REVIEW ARTICLE

Vitamin D Deficiency and Cardiovascular Diseases

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Abstract

Vitamin D is considered a steroid hormone with a broad spectrum of action in the human body. Its action arises from the binding of its active metabolite (1α,25-dihydroxyvitamin D) to its receptor (VDR), which is present throughout the body, including vascular smooth muscle cells and cardiomyocytes. Initially, vitamin D deficiency was related only to changes in the musculoskeletal system, but in recent years, researchers have demonstrated its relationship with several pathologies related to other systems, such as cardiovascular diseases. The objective of this study is to review vitamin D's pathophysiology, describe its relationship with cardiovascular diseases based on the most recent publications, and highlight the results of vitamin supplementation in the prevention of such pathologies.

Introduction

Vitamin D, the fourth vitamin to be described, was initially characterized as a factor capable of curing rickets, a disease characterized by bone demineralization and skeletal deformities.[1]

Currently, vitamin D comprises a group of secosteroid molecules derived from 7-dehydrocholesterol (7-DHC) that includes the active metabolite (1α,25-dihydroxyvitamin D or calcitriol), its precursors (cholecalciferol or vitamin D3, ergocalciferol or vitamin D2 , and 25-hydroxyvitamin D or calcidiol), as well as its degradation products.[2] These molecules, along with their carrier proteins and receptors, comprise an important metabolic axis: the endocrine vitamin D system.[3]

Keywords

Vitamin D Deficiency / physiopathology; Cardiovascular Diseases; Solar Radiation; Calcium; Phosphorus.

The active vitamin D has a fundamental role in regulating bone and mineral physiology, in particular, calcium and phosphorus metabolism. It is also involved in the homeostasis of several other cellular processes, such as the modulation of autoimmunity and synthesis of inflammatory interleukins,[4] blood pressure control,[5] and participation in the process of cell multiplication and differentiation.[6] The spectrum of action of vitamin D is so broad that microarray studies show that 1α,25-dihydroxyvitamin has more than 900 potential gene targets, corresponding to approximately 3% of the human genome.[7]

Epidemiological studies have found that a significant portion of the world population, regardless of age, ethnicity, and geographical location, has low serum levels of vitamin D,[8] as illustrated in Figure 1. Some countries even present rates of vitamin D deficiency above 50%, as observed in Brazil, Denmark, and Germany.

Recent studies have associated inadequate serum vitamin D levels with several diseases unrelated to the musculoskeletal system, such as cancer (colon, prostate, and breast), autoimmune and inflammatory diseases (multiple sclerosis, Crohn's disease), depression, and cardiovascular diseases (CVDs) such as hypertension, coronary artery disease (CAD), and heart failure (HF).[9]

The objective of this study was to review vitamin D's pathophysiology, describe its relationship with CVD based on the most recent publications, and highlight the results of vitamin supplementation in the prevention of such diseases.

Physiology and mechanism of action

In humans, only 10 to 20% of the vitamin D derives from the diet, and the remaining 80% is synthesized endogenously.[10] Few foods have significant amounts of this vitamin, of which the main ones are listed in Table 1.

