Scholars LITERATURE

International Journal of Integrative Cardiology

Review Article

DOI: https://doi.org/10.47275/2690-862X-141
Volume 6 Issue 1

A Review on Vitamin D Deficiency and Risk of Cardiovascular Disease

Utkarsh[1]*, Shaik Mohammad Rafi[2]*, Glady Merigala[3] and Sindhu Kattekola[4]

[1]Bharat Ratna Atal Bihari Vajpayee Medical College, Pune, Maharashtra, India.

[2]Guntur Medical College, Guntur, Andhra Pradesh, India.

[3]Siddhartha Government Medical College, Vijayawada, Andhra Pradesh, India.

[4]Kamineni Institute of Medical Sciences, Narketpally, Telangana, India

Abstract

Calcium and phosphorus metabolism are regulated by vitamin D in skeletal health. Nonskeletal tissues also produce vitamin D metabolites, which influence regulatory pathways via paracrine and autocrine mechanisms. One of vitamin D's active metabolites, 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), binds to the vitamin D receptor and regulates numerous genes that may play a role in heart disease, including cell proliferation, differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, and adhesion. It has been discovered that all kinds of cardiovascular cells, such as cardiomyocytes, arterial wall cells, and immune cells, contain vitamin D receptors (VDRs). Inflammation, thrombosis, and the renin-angiotensin system are all affected by vitamin D metabolites, according to experimental studies. Various manifestations of degenerative cardiovascular disease (CVD), such as vascular calcification, have been associated with vitamin D deficiency in clinical studies. However, vitamin D supplementation has yet to be proven as a means of managing CVD. The purpose of this review is to summarize clinical studies that show associations between vitamin D status and CVD as well as experimental studies exploring the mechanisms underlying these associations.

Keywords: Cardiovascular disease, Vitamin D, Heart failures

***Correspondence to*:** Utkarsh and Shaik Mohammad Rafi, Bharat Ratna Atal Bihari Vajpayee Medical College, Pune, Maharashtra, India and Guntur Medical College, Guntur, Andhra Pradesh, India.

Citation: Utkarsh and Rafi SM, (2024) A Review on Vitamin D Deficiency and Risk of Cardiovascular Disease. Int J Integr Cardiol, Volume 6:1. DOI: https://doi.org/10.47275/2690-862X-141

Received: March 14, 2024; **Accepted:** June 30, 2024; **Published:** July 03, 2024

Introduction

Calcium and phosphate are physiologically absorbed more efficiently by the intestinal tract due to vitamin D. Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the most important components of vitamin D. Among people suffering from CVD, there was a seasonality associated with vitamin D. It has been shown that heart disease is more common during winter, possibly because vitamin D levels are low. With food, you can take cholecalciferol and ergocalciferol. There are two distinct metabolic processes that occur after vitamin D2 is consumed through food. As a result of liver metabolism, vitamin D2 becomes 25-hydroxyvitamin D (25(OH)D), which is converted in the kidney to 1,25$(OH)_2$D (calcitriol) by CYP27B1. Several feedback mechanisms regulate calcitriol production in the endocrine system. A reduction in calcium plasma levels results in the release of parathyroid hormone (PTH), which stimulates calcium calcitriol production. As a result, calcium increases serum calcium levels by directly suppressing PTH gene transcription and subsequent hormone production. Moreover, calcium-sensing receptor gene transcription and protein expression are also upregulated by calcitriol. In addition, vitamin D inhibits CYP27B1 from regulating its own production. Furthermore, cholecalciferol is synthesized by the skin under sunlight exposure. Several factors affect how much sunlight is required to satisfy our vitamin D requirements, including skin pigmentation, age, latitude, season of the year, or time of day. Vitamin D deficiency can contribute to several diseases. Vitamin D deficiency has long been associated with rickets. Moreover, low vitamin D levels can contribute to chronic diseases such as atherosclerosis, heart disease, high blood pressure, heart failure, type 2 diabetes, cancer, and immunological conditions. The results of randomized clinical trials (RCTs) designed to prove vitamin D supplementation's therapeutic effects have been inconclusive despite the pathogenic link between vitamin D deficiency and these diseases. Although the role of vitamin D in CVD pathogenesis is quite complex, it should be noted. Furthermore, vitamin D locally activates autocrine/paracrine pathways in atherosclerotic plaques, which play a supportive role within this context. Human carotid plaques expressing VDRs were associated with less major adverse cardiovascular events (MACEs) [1, 2].

The Role of Vitamin D in Signaling

VDR, a cytosolic receptor protein that activates transcription of targeted genes in response to ligand binding, mediates vitamin D's biological effects. The VDR gene is located on chromosome 12q and belongs to the nuclear receptor transcription factor family. Vitamin D and retinoid X receptors bind to the VDR, activating it. This results in the activated heterodimeric receptor complex translocating into the nucleus where it engages specific nucleotide sequences called vitamin D response elements (VDREs). Within hours or days, the latter regulate vitamin D-sensitive gene transcription. The VDR is also localized at the level of cell membrane, so vitamin D can also affect gene expression quickly through this classical signaling pathway [3]. Histone

modification and other epigenetic mechanisms are likely to trigger these rapid effects. There have been many studies, but the tissue distribution of VDR has not yet been clearly defined. The receptor is certainly expressed in cells of the skeleton, bowel, heart, and endothelium. There are several studies showing the presence of CYP27B1, which allows us to gain a better understanding of how vitamin D affects endothelial and cardiomyocyte functions locally. Atherosclerotic plaques may develop as a result of local deficiency of vitamin D in tissues [4].

