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Vitamin D and Cardiovascular Diseases

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Abstract

Vitamin D deficiency is highly prevalent worldwide and has been implicated in the pathogenesis and complications of cardiovascular disease (CVD). Defining this relationship has been challenging, and the clinical application of vitamin D screening and supplementation for CVD risk prevention and modification remain uncertain. The available evidence includes large observational studies and smaller randomized trials mostly evaluating surrogate endpoints and scarcely directed at CV outcomes as a primary endpoint. Methodological heterogeneity is present among most of these trials. Clarification of the clinical application of this relationship through ongoing large randomized trials should have important implications for public health.

Keywords: vitamin D deficiency, cardiovascular disease, endothelial function, hypertension, vitamin D

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the developed world and is projected to be the leading cause of morbidity and mortality in developing countries by 2020 [1]. In the United States, one in three adults lives with CVD resulting in disability and losses of billions of dollars each year [2]. CVD is a multifactorial disease that embodies a complex interplay between genetic predisposition, environmental factors, and risk factors that tend to be more prevalent in certain ethnic groups and those with lower socioeconomic status. Despite substantial gains in CVD prevention, a significant amount of risk remains despite adequate control and modification of traditional risk factors. Identification of novel risk factors that are easily modifiable has been eagerly sought over the past decade.

The discovery of the vitamin D receptor (VDR) in multiple cell types, including cardiomyocytes and vascular cells [3, 4], has led to increasing interest in vitamin D's role in human health, including cardiovascular, beyond its well-known role in bone health. Deficient vitamin D levels (<20 ng/ml) have been independently linked to increased morbidity and mortality [5–7].

Experimental evidence has linked vitamin D to regulation of multiple pathways involved in the pathogenesis of CVD. Several ecological and epidemiological studies have suggested a relationship between CVD and vitamin D status, as CVD events are higher in the winter, a period when vitamin D levels are lowest [8, 9]. Additionally, certain populations with poor cutaneous production of vitamin D and subsequently lower plasma levels, such as African Americans, tend to be at greater risk for hypertension and cardiovascular disease [3, 8, 10, 11]. These lines of evidence do not prove causality but support a hypothesis for further study.

Randomized controlled trials have mostly been based on surrogate or secondary endpoints for CV risk reduction [12]. Study methodology has been heterogeneous and results are often conflicting. To date, large well-powered randomized trials of vitamin D featuring CV outcomes as a primary endpoint are still ongoing [13, 14]. In the absence of results from these trials, regular supplementation cannot be recommended for cardiovascular risk modulation. Despite the lack of recommendations, use of vitamin D supplements for this purpose has risen dramatically.

The following chapter will provide an overview on the biologic plausibility and current evidence linking vitamin D to CV health and disease. But first, a brief review of the prevalence and definition of vitamin D deficiency and description of vitamin D synthesis and metabolism is necessary.

2. Vitamin D deficiency

Vitamin D deficiency is prevalent in 30–50% of adults in developed countries [10, 15], and it is estimated that more than 1 billion individuals worldwide are vitamin insufficient or deficient [3, 10, 16, 17]. Vitamin D deficiency is prevalent in every segment of the US population but remains under recognized and under treated [15, 18].

Serum levels of 25(OH)D <20 ng/ml indicate deficiency, and levels >30 ng/ml are considered optimal for bone health (**Table 1**) [15, 19]. Vitamin D levels of 30–40 ng/ml are associated with maximal parathyroid hormone suppression [10, 16, 19, 20]. No consensus has been reached on the optimum level of 25(OH)D for purported benefits beyond skeletal health [3, 10, 16, 17, 21]. A recent study suggests a 25(OH)D threshold of 11–14 ng/ml below which signifies increased CVD risk [22].

Levels in the range of 21–29 ng/ml are considered insufficient. Using this definition, the majority of the US population would be labeled as vitamin D insufficient.

