REVIEW ARTICLE

Vitamin D: Popular Cardiovascular Supplement but Benefit Must Be Evaluated

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ABSTRACT

Vitamin D deficiency is prevalent in the United States. Understanding any relationship between this deficiency and cardiovascular disease is essential. Vitamin D, as used, refers to both D_2 and D_3; both are present in over-the-counter supplements, whereas D_2 is the prescription product in the United States. In the liver, both D_2 and D_3 are converted to 25-hydroxyvitamin D, the major circulating metabolite that is measured to assess activity. The actual active form at a cellular level is 1,25-dihydroxyvitamin D; however, it does not correlate well with overall activity. Estimated vitamin D deficiency is, at times, more than 50%. Despite absence of placebo-controlled randomized trials, much information associates vitamin D deficiency with cardiovascular risk and supports benefit from vitamin D supplementation. There are also reports that explain how this benefit from vitamin D may occur. Vitamin D appears to cause only minimal changes in low- and high-density lipoprotein levels. Therefore, any cardiovascular benefit that may exist from vitamin D probably has an explanation other than an effect on levels of these lipoproteins. There is more association of vitamin D deficiency with metabolic syndrome components such as an increase in blood pressure, elevated plasma triglycerides, and impaired insulin metabolism. Possible documentation of cardiovascular benefit from vitamin D includes some evidence for endothelial stabilization and decreased inflammation in arteries. If the clinician decides that recommendation of vitamin D supplementation is warranted, it is reassuring that toxicity is rare. Furthermore, this toxicity involves doses exceeding those of most clinical trials and mainly has involved hypercalcemia. Vitamin D supplementation is easy and can be taken as a dose of 2000 IU daily on an indefinite basis. In 1997, the Food and Nutrition Board of the U.S. Institute of Medicine considered this the safe tolerable upper limit, but this is not based on current evidence. Some practitioners, especially endocrinologists, recommend vitamin D at a dose of 50,000 IU per week for 8 weeks, repeated if necessary to achieve a normal level of vitamin D. It appears appropriate to assess low vitamin D as a possible cardiovascular risk factor, but potential benefit of supplementation must be weighed against the current absence of definitive outcomes studies.

KEYWORDS: Cardiovascular risk, coronary heart disease, low-density lipoproteins, peripheral vascular disease, vitamin D

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Vitamin D deficiency is considered to be present in a significant proportion of the general population of the United States. Increasing data suggest that low levels of vitamin D may be associated with increased risk for cardiovascular (CV) disease. The causes of deficiency and what vitamin D levels equate with significant deficiency must be considered. Another major issue is replacement or supplementation doses to be recommended for vitamin D. Secondary effects of the vitamin must be considered because some of the observed effects may explain cardiovascular risk and others may elucidate mechanisms of benefit. Also, there are other reported possible benefits of the vitamin, the significance of which must be assessed. Vitamin D supplementation appears to be generally safe in the doses evaluated in clinical studies, but outcomes data that prove clinical efficacy are still lacking.

FORMS OF VITAMIN D

There are two basic forms of vitamin D. Vitamin D_2 (ergocalciferol) is found in plants as the product of ultraviolet B irradiation of ergosterol. Vitamin D_3 has its origin from dehydrocholesterol and is the product of ultraviolet B irradiation of this compound after transiently passing through previtamin D_3.[1] The vitamin D_3 can either be synthesized in the human epidermis or consumed from oily fish, fortified foods, or supplements. Vitamin D actually refers to both D_2 and D_3. Both vitamin D_2 and vitamin D_3 are ingredients in over-the-counter vitamin D supplements; however, the form available via high-dose 50,000 IU prescription in the United States is vitamin D_2.

Excessive exposure to sunlight cannot cause vitamin D toxicity because ultraviolet B irradiation converts excess vitamin D_3 to inert isomers; conversely, excessive oral vitamin D intake can cause toxicity.[2] Vitamin D is converted in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite of vitamin D.[1] It is this 25(OH)D that should be measured to evaluate vitamin D status because it reflects both vitamin D intake and production that occurs endogenously. However, the actual active form is 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], and it is this active form that regulates calcium metabolism. Notably, the serum level of $1,25(OH)_2D$ does not correlate well with the overall status of vitamin D and is not considered clinically useful.[1] This active form of vitamin D is actually a hormone because it is produced mainly in a single organ, the kidney, and is closely regulated by plasma parathyroid hormone levels as well as serum calcium and serum phosphorus levels.[1,3] Vitamin D receptors are present in most tissues including endothelium, vascular smooth muscle, and myocardium.[4,5] Of significant note is the possibility that both endothelial cells and vascular smooth muscle cells may be able to convert 25(OH)D to $1,25(OH)_2D$.[6] Whether directly or indirectly, $1,25(OH)_2D$ plays a role in regulating multiple genes such as those involved in the production of insulin and the development of vascular smooth muscle cells.[1] Thus, it is easy to postulate major importance for vitamin D deficiency via deficiency of the active form, $1,25(OH)_2D$, as a possible contributing factor to CV disease (Table 1).

