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Review

Critical reappraisal of vitamin D deficiency

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ABSTRACT

The current surge of interest in vitamin D is fuelled not only by evidence that vitamin D supplementation decreases the risk of osteoporotic fractures but also by vast observational studies indicating a variety of beneficial extraskeletal effects (including decreases in the risks of cancer, inflammatory diseases, and even death). Serum 25-hydroxyvitamin D (25(OH)D) assay is now a highly reliable method for evaluating vitamin D stores in individual patients. Nevertheless, the normal or desirable 25(OH)D range for patients seen in everyday clinical practice needs to be more accurately defined. Maintaining serum 25(OH)D above 75 nmol/L is currently recommended to ensure optimal bone health, but higher levels may be required to obtain some of the extraskeletal benefits. Naturally occurring vitamin D is by far the most widely used form for correcting vitamin D deficiency, and the hydroxylated derivatives have only a few highly specific indications. However, controversy persists about the optimal modalities of natural vitamin D supplementation in terms of the type of vitamin (D2 or D3), schedule (once daily or at wider intervals), and route (oral or injectable). For chronic supplementation to protect against bone loss, a daily dosage of at least 800 IU seems required. Higher dosages (e.g., 100,000 to 200,000 IU every 2 months for 6 months) may be needed to correct established vitamin D deficiency; a repeat 25(OH)D assay after 4 to 6 months may help to assess the treatment response and to adjust the subsequent vitamin D dosage. The current emphasis is on the detection of vitamin D deficiency in the general population and in subgroups at risk for osteoporosis followed by an assessment of severity and the initiation of appropriate treatment. From a public health perspective, supplying at least 800 IU per day seems useful and safe.

Vitamin D – which is not a vitamin, as it can be produced by the body as vitamin D3 derived from 7 dehydrocholesterol – is generating a strong surge of interest fueled not only by its well-known effects on bone but also by recent evidence of extraskeletal effects [1,2]. A reappraisal of the skeletal and systemic effects of vitamin D should include an effort to devise operational definitions of vitamin D deficiency and repletion.

Vitamin D is available either as ergocalciferol (vitamin D2) or as cholecalciferol (vitamin D3). Ergocalciferol, which is derived from plants, is converted by the liver to 25-hydroxyvitamin D2 (25(OH)D2), then by the kidneys to 1,25-dihydroxyvitamin D2 ($1,25(OH)_2$ D2). Similarly, cholecalciferol, from animal sources, is converted to 25(OH)D3 then $1,25(OH)_2$ D3 [1,3,4]. Cholecalciferol is abundant in a few food sources (e.g., fish liver) and is often used as a dietary supplement, either alone or with calcium. Ultraviolet B (UV-B) radiation (290–315 nm) converts 7-dehydrocholesterol in the deep epidermal layers to the provitamin cholecalciferol [4,5].

1. Vitamin D status evaluation

Before the introduction of vitamin D assays, the diagnosis of vitamin D deficiency relied on symptoms of osteomalacia such as pain, muscle fatigability, and impotence. Vitamin D deficiency is still overlooked occasionally and the symptoms mistakenly ascribed to generalized osteoarthritis or aging. Thus, serum vitamin D assays play a crucial role in the diagnosis of vitamin D deficiency.

1.1. 25(OH)D assay

The serum 25(OH)D level reflects the vitamin D stores in the body. An assay that recognizes both 25(OH)D2 and 25(OH)D3 should be used. The result is given in nmol/L (= 2.5 × ng/ml). The 25(OH)D level dips in winter and increases in summer [1,5,6]. Measurement of the active form $1,25\ (OH)_2D$ is not useful in clinical practice.

The normal 25(OH)D values remain ill-defined, for several reasons. Studies have shown considerable interindividual variability in 25(OH)D levels related to differences in sunshine exposure, clothing style, skin pigmentation, skin thickness, age [5], and weight (with lower levels in heavier individuals due to storage

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of vitamin D in fat) [1,2]. In addition, assay methods vary across studies and no standardized assay method is available, which complicates the definition of normal ranges and cutoffs [6,7]. One study found 86% higher values with a competitive protein binding assay than with a high-performance liquid chromatography assay [8]. Moderate vitamin D deficiency is defined as a serum 25(OH)D level lower than 25 nmol/L and mild deficiency (or insufficiency) as a level between 25 and 50 nmol/L [9], although this classification has been challenged [1,2].

