Vitamin D and Calcium Supplements: Helpful, Harmful, or Neutral for Cardiovascular Risk?

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ABSTRACT: Vitamin D has traditionally been known as the "bone vitamin". However, a large body of observational data has also linked low concentrations of serum 25-hydroxyvitamin D (25[OH]D), the primary storage form of vitamin D, to an increased risk of incident cardiovascular disease (CVD) and mortality, garnering public excitement about the purported nonskeletal benefits of vitamin D. Despite this, more recent meta-analyses and randomized clinical trials have failed to find a beneficial effect of vitamin D supplements on CVD and cancer outcomes. These findings, along with the lack of consensus on optimal serum 25(OH)D concentrations, have dampened some of the initial enthusiasm for vitamin D supplements. Residual confounding or reverse causation may explain some of the discrepancy between the observational and trial results. At this time, vitamin D supplements should not be prescribed for the primary purpose of CVD prevention. Adding to this complexity is the fact that many adults take vitamin D and calcium supplements together for bone health, and there is some concern (albeit inconclusive) related to calcium use and increased CVD risk. In this light, it may be best to achieve the recommended daily allowances of calcium intake through food and reserve calcium supplementation only for those at risk for calcium intake deficiency, with the smallest dosage needed after dietary modifications have been exhausted. In this review, we discuss vitamin D and calcium supplementation and how they may affect cardiovascular health.

INTRODUCTION

Vitamin D has been known as the "bone vitamin" ever since its discovery as the unknown factor in cod liver oil that cures rickets and osteomalacia. Through the past century, this label was cemented through numerous discoveries that further linked vitamin D to bone physiology, pathways of calcium homeostasis, and sunlight exposure (the other identified cure for rickets).[1] However, newer discoveries suggest a broader role for vitamin D.[2] Activated vitamin D receptors, which act as transcription factors, could influence the expression of hundreds of genes, including genes crucial in cell-cycle regulation, differentiation, and cancer pathology.[2] Most importantly, low serum concentrations of 25-hydroxyvitamin D (25[OH]D), the primary storage form of vitamin D, have been associated with increased morbidity and mortality from an expansive list of diseases, including the two leading causes of death in the United States—cardiovascular disease (CVD) and cancer. This has sparked much public enthusiasm for the potentially protective effects of supplementation.[3]

However, the pendulum may be swinging the other way, as more recent meta-analyses and randomized clinical trials have failed to find a beneficial effect of vitamin D supplements on CVD and cancer outcomes.[4-7] These findings, along with the lack of consensus on optimal serum concentrations,[8,9] have dampened some of the initial enthusiasm of vitamin D as a potential "do-it-all" vitamin. To add to this conundrum, many adults take calcium supplements along with vitamin D, and there are some concerns (although inconclusive) regarding calcium supplements and increased CVD risk.[10-12]

In this review, we will discuss vitamin D and calcium supplementation and how they may affect cardiovascular health.

METABOLISM AND MEASUREMENT

Vitamin D is the collective of two physiologically inactive precursors to the active 1,25-dihydroxycalciferol ($1,25(OH)_2D$ or calcitriol) steroid hormone: vitamin D2 (ergocalciferol), which is obtained from plants, and vitamin D3 (cholecalciferol), which is produced after the skin is exposed to UVB radiation.[13] While both D2 and D3 can be obtained as dietary supplements, the classification of "vitamin" could be considered a misnomer since the body can produce its required vitamin D3 in the skin when enough sunlight is available. However, this endogenous production is often insufficient, and augmentation with dietary intake is required. Since few foods are naturally rich in vitamin D, and farmed varieties contain lower concentrations, artificially fortified foods and supplements are appealing.[13]