PREVALENCE OF VITAMIN D DEFICIENCY

The prevalence of vitamin D deficiency is surprisingly high and depends on location with regard to seasonal months. Most investigators in the vitamin D field define insufficient vitamin D concentrations as those below 30.0 ng/mL (75.0 nmol/L) and severely deficient concentrations as those below 10.0 ng/mL (25.0 nmol/L). In a general practice in Edinburgh, Scotland, from 2005 to 2007 that involved 99 patients suspected of possible vitamin D deficiency, only 2% had sufficient vitamin D concentration. Severe deficiency was documented in 47%.[7] Of note for 25(OH)D, ng/mL multiplied by 2.496 equals nmol/L.[8]

The National Health and Nutrition Examination Survey (NHANES) data were evaluated by Ginde et al to analyze the demographics of vitamin D insufficiency in the United States from 1988 to 2004.[9] Data obtained on participants showed a marked decrease in serum 25(OH)D from the 1988–1994 period to the

Table 1 Synopsis of Vitamin D Supplements and Active Forms

Forms of Vitamin D	Clinical and Scientific Significance
D_2 (ergocalciferol, from ultraviolet B irradiation of ergosterol)[1]	One of two basic forms of vitamin D. D_2 is the prescription product in the United States.
D_3 (origin from dehydrocholesterol via ultraviolet B irradiation)[1]	The other basic form of vitamin D.
25-Hydroxyvitamin D[3–5]	Abbreviated as 25(OH)D. Major circulating vitamin D metabolite. Used as the clinical measurement of vitamin D activity.
1,25-Dihydroxyvitamin D[3–6]	Actually a hormone produced mainly in the kidneys and is derived from 25(OH)D. It is the active form of vitamin D.

2001–2004 period. The overall mean serum 25(OH)D was 30 ng/mL during the 1988–1994 period and decreased to 24 ng/mL during the 2001–2004 period. The incidence of 25(OH)D levels less than 10 ng/mL increased from 2 to 6% for the more recent interval while 25(OH)D levels of 30 ng/mL or more decreased from 45 to 23%. During 2001–2004, non-Hispanic white males and white females had the lowest percentage of 25(OH)D less than 10 mg/mL with a maximum occurrence (6%) in white females age 60 years and over. For non-Hispanic black males from 2001 to 2004, the percentage of participants with 25(OH)D less than 10 ng/mL ranged from 18 to 27% for the age groups, and the highest percentage of this deficiency occurred in the 20- to 39-year age group. For non-Hispanic black females during the same period, the percentage of participants with 25(OH)D less than 10 ng/mL ranged from 26 to 38% for the age groups, and the highest percentage of this deficiency occurred in the 40- to 59-year age group. For Mexican-American males during 2001–2004, the percentage of participants with 25(OH)D less than 10 ng/mL ranged from 3 to 9% for the age groups, and the highest percentage of this deficiency occurred in the 60 years and over age group. For Mexican-American females during the same period, the percentage of participants with 25(OH)D less than 10 ng/mL ranged from 18 to 20% for the age groups, and the highest percentage of this deficiency occurred in the 12- to 19-year and 20- to 39-year age groups, both having an occurrence of 25(OH)D less than 10 ng/mL in 20% of each age group. These data demonstrate very well some of the population and racial differences that occur.[9]

By synthesizing data from many reports, Holick concluded that probably 1 billion people worldwide may have a deficiency or at least an insufficiency of vitamin D.[1] Furthermore, he assessed from several studies that 40 to 100% of the elderly (both male and female) in the United States and Europe, still living in the community and not in institutional care, are deficient in vitamin D. In a multinational study of 18 countries at various latitudes, Lips et al studied a total of 2606 postmenopausal women with osteoporosis.[10] The mean serum 25(OH)D level was 26.8 ng/mL with the highest mean values in Latin America (29.6 ng/mL) and lowest in the Middle East (20.4 ng/mL). In the entire study, 64% of women had serum levels <30 ng/mL. Women recruited during the winter months in countries not at the equator generally had somewhat lower serum 25(OH)D levels than those entering the study during the summer months. It is therefore evident that low levels of serum 25(OH)D are common in postmenopausal women, a group that is associated with increased CV risk.

