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CURRENT THERAPEUTICS (SL SILVERMAN, SECTION EDITOR)

Vitamin D in the New Millennium

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Abstract The incidence of vitamin D deficiency is rising worldwide, yet in the vast majority of patients, the condition remains undiagnosed and untreated. Current evidence overwhelmingly indicates that supplemental doses greater than 800 IU/day have beneficial effects on the musculoskeletal system, improving skeletal homeostasis, thus leading to fewer falls and fractures. Evidence is also accumulating on the beneficial effects of vitamin D on extraskeletal systems, such as improving immune health, autoimmune disorders, cancer, neuromodulation, diabetes, and metabolic syndrome. The cause-effect relationship of vitamin D deficiency with increasing incidences of nonskeletal disorders is being investigated. Published reports support the definition of sufficiency, serum levels of 25-hydroxyvitamin D [25(OH)D] greater than 30 ng/mL (75 nmol/L). To achieve this, most people need vitamin D supplementation ranging from 600 to 2000 IU/day; consumption up to of 5000 international units (IU) per day of vitamin D is reported as safe. Although light-skinned individuals need 1000 IU/day of vitamin D, elderly and dark-skinned individuals are likely to need approximately 2000 IU/day to maintain serum 25(OH)D levels greater than 30 ng/mL. Other vulnerable patients, such as the obese, those who have undergone bariatric surgery, and those with gastrointestinal malabsorption syndromes, may require higher doses of vitamin D to maintain normal serum levels and be healthy.

Keywords Bone mineral density (BMD) · Fractures · Osteoporosis · Rickets · Supplements · Syndrome · Osteomalacia · Vitamin D

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Introduction

Vitamin D deficiency is one of the most common and underdiagnosed medical conditions in the world. Emerging evidence indicates vitamin D deficiency may be pandemic [1–3]. Vitamin D facilitates the absorption of calcium from the intestines and is essential for skeletal health: bone mineralization, remodeling, and maintenance. Epidemiologic and cross-sectional data suggest that vitamin D sufficiency has beneficial effects on extraskeletal body systems, including promoting immune and metabolic functions and protection from cancer [4–16], especially when comparing the highest and lowest tertiles; only a few authors have reported a lack of association [17–19]. Irrespective of age, adequate vitamin D is essential for optimal human health for everyone.

Children with severe vitamin D deficiency may present with rickets and skeletal deformities. In adults, vitamin D deficiency can lead to osteomalacia, muscle weakness [20–24] and falls [25, 26], osteoporosis, and fractures [27–30]. Humans obtain vitamin D via sun exposure, and from food and dietary supplements. Two forms of vitamin D—vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol)—are available as supplements and included in certain fortified foods. Although both forms can increase available vitamin D levels in the blood, vitamin D_3 generally seems to produce higher amounts of circulatory vitamin D levels secondary to its longer

retention time in the body. Sensible exposure to sunlight and a better intake of dietary and supplemental vitamin D can prevent vitamin D deficiency, cost-effectively. Most adults need between 600 and 2000 international units (IU) of vitamin D per day to maintain physiologic levels of serum vitamin D.

Functions of Vitamin D

The major function of vitamin D is to provide and maintain adequate calcium and phosphorus in the body to facilitate optimal metabolic functions. In addition, vitamin D deficiency impairs reproductive success [5, 6] and the ability to combat infections, in particular, tuberculosis, viral infections, and influenza [7–9]. It may precipitate or worsen autoimmune conditions [31, 32] and increases the incidences of deaths associated with heart disease [33–35], stroke secondary to hypertension [36], inflammatory bowel disease [10], muscle weakness and falls [25, 26], fractures [37••], and cancers of the breast, colon, and prostate [13, 14, 38, 39]. Nevertheless, potential confounders, such as drug interactions, variability in sun exposure and physical activity, intensity of skin pigmentation, vitamin D assay viabilities, and overall nutritional status on reported beneficial outcomes, must be considered carefully [37••].

Prevalence of Vitamin D Deficiency

The NHANES (National Health and Nutrition Examination Survey) has reported a marked decrease in serum 25-hydroxycholecalciferol [25(OH)D] levels in the United States population, from the late 1980s to the early 2000s [2]. Accordingly, approximately 90% of the dark-skinned people in the United States and more than 50% of the white population have vitamin D insufficiency or deficiency. Insufficiency is defined as serum vitamin D levels less than 30 ng/mL. The proactive identification of those who are vulnerable of having vitamin D deficiency and vigorous treatment with therapeutic doses of vitamin D supplementation seem rational and cost-effective in preventing morbidities.