A decline in mean serum vitamin D levels in the US population was detected when comparing data from the National Health and Nutrition Examination Survey (NHANES). The NHANES

survey from 1988 to 1994 (n = 18,883) showed a mean 25(OH)D level of 30 ng/ml as compared to a mean 25(OH)D level of 24 ng/ml in the 2001–2004 (n = 13,369) survey [23, 24]. This difference may have been explained by different assays used during the more current survey as compared to prior surveys, but there still remained a small but significant reduction after accounting for these differences [25]. The decline was likely related to behavioral factors most notably sun avoidance and obesity.

	25(OH)D concentrations (ng/ml)	Symptoms and biochemical consequences
Deficiency	10–20	Severe hypoparathyroidism
–	–	Calcium malabsorption
–	–	Rickets
–	–	Osteomalacia
–	–	Myopathy
Insufficiency	21–29	Elevated PTH
–	–	Low intestinal calcium absorption
–	–	Reduced bone mineral density
–	–	Subclinical myopathy
Sufficiency	>30	–
Toxicity	>150	Hypercalcemia
–	–	Increased intestinal absorption

Based on Lee et al. [15] and Zittermann et al. [7]

Table 1. 25(OH)D concentration and its effects [3, 7, 15].

Risk factors for developing vitamin D deficiency include limited cutaneous synthesis due to inadequate sun exposure (sunscreen use, institutionalized or homebound patients) and low dietary intake [3]. Other risk factors include age >65, smoking, air pollution, dark skin pigmentation, obesity (resulting from storage in adipose tissue), kidney and/or liver disease, disorders affecting fat absorption (e.g., celiac disease, Crohn’s disease, ulcerative colitis, some types of bariatric surgery), and end organ insensitivity to 1,25(OH)₂D [3, 9, 17].

3. Vitamin D metabolism

Vitamin D is a prohormone. Its active form, 1a 25-dihydroxyvitamin D (1,25(OH)₂D), plays an essential role influencing various metabolic pathways [7, 21, 26–30].

Skin synthesis from sunlight exposure (wavelength, 290–315 nm) contributes to 80–90% of vitamin D production in humans under natural conditions (D₃—cholecalciferol) [17]. UV-B irradiation of skin triggers photolysis of 7-dehydrocholesterol (provitamin D₃) in the plasma

membrane of human skin keratinocytes [3], which is then rapidly converted to vitamin D₃ by the skin's temperature (**Figure 1**) [7].