McKenna assessed data from North America, Central Europe, and Western Europe and found that the vitamin D status in both young adults and the elderly varies widely with the country of residence and with the seasons (summer versus winter).[11] Adequate exposure to summer sunlight appeared to be the ideal means to have an adequate vitamin D level; however, overall it appeared that supplementation and/or fortification with vitamin D was necessary to maintain an adequate baseline. The author suggested that all countries should adopt a fortification policy and that it was likely the elderly population could benefit from a daily supplement of 400 IU (10 μg) of vitamin D as well. There is a general consensus that the minimum serum 25(OH)D level, at least for bone health, is 20.0 to 32.1 ng/mL (50.0 to 80.0 nmol/L). Daily intake of vitamin D_3 of at least 800 to 1000 IU appears needed to attain a mean 25(OH)D level of 30.0 ng/mL (75.0 nmol/L).[12]

Despite these observations of vitamin D deficiency, the issue of widespread long-term vitamin D supplementation remains unresolved despite the association of hypovitaminosis D with diabetes, CV disease, and cancer.[13] This may not necessarily mean that vitamin D supplementation will improve health outcomes, as was found, for example, with the failure of benefit from antioxidant vitamin supplementation and also with possible increased mortality from supplementation with vitamin A, β-carotene, and vitamin C.[14] Despite the fact that vitamin D toxicity may not be probable even with large doses, it is essential to resolve any uncertainties by conducting large-scale, randomized controlled trials that compare different doses of vitamin D with placebo.[13] Only then will it be possible to make safe and completely rational recommendations on vitamin D supplementation. Nevertheless, the available evidence appears promising.

VITAMIN D DEFICIENCY AND HIGH-DENSITY/LOW-DENSITY LIPOPROTEINS

Increased CV risk from vitamin D deficiency and CV benefit from supplementation in relation to lipoprotein levels appears problematic. In an addendum to a study on hormone replacement therapy in postmenopausal women, Heikkinen et al found that high-density lipoproteins (HDLs) decreased 5.2% and low-density lipoproteins (LDLs) increased 4.1% in their vitamin D_3 group.[15] In addition, the beneficial effect of hormone replacement therapy on serum LDL level was decreased when vitamin D_3 was added, resulting in a 5.9% decrease in LDL. In contrast, results from the Women's Health Initiative showed that over 5 years, dietary calcium and vitamin supplementation (calcium carbonate 1.0 g with vitamin D_3 400 IU daily) were not associated with any significant changes in total cholesterol, LDL, HDL, and non-HDL.[16] Any CV benefit that may exist from the vitamin probably cannot be explained by an alteration of these lipoproteins.

VITAMIN D OVERDOSE AND INTOXICATION

Vitamin D intoxication can be considered to be present when serum levels of 25(OH)D are greater than 149.8 ng/mL (374.0 nmol/L).[1] A long-standing upper limit for vitamin D supplementation has been an intake of 2000 IU/d as established in 1997 by the Food and Nutrition Board of the U.S. Institute of Medicine.[17] However, this does not appear to be based on current evidence and appears much too restrictive.[18] Based on an assessment of multiple clinical studies, it has been suggested that 10,000 IU/d (250 μg/d) be considered a safe upper limit for continual vitamin D supplementation.[18] The value of data supporting a safe upper level favors a margin of safety rather than advocacy for replacement at such a 10,000 IU per day level and adds confidence in the safety of a continued dose of 2000 IU/d when indicated. Published cases of vitamin D toxicity with hypercalcemia, for which the 25(OH)D concentration and vitamin D dose are known, all involve an intake of $\geq$ 40,000 IU/d.[19] Exposure to sunlight for extended time periods generally does not cause vitamin D toxicity. The reason for this is that in light-skinned individuals, the concentration of vitamin D precursors produced in the skin reaches an equilibrium after ~20 minutes of exposure to ultraviolet light.[19] For individuals with pigmented skin, the period to attain equilibrium is 3 to 6 times longer. Any vitamin D subsequently produced is degraded.[20] Vieth commented that at least four studies support the concept that one full-body exposure to sunlight can be equivalent to an oral vitamin D intake of 250 μg (10,000 IU).[19] Holick cites four studies that exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of ~20,000 IU vitamin D_2.[1] A very recent study using specifically generated ultraviolet B irradiation for 10-minute exposures to the back and chest (24% of body surface) showed a mean increase in 25(OH)D of 23.3 nmol (9.3 ng/mL) with a strong negative correlation with baseline 25(OH)D and a significant positive correlation with baseline total cholesterol levels.[21] Specific results from the sun and other ultraviolet light sources appear difficult to quantitate comparatively, and regular exposure to either is conflicted due to perceived increased risk of skin cancers.

IS THERE ANY SPECIFIC RELATIONSHIP OF VITAMIN D TO ATHEROSCLEROSIS?