More than half of North American postmenopausal women receiving osteoporosis treatments have vitamin D inadequacy [40], and 88% of women with fractures have serum 25(OH)D levels less than 20 ng/mL [41]; other studies also have confirmed these results [42, 43]. Those with African ethnicity and Asians living in Western countries have a three- and twofold higher prevalence, respectively, of vitamin D deficiency than do white Caucasians. A number of these studies also demonstrate the negative effects of low vitamin D levels on bone metabolism, as reflected by lower bone mineral density (BMD), increased markers of bone turnover, and increased serum parathyroid hormone (PTH) levels, especially when serum 25(OH)D concentrations are less than 20 ng/mL [27, 43, 44].

Generation and the Types of Vitamin D

When administered daily, vitamins D_2 and D_3 generally are considered equivalent in humans [45, 46••]. However, when administered intermittently, cholecalciferol is reported to be twice as potent as ergocalciferol in increasing serum 25(OH)D and modulating serum PTH [47, 48], whereas others have reported that 50,000 IU of D_2 or D_3 produced similar increases in the serum vitamin D level [49]. This phenomenon is attributable to the longer serum half-life of D_3 and its affinity to the D-binding protein. Data suggest that equal serum 25 (OH)D levels can be achieved by administering either of the two forms daily or weekly [45]. In light of the half-life differences, it seems logical to use D_3 when supplementing with longer intervals, such as biweekly or once a month [50].

Cholecalciferol, the "sunshine vitamin," is synthesized in the skin after exposure to solar ultraviolet B (UVB) rays, which converts 7-dehydrocholesterol to previtamin D upon photolytic, nonenzymatic reaction. This previtamin D_3 isomerizes in the skin to form vitamin D_3, before moving to the liver. Vitamin D_3 is transported preferentially from the skin to the liver via the vitamin D–binding protein for which vitamin D_3 has severalfold higher affinity than previtamin D [51]. The pathway of generation of vitamin D is illustrated in Fig. 1A.

25(OH)D needs to be hydroxylated to its active form before it facilitates calcium and phosphorus homeostasis. Vitamin D undergoes two hydroxylation reactions. In the liver parenchymal cells, it is hydroxylated into calcidiol [25(OH)D] in a substrate-dependent manner using cytochrome P450 enzymes [52]. In a highly regulated process in the renal tubules, subsequently, mitochondrial hydrolase CYP27B1 converts 25(OH)D via C^1-hydroxylation to 1,25-hydroxyvitamin D [$1,25(OH)_2D$; calcitriol]. This process is stimulated by PTH and inhibited by calcium and fibroblast growth factor-23 (FGF-23).

The serum level of $1,25(OH)_2D$ is 1000-fold less than that of 25(OH)D. $1,25(OH)_2D$ is distributed via the circulation throughout the body and acts on its specific receptors in target cells; thus, it is considered a hormone. Once the serum calcium level is normalized, several mechanisms are activated to downregulate the production of $1,25(OH)_2D$, including FGF-23–associated activation of 24-hydroxylase, which suppress the PTH-driven 1α-hydroxylase axis (Fig. 1B). The 1α-hydroxylase enzyme is also present in extrarenal tissues, including keratinocytes, monocytes, macrophages, and T- and B-lymphocytes, which are not regulated by feedback mechanisms. Therefore, in certain conditions, unregulated