Vitamins D2 and D3 are hydroxylated in the liver to form 25(OH)D, which is the primary circulating form of vitamin D. 25(OH)D reflects both endogenous and exogenous sources and is considered the best marker for assessing vitamin D status. To generate the physiologically active form of vitamin D, 25(OH)D

undergoes hydroxylation by the 1α-hydroxylase enzyme in the kidneys to produce 1,25(OH)$_2$D (calcitriol). However, identification of extra-renal forms of 1α-hydroxylase and the presence of vitamin D receptors in nearly all nonskeletal tissue—including cardiomyocytes, arterial wall cells, and immune cells—have led to speculations of autocrine and paracrine functions for vitamin D in many organ systems, including the cardiovascular system.[2] Currently, circulating 25(OH)D concentrations continue to be the marker of choice for assessing auto/paracrine vitamin D activity, even in the study of nonskeletal effects of vitamin D.[14]

Assays of calcitriol concentration are not useful in assessment of vitamin D reserves since serum concentration of calcitriol is considerably lower than 25(OH)D and tightly regulated by the parathyroid hormone, such that it could be normal or even elevated in vitamin D-deficient individuals. Conversely, this assay is used in the differential diagnosis of hypercalcemia, parathyroid disorders, granulomatous diseases (which are associated with unregulated activation of vitamin D, causing toxicity),[15] and when pathologic inability to activate 25(OH)D into calcitriol is suspected as the cause of phenotypic vitamin D deficiency despite adequate reserves (eg, which could occur in individuals with chronic kidney disease).[16]

ADEQUATE LEVELS OF VITAMIN D INTAKE

Cutaneous vitamin D production depends on many geographical factors such as latitude, season of the year, ambient pollution, and weather conditions as well as individual factors such as age, time spent outdoors, choice of clothing, skin pigmentation, and sunscreen use.[13] Most scientific research sidesteps this quantification problem by studying serum 25(OH)D. As a downfall, few studies relate dietary vitamin D directly to health measures, and most organizations base their guidelines on establishing a sufficient serum 25(OH)D concentration and define adequate dietary intake as the amount of vitamin D intake that would maintain such serum levels with minimum sun exposure.[8]

To our knowledge, all relevant guidelines concede that evidence for nonskeletal benefits of vitamin D are lacking and instead use optimal bone health as the benchmark. Most guidelines agree that serum 25(OH)D concentration < 12 ng/mL (multiply by 2.496 for nmol/L) constitutes frank deficiency and 12 to 20 ng/mL is typically insufficient for optimal bone health. However, establishing an optimal serum 25(OH)D concentration has proven more controversial. Among the two most cited guidelines, the Institute of Medicine (IOM) guidelines chose 20 ng/mL as sufficient for 97.5% of the population and argue that higher levels do not confer additional benefits,[8] while the Endocrine Society classified > 30 ng/mL as satisfactory and 20 to 30 ng/mL as insufficient.[9]

To link these serum concentrations to dietary vitamin D intake, the IOM used a nonlinear dose-response relationship based on results of studies from Antarctica and Northern Europe in winter. To err on the side of caution, the IOM then rounded up the calculated results and recommended a daily intake of 600 IU for individuals between ages 1 and 70 years old and 800 IU for individuals older than 71 years.[8] A notable subtlety of this indirect process is that these values are not calculated so that 97.5% of the population achieves serum 25(OH)D concentrations of 20 ng/mL; rather, they are expected to result in a mean concentration of 20 ng/mL, which is meant to suffice for 97.5% of the population. Hence, it would be expected that significantly more than 2.5% of adherent adults would be classified as deficient (< 20 ng/mL) when tested. Discussions about this subtlety and its appropriateness are other points of controversy.