Any specific biochemical relationship of vitamin D to atherosclerotic vascular disease, peripheral vascular disease (PVD) or coronary heart disease (CHD), needs further definition, but some basic information can be considered. Several mechanisms may explain the relationship of vitamin D deficiency to atherosclerosis, as decreased vitamin D is associated with obesity, diabetes, and hypertension, all of which increase PVD and CHD risk. Additional explanatory mechanisms for this vitamin D association include the fact that vitamin D receptors have a widespread distribution, which includes vascular smooth muscle cells, macrophages, and lymphocytes.[22] Therefore, $1,25(OH)_2D$, as the active form of vitamin D that affects receptors, regulates protein expression relevant to the arterial wall including vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, elastin, and type I collagen. This regulation by vitamin D may decrease atherosclerosis. In contrast, there are some problematic data regarding vitamin D and atherosclerosis. Without question, the right amount of vitamin D appears essential for CV disease prevention, but an excess of the vitamin may be detrimental, especially due to possible harmful effects on elastogenesis and inflammation of the arterial wall.[23] There are data to suggest that if monitored serum levels of 25(OH)D are increased beyond the normal range, vascular calcification may develop, even within normal levels of $1,25(OH)_2D$. High doses of oral vitamin D have been shown to induce vascular calcification in experimental animals. These same high doses increase 25(OH)D but do not always increase serum levels of $1,25(OH)_2D$ because levels of the latter appear to be strictly regulated within a narrow range by parathyroid hormone, despite the nutritional status of vitamin D.[24] How increased 25(OH)D might induce vascular calcification still has to be clarified. Nevertheless, it appears desirable to monitor serum levels of 25(OH)D during vitamin D supplementation and be aware that excess supplementation may be harmful.

VITAMIN D DEFICIENCY AND CARDIOVASCULAR RISK

Vitamin D deficiency has been associated with an increase in high blood pressure, elevated plasma triglycerides, elevated very-low-density lipoproteins, impaired insulin metabolism,[25] and an increase in CV risk.[5] Decreased serum 25(OH)D levels have been documented in patients with myocardial infarction,[26] stroke,[27] congestive heart failure (CHF),[28] PVD,[29] diabetes mellitus, obesity,[30] insulin resistance, pancreatic β-cell dysfunction, and the metabolic syndrome.[31]

Unfortunately, this association of vitamin D deficiency and CV risk remains to be confirmed. This necessity of confirmation of benefit from vitamin D was well analyzed in a comprehensive study just published in 2010. Pittas et al called their extensive study a systematic review of vitamin D and cardiometabolic outcomes.[32] These authors looked at 13 observational studies, which included a total of 14 cohorts, and also at 18 clinical trials. They commented that there does appear to be increasing evidence suggesting that vitamin

D may favorably modify risk for cardiometabolic outcomes as defined by type 2 diabetes, hypertension, and cardiovascular disease. However, it appeared to these authors that most studies that have shown an association between decreased 25(OH)D concentration or decreased vitamin D intake and augmented cardiometabolic risk are cross-sectional, thereby limiting the strength of the conclusions. From their extensive analysis, the authors were only able to conclude that a lower 25(OH)D concentration of vitamin D intake has an indefinite qualification of being possibly associated with increased hypertension and CV disease risk; any association with outcomes related to diabetes was considered unclear. There appeared to be no strong collective data to prove definitively CV benefit from increasing vitamin D supplementation of plasma 25(OH)D concentrations. It appears that this extensive analysis results in an emphasis on the need for well-defined randomized trials and that the effect of vitamin D on cardiometabolic disease can be considered promising but unproven.

In addition, data and trials to control for any relevant normal background deficiency in vitamin D appear very problematic. Experimental data suggest that $1,25(OH)_2D$ appears to affect cardiac muscle in a direct way, control the secretion of parathyroid hormone, regulate the renin-angiotensin system, and temper the immune system.[33] A possible association of vitamin D deficiency with upregulation of the renin-angiotensin-aldosterone system has now been made. Li discovered that deficiency in vitamin D appears very problematic for this association. Experimental data suggest that $1,25(OH)_2D$ functions as a potent negative endocrine regulator for the expression of the renin gene, thereby providing some insights into such a mechanism.[34] Vitamin D deficiency also appears to predispose to left ventricular hypertrophy and vascular smooth muscle cell hypertrophy.[28] Such biologic effects offer an explanation of how vitamin D deficiency can be associated with hypertension and CV disease.