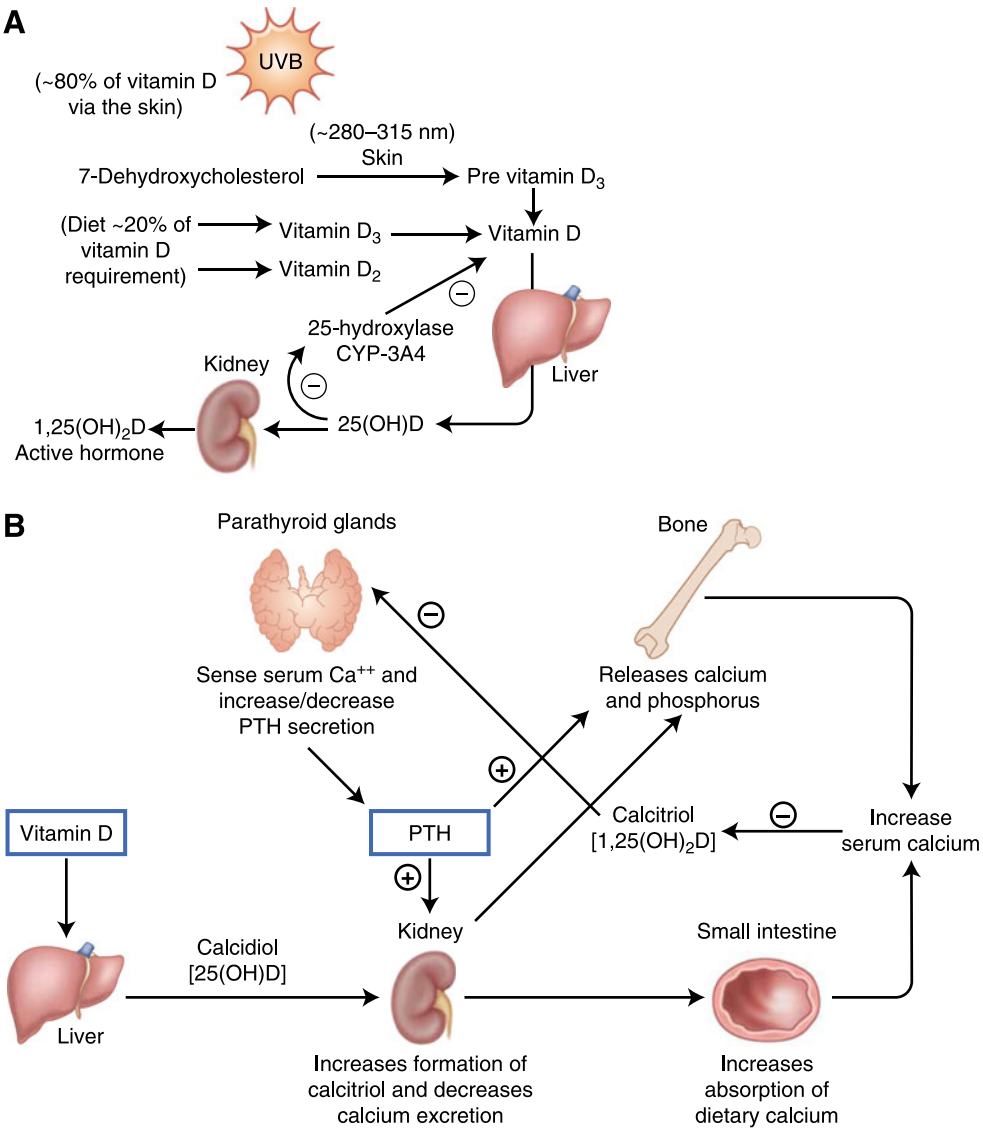

Fig. 1 **a,** The final common pathways of generation of 25 (OH)D and 1,25(OH) $_2$D, the feedback loop, and the roles of skin, liver, and the kidney. Eighty percent of the vitamin D requirements of humans is generated through UVB rays after skin exposure to sunlight. **b,** Illustrate the physiologic role of PTH in the maintenance of serum calcium level. Key target organs for PTH; bone, kidney and intestine, and their feedback interactions with calcium are illustrated. **c,** Feedback hormonal control of calcium metabolism. Low serum ionized calcium enhances the secretion of PTH from parathyroid glands. Subsequently, PTH increases the synthesis of $1,25(OH)_2D$, stimulates calcium absorption from the intestine, and mobilizes calcium from the skeleton to maintain normocalcemia, and negatively regulates PTH synthesis and release. FGF-23—fibroblast growth factor-23; PTH—parathyroid hormone; UVB—ultraviolet B

excess production of $1,25(OH)_2D$ may lead to hypercalcemia. The feedback cycle of the generation of 25(OH) and 1,25 $(OH)_2D$ is shown in Fig. 1C.

$1,25(OH)_2D$'s interactions with its receptors modulate a large number of genes that lead to its biological actions, such as the absorption of calcium and phosphorus in the intestinal epithelium, activation of enzymes, and neural activity [53]. $1,25(OH)_2D_3$ is the high-affinity ligand for the vitamin D receptor (VDR) in key target tissues, such as the intestine, parathyroid cells, kidney, and bone, where it modulates the expression of vitamin D–dependent genes. The VDR is involved in many classic actions of $1,25(OH)_2D$, such as calcium transportation, antiproliferative, prodifferentiating, and immunomodulatory activities. $1,25(OH)_2D$ is also required for nongenotropic actions [54, 55], including rapid activation of protein kinases and modulation of the electrical state of cells (eg, activating calcium and chloride membrane ion channels) [56, 57].

