Kanem J Med Sci 2025; 19(1): 1-21

ISSN 2006-4772
https://doi.org/10.36020/kjms.2025.1901.001

Review Article

Non-calcitropic roles of calcitriol in the cardiovascular system — a narrative review

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Abstract

Background: Vitamin D is a secosteroid with the elemental formula of $C_{27}H_{44}O$, and vitamin D_2 and D_3 are its two distinct forms. Cutaneous synthesis and diet are two main sources of delivering vitamin D. It is converted into its active hormonal form to exert its biological actions and plays an important, pleiotropic role, as the diverse activities of vitamin D are mediated through both genomic and non-genomic pathways. Aside from its traditional roles in the regulation of mineral homeostasis, vitamin D has also been shown to mediate a number of additional non-genomic or "rapid" actions at the non-transcriptional level in a variety of tissues. It has been shown to protect against endothelial dysfunction, smooth vascular muscle cell proliferation and migration, and modulation of the immune system, as well as the inflammatory response. Although some vitamin D is essential for cardiovascular health, excess may have detrimental effects, particularly on elastogenesis and inflammation of the arterial wall. The detection of Vitamin D receptors in almost all tissues of the body spurred wide interest in its physiological functions. The primary purpose of this review was to provide an overview of the metabolism, mechanism of actions, homeostatic regulations, and non-calcitropic roles of Vitamin D in the vasculature. **Methodology:** Literature search using the combination(s) of the following key terms: "*cardiovascular System,*" "*Metabolism,*" "*Non-calcitropic Role,*" "*Regulation,*" *and* "*Vitamin D*" was used to identify relevant studies that were used for this review. The search was restricted to articles written in English language, but no time limit restriction was used. Out of the retrieved studies, only those the relevant information as assessed by the authors were used to write this review.

Keywords: *Cardiovascular System, Metabolism, Non-calcitropic Role, Regulation, Vitamin D*

Introduction

A newborn with excessive birth weight is referred to Historically, vitamin D (alphabetically named 'D' as the fourth known vitamin) was discovered by McCollum *et al* in 1922 from cod liver oil as the substance that cured rickets. [1,2] Vitamin D is a prohormone classified under a group of fat-soluble molecules with the elemental formula of $C_{27}H_{44}O$.. [3] Cutaneous synthesis and diet are two main sources of delivering vitamin D, which has two distinct forms: vitamins D_2 and D_3. [4,5] Vitamin D_2 is a 28-carbon molecule derived from ergosterol, whereas vitamin D_3 is a 27-carbon molecule derived from cholesterol. [6] In a human being, 80 to 90% of the required vitamin D is supplied by cutaneous synthesis in the form of vitamin D_3. [7] In a classical sense, vitamin D_3 is not a true "vitamin" because it is produced from 7-dehydrocholesterol. [8,9] It has been estimated that a 10-minute sunlight exposure (solar UVB radiation between wavelengths of 290 and 320nm, with peak synthesis occurring within 295 and 297nm) of just the uncovered hands and face suffices to produce sufficient vitamin D_3 (Fig. 1). [10,11] Prolonged exposure to sunlight would not produce toxic amounts of vitamin D_3 because of the photoconversion of pre-vitamin D_3 to lumisterol and tachysterol and photodegradation into other inactive metabolites such

Cite this article as: Leta Melaku, Bedasa Elias. Non-calcitropic roles of calcitriol in the cardiovascular system — a narrative review. Kanem J Med Sci 2025; 19(1): 1-21.

Received: 5th January 2025 **Accepted: 19th March 2025** **Published: 30th June 2025**

as 5, 6-trans-vitamin D_3, suprasterol 1, and suprasterol 2. [12] Subsequently, under dark conditions and as pre-vitamin D_3 declines, lumisterol and tachysterol can undergo reversible conversion back to pre-vitamin D_3, which serves as a reservoir (Fig. 1). [3,13] The slow conversion of previtamin D_3 to vitamin D_3 ensures adequate supplies when the exposure is brief. [14] Therefore, only when exposure to sunlight is inadequate does vitamin D_3 become a vitamin in the historical sense. In the blood, vitamin D_3 is transported in the bounded form by binding primarily to a protein known as vitamin D binding protein (VDBP).[4] This protein selectively removes vitamin D_3 from the skin due to its low affinity it has for 7-dehydrocholesterol, previtamin D_3, lumisterol, and tachysterol. [15,16]

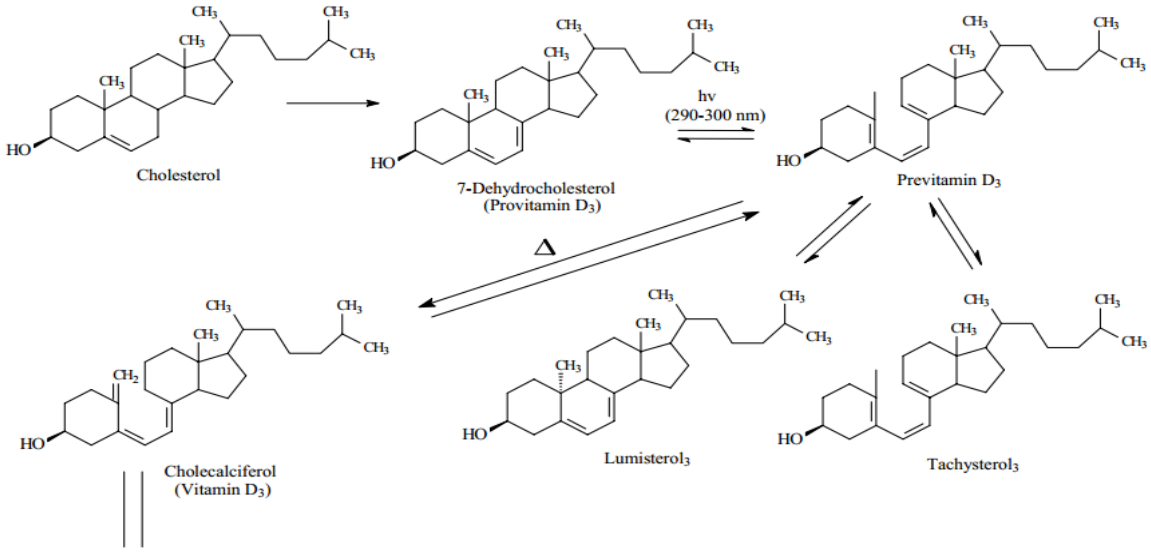

Figure 1: Vitamin D_3 biosynthesis

Apart from exposure to sunlight, a smaller portion of vitamin D (10.0% to 20.0% of circulating levels) is ingested from the diet. [5,17,18] Vitamin D_3 may be absorbed better than vitamin D_2. [19] Vitamin D_2, which is mostly synthesized by invertebrates and plants after exposure to ultraviolet radiation (Fig. 2),[5] is most often used in commercial products and to fortify foods. [17] These two vitamins differ chemically only in their side chains. This difference alters their binding to the vitamin D-binding protein and their metabolism. [19,20]

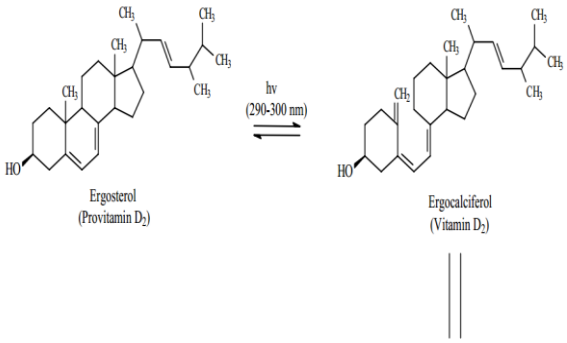

Figure 2: Vitamin D_2 biosynthesis.