In a study of 1739 Framingham Offspring Study participants (mean age 59 years, 55% women, all white) with no previous CV disease, Wang et al found increased CV disease in those participants with low levels of vitamin D.[5] Vitamin D status was assessed by measuring 25(OH)D levels. Specific thresholds were used to characterize 25(OH)D deficiency, and these were <15 ng/mL and <10 ng/mL. Overall, 28% of individuals had levels <15 ng/mL and 9% had levels <10 ng/mL. During a mean follow-up of 5.4 years, 120 of the 1739 participants developed a first CV event. Individuals with 25(OH)D <15 ng/mL had a multivariable-adjusted hazard ratio of 1.62 (95% confidence interval of 1.11 to 2.36, $p = 0.01$) for CV events compared with those with 25(OH)D $\geq$ 15 ng/mL. This first CV event effect for the collective hypovitaminosis D was noted specifically with a hazard ratio of 2.13 (95% confidence interval of 1.30 to 3.48) in the presence of hypertension but not in the absence of hypertension where the hazard ratio was 1.04 (95% confidence interval of 0.55 to 1.96). There was an inverse association of CV risk across levels of 25(OH)D that included hazard ratios of 1.53 (95% confidence interval of 1.00 to 2.36) for 25(OH)D <15 ng/mL and 1.80 (95% confidence interval of 1.05 to 3.08) for 25(OH)D <10 ng/mL (linear trend, $p = 0.01$).

In the meta-analysis of Autier and Gandini, a total of 18 independent randomized controlled trials were identified (12 placebo-controlled and 6 open-label trials) involving a total of 57,311 participants.[35] In the trials, vitamin D supplements ranged from 300 to 2000 IU (most daily doses ranged between 400 and 833 IU) and the study size-adjusted mean daily vitamin D dose was 538 IU. The results of the 18 trials pointed to a significant 7% decrease in total mortality risk using vitamin D although it was not possible to consider the specific causes of death in the analysis (summary relative risk, 0.93; 95% confidence interval, 0.87 to 0.99). All-cause mortality was calculated from the trials and analyzed as summary relative risk. The authors made the conclusion that vitamin D in common doses seemed to be related to a reduction in total mortality. They considered that there was no indication for heterogeneity or publication bias involving the studies analyzed. However, the conclusion was qualified with the comment that future studies involving total mortality as the main end point in population-based, placebo-controlled randomized trials are essential for confirmation.

There is a well-known and very high association of PVD with CHD. In a study of 155 patients with low ankle-brachial index, Sukhija et al found that 84% of the patients had 3- or 4-vessel CHD.[36] The CV association then extends further, in that there is a strong connection between PVD and metabolic syndrome, which is itself a major CV risk factor. Maksimovic et al found in one study involving 388 PVD patients that 59.8% of them had metabolic syndrome.[37] These CV interrelationships then transfer to the subject at hand in that low levels of vitamin D have also been associated with increased risk of PVD. Melamed et al, reporting on a study by the NHANES involving 4839 participants, noted the relationship between 25(OH)D and PVD (defined as ankle-brachial index <0.9).[29] Using quartiles of 25(OH)D, from lowest to highest, the prevalence of PVD was 8.1, 5.4, 4.9, and 3.7% (p trend <0.001). After multivariate adjustment for demographics, comorbidities, physical activity level, and laboratory measures, the prevalence ratio of PVD for the lowest (<17.8 ng/mL) compared with the highest ($\geq$ 29.2 ng/mL) quartile of 25(OH)D was 1.80 (95% confidence interval of 1.19 to 2.74). For each 10 ng/mL decrease in the 25(OH)D level, the multivariate-adjusted prevalence ratio for PVD was 1.35 (95% confidence interval of 1.15 to 1.59). These data support the conclusion that low serum 25(OH)D levels

are associated with a higher prevalence of PVD, and in conjunction, other available data confirm the interrelationship between PVD, CHD, diabetes mellitus,[38] and metabolic syndrome. Therefore, any significant CV effect of vitamin D deficiency appears relevant to the entire CV continuum.

Over a winter, Sugden et al studied the effect of vitamin D supplementation in 34 subjects with type 2 diabetes mellitus and low serum 25(OH)D levels in a placebo-controlled, randomized trial.[39] A single dose of 100,000 IU vitamin D_2 or placebo was administered to enrolled patients if their baseline 25(OH)D level was <20.0 ng/mL (50.0 nmol/L), and they were studied 8 weeks later. Relative to placebo, vitamin D_2 administration increased 25(OH)D levels by 6.1 ng/mL (15.3 nmol/L), significantly improved flow-mediated vasodilation of the brachial artery by 2.3%, and decreased systolic blood pressure by 14 mm Hg. The authors considered that their study was an indication that a single large dose of oral vitamin D_2 improved endothelial function in patients with type 2 diabetes mellitus and vitamin D insufficiency. In a short-term study of vitamin D_3 and calcium effects on blood pressure, Pfeifer et al found that 60 (80%) subjects in their 8-week vitamin D_3 plus calcium group showed a decrease in systolic blood pressure of 5 mm Hg or more ($p = 0.04$) compared with their 8-week calcium-alone group.[40] No significant difference was observed for diastolic pressure.