Vitamin D Deficiency and its Diagnosis

Vitamin D deficiency is diagnosed by the measurement of total serum 25(OH)D levels (ie, the combination of D_2 plus D_3) at or below 20 ng/mL (≤50 nmol/L) [58, 59], and insufficiency is defined as serum 25(OH)D of 20 to 29 ng/mL (50 to 74 nmol/L) (Table 1). Levels ≤10 ng/mL (≤25 nmol/L) are considered severe vitamin D deficiency and may be associated with signs and symptoms [60]. In general, immunoassays measure $25(OH)D_2$ and $25(OH)D_3$ equally [61]. Most reports during the past decade have suggested the minimum desirable serum 25(OH)D level between 28 and 32 ng/mL (~75 nmol/L) [58, 60, 62, 63]. The current definitions and the cutoff levels for diagnosis of vitamin D deficiency, insufficiency, and adequacy are illustrated in Table 1.

Vitamin D deficiency leads to a compensatory increase of PTH secretion, leading to secondary hyperparathyroidism (Fig. 1B), which stimulates the renal tubular 1α-hydroxylase

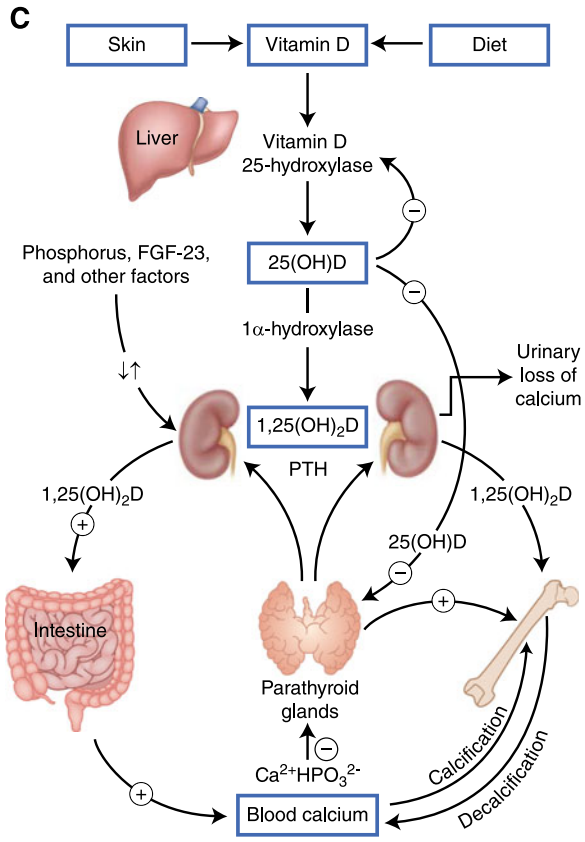

Fig. 1 (continued)

activity and a subsequent increased production and release of $1,25(OH)_2D$ into the circulation. Thus, only at very low levels of 25(OH)D do the serum $1,25(OH)_2D$ levels begin to decline; so the serum $1,25(OH)_2D$ level is not a useful marker in diagnosing vitamin D deficiency [64].

The methodologies used to measure serum 25(OH)D include immuno-based vitamin D assays, such as radioimmunoassay, enzyme-linked immunosorbent assay, and chemiluminescent immunoassays [65]. However, these assays are associated with biases. Such tendencies can be minimized by using physical methods, such as high-performance liquid chromatography and liquid chromatography—tandem mass spectrometry (LC/MS/MS) technology [66, 67]. Recent advances in the LC/MS/MS assay methodology have further refined the accuracy and precision of these measurements [68, 69, 70•].

Risk Factors for the Development of Vitamin D Deficiency

Insufficient exposure or avoidance of sunlight exposure [71]; being homebound or nonambulatory; poor conversion of precursor to vitamin D in aged skin, such as in the elderly or dark-skinned people [72]; being institutionalized [44, 71, 73]; and the long-term use of some medications, such as anticonvulsants, glucocorticoids, or any medications that enhance vitamin D catabolism or decrease its absorption, are some of the key risk factors for development of vitamin D deficiency [74–77].

Modern Western diets are low in calcium and rich in phosphorus. Moreover, recent human behaviors, including sunlight avoidance, relative inactivity, longevity, and the associated aging process further diminish the ability of the skin to generate vitamin D, which then decreases intestinal absorption of calcium. Burn injuries cause skin damage and long-term musculoskeletal complications. Burn scars and even the normal skin adjacent to burn scars have less ability to transform 7-dehydrocholesterol into previtamin D. This may explain in part the consistently low serum vitamin D levels, decreased bone formation, and low bone mass reported in children even several years following their burn injuries [78].

Asians who immigrate to Europe and North America are known to have lower serum 25(OH)D levels and a higher incidence of rickets and osteomalacia than do white Caucasians [79, 80]. Others who are vulnerable to vitamin D deficiency include those with gastrointestinal diseases such as celiac disease, malabsorption syndromes, obesity, and developmental disabilities [75, 76]. Those who have had rapid weight loss after dieting or bariatric surgery are particularly vulnerable to vitamin D deficiency [81].

