



VITAMIN D DEFICIENCY -ROLE IN CAD AND CARDIOVASCULAR DISEASE

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ABSTRACT

Vitamin deficiency may become more significant factor leading to cardiovascular disease. This review is an overview of the current body of literature, and presents evidence of the mechanisms through which vitamin D deficiency affects the cardiovascular system in general and the heart in particular. Available data indicate that the majority of congestive heart failure patients have 25-hydroxyvitamin D deficiency. Furthermore, the low serum 25-hydroxyvitamin D level has a higher impact on hypertension, coronary artery disease and on the occurrence of relevant cardiac events. A serum 25-hydroxyvitamin D level below 75 nmol/l (30 ng/l) is generally regarded as vitamin D insufficiency in both adults and children, while a level below 50 nmol/l (20 ng/l) is considered deficiency. Levels below 50 nmol/l (20 ng/l) are linked independently to cardiovascular morbidity and mortality. Low vitamin D levels favor atherosclerosis enabling vascular inflammation, endothelial dysfunction, formation of foam cells, and proliferation of smooth muscle cells. The antihypertensive properties of vitamin D include suppression of the renin-angiotensin-aldosterone system, renoprotective effects, direct effects on endothelial cells and calcium metabolism, inhibition of growth of vascular smooth muscle cells, prevention of secondary hyperparathyroidism, and beneficial effects on cardiovascular risk factors. Vitamin D is also involved in glycemic control, lipid metabolism, insulin secretion, and sensitivity, explaining the association between vitamin D deficiency and metabolic syndrome. Vitamin D deficit was associated in some studies with the number of affected coronary arteries, post-infarction complications, inflammatory cytokines and cardiac remodeling in patients with myocardial infarction, direct electromechanical effects and inflammation in atrial fibrillation, and neuroprotective effects in stroke. In peripheral arterial disease, vitamin D status was related to the decline of the functional performance, severity, atherosclerosis and inflammatory markers, arterial stiffness, vascular calcifications, and arterial aging. Vitamin D supplementation should further consider additional factors, such as phosphates, parathormone, renin, and fibroblast growth factor 23 levels.

KEYWORDS: 25-hydroxyvitamin D, atherosclerosis, insulin secretion, parathormone, neuroprotective effects, renoprotective.

INTRODUCTION

Though vitamin D has been traditionally associated with bone health, adequate levels are also important for optimal cardiovascular (CV) function. The quest to identify new predictors of CV disease has focused the attention on vitamin D, given its association with various established risk factors for CAD, including hypertension, diabetes, obesity, metabolic syndrome, congestive heart failure, and prevalent coronary artery disease.^[1,2] Vitamin D deficiency has also been linked to increased risk of adverse CV events including higher risk of myocardial infarction, CV death, and overall mortality.^[3-5] However, other studies have reported absence of a significant correlation of vitamin D with CVD and the overall epidemiologic evidence is inconclusive, necessitating further studies to corroborate a potential link between the two.^[6-9] Endothelial dysfunction is an important antecedent event in the

development of CHD and atherosclerosis.^[10,11] Vitamin D is known to affect vascular endothelium directly or indirectly through up-regulation of the renin-angiotensin system or via induction of smooth muscle proliferation and a pro-inflammatory state.^[1,4] Hence, it is important to study the relationship between vitamin D deficiency and endothelial dysfunction assessed by brachial artery flow mediated vasodilatation, given their role in the development of CVD. Vitamin D exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3, "the sunshine vitamin," is synthesized in the human epidermis via ultraviolet irradiation, or it may be consumed in the form of oily fish or supplements. Vitamin D2 is found in plants, as a product of irradiation of ergosterol.^[1] The vitamin is converted in the liver and kidney to calcidiol and calcitriol, respectively, and acts on specific target tissues via vitamin D receptors. Calcitriol, the active form of vitamin D, binds to vitamin

