Vitamin D Deficiency

An Important, Common, and Easily Treatable Cardiovascular Risk Factor?

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Vitamin D deficiency is a highly prevalent condition, present in approximately 30% to 50% of the general population. A growing body of data suggests that low 25-hydroxyvitamin D levels may adversely affect cardiovascular health. Vitamin D deficiency activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. Epidemiologic studies have associated low 25-hydroxyvitamin D levels with coronary risk factors and adverse cardiovascular outcomes. Vitamin D supplementation is simple, safe, and inexpensive. Large randomized controlled trials are needed to firmly establish the relevance of vitamin D status to cardiovascular health. In the meanwhile, monitoring serum 25-hydroxyvitamin D levels and correction of vitamin D deficiency is indicated for optimization of musculoskeletal and general health. (J Am Coll Cardiol 2008;52: 1949–56) © 2008 by the American College of Cardiology Foundation

Traditionally, vitamin D has been associated primarily with bone health, and it is well understood that vitamin D deficiency leads to rickets in children and osteomalacia and osteoporosis in adults [1]. However, it is now known that adequate vitamin D status is important for optimal function of many organs and tissues throughout the body, including the cardiovascular (CV) system [2]. Vitamin D receptors (VDRs) are present on a large variety of cell types, including myocytes, cardiomyocytes, pancreatic beta-cells, vascular endothelial cells, neurons, immune cells, and osteoblasts [1]. Vitamin D deficiency or insufficiency is prevalent in practically every segment of the U.S. population, including children and young adults [1]. This worldwide pandemic remains generally unrecognized and untreated.

Evolving data indicate that vitamin D deficiency is playing an important role in the genesis of coronary risk factors and CV disease. Vitamin D deficiency seems to predispose to hypertension, diabetes and the metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation [1,2]. Epidemi-ologic studies have also recently linked vitamin D deficiency with increased risk of major adverse CV events [3]. A study of male health professionals showed a 2-fold risk of myocardial infarction (MI) in subjects who were vitamin D deficient compared with those in the sufficient range [4]. Similarly, a recent prospective cohort study measured the vitamin D levels in 3,258 German adults who were undergoing elective cardiac catheterization. During a mean follow-up of 7.7 years, individuals in the lowest quartile for baseline serum 25-hydroxyvitamin D [25(OH)D] had a risk-adjusted 2-fold increased risk of death, especially CV death, compared with those in the highest quartile of vitamin D [5].

This review focuses on the relationship between 2 widespread problems: vitamin D deficiency and CV disease. The issues addressed will include: 1) the role of vitamin D deficiency in the genesis of coronary risk factors and adverse CV events; 2) how repletion of vitamin D stores may improve CV health and prognosis; and 3) practical and specific recommendations for restoring and maintaining a healthy vitamin D status in CV patients, because no guidelines have been published on this topic yet.

Vitamin D Basics

Vitamin D comes in 2 forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2, found in plants, is the product of ultraviolet B (UVB) (290 to 315 mm) irradiation of ergosterol, and can be consumed as

Abbreviations and Acronyms

25(OH)D = 25-hydroxyvitamin D

CV = cardiovascular

MI = myocardial infarction

PTH = parathyroid hormone

UVB = ultraviolet B

VDR = vitamin D receptor

a supplement or in fortified foods (1). Vitamin D_3, a product of UVB irradiation of 7-dehydrocholesterol, is synthesized in the human epidermis or consumed in the form of oily fish, fortified foods, or a supplement. Excessive sunlight exposure cannot cause vitamin D toxicity because UVB converts excess vitamin D_3 to biologically inert isomers (1); however, excessive oral vitamin D intake can cause toxicity at very high doses (6).

Vitamin D is converted in the liver to 25(OH)D, which is the major circulating metabolite of vitamin D. Serum 25(OH)D concentrations, which reflect both vitamin D intake and endogenous production, should be measured to clinically assess vitamin D status (1). In the kidney, 25(OH)D is converted by 1α-hydroxylase to its active form, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], which plays a vital role in maintaining bone and muscle health by regulating calcium metabolism. Although 1,25(OH)$_2$D is the active form of vitamin D, its serum level does not correlate with overall vitamin D status and thus is generally not clinically useful (1).

