Low Vitamin D Status: Definition, Prevalence, Consequences, and Correction

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KEYWORDS

• Vitamin D • 25-Hydroxyvitamin D • Supplementation
• Deficiency • Insufficiency

Vitamin D is obtained either by ingestion or cutaneous production. When skin is exposed to ultraviolet B radiation, 7-dehydrocholesterol is converted to vitamin D_3 (cholecalciferol). Dietary sources may provide either vitamin D_3 or vitamin D_2 (ergocalciferol).[1,2] However, few foods contain appreciable amounts of vitamin D, as such dietary intake is often low. Combining low intake with indoor lifestyle and sun-avoiding behaviors including sunscreen use, it is not surprising that low vitamin D status is endemic.[3–6] The skeletal health consequences of vitamin D deficiency (calcium malabsorption and skeletal fragility) have long been recognized. More recently it has become appreciated that low vitamin D status leads to muscle weakness, falls, and potentially a multitude of nonskeletal morbidities.[7,8] This review considers the definition and prevalence, potential health consequences, and approaches to correcting low vitamin D status.

VITAMIN D BACKGROUND AND ASSESSMENT

Vitamin D must be metabolized to become physiologically active. Specifically, vitamin D (either D_2 or D_3) is converted to 25-hydroxyvitamin D (25(OH)D) in the liver and subsequently to the active or ''hormonal'' form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in the kidneys.[9] Measurement of 25(OH)D is the accepted indicator of an individual's vitamin D status.[10] This evaluation is not intuitive, as it would seem logical that measurement of the active form, $1,25(OH)_2D$, would be the appropriate measure of an individual's vitamin D status. It is not rare anecdotally to see health

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care providers obtain measurement of $1,25(OH)_2D$ purportedly to evaluate an individual patient's vitamin D status. However, measurement of circulating $1,25(OH)_2D$ does not provide a useful assessment of an individual's vitamin D status, as vitamin D deficiency leads to parathyroid hormone (PTH) elevation, which enhances renal 1α-hydroxylase activity thereby promoting conversion of available 25(OH)D to $1,25(OH)_2D$. As 25(OH)D is present in much higher concentration than $1,25(OH)_2D$ (ng/mL vs pg/mL) given the enhanced conversion induced by PTH elevation, $1,25(OH)_2D$ may be normal even in the setting of low vitamin D status.

The clinical measurement of 25(OH)D has been problematic, with substantial variability present between laboratories.[11,12] It is not the purpose of this review to detail approaches to and challenges with vitamin D measurement; this topic is reviewed elsewhere in this issue. Suffice it to say that current evaluations find that clinical 25(OH)D measurement has improved,[13] allowing health care providers to have reasonable confidence in clinical 25(OH)D measurements. Moreover, the recent availability of standard reference materials from the National Institute of Standards and Technology seems destined to further improve between-laboratory agreement. However, despite 25(OH)D assay improvements, health care providers must appreciate that assay variability is present for all laboratory results. The analytical imprecision and inaccuracy present in all quantitative medical procedures is due to method, human, and instrument limitations that confound application of rigid diagnostic cutpoint approaches. For example, if one were using a 25(OH)D value of 30 ng/mL to differentiate ''low'' from ''optimal'' vitamin D status, it must be recognized that a laboratory result of 29 ng/mL does not differ from 31 ng/mL.[14]

LOW VITAMIN D STATUS: DEFINITION AND PREVALENCE

A spectrum of vitamin D status has been proposed wherein individuals whose serum 25(OH)D value is less than approximately 10 ng/mL are classified as deficient and may sustain impaired bone mineralization (rickets/osteomalacia), while those with a value less than approximately 30 ng/mL are identified as insufficient (**Fig. 1**) and may sustain long-term adverse health consequences.[15] However, the cutpoint values selected, and even the verbiage to describe low vitamin D status, remain controversial. For example, terminology including deficiency, insufficiency, inadequacy, and hypovitaminosis has been variously, and interchangeably, applied to describe low vitamin D status. To avoid what seems to be a nonproductive debate, the terminology ''low vitamin D status'' is used here. Moreover, as noted above, 25(OH)D assay variability and absence of accepted standards has confounded agreement on a single definition of ''low.''