Presentation of Patients with Vitamin D Deficiency

The nonspecific nature of clinical signs and symptoms of vitamin D deficiency leads to difficulty in making a clinical diagnosis. The serum levels must be very low for a long period before a patient exhibits classic clinical signs and symptoms of vitamin D deficiency, such as rickets in children, and proximal myopathy or osteomalacia in adults. Other signs and symptoms of vitamin D deficiency include lethargy; increased incidence of infection; exacerbation of existing or worsening chronic diseases such as inability to lose weight, rheumatoid arthritis, generalized pains; low back pain, muscle aches, and bone pain [82, 83]. Occasionally, routine x-rays may reveal painful skeletal sites visualized as pseudo-fractures [84]. Vitamin D deficiency is increasingly recognized in patients with chronic renal disease and those with frequent falls and impaired physical function [71, 85, 86].

Vitamin D Deficiency and Falls

Evidence is mounting to support that appropriate vitamin D supplementation reduces falls, improves body sway and reflexes [26, 87], and decreases risk of falls [27, 71, 88,

Table 1 Vitamin D status and the terminology

Status—Terminology	Serum 25(OH)D levels[a]	
	ng/mL	nmol/L
Severe deficiency: Leading to rickets in infants and children and osteomalacia in adults	<10	<25
Deficiency: Inadequate for skeletal and overall health; thought to increase morbidities due to various illnesses	10–19	25–49
Insufficiency: May impair skeletal health and overall health	20–29	50–74
Optimal (healthy) range	30–60	75–150
Intoxication: Considered potentially toxic, as indicated by hypercalcemia and hyperphosphatemia, etc.	≥ 100	> 250

[a] Depending upon the laboratory/country, serum concentrations of 25(OH)D are reported in nanograms per milliliter (ng/mL) or nanomoles per liter (nmol/L) (1 ng/mL=2.5 nmol/L). One microgram of vitamin D increases circulatory vitamin D by approximately 1 nmol/L (~0.4 ng/mL). 100 IU of vitamin D is expected to increase the serum vitamin D level by 1 ng/mL

89] and fractures in the elderly [90]. Improving vitamin D status is an important modifiable risk factor for reducing falls and fractures. Nevertheless, because the half-life of vitamin D is days, to be effective in fall reduction, the vitamin D needs to be administered more frequently than once every 6 months or once a year. Because muscle weakness and muscular incoordination are important risk factors for falls and fractures, vitamin D deficiency should be rectified in all osteoporotic and fracture patients. Taking these data together, it is logical to initiate programs to supplement all residents of nursing homes and developmental disability facilities, and most of our elderly population, even without measurement of serum 25(OH)D levels.

Vitamin D and Skeletal Health

Vitamin D is essential for calcium absorption, mineralization, and maintenance of the skeleton [37••]. Suboptimal levels of vitamin D are associated with reduced BMD [91, 92], osteoporosis [93], and fractures [30, 94–96]. Nevertheless, osteoporosis treatments primarily focus on pharmacologic antiosteoporosis therapies, instead of inexpensive healthy lifestyles changes, weight-bearing exercises, and correction of vitamin D deficiency [37••].

Vitamin D supplementation with or without calcium decreases serum PTH levels, alleviates secondary hyperparathyroidism [97], decreases bone turnover, improves muscle function, reduces falls among aged care residents [71, 98], and reduces risks of hip and other osteoporotic fractures [27, 44, 99]. Moreover, vitamin D and calcium have been shown to decrease the incidence of hip and other peripheral fractures in nursing home residents [93]. Figure 1B illustrates the sequence of events that leads to development of secondary hyperparathyroidism and consequent negative calcium balance, poor bone quality, osteoporosis, and fragility fractures.

Bone Metabolism

Treatment of vitamin D insufficiency in patients with low bone mass results in a rapid increase in BMD [100], perhaps due to mineralization of the accumulated excess osteoid tissue. It is possible that the levels of serum $1,25(OH)_2D$ necessary to trigger optimum intestinal calcium absorption may not be the same as those required for calcium released from bone or skeletal mineralization [101, 102]. Moreover, using VDR-knockout mice, VDR-independent but calbindin-D9k–dependent intestinal calcium absorption has been reported [103–105]. Others have reported active intestinal calcium transportation even in the absence of calbindin-D9k [106, 107].