A Deficiency of Vitamin D and an Excess of It

The definition of vitamin D deficiency (also known as hypovitaminosis D), levels of 25(OH)D that are appropriate for health, and requirements for vitamin D in the diet have all been the subject of controversy. Vitamin D deficiency is defined as levels of 25(OH) D below 50 nmol/L (20 ng/ml) and insufficiency as levels of 52.5 to 72.5 nmol/L, according to the Endocrine Society Clinical Practice Guidelines. A 25(OH)D deficiency is defined as a level of 25 nmol/L, an insufficiency as 50 nmol/L, and a target level of 75 nmol/L according to the International Osteoporosis Foundation. For bone health, a target level of 50 nmol/L is recommended by the Institute of Medicine [5]. Vitamin D status and CVD are complicated by this lack of consensus, as well as seasonal fluctuations and dietary changes. In addition to the lack of consensus between guidelines, the variability of serum 25(OH)D measurements exacerbates the problem. As a result, local concentrations of vitamin D metabolites within the arterial wall may differ from circulating levels due to the presence of CYP27B1, which produces $1,25(OH)_2D$ from 25(OH)D in smooth muscle cells, endothelial cells, macrophages, and dendritic cells [6].

Several genes in the biosynthetic and activation pathways of vitamin D have been identified as being associated with variation in serum levels through twin and genetic studies (estimated to be 23% - 77%). Recent genome wide association studies have also highlighted the heritability of circulating 25(OH)D levels. VDR genetic variability was also evaluated in these studies. CVD is not yet understood to be caused by these variants [7].

The most common cause of vitamin D deficiency is reduced skin synthesis due to aging and environmental factors. As with CVD, vitamin D deficiency is highly prevalent in many subgroups, especially the elderly, although prevalence varies with sex, age, latitude, ethnicity, and culture. CVD sufferers are more likely to be vitamin D deficient. Among whites, 88% of Hispanics, and 97% of blacks with CVD in the National Health and Nutrition Examination Survey 2001 - 2004, approximately 68% had 25(OH)D levels of 75 nmol/L (less than the recommended concentration of the International Osteoporosis Foundation) [8].

Vitamin D deficiency has been a major concern in recent decades. In view of epidemiological evidence that deficiency is a significant public health issue, this is appropriate [9]. A high intake of vitamin D, however, can cause kidney stones, renal impairment, malignancy, and possibly some cardiovascular manifestations.

The VDR

VDREs are found in the promoters of many genes regulated by VDR, which belongs to the nuclear receptor superfamily. In addition to proliferating and diffusing cells, these genes are involved in growing, dividing, apoptosing, oxidative stress, membrane transport, matrix homeostasis, tissue mineralization, and adhesion. Cardiomyocytes, VSMCs, ECs, and most immune cells, along with platelets, contain VDRs [5, 10].

With high affinity and specificity, VDR binds $1,25(OH)_2D$ and heterodimerizes mainly with retinoid X receptors. An N-terminal domain of VDR contains two zinc fingers which confer specificity for VDREs and provide a site for heterodimerization before the DNA-binding domain. At the C-terminal, a lipophilic $1,25(OH)_2D$-binding domain is found, and the rest of the molecule contains the lipophilic $1,25(OH)_2D$-binding domain. A tissue-specific coactivator, including the steroid receptor coactivator, and the silencing of corepressors that modify chromatin structure are necessary for gene expression; the DNA-binding domain is small, and contact with the open DNA groove is limited to 6 nucleotides. In CVD, these protein complexes may have relevance, for example, mothers against decapentaplegic homolog 3 coactivates transducin causing transcription. Parathyroid hormone and CYP27B1 genes are downregulated by VDR (Figure 1) [5].

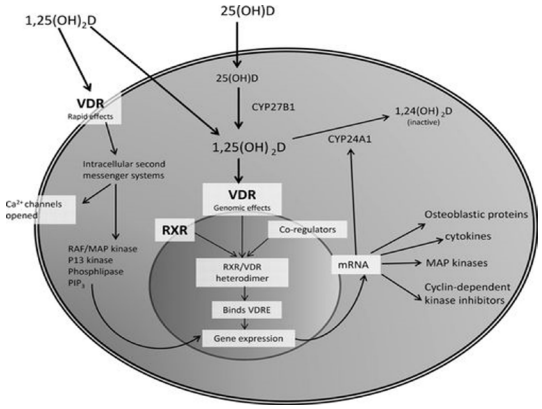

Figure 1: VDR effects on the cell membrane and genome [5].

Vitamin D metabolites may have epigenetic effects, with evidence emerging that VDR activation can generate microRNAs that can influence post-translational events. The VDR displays nongenomic effects that involve transmembrane calcium transport and the release of various second messengers, which can modulate gene expression in a similar way to certain other nuclear receptors. CVD signaling is poorly understood regarding its importance.

Vitamin D and Renin–Angiotensin–Aldosterone System (RAAS)