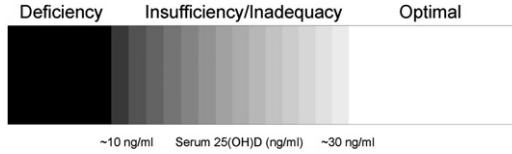

Fig. 1. Spectrum of vitamin D status. The spectrum of low vitamin D status is depicted. At very low vitamin D levels, (25(OH)D of approximately 10 ng/mL or less) calcium malabsorption, osteomalacia/rickets and myopathy occur. Less marked vitamin D deficiency (often referred to as inadequacy or insufficiency) has been associated with a variety of adverse health consequences. Consensus regarding an "optimal" 25(OH)D concentration continues to evolve; however, there seems to be increasing agreement that values greater than approximately 30 to 32 ng/mL are associated with optimal physiologic function.

Recognizing that controversy exists, there seems to be increasing consensus that circulating 25(OH)D values less than approximately 30 to 32 ng/mL indicate less than ideal vitamin D status.[16] These cutpoint values were suggested based on the long-established role of vitamin D to facilitate calcium and phosphorus absorption with deficiency leading to rickets/osteomalacia.[17–19] Thus, less severe vitamin D ''deficiency'' appears to cause calcium malabsorption, leading to secondary hyperparathyroidism with resulting elevated bone turnover and ultimately, bone loss.[20] The 25(OH)D to PTH relationship has been extensively reported, with various studies finding an apparent inflection point at around 20 to 30 ng/mL.[16,21] Moreover, some work demonstrates improved calcium absorption at 25(OH)D levels within what had previously been accepted as the ''normal'' range.[22] However, others have challenged this seemingly cardinal tenant of low vitamin D status by reporting that calcium malabsorption does not occur until severe vitamin D deficiency is present, due to PTH-mediated maintenance of 1,25-dihydroxyvitamin D levels.[23,24] Finally, it has recently been suggested by Heaney and colleagues[25] that the point at which hepatic 25(OH)D production becomes zero order could be used to define the lower end of normal vitamin D status. In this work, the investigators found serum 25(OH)D to rapidly increase as circulating vitamin D_3 (cholecalciferol) increased. When circulating vitamin D_3 exceeds approximately 5.8 ng/mL, the hepatic 25-hydroxylase appears to become saturated and this reaction switches from first order to zero order. Taking this approach would define the lower limit of normal at approximately 35 ng/mL,[25] obviously quite close to the 30 to 32 ng/mL suggested by other end points such as the relationship with PTH.

It is plausible that some of the debate surrounding what value defines ''optimal'' 25(OH)D status is being confounded by different levels for various tissues and end points; that is, the cutpoint for various nonclassic targets of vitamin D might vary from that for bone.[26] Furthermore, it is possible that the 25(OH)D value for ''optimal'' physiologic functioning might differ between individuals. Having a range of ''normal'' for virtually all clinically measured biologic parameters is well known by clinicians. As vitamin D is, in essence, an endogenously produced hormone, it is not surprising that between-individual variability and regulation would exist. In this regard, the skin of humans,[27] and other animals,[28] possesses the ability to regulate cholecalciferol production. Moreover, limited data suggest that variation in vitamin D degradation may exist, in that differences in 24-hydroxylase capacity between individuals may be based on race.[29] Data from a study of adults in Hawaii supports between-individual differences despite abundant sun exposure.[30] In fact, inspection of serum 25(OH)D concentration in that cohort reveals a virtually normal or Gaussian distribution (**Fig. 2**). Indeed, other studies of highly UV-exposed adults[31,32] find some individuals with ''low'' 25(OH)D despite high UV exposure and a fairly broad range of what it would seem logical to define as ''normal,'' as noted in **Fig. 2**. Thus, it seems likely that some of these people with ''low'' 25(OH)D levels could in fact be ''optimal'' for them. It is clearly accepted that a range exists for multiple physiologic functions that is considered ''normal'' for healthy adults; it is not known whether the same should apply to 25(OH)D.