Vitamin D in the form of 1,25(OH)$_2$D is a hormone, because it is produced primarily in 1 organ (the kidney) and then circulates throughout the body, where it exerts wide-ranging effects. The VDR is present in most tissues, including endothelium, vascular smooth muscle, and myocardium (2). In addition, both vascular smooth muscle and endothelial cells may have the ability to convert 25(OH)D to 1,25(OH)$_2$D (7). Circulatory 1,25(OH)$_2$D crosses the cell membrane and cytoplasm and reaches the nucleus, where it binds to the VDR. The VDR-bound 1,25(OH)$_2$D in turn binds to the retinoic acid x-receptor and serves as a nuclear transcription factor, altering gene function and inducing protein synthesis (1). Directly or indirectly, 1,25(OH)$_2$D regulates over 200 genes, including those involved in renin production in the kidney, insulin production in the pancreas, release of cytokines from lymphocytes, production of cathelicidin in macrophages, and growth and proliferation of both vascular smooth muscle cells and cardiomyocytes (1).

Definition and Prevalence of Vitamin D Deficiency

Although a consensus regarding the optimal level of serum 25(OH)D has not yet been established, most experts define vitamin D deficiency as a 25(OH)D level of <20 ng/ml (50 nmol/l) and vitamin D insufficiency as 21 to 29 ng/ml (Table 1). For all studied end points to date, the optimal concentration of 25(OH)D is at least 30 ng/ml (8).

A rapidly evolving knowledge base indicates that vitamin D deficiency is much more prevalent than previously rec-

ognized and is present in up to 50% of young adults (9) and apparently healthy children (1). The Third National Health and Nutrition Examination Survey (NHANES III) reported the prevalence of vitamin D deficiency in the U.S. to be between 25% and 57% of adults (10).

The prevalence of vitamin D deficiency increases in proportion to distance from the equator because of increased atmospheric filtering of UVB radiation caused by the oblique angles of the sun's rays at higher latitudes. Additionally, ethnic groups with darker skin require proportionally more sun exposure to synthesize equivalent amounts of vitamin D compared with people with lighter skin coloration (11).

Modern human cultures produce less vitamin D cutaneously, in part because of increasingly indoor lifestyles and efforts to minimize sun exposure by using sunscreens and other sun avoidance strategies. Sunscreen with a sun protection factor of 15 blocks approximately 99% of the cutaneous vitamin D production (12). Additionally, obesity is associated with vitamin D deficiency (13), probably because of a decreased bioavailability of vitamin D that is sequestered in the fat of individuals with excess adipose tissue (14). After equivalent exposure to UVB radiation or a bolus dose of vitamin D_2, obese individuals showed 50% lower blood levels of vitamins D_3 and D_2 compared with nonobese individuals, probably because of sequestering of 25(OH)D in adipose tissue (14). Older age also reduces the capacity for UVB-induced cutaneous synthesis of vitamin D. After equal doses of sunlight exposure, a 70-year-old person produces 75% less vitamin D_3 than a 20-year-old person (15). Other risk factors for vitamin D deficiency are listed in Table 2.

Vitamin D Deficiency and CV Disease

Epidemiological studies report that the rates of coronary heart disease, diabetes, and hypertension, like vitamin D deficiency, increase in proportion to increasing distance from the equator (16). Deficient or insufficient serum 25(OH)D levels have been documented in patients with myocardial infarction (17), stroke (18), heart failure (2), diabetic CV disease (19), and peripheral arterial disease (20). Recently, the relationship between CV risk factors and 25(OH)D levels was explored among the 15,088 subjects from the NHANES III national cohort registry. In this cross-sectional study, 25(OH)D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia, and obesity (21). Other cross-sectional studies have

Vitamin D Status

Serum 25-Hydroxyvitamin D (ng/ml)	Vitamin D Status
≤10	Severe deficiency
10–20	Deficiency
21–29	Insufficiency
≥30	Sufficiency
>150	Toxicity