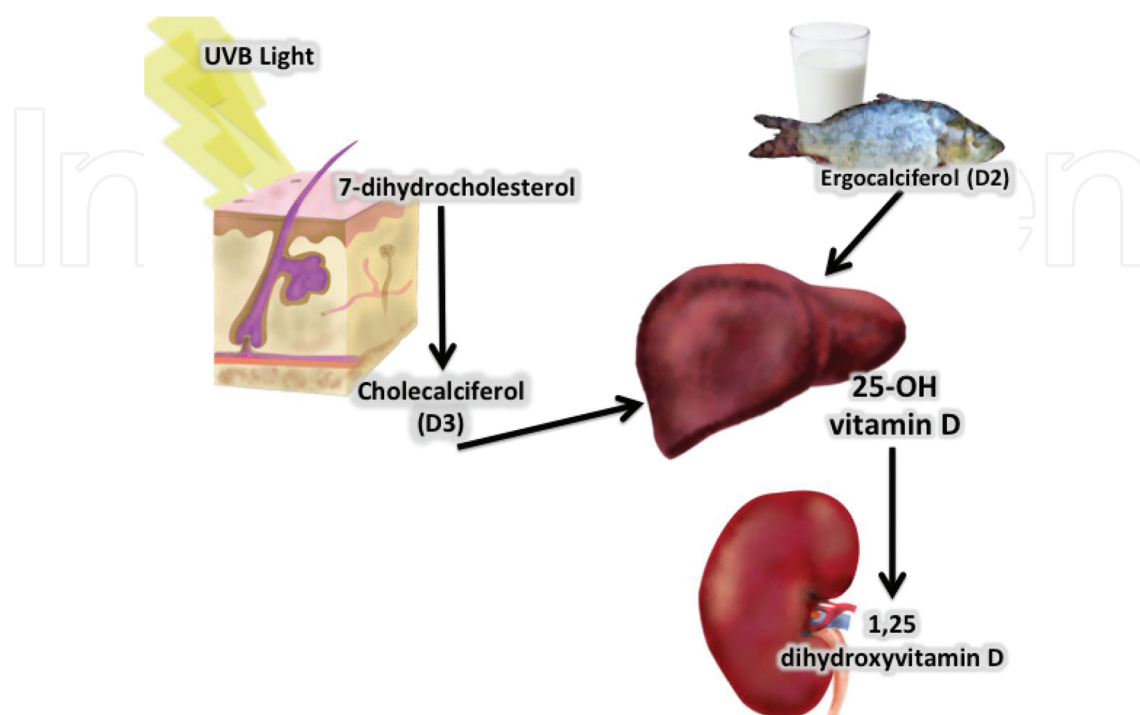


Figure 1. Vitamin D synthesis and metabolism [17].

The dietary supply of vitamin D (D₂—ergocalciferol) contributes 10–20% to the total amount of vitamin D in the body [31].

D₃ from the skin and D₂ from the diet undergo two sequential hydroxylations: 25 hydroxylation in the liver followed by 1,25-dihydroxylation in the kidney by 1- α hydroxylase (CYP27B1) (**Figure 1**). The major circulating metabolite of vitamin D is 25(OH)D, which should be measured clinically to assess vitamin D status, reflecting both intake and endogenous production [15, 31, 32]. 1,25(OH)₂D₃ is the biologically active form. The hydroxylation of 25(OH)D to its biologically active form is under control of parathyroid hormone (PTH) [7, 15].

The majority of 25(OH)D and 1,25(OH)₂D₃ in the circulation is bound to vitamin D-binding protein (DBP) (80–90%) and albumin (1–20%), while a small fraction is free. Production and levels are regulated by a feedback loop that includes serum PTH, calcium, and phosphate [3, 10, 16, 32].

Most of the known biological effects of 1,25(OH)₂D₃ are mediated through the vitamin D₃ receptor (VDR), a member of the superfamily of nuclear hormone receptors, which mediates transcriptional gene regulation [3, 7, 33–35].

1,25(OH)₂D₃ enters the cell and interacts with its nuclear VDR. It then forms a heterodimeric complex with the retinoic acid X receptor. Once the receptor complex binds to vitamin D-

responsive elements, a variety of transcriptional factors bind to it, resulting in gene expression [17] (Figure 2).