Studies found high prevalences of vitamin D deficiency in a variety of populations, regardless of the definition used. In the northern US, nearly 40% of pregnant women had vitamin D deficiency [10]. Mild-to-moderate vitamin D deficiency has been reported in children, adolescents, and young adults. Among teenagers in Boston (MA, USA), 42% had 25(OH)D levels $\leq$ 50 nmol/L, 24.1% $\leq$ 37.5 nmol/L, and 4.6% $\leq$ lower than 20 nmol/L [11]. A study of 175 male teenagers in a rural area north of Paris (France) showed that the mean 25(OH)D level was 58.5 $\pm$ 18.0 nmol/L in late summer and 20.6 $\pm$ 6.0 nmol/L in late winter (P = 0.0001) and that the serum level of intact parathyroid hormone reached a plateau when the 25(OH)D level was above 82 nmol/L [12]. Among 1569 healthy in France, 14% had 25(OH)D levels $\leq$ 30 nmol/L [13]. In a population of patients seen for osteoporosis advice, serum 25(OH)D was < 50 nmol/L in 32% and lower than 75 nmol/L in 72% of individuals [14]. 25(OH)D levels were $\leq$ 75 nmol/L in 64% of women with osteoporosis [15] and in 97% of women admitted for osteoporotic fractures, among whom 21% had levels < 15 nmol/L [16]. Similarly, among women with osteopenia or osteoporosis in France, nearly 90% had 25(OH)D levels < 75 nmol/L and more than 50% had levels < 50 nmol/L [17]. In a clinical trial of bazedoxifene, 25(OH)D was assayed in 7441 postmenopausal women with osteoporosis living in 29 countries at various latitudes [18]. 25(OH)D was < 25 nmol/L in 5.9% of patients in winter and 3.0% in summer and was > 75 nmol/L in only 21.2% of patients in winter and 27.5% in summer. 25(OH)D levels were higher in the Scandinavian countries than elsewhere in Europe, as a result of greater use of multivitamin supplements (and of cod-liver oil in Iceland) [19].

1.2. Indirect evaluation based on the effects of vitamin D deficiency

A number of indirect criteria can be used to evaluate the prevalence of vitamin D deficiency such as the 25(OH)D cutoff below which hyperparathyroidism or PTH elevation occurs [13] or the cutoff below which clinical symptoms develop [1,2,20].

1.2.1. Vitamin D and intestinal absorption of calcium

Vitamin D plays a pivotal role in intestinal calcium absorption, and decreased absorption of dietary calcium is one of the main deleterious effects of vitamin D deficiency [21]. In one study, calcium absorption was measured from the area under the curve of the serum calcium increase induced by an oral calcium load (a controversial technique), in the spring, with and without pretreatment with 25(OH)D [22]. The serum 25(OH)D level was 86.5 $\pm$ 25 nmol/L with pretreatment and 50.2 $\pm$ 15 nmol/L without pretreatment; both ranges were considered normal. All participants received 500 mg of calcium per day orally. Calcium absorption efficiency was 65% greater with than without pretreatment and the authors concluded that the lower 25(OH)D values (50.2 $\pm$ 15 nmol/L) were associated with suboptimal calcium absorption [22]. In healthy men, calcium absorption showed very little difference when the 25(OH)D level decreased from 122 nmol/L after a summer of outdoor activity (the equivalent of 2800 IU vitamin D per day) to 74 nmol/L in late winter [23]. Calcium absorption efficiency may improve with rising 25(OH)D concentrations up to 80 nmol/L and level off subsequently [21]. Uncertainties remain, however, about the relation between the 25(OH)D level and calcium absorption. Whether 25(OH)D directly influences absorption is unclear; variations in 25(OH)D levels are not associated with significant variations in 1,25$(OH)_2$ D levels and, in osteomalacia, calcium absorption may be profoundly diminished despite normal or elevated levels of 1,25$(OH)_2$ D [21]. One study suggests that calcium malabsorption may occur only when the (25(OH)D) level is insufficient to maintain the 1,25$(OH)_2$D level despite secondary hyperparathyroidism [24].