─ ▪▪▪▪ ─ Risk Factors for Vitamin D Deficiency
Elderly
Darkly pigmented skin
Institutionalized or homebound
Increased distance from equator
Winter season
Cover-up clothing and/or sunscreen
Air pollution
Smoking
Obesity
Malabsorption
Renal disease
Liver disease
Medications: anticonvulsants, glucocorticoids, antirejection, and human immunodeficiency virus medications

confirmed the links between vitamin D deficiency and both hypertension and diabetes (22,23). Additionally, vitamin D deficiency predisposes to insulin resistance, pancreatic beta cell dysfunction (24), and the metabolic syndrome (24,25). One study reported that a daily intake of 800 IU of vitamin D compared with a daily intake of <400 IU of vitamin D reduced the risk of type 2 diabetes by one-third (26). A study of 10,366 Finnish children who were given 2,000 IU of vitamin D_3 per day throughout the first year of life experienced a 78% reduced risk of type 1 diabetes over the ensuing 31 years of follow-up (27). Subsequently, this finding has been confirmed by a meta-analysis performed on 5 observational studies by a group in England (28).
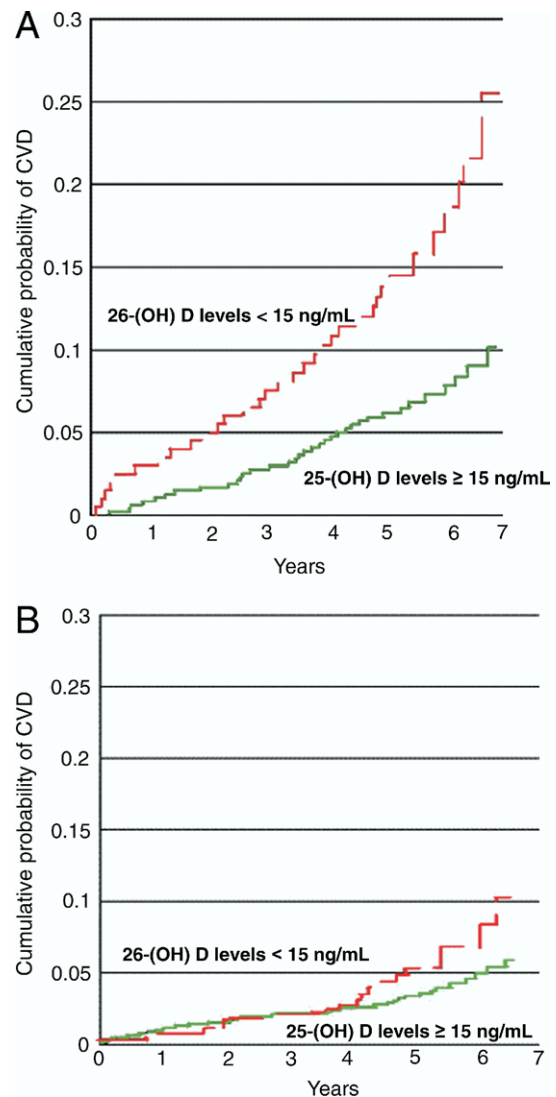
A correlation between vitamin D deficiency and subsequent major adverse CV events was found among the 1,739 Framingham Offspring Study participants who were free of CV disease at baseline (3). In this prospective observational study, 25(OH)D levels were measured at baseline and subjects were followed up for a mean of 5.4 years. The rate of a composite CV end point (fatal or nonfatal MI, ischemia, stroke, or heart failure) was 53% to 80% higher in people with low vitamin D levels. The increased CV risk associated with vitamin D deficiency was magnified in the cohort of Framingham offspring with hypertension (Figs. 1 and 2).

Vitamin D deficiency predisposes to up-regulation of the renin-angiotensin-aldosterone system and hypertrophy of both the left ventricle and vascular smooth muscle cells (2) (Fig. 3). In vitamin D-deficient animals there is an increased incidence of hypertension, left ventricular hypertrophy, and atherosclerosis (29). Human studies indicate that $1,25(OH)_2D$ inhibits renin synthesis, which may lower blood pressure (30). Krause et al. (31) showed that increased exposure to UVB radiation in a tanning bed 3 times per week for 3 months led to a 180% increase in 25(OH)D levels and a 6-mm Hg reduction in both systolic and diastolic pressures. A small, randomized, placebo-controlled study of patients with type 2 diabetes and low baseline 25(OH)D levels showed that a single dose of 100,000 IU of vitamin D_2 reduced systolic blood pressure by a mean of 14