D receptors in the intestines, bones, and kidneys to increase calcium absorption from the intestines, promote calcium deposition in bones, and decrease parathyroid hormone concentrations (PTH). Its extrasosseous effects are less known. Vitamin D receptors were found in other tissues, as well, including the brain, cardiomyocytes, vascular smooth muscle cells, endothelial cells, pancreatic beta-cells, skeletal muscle, breast, prostate, colon, macrophages, and skin, exerting several pleiotropic effects, and their expression decreases with age. The vitamin D receptor is closely related to the thyroid, retinoid, and peroxisome proliferator-activator receptors.^[2] Recent studies have found active 1 alpha hydroxylase in several extra renal tissues, such as the heart and vascular smooth muscle cells.^[3,5] Activated vitamin D may influence cellular growth, proliferation and apoptosis, oxidative stress, membrane transport, matrix homeostasis, cell adhesion, and immune system functions and may regulate a large number of genes and healthy aging. Despite abundant sunshine, vitamin D deficiency is frequent among Indians.^[15] This is due to lack of vitamin D supplementation in the diet, malnutrition and high degree of coverage of the body with clothing, thus precluding adequate synthesis of the vitamin. Moreover, a darker skin pigmentation, as noted with Asians, requires greater degree of exposure to the sun to be able to synthesize equivalent amounts of vitamin D compared to people with lighter skin color.^[6] Despite the rising prevalence of CAD in Asian

Indians, studies of vitamin D levels in patients with angiographically documented CAD in such patient populations are limited and have reported conflicting results.^[8] We prospectively studied the prevalence of vitamin D deficiency in 100 consecutive patients undergoing coronary angiography at our institution for suspected CAD, and also tested the hypothesis of whether vascular endothelial function, assessed by endothelium-dependent dilation, is related to serum 25 (OH) D statuses. Recent research has linked inadequate vitamin D status to nonskeletal major chronic diseases, especially cardiovascular diseases.^[8] Existing data from laboratory studies, epidemiologic and experimental research and prevention trials, suggest that vitamin D reduces the risk of cardiovascular disease, and a large, randomized, primary prevention trial, with adequate dosing, combining cholecalciferol and omega-3 fatty acids, is ongoing: the VITAL study. Poor vitamin D status was associated with cardiovascular and overall mortality, despite unconvincing results of vitamin D supplementation on mortality.^[3] Food-based strategies for enhancement of vitamin D status in the population could lower cardiovascular risk if a causal link between low vitamin status and cardiovascular pathology would be demonstrated.^[4] The **aim** of the present paper was to review the most important mechanisms explaining the possible association of vitamin D deficiency and cardiovascular diseases, focusing on recent experimental and clinical data.

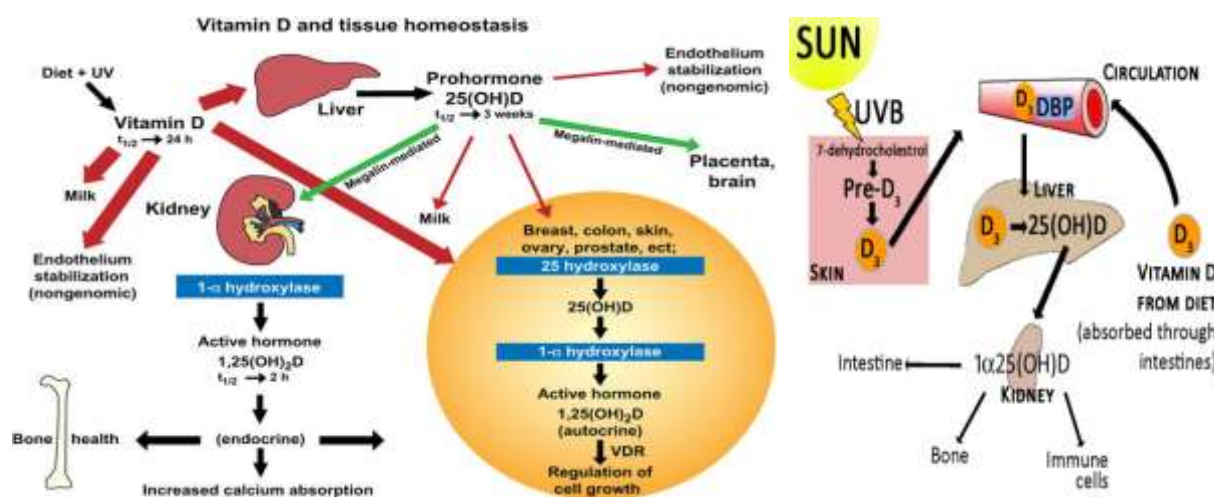


Fig.-1: Synthesis & target organs of vit.d.