Blood pressure is greatly influenced by the RAAS, and several antihypertensive drugs work on this system. Feedback pathways in this system regulate fluid volume homeostasis, electrolyte plasma levels, and vascular resistance. Various conditions, such as hypoperfusion of the kidneys and the activation of the sympathetic nervous system, induce the synthesis of renin in nephrons [6, 7]. Angiotensinogen produced in the liver is converted into angiotensin I by renin, which in turn is converted into angiotensin II by angiotensin-converting enzyme expressed in the lungs. This molecule binds to its receptor, exerting several biological effects in multiple areas, such as the brain, the heart, the kidney, the adrenal glands, and the peripheral vessels. Several studies were conducted to measure possible changes in the activity of RAAS by disrupting vitamin D pathways *in vivo* and *in vitro*, with the goal of demonstrating the relationship between vitamin D and RAAS. RAAS is currently thought to be negatively regulated by vitamin D. Compared with wild-type mice, the levels of renin and angiotensin II are elevated in genetic models of VDR null mice. In addition, VDR null mice had higher systolic and diastolic blood pressures than wild-type mice. A hypertrophied heart also resulted in increased weight in null mice. As a result of overexpression of renin and angiotensin II in arterial hypertension, both null mice and wild-type animals exhibited similar decreases in blood pressure when treated with captopril. Furthermore, angiotensin II regulates thirst and salt craving, as well

as water and salt absorption in the intestinal tract. Under normal electrolyte plasma levels, VDR null mice drank twice as much as wild-type mice. In terms of food intake, no difference was observed. There was a 39% higher sodium excretion in the urine of VDR null mice compared to normal mice, as well as a 19% higher potassium excretion; thus, null mice seem to have angiotensin II overexpression, which leads to a greater water and salt absorption. Strontium, a substance capable of blocking vitamin D production, was used as an experimental dietary model of vitamin D suppression. When mice fed with a normal diet were subjected to strontium ingestion, renin levels were increased. Furthermore, 4.1 cells were used *in vitro* models to study the effects of SV40T antigen transgenic mice on kidney tumors. Vitamin D has the ability to negatively regulate renin levels by reducing renin messenger RNA expression. Experimental models of vitamin D deficiency exhibit cardiac hypertrophy and hypertension as well-known consequences of excessive RAAS activation. In nongenetic vitamin D deficiency models, similar results have been observed [2, 8]. An experiment using vitamin D-free diet mice and vitamin D-included diet mice induced hypovitaminosis D through dietary deprivation was carried out. As compared to the subgroup fed with vitamin D, the subgroup of rats on vitamin D-free diet had higher systolic blood pressure and myocardial/vascular contractility. During a vitamin D3-deficient diet, where calcium and phosphate levels were normal, a group of rats was tested to exclude hypocalcemia caused by hypovitaminosis D [9]. The blood pressure and heart/vasculature contractility were found to be similar under these experimental conditions. In a study of normo-glycemic individuals with newly diagnosed hypertension, hypovitaminosis D was found to have a strong inverse relationship with 1 h post-load glucose. Multiple subclinical organ damage was seen in patients with hypovitaminosis D and glucose levels >155 mg/dl at 1 h post-load glucose. Vitamin D supplementation and ultraviolet radiation have not been exhaustively studied for their effects on blood pressure. In hypertensive patients with low vitamin D levels, vitamin D supplementation lowers blood pressure, according to two RCTs. Vitamin D supplementation may lower blood pressure in hypertensive patients with vitamin D deficiency, unlike normal subjects with physiologic vitamin D levels. In order to gain a deeper understanding of the issue, additional studies will be required. In addition to RAAS hyperactivation, vitamin D deficiency could contribute to arterial hypertension through endothelial dysfunction and atherosclerosis [10-12].

Defining Matrix Homeostasis

The role of vitamin D metabolites in matrix homeostasis is supported by various lines of evidence. The role of inflammation, matrix destruction, and proteolysis in aneurysmal disease may be significant. Various cell types have shown that $1,25(OH)_2D$ inhibits matrix-metalloproteinase (MMP) production in vitro, and it has been shown that VDR knockout mice have lowered expressions of MMP-1 and MMP-3, whereas expressions of MMP-2 and MMP-9 are upregulated. MMP-2 and MMP-9 circulating levels are associated with vitamin D insufficiency in some clinical studies [13-17].

Marfan syndrome patients showed decreased expression of VDR gene in cultured skin fibroblasts. In view of the fact that the VDR acts as a negative regulator of transforming growth factor-β transcriptional activation, this could contribute to aneurysmal phenotype. A post-transcriptional mechanism is also known to repress elastin gene expression by vitamin D metabolites. It has been hypothesized that excessive vitamin D exposure during fetal life could influence the elastin deposition in the developing aorta, which would lead to aneurysm formation later in life, since most aortic elastin is synthesized during the fetal and early postnatal period [18]. Aortic aneurysms are associated with low vitamin D levels in adults. Currently, humans are not exposed to excessive vitamin D. As a result, it is uncertain whether this hypothesis holds true [19].

Aneurysmal disease and vitamin D deficiency are associated with some epidemiological evidence, as with occlusive arterial disease. The level of 25(OH)D correlated with aneurysmal diameter in a dose-response manner in a large population-based study of older men (n = 4233). Patients with abdominal and thoracic aneurysms (n = 236) also demonstrated a similar finding [5, 20].