Whether it is derived from the diet or synthesized cutaneously, vitamin D requires two hydroxylation reactions in the body to gain its full hormonal activity (Fig. 4).[21,22] The first biological activation occurs in the liver, where vitamin D is converted to 25(OH)D (calcidiol) by the enzyme vitamin D_3-25-hydroxylase (25-OHase)(23). 25(OH)D is a biologically inactive form and recirculates in the blood in free form (<0.05%), and the rest is bound to serum proteins. [5] Recent studies have shown that vitamin D3 is significantly more effective than vitamin D2 at increasing serum 25(OH)D concentrations; [24,25] therefore, vitamin D_3 is considered to be a better form of supplementation. [26,27] However, excessive oral supplementation of vitamin D can lead to toxicity by raising plasma 25(OH)D concentrations that exceed Vitamin D-Binding Protein (VDBP) binding capacity. [12,28]

The next step of the vitamin D bio-activation is the hydroxylation of 25(OH)D to the active hormonal form of 1, $25(OH)_2D$ (calcitriol) by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase), which mainly occurs in the epithelial cells of renal proximal convoluted tubules (Fig. 3).[13] Apart from renal, several other cell types can express 1α-hydroxylase, enabling extrarenal activation of circulating 25(OH)D to the active hormonal form.29,30 These include skin cells, monocytes/macrophages, placenta during pregnancy, colon cells, endothelial cells, VSMCs,

breast cells, pancreatic islets, and prostate cells. [31] According to a widely accepted hypothesis, the local conversion of 25(OH)D to 1, 25$(OH)_2$D seems to determine tissue levels of 1, 25$(OH)_2$D in various organs, [32] as well as acting in a paracrine/autocrine fashion to regulate cell growth and differentiation. [22] Furthermore, only in the case of excessive local production does 1, 25$(OH)_2$D spill over into the general circulation. [33] Therefore, activity of renal 1α-hydroxylase, unlike that of extrarenal 1α-hydroxylase, [20,34] is under close modulation by a tight feedback mechanism that keeps calcitriol levels within a narrow range. [21] The strong bio-efficacy of 1, 25 $(OH)_2$D is also controlled by countervailing 25–hydroxyvitamin D_3-24-hydroxylase (24-OHase) enzyme, which leads to deactivation of 1, 25$(OH)_2$D or 25(OH)D and the resulting vitamin D metabolites [e.g. 1, 24, 25$(OH)_3$D or 24, 25$(OH)_2$D] which are subsequently converted to calcitroic acid and excreted via the urine (Fig. 3).[35–37] It is the most important mechanism by which the 1, 25(OH) $_{2D\text{-mediated}}$ endocrine or intracrine signal is terminated in all target cells. [38] In general terms, vitamin D metabolism is self-regulated through negative feedback mechanisms, serum phosphate and calcium, FGF-23, and PTH. [3,39] The vitamin D intracrine system, in contrast, appears to be dependent more on the availability of ample 25(OH)D substrate to generate local 1, 25$(OH)_2$D to lower the risk of chronic diseases. [40]

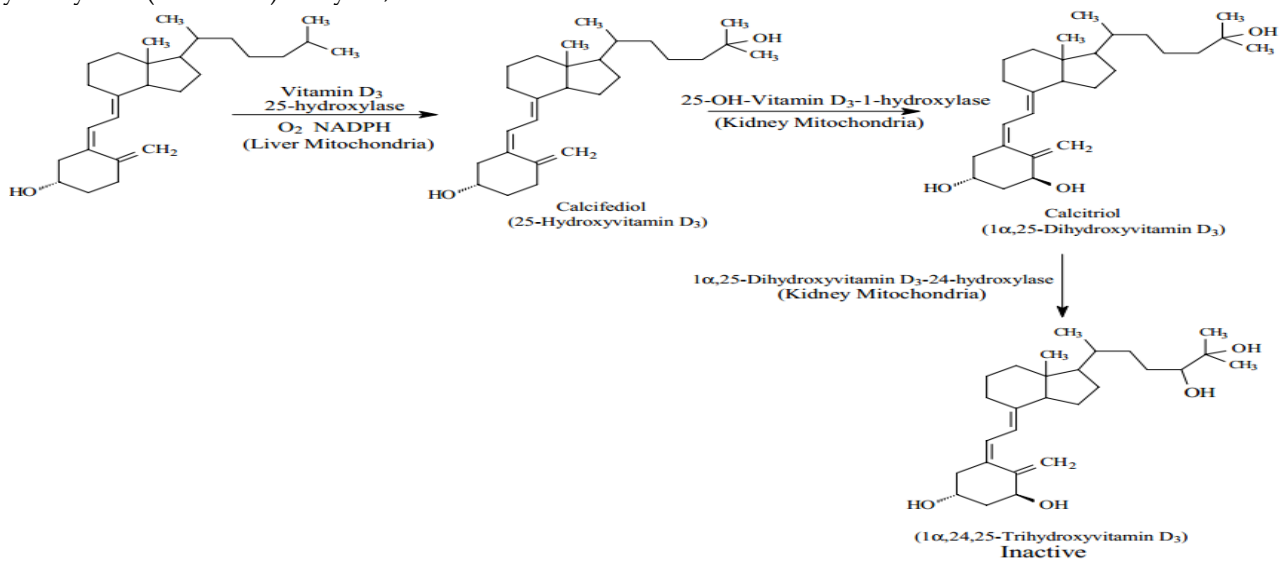

Figure 3: Vitamin D activation and inactivation

It is well known that vitamin D exerts pleiotropic actions in multiple organs and tissues, ranging from regulation of the immune system to that of mineral metabolism. [41] It is generally assumed that most of the vitamin D's action occurs through the binding of its active metabolite, 1, 25$(OH)_2$D (calcitriol) to the vitamin D receptor (VDR), although effects mediated by other metabolites such as 25(OH)D and 24, 25$(OH)_2$D are also possible. [15,42] The VDR has two variant isoforms, one with 424 amino acids (VDRm) and the other with 427 amino acids (VDRn).[43,44] Liganded VDRn forms a heterodimeric complex with Retinoid-X-Receptor (RXR) and either up-regulates or down-regulates the expression of target genes through binding to promoter sequences termed vitamin D responsive elements (VDREs).[45] Classically, the genomic effects of 1, 25$(OH)_2$D are thought to be mediated by its interaction with a nuclear vitamin D receptor (VDRn)(Fig. 4), a member of the nuclear receptor superfamily of ligand-activated transcription factors. [46] The existence of a VDRm and its role in the non-genomic actions of 1, 25$(OH)_2$D are also well-accepted. [46,47] It is recognized that 1, 25$(OH)_2$D also exerts non-genomic actions, in the main, as the activation of signalling molecules, such as phospholipase C and phospholipase A_2 (PLA_2), phosphatidylinositol-3 kinase (PI3K) and p21ras, and the rapid generation of second messengers (Ca^{2+}, cAMP, fatty acids and IP_3), accompanied by the activation of protein kinases, such as Protein Kinase A (PKA), src, Mitogen-Activated Protein Kinase (MAPK), Protein Kinase C (PKC) and Ca^{2+}-calmodulin kinase II (Fig. 4).[48–50] The non-genomic actions also include the opening of Ca^{2+} and Cl^- channels. [51]