Deficiency

Optimal serum concentration of 25-hydroxyvitamin D considers only bone health and was defined as the concentration that maximally suppresses serum parathyroid hormone.^[14,5] Most experts define vitamin D deficiency as a calcidiol level of <20 ng/mL and insufficiency as 21–29 ng/mL.^[1,6] Vitamin D is sufficient if >30 ng/mL, and vitamin D intoxication is considered if >150 ng/mL.^[6] There are variations among professional bodies regarding the cut-off values for insufficient or deficient vitamin D level.^[7] According to a report of the Institute of Medicine (IOM), vitamin D at doses of

600 IU/day is beneficial for the bones, but it is not certain if higher doses could reduce the risk of chronic diseases, including cancer and cardiovascular pathology.^[7] A threshold effect between vitamin D status and cardiovascular risk was suggested.^[1] Zittermann et al. found a vitamin D level of 30–35 ng/L as the best choice for risk reduction in cardiovascular mortality.^[1,8]

Renin-Angiotensin-Aldosterone system and Vit.D Deficiency

The renin-angiotensin-aldosterone system (RAA) maintains vascular resistance, due to angiotensin II

synthesis, and extracellular fluid volume homeostasis, considering the release of aldosterone.^[9] Studies by different groups, in both animals and humans, demonstrated that vitamin D *decreases RAA activity*^[2],

suppressing *renin gene expression*¹. Vitamin D regulates the genes involved in renin production, through a *cis*-DNA element in the renin gene promoter^[6], downregulating the RAA system.

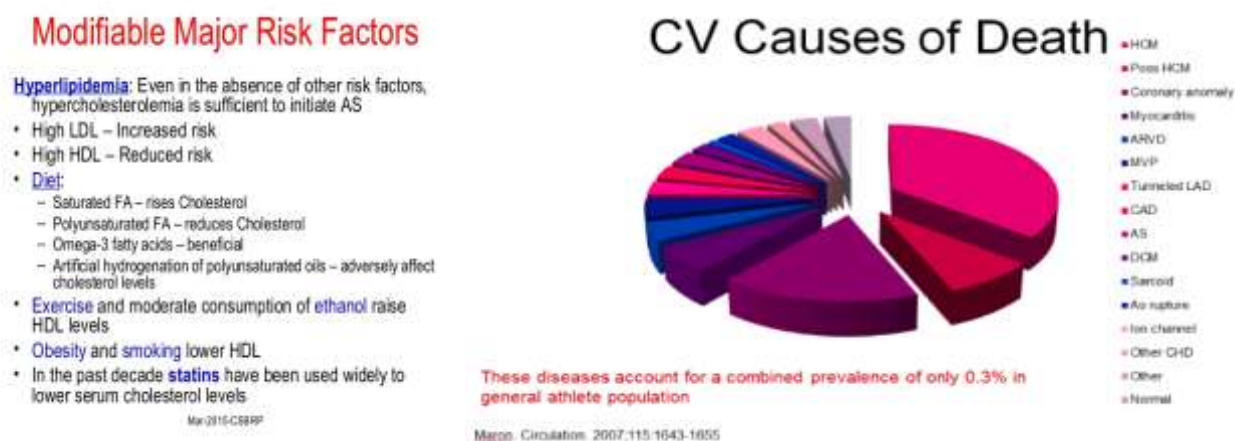


Fig:-2,3.