Given these data, it is not surprising that an exact 25(OH)D cutpoint to define suboptimal vitamin D status remains somewhat controversial.[33] Despite this, there is increasing agreement that values less than approximately 30 to 32 ng/mL be identified as ''low.''[34,35] When this cutpoint is applied, low vitamin D status is extremely common worldwide. For example, recent reports classify 52% to 77% of the studied cohorts as ''low'' using 30 ng/mL as a cutpoint.[21,36–38] Even the more restrictive cutpoint of less than 20 ng/mL identifies 18% to 36% as ''low'' (**Fig. 3**). It is not surprising that studies report a variable prevalence of low vitamin D status as the studied cohorts differ in

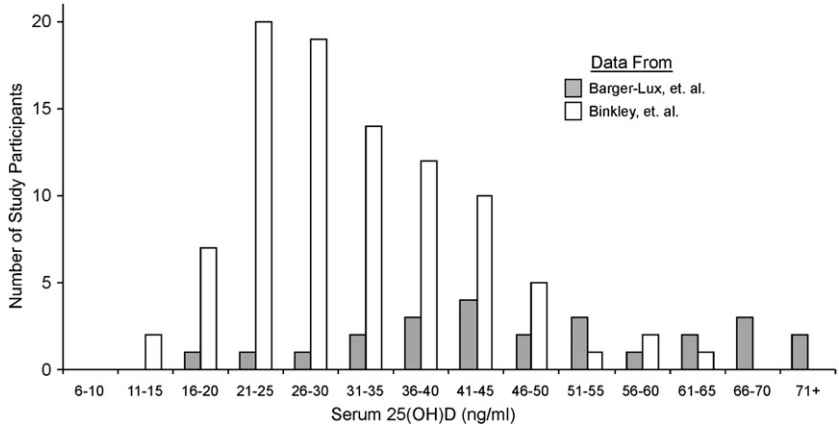

Fig. 2. Distribution of serum 25(OH)D in highly sun-exposed adults. In these 2 studies in which the average total body sun exposure was approximately 11 hours per week, a broad, and somewhat Gaussian, distribution of circulating 25(OH)D is apparent. Note that the study by Barger-Lux and colleagues used a 25(OH)D assay that measures approximately 10% higher than the HPLC assay used in the report by Binkley and colleagues. (*Data from* Binkley N, Novotny R, Krueger D, et al. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab 2007;92:2130–5; and Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 2002;87:4952–6.)

age, sex, race, body mass index, and dietary vitamin D intake. Although it is often assumed that some of the variable prevalence of low vitamin D reflects limited availability of sun exposure due to living at higher latitudes, it is of interest that a recent meta-analysis involving 394 studies comprising more than 32,000 subjects found no