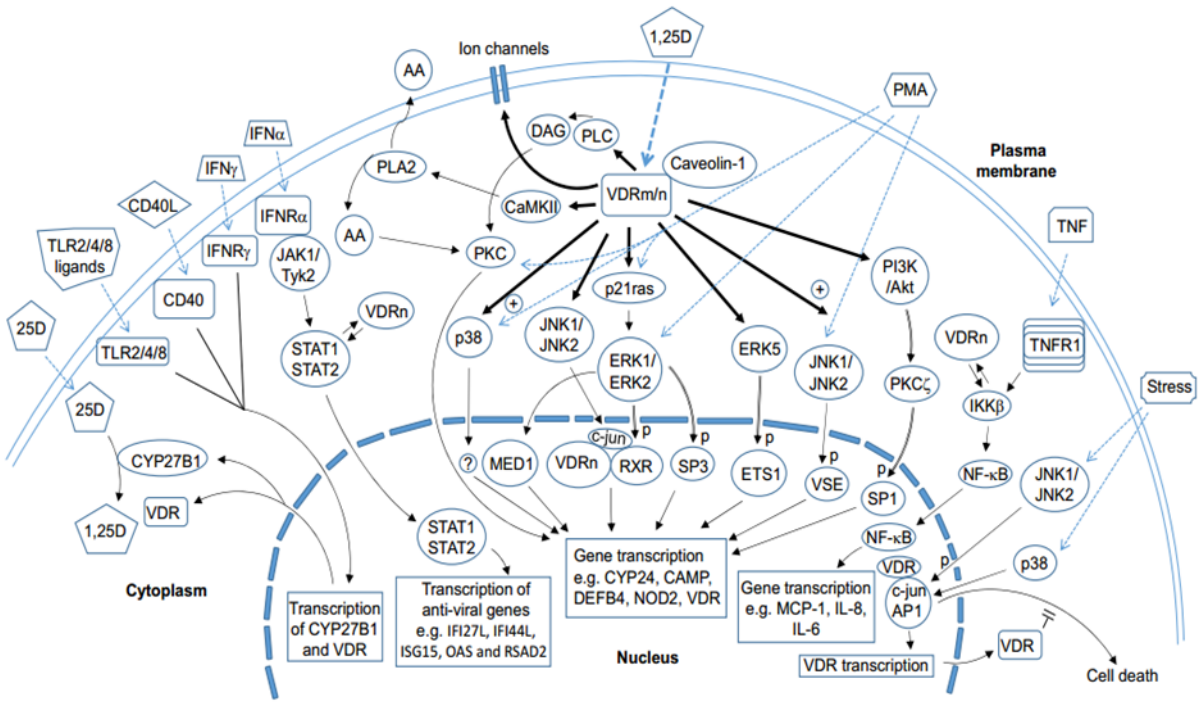

Figure 5: The molecular mechanism of actions of 1, 25(OH)$_2$D via both genomic and non-genomic actions. *Dotted arrows denote ligand binding to their receptors. Reversible arrows indicate protein-protein interaction. Arrows with double lines indicate a kinase-substrate relationship. "p" denotes phosphorylation; "+" denotes enhancement*

1. Effects of Vitamin D on Endothelial Cells of Blood Vessels

The healthy endothelium responds to physical and chemical signals by producing factors that regulate vascular tone, cellular adhesion, thrombosis, smooth muscle proliferation, and vessel wall inflammation. [52] In normal vascular physiology, nitric oxide (NO) plays a key role in maintaining the vascular tone under laminar shear stress in a quiescent state by inhibition of inflammation, cellular proliferation, and thrombosis. [53] Prolonged exposure to cardiovascular risk factors can ultimately exhaust the protective effect of endogenous anti-inflammatory and antioxidant systems within endothelial cells and thus contribute to vascular disease by sustained endothelial activation. [54] Endothelial activation is a switch from a quiescent state, mostly regulated by NO-mediated silencing of cellular processes, to an activated endothelium mediated by redox signaling. [55] Upon endothelial activation:

A. eNOS uncoupling occurs; ROS, such as H_2O_2, will diffuse into the endothelial cell. This leads to expression of adhesive ligands (inclusive of von-

B.

C. Willebrand factor (vWF) and P-selectin) on the endothelium. Platelet adhesion also occurs through binding of platelets via platelet-fibrinogen complexes and intercellular adhesion molecule-1 (ICAM-1). These adherent platelets secrete numerous bioactive substances that alter the adhesive properties. [53]

D. NF-κB dissociates from Ikβ (a regulatory protein that inhibits NF-κB by complexing with and trapping it in the cytoplasm) and translocates into the cell nucleus. Through interactions with CD40, platelets also release interleukin-1 beta (IL-1β), which can stimulate endothelial cells via NF-κB to release interleukins, IL-6 and IL-8, and increase the expression of ICAM-1, VCAM-1, P-selectin and E-selectin. As such, these cytokines and tissue factor release fuel a feed-forward chain reaction, which further decreases NO release. [56]

E. The innate inflammatory process is triggered. The prolonged interaction between ROS and NO sets up a vicious circle, which results in further endothelial activation and inflammation. [53,57]

Several experimental studies reveal ECs express VDRs and can synthesize calcitriol because they express 1α-hydroxylase. [58] The coexistence of these 2 crucial elements of vitamin D metabolism strengthened the hypothesis of an autocrine/intracrine mechanism of vitamin D action as a modulator of endothelial

functions. [59] Vitamin D exerts protective effects on endothelial activation/dysfunction through both genomic and nongenomic mechanisms. It was observed that the vitamin D interaction with VDR caused the phosphorylation of p38, Akt, and ERK, leading to eNOS activation and increased NO formation (Fig. 5).[60] This effect was dose-dependent, VDR-mediated, and accompanied by a significant increase in the level of phosphorylation of intracellular kinases. [60,61] Vitamin D also works as an antioxidant as it protects the endothelium from H_2O_2 oxidant injury through the activation of the MEK/ERK-Sirt-1 axis. [62] *In vivo* and *in vitro* experiments have recently demonstrated that a vitamin D analog (22-oxacalcitriol) significantly suppressed the elevated expression of p22 (phox) and NADPH oxidase subunit and improved endothelial NO synthase coupling, thus reducing oxidative stress in the endothelium. [63] Moreover, vitamin D protected ECs against H_2O_2 oxidative stress, counteracting superoxide anion generation and apoptosis and blocking the extrinsic caspase cascade by positively controlling the level of phospho-active extracellular signal-regulated kinases. [64] In a recent study, it has also been seen that vitamin D protects human endothelial cells from oxidative stress through modulation between apoptosis and autophagy by reducing apoptosis-related gene expression and enhancing autophagy by activation of pro-autophagic Beclin 1 and phosphorylation of ERK 1/2 and Akt. [65]

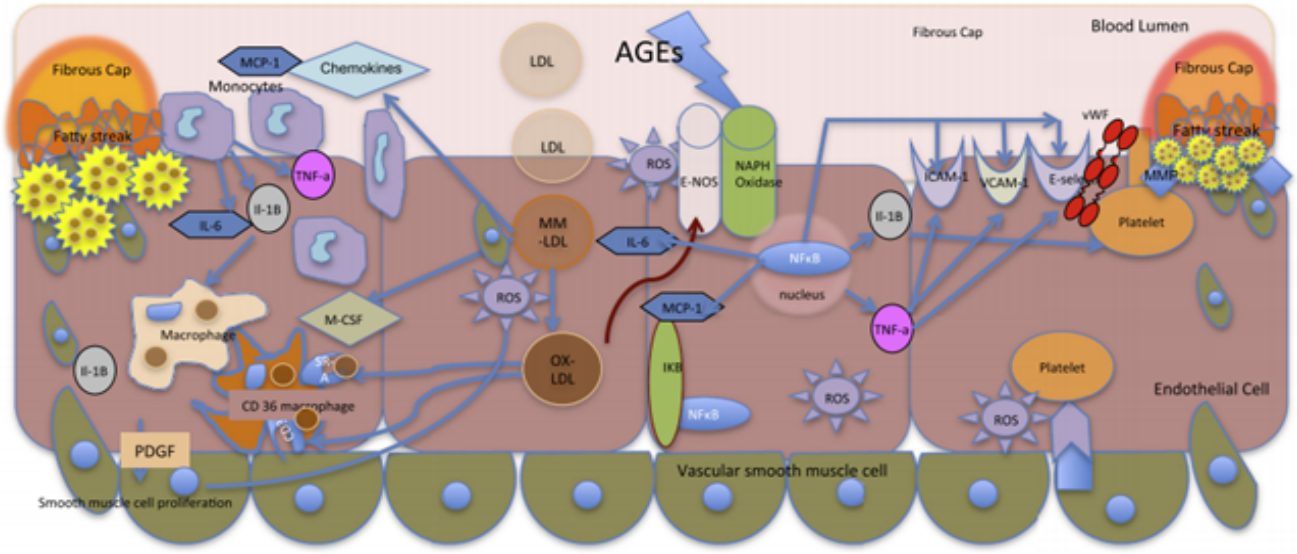

Figure 5: Schematic representation of advanced glycation end-products associated with increased oxidative stress induced endothelial activation and lipid peroxidation, formation of foam cells, smooth muscle migration, formation of fatty streak, thrombus and fibrous cap.