Vit.D & atherosclerosis

Vitamin D suppresses inflammation via several pathways, such as inhibition of prostaglandin and cyclooxygenase pathways, upregulation of anti-inflammatory cytokines, decrease of cytokine induced expression of adhesion molecules, reduction of matrix metalloproteinase^[9], and downregulation of the RAA.^[5] Vitamin D deficiency stimulates *systemic and vascular inflammation*, enabling atherogenesis.^[1] On the other hand, as already mentioned, hypertension is also associated with lack of vitamin D, due to activation of the RAA system, enabling *endothelial dysfunction*, the first step in plaque formation. The proinflammatory nuclear factor κ B mediates partly the association between endothelial dysfunction and low vitamin D status.^[11] Vascular smooth muscle cells and endothelial cells express receptors for vitamin D, enabling conversion of calcidiol to calcitriol^[2], and vitamin D is involved in regulation of growth and proliferation of smooth muscle cells and cardiomyocytes. Vitamin D inhibits proliferation of vascular smooth muscle cells by acute influx of calcium into the cell and increases calcification of smooth muscle cells.^[3,4] The cardiovascular protective effects of vitamin D include also the anti-inflammatory effects, inhibition of vascular smooth muscle cells proliferation, suppression of proatherogenic T lymphocytes, preservation of endothelial function and protection against advanced glycation products.^[2] Vitamin D deficiency was associated with *vascular stiffness*, which is a known predictor of cardiovascular morbidity and mortality^[11] and a marker of subclinical atherosclerosis.

Deficiency and hypertension

Ultraviolet light exposure enables vitamin D synthesis and has blood pressure lowering effects.^[5] Hypertensive patients exposed to a tanning bed significantly raised their concentration of 25-hydroxyvitamin D after 3

months and became normotensive. Calcitriol exerts a protective effect on human renovascular function, restoring the impaired *endothelium-dependent relaxation* in renal arteries, accompanied by the normalization of oxidative-stress related proteins.^[2] The augmented production of *reactive oxygen species* is induced by angiotensin II in human renal arteries and endothelial cells and impairs vascular function enabling the development of hypertension.^[2] Vitamin D metabolites reduced endothelium-dependent v The relation of vitamin D deficiency and *preeclampsia* is controversial. Vitamin D deficiency in pregnancy has been associated with an increased risk of preeclampsia.^[6] suggesting that vitamin D supplementation in early pregnancy could prevent preeclampsia^[6,4] and decreased calcidiol was found at diagnosis of early onset severe preeclampsia.^[6] vascular smooth muscle contractions and vascular tone in hypertensive rats by affecting calcium influx across endothelial cells. Serum levels of vitamin D should be checked during the evaluation of those patients, considering that orthostatic hypotension is associated with falls, fractures, cardiovascular events, and significant mortality in the elderly.^[4,6] Vitamin D receptors are found in vascular smooth muscle, endothelial and cardiac cells, enabling involvement in the cardiac and vascular response during orthostasis^[7], and vitamin D deficiency downregulates the RAA system and was also associated with endothelial dysfunction.^[4,6] On the other hand, both orthostatic hypotension and vitamin D deficiency are more prevalent in the elderly. The *parathormone (PTH)* is a crucial regulator of calcium and phosphate balance. Higher PTH concentrations were associated with several cardiovascular risk factors, including hypertension and arterial stiffness. The *parathormone (PTH)* is a crucial regulator of calcium and phosphate balance. Higher PTH concentrations were associated with several cardiovascular risk factors, including hypertension and

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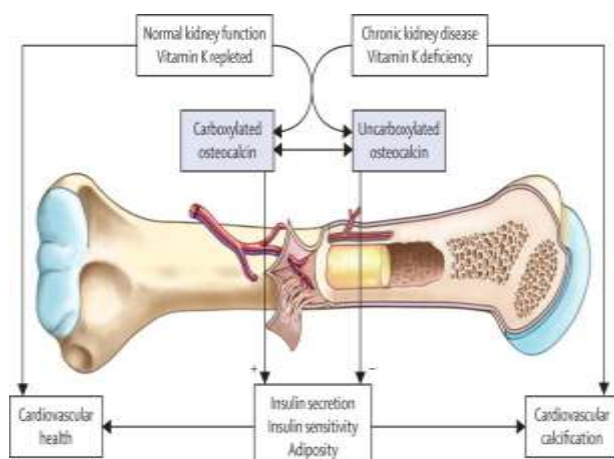


Fig.-4: Bone-a new endocrine organ.