Vitamin D and Endothelial Dysfunction

VDR+ endothelial and smooth muscle cells in the vascular system respond to vitamin D. In this respect, vitamin D plays a significant role in vascular contractility and the development of vascular calcifications. Vascular structure and function can be affected by vitamin D in different ways. In addition to vitamin D and its receptor, nitric oxide is well known for its potent vasodilating and vasoprotective properties. Nitric oxide synthesis may be regulated by vitamin D and its receptor, according to some studies. Vitamin D deficiencies are associated with increased oxidative stress, or a decrease in antioxidant capacity. In a study of chronic kidney disease patients receiving conservative treatment, serum 25(OH)D levels were found to be inversely correlated with artery dilation, measured by assessing brachial artery flow. Vitamin D circulating levels are thus inversely correlated with arterial size. Furthermore, hypovitaminosis D patients have higher plasma levels of pro-atherosclerosis cytokines. When compared to subjects with normal vitamin D levels, soluble vascular cell adhesion molecule-1 and soluble E-selectin levels were higher in vitamin D deficient subjects [21-24]. In a similar study, acetylcholine vasodilator response deteriorated when VDR expression was absent. Both endothelial cells and cells derived from activated vitamin D may also participate in this process. Vasodilatory and antithrombotic gene programs are activated by vitamin D. In fact, $1,25(OH)_2D$ decreases thrombogenic gene expression while increasing fibrinolytic gene expression in coronary vascular smooth muscle cells. Hypercoagulability is also associated with genetic models of VDR mice. According to a study, VDR null mice with normal levels of calcium plasma were able to increase ADP-induced platelet aggregation. Hemostasis was affected by changes in a variety of substances in this model. Antithrombin and thrombomodulin gene expression was downregulated, whereas prothrombotic tissue factor gene expression was upregulated. Under normal and low plasma calcium levels, the same study evaluated the differences between wild-type mice and VDR null mice after a prothrombotic insult. In spite of the plasma calcium levels, exogenous lipopolysaccharide caused an exacerbation of multiorgan thrombosis, associated with elevated tissue factor levels and decreased antithrombin and thrombomodulin levels. Through its receptor, vitamin D influences the endothelial system by modifying pro- and anti-thrombotic substances produced by endothelial cells [25].

The Relationship Between Vitamin D, Inflammation, and Atherosclerosis

There is currently evidence that vitamin D is related to atherosclerotic plaque development, perhaps through modulation of immune responses. VDR and CYP27A1 and CYP27B1 hydroxylases are expressed within immune system cells, explaining these interactions. They play an autocrine/paracrine role in the pathobiology of atherosclerotic plaques by activating vitamin D. Active vitamin D acts on macrophages and other immune cells, including dendritic cells. Vitamin D, in particular, drives cellular commitment to the M1 phenotype by promoting monocyte to macrophage transition. Toll-like receptors (TLR) TLR2, TLR4 and TLR-9 are inhibited by this receptor,

along with the production of immunosuppressant cytokines such as prostaglandin E2 [26]. Due to the downregulation of MHC class two antigens at the cell surface, the synthesis of inflammatory cytokines is decreased. Vitamin D inhibits the proliferation of B lymphocytes, their maturation into plasma cells, and their production of immunoglobulins in addition to regulating adaptive immune cells. T lymphocytes are suppressed by vitamin D from undergoing Th1 or Th17-dependent proinflammatory responses, and their immunomodulatory activity is also enhanced by vitamin D [27, 28]. Using vitamin D and VDR together, diabetics were able to downregulate the expression of scavenger receptors on macrophage surfaces, which prevented LDL cholesterol from passing into foam cells and preventing atherosclerosis. An additional anti-atherosclerotic mechanism is mediated by VDR activation, leading to the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) gene expression, associated with the downregulation of pro-inflammatory and pro-thrombogenic cytokines such as interleukin-6, as well as with the upregulation of thrombomodulin and interleukin-10. By inhibiting foam cell formation, this endothelial modulation suppresses vascular calcification and prevents atherosclerotic plaque formation. NF-B expression can be downregulated by adequate levels of vitamin D in pigs by inhibiting kariopherin-A4 (KPNA4), a protein that promotes it. These autocrine/paracrine pathways are characterized by their independence from calcium, PTH, and $1,25(OH)_2D$ levels in the body [29]. Thus, vitamin D supplementation's inconclusive results may be explained by disengagement from these classical regulatory mechanisms. There are several reasons why VDR expression can be correlated with the *in vivo* burden of atherosclerotic plaques. The presence of atherosclerotic lesions was detected in transgenic rats overexpressing 24-hydroxylase, which inactivates $1,25(OH)_2D$. Furthermore, endarterectomy patients

Table 1: Autocrine and paracrine $1,25(OH)_2D$ signaling in cardiovascular cells [2].

Cell type	Effect on gene expression and cell metabolism	Functional outcome	Cardiovascular significance
EC	↓ NFKB, ↓IL-6 expression	↓ Endothelial inflammation, improved flow-mediated dilation	↓ Atherosclerosis
	↓ Ca^{2+} influx, ↑ NO production	-	-
	↓ AII-induced ROS generation	↓ Endothelium-dependent contraction; optimal blood pressure	↓ Hypertension
	↓ Cyclin-dependent kinase	↓ Proliferation, ↑ monocyte adhesion	Unclear relevance to atherosclerosis
SMC	p38 MAP kinase, p21, p38, Cdk2	Modulation of proliferation and migration	↓ Atherosclerosis and intimal hyperplasia
	Altered expression of osteoblastic genes (alk phos, MGA, OP, ON, PTH-rP, Msx2, BMP2, Runx2, OC, Osterix)	Altered tissue mineralization	Variable dose-dependent influence of vascular calcification
	↓ Elastin expression	Aortic elastin content	Unclear relevance to aneurysmal phenotype
	↓ TF, ↓PAI-1, ↓ THSP1, ↑ TM)	Physiological balance of thrombosis and hemostasis	↓ Thrombogenicity
	↓ TGF-β expression	Matrix homeostasis	↓ Aneurysmal phenotype
	↓ Oxytocin receptor, ↑ type-B endothelin receptor expression	NO release, physiological vascular tone	↓ Hypertension
	↑ VEGF expression	Improved endothelial repair	↓ Atherosclerotic plaque initiation
	↑ CYP24A1	Autoregulation of local $1,25(OH)_2D$ production	Prevention of local $1,25(OH)_2D$ toxicity
Macrophage	↓ bic expression and microRNA-155 production	↑ SOCS	↓ Inflammation
	↑ IL-4, IL-10	↑ Anti-inflammatory	↓ Atherosclerosis
	↓ IL-6, IL-1, IL-23, TLR, TNFα, IFN-γ	↓ Proinflammatory gene expression	
	↓ TF, ↑ TM	Physiological balance of thrombosis and hemostasis	↓ Thrombogenicity
	↓ RAS activation, ↓ ER stress	↓ Cholesterol uptake and foam cell formation	↓ Atherosclerosis
	↑ CYP24A1	Autoregulation of local $1,25(OH)_2D$ production	Prevention of local $1,25(OH)_2D$ toxicity
Dendritic cell	↓ Proliferation and maturation	Induction of tolerogenic phenotype	↓ Vulnerable atherosclerotic plaque
	↓IL-12, ↑IL-10	↓ T cell stimulation	-
	-	↓ Inflammatory response	Effect on aneurysmal phenotype
T cell	↓T_H1, ↓T_H1, ↑T_{REG}, ↑T_H2	Tolerogenic adaptive immune response	↓ Atherosclerosis
	↑ IL-5, ↑ IL-10	↓ Inflammatory response	-
Cardiomyocyte	↑TIMP-1 and -2, ↓MMP-2 and -9	Physiological matrix turnover and cardiac remodeling	↓ Cardiac hypertrophy
	↓c-myc expression, ↓RAS activation	-	↓ Heart failure
	↓ANP, ↑ type 1 natiuretic peptide receptor A	↓ RAS, ↓ Proliferation/ventricular hypertrophy	-
	Myosin expression, sarcomere function	Cardiac contractility	Optimal diastolic coronary perfusion
Aortic valve fibroblast	Osteogenic factors ↓BMP2	↓ Matrix calcification	↓ Valve calcification

