

New Insights About Vitamin D and Cardiovascular Disease

A Narrative Review

Cora McGreevy, MB, BCh, BAO, and David Williams, MB, BAO, BCh, PhD

The worsening worldwide trend toward nutritional insufficiency and the emerging knowledge of the nonhormonal actions of vitamin D and its metabolites have increased interest in the synthesis, metabolism, and action of vitamin D. Vitamin D deficiency has been linked with hypertension, myocardial infarction, and stroke, as well as other cardiovascular-related diseases, such as diabetes, congestive heart failure, peripheral vascular disease, atherosclerosis, and endothelial dysfunction.

This review discusses the physiology and definition of vitamin D deficiency, evaluates the worldwide prevalence of vitamin D defi-

ciency, and discusses recent evidence for the association between hypovitaminosis D and cardiovascular disease. Few randomized, controlled trials have evaluated the effect of vitamin D replacement on cardiovascular outcomes, and the results have been inconclusive or contradictory. Carefully designed randomized, controlled trials are essential to evaluate the role of vitamin D supplementation in reducing cardiovascular disease.

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For author affiliations, see end of text.

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Vitamin D is a collection of fat-soluble steroids, the 2 dominant forms of which are vitamins D₂ (ergocalciferol) and D₃ (cholecalciferol). Vitamin D₂ is manufactured by invertebrates and plants after exposure to ultraviolet radiation. Vitamin D₃ is naturally present in a small range of foods and is also made endogenously in the skin when 7-dehydrocholesterol is exposed to ultraviolet B light between wavelengths of 270 to 300 nm. Apart from exposure to sunlight, vitamin D₃ can also be obtained by dietary intake or pharmaceutical supplementation. Dietary vitamin D typically comprises only 10% to 20% of circulating levels of vitamin D (1).

Exogenously acquired vitamin D is biologically inactive and requires 2 hydroxylation reactions in the body for activation (2). The first occurs in the liver, where 25-hydroxyvitamin D ([OH]D) is produced (Figure); this is the major circulating form of vitamin D in the blood. The second takes place in the kidneys, where it is converted to 1,25-(OH)D. Because of its long half-life, 25-(OH)D measurements are clinically useful for assessing vitamin D status in patients (3).

In conjunction with parathyroid hormone, vitamin D is responsible for the regulation of calcium and phosphate homeostasis. Vitamin D deficiency leads to calcium deficit, myopathy, and osteomalacia in adults and rickets in children. Increasing evidence also indicates that vitamin D controls the secretion of parathyroid hormone, plays a role in the renin-angiotensin-aldosterone system, regulates the immune system, and may directly affect cardiac muscle (4).

Here, we discuss the worldwide prevalence of vitamin D deficiency and elaborate on recent evidence for the association between hypovitaminosis D and cardiovascular disease.

METHODS

Studies were identified by searching PubMed for English-language articles from 1985 through August 2011 by using the Medical Subject Heading terms and keywords *vitamin D*, *stroke*, and *cardiovascular disease*, alone or in combination. The reference lists of published reports were also searched. Both authors critically reviewed the design, population characteristics, and findings of the selected studies. For prevalence of vitamin D deficiency, we reviewed community-based studies that used standardized techniques to assess serum 25-(OH)D level. For data on risk factors and associations, we considered systematic reviews and original studies of any design in humans.

DEFINING VITAMIN D DEFICIENCY

Considerable controversy surrounds the definition of vitamin D deficiency. Current International Osteoporosis Foundation guidelines (5) define vitamin D insufficiency as 25-(OH)D levels less than 50 nmol/L and deficiency as levels less than 25 nmol/L.

No universal consensus has been reached on which level of serum 25-(OH)D reflects optimum vitamin D status. A recent position statement from the International Osteoporosis Foundation (5) recommended a target level of 75 nmol/L, which is associated with maximal suppression of parathyroid hormone. However, a report from the Institute of Medicine (6) that revised the dietary reference intakes for vitamin D and calcium for the United States and Canada concluded that a serum 25-(OH)D level of 50 nmol/L was sufficient to ensure bone health. The Institute of Medicine report does not support the recommendation that all adults should have vitamin D levels greater than 75 nmol/L and concludes that current evidence does not support any nonskeletal benefits for vitamin

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Vitamin D deficiency is prevalent worldwide, particularly in Northern Europe, Africa, and the Middle East.