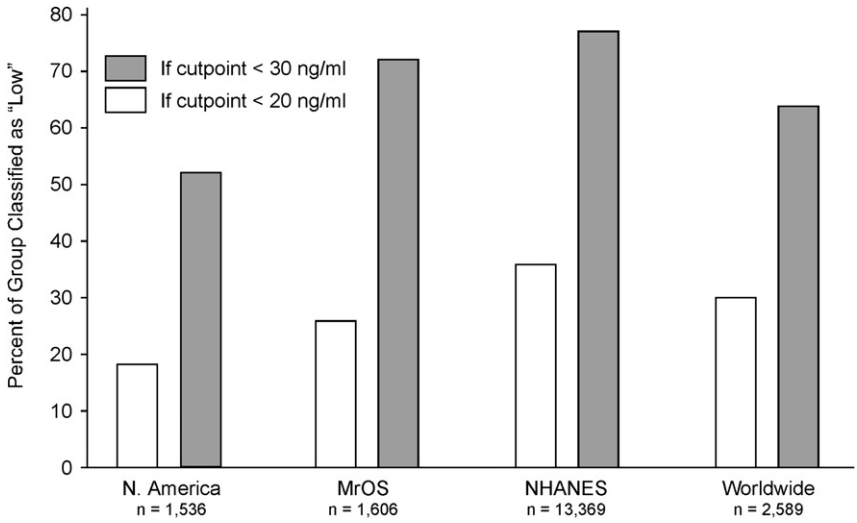

Fig. 3. Prevalence of low vitamin D status in various populations. In these recent cohort studies, low vitamin D status, whether defined as a 25(OH)D level below 20 ng/mL or below 30 ng/mL, is extremely common. (*Data from* Refs.[21,36–38].)

influence of latitude on 25(OH)D concentration.[39] It seems likely that the absence of an effect based on latitude reflects current human indoor lifestyles, clothing, and sun-avoidance behavior. Moreover, it is probable that these factors are contributing to worsening population vitamin D status. Although measurement issues confound data interpretation, recent National Health and Nutrition Examination Survey data report a decline in mean 25(OH)D concentration from the 1988 to 1994 data collection to that of 2000 to 2004.[36,40] In summary, despite variation in 25(OH)D methodology, cutpoint selected, and cohort studied, it is clear that low vitamin D status is common worldwide.

LOW VITAMIN D STATUS: CONSEQUENCES

Bone

Low vitamin D status has long been associated with osteomalacia/rickets, and a role in osteoporosis pathogenesis via calcium malabsorption and secondary hyperparathyroidism has more recently been suggested. Consistent with an important role of low vitamin D status in osteoporosis, recent meta-analyses find low 25(OH)D to be associated with higher fracture risk.[41–43] In addition, a dose effect was reported, with greater vitamin D intakes and higher achieved 25(OH)D concentrations providing superior fracture reduction benefit.[43] In summary, while one can debate the cutpoint, low vitamin D status leads to adverse bone consequences.

Muscle Function and Falls

Both genomic and nongenomic effects of vitamin D on muscle have been proposed.[44,45] Regardless of the mechanism, patients with osteomalacia due to vitamin D deficiency develop muscle pain and weakness that is improved with vitamin D therapy.[46–48] Muscle biopsy in such people reveals atrophy of the fast twitch (type II) fibers. As type II fibers are first to be recruited to avoid falling, this observation may explain the increased falls risk in vitamin D deficient individuals.[49] Of note, randomized prospective studies find vitamin D to reduce risk of falls by more than 20%.[50] It seems likely that reducing falls contributes in a major way to the fracture reduction efficacy observed with vitamin D.[51] Moreover, similar to the relationship observed with fracture, a higher vitamin D dose provides greater reduction in the risk of falls.[52] The 25(OH)D concentration needed to optimize leg function has been explored, with various cutpoints (eg, 16–24 ng/mL) suggested.[35,53] A recent review finds 25(OH)D concentrations less than approximately 16 ng/mL to be associated with substantially poorer leg function, but additionally finds values greater than approximately 36 to 40 ng/mL to be optimal.[26]

Cancer

Vitamin D has antiproliferative and prodifferentiating effects on many cell types.[54] It has been proposed that these effects are related to local production of 1,25-dihydroxyvitamin D, thus favorably impacting genes affecting cellular proliferation/differentiation and thereby reducing cancer risk.[7] Consistent with this, an extensive, albeit largely associational, literature exists relating higher latitude, low vitamin D intake, and/or less sunlight exposure to increased risk of, or mortality from, multiple types of cancer.[55–59] Prospective trials of vitamin D supplementation with cancer as an end point are very limited; the Women's Health Initiative did not demonstrate a reduction in colon cancer risk, perhaps related to the low daily dose (400 IU) of vitamin D used.[60] However, a smaller prospective study of postmenopausal women found calcium plus vitamin D_3 (1100 IU daily) to reduce overall cancer risk by approximately

60%.[61] To summarize, physiologically logical hypotheses, observational data, and one small randomized trial find low vitamin D status to be associated with higher cancer risk. Additional prospective studies are needed.