VITAMIN D AND CVD IN OBSERVATIONAL STUDIES

The earliest reports of an association between vitamin D and CVD were ecologic studies in which mortality from CVD was found to differ based on an individual's distance from the equator and seasonal changes, such that less sunshine exposure was associated with higher cardiovascular risk.[17,18] In NHANES III, participants with the lowest quartile of 25(OH)D (serum concentrations < 17.8 ng/mL) were found to have 26% higher all-cause mortality compared to the highest quartile after adjustment for other risk factors (RR 1.26; 95% CI, 1.08-1.46).[19] Subsequent prospective community-based cohort studies have linked low serum 25(OH)D concentrations to increased risks of incident coronary heart disease (CHD), stroke, heart failure, and total CVD. [20-24]

In a large meta-analysis of cohort studies from Europe and the United States, concentrations of serum 25(OH)D in populations experiencing all-cause mortality, cardiovascular mortality, and cancer mortality all showed an inverse dose-response relationship (~50% increase in cardiovascular death in the lowest quintile compared to the highest quintile).[25] Several other studies and meta-analyses have found both low and high serum 25(OH)D to confer increased risk.[19,24,26,27]

Of course, observational studies are innately limited in establishing causality and cannot predict the effects of intervention. In the case of vitamin D, there were at least two other possible explanations for these observations (Figure 1):

Confounding: Many risk factors for CVD and poor health outcomes are also risk factors for vitamin D deficiency and poor vitamin D bioavailability. For example, vitamin D is fat soluble and is sequestered in the adipose tissue of obese individuals, leading to lower available levels in the serum.[28] Obesity can

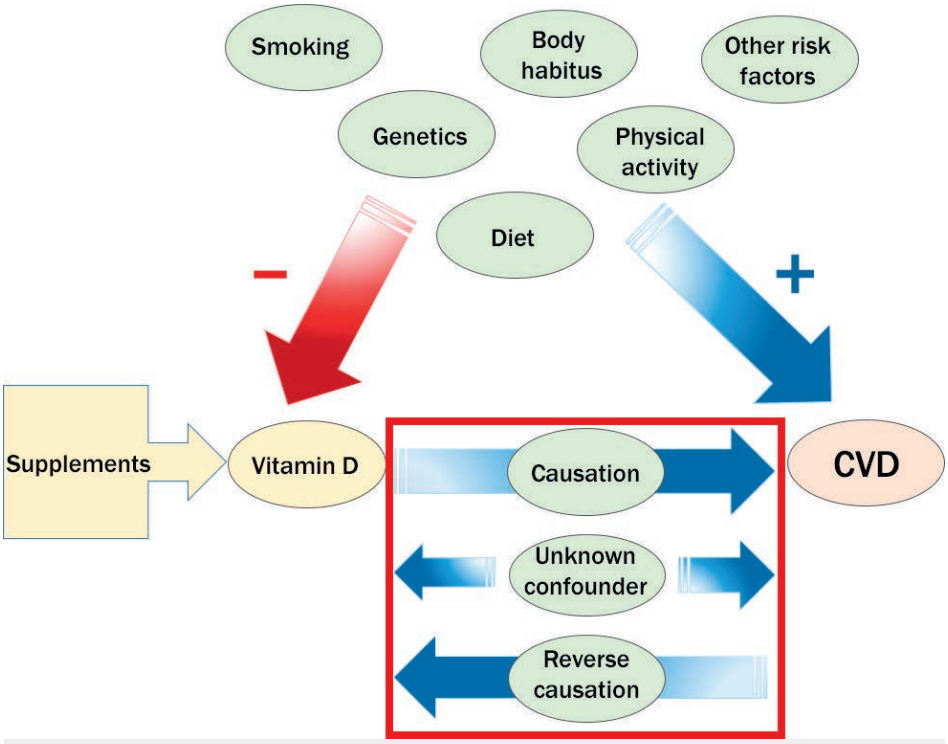

Figure 1.
There are many possible pathways that could explain how low 25(OH)D and poor cardiovascular outcomes can be correlated, but only a causal relationship would mean that vitamin D supplementation can improve outcomes for cardiovascular disease (CVD). Unaccounted confounding and reverse causation can also result in associations in observational studies, but this would mean that improving vitamin D status through supplementation does not improve cardiovascular health. These correlative relationships aren't necessarily mutually exclusive, and even all can be present at the same time, making them hard to control for in observational settings and reinforcing the need for randomized controlled trials to establish causal effect.