Experimental data have shown that vitamin D deficiency may be linked with hypertension, myocardial infarction, and stroke.

Vitamin D deficiency has also been implicated in the development of atherosclerosis and endothelial dysfunction, which may be mediated through the action of osteoprotegerin, a protein component of the arterial wall.

A few randomized, controlled trials have evaluated the effect of vitamin D replacement on cardiovascular outcome, but the results have been inconclusive or contradictory.

Until further robust research is completed, vitamin D cannot be recommended as a treatment for cardiovascular disease.

D or calcium. The report also notes that higher levels of both may lead to adverse health outcomes, including kidney stones and renal impairment (6).

WORLDWIDE PREVALENCE OF VITAMIN D DEFICIENCY

Vitamin D deficiency is prevalent worldwide, particularly at northern latitudes, because of the low levels of ultraviolet B light in winter at these latitudes. Europe's largely northern latitude, coupled with the relatively short (4- to 6-week) half-life of 25-(OH)D (7) result in substantial decreases in levels in winter and early spring. A 2007 British study (8) found that almost one half of the 7437 participants (all aged 45 years) had 25-(OH)D levels less than 40 nmol/L during the winter and spring. A Europe-wide review (9) reported a prevalence of vitamin D deficiency (serum 25-[OH]D levels <25 nmol/L) in 2% to 30% of adults but found that it increased to 75% or more in institutionalized older persons.

Several European studies (10–12) have shown variation in vitamin D status within countries, which could be explained by reduced sunlight exposure, low dietary intake of vitamin D–rich foods, low physical health status, limited fortification of food with vitamin D, or differences in biochemical assays used to measure vitamin D levels (13). In the United States, several recent studies (14, 15) have described a high prevalence of 25-(OH)D deficiency (defined as levels <50 nmol/L) and insufficiency (levels between 50 and 75 nmol/L) in the general population, with higher rates in older persons and racial and ethnic minorities.

A 2009 study of global vitamin D status (1) found that although the exact definitions of vitamin D insufficiency and deficiency and the assay techniques for 25-

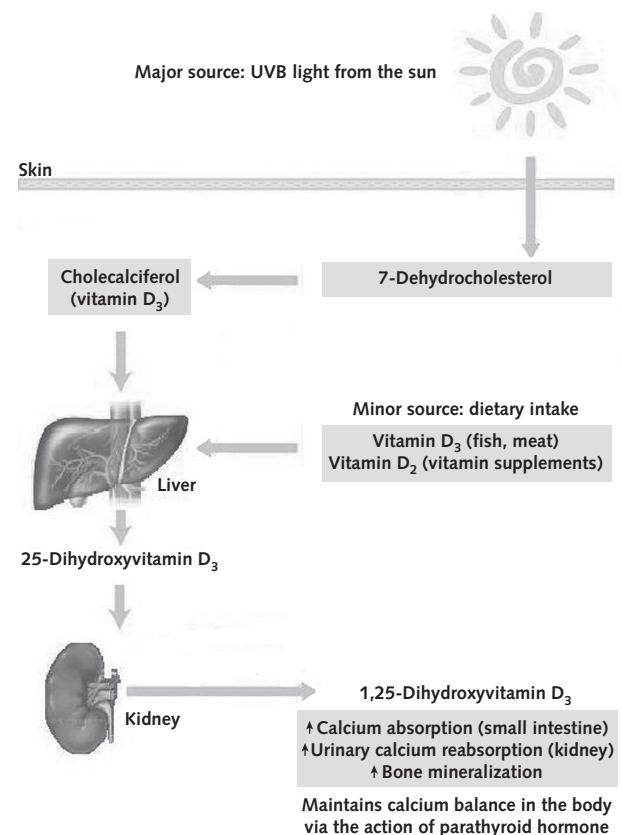
(OH)D all vary, serum levels below 75 nmol/L prevailed in every region studied. Levels below 75 nmol/L ranged from 42% in postmenopausal Brazilian women to 92% in postmenopausal women in South Korea (16, 17). Very deficient levels (≤ 25 nmol/L) are most prevalent in South Asia and the Middle East (1, 18), possibly because of cultural dress that limits sun exposure and extended periods of breastfeeding without vitamin D supplementation.