Note: ANP: Atrial natriuretic peptide; BMP2: Bone morphogenetic protein 2; Cdk2: Cyclin-dependent kinase 2; CYP24A1: 24-hydroxylase; EC: Endothelial cell; IFN-γ, Interferon-γ; IL: Interleukin; MAP: Mitogen-activated protein; MGA: Matrix gla protein; MMP: Matrix-metalloproteinase; NFκB: Nuclear factor κB; OC: Osteocalcin; ON: Osteonectin; PAI-1: Plasminogen activator inhibitor-1; PTH-rP: Parathyroid-related protein; RAS: Renin–angiotensin system; ROS: Reactive oxygen species; SMC: Smooth muscle cell; SOCS: Suppressors of cytokine signaling; TF: Tissue factor; TGF-β: Transforming growth factor-β; TIMP-1: Tissue inhibitor of matrix metalloproteinase-1; TLR: Toll-like receptor; TM: Thrombomodulin; TNF-α: Tumor necrosis factor-α; and VEGF: Vascular endothelial growth factor.

with carotid stenosis have undergone interesting studies on human plaques. Observations showed a correlation between intraplaque VDR levels and M1 macrophage phenotype expression. Carotid plaques with low VDR levels are more likely to cause MACE than those with high plasma vitamin D levels. Similarly, vitamin D may contribute to cardiometabolic dysfunction by regulating visceral and ectopic fat deposition. According to some clinical trials, vitamin D and calcium supplementation may decrease fat deposition and reduce the risk of cardiovascular and metabolic disorders [30].

Vitamin D Supplementations and Cardiovascular Health

In a recent RCT, the Vitamin D and Omega-3 Trial (VITAL) investigates the effects of omega-3 or vitamin D supplements on cardiovascular outcomes in the general population. Twenty-five thousand eight hundred seventy-one participants were recruited throughout the United States, getting either a placebo or a daily dose of 2.000 IU of vitamin D. A median of 5.3 years was used to monitor reductions in myocardial infarctions, strokes, and cardiovascular death. A significant benefit on cardiovascular outcomes was not found in the VITAL trial [31, 32]. Compared to the placebo group, vitamin D treatment only had a minor impact on cardiovascular events. Vitamin D supplementation did not result in any cardiovascular benefits in the Women's Health Initiative Calcium and Vitamin D Trial (WHI CaD). In the DIMENSION trial, cholecalciferol supplementation for 16 weeks was evaluated for its potential impact on endothelial function. A particular focus was on the improvement of vascular biomarkers and the reactive hyperemia index. The treatment arm showed significant increases in vitamin D levels [33]. A multivariate regression analysis, however, revealed no effect on endothelial function. In addition, cholecalciferol administered before a percutaneous coronary procedure did not result in any change in MACE compared to a control arm in a study that examined the possible protective effects of vitamin D on markers of heart disease. As part of the BEST-D trial, the authors studied the effects of cholecalciferol supplementation in healthy subjects over a 1-year period. This trial also had fewer encouraging results than the above-mentioned trials. There was an increase in serum 25(OH) D concentrations when vitamin D supplementation was administered, but no significant changes were found in CVD risk factors, blood pressure, arterial stiffness, or blood lipid levels [34]. Over 21,000 subjects participated in the D-Health Trial, which assessed vitamin D supplementation's effectiveness in preventing cancer and mortality. Based on access to health records and death records, this RCT assessed the effects of either placebo or cholecalciferol administrations for a 5-year period followed by passive monitoring for another 5 years. There was no clear evidence that vitamin D supplementation reduced cancer and mortality risk in this study, and the authors concluded that observational data do not support the utilization of vitamin D as a protective agent in healthy individuals [35, 36]. Supplementation with cholecalciferol did not reduce the risk of CVD. In another double-blind, placebo-controlled trial in healthy subjects, cholecalciferol supplementation was explored to see if it could lower blood pressure, heart rate, and CVD risk markers for 12 weeks. The CVD risk did not improve despite an increase in serum 25(OH)D levels. CVD incidence and serum 25(OH)D levels were correlated in a recent meta-analysis. In spite of low vitamin D levels being linked to a significant increase in CVD (incidence and mortality combined), and an increased mortality associated with CVD, no significant relationship was found. In another meta-analysis, 21 RCTs were included to assess whether vitamin D supplements are beneficial to heart health over a one-year period, regardless of whether calcium is taken [5, 37]. In this study, MACEs were combined as the primary endpoint. In addition to endpoints related to myocardial infarction, strokes, and cerebrovascular accidents, secondary endpoints included cardiovascular mortality and mortality from all causes. MACE, stroke, cardiovascular mortality, or all-cause mortality were not significantly affected by vitamin D supplementation, based on this meta-analysis. Studies like the ones above confirm the evidence that vitamin D supplementation does not affect cardiovascular health in a meaningful way. Supplemental vitamin D may cause acute toxic effects, but only at very high doses can vitamin D toxicity occur [2, 38-41]. Hypercalcemia is one of vitamin D's toxic effects, which can cause cardiac arrhythmias caused by shortened QT intervals.