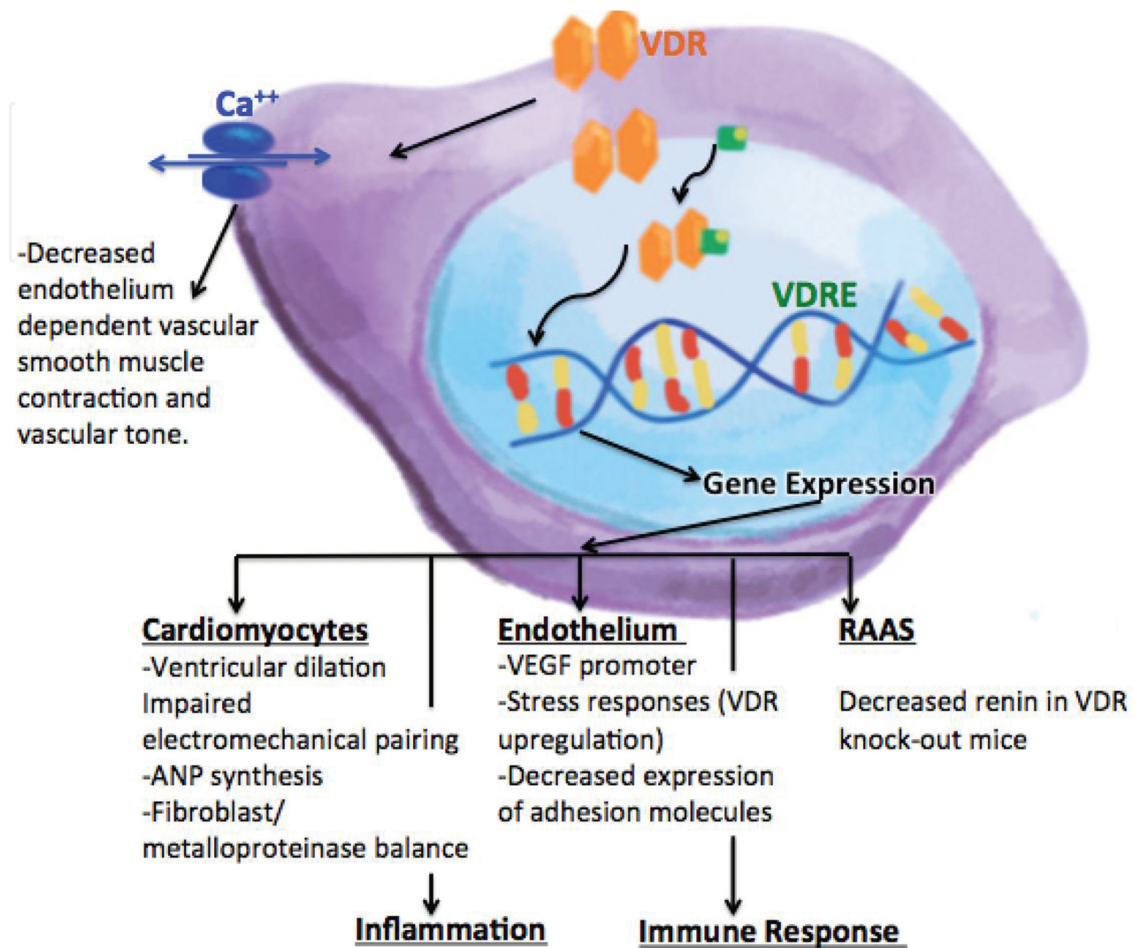


Figure 2. Cellular effects of vitamin D.

Over 200 genes are regulated by $1,25(\text{OH})_2\text{D}_3$. These include genes directly or indirectly responsible for renin and insulin production [15, 36], cytokine release [34], and vascular smooth muscle cell (VSMC) and cardiomyocyte proliferation [37].

$1,25(\text{OH})_2$ is also involved in non-genomic mediated intracellular signaling demonstrating immunomodulatory, antiproliferative, and prodifferentiative activities in experimental settings [17, 31, 38].

4. Biologic plausibility

Although biologically plausible, the characterization of vitamin D deficiency as a primary risk factor for CVD is challenging because of the complexity and number of interplaying pathways vitamin D is involved with.

The vitamin D receptor is nearly ubiquitous. It has been found in many cells including vascular smooth muscle cells (VSMC), endothelial cells, cardiac myocytes, and juxtaglomerular and most immune cells, all of which have been implicated in the pathogenesis and progression of CVD [3, 6, 10, 15–17, 32, 37–41].

Activated CD4+ and CD8+ T cells, B cells, neutrophils, macrophages, and dendritic cells all possess the capacity to convert 25(OH)D₃ into its active form 1,25(OH)₂D₃. Moreover, it is known that the rate-limiting enzyme in this pathway, 1,25 hydroxylase, is also present in activated macrophages [41, 42]. VSMC [37] and endothelial cells also express their own 1,25 hydroxylase, suggesting that these cells contain an autocrine mechanism to modulate the effects of vitamin D on the vasculature [43].

