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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Vitamin D and Cardiovascular Disease

## Controversy Unresolved

Ibhar Al Mheid, MD,[a,b] Arshed A. Quyyumi, MD[a,b]

**ABSTRACT**

Vitamin D deficiency is typically caused by inadequate cutaneous synthesis secondary to decreased exposure to sunlight. Serum levels of 25-hydroxyvitamin D l <20 ng/ml are diagnostic of vitamin D deficiency. Vitamin D has various cardiovascular pleiotropic effects by activating its nuclear receptor in cardiomyocytes and vascular endothelial cells and by regulating the renin-angiotensin-aldosterone system, adiposity, energy expenditure, and pancreatic cell activity. In humans, vitamin D deficiency is associated with the following: vascular dysfunction; arterial stiffening; left ventricular hypertrophy; and worsened metrics of diabetes, hypertension, and hyperlipidemia. It is also linked with worse cardiovascular morbidity and mortality. However, meta-analyses of vitamin D supplementation trials have failed to show clear improvements in blood pressure, insulin sensitivity, or lipid parameters, thus suggesting that the link between vitamin D deficiency and cardiovascular disease may be an epiphenomenon. Ongoing larger randomized trials will clarify whether monitoring and supplementation of vitamin D play roles in cardiovascular protection.
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## PHOTOSYNTHESIS, DIETARY INTAKE, AND METABOLISM OF VITAMIN D

Vitamin D consists of a group of fat-soluble molecules called secosteroids, which are similar to steroids, but with “broken” rings, and that exist in several forms (Figure 1). Its designation as a vitamin is a misnomer given that human skin synthesizes cholecalciferol, or vitamin $D_3$, by the photochemical cleavage of cutaneous 7-dehydrocholesterol, which is most efficient at ultraviolet (UV) wavelengths. The ability to convert 7-dehydrocholesterol into vitamin D in the skin decreases with age and with increasing skin pigmentation or sunscreen use, and it is also affected by seasonal changes, distance from the Equator, and altitude, as well as the degree of ambient pollution and cloud cover. Vitamin $D_3$ is also found naturally in fatty fish, fish oils, and egg yolks and is also industrially manufactured. A second form of vitamin D, ergocalciferol (or vitamin $D_2$) is produced by irradiation of ergosterol, a membrane sterol found in the ergot fungus.

Whether derived from the diet or synthesized cutaneously, vitamins $D_2$ and $D_3$ are biologically inert and require activation by successive hydroxylation steps, first by hepatic mitochondrial and microsomal enzymes, yielding 25-hydroxyvitamin D (25-OH D). This step is loosely regulated, if at all, and excessive intake (i.e., pharmacological preparations) of vitamin $D_2$ or vitamin $D_3$ causes a proportional and unchecked rise in serum 25-OH D levels (1). In contrast, cutaneous synthesis raises serum 25-OH D to a plateau level above which further sun exposure results in spontaneous 25-OH D degradation (2). The second step is catalyzed and tightly regulated by renal 1-α-hydroxylase and yields the hormonal form 1,25-dihydroxyvitamin D (1,25-OH vitamin D or calcitriol). Although 25-OH D may bind and activate the vitamin D receptor (VDR), 1,25-OH vitamin D is by far the most potent vitamin D analogue that mediates most known functions of vitamin D.

Listen to this manuscript’s audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Emory Clinical Cardiovascular Research Institute, Atlanta, Georgia; and the [b]Emory University School of Medicine, Atlanta, Georgia. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**ABBREVIATIONS AND ACRONYMS**

