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REVIEW ARTICLE

Vitamin D Deficiency and Heart Health: A Narrative Review

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Abstract

Vitamin D deficiency has developed into a global issue, impacting an estimated one billion people worldwide. Lack of sunlight exposure is the major cause of vitamin D deficiency, as very few foods contain natural vitamin D. Several epidemiological and random clinical trials have reported a close association between low vitamin D levels and cardiovascular disease development. This paper aims to discuss vitamin D deficiency and its role in developing cardiovascular disease. Vitamin D is an essential fat-soluble vitamin which plays an important role in skeletal maturation. Vitamin D deficiency is highly prevalent globally and is linked to a spectrum of cardiovascular disorders and is thought to promote atherogenesis. We have done a thorough review of the literature using a Pubmed search. Different keywords like vitamin D deficiency, cardiovascular diseases, coronary artery disease, atherosclerosis, heart failure were used to write the review. Here we report according to current evidence, vitamin D deficiency is associated with a higher risk of cardiovascular diseases. However, further study is necessary to evaluate whether vitamin D supplementation has a beneficial effect on cardiovascular outcomes.

Keywords: Vitamin D deficiency; Cardiovascular diseases; Cholecalciferol; Coronary heart disease; Heart failure

Introduction

Vitamin D is a fat-soluble vitamin that functions as a steroid hormone that helps in mineral homeostasis and skeletal health. It also acts as an immunomodulator and modulates the immune response in the body[1]. The most common form of vitamin D is vitamin D3 (Cholecalciferol). Vitamin D levels can be influenced by multiple factors, including nutrition, sunlight exposure, outdoor physical activity, and pigmented skin colour. The majority of vitamin D (80%) in the human body is synthesised in the skin in response to ultraviolet rays from 7-dehydrohydrochesterol by non-enzymatic reactions. Vitamin D is also naturally contained in some foods, such as fish oil, mushrooms, egg yolks, fortified milk, and cereals[2]. Vitamin D from the diet and skin is hydrolyzed in the liver by mitochondrial and microsomal enzymes to 25- hydroxyvitamin D [25-(OH)D], which is further metabolised in the proximal convoluted tubules of kidneys into its active form 1,25- hydroxyvitamin D [1.25 (OH)D] by 1-alpha-hydroxylase (CYP27B1)[3].

Vitamin D is primarily known to have its role in controlling skeletal physiology by regulating calcium and phosphorus and bone remodelling along with other calcium-regulating hormones like parathyroid hormone and calcitonin. However, several active metabolites of vitamin D also exert both direct actions, mainly via vitamin D3 receptor trans-activation and indirect actions on several other tissues in endocrine, autocrine and paracrine manners[4].

The best marker to assess vitamin D deficiency is serum 25- (OH) D levels. According to Endocrine Society Task Force on Vitamin D, serum concentration of 25-(OH) D below 50 nmol/L (or 20 ng/ml) is considered vitamin D deficiency, and levels <30 nmol/L (or 12 ng/ml) is considered as severe vitamin D deficiency. The prevalence of 25-(OH) D below 50 nmol/L (or 20 ng/ml) is estimated at 24% in the US, 37% in Canada, and 40% in Europe. Whereas the prevalence of 25-(OH) below 30 nmol/L (or 12 ng/ml) is estimated at 5.9% in the US, 7.4% in Canada, 13% in Europe, and >20% in India, Tunisia, Pakistan, and Afghanistan.[5]

Vitamin D deficiency not only causes rickets and osteoporosis but has been also associated with an increased risk of cancer (eg colon, prostate, and breast cancer), autoimmune illnesses (eg type I diabetes, multiple sclerosis), and infectious diseases (eg tuberculosis).[6] Along with calcium and phosphate homeostasis, 1,25(OH)2D3 exerts antiproliferative and pro-differentiating effects on a wide variety of cell types and induces apoptosis of cancer cells to slow their proliferation. Studies have shown that deficiency of vitamin D decreases insulin secretion whereas vitamin D supplementation may improve the synthesis of denovo proteins by Islets of Langerhans leading to the conversion of proinsulin to insulin.[7] Vitamin D deficiency has been linked to cardiovascular diseases such as congestive heart failure, myocardial infarction, peripheral vascular disease, hypertension, and abdominal aortic aneurysm. It has been associated with activation of the pro-inflammatory mechanism, promoting atherogenesis.[4] Vitamin D receptors (VDRs) are nuclear steroid hormone receptors present broadly in all body tissues. The presence of VDR on cardiac myocytes and endothelial cells suggests the direct involvement of vitamin D in the progression of cardiovascular disease. The other possible mechanism of vitamin d deficiency causing cardiovascular diseases is its effects on the renin-angiotensin-aldosterone system (RAAS).[7] In this narrative review, we aim to highlight the role of vitamin D in cardiovascular diseases focusing on hypertension, hypercholesterolemia, and heart failure by exploring various cross-sectional studies and clinical trials Table 1[3].

