating cholesterol. A combination of vitamin D and nicotine, causing hypercalcemia, results in stiffer rat conductance arteries and exacerbates the atherosclerotic effects of cholesterol feeding. The relevance of any of these models to the development of cardiovascular disease in humans is uncertain.

Another possible link between vitamin D and peripheral arterial disease has been found in a study of transgenic rats that constitutively express vitamin D-24-hydroxylase [which catalyzes the conversion of 25(OH)D3 to 24,25(OH)2D3]. These rats had low levels of plasma 24,25(OH)2D3 and developed hyperlipidemia and aortic atherosclerosis. This is an example of the complexity of the relationship between differing vitamin D metabolites and the arterial wall.

Summary
In addition to its role in calcium and phosphate homeostasis, vitamin D is important in many physiological and pathological processes relevant to peripheral arterial disease. Vitamin D is essential for the development and maintenance of a healthy arterial tree. 1α,25(OH)2D3 influences the migration, proliferation, gene expression of VSMCs, elastogenesis, and immunomodulation, all processes which are involved in the pathogenesis of atherosclerotic and aneurysmal arterial disease. 1α,25(OH)2D3 has additional, poorly understood, nongenomic effects on vessel contractility in essential hypertension and is likely to have a pivotal role in the paradoxical association between osteoporosis and vascular calcification. New clinical studies are required to fully understand the contribution of vitamin D to the health of peripheral arteries.

References
27. Linden V. Vitamin D and myocardial infarction. BMJ. 1974;467–465.


80. Hatton D, Xue H, DeMerritt H, McCarron D. 1,25 (OH)2 Vitamin D3 modifies the expression of 1,25-


88. Bukoski R, DeWan P, McCarron D. 1,25 (OH)2 Vitamin D3 has a direct effect on naive CD4

89. Veldman C, Cantorna M, DeLuca H. Expression of 1,25-


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In the January 2005 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the Brief Review entitled “Vitamin D, Shedding Light on the Development of Disease in Peripheral Arteries” by Norman and Powell (*Arterioscler Thromb Vasc Biol*, 2005;25:39–46), there was a typographical error in the section entitled “Vitamin D and Peripheral Arterial Calcification.” On page 42, in the fourth line from the bottom of the left column, “… anatagonist (paricalcitol) improves survival…” should have read “… agonist (paricalcitol) improves survival…”

In the February 2005 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the article entitled “Matrix Metalloproteinase-9 (MMP-9), MMP-2, and Serum Elastase Activity Are Associated With Systolic Hypertension and Arterial Stiffness” by Yasmin et al (*Arterioscler Thromb Vasc Biol*, 2005;25:372–378), the order of authorship was listed incorrectly. The correct order of authorship is as follows: Yasmin, Carmel M. McEniery, Sharon Wallace, Zahid Dakham, Pawan Pusalkar, Kaisa Maki-Petaja, Mike J. Ashby, John R. Cockcroft, Ian B. Wilkinson. We apologize for these errors.