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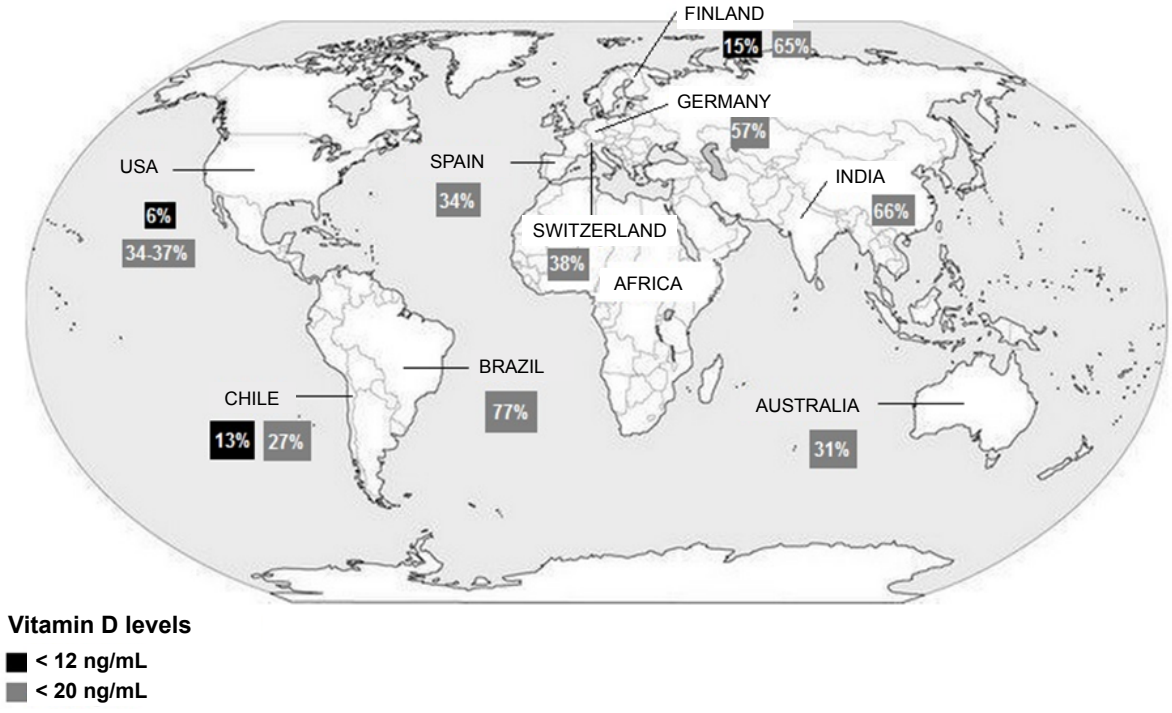

Figure 1 - Global prevalence of vitamin D deficiency in adults.
Adapted from: Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014 October; 144PA: 138–145. doi:10.1016/j.jsbmb.2013.11.003.

Table 1 - Some food sources of vitamin D. Adapted from the Brazilian Society of Endocrinology and Metabolism[11]

Food	Portion	Amount of vitamin D per portion
Wild salmon	100 g	600 – 1,000 IU of vitamin D_3
Farmed-raised salmon	100 g	100 – 250 IU of vitamin D_3
Canned sardines	100 g	300 IU of vitamin D_3
Canned mackerel	100 g	250 IU of vitamin D_3
Canned tuna	100 g	230 IU of vitamin D_3
Cod liver oil	5 mL	400 – 1,000 IU of vitamin D_3
Egg yolk	1 unit	20 IU of vitamin D_3
Fresh mushrooms	100 g	100 IU of vitamin D_2
Sun-dried mushrooms	100 g	1,600 IU of vitamin D_2

The molecular structure of vitamins D2 and D3 is very similar. Ergocalciferol differs from cholecalciferol by a double bond between carbons 22 and 23 and a methyl group on carbon 24, as shown in Figure 2. Both vitamins are synthesized from energy derived by photolysis (solar radiation) on their precursors: ergosterol (vitamin D2) and 7-DHC (vitamin D3). Following ingestion by humans, both vitamins follow the same metabolization pathway in the liver and are converted into 25-hydroxyvitamin D.[11]

Synthesis of endogenous vitamin D starts in the deep layers of the epidermis, where the precursor 7-DHC is stored in the double lipid layer of the cell membrane. Ultraviolet B (UVB) radiation promotes 7-DHC photolysis, leading to the formation of a secosteroid molecule: previtamin D3. This molecule is thermally unstable and undergoes an isomerization reaction induced by heat, converting it into vitamin D3. Skin melanin competes for the radiation photon, decreasing the availability of photons for 7-DHC photolysis, hence the observation of lower vitamin D levels in blacks.[11]