1.2.2. Relations between 25(OH)D levels and bone status

The presence of bone alterations can be used as an indirect criterion of vitamin D status. Secondary hyperparathyroidism is a classic sign of vitamin D deficiency. In a study of 1569 individuals in 20 cities in France, PTH values were stable as long as the 25(OH)D level was above 78 nmol/L but increased gradually as the level fell below this cutoff [13]. In a rural population of postmenopausal women in Nebraska, 25(OH)D showed an inverse curvilinear relationship with PTH, and the inflection point of the curve was at about 80 nmol/L [25]. However, another study of postmenopausal women conducted using a different statistical analysis strategy showed that the PTH plateau was obtained only when the 25(OH)D level rose above 100 to 120 nmol/L, a value found in only a small minority of individuals [18].

1.2.3. Influence of calcium intake

At the individual level, the relationship between the 25(OH)D level and the PTH level may depend on calcium intake [21]. Dietary calcium intake influences the PTH level and, in turn, variations in PTH levels can influence the turnover rate of vitamin D metabolites [18,19]. Low calcium intake is associated with elevations in PTH and 1,25$(OH)_2$ D levels and with a decrease in 25(OH)D half-life. Thus, calcium deficiency may worsen vitamin D deficiency, whereas a high calcium intake may exert a vitamin D-sparing effect. In a study of 944 healthy adults in Iceland, PTH levels were evaluated in various subgroups defined based on age, calcium intake, or 25(OH)D level [19]. Again, PTH was inversely related to 25(OH)D and, in vitamin D-replete individuals, calcium intake levels greater than 800 mg/day were not necessary to maintain normal PTH levels [19]. Magnesium deficiency, which is present in some individuals with vitamin D deficiency, may contribute to a blunted PTH response in patients with osteoporosis [26].

2. Effects on bone mineral density

In cross-sectional studies, low 25(OH)D levels were associated with low BMD values even after adjustment for age, body mass intake, and calcium intake. In a population-based survey (NHANES III) of 13,432 US residents, 25(OH)D levels correlated positively with BMD values [27]. The correlation was statistically significant for 25(OH)D levels between 22.5 and 94 nmol/ml both in individuals younger than 50 years and in those aged 50 years or older. In a clinical trial in postmenopausal women with osteoporosis, 25(OH)D levels correlated positively with various BMD parameters at a threshold of 50 nmol/(18). Differences across studies in vitamin D dosages and administration modalities complicate the interpretation of data on the relation between vitamin D status and BMD. A 2007 meta-analysis showed that combined vitamin D and calcium supplementation was associated with small reductions in the bone loss rate, of 0.54% at the hip and 1.19% at the lumbar spine [28]. Vitamin D supplementation alone failed to effectively and consistently prevent bone loss in postmenopausal women, patients with osteoporosis, or glucocorticoid users [2].

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3. Effects on fractures

In a prospective study of 986 women with a mean age of 75 years, the relative risk of sustaining a fracture during the 3-year follow-up was 2.04 (95% confidence interval, 1.04 – 4.04) in the group with 25(OH)D levels lower than 50 nmol/L [29]. In the Women's Health Initiative study of 39,795 postmenopausal women, the hip fracture risk was higher in the group with low 25(OH)D levels [30]. Several studies suggest that vitamin D supplementation may help to prevent fractures. A 100,000 IU dose of vitamin D every 4 months decreased the risk of osteoporotic fracture [31]. A meta-analysis indicated benefits with 700 IU per day but not 400 IU/day of vitamin D [32] and another that 800 IU of vitamin D with 1200 mg of calcium per day decreased the fracture risk by 24% provided adherence was greater than 80% [28]. In contrast, a review of 15 randomized controlled trials of vitamin D supplementation showed a substantial decrease in the risk of falls but only a small effect in preventing fractures [33].

4. Effects on muscle function

Low 25(OH)D levels are associated with impaired muscle function, which increases the risk of falls [2]. In 4100 ambulatory individuals older than 60 years of age in NHANES III, impaired muscle function was noted in the group with serum 25(OH)D levels lower than 100 nmol/L [34]. A randomized controlled trial of 139 ambulatory patients aged 65 years or older who had a history of falls and 25(OH)D levels lower than 20 nmol/L showed that a single intramuscular injection of ergocalciferol improved balance tests and the reaction time compared to a placebo but had no statistically significant effect on muscle strength [35]. In a meta-analysis of six randomized controlled trials with a total of 1237 community-dwelling or institutionalized elderly women, vitamin D supplementation decreased the risk of falls by 22% [36].