Vitamin D has direct and indirect cardiovascular effects. In a direct manner, 1,25(OH)₂D₃ enhances proliferation of vascular smooth muscle cells and expression of vascular endothelial growth factor via the VDR and CYP27B1 expression in VSMCs and endothelial cells [37]. It also plays an important role in inflammation and thrombosis. Inverse associations between vitamin D deficiency and thrombogenicity, vascular inflammation, and vascular calcification have been demonstrated [7, 38]. Cardiac and smooth muscle contractility is controlled partly by intracellular handling of calcium that depends on extracellular calcium which is regulated by vitamin D. 1,25(OH)₂D₃ has an inhibitory effect on hypertrophy and proliferation of VSMCs *in vitro* and in cultured cardiac myocytes, ultimately inducing apoptosis [37]. (**Figure 2**) The lack of VDR signaling results in chronically low nitric oxide production, caused by defective NO synthase.

Indirectly, the expression of renin *in vivo* is strongly regulated by vitamin D, and an inverse relationship between vitamin D levels and renin expression has been demonstrated experimentally [6, 27, 39, 40, 44, 45]. 1,25(OH)₂D₃ binds to the renin promoter region and inhibits renin transcription, thus reducing plasma renin activity [27, 40]. VDR knockout mice were proven to have increased levels of renin and angiotensin II and therefore higher prevalence of hypertension [27, 28, 40, 44, 45]. Thus, vitamin D may indirectly regulate blood pressure and affect cardiac hypertrophy through this mechanism.

Another indirect effect of vitamin D on CVD involves the production of matrix metalloproteinase 2 and 9, which promote insulin uptake beta-cell function and suppress pro-inflammatory cytokine release while increasing anti-inflammatory cytokine levels (IL-10) [34, 46]. These mechanisms help delay the inflammatory pathways implicated in coronary artery disease, by maintaining glycemic control and hindering secondary hyperparathyroidism and the formation of vascular calcification [33].

Vitamin D deficiency may also indirectly act deleteriously by inducing hyperparathyroidism. Parathyroid hormone (PTH) controls calcium homeostasis through specific receptors that are also present within vessel walls and the myocardium. PTH may promote the release of inflammatory cytokines, modulate vascular remodeling and lead to impaired glucose metabolism [47]. Several studies have demonstrated an association between high PTH levels and hypertension, myocardial dysfunction and vascular disease. In addition, hyperparathyroidism is also associated with increased mortality [6, 47, 48].

Lastly, increased biosynthesis and hyperlipidemia have also been associated to vitamin D deficiency. This is thought to result from decreased transcriptional activity of the VDR leading to the downregulation of insulin-induced gene-2 (Insig-2) expression. This ultimately results in increased 3-hydroxy-3-methylglutaryl-coenzyme reductase expression [49].

5. The clinical evidence

Vitamin D deficiency is a common finding in patients with CVD [15]. An inverse association between suboptimal 25(OH)D₃ and poor outcomes in CV health has been demonstrated by multiple trials. Most of these studies are observational, hindering the establishment of a causal relationship.

Significant differences across studies such as varying definitions vitamin D deficiency, lack of seasonal adjustment, and properly defined CV outcomes also hamper our ability to make valid and consistent conclusions. Additional questions arise from use of a single baseline measurement of vitamin D (which may not be an accurate indicator of vitamin D status overall), underestimating or poorly understanding the role of high PTH on CVD, and the confounding use of other disease-modulating drugs such as calcium and statins in both active and placebo groups.

6. Observational data

Several large-scale observational studies have been completed over the past decades.

The NHANES III national cohort registry analyzed 15,088 subjects using a cross-sectional design and found that 25(OH)D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia, and obesity [5, 35].

Similar conclusions were obtained in the prospective analysis of 41,504 patients from The Intermountain Heart Collaborative Study Group, in which serum 25(OH)D levels <30 ng/ml were associated with highly significant increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Serum 25(OH)D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, stroke, and incident death [18].