RISK FACTORS FOR VITAMIN D DEFICIENCY

A recent review (1) examined the effects of various factors on vitamin D status, including age, sex, ethnicity, location, nutritional status, housing conditions, and physical fitness. The Table lists risk factors for vitamin D deficiency.

Groups that seem particularly prone to severe deficiency worldwide include elderly persons, women, institutionalized persons, and children in susceptible geographic areas who are exclusively breastfed (1). Recurrent predictors of hypovitaminosis D throughout the Middle East are older age, female sex, multiple births, conservative dress, lower-income group, and urban living (1). Vitamin D de-

Figure. Process of vitamin D activation in the body.



UV = ultraviolet.

Table. Risk Factors for Vitamin D Deficiency

Advanced age
Institutionalized or home-bound
Use of sunscreen with sun protection factor >15
Heavily pigmented skin
Air pollution
Prolonged, exclusive breastfeeding
Northern latitudes
Smoking
Obesity
Malabsorption syndromes
Renal or liver disease
Antiepileptic or HIV medications

iciency is also prevalent in the Oceanic region, both in nursing home residents and children of immigrant parents (19–21).

After similar exposure to ultraviolet B sunlight, a person aged 70 years produces 75% less vitamin D₃ than a person aged 20 years (22). Aging has been shown to halve the capacity of the skin to produce 7-dehydrocholesterol because of structural changes that occur in the dermis, including shrinkage and decreased elasticity of the papillary dermis and a decrease in superficial capillary loops on the papillary body beneath the dermis (23).

Other risk factors for vitamin D deficiency include the use of sunscreen with a sun protection factor of 15 or more, which has been shown to prevent approximately 99% of dermal vitamin D production (24). Persons with a high body mass index are also susceptible to low vitamin D levels because of the decreased bioavailability of vitamin D that is stored in excess adipose tissue (25).

Differing food supplementation policies worldwide may also contribute to the variations in worldwide vitamin D levels. For example, the United States and Canada fortify milk and other dairy products and have a formal supplementation program for infants that recommends 400 IU (10 mcg) all year and 800 IU (20 mcg) in winter for high-risk infants (6). Both the United States and Canada mandate fortification of infant formula with vitamin D (6). In Australia, margarine, some milk, and milk products are currently fortified with vitamin D. In New Zealand, fortification of margarine is not mandatory, but voluntary fortification of margarine, fats, and dairy food items has been permitted since 1996 (26).

Drug therapy, including long-term treatment with such antiepileptic drugs as phenytoin, carbamazepine, and phenobarbital, can lead to osteomalacia due to induction of 1,25-(OH)D catabolism (27). Nonnucleoside reverse transcriptase inhibitors, used to treat HIV infection, have also been implicated as a risk factor for vitamin D deficiency because they seem to increase the catabolism of 25-(OH)D through induction of the CYP450 system (28).

VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Rates of vitamin D deficiency and cardiovascular disease increase with distance from the equator, with higher rates of ischemic heart disease noted in countries with lower levels of ultraviolet B exposure (29). Vitamin D levels have been shown to be seasonal, with higher levels in summer (30), and the rate of ischemic heart disease can display similar seasonal patterns (31). Epidemiologic studies (32, 33) have reported a trend toward higher prevalence of ischemic heart disease and hypertension with increasing distance from the equator, and these higher rates are attributed to the higher rates of vitamin D deficiency in regions with less exposure to sunlight.