One of the postulated mechanisms by which vitamin D may be important in decreasing CV risk is in decreasing inflammation. Over a 9-month period, Schleithoff et al studied 123 CHF patients who were randomized to receive either 2000 IU (50 μg) vitamin D_3 plus 500 mg calcium per day or a placebo plus 500 mg calcium per day.[41] In the 93 patients who completed the study, significant treatment effects were observed on serum concentrations of 25(OH)D ($p = 0.001$), parathyroid hormone ($p = 0.007$), TNF-α ($p = 0.006$), and IL-10 ($p = 0.042$). The level of 25(OH)D increased by 26.8 ng/mL in the vitamin D plus calcium group but increased only by 3.6 ng/mL in the placebo plus calcium group. Compared with baseline, parathyroid hormone was significantly lower and the anti-inflammatory cytokine IL-10 was significantly higher in the vitamin D plus calcium group after 9 months. The proinflammatory cytokine TNF-α increased in the placebo plus calcium group but remained constant in the vitamin D plus calcium group. This study involving CHF patients supports a possible reduction of inflammatory risk by vitamin D.

Low serum 25(OH)D levels (<32 ng/mL) have been associated with the development of a statin-associated myopathy. Ahmed et al studied 621 patients taking a statin.[42] Of these patients, 128 patients had myalgia at entry and 493 were asymptomatic. Serum 25(OH)D was low in 82 of 128 (64%) patients with myalgia versus 214 of 493 (43%) of the asymptomatic patients ($\chi^2 = 17.4$, $p < 0.0001$). Of the 82 vitamin D-deficient patients with myalgia, 38 were given vitamin D in a dose of 50,000 IU/week for 12 weeks while continuing their statin. There was a resultant increase in serum vitamin D from 20.4 ± 7.3 to 48.2 ± 17.9 ng/mL ($p < 0.0001$) and resolution of myalgia in 35 (92%). (Note: The ± numbers are the standard deviation.) The authors speculate that there may be a reversible interaction between vitamin D deficiency and statins in skeletal muscle. By potentially increasing statin usage, this represents another mechanism by which vitamin D deficiency may decrease CV risk (Table 2).

ARE THERE POSSIBLE RISKS TO SUPPLEMENTATION?

As with all CV management, any downside risk must be considered. Oh et al in 2009 studied foam cell formation and macrophage cholesterol uptake in 76 diabetic patients considered to have vitamin D deficiency whose 25(OH)D level was less than 80 nmol/L (32.1 ng/mL).[43] The patients were also hypertensive and obese. Macrophages were obtained from these patients and from four control groups: (1) patients with normal vitamin D who had diabetes, obesity, and hypertension; (2) vitamin D-deficient patients without diabetes but with obesity and hypertension; (3) vitamin D-deficient patients who did

Table 2 Association of Vitamin D Levels, Measured as 25(OH)D, with Specific Cardiovascular Diseases and the Potential Benefit of Supplementation

Decreased Serum 25(OH)D Levels Documented in:	Potential Cardiovascular Benefits of Vitamin D Supplementation:
Myocardial infarction[26]	Direct effect on cardiac muscle[33]
Stroke[27]	Favorable regulation of renin-angiotensin system[33]
CHF[28]	Tempering of immune system[33]
PVD[29]	Decreased hypertension[5,39]
Diabetes mellitus[30]	Decreased total mortality[35]
Obesity[30]	Improved endothelial function[39]
Insulin resistance[31]	Decreased inflammation[41]
Metabolic syndrome[31]	Decreased statin-related myopathy[42]

CHF, congestive heart failure; PVD, peripheral vascular disease

not have diabetes, obesity, or hypertension; and (4) patients with normal vitamin D without diabetes, obesity, or hypertension. Macrophages from all patients were cultured in vitamin D-deficient or $1,25(OH)_2D$-supplemented media and exposed to modified (oxidized or acetylated) LDL. The $1,25(OH)_2D$ suppressed foam cell formation by reducing acetylated or oxidized LDL uptake in diabetic subjects only, which would appear to indicate a beneficial CV effect. In contrast, deletion of the vitamin D receptor in macrophages from diabetic patients resulted in accelerated foam cell formation by the modified LDL.[43] One interpretation in terms of potential CV risk is the possibility of increased macrophage foam cell formation and accelerated CV disease in diabetics who happen to have a vitamin D receptor deficiency. Unfortunately, identification of this by practical clinical analysis does not currently appear possible.