Vitamin D and Heart Failure

Cardiomyocytes express both VDR and hydroxylases necessary for forming active vitamin D. As a result of the loss of activity of the vitamin D signaling pathway, cardiomyocytes and the extracellular matrix are remodeled *in vivo* [42-44]. In addition to acled on the anatomical, functional, molecular, and genetic aspects of cardiac hypertrophy and dysfunction that lead to heart failure with preserved ejection fraction (HFpEF), vitamin D can reduce or prevent this remodeling by administrating the active form of vitamin D. Heart failure with preserved ejection fraction (HFpEF) is characterized by an increased filling pressure, cardiac hypertrophy, and diastolic dysfunction [45, 46]. Researchers found that PC reduced left ventricular hypertrophy in a mice model of hypertension and left ventricular hypertrophy, induced by high-salt diets. Additionally, the interventional group demonstrated a reduction in the interventricular septum, posterior wall, and mass of the left ventricle [47]. Also, in this setting, PC was found to reduce the signs of cardiac hypertrophy in patients with end-stage renal disease. For seven consecutive days, continuous wireless telemetry was performed to exclude the possibility that these findings were due to a different pressure overload between the two groups [48]. As well as reducing BNP and ANF, PC also decreased a variety of molecular markers of heart failure. Vitamin D appears to improve cardiac function by activating intracellular pathways that lead to altered gene expression, but its mechanism is not fully understood. Using microarray gene analysis, it was found that mice in the PC-group had reduced levels of those genes related to hypertrophy. As a result of transverse aortic constriction induced cardiac hypertrophy in mice, gene expression was shown to change by PC or losartan treatment [49]. The expression of collagen III, fibronectin, and tissue inhibitor-1 of MMPs were reduced. Activation of the vitamin D pathway appears to stimulate calcium uptake in wild type mice, increase contractility in VDR knockout mice, and improve diastolic function in VDR knockout mice. Hypertrophy and cardiomegaly are observed in VDR knockout animal models. Researchers found that hypovitaminosis D was a significant predictor of increased left ventricular mass index in newly diagnosed hypertensive patients. Extracellular matrix can also be affected by vitamin D by interfering with collagen and metalloproteinase production [50]. In mice lacking vitamin D, extracellular space and collagen increase, resulting in cardiomegaly. In addition, VDR knockout mice display high MMP levels and low tissue inhibitors of metalloproteinases concentrations, as well as increased fibrosis.

Cardiovascular Risks Associated with Calcium and Phosphate

It is quite natural that changes in the levels of calcium/phosphate metabolites and the overall cardiovascular risk could be correlated due to vitamin D's role in regulating calcium/phosphate absorption and metabolism. The pathogenesis of CVDs may be influenced by calcium, phosphate, and vitamin D, according to a number of experimental and clinical studies [2, 51]. In light of the close connections between

calcium, phosphate, and vitamin D, they constitute a biological axis that should be considered with regard to all three components. It is still unclear how their coordinated functions affect cardiovascular disorders' development and progression. Clinical trials designed to unravel the real effects of calcium/phosphate/vitamin D deficiencies or supplementation have been unable to do so in the very complex scenario of the global cardiovascular risk [52, 53].