When reaching the liver, vitamins D2 and D3 undergo hydroxylation by cytochrome P450 and originate 25-hydroxyvitamin D, which is the form of the vitamin that predominates in the circulation. In the blood, about 85 to 90% of the 25-hydroxyvitamin D is bound to vitamin

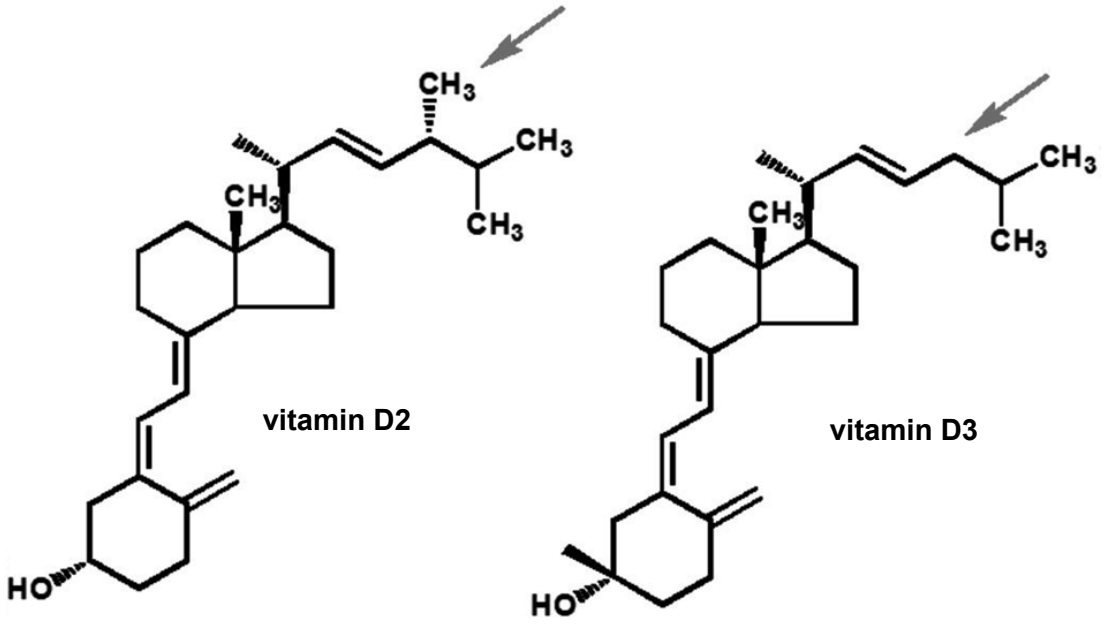

Figure 2 - Vitamin D2 and D3 molecules, showing the difference in methyl group (CH3), which is present in the former and absent in the later (arrows).
Extracted from: Peixoto PV et al. Hypervitaminosis D in animals [Hipervitaminose D em animais]. Pesq. Vet. Bras. 32(7):573-594, julho 2012.

D-binding protein (VDBP), 10 to 15% to albumin, and the remaining (less than 1%) circulate in a free form. There are few data in the literature on the bioavailability of vitamin D bound to albumin; therefore, the expression "vitamin D bioavailability" is used for the 25- hydroxyvitamin D form not bound to VDBP.[12]

When reaching target tissues, 25-hydroxyvitamin D is converted by the enzyme 1α-hydroxylase into 1α,25-dihydroxyvitamin D, which is the metabolically active form of the vitamin.

The effects of 1α,25-dihydroxyvitamin D are mediated by its receptor, VDR, which belongs to the family of nuclear receptors 1. Both the enzyme 1α-hydroxylase and the VDR receptor are found in almost all human cells, including cardiomyocytes[13] and vascular smooth muscle cells.[14] Experimental models with absence of VDR allow the understanding of the tissue-specific activity of the receptor. As an example, the absence of VDR results in increased ventricular mass, increased brain natriuretic peptide (BNP) levels and deregulation of cardiac metalloproteinases and fibroblasts, promoting a fibrotic extracellular matrix and leading to ventricular dilation and electromechanical uncoupling.[15] After the binding of vitamin D to the VDR, the complex promotes gene activation or suppression, with the help of coregulator proteins. On the other hand, the VDR also presents prompt nongenomic responses by inducing voltage-dependent calcium channels, leading to increased cell inflow of calcium and activation of other messengers, such as cyclic AMP, protein kinase A, and phospholipase C.[16]