Vitamin D appears also to be implicated in the modulation of the vascular tone via regulation of the release of vasoconstrictor metabolites of arachidonic acid called endothelium-derived contracting factors (EDCFs)(66). Of note, vitamin D acutely modulated vascular tone by reducing calcium influx into the ECs and hence decreasing the production of EDCFs (Fig. 6).[67]. However, a recent study also recognized calcium-independent mechanism through a direct effect of vitamin D down-regulating the expression of cyclooxygenase-1, the major source of EDCFs, in ECs. [68] In addition to their effects on vascular tone, vitamin D effects on prostaglandin metabolism and signaling appear to play important role in the inflammatory component. It is noteworthy that calcitriol significantly repressed the mRNA and protein expression of cyclooxygenase-2 but upregulated the expression of 15-hydroxyprostaglandin dehydrogenase, the enzyme initiating prostaglandin catabolism, thereby reducing the level of prostaglandins and suppressing the production of several proinflammatory cytokines. This could successfully prevent the immune-mediated changes in the ECs. [69]

Vitamin D treatment *in vitro* has been documented to modulate levels of systemic inflammatory cytokines, such as TNF-α and IL-6 as well as inhibit lipopolysaccharide (LPS) induced activation and vasodilatation of vascular endothelium (Fig. 6).[70]. Equils *et al,* [70] also demonstrated an effect of 1,

$25(OH)_2D$ on microbial antigen-induced EC activation. According to their data, lipopolysaccharide stimulation led to the release of proinflammatory cytokines, which induced 1α-OHase activity and consequently calcitriol expression. Calcitriol in turn inhibited interleukin (IL)-6, IL-8, and RANTES (regulated on activation, normal T cell expressed, and secreted) expression through inhibition of nuclear factor-κB (NF-κB) in an autocrine/paracrine fashion to "switch off" the immune activation. [71] Talmor *et a,l* [72] demonstrated inhibitory effects of calcitriol on the expression of ICAM-1, platelet EC adhesion molecule-1, and IL-6 in ECs, effects mediated through NF-κB and p38 MAPK. Moreover, multiple studies have revealed that pretreatment with 1, $25(OH)_2D$ significantly inhibited the TNF-α–induced expression of E-selectin, vascular cell adhesion molecule-1, and IL-8 on human coronary arterial ECs via inhibition of NF-κB. [73,74.] Recent studies showed that the tumor necrosis factor-α induced increase in protein levels of ICAM-1 and VCAM-1 was significantly abolished after incubation of human ECs with 1, $25(OH)_2D$, an effect independent of NF-κB activation. [75,76] The expression of CD40L and CD62P in platelets, the expression of ICAM-1, VCAM-1, the urokinase receptor (uPAR) and membrane type 1 matrix metalloproteinase (MT1-MMP) in endothelial cells and endothelial cell ROS generation were significantly reduced through pre-incubation with 1, $25(OH)_2D$. [76,77] Finally, calcitriol may also act as a vascular protective agent counteracting the deleterious effects of advanced glycation end products on endothelial function. [78] Calcitriol acting via VDR has been found to decrease the expression of genes involved in advanced glycation end products–activated inflammatory pathway such as RAGE, IL-6, and IL-8 through an NF-κB–mediated mechanism. [79] 1, $25(OH)_2D$ has been seen to ameliorate the effects of AGEs seen in diabetes mellitus on the endothelial cells by blunting the AGEs-induced elevation of NF-κB-p65 DNA binding activity, a phenomenon related to an increased expression of IkB alpha as seen in an in vitro study. [78] Confirming the *in vitro* data, several clinical studies showed both an inverse relationship between vitamin D levels and endothelial dysfunction and favorable effects of the vitamin D replacement on endothelial function. [71,80,81]

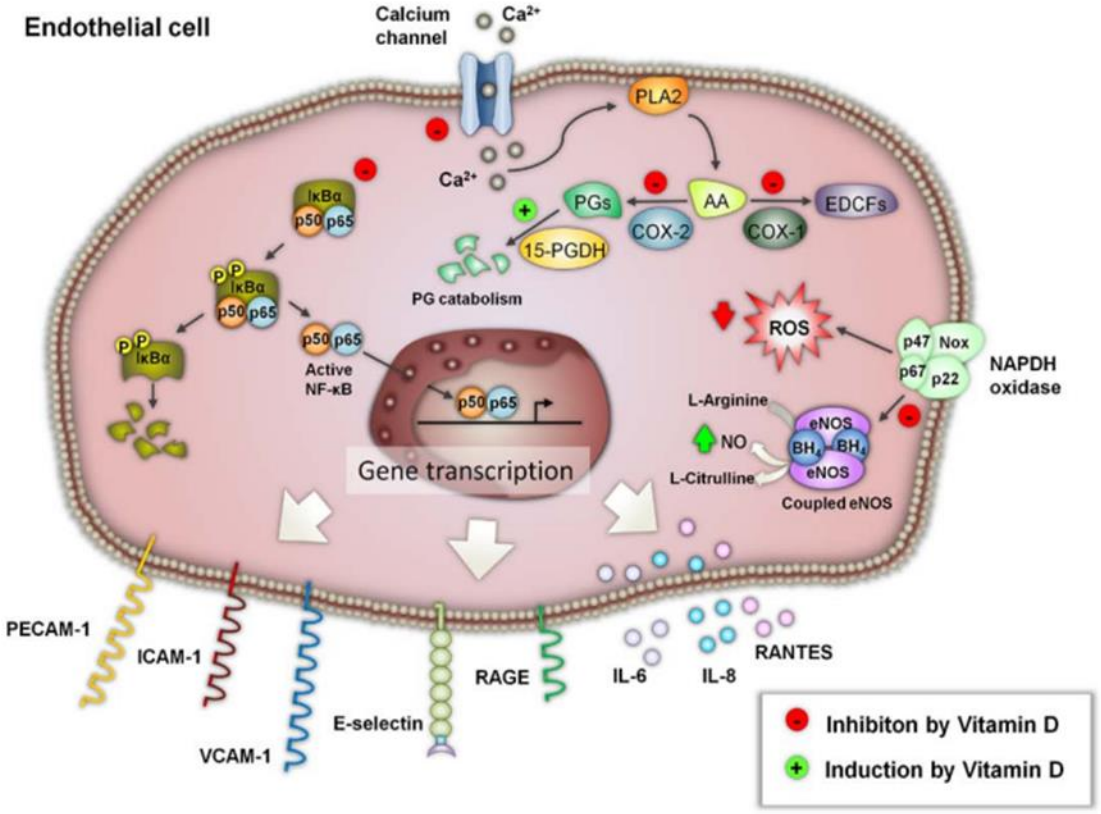

Figure 6: Vitamin D exerts protective effects on endothelial activation/dysfunction.