also indirectly contribute to low serum 25(OH)D because heavyset individuals may be less likely to participate in outdoor physical activities. Similarly, smoking has been shown to correlate with vitamin D status and calcium metabolism independent of lifestyle factors such as age, sex, dietary intake, and physical exercise.[29] Hence, confounding and effect modification by known and unknown risk factors could alter both vitamin D status and health outcomes, resulting in a misleading association.

Reverse causation: Instead of low vitamin D being the driving factor for poor health, unhealthiness could cause a decrease in vitamin D reserves by affecting the diet, time spent outdoors, and the ability to absorb and metabolize nutrients. This culminates in a subpopulation that has both low 25(OH)D concentrations and an increased risk of disease.

EFFECTS OF VITAMIN D SUPPLEMENTATION ON CARDIOVASCULAR DISEASE

Until recently, randomized clinical trials (RCTs) studying vitamin D had focused on bone health as the primary outcome, and their findings regarding CVD were mixed and unconvincing. In the past few years, data from two completed major trials have provided high-quality evidence, and another large RCT in Australia (D-Health) is still ongoing.[4,5,30]

The Vitamin D Assessment (ViDA) study was a double-blind placebo-controlled trial in New Zealand,[5] where more than 5,000 community residents aged 50 to 84 years were given placebo or vitamin D3, with an initial dose of 200,000 IU followed by monthly doses of 100,000 IU for a median of 3.3 years. Median deseasonalized 25(OH)D concentration at baseline was 26.5 ng/mL, and 1,270 participants (24.9%) were deficient in vitamin D. Compared to placebo, the treatment regimen increased serum 25(OH)D by more than 20 ng/mL but had a nonsignificant hazard ratio of 1.02 (95% CI, 0.87-1.20) for cardiovascular events. Similar results were seen for participants with baseline 25(OH)D deficiency.[5] The high-dose monthly supplementation regimen used in that study may also affect its generalizability since daily supplementation at doses less than 2,000 IU per day is more common in the general public, and it is unclear if pharmacokinetic differences between these dosing methods could affect outcomes.

The Vitamin D and Omega-3 Trial (VITAL) is the most definitive RCT to date to investigate the effects of vitamin D supplementation on cardiovascular events and cancer in the general population.[4] VITAL was a double-blind placebo-controlled trial that recruited healthy participants throughout the United States with intentional oversampling of African Americans. A total of 25,871 participants (5,106 African Americans) including men aged ≥ 50 years and women aged ≥ 55 years were randomized to receive either a 2,000 IU daily dose of vitamin D or a placebo, and primary CVD end points of myocardial infarction (MI), stroke, and death from cardiovascular causes were tracked for a median of 5.3 years. Baseline serum 25(OH)D concentrations were measured in 15,787 participants

and demonstrated a 12.7% prevalence of deficiency (25[OH]D < 20 ng/mL). More than 40% of the participants personally used vitamin D supplements, but supplementation with > 800 IU/day was an exclusion criterion. VITAL found no significant benefits in CVD outcomes, with a statistically insignificant hazard ratio of 0.97 (95% CI, 0.85-1.12) for cardiovascular events in the treatment group compared to the placebo. These findings were independent of race. Even for the subgroups found to be deficient at baseline—those with serum 25(OH)D < 20 ng/mL or below the median < 31 ng/mL—no cardioprotective effects with supplementation were noted.[4] These results were in line with and complementary to results from the Women's Health Initiative Calcium and Vitamin D Trial (WHI CaD), which found no cardiovascular benefits with 400 IU daily vitamin D supplementation.[31] A recent meta-analysis of vitamin D RCTs confirmed the consistency of these findings across different trials and the lack of benefit from vitamin D supplements for the prevention of cardiovascular events.[32]