Vitamin D deficiency

The American guideline for evaluation, prevention, and treatment of vitamin D deficiency[17] establishes that the body pool of the vitamin should be determined by measurement of serum 25-hydroxyvitamin D with the following cutoff points: (i) deficiency, when below or equal to 20 ng/mL, (ii) insufficiency, when between 20 and 30 ng/mL, and (iii) sufficiency when greater than 30 ng/mL.

Some risk factors for vitamin D deficiency have been observed and relate to sun exposure, dietary habits, and intestinal absorption. These include an indoor lifestyle (sun deprivation), use of sunscreens, advanced age, distance from the Equator, black skin, air pollution, smoking, poor food absorption (malabsorption syndromes), drugs (anticonvulsants, glucocorticoids), and kidney and liver disease.[10,17]

Despite the increased prevalence of vitamin D deficiency in the adult population and the growing evidence of its association with CVD, both American and Brazilian guidelines recommend that serum 25-hydroxyvitamin D levels should not be measured routinely in the general population and should only be measured in patients of populations considered at risk for deficiency of this vitamin.[10,17]

Association of vitamin d deficiency and cardiovascular diseases

Although numerous studies have confirmed an association between vitamin D and CVD, a cause-effect relationship between both remains unclear.

In this review, we discuss the association of vitamin D deficiency with the main cardiovascular pathologies and, subsequently, we analyze some outcomes with vitamin replacement.

Hypertension

The association of vitamin D deficiency and hypertension has its basis on the renin-angiotensin-aldosterone system (RAAS). Renin is synthesized by renal juxtaglomerular cells and stimulates the production of angiotensin II (from angiotensin I) and aldosterone, which increase blood pressure (BP) directly by vasoconstriction and indirectly by fluid and salt retention.[18] Inappropriately increased RAAS activation has been reported in studies with VDR and 1α-hydroxylase knockout mice.[19] Vitamin D acts by inhibiting renin gene expression, decreasing the synthesis of renin and, thus, preventing hyperstimulation by this system.[20]

The Third National Health and Nutrition Examination Survey (NHANES III),[21] a large population study that analyzed a sample of 12,644 North-Americans, has shown that systolic BP and pulse pressure correlate inversely with levels of 25-hydroxyvitamin D. These results have been confirmed by subgroup analyses in which increases in BP associated with age were significantly lower in vitamin D sufficient individuals.[22] The prevalence of hypertension was also associated with vitamin D deficiency in other large studies such as the German National Interview and Examination Survey[23] and the British Birth Cohort.[24] A study carried out in Brazil with 91 hypertensive elderly patients has shown that the serum concentrations of 25-hydroxyvitamin D is inversely associated with BP and positively associated with the weekly frequency of fish consumption.[25]

Few prospective studies have evaluated the association between vitamin D and changes in BP or emergence of hypertension. In 2015, van Ballegooijen et al.[26] followed up 5,066 individuals without hypertension at the Dutch city of Groningen; the individuals had their serum vitamin D level measured and were followed up for 6.4 years. At the end of follow-up, 1,036 (20.5%) developed hypertension and, as expected, low levels of vitamin D were associated with a greater risk of development of the disease.[26]

Diabetes mellitus

Type 1 diabetes occurs due to an autoimmune destruction of pancreatic beta cells leading to complete deficiency of insulin production. As for the development of type 2 diabetes, the major mechanisms involved are beta cell dysfunction, peripheral insulin resistance, and systemic inflammation. According to evidence, vitamin D deficiency is associated with all these processes.[27]