2. Effects of Vitamin D on Vascular Smooth Muscle Cells

The vascular smooth muscle cells (VSMCs) regulate the active component of vascular tone by varying the diameter of the arterial lumen under the control of circulating hormones, paracrine substances, and neurotransmitters. [82] The presence of VDRs in the VSMCs, which also express an enzymatically active 1α-hydroxylase, highlights the biological importance of 1, 25$(OH)_2$D in the regulation of VSMC homeostasis and function. [83,84] Antiproliferative effects of 1, 25$(OH)_2$D on VSMCs have been demonstrated by several studies. [85–87] 1, 25$(OH)_2$D inhibits the proliferative effects of both epidermal growth factor and endothelin on VSMCs, the latter via decreasing cyclin-dependent kinase 2 activity, which actually regulates the cell cycle machinery. [85,88] Calcitriol also inhibited proliferation by an acute influx of Ca^{2+} into the VSMCs (Fig. 7).[89] The effects of 1, 25$(OH)_2$D on VSMC migration appear to be divergent. At high doses, calcitriol can induce VSMC migration, an effect that involves both nongenomic (through activation of the PI3K pathway) and genomic (through reducing the expression of β1-integrin receptors on the VSMC surface) actions. [90,91] However, in physiological doses, 25(OH)D and calcitriol inhibited VSMC migration and proliferation by reducing the activity of vitamin D binding protein, an effect mediated through the attenuation of extracellular signal-regulated kinase 1/2 phosphorylation. [92] Other aspects of VSMC biology besides proliferation and migration are also affected by vitamin D. Vitamin D appears to exert morphological effects, including increased elastogenesis and stabilization of the musculoelastic multilayer of VSMCs, via regulation of the production of proteins that are related to the vascular wall, including myosin, collagen type 1, matrix metalloproteinase-9, and elastin. [93] Furthermore, 1, 25$(OH)_2$D has been shown to enhance prostacyclin production, a prostanoid that inhibits the aggravation of atherosclerosis, in VSMCs via the cyclooxygenase pathway. [94] 1, 25$(OH)_2$D increased the superoxide dismutase activity in VSMCs via stimulation of the expression of IκB-α, thus reducing vascular cell–mediated oxidation of low-density lipoprotein. [95] Moreover, it improved the recovery of stressed VSMCs and their viability via regulating heat-shock protein 70 and possibly via increasing telomerase activity. It has recently been shown that vitamin D_3 supplementation improved telomerase maintenance and prevented peripheral blood mononuclear cells' senescence. [96]

In accordance with the aforementioned *in vitro* data, a 16-week clinical trial showed that a 2000 IU daily vitamin D_3 supplement counterbalanced the progression of arterial stiffness, as estimated by the carotid-femoral pulsed-wave velocity. [97] Vitamin D also regulates the expression of profibrotic and antifibrotic factors (98). Plasminogen activator inhibitor-1, which is produced by a broad range of cells such as vascular ECs and VSMCs, [99] is considered an inflammatory response gene that is associated with increased risk for thrombosis and atherosclerosis. [100,101] Activated vitamin D analogs (calcitriol and paricalcitol) have been reported to suppress plasminogen activator inhibitor-1 by blocking NF-κB activation. [87,102] Additionally, vitamin D has been found to regulate the expression of antifibrotic factors. It was demonstrated that exposing mesenchymal multipotent cells to 1, 25$(OH)_2$D increased through VDR-mediated genomic effects the expression of bone morphogenetic protein-2 and BMP7 (transforming growth factor-β1 antagonists), matrix metalloproteinase-8 (a collagen breakdown inducer), and follistatin (an inhibitor of the profibrotic factor myostatin) and decreased the expression of collagen I and III, which define a fibrotic process. [98,103]

Data on the role of vitamin D in vascular calcification are conflicting (Fig. 7).[104,105] In vitro experiments support that VSMCs undergo calcification when treated with 1, 25$(OH)_2$D through three pathways: stimulation of calcium influx. [106,107] interference with the basic cellular housekeeping machinery, [105] and activation of protein kinase–mediated pathways (Fig. 7).[90,108] Once activated, these signal transducers, in concert with cytokines and growth factors, including angiotensin II, induce cell dedifferentiation, promote cell migration, and increase oxidative stress, thereby leading to the structural disintegration and stiffening of the arterial wall. [108] On the other hand, the protective effects of calcitriol and other VDR agonist on vascular calcification have also been recognized *in vitro.* [99] Among the proposed mechanisms is upregulation of the expression of matrix Gla protein and osteopontin by VSMCs, which are both potent inhibitors of vascular calcification. [109,110] Moreover, a recent study showed that VDR agonists (both calcitriol and maxacalcitol) suppressed the TNF-α–induced expression of the runx2, osteocalcin, and MMP-2 genes in VSMCs.[111] It is important to note that the

protective or harmful effect of active vitamin D on vascular calcification remains a contentious issue, presumably because of the differences in the experimental model or the dose, or type of active vitamin D used. [112–114]

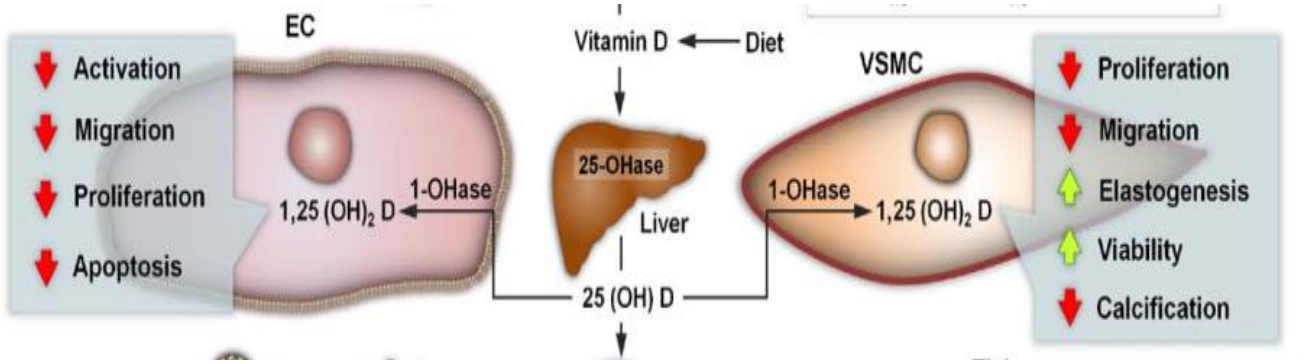

Figure 7: Schematic representation illustrating the actions of vitamin D in vasculature.

2. ***Effects of vitamin D on immune cells and atherosclerosis***

Several subsets of T cells, such as naive, T helper (Th)1, Th2, T regulatory cells, Th17, and B cells, along with leucocytes and transformed monocytes, are present within atherosclerotic lesions. [115] Interestingly, the Th1 subtype primarily drives the inflammatory response in the atherogenesis process by producing cytokines such as interferon-γ, TNF-α, IL-6, and IL-12, which are known to be proatherogenic. [116,117] Although the exact role of IL-17 and its producing Th17 cells has not been fully addressed, recent studies have demonstrated the existence of IL-17A$^+$ cells within atherosclerotic lesions, suggesting a potential role in atherosclerosis. [118] Actually, the IL-17A–dependent response was found to occur in parallel with the Th1-dominant and unfavorable immune response during the atherogenic process. [99] On the other hand, Th2 by secreting antiatherogenic cytokines such as IL-5, IL-10, and IL-13 neutralizes the Th1 effect. [119] It has been demonstrated that 1, 25$(OH)_2$D shifts the immune response away from a Th1 and toward a Th2 profile, thus promoting an antiatherogenic immune profile. [120] Furthermore, treatment of T cells *in vitro* with 1, 25$(OH)_2$D suppressed the development of Th17 and inhibited IL-17 production via a posttranscriptional mechanism (Fig. 8).[121] It has been shown that vitamin D is carried by low-density lipoprotein particles and is internalized by various cells, including monocytes, through the low-density lipoprotein receptor either in its active form or as 25(OH)D. Once monocytes migrate transendothelially and are transformed into foam cells, 25(OH)D is accumulated in the subendothelial space or in the atherosclerotic plaque and may be converted to its active form by 1α-hydroxylase, which is expressed by monocyte derived cells. [122,123] In turn, 1, 25$(OH)_2$D may alter macrophage gene expression, influencing the expression of a variety of factors that are implicated in the atherosclerosis process (eg, type I collagen, vascular endothelial growth factor, matrix metalloproteinases, and elastin) by ECs and VSMCs. [99] The physiological role of vitamin D–VDR in the maintenance of antithrombotic homeostasis has been confirmed with VDR knockout mice. [124] Interestingly, 1, 25$(OH)_2$D supplementation suppressed cholesteryl ester formation and enhanced cholesterol efflux in macrophages compared with vitamin D–D-depleted cells, suggesting facilitation of cholesterol egress in the presence of 1, 25$(OH)_2$D. [125] Moreover, 1, 25$(OH)_2$D acting as a natural endoplasmic reticulum stress reliever was found to induce an M1 antiatherogenic macrophage/monocyte phenotype over M2 (with increased cholesterol uptake and deposition) and to decrease mRNA expression of the monocyte adhesion molecules PSGL-1, β(1)-integrin, and β(2)-integrin, resulting in an increase of monocyte adhesion to activated endothelium. [126] Moreover, 1, 25$(OH)_2$D dose-dependently inhibited the production of IL-6 and TNF-α by monocytes, an effect exerted at a posttranscriptional level, and possibly contributed to the aforementioned suppression of Th1 proatherogenic immune response. [127] In addition to their immunoregulatory effects, monocytes are implicated in the development of atherothrombotic lesions by regulating coagulant and anticoagulant factors. It has been demonstrated that vitamin D, via VDR, up-regulates the expression of the anticoagulant