Other Conditions

It is likely that vitamin D has immune modulating effects. It has long been recognized that vitamin D deficiency is associated with respiratory infections, which perhaps contributed to the use of cod liver oil in antituberculous therapy.[62,63] More recently, it has become appreciated that calcitriol enhances monocyte mycobacterial killing, likely by facilitating production of the antimicrobial protein, cathelicidin.[64] Moreover, helper type 1 and 2 cells are vitamin D targets, with vitamin D causing a shift toward an anti-inflammatory profile.[65–68] Thus, it is not surprising that low vitamin D status is associated with an increased risk of autoimmune and potentially infectious diseases.[69–71] In addition, inflammation is increasingly being recognized as a contributor to the pathogenesis of various diseases, and vitamin D modulates inflammatory cytokine production.[72–74]

It has been suggested that endemic low vitamin D status is contributing to the increased prevalence of diabetes mellitus. Multiple potential mechanisms have been proposed, including vitamin D increasing insulin production/secretion.[75–77] In addition, observational studies associate low vitamin D status with diabetes type 1 and type 2.[78–80] Prospective studies of vitamin D supplementation are clearly indicated; however, on the whole it appears that low vitamin D status impairs glucose metabolism.[78]

Observational studies report an association between low vitamin D status and cardiovascular disease.[81–85] Potential mechanisms include a vitamin D effect on the endothelium,[86] vascular smooth muscle,[87,88] and/or cardiomyocytes,[89] all of which possess the vitamin D receptor. Prospective studies to further evaluate this reported association are needed.

In summary, low vitamin D status has been associated with a variety of diseases, and biologically plausible hypotheses exist to suggest a possible causal role. However, until confirmed by randomized studies, it is wise to be cautious and recognize that association does not prove causation.

WHEN SHOULD VITAMIN D STATUS BE ASSESSED?

Given the multitude of potential adverse health consequences ascribed to low vitamin D status, it is not surprising that screening 25(OH)D measurement has been advocated.[90,91] Such screening may in fact be appropriate, if it becomes established that low vitamin D status contributes in a causal manner to multiple adverse health outcomes, for example, cardiovascular disease, diabetes, hypertension, and so forth, with which it is currently associated. However, in the absence of randomized trials documenting benefit for these varied outcomes, population-based screening seems premature.

At this time, rather than advocating a population screening approach, it seems reasonable to measure 25(OH)D in those identified as being at high risk of vitamin D deficiency and those for whom a prompt musculoskeletal response to optimization of vitamin D status could be expected. Such groups include those with osteoporosis, a history of falls or with high risk of falls, malabsorption (eg, celiac disease, radiation enteritis, bariatric surgery, and so forth), individuals with liver disease, and those requiring medications known to alter vitamin D status, for example, certain anticonvulsants. Given the relationship of low vitamin D status with cancer, it also seems rational to measure 25(OH)D in those with malignancy.[92]

Alternatively, it could be argued that simple treatment of all individuals with vitamin D should be advocated, thereby making 25(OH)D measurement unnecessary. Although this approach is attractive, it is unfortunately problematic in that no expert consensus exists regarding a recommended dose. For example, the National Osteoporosis Foundation recommends 800 to 1000 IU daily,[93] whereas some vitamin D experts suggest values over 2000 IU.[94] Moreover, as discussed later, vitamins D_2 and D_3 appear to not be equally potent in maintaining 25(OH)D.[95,96] As such, daily intake of 1000 IU of vitamin D_2 may well not be equal to 1000 IU of vitamin D_3. In addition, vitamin D dosing may differ by age in that older adults likely require higher vitamin D intakes because of to the lower capability of skin to produce vitamin D with advancing age.[97] Similarly, clear differences exist between races, with African Americans requiring higher intakes than Caucasian Americans; Hispanic individuals may have intermediate requirements.[98] Some of these differences in required intake may reflect differences in cutaneous melanin content[99]; however, other less well understood between-individual differences in vitamin D absorption and subsequent metabolism may well play a role. In this regard, even among individuals of similar age and race/ethnicity, substantial between-individual variability in response to equal vitamin D intake is noted (**Fig. 4**). Thus, if a health care provider wishes to assure optimal vitamin D status in an individual patient, it is necessary to obtain a 25(OH)D measurement.