Conclusion

Secosteroids such as vitamin D are involved in calcium and phosphate metabolism. To reach sufficient levels of vitamin D, adequate food intake and sunlight exposure are needed. It is not just bone and calcium metabolism diseases that are associated with low vitamin D levels. Current evidence suggests that hypovitaminosis D directly contributes to CVD. Atherosclerotic plaque development was favored by vitamin D deficiency both *in vitro* and *in vivo* in animal models. The reintegration of vitamin D restored or improved cardiovascular impairment in animal reversible models by restoring endothelial dysfunction and RAAS modulation. Animal models of vitamin D deficiency also display biochemical and echocardiographic changes similar to those observed in patients with HFpEF due to heart hypertrophic remodeling. It is well established in animal models that hypovitaminosis D is associated with cardiovascular disease, but a number of trials and meta-analyses have failed to confirm that vitamin D supplementation will improve cardiovascular health in humans, thus never reaching significant results regarding MACE. Therefore, vitamin D supplementation needs to be further investigated before the supposed benefits can be proven.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357: 266-281. https://doi.org/10.1056/NEJMra070553
2. Condoleo V, Pelaia C, Armentaro G, Severini G, Clausi E, et al. (2021) Role of vitamin D in cardiovascular diseases. Endocrines 2: 417-426. https://doi.org/10.3390/endocrines2040037
3. Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, et al. (2012) The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. Endocr Rev 33: 456-492. https://doi.org/10.1210/er.2012-1000
4. Weishaar RE, Simpson RU (1987) Vitamin D3 and cardiovascular function in rats. J Clin Invest 79: 1706-1712. https://doi.org/10.1172/JCI113010
5. Norman PE, Powell JT (2014) Vitamin D and cardiovascular disease. Circ Res 114: 379-393. https://doi.org/10.1161/CIRCRESAHA.113.301241
6. Scragg R (1981) Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. Int J Epidemiol 10: 337-341. https://doi.org/10.1093/ije/10.4.337
7. Motiwala SR, Wang TJ (2012) Vitamin D and cardiovascular risk. Curr Hypertens Rep 14: 209-218. https://doi.org/10.1007/s11906-012-0262-y
8. Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, et al. (2013) Effect of vitamin D supplementation on blood pressure in blacks. Hypertension 61: 779-785. https://doi.org/10.1161/HYPERTENSIONAHA.111.00659
9. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB (2012) Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. Am J Hypertens 25: 1215-1222. https://doi.org/10.1038/ajh.2012.111
10. Witham MD, Nadir MA, Struthers AD (2009) Effect of vitamin D on blood pressure: a systematic review and meta-analysis. J Hypertens 27: 1948-1954. https://doi.org/10.1097/HJH.0b013e32832f075b
11. Legarth C, Grimm D, Wehland M, Bauer J, Krüger M (2018) The impact of vitamin D in the treatment of essential hypertension. Int J Mol Sci 19: 455. https://doi.org/10.3390/ijms19020455
12. Victor VM, Rocha M, Sola E, Banuls C, Garcia-Malpartida K, et al. (2009) Oxidative stress, endothelial dysfunction and atherosclerosis. Curr Pharm Des 15: 2988-3002. https://doi.org/10.2174/138161209789058093
13. Zhang QY, Jiang CM, Sun C, Tang TF, Jin B, et al. (2015) Hypovitaminosis D is associated with endothelial dysfunction in patients with non-dialysis chronic kidney disease. J Nephrol 28: 471-476. https://doi.org/10.1007/s40620-014-0167-8
14. Napoli C, de Nigris F, Williams-Ignarro S, Pignalosa O, Sica V, et al. (2006) Nitric oxide and atherosclerosis: an update. Nitric Oxide 15: 265-279. https://doi.org/10.1016/j.niox.2006.03.011
15. Zehnder D, Bland R, Chana RS, Wheeler DC, Howie AJ, et al. (2002) Synthesis of 1,25-dihydroxyvitamin D3 by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. J Am Soc Nephrol 13: 621-629. https://doi.org/10.1681/ASN.V133621
16. Cardus A, Parisi E, Gallego C, Aldea M, Fernandez E, et al. (2006) 1,25-Dihydroxyvitamin D_3 stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway. Kidney Int 69: 1377-1384. https://doi.org/10.1038/sj.ki.5000304
17. Wu-Wong JR, Nakane M, Ma J, Ruan X, Kroeger PE (2006) Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. Atherosclerosis 186: 20-28. https://doi.org/10.1016/j.atherosclerosis.2005.06.046
18. Aihara KI, Azuma H, Akaike M, Ikeda Y, Yamashita M, et al. (2004) Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem 279: 35798-35802. https://doi.org/10.1074/jbc.M404865200
19. Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, et al. (2009) Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J Immunol 182: 4289-4295. https://doi.org/10.4049/jimmunol.0803736
20. Quinn CM, Jessup W, Wong J, Kritharides L, Brown AJ (2005) Expression and regulation of sterol 27-hydroxylase (CYP27A1) in human macrophages: a role for RXR and PPARγ ligands. Biochem J 385: 823-830. https://doi.org/10.1042/BJ20041776
21. Dickie LJ, Church LD, Coulthard LR, Mathews RJ, Emery P, et al. (2010) Vitamin D3 down-regulates intracellular Toll-like receptor 9 expression and Toll-like receptor 9-induced IL-6 production in human monocytes. Rheumatology 49: 1466-1471. https://doi.org/10.1093/rheumatology/keq124
22. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, et al. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311: 1770-1773. https://doi.org/10.1126/science.1123933
23. Chen S, Sims GP, Chen XX, Gu YY, Chen S, et al. (2007) Modulatory effects of 1,25-dihydroxyvitamin D_3 on human B cell differentiation. J Immunol 179: 1634-1647. https://doi.org/10.4049/jimmunol.179.3.1634
24. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, et al. (2001) 1α,25-Dihydroxyvitamin D_3 has a direct effect on naive $CD4^+$ T cells to enhance the development of Th2 cells. J Immunol 167: 4974-4980. https://doi.org/10.4049/jimmunol.167.9.4974
25. Oh J, Weng S, Felton SK, Bhandare S, Riek A, et al. (2009) $1,25(OH)_2$ vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation 120: 687-698. https://doi.org/10.1161/CIRCULATIONAHA.109.856070
26. Yin K, You Y, Swier V, Tang L, Radwan MM, et al. (2015) Vitamin D protects against atherosclerosis via regulation of cholesterol efflux and macrophage polarization in hypercholesterolemic swine. Arterioscler Thromb Vasc Biol 35: 2432-2442. https://doi.org/10.1161/ATVBAHA.115.306132
27. Chen S, Swier VJ, Boosani CS, Radwan MM, Agrawal DK (2016) Vitamin D deficiency accelerates coronary artery disease progression in swine. Arterioscler Thromb Vasc Biol 36: 1651-1659. https://doi.org/10.1161/ATVBAHA.116.307586
28. Kasuga H, Hosogane N, Matsuoka K, Mori I, Sakura Y, et al. (2002) Characterization of transgenic rats constitutively expressing vitamin D-24-hydroxylase gene. Biochem Biophys Res Commun 297: 1332-1338. https://doi.org/10.1016/S0006-291X(02)02254-4
29. Neeland IJ, Poirier P, Després JP (2018) Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 137: 1391-1406. https://doi.org/10.1161/CIRCULATIONAHA.117.029617