Vitamin D may exert effects on beta cell function through a direct connection to VDR receptors and by local expression of the enzyme 1α-hydroxylase. Vitamin D may also increase insulin sensitivity by stimulating VDR expression in peripheral tissues and activating peroxisome proliferator-activated receptor-gamma (PPAR) receptors, a factor that is involved in regulating the metabolism of fatty acids in skeletal muscles and adipose tissue. On the other hand, vitamin D may also act through indirect pathways in insulin secretion and sensitivity by regulating calcium concentration and flux in beta cell membranes and peripheral tissues.[27]

Observational studies have shown that the incidence and prevalence of type 1 diabetes are higher in countries with higher latitude and that the disease is most often diagnosed in the winter months.[28] Some studies have related vitamin D deficiency in pregnant women with the incidence of type 1 diabetes in children after birth.[29] Other studies have evaluated the protective role of vitamin D supplementation in early childhood against the development of type 1 diabetes, showing a lower incidence of the disease in children who received vitamin supplementation.[30]

With respect to insulin resistance and type 2 diabetes, the results have been conflicting. Some studies have associated low concentrations of 25-hydroxyvitamin D with insulin resistance and dysfunction of pancreatic

beta cells in western populations.[31] While studying 1,807 healthy Korean individuals, Ock et al.[32] have recently reported that vitamin D has an inverse association with insulin resistance.[32] While analyzing the relationship between vitamin D deficiency, diabetes, and CAD, Nardin et al.[33] evaluated 1,859 patients undergoing elective angiography for evaluation of CAD and concluded that diabetes is not an independent predictor of vitamin D deficiency, but diabetic patients with vitamin D deficiency presented increase CAD prevalence and severity.[33] In a recent study, Schafer et al.[34] followed up more than 5,000 elderly women for 8.6 ± 4.4 years to investigate a possible relationship between vitamin D levels and the emergence of type 2 diabetes; the authors concluded that the serum levels of vitamin D were not independent predictors of the incidence of type 2 diabetes in this population.[34]

Obesity

Recent evidence suggests that vitamin D deficiency is associated with obesity and other components of the metabolic syndrome.[35]

Low levels of 25-hydroxyvitamin D are common in obese individuals, and many studies have demonstrated an inverse relationship between serum vitamin D levels and body mass index (BMI).[36] Vitamin D has also been associated with regional fat distribution, and high levels of the vitamin have been associated with a lower amount of visceral and subcutaneous fat.[37] Some of the explanations proposed for this association are: differences in dietary intake between obese and nonobese individuals, decreased sun exposure among obese individuals, lower vitamin D bioavailability in obesity, and altered vitamin D metabolism in obese individuals.[38]

Wortsman et al.[39] proposed the hypothesis of sequestration of vitamin D by fat tissue to explain the prevalence of low levels of this vitamin in obese individuals.[39] They demonstrated that obese individuals presented a lower increase in serum 25-hydroxyvitamin D when compared with nonobese individuals under the same conditions of exposure to sunlight and vitamin intake. Since vitamin D is liposoluble, they proposed that the vitamin must accumulate in fatty tissue and not be readily available in the circulation, which would lead to low serum levels of this vitamin.

On the other hand, Drincic et al.[40] suggested that the difference in serum levels of vitamin D between obese and nonobese individuals is related to the distribution volume of this vitamin, which is greater in obese individuals and would justify its lower serum levels in these individuals.[40]

Smoking and lifestyle habits

Smoking is a risk factor for CVD and systemic inflammation, and vitamin D has been associated with both these conditions. Lee et al.[41] studied 560 Korean individuals aged 60 years or older to investigate the association between vitamin D and inflammatory markers and evaluate whether this association would change with the smoking profile of the patients.[41] The authors observed a significant association between vitamin D deficiency and high-sensitivity C-reactive protein (hsCRP) and a modifying effect of smoking on this association, in which smokers show a stronger association between vitamin D deficiency and hsCRP than nonsmokers.[41]