In the Health Professionals Follow-up Study, men deficient in 25(OH)D (<15 ng/ml) were at increased risk for myocardial infarction compared with those considered to be vitamin D sufficient (>30 ng/ml) RR, 2.09; 95% CI, 1.24–3.54; *P* = 0.02 for trend) even after risk factor adjustment [50]. It could be hypothesized that this increased risk may be explained by a pro-inflammatory state induced by vitamin D deficiency.

In contrast, other prospective studies have had discordant results. The MIDSPAN family study followed 2338 subjects prospectively for a median of 14.4 years. Plasma levels of 25(OH)D

<15 ng/ml were not associated with a risk of cardiovascular diseases, but did relate to all-cause mortality. There was an association between 25(OH)D levels and incidence of type 2 diabetes, but there was no evidence that vitamin D supplementation improved outcomes in these subjects [51]. Follow-up of 3135 patients from the Osteoporotic Fractures in Men (MrOS) study and included in the MrOS Sleep Study failed to establish a significant association between circulating 25(OH) vitamin D and risk of CVD events [52].

Aside from actual CVD events and mortality, other endpoints using surrogate markers have been studied. In a prospective Austrian cohort of 3258 patients referred for coronary angiography and followed up for 7.7 years, low 25(OH)D levels correlated inversely with markers of inflammation (C-reactive protein and interleukin-6), oxidative burden (serum phospholipid and glutathione), and cell adhesion (vascular cell adhesion molecule-1 and intercellular adhesion molecule-1) [6].

A myriad of observational data relates low vitamin D status to an increased prevalence of hypertension. In the Third National Health and Nutrition Examination Survey (NHANES-III), systolic blood pressure (BP) had a significant inverse correlation to 25(OH)D levels. Mean systolic and diastolic BP were 3.0 and 1.6 mm Hg ($P < 0.05$) lower for participants in the highest quintile compared with the lowest, after adjusting for potential confounders. Age-adjusted systolic BP was significantly lower in individuals with vitamin D sufficiency [5].

A prospective analysis among 1211 non-hypertensive US men found an inverse relationship between vitamin D levels and development of hypertension over a 15-year follow-up period. VDR BsmI and FokI polymorphisms were also associated with increased risk of hypertension [53].

Additionally, a more recent study involving 746 patients failed to demonstrate significant relationship between serum vitamin D levels and the severity and extent of coronary artery disease [54].

Aside from the link between developing hypertension and low vitamin D levels, the Framingham Offspring Study suggested that low serum vitamin D levels may augment the risk associated with existing hypertension to dramatically raise the risk of future cardiovascular events [55].

7. Randomized controlled trials

Many randomized interventional studies have focused on improving surrogate endpoints rather than hard CV outcomes. Those focusing primarily on CV outcomes are sparse. Most of the available studies have varied methodologically in defining baseline vitamin D status, dose used, and definition and ascertainment of outcomes.

These flaws are seen in studies that evaluate all-cause mortality and those evaluating CVD outcomes.

A meta-analysis of randomized placebo control trials with varying levels of vitamin D using mortality as a secondary endpoint found a significant 8% reduction in mortality in individuals

receiving vitamin D. This study was limited by the inability to evaluate cause-specific mortality [56].

In another meta-analysis, individuals who took vitamin D at daily doses ranging from 300 to 2000 IU (average dose 528 IU) for an average of 5.7 years had a 7% lower risk of death (from all causes) than those who did not.

The relatively low dose of vitamin D and the short treatment period may have led to an underestimation of its effect. It was noted that the clinical evolution of chronic conditions may take longer to be influenced by vitamin D supplementation; hence, very long-term follow-up would be required to observe the full effect [57].