Vit.D & Metabolic Syndrome

Cardiovascular risk factors such as hyperlipidemia, abdominal obesity, hypertension, and diabetes often cluster in the same individual.^[2] A small cross-sectional study, including middle-aged men, found that vitamin D metabolites were related to lipid and glucose metabolism and serum urate.^[7] Serum calcitriol was inversely correlated to the blood pressure and triglycerides and calcidiol to fasting insulin and lipoprotein lipase activity both in adiposal tissue and in skeletal muscle.^[7] Obese individuals are at higher risk of hypertension, hypercholesterolemia, diabetes, cardiovascular mortality, and vitamin D deficiency. Besides vitamin D sequestration in subcutaneous fat and making stores less available to become biologically activated, obese persons may have a sedentary lifestyle and be less active outdoors, and skin production of vitamin D may be impaired due to clothing habits. An inverse association between circulating 25-hydroxyvitamin D and incident type 2 diabetes was demonstrated by a systematic review and meta-analysis, including only prospective studies.^[8] The plausible mechanisms explaining the mentioned associations involve vitamin D receptors in pancreatic beta-cells influencing insulin secretion and vitamin D effects on insulin sensitivity, or through the effects of vitamin D on calcium metabolism, but there is no demonstrable evidence of causality yet. Sun exposure implies greater outdoor physical activity, improving insulin sensitivity.

Vit.D, Coronary Heart Disease & Heart Failure

A strong association was found between vitamin D deficiency and *slow coronary flow, endothelial dysfunction and subclinical atherosclerosis*, in patients with normal or near-normal coronary arteries at coronary angiography^[8]. Decreased levels of vitamin D binding protein were found in the plasma of survivors of a

myocardial infarction at young age, statistically correlated with the number of affected coronary arteries.^[8] Low vitamin D levels have been linked to inflammation, *higher coronary artery calcium scores, increased mean platelet volume, and increased vascular stiffness*.^[1] Abnormally high mean platelet volume has been associated with cardiovascular diseases, considering the higher risk to block arteries, due to the ability to aggregate more rapidly with collagen, the higher thromboxane A2 level. Vitamin D deficiency was associated with coronary heart disease and myocardial infarction^[8] and was found in a high proportion of patients with myocardial i. The majority of congestive heart failure patients have insufficient vitamin D, due to reduced sunlight exposure, difficult mobilization and outdoor activity, nutritional factors, and malabsorption of vitamin D due to intestinal edema in severe right heart failure and comorbidities, such as obesity and renal and hepatic failure.^[10] Lack of vitamin D causes hypocalcaemia and *secondary hyperparathyroidism*. Indeed, serum parathormone (PTH) was elevated in patients with congestive heart failure due to ischemic or dilated cardiomyopathy and hypovitaminosis D was present.^[6] Osteomalacia and osteoporosis and fracture rates should be, probably, evaluated in individuals with congestive heart failure.^[1] Infarction. Vitamin D level was not associated with the severity of coronary lesions in patients with ST-segment elevation myocardial infarction.

Vit.D & Left ventricular Hypertrophy

Considering *hypertension* associated with low vitamin D levels, left ventricular hypertrophy could also be a consequence. Vitamin D reduces cardiac hypertrophy in spontaneously hypertensive rats^[2] and in salt-sensitive rats via modulation of several protein kinase pathways.^[5] Among the proposed cardioprotective effects of vitamin D, reduced expression of mediators of myocardial hypertrophy, including atrial natriuretic peptides, and growth factors promoting cell proliferation were mentioned.^[10] Intravenous calcitriol treatment, used to control secondary hyperparathyroidism in hemodialysis patients, caused regression of myocardial hypertrophy and reduction of QT interval dispersion, suggesting a cardioprotective effect of vitamin D.