With the aim of relating lifestyle characteristics with vitamin D deficiency, Skaaby et al.[42] conducted a longitudinal study with 4,185 individuals with a follow-up time of 5 years. In this study, multivariate analyses of repeated serum measurements 25-hydroxyvitamin D were used to evaluate the association of this vitamin deficiency with BMI, practice of physical activity, type of diet (more healthy *versus* less healthy), alcohol consumption, and smoking. As a result, lower serum levels of vitamin D were associated with higher BMI, lower levels of physical activity, consumption of a less healthy diet, increased alcohol consumption, and smoking.[42]

Coronary artery disease

The occurrence of CAD has been associated with vitamin D deficiency, but the pathophysiological mechanisms of this association have not been well understood yet. The main evidence to suggest such an association is the VDR presence in both the myocardium and vascular cells, and the demonstration by epidemiological studies that the incidence of both CAD and vitamin D deficiency increase in winter months and in countries furthest from the Equator.[43]

Vitamin D deficiency appears to be common in acute myocardial infarction (AMI), and preliminary studies indicate a possible association of vitamin deficiency with AMI prognosis in the short and long term.[43] Moreover, vitamin D deficiency seems to predispose to recurrent adverse cardiac events, due to its association with the number of affected coronary arteries, AMI complications, and cardiac remodeling.[44]

The Health Professionals Follow-up Study followed up 18,225 men during 10 years and observed an association between low vitamin D levels and increased AMI risk, even after adjustment for other risk factors.[45] Prospective studies have also found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study carried out with 239 patients with acute coronary syndrome (ACS) showed that 96% of the individuals had low vitamin D levels at hospital admission.[46]

Some studies show a potential independent association between severe vitamin D deficiency and intrahospital mortality in patients with ACS. Correia et al.[47] studied 206 patients with ACS and found that individuals with serum vitamin D levels lower than 10 ng/mL had a 24% rate of intrahospital cardiovascular mortality, which was significantly higher than that observed in the remaining patients (4.9%).[47]

Heart failure

HF has been associated with vitamin D deficiency. Shane et al. demonstrated a high prevalence of vitamin D deficiency in patients with HF, as well as an inverse correlation between serum levels of vitamin D with left ventricular function and disease severity.[48]

Vitamin D deficiency has been associated with severe adverse events, such as hospitalization due to HF and mortality. Liu et al.[49] reported in a study with 548 patients that low levels of 25-hydroxyvitamin D were associated with higher BNP levels, as well as a higher rate of hospitalization due to HF and increased mortality rate from all causes.[49] In the LURIC study, a prospective cohort study with 3,299 patients undergoing coronary angiography, the levels of N-terminal (NT)-proBNP related inversely to the levels of vitamin D.[50]

In regards to HF with normal ejection fraction (HFNEF), studies have shown conflicting results in terms of its association with vitamin D deficiency. In 2013, Lagoeiro et al. studied 85 outpatients with suspected HFNEF, of whom 32 had confirmed HFNEF, and observed a negative correlation between vitamin D deficiency and E/E' ratio.[51] On the other hand, Pandit et al.[52], in 2014, conducted a retrospective study with 1,011 patients and found no significant association between vitamin D levels and left ventricular diastolic performance.[52]

Despite evidence demonstrating an association between vitamin D and HF, the exact mechanism by which this vitamin's deficiency leads to worse clinical outcomes in patients with HF has not been clearly established yet. A potential mechanism could be through the occurrence of cardiorenal syndrome or worsening of renal function.[53] It is well known that the cardiovascular and renal systems are interrelated and that a decline in one of them could influence the other. Progression of cardiorenal syndrome involves hyperactivation of RAAS and sympathetic nervous system, as well as systemic inflammation, which may lead to electrolyte disturbances and disorders in fluid regulation, causing endothelial dysfunction, potentially leading to left ventricular remodeling and myocardial fibrosis. These changes generate a vicious cycle in which a decline in a system's function contributes to its further deterioration.[54]

Evidence supports vitamin D as an important regulator in the progression of cardiorenal syndrome. Deregulations in vitamin D metabolism due to reduced activity of the enzyme 1α-hydroxylase and depletion of VDBPs due to proteinuria are responsible for vitamin D deficiency in chronic renal patients; given the high prevalence of chronic renal insufficiency in patients with HF, such changes can be prevalent in these patients.[55]