mm Hg and significantly improved endothelial function as measured by forearm blood flow (32). In the NHANES III study, the mean systolic blood pressure was about 3 mm Hg lower in those in the individuals in the highest quintile of serum 25(OH)D levels compared with those in the lowest quintile (22).
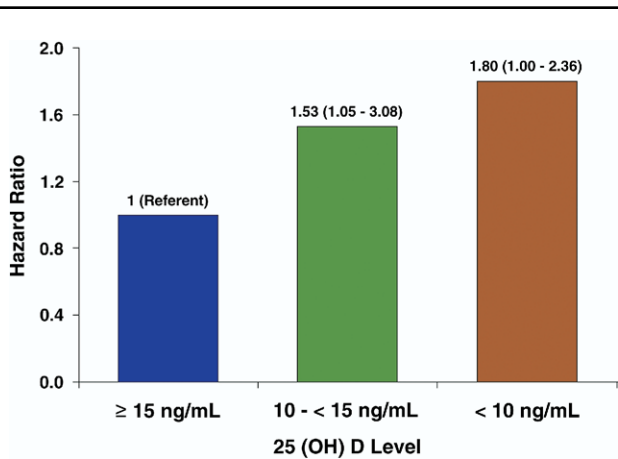
Hyperparathyroidism Increases CV Risk

Chronic vitamin D deficiency causes secondary hyperparathyroidism, which in turn may mediate many of the detrimental CV effects of inadequate vitamin D levels. The

─ ▪▪▪▪ ─ Vitamin D Levels Associated With CVD

Vitamin D deficiency increases CV risk. Kaplan-Meier curves show the probability of major adverse CV events in participants with 25(OH)D levels ≥15 ng/ml **(green lines)** and 25(OH)D levels <15 ng/ml **(red lines)**. The increased CV risk was more apparent in patients with **(A)** than in patients without **(B)** hypertension. Reprinted, with permission, from Wang et al. (3). 25(OH)D = 25-hydroxyvitamin D; CV = cardiovascular; CVD = cardiovascular disease.
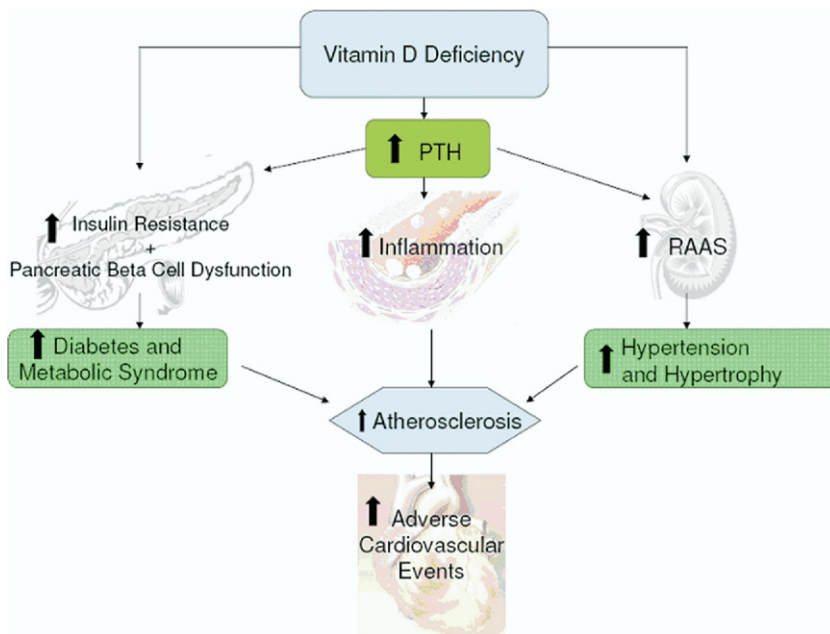
Hazard Ratio for CVD by Vitamin D Levels

Multivariable adjusted hazard ratios for major adverse CV events. Data from Wang et al. (3). Abbreviations as in Figure 1.

threshold for elevation of parathyroid hormone (PTH) is a 25(OH)D level of <30 ng/ml. Further decreases in serum 25(OH)D levels will result in proportionally higher PTH levels to maintain serum and total body calcium (Fig. 4). Vitamin D deficiency reduces intestinal calcium absorption by more than 50% (1). The attendant decrease in serum calcium levels triggers PTH release, which quickly corrects the calcium level by mobilization of calcium from bone, increased renal tubular calcium reabsorption, and increased renal production of 1,25(OH)$_2$D.