Clinical studies support a role for vitamin D in maintaining cardiovascular health through both the direct action of the vitamin on cardiomyocytes and the indirect actions on circulating hormone and calcium levels (34). The vitamin D receptor is found in several tissue types throughout the body, such as lymphocytes, colonic cells, hepatocytes, and cardiac myocytes (4, 35). Previous studies (36–39) have demonstrated associations between low vitamin D levels and increased plasma renin activity, coronary artery calcification, blood pressure, and cardiovascular disease. Wang and colleagues' recent meta-analysis (40) of 17 prospective cohort studies and randomized trials found that moderate to high doses of vitamin D supplements may reduce the risk for cardiovascular disease, with benefits mainly seen in patients receiving dialysis. However, only 1 study involving the general population (41) showed consistent reductions in cardiovascular disease after vitamin D supplementation. A systematic review of 13 observational studies examining the association of vitamin D status with cardiometabolic outcomes (type 2 diabetes, hypertension, or cardiovascular disease) concluded that the association is uncertain and the results were hampered by the heterogeneity of studies (42). Of the 13 trials, 4 (43–46) found that vitamin D supplementation had no effect on cardiovascular outcomes. A recent meta-analysis of 51 trials examining vitamin D and cardiovascular outcomes (47) similarly found that trial data could not demonstrate a statistically significant reduction in mortality or cardiovascular risk in relation to vitamin D status.

Wang and colleagues (48) studied more than 1700 Framingham Offspring Study participants (mean age, 59 years) with no previous cardiovascular disease and measured their 25-(OH)D levels. Participants with levels less than 37 nmol/L had a hazard ratio for incident cardiovascular events of 1.62 (95% CI, 1.11 to 2.36; $P = 0.01$) compared with those with higher 25-(OH)D levels (48). The investigators concluded that low vitamin D levels are linked with incident cardiovascular disease and proposed several potential mechanisms to explain their findings, including the role of 1,25-(OH)D in the renin–angiotensin axis by direct inhibition of renin gene expression and the

potential role of vitamin D in vascular function, including inflammation, smooth muscle growth, and thrombosis. Because positive findings were found only in patients with hypertension, the investigators proposed that hypertension could enhance the adverse effects of hypovitaminosis D on the cardiovascular system because of their joint roles in vascular remodeling (48).

A prospective case–control study of more than 18 000 men (49) found a statistically significant correlation between low 25-(OH)D levels and an increased risk for myocardial infarction, even after adjustment for traditional cardiovascular risk factors. This study confirmed the findings of other, smaller studies (50–53) that looked at the association between vitamin D status and cardiovascular outcomes.

VITAMIN D DEFICIENCY AND ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is characterized by a change in the properties of the endothelium toward decreased vasodilation and the creation of a proinflammatory and prothrombotic state (54). It plays an important role in the pathogenesis of atherosclerosis; in vivo evidence indicates that it contributes to plaque initiation and progression (54). Endothelial dysfunction is also associated with increasing arterial stiffness (55). Previous studies (56, 57) that examined the association between hypovitaminosis D and endothelial dysfunction found that supplementation of patients with vitamin D deficiency led to a statistically significant improvement in arterial stiffness compared with placebo.

A recently published study (58) demonstrated that vitamin D supplementation decreased the mean pulse wave velocity from 5.41 m/s (SD, 0.73) at baseline to 5.33 m/s (SD, 0.79) ($P = 0.031$), thus reducing arterial stiffness. Vitamin D deficiency is also associated with higher circulating concentrations of matrix metalloproteinase-9, which controls vascular wall remodeling. Circulating plasma matrix metalloproteinase-9 concentrations increase in patients with cardiovascular disease (59, 60). Vitamin D supplementation has been shown to decrease serum matrix metalloproteinase-9 concentrations by 68% (61).

VITAMIN D AND ATHEROSCLEROSIS

Previous studies (62–64) have revealed an inverse association between 25-(OH)D levels and subclinical atherosclerosis, as measured by carotid intima–media thickness and computed tomography–derived calcified atherosclerotic plaque.

Several bone proteins, including osteopontin, osteocalcin, matrix gla proteins, and osteoprotegerin, have also been found to be components of the arterial wall. More recently, osteoprotegerin has attracted the most interest for its role in vascular calcification. Osteoprotegerin inhibits

the binding of the receptor activator of nuclear factor- κ B ligand to the receptor activator of nuclear factor- κ B receptor, thereby blocking intercommunication between osteoblast cells and osteoclast precursors. This action prevents the differentiation of the osteoclast precursor into a mature osteoclast (65).

Clinical studies (66, 67) suggest that serum osteoprotegerin levels may increase with calcification of vessels, ischemic heart disease, or stroke. This has led to increased interest in osteoprotegerin as a potential biomarker of vascular disease. Although animal models suggest a protective role for osteoprotegerin, the exact role of elevated osteoprotegerin levels as a marker of vascular damage has not been fully explored.