Vit.D & Stroke

Epidemiological studies have shown that vitamin D deficiency is an independent risk factor for arterial hypertension and stroke.^[11] A recent “umbrella” review stated that the association between high vitamin D level and low stroke risk is possible, but not convincing.^[1]

Renal Implications of Deficiency of Vit.D deficiency related to Cardiovascular Pathology

The kidneys are involved in the synthesis of the metabolically active form of vitamin D, since the second hydroxylation, stimulated by the parathyroid hormone, occurs in the kidneys. Serum phosphate levels influence the renal hydroxylation of vitamin D through a negative

feedback mechanism.^[2] Individuals with renal disease have a deficiency of 1, 25-dihydroxyvitamin D, impairing calcium and phosphate balance.^[12] Cardiovascular diseases are more prevalent in patients with chronic kidney disease compared to patients with normal kidney function, and several links between vitamin D deficiency and poor cardiovascular outcomes were described in patients with renal disease. Vitamin D deficient patients with chronic renal failure had *enhanced atherosclerotic lesions* with arterial stiffening and reduced flow-mediated dilatation. *Elevated PTH* contributes probably to the development of *uremic cardiomyopathy*, considering the correlations between PTH and left ventricular hypertrophy in chronic renal failure.^[12] Vitamin D given in hemodialysis patients enabled regression of myocardial hypertrophy and reduction of QT interval dispersion, a marker of ventricular arrhythmia risk.^[1]

Cause of opposite theories

It is still not clear if vitamin D supplementation is needed only if vitamin D is deficient in order to exert its cardioprotective effects. Which type of vitamin D or vitamin D analogue is effective is another question still requiring an answer. Lower doses in vitamin D2 supplementation and shorter intervention periods were associated with a higher mortality.^[6] The question about the benefit of vitamin D supplementation for cardiovascular outcomes cannot be answered certainly for the moment^[7,6] but perhaps the outcomes of the VITAL prevention trial and J-DAVID trial will provide more answers. Another concern is related to the vitamin D level with benefic effects for cardiovascular disease, considering that doses recommended for osteoporosis treatment are neither beneficial nor harmful in cardiovascular disease.^[2] Consumption of high amounts of vitamin D may interfere with the regulation of phosphate metabolism by fibroblast growth factor 23 and the Klotho gene product.^[1,3] It is therefore important to identify and use new markers for phosphate homeostasis, such as salivary phosphate secretion¹⁰ during vitamin D therapy. It still remains uncertain whether the association between low vitamin D status and cardiovascular diseases is causal or just a bystander. It is likely that unidentified factors and relationships with other endocrine networks are also involved in vitamin D biology, emphasizing the need of further research in this area.

CONCLUSION

Observational data support the link between vitamin D status and cardiovascular diseases, and vitamin D deficiency can be considered a cardiovascular risk marker. Vitamin D exerts its cardiovascular effects by reducing the activity of the renin-angiotensin-aldosterone system, lowering blood pressure values, and having an anti-inflammatory, antiproliferative, antihypertrophic, antifibrotic, antidiabetic, and antithrombotic effect and beneficial modulation of classical cardiovascular risk factors. The mentioned effects might be very important

for public health, considering the high prevalence of vitamin D deficiency, the aging population, and the indoor oriented lifestyle. Vitamin D deficiency is treatable and supplementation is inexpensive. Vitamin D could be combined with antihypertensive agents in order to control blood pressure, as a simple, inexpensive, and important prophylactic method in order to prevent cardiovascular morbidity, especially in the elderly. Large randomized controlled trials could confirm the promising findings of observational studies, considering endothelial function, arterial stiffness, and patients undergoing percutaneous coronary interventions. Vitamin D supplementation should further consider additional factors, such as phosphates, PTH, RAA, and fibroblast growth.

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