Table 1. Major risk factors that lead to vitamin D deficiency

Major Risk factors for Vitamin D deficiency
Increased distance from equator
Winter seasons
Aging
Smoking
Pigmented skin colour
Obesity
Fat malabsorption
Renal and liver disease
Medications such as glucocorticoids and antiepileptic drugs

Discussion

Vitamin D metabolism

Vitamin D has an interesting metabolism as it can be both ingested orally as well as synthesised in the skin by exposure to ultraviolet-B light that converts 7-dehydrocholesterol to cholecalciferol or reversely metabolised to vitamin D-inactive substances such as Lumisterol and Tachysterol.[8] Both ingested or synthesised cholecalciferol binds to vitamin-D binding protein and is transferred to the liver. In the liver, the hepatic enzyme CYP2R1 (25-hydroxylase) converts vitamin D into 25-hydroxyvitamin D (25(OH)D), which is then converted into 1,25 dihydroxy vitamin D ($1,25(OH)_2D$) by 1α-hydroxylase (CYP27B1) in the kidneys.[9] In the circulation, $1,25(OH)_2D$ is transported by vitamin D binding proteins (DBP)[8]. Vitamin D is considered a steroid hormone as it exerts its effects mainly through vitamin d receptors (VDR) in the cells. The 1,25(OH)D has a high affinity for VDR, which acts as a ligand-activated transcription factor. VDR is an intracellular receptor found on various cells such as cardiac myocytes, endothelial cells, vascular smooth muscle cells, macrophages, and dendritic cells.[10]

Vitamin D binds to the membrane bound receptors which induces a conformational change in the VDR. This conformational change causes heterodimerization of VDR with retinoid X receptors. The complex translocates into the nucleus and binds to Vitamin D response elements in the promoter region of target genes.[4,8,9]

The metabolism of vitamin D is strongly regulated by calcium, phosphate, fibroblast growth factor 23, and parathyroid hormone.[11]

Vitamin D deficiency and cardiovascular diseases

In recent years, Vitamin D deficiency has also been associated with a wide variety of extraskeletal conditions, including the regulation of cell proliferation and differentiation and the regulation of cardiac contractility and hypertrophy.[12] Cardiovascular diseases are the leading cause of death in the United States. About 697,000 people in the United States died from heart disease in 2020.[13]

Vitamin D deficiency is linked with an increased risk of several cardiovascular diseases like arterial stiffness, left ventricular hypertrophy, and vascular dysfunction, as well as coronary artery disease, stroke, atherosclerosis, ischemia, heart failure, and hypertension.[14,15] Activation of the renin-angiotensinogen-aldosterone system (RAAS), oxidative stress, altered inflammation, and abnormal nitric oxide regulation, contribute to these effects.[16] Furthermore, the prospective study of the Integrated Intermountain Healthcare system database showed that deficiency of vitamin D is associated with an increase in the prevalence of HTN, peripheral vascular disease (PVD), and hyperlipidemia ($P < 0.0001$) as well as heart failure (HF), coronary artery disease/myocardial infarction, stroke and their composites.[17] In addition, patients with heart transplants had low vitamin D levels. Its level (below 10 ng/mL) was found in 10% of transplant group patients and 55% of orthotopic heart transplant recipients.[18]

Vitamin D modulates inflammatory response by decreasing the expression of TNF-alpha, Interleukin-6 (IL-6), IL-1, and IL-8.[19] Lower levels of IL-6 are associated with the decreased synthesis of the acute-phase inflammatory marker, C-reactive protein (CRP). High levels of CRP serum concentrations are associated with increased levels of inflammation and serve as a predictor for cardiovascular events.[20] Vitamin D deficiency increases the risk of coronary artery disease development through chronic inflammation of epicardial adipose tissue by up regulation of karyopherin alpha 4 (KPNA4), which increases NF-kB activation.[21]