The effects of primary hyperparathyroidism on CV outcomes were shown in a study that reported approximately 40% lower relative risks of MI, stroke, and death in patients who had surgical parathyroidectomy compared with observation (33). This link between increased PTH and CV disease was further corroborated by a study of patients with renal failure and secondary hyperparathyroidism [caused by decreased conversion of 25(OH)D to 1,25(OH)$_2$D]. In this study, patients with a PTH level ≥250 pg/ml had a 2-fold risk of CV disease compared with those with PTH levels <250 pg/ml (34). Additionally, a recent observational study found that elevated PTH levels in elderly individuals was associated with a doubling of mortality during follow-up compared with those with normal PTH levels (35).
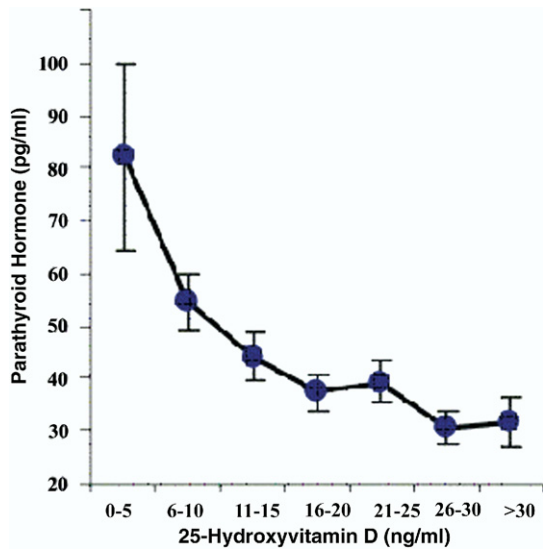
An increased PTH level is associated with increases in both blood pressure (36) and myocardial contractility, which eventually lead to hypertrophy, apoptosis, and fibrosis of both the left ventricle and vascular medial smooth muscle (2). Vitamin D deficiency and/or increased PTH also predispose to calcification of heart valves, mitral annulus, and myocardium, especially in patients with moderate or severe chronic kidney disease (37).

Chronic kidney disease is associated with markedly increased CV risk (38), which may in part be mediated by inadequate vitamin D levels. Vitamin D deficiency is associated with increased mortality rates in the setting of chronic kidney disease (39), and repleting vitamin D in such patients improves outcomes. Recent observational studies of patients with chronic kidney disease and hyperparathyroidism found that the oral administration of 1,25(OH)$_2$D$_3$

Potential Mechanisms for CV Toxicity of Vitamin D Deficiency

Possible mechanisms of increased cardiovascular (CV) risk from vitamin D deficiency. PTH = parathyroid hormone; RAAS = renin-angiotensin-aldosterone system.

**Relationship of Serum Levels
of Parathyroid Hormone and Vitamin D**

The inverse relationship between serum 25-hydroxyvitamin D levels and serum parathyroid hormone levels. Reprinted, with permission, from Zittermann et al. (2).

(also known as activated vitamin D or calcitriol) was associated with significantly improved survival (40). A placebo-controlled study of 30 pre-dialysis renal failure patients with secondary hyperparathyroidism showed that treatment with $1,25(OH)_2D_3$ improved left ventricular diastolic function (41). Vitamin D analogs used in patients on dialysis have been shown to improve survival at all doses tested thus far (42).

Low 25(OH)D levels and increased PTH levels increase both inflammation and the risk of adverse CV events (36). Vitamin D deficiency increases systemic inflammation, as documented by elevated levels of C-reactive protein and interleukin-10 (2). Furthermore, administration of $1,25(OH)_2D$ to vitamin D-deficient individuals down-regulated inflammatory markers (C-reactive protein, and so on) and conferred an antiproliferative effect (43). Extrarenal synthesis of $1,25(OH)_2D$ occurs through cytokine stimulation (7) and is locally important in the paracrine regulation of cellular growth, differentiation, and function (44). This may explain why vitamin D deficiency has been associated with type 1 diabetes, cancer, and multiple sclerosis (45).