The Women's Health Initiative Investigators in 2007 randomized 36,282 postmenopausal women to calcium carbonate 500 mg with vitamin D 200 IU two times a day versus placebo.[44] As assessed by the occurrence of myocardial infarction, CHD death, or stroke, the supplement containing vitamin D did not increase or decrease these results of CV risk in these women followed over 7 years. Even if the participants took an additional 400 IU vitamin D, as allowed by the protocol, the dose level may have been too low to expect therapeutic results because only 13% of women with incident fractures ($n = 1589$) consuming an average of 365 IU vitamin D each day and 15% of matched controls had 25(OH)D levels greater than 75 nmol/L (30 ng/mL). This large study showed no benefit, but it has to be considered that the vitamin D dose used was possibly too low.

VITAMIN D SUPPLEMENTATION: DAILY AND REPLACEMENT

Treatment for vitamin D deficiency can be initiated with vitamin D_2 or D_3 at a prescribed dose of 50,000 IU weekly for 8 to 12 weeks.[28] This can be followed by repetition of the same regimen if significant deficiency still persists. Subsequently, maintenance therapy can include 50,000 IU vitamin D_2 or D_3 every 2 weeks or a regimen of 1000 to 2000 IU/d vitamin D_3.[28] Endocrinologists have especially had a strong interest in higher dosages over a limited term. A recommended serum goal for 25(OH)D is at least 32.1 ng/mL (80.0 nmol/L). It has been reported that 25(OH)D levels above these limits are associated with a reduced risk of bone fractures, reduced incidence of several cancers, and decreased type 1 diabetes mellitus. Aloia et al pointed out that determination of the vitamin D intake required to attain a desired serum 25(OH)D concentration of 30.0 ng/mL (75.0 nmol/L) needs to take into account the extensive variability in dose–response curves and basal 25(OH)D concentrations.[45] These authors projected dose–response curves observed in a small study of 138 subjects onto the population of the third NHANES. From this, they said that it appeared appropriate to suggest that daily doses of vitamin D include 3800 IU (95 μg) for individuals above a 25(OH)D level of 22.0 ng/mL (55.0 nmol/L) and 5000 IU (125 μg) for individuals below 22.0 ng/mL. Pietras et al, in their clinic specializing in metabolic bone disease, reported their experience over 6 years.[8] They found that vitamin D_2 in a dose of 50,000 IU each week for 8 weeks treated vitamin D deficiency effectively. They then found that vitamin D_2 continued at a dose level of 50,000 IU every other week for up to 6 years prevented recurrent vitamin D deficiency in most patients although 16% of their patients remained deficient or insufficient in vitamin D. Their results show the variable and high supplementation dose that may be necessary, its relative safety, and the relatively low cost (e.g., $66 per year for maintenance therapy). Variable dose–response studies help elucidate safe doses such as vitamin D 2000 IU/d, a dose level for which there appears to be a wide margin of safety above this long-term dose advocated in 1997 by the Food and Nutrition Board.[18] Such management provides an inexpensive and easy way to manage and prevent vitamin D deficiency.

CLINICAL RECOMMENDATIONS FOR VITAMIN D

The data appear to indicate some promise for CV benefit of vitamin D although this has not been established with definitive outcomes studies. Placebo-controlled randomized trials need to be performed but are unlikely to happen without government-supported research, as there is no financial incentive for pharmaceutical company support. However, until the issue is more definitively resolved, it still appears appropriate to check vitamin D levels in the plasma and, if deficient, to discuss with the patient the pros and cons of a regular continuing supplement such as 2000 IU/d. For the most major deficiencies, it also appears appropriate to consider higher short-term supplements to correct major deficiencies as appears to be preferred by many endocrinologists. Vitamin D supplementation appears to be safe and is inexpensive. The problem of deficiency is widespread and extensive, especially during prolonged inclement weather. The potential CV benefit appears to warrant regular assessment of vitamin D levels and discussion of possible supplementation with the individual patient when significant deficiency is present.

CONCLUSION

There is much interest in vitamin D among some medical groups but a major lack of interest among

many others. Vitamin D deficiency without supplementation is common in developed societies in more northern climates. For now, it is indicated to think of vitamin D supplementation for the primary purpose of ensuring proper bone mineralization. For those clinicians who insist on hard data from conclusive outcomes studies, supplementation will not be recommended for CV concerns. Nevertheless, a review of available information provides much concern about CV disease associated with vitamin D deficiency and the possible associated benefit from supplementation. It appears appropriate to measure vitamin D as a potential CV risk factor. However, until definitive outcomes studies are available, supplementation with vitamin D has to be at the discretion of the individual clinician after discussion with his or her individual patient. In addition, it must be kept in mind that excess vitamin D supplementation may actually contribute to atherosclerosis, but the associated toxic dose appears to be long-term supplementation in excess of 10,000 IU/d. Fortunately, there is a relatively low cost and low risk associated with moderate vitamin D supplementation. Unfortunately, with the lack of pharmaceutical company financial incentive, extensive outcomes studies will not occur unless specific government or nonprofit-granting agencies decide to facilitate definitive placebo-controlled randomized trials. Hopefully, the Vitamin D and Omega-3 Trial (VITAL), scheduled to have begun in early 2010, can help fulfill this role.[46] It is intended to evaluate whether vitamin D (~2000 IU) or fish oil supplements (~1 g of omega-3 fatty acids) may play a role in the primary prevention of cancer, heart disease, and stroke. It is hoped the data obtained in studies such as VITAL can facilitate decisions on the CV value of vitamin D supplementation when deficiency is present.