PTH-mediated bone resorption may require calcium-stimulated calcium-sensing receptor (CaSR)–mediated enhancement of osteoclastic activity [108]. This suggests interactions between the CaSR, 25(OH)D, and 1α-hydroxylase–modulating skeletal growth and bone turnover. Evidence suggests that such interactions are mediated by stimulation of osteoblast/stromal cell production of receptor activator of nuclear factor-κB ligand (RANKL), the key regulator of osteoclast recruitment and differentiation [109, 110]. However, in vitro osteoblasts from VDR-knockout mice cannot enhance osteoclast differentiation from progenitors in the presence of $1,25(OH)_2D$ but can do so in the presence of PTH and interleukin-1α, suggesting that vitamin D has specific effects on osteoclasts.

Reduction of Fractures with Vitamin D

Several studies have suggested that higher-dose vitamin D supplementation prevents fractures [27, 28, 89]. A meta-analysis of eight randomized trials involving 2426 older patients demonstrated that daily doses of vitamin D (700–1000 IU) lowered fracture risk by 19% [111]. In addition,

the Women's Health Initiative study suggested that every 10-ng/mL decrease in serum vitamin D level doubles the risk of hip fractures, especially when the levels are less than 30 ng/mL [95]. The analysis by Bergman et al. [112] supports the use of cholecalciferol 800 IU daily to reduce the incidence of osteoporotic fractures in women older than 50 years.

Another meta-analysis that consisted of five randomized clinical trials (RCTs) (n=9294) of hip fracture and seven RCTs (n=9820) of nonvertebral fractures with oral vitamin D with or without calcium reported a significant reduction of fractures [27]. Vitamin D in doses in excess of 700 to 800 IU/day reduced the risk of hip and nonvertebral fracture by 26%, compared with calcium alone, placebo, or low doses of 400 IU of vitamin D per day [27]. Many studies have reported that vitamin D sufficiency is associated with a low incidence of fractures [29, 30, 96]. Nevertheless, one study failed to confirm the fracture benefits of treating ambulatory patients 65 to 71 years old using 800 IU of cholecalciferol [113], but fracture data were collected by telephone interviews. A Cochrane review also reported that vitamin D_3 reduced hip fractures [29]. Overall, the Cochrane reviews [29, 90, 111, 114] suggest higher doses of vitamin D are more effective and provision of calcium with vitamin D is helpful.

Although the fractional calcium absorption may increase following the normalization of serum vitamin D levels, calcium supplementation may be indicated when the dietary calcium intake is insufficient. Calcium intake over 800 mg per day may be beneficial for improved BMD, only when 25 (OH)D levels are less than 20 ng/mL (<50 nmol/L) [94]. In this study, 25(OH)D status was found to be more important than increasing dietary calcium intake for improving hip BMD. Another meta-analysis reported that calcium supplementation alone or in combination with vitamin D was effective in the prevention of osteoporotic fracture [115]; whereas another showed no reduction in hip fracture risks with calcium supplementation [116]. Overall, the relative reduction of fracture risk was greater in individuals who were elderly, living in institutions, and had a low baseline calcium intake.

Optimization of Serum Vitamin D Levels

The 2010 Institute of Medicine (IOM) report on vitamin D suggests a serum level of 20 ng/mL (50 pmol/L) is adequate for health [117••], but many other studies indicate that at least 30 ng/mL is necessary to obtain its physiologic benefits [2, 100]. Others have suggested that supplementation with 2600 IU/day of oral vitamin D would ensure 97% of the elderly patient population achieve the desired serum vitamin D level [58, 101]. Supplementation of 2000 and 4000 IU vitamin D per day may be necessary to reduce the risks of autoimmune diseases and cancer [64, 118]. Meanwhile, the IOM [117••] and the Endocrine Society reports [46••] recommend increasing the upper limit of intake of vitamin D to 4000 IU/day, demonstrating its safety.

Many individuals in temperate and colder climates do not get adequate sunlight exposure or oral vitamin D through their diet to protect skeletal health. To produce enough vitamin D in a fair-skinned person, it is necessary to expose 15% of the body surface—hands, face, and arms or equivalent area of skin—to sunlight for 10 to 15 min, four to six times a week [50, 119–125], but this is dependent on the level of its precursor, 7-dehydrocholesterol, present in the skin [126] (Fig. 1A). In light-skinned persons with optimal sun exposure and a minimal erythemal dose, the skin would generate approximately 10,000 IU of vitamin D_3 within 24 h of exposure. Generally, it takes about 7 to 14 days to peak the serum vitamin D level after exposure to sunlight.