Outcome Studies

A recent meta-analysis of 18 randomized controlled trials comprising 57,000 individuals showed that a vitamin D intake >500 IU/day improved all-cause mortality, in part by decreasing CV deaths (46). Moreover, the data regarding both efficacy and CV safety for vitamin D appear to be superior to that for calcium supplements. Indeed, calcium supplementation has recently been implicated as possibly increasing the risk of adverse CV events, particularly in

patients with chronic kidney disease (47,48). Calcium supplements acutely increase serum calcium levels, which might accelerate arterial calcification (49). In contrast, serum vitamin D levels are inversely associated with coronary artery calcification (50).

Osteoporosis and atherosclerotic CV disease share many common risk factors, and a pathologic link between these 2 highly prevalent age-related diseases has been suggested (51). A large number of middle-aged to elderly individuals at risk for both CV disease and osteoporosis may benefit from therapies that are likely to improve both conditions, such as an anti-inflammatory diet, daily exercise (especially weight-bearing forms), avoidance of both tobacco and heavy alcohol intake, and possibly vitamin D supplementation.

Vitamin D and Myopathy

Myalgias are generally the first manifestation of vitamin D deficiency. Severe vitamin D deficiency with corresponding elevations of PTH were reported in 88% of women who presented with muscle pains and weakness (52). Another study investigated 150 patients with nonspecific musculoskeletal pains and reported that 25(OH)D levels were insufficient in 93% of individuals and severely deficient in 28% (53). A meta-analysis of 5 randomized clinical trials reported that vitamin D supplementation reduced the risk of falls, most likely from improved muscle function and strength (54). Myalgia, the most common complaint reported by patients on statin therapy, may be at least in part caused by underlying vitamin D deficiency. Anecdotally, we have observed that repletion of 25(OH)D levels predictably improves or resolves statin-related myalgias.
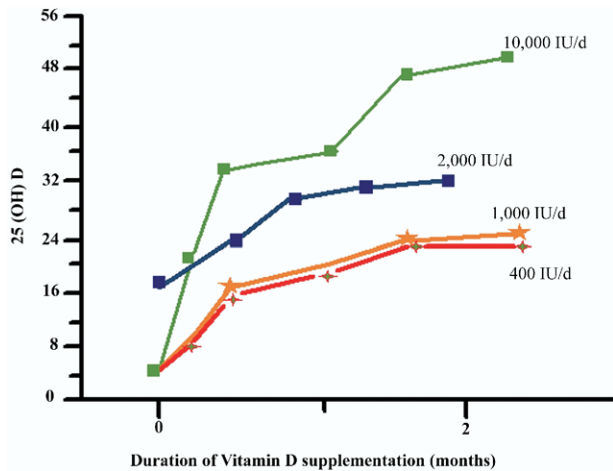
Supplementing Vitamin D

Traditionally, up to 95% of the body's vitamin D requirement comes from the synthesis in the epidermis on sun exposure, with the remainder ingested from dietary sources (Table 3) (55). The U.S. government's current recommendation for oral vitamin D is 200 IU daily for individuals age <50 years, 400 IU daily for individuals between age 50 and 70 years, and 600 IU for those older than age 70 years. Studies indicate that the average U.S. adult consumes about 230 IU vitamin D per day (56). However, it has been

Selected Food Sources of Vitamin D

Food	IU per Serving
Cod liver oil, 1 tablespoon	1,360
Wild-caught salmon, 3 oz	600–1,000
Farmed salmon, 3 oz	100–250
Mackerel, cooked, 3 oz	345
Tuna fish, canned in oil, 3 oz	200
Sardines (with bones), canned in oil, drained, 1 oz	250
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98

Data from Holick (1) and the National Institutes of Health (55).