Vitamin D is paramount for calcium homeostasis. It is also essential to maintain the diastolic function of the heart. Vitamin D induces increased phosphorylation of protein kinase C, which targets phospholamban B and cardiac troponin I, both of which, through modulation of intracellular Ca^{2+}, accelerate the relaxation of cardiac myocytes[22]. Reduced relaxation of cardiac myocytes due to vitamin D deficiency and subsequent impaired filling of ventricles is the primary pathologic finding in diastolic heart failure[23]. The RAAS plays a crucial role in the regulation of blood pressure. Vitamin D deficiency stimulates the expression of renin in normal mice. On the contrary, 1,25(OH)D injection decreases renin synthesis. In addition, a marked increase in the production of renin and angiotensinogen II is seen in VDR knockout mice, inciting hypertension and left ventricular hypertrophy. In contrast, treatment of VDR knockout mice with 1,25(OH)D leads to partial suppression of hypertrophy[24]. Moreover, vitamin D deficiency leads to sustained RAAS activation resulting in increased angiotensinogen II levels, arterial hardening, and endothelial dysfunction. This ultimately results in elevated blood pressure. However, random control trials to establish a causal relationship between vitamin D supplementation and improved CVD risk factors as well as its effects on arterial hypertension have been inconclusive.[17]

Atherosclerosis

Atherosclerosis is caused by multiple genetic and environmental factors. The most common factors promoting atherogenesis are hypertension and elevated low-density lipoproteins in the blood. There is some evidence from experimental and clinical studies that vitamin D signalling may modulate the pathogenesis of atherosclerosis. Endothelial injury and inflammation are the first steps in the pathogenesis of atherosclerosis. Vitamin D modulates the inflammation by reducing the levels of TNF *a*, IL-6, IL-1, and IL-8 in the monocytes, thus influencing the development of atherosclerosis. Additionally, Vitamin D can also decrease cholesterol accumulation in macrophages (reduce foam cell formation) and decrease uptake of LDL in atheromas.[9] Depletion of VDR and a low Vitamin D diet stimulate osteoblast-like cell formation of vascular smooth muscle cells and aortic calcification hypertrophy.[24]

There are several conflicting experimental as well as clinical studies about the role of vitamin D signalling in atherosclerosis but based on certain experimental settings, it can be concluded that vitamin D signalling may have a beneficial effect on the pathogenesis of atherosclerosis through its anti-inflammatory actions.[9]

Coronary heart disease

Vitamin D deficiency is associated with coronary heart disease (CHD)[17,25]. It increases the risk of coronary artery disease development through chronic inflammation of epicardial adipose tissue by upregulation of karyopherin alpha 4 (KPNA4), which increases NF-kB activation.[21] Low levels of vitamin D are associated with coronary artery calcium stones.[26] The results of a meta-analysis of L. Wang

et al showed a relative risk of 1.4 for coronary artery disease (CAD) when comparing the lowest to the highest levels of vitamin D in the patients.[14] Vitamin D deficiency not just increases the risk of CAD but also makes it worse.[27,28] Despite these observations, Vitamin D supplementation is not yet proven as a beneficial treatment for acute myocardial infarction patients, nor have trials been conducted to determine the efficacy of early vitamin D administration to patients with a high risk of CHDs.[29–31]

Heart failure

Vitamin D deficiency is also associated with HF. Several studies have reported lower vitamin D levels in patients with HF compared to a control. It has been linked to a higher rate of hospitalised HF patients with preserved ejection fraction.[32] The serum level of vitamin D is inversely correlated with the risk of HF of 1.3 for low levels (16–30 ng/mL) and 2.0 for very low levels ($\leq$15 ng/mL).[17] In the VINDICATE trial, Witte et al. demonstrated a significant improvement in left ventricular function when high-dose vitamin D was administered for 1-year in chronic HF patients with vitamin D deficiency but more clinical trials are still required to provide an adequate answer to the question of whether vitamin D benefits HF patients.[32]