High quantities of vitamin D are found naturally in a limited number of foods, including fatty fish and irradiated mushrooms. However, in some industrialized countries, vitamin D is added to certain foods, such as milk, milk powder, yogurt, orange juice, margarine, infant formula, and breakfast cereals. Some calcium supplements and most multivitamins contain small amounts of vitamin D. Most multivitamin tablets contain between 200 and 400 IU of vitamin D and 200 mg of calcium. Calcium and vitamin D combination tablets are commonly available; each tablet supplies 200 to 600 IU of vitamin D and 200 to 600 mg of calcium. Some recently introduced multivitamin preparations contain 1000 IU of vitamin D. Calcium supplementation exceeding more than 1000 mg a day may not be safe. The current recommendation is to keep the total calcium intake, dietary and calcium supplements together, between 1200 and 1500 mg per day. One needs to be aware that some supplements and multivitamins also contain vitamin A, which can be toxic if intake exceeds the recommended dietary allowance (RDA).

Clinical Guidance for Vitamin D Supplementation

Measurement of serum vitamin D levels 3 to 4 months after completion of therapeutic doses can determine whether a patient needs additional high-dose vitamin D therapy or whether the maintenance vitamin D doses are adequate. The goal is to achieve a minimum stable serum vitamin D level of 30 ng/mL (75 nmol/L). However, one needs to be watchful, as correction of secondary hyperparathyroidism in some patients may take several months. If the serum PTH is not normalized after the serum 25(OH)D level is normalized, it is necessary to exclude the possibility of coexisting primary hyperparathyroidism [127]. The use of artificial

UVB irradiation or lamps to raise serum vitamin D levels has been explored in patients with several disorders [128–131]. These studies are of short duration; thus, the longer-term safety of using artificial ultraviolet exposure as a therapeutic modality to raise serum vitamin D levels, albeit possible, is not yet established.

Children, pregnant women, institutionalized patients, obese patients, and those who have experienced rapid weight loss, gastric bypass patients, those taking antiepileptic drugs, those living in northern latitudes during winter months, people with darker skin who live in northern latitudes, and those who avoid sunlight should be considered for routine supplementation with vitamin D [24, 132–134]. Patients with celiac disease, inflammatory bowel syndrome, cystic fibrosis, recurrent infections, or chronic liver and kidney disease and those receiving antiretroviral or long-term glucocorticoid therapies also should be considered for longer-term supplementation with vitamin D. Such interventions are simple, safe, and likely to be cost-effective in decreasing disease burdens.

After an oral dose of 50,000 IU of vitamin D, a peak serum 25(OH)D level is achieved in approximately 3 days. There are many ways one can supplement vitamin D. There are two easy and practical regimens for administering therapeutic doses of vitamin D. Regimen 1): For patients with serum vitamin D level less than 10 ng/mL, administer 50,000 IU three times a week; for a level between 11 and 20 ng/mL, administer 50,000 IU twice a week; and between 21 and 29 ng/mL, administer 50,000 IU once a week for 6 to 10 weeks. Regimen 2): Administer a varying loading dose followed by 50,000 IU twice a week, as illustrated in Table 2.

Some suggest giving extra an 100 IU for each nanogram per milliliter decrement in 25(OH)D, whereas others prefer to correct the deficiency quickly. Because of marked depletion of vitamin D stores in the body, several months of low-dose daily treatment is required to normalize serum vitamin D levels, whereas therapeutic doses such as 50,000 IU once a week would rapidly bring the serum vitamin D levels to the normal range. In patients with vitamin D deficiency, the deficits of vitamin D are in the range of half to one million international units, or more. Thus, there is no reason to be fearful of prescribing higher doses of vitamin D for patients with deficiency, for short periods.

Vitamin D Supplementation

At-risk individuals may need vitamin D supplements in higher-than-usually-accepted doses (eg, 2000 IU/day or 50,000 IU every 2 to 4 weeks) to maintain physiologic levels of serum vitamin D and health [135]. In a few patients, serum 25(OH)D levels may not normalize for reasons that include nonadherence to therapy, malabsorption, sequestration in fat, or increased catabolism. Such patients may require 50,000 IU once or twice a week for several months or years to maintain normal serum vitamin D levels. Another category of patients who require such high doses of vitamin D are the obese and those who have undergone bariatric surgery.

Once the target serum vitamin D level is reached, most patients need a maintenance dose of vitamin D between 1000 and 2000 IU a day, or 10,000 IU once a week, or 50,000 IU of vitamin D_3 once a month. Without such maintenance doses, serum vitamin D levels will revert to insufficient levels in the vast majority of patients, within a few months. Parenteral vitamin D (marketed as 300,000 IU/mL) is available in some countries but not in the United States.