glycoprotein thrombomodulin and down-regulates the expression of a critical coagulation factor, tissue factor, in human peripheral monocytes. [128] Moreover, NF-κB appears to play a crucial role in mediating many of the beneficial effects of vitamin D. However, other signaling pathways, either genomic or nongenomic, appear to be implicated (Fig. 8).[99] In summary, the beneficial action of vitamin D on endothelial dysfunction, VSMC proliferation and migration, and calcification, as well as on the inflammatory/immune process of atherosclerosis, is well documented in the literature, even though the signal mechanisms by which these responses are elicited need to be fully characterized.

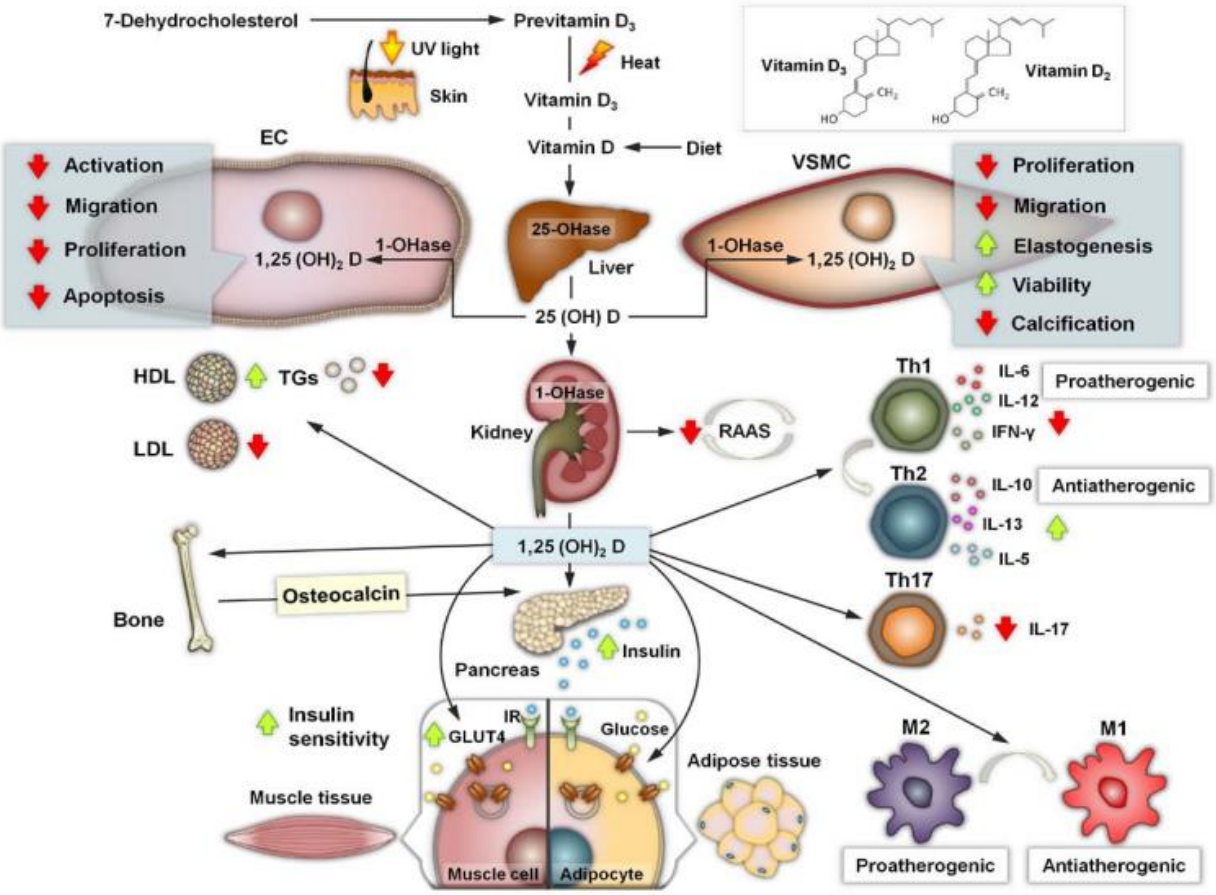

Figure 8: The metabolism and actions of vitamin D in cells and tissues that are implicated directly and indirectly in the atherogenic process.

2. Role of Vitamin D in the Renin Angiotensin System

In an experimental studies, inhibition of 1, 25$(OH)_2$D synthesis led to an increase in renin expression, accompanied by increased plasma angiotensin II levels, hypertension, and cardiac hypertrophy. [129] whereas 1, 25$(OH)_2$D injection led to renin suppression in the juxtaglomerular apparatus, independently of parathyroid hormone and calcium metabolism. [130–132] On a molecular level, calcitriol binds to the VDR and subsequently blocks formation of the CRE-CREB-CBP complexes in the promoter region of the renin gene, reducing its level of expression (Fig. 9).[129,131,133] These data suggest that vitamin D analogs and supplements may potentially be agents for controlling renin production and blood pressure. Corroborating this hypothesis, Fryer et al (134) evaluated the effects of paricalcitol and calcitriol on renin expression in C57/BL6 mice and showed that paricalcitol produces significant dose-dependent reductions in renin/GAPDH expression and calcitriol produced renin suppression. Moreover, Zhou *et al* [135] demonstrated regulation of the renin-angiotensin system through supplementation of 1, 25$(OH)_2$D in 1-α hydroxylase knockout mice free of enzyme. Taken together, the

associations found in clinical studies and the supporting mechanistic studies make it plausible that vitamin D deficiency could indeed contribute to an inappropriately activated RAAS, as a mechanism for progression of cardiovascular disease. [131] Conversely, vitamin D metabolites may exert several renoprotective effects such as suppression of the renin–angiotensin–aldosterone system, antiproteinuric effects, as well as anti-inflammatory and immunomodulatory properties with up-regulation of regulatory T cells (Tregs) that protect against autoimmunity. [136–138] Interactions between vitamin D and other RAAS components have been studied as well. There is cross talk between mineralocorticoid receptor used by aldosterone and vitamin D agonists could potentially exist, but this has not been studied so far. [132] Vitamin D analogues may also have cardioprotective effects in association with suppression of renin in the kidney and heart. [139,140]

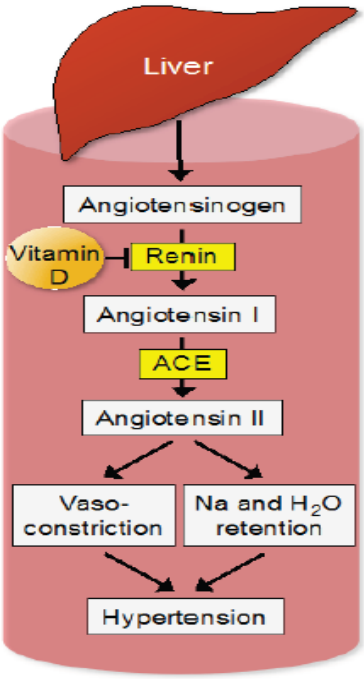

Figure 9: The effects of vitamin D on the renin-angiotensin system. *1, 25-dihydroxyvitamin D suppresses renin gene expression, thereby inhibiting the renin-angiotensin system.*