5. Other effects

Vitamin D exerts many other health effects [1,2]. Multiple sclerosis and cancer are two examples of diseases that may be affected by vitamin D. However, two important points should be borne in mind: evidence of a link between these diseases and vitamin D rests chiefly on epidemiological studies, and the 25(OH)D levels needed to influence the risk of these disease are probably higher than those needed to prevent bone loss. Controlled interventional studies are impatiently awaited to clarify the effects of vitamin D on the risk of multiple sclerosis, cancer, and other diseases.

5.1. Vitamin D and multiple sclerosis

In a study of seven million US military personnel, 25(OH)D levels higher than 99.1 nmol/L were associated with a 62% decrease in the risk of multiple sclerosis [37]. In the Nurses's Health Study, women who took at least 400 IU of vitamin D per day had a 41% decrease in the risk of multiple sclerosis compared to those who took no supplemental vitamin D [38].

5.2. Vitamin D and cancer

A protective effect of vitamin D against cancer is suggested by observational data from patients with colon cancer (30 studies), breast cancer (13 studies), and prostate cancer (26 studies) [1,39]. In an 8-year longitudinal study of 25,620 volunteers, 25(OH)D levels greater than 50 nmol/L were associated with a decreased risk of colorectal cancer [40]; and in a meta-analysis the risk of colorectal cancer was decreased by 50% in individuals whose 25(OH)D levels were greater than 82.5 nmol/L compared to those with levels lower than 30 nmol/L [41]. For breast cancer, a 50% risk reduction was seen for a considerably higher 25(OH)D level of 130 nmol/L, corresponding to a vitamin D intake of 4000 IU/day [42]. These data were produced by epidemiological and experimental studies, and the potential benefits of vitamin D in cancer prevention need to be further evaluated by randomized controlled trials [2].

5.3. Other effects

Significant associations may exist between vitamin D intake and the risk of death, infection, inflammatory disease, diabetes, cardiovascular disease, osteoarthritis, and other diseases [2].

6. Vitamin D supplementation modalities

The beneficial effects of vitamin D and the adverse effects of vitamin D deficiency have led to the recommendation that vitamin D supplements be given as a preventive measure. However, the optimal modalities of vitamin D supplementation are not agreed on [1,2,20,28,43].

6.1. Sunshine exposure and dietary intake of vitamin D

Exposure to UV-B radiation is a simple means of increasing the synthesis of 25(OH)D in the body. There is no risk of intoxication, as any excess of vitamin D3 and provitamin D3 is converted to inactive metabolites [5]. Exposure of the four limbs to sunshine for 5 to 30 minutes twice a week between 10 am and 3 pm in spring, summer, and fall leads to a significant increase in 25(OH)D levels [1,44]. The minimum erythema dose of UV-B radiation to the entire body supplies 20,000 IU of vitamin D in a single day [1]. The use of ultraviolet lamps has been suggested [1,5]. However, vitamin D production in the skin varies with the season, latitude, time of exposure, and age (with a four-fold lower level of production at 70 than at 20 years of age) [44]. Compared to Caucasians, blacks had a decrease in vitamin D production after UV-B exposure equivalent to a sun protection factor of 15 [45]. The main adverse effect of UV-B exposure is an increase in the melanoma risk. Vitamin D supplementation may produce major economic benefits, as the cost of vitamin D deficiency in the US has been estimated at 40 to 53 billion dollars, compared to only 5 to 7 billion dollars for excessive UV-B radiation [18].

6.2. Exogenous vitamin D

6.2.1. Vitamin D2 or D3

Vitamin D3 was more effective than vitamin D2 in restoring adequate 25(OH)D levels in some studies [46,47] but not in others [48].

6.2.2. Administration modalities

A randomized controlled trial compared equivalent vitamin D3 dosages of 600 IU daily, 4200 IU weekly, and 18,000 IU monthly for 4 months in nursing home residents having a baseline mean serum 25(OH)D level of 25.0 ± 10.9 nmol/L [49]. The mean increases in serum 25(OH)D levels were 69.9 nmol/L with daily dosing, 67.2 nmol/L with weekly dosing, and 53.1 nmol/L with monthly dosing ($P < 0.001$) [49]. In another study, however, the serum 25(OH)D response was not significantly different in elderly hip-fracture women (mean age, 81 ± 8 years) across three equivalent vitamin D3 dosages of 1500 IU daily, 10,500 IU weekly; and 45,000 IU monthly; the serum 25(OH)D increases at 2 months in the three groups were 33.2 ± 8.5, 29.2 ± 8.9, and 37.1 ± 10.3 nmol/L, respectively [50]. In healthy adults, a single oral cholecalciferol dose of 100,000 IU was found to be safe and effective in increasing serum