REFERENCES

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266–281
2. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. N Engl J Med 2001;345:66–67
3. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80(6, Suppl): 1689S–1696S
4. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol 2006;92:39–48
5. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117: 503–511
6. Zehnder D, Bland R, Chana RS, et al. Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. J Am Soc Nephrol 2002;13:621–629
7. Rhein HM. Vitamin D deficiency is widespread in Scotland. BMJ 2008;336:1451
8. Pietras SM, Obayan BK, Cai MH, Holick MF. Vitamin D2 treatment for vitamin D deficiency and insufficiency for up to 6 years. Arch Intern Med 2009;169:1806–1808
9. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626–632
10. Lips P, Hosking D, Lippuner K, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med 2006;260:245–254
11. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. Am J Med 1992; 93:69–77
12. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713–716
13. Witham MD. Vitamin D deficiency: more evidence is needed before general supplementation. BMJ 2008;336:1451
14. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 2008;(2):CD007176
15. Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen M, Penttilä I, Saarikoski S. Long-term vitamin D3 supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. Eur J Endocrinol 1997;137:495–502
16. Rajpathak SN, Xue X, Wassertheil-Smoller S, et al. Effect of 5 y of calcium plus vitamin D supplementation on change in circulating lipids: results from the Women's Health Initiative. Am J Clin Nutr 2010;91:894–899
17. Food and Nutrition Board. Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: National Academy Press; 1997
18. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. Am J Clin Nutr 2007;85:6–18
19. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999;69:842–856
20. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995;61(3, Suppl):638S–645S
21. Bogh MKB, Schmedes AV, Philipsen PA, Thieden E, Wulf HC. Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. J Invest Dermatol 2010;130:546–553
22. Mascitelli L, Goldstein MR, Grant WB. Does vitamin D have a role in reducing the risk of peripheral artery disease? Mayo Clin Proc 2010;85:1058–1059; author reply 1059–1060
23. Norman PE, Powell JT. Vitamin D, shedding light on the development of disease in peripheral arteries. Arterioscler Thromb Vasc Biol 2005;25:39–46
24. Jono S, Nishizawa Y, Shioi A, Morii H. 1,25-Dihydroxyvitamin D3 increases in vitro vascular calcification by modulating secretion of endogenous parathyroid hormone-related peptide. Circulation 1998;98:1302–1306
25. Lind L, Hänni A, Lithell H, Hvarfner A, Sörensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 1995;8:894–901

26. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol 1990;19:559–563
27. Poole KE, Loveridge N, Barker PJ, et al. Reduced vitamin D in acute stroke. Stroke 2006;37:243–245
28. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol 2008;52:1949–1956
29. Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arterioscler Thromb Vasc Biol 2008;28:1179–1185
30. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2007;167:1159–1165
31. Riachy R, Vandewalle B, Moerman E, et al. 1,25-Dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. Apoptosis 2006;11:151–159
32. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307–314
33. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. Pharmacotherapy 2009;29:691–708
34. Li YC. Vitamin D regulation of the renin-angiotensin system. J Cell Biochem 2003;88:327–331
35. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167:1730–1737
36. Sukhija R, Aronow WS, Yalamanchili K, Peterson SJ, Frishman WH, Babu S. Association of ankle-brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. Cardiology 2005;103:158–160
37. Maksimovic M, Vlajinac H, Radak D, Marinkovic J, Jorga J. Relationship between peripheral arterial disease and metabolic syndrome. Angiology 2009;60:546–553
38. Alexander CM, Landsman PB, Teutsch SM, Haffner SM; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210–1214
39. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med 2008;25:320–325
40. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 2001;86:1633–1637
41. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2006;83:754–759
42. Ahmed W, Khan N, Glueck CJ, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. Transl Res 2009; 153:11–16
43. Oh J, Weng S, Felton SK, et al. 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation 2009;120:687–698
44. Hsia J, Heiss G, Ren H, et al; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846–854
45. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr 2008;87:1952–1958
46. The Vitamin D and Omega-3 Trial (VITAL). Available at: http://www.vitalstudy.org/. Accessed March 22, 2010