**1,25-OH vitamin D** = 1,25-dihydroxyvitamin D (calcitriol)

**25-OH D** = 25-hydroxyvitamin D

**BP** = blood pressure

**CVD** = cardiovascular disease

**DM** = diabetes mellitus

**LDL** = low-density lipoprotein

**PTH** = parathyroid hormone

**RAAS** = renin-angiotensin-aldosterone system

**UV** = ultraviolet

**VDR** = vitamin D receptor

The clinical properties of vitamin D have been most extensively studied as an antirachitic factor, including its effects on intestinal and renal handling of mineral ions and regulation of osteoblast activity. Vitamin D deficiency causes a net reduction in intestinal absorption and renal reabsorption of calcium, which, in turn, raises parathyroid hormone (PTH) levels and is accompanied by osteocyte activation and accelerated bone demineralization to maintain eucalcemia. More recently, the identification of fibroblast growth factor 23, a secretory protein expressed in osteoblasts and osteocytes, demonstrated a complex feedback loop along a bone-kidney axis, with pivotal roles in phosphate and vitamin D metabolism. Indeed, elevated fibroblast growth factor 23 is associated with vascular dysfunction, ventricular hypertrophy, and incident CVD and is believed to represent the other side of the same coin as vitamin D deficiency.

Following chronic and severe vitamin D deficiency, frank hypocalcemia ensues, but patients rarely present with the acute symptoms (e.g., tingling or tetany) that are classically observed following surgical resection of parathyroid glands, as this usually develops over an extended period. Rather, isolated vitamin D deficiency commonly manifests as a constellation of vague, local, or diffuse musculoskeletal aches and pains, accompanied by low serum calcium and phosphorus and elevated alkaline phosphatase and PTH levels. The diagnosis is confirmed by low serum 25-OH D levels.

## VITAMIN D STATUS: DEFICIENCY VERSUS INSUFFICIENCY

The most suitable metabolite for assessment of vitamin D status is serum 25-OH D, given its long half-life (weeks vs. hours for 1,25-OH vitamin D) and its reflection of both dietary intake and cutaneous synthesis. Serum 25-OH D levels >12 ng/ml are generally required to maintain 1,25-OH vitamin D within its narrow physiological range and to suppress PTH, and most current guidelines agree that levels <20 ng/ml are inadequate for maintaining bone health and are therefore diagnostic of vitamin D deficiency. However, a consensus is yet to be reached regarding an optimal level for maintaining nonskeletal health and reaping possible cardiovascular and cancer preventive benefits. Although some consider levels >20 ng/ml to be sufficient, others categorize levels between 20 and 29 ng/ml as vitamin D insufficiency and/or even diagnose vitamin D deficiency at any level <30 ng/ml.

## VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASES: EPIDEMIOLOGY

Population studies demonstrate an unequivocal association between vitamin D deficiency and the prevalence of many chronic morbid conditions, including cardiovascular disease (CVD) and its risk factors. Notable examples include the third National Health and Nutrition Examination, as well as large European cohorts that showed a cross-sectional inverse relationship between 25-OH D levels and the prevalence of hypertension, insulin resistance, frank type 2 diabetes mellitus (DM), and dyslipidemia, despite careful adjustment for potential confounders. Moreover, vitamin D deficiency has been implicated as an independent risk factor for the prospective development of CVD or its risk factors, as well as incident all-cause and CVD morbidity and mortality in several cohort studies that followed hundreds of thousands of subjects for nearly 2 decades (3).

## VITAMIN D AND CVD: MECHANISMS

Epidemiological studies linking vitamin D status and CVD risk were paralleled by experimental studies elucidating mechanisms by which vitamin D deficiency may confer increased CVD risk (**Central Illustration**). Both the VDR and 1-α-hydroxylase, which converts vitamin D into the hormonal 1,25-OH vitamin D form, are found in cardiovascular tissues, and experimental models lacking VDR highlight its tissue-specific activity. For example, VDR knockout results in increased ventricular mass and atrial natriuretic peptide levels and dyshomeostasis of cardiac metalloproteinases and fibroblasts, thereby promoting formation of a fibrotic extracellular matrix and leading to ventricular dilation and impaired electromechanical coupling (4,5).

Endothelial cells also express VDR, which is up-regulated under stress; VDR activation modulates response elements in the vascular endothelial growth factor (VEGF) promoter and affects calcium influx across the cell membrane, as well as endothelium-dependent vascular smooth muscle contractions and vascular tone in hypertensive models (6). Importantly, the role of 1,25-OH vitamin D as a negative regulator of the renin-angiotensin-aldosterone system (RAAS) was demonstrated in VDR knockout models (7). Other potential consequences of impaired vitamin D metabolism on human vasculature include exacerbation of atherogenesis and acceleration of arterial calcification. For example, the established