SAFETY OF VITAMIN D SUPPLEMENTATION

Acute vitamin D toxicity is theoretically life threatening (eg, along with anticoagulants, vitamin D3 is the most commonly used active ingredient in rodenticides). However, it hardly ever occurs with supplementation and requires extremely high doses.[33] Vitamin D toxicity is associated with hypercalcemia and low serum parathyroid hormone levels. Because hypercalcemia is the primary issue, patients could present with clinical signs of "stones, groans, thrones, muscle tone, and psychiatric overtones" for nephrolithiasis, abdominal symptoms such as pain, anorexia and nausea/vomiting, polyuria and polydipsia, hypotonicity and hyporeflexia, and neuropsychiatric issues.[34] Hypercalcemia can also affect cardiovascular conduction (shorten QT interval), cause arrhythmias, and even mimic acute myocardial infarction on electrocardiography.[35] While vitamin D toxicity is rare (anecdotal evidence suggests > 10,000 IU/day is required for acute toxicity), some argue that high-dose supplementation could still contribute to adverse outcomes, especially in at-risk individuals.

In an RCT of 400 heart failure patients, daily supplementation with 4,000 IU vitamin D3 for 3 years was associated with secondary outcome of increased need for mechanical support (15.4% vs 9.0% on placebo; $P = .03$) and doubled the incidence of hypercalcemia (6.2% vs 3.1% on placebo), although the latter was not statistically significant.[36] In a large RCT, vitamin D supplements were associated with an increased incidence of sessile serrated adenomas or polyps in the colon (22 events in 216 participants who received treatment vs 5 events in 201 participants on placebo; adjusted $P = .02$), although this effect only reached statistical significance when calcium supplements were also used.[37] Interestingly, these associations had not reached statistical significance during the treatment phase of the RCT and were noted with a latency of 6 to 10 years.[37] It should be noted that the previously discussed VITAL trial did not find any increase in the rate of colorectal cancer during its 5-year course and reported a generally benign side-effect profile with continued daily supplementation using 2,000 IU of oral vitamin D.

On the other hand, another recent meta-analysis of RCTs that investigated the effects of various dietary and supplement interventions on cardiovascular health found an increased risk for stroke (RR 1.17; 95% CI, 1.05-1.30) among those taking vitamin D plus calcium supplements but not vitamin D alone.[38] Moreover, increased susceptibility to kidney stone formation has also been reported in several studies, especially in conjunction with calcium supplements.[39] While these findings have not been universally reproduced, we encourage physicians to carefully assess the detrimental effects of vitamin D deficiency on bone health and potential side effects of supplementation on a patient-by-patient basis, taking into account any history of granulomatous diseases, nephrolithiasis, and other such risk factors.

CALCIUM SUPPLEMENTATION

Per the IOM, the recommended daily intake for calcium is 1,000 mg/day for women aged 19 to 50 years and men aged 19 to 70 years and 1,200 mg/day for women aged ≥ 50 and men aged ≥ 70 years.[8] It is best to achieve this amount of calcium through food sources, but approximately 40% of the US population also ingest calcium in the form of supplements.[40]

Due to their interlinked physiology, vitamin D and calcium supplements are often used in conjunction, especially in individuals with increased risk of bone loss, such as the elderly or postmenopausal women. However, the same population is also at increased risk of CVD, which leads to concerns about the effects of supplementation on the cardiovascular system since use of calcium supplements has been suggested to increase cardiovascular risk and mortality. This topic generated concern after a meta-analysis by Bolland et al. in 2010 found a 27% increase in the risk of MI in women taking calcium supplements.[11] Those findings proved controversial and led to many other publications challenging its methods and generalizability. The debate generated more controversy when Bolland et al. re-analyzed data from the WHI CaD study and reported that the calcium-naïve subpopulation had a 22% increased rate of MI during the trial, arguing that the effect was masked by a high prevalence of baseline calcium supplement users in the original analysis.[12]