Other evidence supporting the role of vitamin D deficiency in the pathogenesis of cardiorenal syndrome relates to the involvement of RAAS and inflammatory cytokines. Vitamin D deficiency leads to RAAS hyperactivation, contributing to left ventricular remodeling and emergence or worsening of HF.[56] Vitamin D deficiency can lead to increased production and release of inflammatory cytokines, which may have a direct or indirect negative effect in the myocardium, contributing to cell apoptosis, hypertrophy, fibrosis, ventricular remodeling, and negative inotropic effects, in addition to increased renal fibrosis and renal insufficiency.[57]

Vitamin D deficiency and myalgia induced by statins

Statins are very effective agents in primary and secondary cardiovascular prevention in high-risk patients.[58] However, the side effects most frequently observed in the musculoskeletal system, such as myalgia, have been commonly observed in patients treated with statins, and these effects directly affect the adherence to treatment using these medications.

Observational studies show that myalgia may occur in approximately 15 to 20% of the individuals treated with statins.[59] However, evidence from daily clinical practice shows that this prevalence is even greater. VDRs are present in muscle cells, and low vitamin D levels are

associated with hypotonia, proximal muscle weakness, and nonspecific musculoskeletal pain.[60] Recent studies have reported that vitamin D deficiency is associated with a higher prevalence of myalgia induced by statins.[61]

In 2014, Shantha et al.[62] performed a retrospective study with 5,526 patients followed by a prospective analysis in which the patients were followed up for 7 years. The patients with measured serum vitamin D levels who started treatment with statins were considered as the exposure group. The aim was to analyze the association between statin-induced myalgia and vitamin D levels, as well as to establish a cutoff level for vitamin D that would demonstrate a high accuracy for the emergence of myalgia. The authors concluded that low levels of vitamin D were associated with myalgia and that a cutoff level of 15 ng/mL for vitamin D showed a high accuracy in predicting the emergence of myalgia induced by statins.[62]

In 2015, Morioka et al.[63] performed a study with 5,907 patients to analyze if the level of vitamin D would modify the association between the use of statin and the emergence of musculoskeletal pain. The authors concluded that the group with vitamin D level below 15 ng/mL and using statins presented an approximately two-fold greater chance of developing musculoskeletal pain than patients who also had vitamin D levels below 15 ng/mL but were not treated with statins.[63]

Prospective and randomized studies are needed to confirm the actual association between vitamin D deficiency and the emergence of myalgia induced by statins. In addition, the pathophysiological mechanism that could explain this association still needs to be elucidated.

Genetic factors of vitamin D and its implications in cardiovascular disease

The increased worldwide prevalence of vitamin D deficiency, or at least of its measurable circulating form, 25-hydroxyvitamin D, can be explained in part by genetic determinants. In 2010, an important multicenter study carried out by Wang et al. pointed out that serum vitamin D levels may be influenced by genetic variations involving its synthesis (7-DHC), hydroxylation (CYP2R1, CYP24A1), and transport protein (VDBP).[64]

Most studies analyzing the association between vitamin D deficiency and CVD are epidemiological, which prevents discrimination between association and causality. In this context, Mendelian randomization (MR) is an alternative approach to estimate the causal relationship between modifiable biological exposures and clinical outcomes of interest using genetic variants (single nucleotide polymorphisms, SNPs) as instrumental variables. Thus, MR using summarized data allows the combination of results already published in previous studies, becoming a relevant alternative to investigating causality.[65]

Some studies have used MR to investigate a possible causal relationship between vitamin D deficiency and CVD. With respect to hypertension, Vimaleswaran et al.[66] found that increased vitamin D levels could reduce the risk of development of CVD, showing a causal relationship.[66] On the other hand, the results of MR studies have not demonstrated a causal relationship for diabetes mellitus[67] and CAD,[68] in which vitamin D deficiency appears to be a confounding factor.