Potential Toxicity

Because of the potential for the development of hypercalcemia and hypercalciuria, vitamin D supplementation should

Table 2 Guidelines for using therapeutic doses of 50,000 IU of vitamin D oral supplementation

Serum vitamin D (ng/mL)	Frequency of administration	Duration of therapy (weeks)	Total dose for correction[a] (IU millions)
≤5	300,000 IU, one dose; and 2 times/week	12	1.5
6–10	2 times/week	12	1.2
11–15	2 times/week	10	1.0
16–20	2 times	8	0.8
21–25	1 time	12	0.6
26–30	1 time	8	0.4
31–40	50,000 IU	Monthly	Maintenance
	or 1000 IU	Daily	Maintenance
Those with low initial levels (<15 ng/mL) likely to require higher maintenance doses		2000 IU daily	Maintenance dose

[a] Normalizing serum vitamin D levels as well as the body's vitamin D stores

be used sparingly in patients with granulomatous diseases, metastatic bone disease, sarcoidosis, and Williams syndrome [136, 137]. Vitamin D intoxication has also been associated with recurrent pancreatitis secondary to hypercalcemia [138]. Careful supplementation is necessary for these patients to prevent manifestations of vitamin D deficiency while preventing hypercalcemia and hypercalciuria.

Because vitamin D is a fat-soluble compound, there are concerns regarding potential toxicity from excessive intake. However, toxicity is unlikely to occur with dosages of less than 5000 IU/day even with longer-term treatment [117••, 139]. In fact, some studies have shown it is safe to take as much as 10,000 IU/day of vitamin D [140]. Isolated cases of vitamin D toxicity have occurred [141, 142]. The half-life of $1,25(OH)_2D$ is 4 h, but 25(OH)D in the circulation lasts for many days. Therefore, depending on the toxicity levels, it takes many weeks or sometimes months to normalize serum calcium levels in such patients. Signs and symptoms of vitamin D toxicity mirror those of hypercalcemia: headache, irritability, metallic taste, nephrocalcinosis, vascular calcinosis, renal impairments, pancreatitis, dehydration, nausea, and vomiting.

Achieving Vitamin D Sufficiency

Until 2010, the RDA of vitamin D was 400 IU [143]; the level has been increased to 600 IU/day but still is far from adequate [144–146]. In most patients, in the absence of exposure to sunshine, such doses will not maintain circulating serum 25(OH)D levels above 30 ng/mL [139, 147]. In 2010, the North American IOM report recommended the 600-IU/day dosage with calcium 1000 to 1200 mg/day in diet plus supplements [117••]. The broader evidence indicates that these dosages may not be sufficient to overcome vitamin D deficiency in many patients.

Conclusions and Recommendations

Formal studies and clinical observations support the role of vitamin D in promoting a variety of health indices and good bone health [148–150]. Sunlight exposure often is limited by lifestyle and other choices, making it difficult to obtain enough vitamin D from diet alone; these patients are likely to require long-term supplementation. Considering the available facts, the introduction of a national policy to provide routine supplementation of vitamin D to vulnerable populations, such as residents of nursing homes or developmental disability centers, not only would reduce various morbidities, falls, and fractures, but also would eliminate other morbidities with minimal cost. Considering the cost of measurement of serum vitamin D, the high safety margin of supplementation, and the high incidence of vitamin D insufficiency, it would be practical, convenient, and cost-effective to supplement such vulnerable populations with 50,000 IU of vitamin D once or twice a month on a long-term basis, which would cost approximately $10 to $15, per patient, per year. Meanwhile, the use of sunscreen with greater than 12 sun protection factor (SPF) prevents the generation of vitamin D in the skin [37••, 151].

Extra vitamin D should be provided to premature infants and those who are exclusively breast-fed. Serum 25(OH)D levels are inversely associated with being overweight, abdominal obesity, metabolic syndrome, systolic blood pressure and stroke, and plasma glucose concentrations [152]. Vitamin D deficiency is associated with secondary hyperparathyroidism [153], higher systolic blood pressure, lower serum calcium, lower high-density lipoprotein levels, and increased incidence of insulin resistance [132]. Moreover, lower serum 25(OH)D levels are associated with increased morbidity and mortality [154], all-cause mortality [155–157], myocardial infarction [158], and diabetes [159–162]. Normalization of vitamin D reverses some of these negative phenomena.

Older adults can safely take more than 100% of the daily RDA of vitamin D. Daily consumption of vitamin D–fortified foods, such as skim milk and other dairy products, is encouraged. However, to maintain serum vitamin D levels$\geq$ 30 ng/mL ($\geq$ 50 nmol/L), 1000 IU (25 μg) of vitamin D per day for adults and 2000 IU (50 μg) per day for adults older than 65 years are necessary.

Disclosure Conflicts of interest: S.J. Wimalawansa: has published a book for primary care physicians on vitamin D; no sponsorships to date, and no other conflicts exist.

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