The National Health and Nutrition Examination Survey (68) examined the link between vitamin D and atherosclerosis and reported that low serum 25-(OH)D levels were associated with higher levels of peripheral arterial disease. Hypovitaminosis D is also associated with decreased levels of high-density lipoprotein cholesterol–associated apolipoprotein A-I (69), and vitamin D supplementation has been shown to have a beneficial effect on the elastic properties of the arterial wall in a randomized, placebo-controlled intervention study in postmenopausal women (70).

VITAMIN D AND HYPERTENSION

Several observational studies (38, 71) have suggested links between low 25-(OH)D levels and a subsequent higher risk for hypertension. However, randomized, controlled trials of vitamin D that examined supplementation and blood pressure (72, 73) have shown inconsistent results, possibly because of differences in sample sizes, vitamin D preparations used, and study duration. The proposed mechanism for the link between vitamin D and high blood pressure involves the role of vitamin D in the inhibition of the renin–angiotensin–aldosterone system. These data are mainly derived from in vitro and animal studies (36, 74).

Increasing evidence indicates that secondary hyperparathyroidism and hypocalcemia, which are commonly seen in patients with hypovitaminosis D, may be an alternative explanation for the association between vitamin D deficiency and hypertension. Previous observational studies (75, 76) have shown an association between parathyroid hormone and hypertension. The pathogenesis for this correlation is unclear, but a recent review (77) suggests that parathyroid hormone may increase arterial stiffness and induce atherosclerotic changes by acting on smooth-muscle cells in the endothelium. One double-blind, randomized, controlled trial involving 148 women (78) found that supplementation with a combination of vitamin D and calcium resulted in a significant increase in serum 25-(OH)D levels of 72% ($P < 0.01$) and a decrease in serum parathyroid hormone levels of 17% ($P = 0.04$), along with signif-

icant decreases in systolic blood pressure and heart rate, compared with calcium supplementation alone.

CONFOUNDING EVIDENCE FOR LINKS BETWEEN VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Many observational studies have reported inverse relationships between serum 25-(OH)D levels and the risk for a wide range of conditions, including vascular disease (56), autoimmune disease (22), type 2 diabetes mellitus (53), obesity (25), and (more recently) cognitive impairment (79). A recent study (79) has demonstrated that the Mini Mental State Examination scores of patients with lower baseline levels of serum 25-(OH)D (<25 nmol/L) decreased by an additional 0.3 point per year compared with those with sufficient levels (>75 nmol/L) at baseline. Of note, other markers of poor health status, such as impaired mobility, depressive symptoms, and lower total energy intake, were more commonly seen in the vitamin D–deficient group, which suggests that deficiency may be a marker of poorer health status in general (79).

In a recent editorial, Grey and Bolland (80) commented that “it seems intuitively unlikely that a single hormone could play a substantial role in preventing or ameliorating the diverse range of diseases that have been linked to low levels of vitamin D.” Several possible scenarios, including the influence of confounders, may explain these associations. For example, vitamin D deficiency may only act as a surrogate marker for poor health status because it reflects an inability to get outdoors for ultraviolet B exposure due to increased body mass index, multiple comorbid conditions, or poor exercise tolerance.

CONCLUSION

Emerging evidence indicates that vitamin D deficiency, cardiovascular disease, and endothelial dysfunction are linked by biological associations. However, no clear evidence indicates that vitamin D supplementation has a role to play in the prevention of cardiovascular disease, outside of clinical studies. Despite some concerns that vitamin D may merely be a surrogate marker for poor health status, further (preferably large) studies are needed to evaluate the efficacy of vitamin D supplementation. These trials should aim to test the hypotheses generated by multiple observational studies and provide evidence on whether vitamin D supplementation may play a role in cardiovascular protection.

From Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland.

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Requests for Single Reprints: Cora McGreevy, MB, BCh, BAO, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland; e-mail, coramcgreevy@rcsi.ie.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. McGreevy and Williams: Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland.

Author Contributions: Conception and design: C. McGreevy, D. Williams.
Analysis and interpretation of the data: D. Williams.

Drafting of the article: C. McGreevy, D. Williams.

Critical revision of the article for important intellectual content: C. McGreevy, D. Williams.

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