30. Hin H, Tomson J, Newman C, Kurien R, Lay M, et al. (2017) Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. Osteoporos Int 28: 841-851. https://doi.org/10.1007/s00198-016-3833-y

31. Neale RE, Armstrong BK, Baxter C, Romero BD, Ebeling P, et al. (2016) The D-Health Trial: a randomized trial of vitamin D for prevention of mortality and cancer. Contemp Clin Trials 48: 83-90. https://doi.org/10.1016/j.cct.2016.04.005

32. Legarth C, Grimm D, Krueger M, Infanger M, Wehland M (2019) Potential beneficial effects of vitamin d in coronary artery disease. Nutrients 12: 99. https://doi.org/10.3390/nu12010099

33. Seibert E, Lehmann U, Riedel A, Ulrich C, Hirche F, et al. (2017) Vitamin D_3 supplementation does not modify cardiovascular risk profile of adults with inadequate vitamin D status. Eur J Nutr 56: 621-634. https://doi.org/10.1007/s00394-015-1106-8

34. Gholami F, Moradi G, Zareei B, Rasouli MA, Nikkhoo B, et al. (2019) The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord 19: 248. https://doi.org/10.1186/s12872-019-1236-7

35. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, et al. (2019) Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol 4: 765-776. https://doi.org/10.1001/jamacardio.2019.1870

36. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, et al. (2021) Vitamin D and cardiovascular health. Clin Nutr 40: 2946-2957. https://doi.org/10.1016/j.clnu.2020.12.025

37. Brown RB, Haq A, Stanford CF, Razzaque MS (2015) Vitamin D, phosphate, and vasculotoxicity. Can J Physiol Pharmacol 93: 1077-1082. https://doi.org/10.1139/cjpp-2015-0083

38. Heine GH, Nangaku M, Fliser D (2013) Calcium and phosphate impact cardiovascular risk. Eur Heart J 34: 1112-1121. https://doi.org/10.1093/eurheartj/ehs353

39. Karlic H, Varga F (2011) Impact of vitamin D metabolism on clinical epigenetics. Clin Epigenetics 2: 55-61. https://doi.org/10.1007/s13148-011-0021-y

40. Huhtakangas JA, Olivera CJ, Bishop JE, Zanello LP, Norman AW (2004) The vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25$(OH)_2$-vitamin D_3 *in vivo* and *in vitro*. Mol Endocrinol 18: 2660-2671. https://doi.org/10.1210/me.2004-0116

41. Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, et al. (2012) Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 188: 2127-2135. https://doi.org/10.4049/jimmunol.1102412

42. Jones G (2013) Extrarenal vitamin D activation and interactions between vitamin D_2, vitamin D_3, and vitamin D analogs. Annu Rev Nutr 33: 23-44. https://doi.org/10.1146/annurev-nutr-071812-161203

43. Jablonski KL, Chonchol M, Pierce GL, Walker AE, Seals DR (2011) 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension 57: 63-69. https://doi.org/10.1161/HYPERTENSIONAHA.110.160929

44. Mill C, George SJ (2012) Wnt signalling in smooth muscle cells and its role in cardiovascular disorders. Cardiovasc Res 95: 233-240. https://doi.org/10.1093/cvr/cvs141

45. Wong MS, Delansorne R, Man RY, Vanhoutte PM (2008) Vitamin D derivatives acutely reduce endothelium-dependent contractions in the aorta of the spontaneously hypertensive rat. Am J Physiol Heart Circ Physiol 295: H289-H296. https://doi.org/10.1152/ajpheart.00116.2008

46. Dong J, Wong SL, Lau CW, Lee HK, Ng CF, et al. (2012) Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. Eur Heart J 33: 2980-2990. https://doi.org/10.1093/eurheartj/ehr459

47. Chen S, Law CS, Gardner DG (2010) Vitamin D-dependent suppression of endothelin-induced vascular smooth muscle cell proliferation through inhibition of CDK2 activity. J Steroid Biochem Mol Biol 118: 135-141. https://doi.org/10.1016/j.jsbmb.2009.11.002

48. Latic N, Erben RG (2020) Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. Int J Mol Sci 21: 6483. https://doi.org/10.3390/ijms21186483

49. Mitsuhashi T, Morris RC, Ives HE. 1991. 1,25-dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. J Clin Invest 87: 1889-1895. https://doi.org/10.1172/JCI115213

50. Rebsamen MC, Sun J, Norman AW, Liao JK (2002) 1α,25-Dihydroxyvitamin D_3 induces vascular smooth muscle cell migration via activation of phosphatidylinositol 3-kinase. Circ Res 91: 17-24. https://doi.org/10.1161/01.RES.0000025269.60668.0F

51. Molinari C, Uberti F, Grossini E, Vacca G, Carda S, et al. (2011) 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. Cell Physiol Biochem 27: 661-668. https://doi.org/10.1159/000330075

52. Bukoski RD, DeWan P, McCarron DA (1989) 1,25$(OH)_2$ vitamin D_3 modifies growth and contractile function of vascular smooth muscle of spontaneously hypertensive rats. Am J Hypertens 2: 553-556. https://doi.org/10.1093/ajh/2.7.553

53. Lamawansa MD, Wysocki SJ, House AK, Norman PE (1996) Vitamin D_3 exacerbates intimal hyperplasia in balloon-injured arteries. Br J Surg 83: 1101-1103. https://doi.org/10.1002/bjs.1800830820