In the CVD arena, a double-blinded, placebo-controlled, randomized trial in the United Kingdom, including 2686 patients between the ages of 65 and 85, showed no benefits on CVD outcomes in the group that received 100,000 IU of supplemental vitamin D₃ every 4 months (833 IU daily) for 5 years [58]. A systematic review of 14 prospective studies and 18 randomized trials examining supplementation with vitamin D, calcium, or both and subsequent cardiovascular events concluded that vitamin D supplementation might reduce the risk of CVD. Separate analysis of the eight randomized trials found a non-significant reduction in CVD risk with vitamin D supplementation [30].

Results from the Women's Health Initiative (WHI) suggests that postmenopausal women receiving 400 IU/day of oral vitamin D₃ combined with calcium 1000 mg/day had no reduction in their risk of CHD events or stroke. In a subanalysis of the WHI, calcium and vitamin D₃ supplementations were not found to improve blood pressure or coronary artery calcium score. Furthermore, after 7 years of follow-up, there was no decrease in incident hypertension or prevention of the metabolic syndrome, diabetes, or decreases in cerebrovascular risk [59].

8. Hypertension

Contrary to observational evidence, randomized controlled trials have failed to demonstrate significant changes in blood pressure in individuals with prehypertension or stage I hypertension and vitamin D deficiency after supplementation [60–62].

In a trial involving 283 blacks (median age, 51 years) randomized into a four-arm, double-blind trial for 3 months of placebo, 1000, 2000, or 4000 UI/day of vitamin D, no effect was found on diastolic blood pressure, but there was a slight effect in lowering systolic blood pressure [63].

In VitDISH, a double-blind, placebo-controlled randomized trial, including 159 patients, vitamin D supplementation did not improve blood pressure or markers of vascular health in older patients with isolated systolic hypertension [64]. A study including patients with resistant hypertension who received vitamin D₃ supplementation for 6 months also showed similar results. Effects on left ventricular hypertrophy were also negligible, although the short-term follow-up may have been a limitation in assessing this outcome variable [65].

9. Diabetes

A meta-analysis of 11 prospective studies involving 3612 cases and 55,713 non-case participants suggested a strong inverse association between serum 25(OH)D concentration and incidence of type 2 diabetes. Results suggested that optimal levels may reduce the risk of future diabetes by 41% [66].

Other contrasting meta-analysis of 15 trials did not find sufficient evidence to recommend vitamin D supplementation for improving glycemia or insulin resistance in obese patients with diabetes, normal fasting glucose levels, or impaired glucose tolerance [67].

10. Endothelial dysfunction

Vitamin D deficiency has been associated with endothelial dysfunction as measured by flow-mediated dilation (FMD) and reactive hyperemia peripheral arterial tonometry (RH-PAT) [68].

A small study involving 23 asymptomatic subjects demonstrated that subjects with significant vitamin D deficiency had impaired brachial artery FMD, which improved after vitamin D replacement therapy. Recently, a stepwise change in FMD according to vitamin D status was demonstrated and an inverse association between serum 25(OH)D levels and vascular inflammatory markers was observed [33].

A prospective placebo-controlled pilot study evaluated the effects of vitamin D repletion on endothelial function and inflammation in subjects with both vitamin D deficiency and CAD. The study was conducted over a 12-week period in 90 subjects. RH-PAT was used to estimate endothelial function. No significant differences between groups were found in reactive hyperemia index, blood pressure, and levels of hs-CRP, IL-6, IL-12, interferon-gamma (INF-gamma), and CXCL-10 [68].

Similar results were obtained on a larger scale, the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS), that studied 852 men and found no significant relationship between vitamin D levels and endothelium-dependent vasodilation, flow-mediated vasodilation, and reflectance index. However, serum 25(OH)D level showed a negative correlation with SYNTAX score (angiographic grading tool to determine severity of coronary disease) and high-sensitivity C-reactive protein (hsCRP) level. Logistic regression analysis identified 25(OH)D as an independent factor related to high SYNTAX scores. Patients whose vitamin D levels were in the lowest 25(OH)D category (<20 ng/ml) were more often in the high SYNTAX scores group, with their incidence about twofold higher than those in the highest 25(OH)D category (>30 ng/ml) [69].