The most common cause for mortality in patients suffering from chronic kidney disease is of cardiovascular origin. It was shown that treatment of patients with chronic kidney disease with vitamin D analogues reduces cardiovascular mortality, and it can lead to regression of LVH.[33]

Over the years a large number of trials and studies have been conducted to assess the effects of vitamin D supplementation on CVD and deaths related to CVD. A 'Vitamin D assessment study' which included 5108 individuals between the age of 50 to 84 years of age was conducted in 2017 to investigate whether monthly high doses of Vitamin D supplementation prevented CVD. The participants were randomised to initially receive either bolus of 200,000 IU oral vitamin D3 or placebo followed by 100,000 IU oral vitamin D3 or placebo monthly for a median follow-up of 3.3 years. The primary end point was decided as incident CVD and death. The incidence for primary outcome of CVD in vitamin D group (11.8%) and placebo (11.5%) were noted and thus it was concluded that monthly high-dose vitamin D supplementation does not prevent CVD.[34]

A RCT using two-by-two factorial design was conducted by Manson et al which included 25,871 people (men aged $\geq$ 50 years and $\geq$ 55 years women) from the United States. The participants were randomly given vitamin D3 (2000 IU per day), and a dose of 1 g omega-3 fatty acids per day and followed for a median of 5.3 years. It was observed that major cardiovascular events occurred in 396 in the vitamin D group and 409 in the placebo group therefore making it evident that supplementation with vitamin D did not result in a lower incidence of cardiovascular events than placebo.[35]

The DO-Health RCT concluded that among adults without major comorbidities aged 70 years or older, treatment with vitamin D_3, omega-3s, or a strength-training exercise program did not result in statistically significant differences in improvement in systolic or diastolic blood pressure.[36]

In 2022, a 5-year, randomised, placebo-controlled trial was conducted among 2495 Finnish male $\geq$60 years and Finnish post-menopausal female participants $\geq$65 years who were free of prior CVD. The participants were divided into 3 groups, given placebo,1600 IU/day, or 3200 IU/day vitamin D3 and an annual follow up was done. The primary endpoint was incidence of major CVD whereas the secondary endpoints included individual components of the primary endpoints like myocardial infarction, stroke, and CVD mortality. The trial concluded that vitamin D3 supplementation did not significantly lower the incidence of major CVD among the older population possibly because of sufficient vitamin D status at baseline.[37]

The meta-analysis conducted by Barbarawi et al included more than 83,000 individuals in 21 RCT. The results of this meta-analysis were consistent with the above mentioned clinical trials with respect to supplementation of vitamin D and CVD as primary endpoints. However, additional trials with high dose vitamin D supplementation needs to be conducted targeting older age groups with baseline lower levels of vitamin D and also evaluating other CVD endpoints like heart failure.[38]

Conclusion

Vitamin D deficiency is the most prominent nutrient deficiency in the world. A low serum vitamin D level leads to adverse health-related problems. According to current evidence, along with causing rickets and osteoporosis, Vitamin D deficiency causes increased risk of cancer, autoimmune diseases like diabetes mellitus and infectious diseases like TB, it is also associated with a higher risk of cardiovascular diseases. In addition, low vitamin D levels are linked with hypertension and higher rates of cardiovascular and all-cause mortality. However, whether vitamin D supplementation has a beneficial effect on cardiovascular outcomes is still unclear. Therefore, randomised clinical trials of vitamin D supplementation are needed to evaluate whether it reduces the severity of such high health problems.

Declarations

Competing interests

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Authors' contribution

All authors meet the authorship criteria and have contributed equally to the manuscript. Nour Shaheen, Abdelraouf Ramadan, Meet A Patel, and Kinna Parikh did the literature review and wrote the first draft of the manuscript. Vasu Gupta, Sunita Kumawat, Fatima Labiebm, FNU Anamika, and Puneetraj Kaur did the literature review, editing and proof reading of the manuscript. Puja Patel, Nazar Mohammad and Talha Mahmood did the literature review and Sachin Gupta and Rohit Jain gave the concept of the paper and final approval.

Abbreviations

Vitamin D receptor (VDR); Retinoid X receptor (RXR); C reactive protein (CRP); Renin angiotensinogen aldosterone system (RAAS); Hypertension (HTN); Coronary heart diseases (CHD); Heart failure (HF).

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