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25(OH)D levels, and a dosing interval of no more than 2 months was needed to maintain the 25(OH)D increase [51]. The vitamin D intake needed to achieve or maintain a given 25(OH)D concentration was assessed in 67 men, who received daily cholecalciferol doses of 25 μg (1000 IU), 125 μg, or 250 μg for 20 weeks during the winter in Nebraska [52]. Each additional microgram of oral cholecalciferol was associated with a 0.70 nmol/L increase in serum 25(OH)D. In the fall before the study, the oral vitamin D intake was estimated at 500 IU/day and the total vitamin D input from all sources at 3800 IU/day. The authors concluded that currently recommended dosages of supplemental vitamin D are inadequate [52]. Six experts estimated that the minimum serum 25(OH)D level required for fracture prevention was 50 to 80 nmol/L and among them five felt that levels in the 70–80 nmol/L range were desirable [53]. However, the optimal serum 25(OH)D level varies with the desired preventive effect. For instance, a level of 25 nmol/L effectively prevents osteomalacia [18] but fails to produce other benefits associated with vitamin D repletion. The daily intakes recommended by public health institutions are inadequate to maintain the currently acceptable minimum serum 25(OH)D level of 50 nmol/L [9,53,54]. For example, individuals who are not exposed to UV-B radiation from sun or other sources must take 1000 IU of vitamin D daily to maintain their 25(OH)D levels between 75 and 125 nmol/L [55]. Experts participating in a round table discussion recommended a mean oral vitamin D intake of 871 IU (400 to 2000 IU) per day in healthy adults to maintain serum 25(OH)D at 72 nmol/L and 1068 IU/day in patients with osteoporosis to maintain serum 25(OH)D at 75 nmol/L [54]. To improve muscle function and to decrease falls and fractures, serum 25(OH)D levels of 75 to 100 nmol/L with regular vitamin D3 dosages of 800 to 1000 IU/d seem required [2,56].

Patients with low serum 25(OH)D levels of less than 25 or 50 nmol/L can benefit from a monthly dose of 100,000 IU of vitamin D for 3 consecutive months. A 4-month dosing interval is too long [56], and an interval of 2 months or less has been found necessary to maintain an optimal serum 25(OH)D level of 75 nmol/L or more [51]. Older individuals and overweight patients may require higher doses to maintain adequate 25(OH)D levels [1,2,57]. The 25(OH)D increase in response to vitamin D supplementation is inversely related to the baseline level: thus, 400 IU/day of vitamin D produces a mean increase of 12 nmol/L in vitamin D-deficient patients compared to only 7 nmol/L in patients with a baseline level of 70 nmol/L [52,58]. Obtaining a serum 25(OH)D assay 3 to 6 months after initiating vitamin D supplementation may be useful to check that the dosage is neither too low nor too high. Combined calcium supplementation has been recommended in patients with osteoporosis [59]. Some studies, however, suggest that a calcium intake of 800 mg/day is adequate provided vitamin D repletion is obtained [1,2].

7. Vitamin D overdose

Vitamin D overdose is an uncommon event usually defined as a serum 25(OH)D level greater than 374 nmol/L. No adverse effects were seen in individuals given 10,000 IU of vitamin D per day for 5 years [31,52]. This dose of 10,000 IU/day is considered the safe tolerable upper intake level for vitamin D [60].

Sound evidence that vitamin D deficiency leads to adverse systemic effects is now available. The most severe bone manifestations of vitamin D deficiency are rickets and osteomalacia. More often, patients with vitamin D deficiency exhibit secondary hyperparathyroidism (with an inverse correlation between serum 25(OH)D and PTH levels) and accelerated bone turnover. There is direct evidence that vitamin D deficiency is associated with bone loss, which can be partially prevented by providing sufficient vitamin D. The minimum serum 25(OH)D level is 50 to 75 nmol/L, which requires at least 800 to 1000 IU of vitamin D per day. Higher dosages of 100,000 to 300,000 IU may be needed during the first few months in patients with severe vitamin D deficiency. Epidemiological data suggest an association between vitamin D status and the risk of various diseases including cancer and inflammatory disorders. Higher 25(OH)D levels may be required to provide these benefits. Interventional studies are needed to clarify the potential benefits of vitamin D supplementation for preventing extraskeletal diseases.

Conflicts of interest

The authors have no conflicts of interest to declare.

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