In cross-sectional analyses, low 25(OH)D (<20 ng/ml) was not associated with stiffer arteries after adjustment for cardiovascular disease risk factors ($P > 0.4$). PTH >65 pg/ml was associated with stiffer arteries after adjustment for cardiovascular disease risk factors, other than systolic blood pressure [70].

Black normotensive teenagers who received 2000 IU/d of vitamin D₃ were compared with those who received 400 IU/d for 16 weeks in an RCT. Teenagers who received 400 IU/d of vitamin D₃ increased their levels of 25(OH)D from 13.6 ± 4.2 to 23.9 ± 7.2 ng/ml and showed no reduction in arterial stiffness. In contrast, teenagers who received 2000 IU/d of vitamin D₃ increased their mean levels of 25(OH)D from 13.2 ± 3.4 to 34.2 ± 12.1 ng/ml and significantly lowered their arterial wall stiffness. This is supported by the observation that serum 25(OH)D levels <30 ng/ml were strongly associated with hypertension, elevated blood glucose, and metabolic syndrome in adolescents [63].

11. Recommended daily allowances and supplementation

The Institute of Medicine (IOM) concluded that there is sufficient evidence to support a role for vitamin D in maintaining skeletal health, but a lack of evidence to support beneficial effects on non-bone-related health outcomes [19]. The Endocrine Society also does not recommend screening for vitamin D deficiency in individuals who are not at risk for vitamin D deficiency [16].

The recommended dietary intake (RDI) of vitamin D is 400 IU/d for 0–12 months, 600 IU/d for ages 1–70 years, as well as for pregnant and lactating women, and 800 IU/d for ages 71 years and older [16, 20, 71, 72]. Measurement of 25(OH)D serum level is the best indicator for overall vitamin D status in the clinical setting, since it has a longer half-life (10–27 days after administration) [21].

Vitamin D can be found in foods such as oily fish (salmon, sardines, and mackerel—400 IU/3.5 oz), cod liver oil (400 IU/tsp), egg yolk (20 IU), fortified milk, orange juice, cereals, cheese, and mushrooms. (100 IU/8oz) [3, 10, 15–17].

In terms of supplements, for every 100 IU of vitamin D ingested, blood 25(OH) level increases by around 1 ng/ml (2.5 nmol/l).

Vitamin D supplementation has dose-dependent side effects, which are fairly rare, such as hypercalcemia, hypercalciuria, renal calcification, and increased bone resorption. Significant increase in triglyceride has also been described [62].

12. Future directions

Several large-scale randomized trials of moderate-to-high dose vitamin D supplementation for cardiovascular disease prevention are currently being conducted. The Vitamin D and Omega-3 Trial (VITAL) is a randomized, double-blind, placebo-controlled clinical trial among more than 20,000 US men and women above age 50, testing 2000 IU/day of oral vitamin D₃ and omega 3 fatty acid supplements in a 2 × 2 factorial design, with cardiovascular disease and cancer as primary prespecified outcomes. Results are expected in 2017 [13]. Another large

randomized trial of CVD prevention, the VIDA trial, is evaluating a higher dose of vitamin D (100,000 IU a month) over 3.3 years and expects results in late 2016 [14].

Evaluating whether common polymorphisms in the VDR receptor modifies the association between 25(OH)D concentrations and individual CVD risk has been proposed. A recent trial evaluating two previously studied VDR polymorphisms failed to reveal a significant role to this end; however, further study may be warranted [73].

13. Conclusions

Vitamin D deficiency has increasingly been implicated in the pathogenesis and complications of cardiovascular disease (CVD). Evidence supporting this relationship and the use of supplementation to prevent or treat CVD is inconclusive and divergent.

Clarification of the clinical application of this relationship through ongoing large randomized trials should have important implications for public health.

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