This concern was further bolstered by observational analyses in which calcium supplement use was found to be associated

with an increased risk of incident coronary artery calcium assessed by cardiac computed tomography and incident MI.[10,41] Interestingly, this trend was exclusive to supplementary calcium and was not observed with dietary calcium from natural sources.[10,41]

To our knowledge, no RCTs have investigated a link between calcium supplement use and cardiovascular events as the primary outcome. However, a recent meta-analysis by Jenkins et al. found a trend for increased risk of cardiovascular events with calcium supplementation, although it was not statistically significant.[6] As mentioned above, another recent meta-analysis of RCTs found an increased risk of stroke when calcium supplements were used in combination with vitamin D.[38] The mechanism for these observations is incompletely understood. However, it may be that a transient elevation in serum calcium concentration following ingestion of calcium supplements—which are often taken in larger doses in a single setting than when calcium is ingested from food—can affect nonskeletal calcium pathways, such as thrombotic pathways and vascular calcium deposition. As mentioned above, calcium supplements in RCTs have been linked to an increased risk of kidney stones and colon polyps, perhaps through decreased gut motility.[37,39] Therefore, even though the association with CVD outcomes is inconclusive, calcium supplements may not be entirely benign for other health outcomes.

FRACTURES, FALLS, AND MUSCULOSKELETAL OUTCOMES

While this review focuses on vitamin D and calcium supplements with regard to their effects on cardiovascular outcomes, most individuals take these supplements primarily for bone health, not cardiovascular health. In this context, however, it important to note that even their role in fracture reduction has been questioned in recent studies.[39,42,43] This led to the US Preventive Services Task Force giving only an "Insufficient" recommendation for the use of calcium and vitamin D supplements for fracture prevention among community dwelling adults.[44] So despite their widespread use, calcium and vitamin D supplements may not be indicated broadly for fracture reduction in the general population. An RCT examining whether vitamin D supplementation can reduce falls in older adults is currently ongoing.[45]

CONCLUSION

In sum, despite an association between serum 25(OH)D deficiency and higher mortality and incidence of CVD, supplementation with vitamin D has not shown observable CVD benefits in RCTs. Therefore, 25(OH)D concentrations should not be routinely tested, and vitamin D supplements should not be prescribed or recommended for the purpose of preventing cardiovascular events. Instead, we would recommend a healthy diet and active lifestyle as the optimal way to improve vitamin D status and promote cardiovascular health. However, since there is no convincing evidence of cardiovascular harm from vitamin D supplementation, the lack of benefit for CVD outcomes should not hinder their use for other indications.

While inconclusive, the current evidence for calcium supplementation is concerning for increased CVD risk. In this light, we suggest that the recommended daily allowances of calcium be achieved through dietary sources when possible, and that the smallest effective supplemental doses be considered in populations at risk of osteoporosis only after dietary modifications have been exhausted.

KEY POINTS

- For optimal bone health, the recommended dietary intake of vitamin D is 600 IU/day for adults aged 19 to 70 years and 800 IU/day for adults aged > 70 years. The recommended dietary intake of calcium is 1,000 mg/day for adults aged 19 to 50 years and for men aged 51 to 70 years and 1,200 mg/day for women aged ≥ 51 years and for all adults > 70 years.
- Large randomized controlled trials have shown no cardiovascular benefits conferred by vitamin D supplementation even in the case of insufficiency (< 20 ng/mL), suggesting that previously seen associations were due to confounding/reverse causation.
- Vitamin D testing/supplementation aimed solely at improving cardiovascular health is not recommended.
- There is some concern that calcium supplements (but not food sources) could increase the risk for cardiovascular events, but the evidence is inconclusive.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:
vitamin D, calcium, supplements, cardiovascular risk

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