Vitamin D replacement

Based on growing evidence of an association between vitamin D deficiency and CVD, many authors have investigated the role of vitamin D supplementation in the prevention and treatment of these pathologies.

A randomized study conducted by Hsia et al.[69] with 36,282 postmenopausal women evaluated the supplementation of vitamin D 200 IU plus calcium carbonate twice a day or placebo during a follow-up of 7 years and found that supplementation of vitamin D was unable to reduce cardiovascular risk.[69] This was one of the few randomized studies that evaluated the impact of vitamin D in reducing hard outcomes, namely, incidence of AMI, stroke, and CAD-related death.

With regard to hypertension, studies with vitamin D replacement have shown conflicting results. An important systematic review and meta-analysis published by Wu et al.[70] comprising 36,806 patients showed no significant effect of calcium plus vitamin D supplementation in variations in systolic and diastolic BP when compared with lack of supplementation of both.[70]

In diabetes mellitus, studies involving vitamin D supplementation have proved disappointing. A study involving 70 children with type 1 diabetes of recent onset, supplementation with calcitriol had a modest effect on the residual function of pancreatic beta cells, but the reduction of glycated hemoglobin after 1 year of treatment was not statistically significant.[71] With respect to type 2 diabetes, study results are conflicting, perhaps due to lack of standardization of the supplemented vitamin D dose or the use of small samples in these studies. A meta-analysis involving 35 controlled studies evaluated the impact of vitamin D supplementation

in healthy patients and individuals with vitamin D deficiency, obesity, prediabetes, and diabetes. Compared with placebo, vitamin D had no effect on insulin resistance, insulin secretion, or glycated hemoglobin.[72]

In regards to obesity, several studies have evaluated the effect of vitamin D supplementation with and without the addition of calcium on weight and body composition. Most of these studies showed no significant effect of vitamin D on BMI or body composition.[73]

Additionally, CAD does not seem to be significantly influenced by vitamin D supplementation. An important study named RECORD[74] involving 5,292 individuals compared the effects of vitamin D, calcium, vitamin D *plus* calcium, or placebo on cardiovascular events. The results showed that although vitamin D can exert a protective role on HF, it does not seem to protect against AMI and stroke. A meta-analysis of 51 controlled studies found that supplementation of vitamin D has no significant impact on AMI.[75]

Vitamin D supplementation seems to have some benefits on HF, although the mechanisms of action have not been well established. Recent studies have reported that in individuals with established HF and vitamin D deficiency, vitamin supplementation is associated with improved survival.[76]

Conclusions

CVDs remain the main cause of mortality in several countries worldwide. An understanding of the pathophysiological mechanisms involved, as well as their risk factors, is essential for planning of prevention and treatment strategies.

In recent years, many studies have shown a relationship between vitamin D deficiency and CVDs, with a direct influence on prognosis. Based on the understanding of this association, the focus of researchers has been in the correction of vitamin deficiency with the aim of preventing diseases and improving the prognosis of established diseases. However, there are still no consistent data to recommend vitamin D replacement in the context of cardiac diseases.

One point that deserves attention is the broad worldwide variation in the prevalence of vitamin D deficiency. Since endogenous vitamin D synthesis is dependent on solar exposure, which in turn varies according to latitude, perhaps the reference level for serum vitamin D also differs among countries depending on sunlight exposure.

It is unclear whether the disappointment of the results of studies with vitamin D supplementation is due to an inability of the vitamin in exerting effects on established disease, or use of inappropriate supplementation doses. It is important to understand the doses required to maintain the serum levels of vitamin D above the desired level, as well as serial measurements of 25-hydroxyvitamin D with the aim of maintaining adequate levels of this vitamin during the entire follow-up duration.

Author contributions

Conception and design of the research: Jorge AJL, Cordeiro JR. Acquisition of data: Cordeiro JR. Writing of the manuscript: Jorge AJL, Cordeiro JR, Bianchi DBC. Critical revision of the manuscript for intellectual content: Jorge AJL, Rosa MLG.Supervision / as the major investigador: Jorge AJL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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