**Response of Serum
Vitamin D Levels to Supplementation**

Effect of dose and duration of vitamin D supplementation on the mean serum 25-hydroxyvitamin D [25(OH)D] concentration achieved. Data from Vieth et al. (62).

estimated that 1,000 to 2,000 IU is necessary to satisfy the body's needs for most people (8). Many experts in the field suggest the recommended daily intake of vitamin D be increased to at least 800 to 2,000 IU of vitamin D daily, doses that are difficult to achieve without supplementation, particularly in higher latitudes and in areas of extreme winter climate. A dose of vitamin D_3 up to 2,000 IU daily has been deemed by the U.S. Food and Drug Administration's nutritional guidelines to be generally recognized as safe. A recent review concluded that the safe upper limit f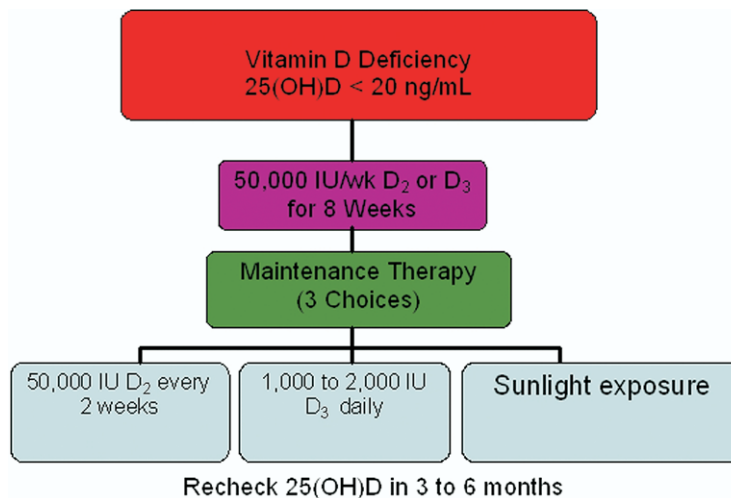or vitamin D consumption is 10,000 IU per day (57); doses above this increase risk of renal calculi formation, especially in patients with absorptive hypercalcuria and end-stage renal disease patients on dialysis (58).

A study of 340 children ages 10 to 17 years found that increasing the intake of oral vitamin D 10-fold, from the currently recommended dose of 200 to 2,000 IU daily, was required to reach a 25(OH)D level of 30 ng/ml (the lower end of the optimal range) (59). The investigators concluded that doses equivalent to 2,000 IU of vitamin D_3 daily were not only safe for adolescents, but also necessary for achieving the desirable vitamin D levels.

The most potent sources of vitamin D are sunlight (about 3,000 IU vitamin D_3 per 5 to 10 min of mid-day, midyear exposure of arms and legs for a light-skinned Caucasian) or prescription oral supplements of 50,000 IU capsule of either vitamin D_2 or D_3 every 2 weeks (1). Among foods, oily fish have the highest content of vitamin D_3, which ranges from 100 to 1,000 IU per 3.5 oz (1,60), whereas other sources such as milk or orange juice fortified with vitamin D contain up to 100 IU per serving.

As a general rule, every 100 IU vitamin D ingested daily increases the 25(OH)D level by about 1 ng/ml (61,62) (Fig. 5). Over-the-counter dietary supplements of vitamin D_2 and D_3 typically contain 400 to 5,000 IU per capsule. Oral supplementation with either vitamin D_2 or D_3 initially will increase vitamin D levels equally well (63), although the increases in serum 25(OH)D levels seem to persist longer after a bolus dose of vitamin D_3 than D_2 (64).

Treatment of vitamin D-deficient individuals should be initiated with 50,000 IU of vitamin D_2 or D_3 weekly for a period of 8 to 12 weeks. Once the initial repletion phase is complete, maintenance therapy can be continued in 1 of 3 ways: 1) 50,000 IU vitamin D_2 or D_3 every 2 weeks; 2)

Treatment Recommendations for Vitamin D Deficiency

25(OH)D = 25-hydroxyvitamin D.

1,000 to 2,000 IU vitamin D_3 daily; and 3) sunlight exposure for 5 to 10 min for Caucasians (longer times required for people with increased skin pigmentation) between the hours of 10 AM to 3 PM (spring, summer, and fall) (1,61) (Fig. 6).

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