3. *Effects of Vitamin D on the Heart*

Vitamin D Receptor (VDR) and 1α-hydroxylase knockout mice with normalized calcium levels display a cardiac phenotype characterized by myocardial hypertrophy, increased contractility, and impaired systolic function. [129,135,141–143] These abnormalities can be reversed by blocking the RAS. [37] This suggests that increased RAS activation is mainly responsible for myocardial damage in these knockout models. In line with these ideas, Li *et al* [129] and Yuan *et al* [133] also demonstrated that 1, 25$(OH)_2$D is a negative regulator of renin and, in concert with much older data suggesting that vitamin D exerts direct effects on (or maybe via) the cardiomyocytes. [144] A clinically significant association between vitamin D deficiency and heart disease is supported by several case reports of children with rickets who suffered from cardiomyopathies but could be successfully cured by vitamin D and calcium supplementation. [145,146] Detailed studies in cultured cardiomyocytes showed profound antihypertrophic and antiproliferative actions of vitamin D metabolites (Fig. 10).[147–149] The VDR itself was shown to be regulated by the occurrence of cardiac hypertrophy per se, suggesting that not only does circulating vitamin D dictate vitamin D signaling, but also VDR expression may be of importance. [150] Furthermore, contractility and electrophysiology of the heart may be significantly modulated by vitamin D effects on myocardial calcium handling. [145,151–153] 1, 25$(OH)_2$D also induces an accelerated relaxation of cardiomyocytes, which may improve the diastolic function of the heart. [151] Apart from this, vitamin D metabolites regulate myocardial extracellular matrix turnover by modulating the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases. [154,155] Other proposed vitamin D effects on the myocardium, such as regulation of energy metabolism or myosin expression, still require further in-depth studies (Fig. 10).[145] Detailed analyses of specific CV events among diabetic hemodialysis patients showed that low 25(OH)D levels were particularly associated with sudden cardiac death. [156] Hence, a poor vitamin D status indicates an increased CV risk, but it remains to be determined whether vitamin D deficiency is the cause or the consequence. In this context, the possibility of reverse causation should be considered, that is, the fact that heart disease-associated limitations in sunlight exposure may underlie the association of vitamin D deficiency and CV risk. [157–160]

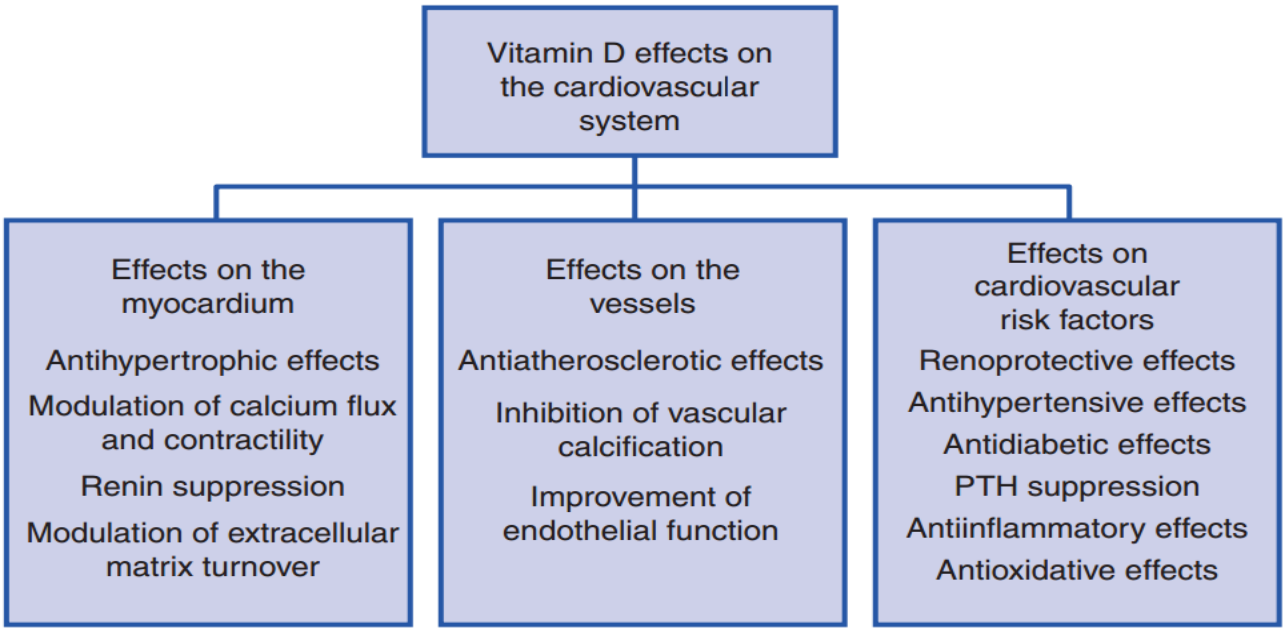

Figure 10: Proposed vitamin D effects on the heart

2. Vitamin D and the Autonomic Nervous System

Interestingly, activated 1, 25$(OH)_2$D has been shown to coordinate biosynthesis of neurotransmitters in brain areas that regulate cardiovascular activity. [161,162] Specifically, the mid-brain and brainstem, in which neurons for the ANS are located in have been shown to have an extremely high concentration of VDR, thus leading to the hypothesis that vitamin D plays a specific, non-calcium-related role in regulating the ANS (Fig. 11).[161–164] Several observational studies and meta-analyses of these studies have demonstrated striking associations between vitamin D deficiency and patient-level outcomes, including CVD and CVD-related death, namely sudden arrhythmic death, in both healthy populations and in the high-risk CKD population. [156,165–168] Conversely, in healthy humans, increasing vitamin D levels with 4 weeks of high-dose vitamin D_3 supplementation (10,000 IU cholecalciferol) was associated with a significant improvement in cardiac ANS balance, specifically enhancing cardioprotective vagal activity, in response to an external stressor. [169,170] Krause, [171] demonstrated that exposure to short-term artificial sunlight heliotherapy not only increased serum 25(OH)D levels and control of mineral metabolism, but significantly increased measurements of cardioprotective vagal activity, which were severely depressed at baseline. Taken together, these data suggest that vitamin D deficiency directly influences CVD and CVD-related mortality risk by mediating activity of the ANS outside the realm of generic mineral metabolism (Fig. 11). Plus, vitamin D supplementation appears to possess genomic and nongenomic mechanisms that may influence activity of the ANS, presenting an attractive therapeutic option.

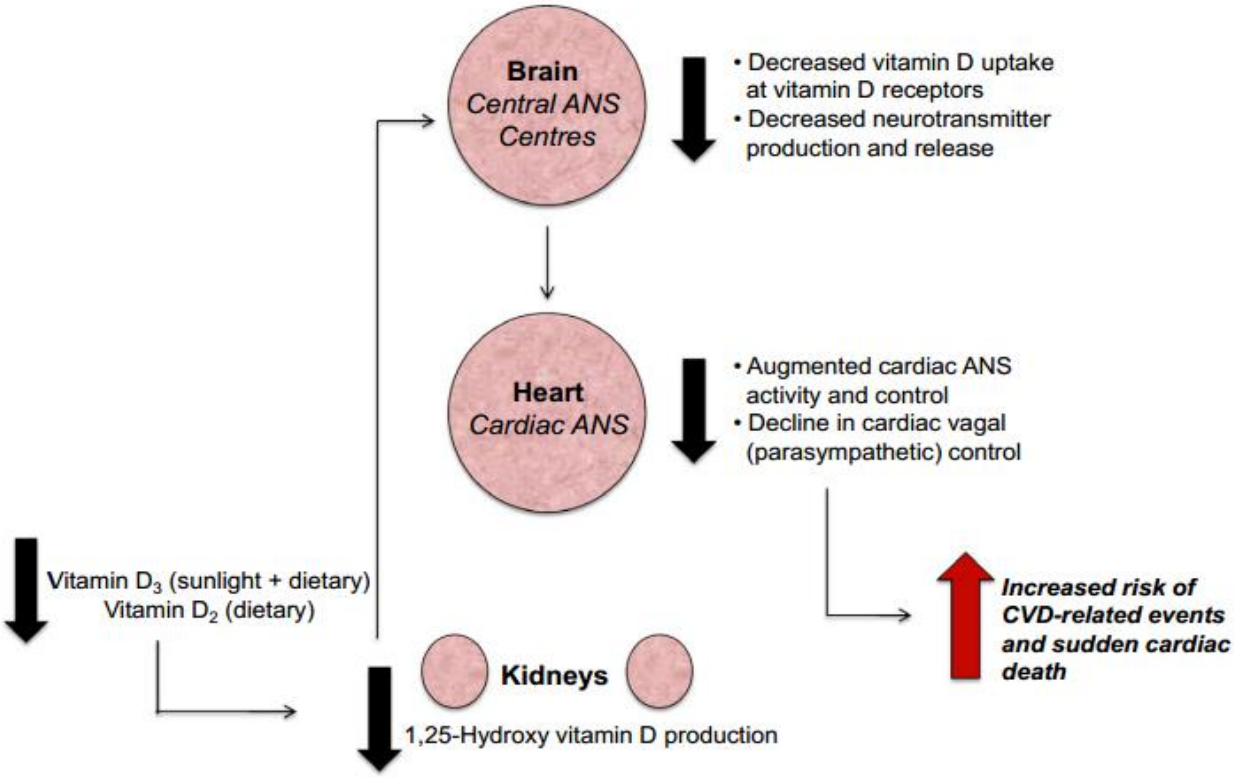

Figure 11: Hypothesized implication of vitamin D deficiency on cardiovascular risk via interaction with the autonomic nervous system

Conclusion and remarks

Aside from role in calcium and phosphate homeostasis, vitamin D is important in many physiological and pathological processes relevant to cardiovascular system. 1, 25$(OH)_2$D influences the migration, proliferation, gene expression of VSMCs, elastogenesis, cytokines, profibrotic, proinflammatory pathways and immunomodulation through the VDR dependent mechanism (Fig. 12). Plus, it may influence blood pressure by functioning as an endogenous inhibitor of the RAAS. Interestingly, calcitriol can permeate the blood-brain barrier and bind to vitamin D receptors located within the cardiovascular centres. Thus, it is essential for the development and maintenance of a healthy cardiovascular function. However, VDD is associated with increased risk of cardiovascular disease, and this may be due to the relationship between low vitamin D levels and obesity, diabetes mellitus, dyslipidaemia, endothelial dysfunction, and hypertension. Therefore, vitamin D may well be relevant for therapeutic purposes.

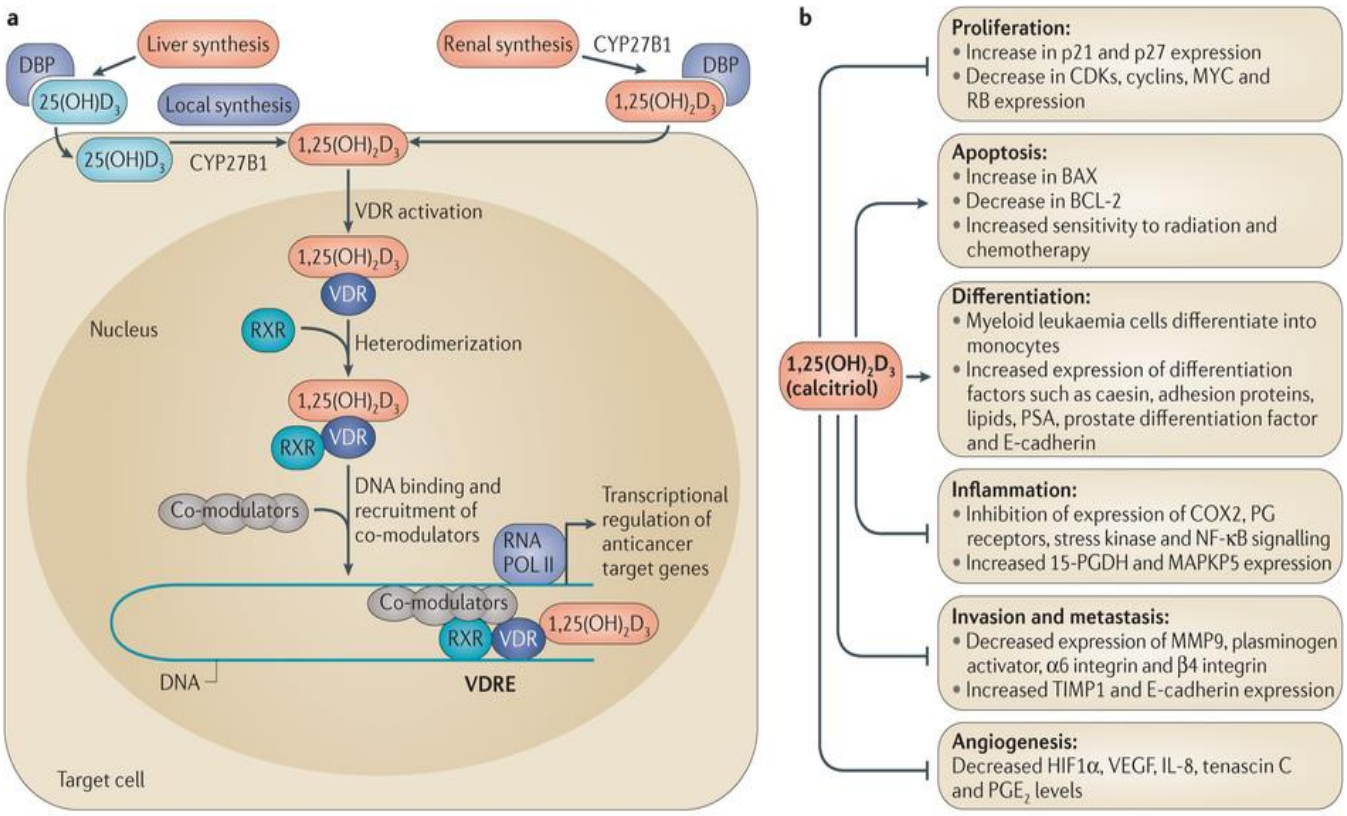

Figure 12: A schematic diagram describing the mechanism and application of the vasculoprotective effect of Vitamin D.

Abbreviations

1, 25(OH)$_2$D – 1,25-Dihydroxyvitamin D (calcitriol)
25(OH)D – 25-Hydroxy Vitamin D (calcidiol)
AGE – Advanced Glycation End-products
CV risk – Cardiovascular Risk
CVD – cardiovascular disease
CKD – chronic kidney disease
ECs – Endothelial Cells
FGF-23 – Fibroblast Growth Factor-23
ICAM-1 – Intercellular Adhesion Molecule 1
NF-κB – Nuclear Factor-κB
NADPH oxidase – Nicotinamide Adenine Dinucleotide Phosphate Oxidase
PTH – Parathyroid Hormone
RAAS – Renin-Angiotensin-Aldosterone System
TNF-α – Tumor Necrosis Factor-α
UVB – Ultraviolet B
VCAM-1 – Vascular Cell Adhesion Molecule 1
VDD – Vitamin D deficiency
VDRm – Membrane Vitamin D Receptor
VDRn – Nuclear Vitamin D Receptor
VSMCs – Vascular Smooth Muscle Cells

Declarations

Ethics Approval and Consent to Participate: Not applicable.

Consent For Publication: Not applicable.

Availability of Data and Materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The author declares that there is no conflict of interest regarding the publication of this paper.

Funding: Nil support in financial or any other manner

Authors' Contributions: LM and BE had participated in the design of the study, data analyses, and manuscript preparation; and the authors could have read and approved the final manuscript.

Acknowledgements: The Author is grateful to the College of Health Sciences Research and

Community Office of Arsi University, as well as researchers whose documents were used in the preparation of the review.

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