APPROACHES TO VITAMIN D REPLETION/SUPPLEMENTATION

Increasing exposure to sunlight would be an effective and free approach to improving vitamin D status. However, this does not seem to be a viable approach, given

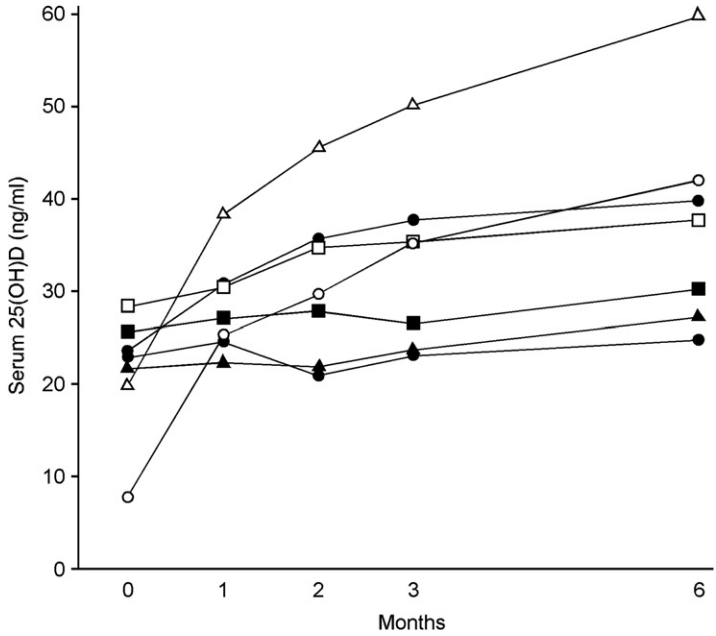

Fig. 4. Variable response to daily vitamin D_3. In these 7 Caucasian older adults (age 66–88 years), all of whom started the study with a 25(OH)D level less than 30 ng/mL, the variable response to daily administration of 1600 IU vitamin D_3 is apparent. (*From* Binkley N, Gemar D, Woods A, et al. Effect of vitamin D_2 or vitamin D_3 supplementation on serum 25OHD. J Bone Miner Res 2008;23(Suppl 1):S350; with permission.)

widespread sun-avoidance campaigns[100–103] based on the association of UV exposure with skin cancer.[104] Sun avoidance and sunscreen use [55,100,105,106] reduce skin exposure to UV radiation and thereby reduce skin vitamin D production.[2,107] In the face of such pervasive and powerful efforts, advocating sun exposure as a population-based measure to improve vitamin D status faces grave obstacles. Despite this, exposure to sunlight in moderation, perhaps for 15 minutes prior to sunscreen application, seems reasonable and is free. It should be noted that due to differences in skin pigmentation, season, latitude, time of day of sun exposure, and amount of body surface exposed, simple recommendations such as ''15 minutes of sun on the hands and face'' are overly simplistic and will not assure optimal vitamin D status in all people.

Higher dose vitamin D treatment approaches to the clinical correction of vitamin D deficiency, and when to monitor 25(OH)D status during and following vitamin D treatment/supplementation, have received surprisingly little attention. Various ''high-dose'' repletion approaches, for example, 50,000 IU 3 times weekly, weekly or monthly, have been evaluated.[108–111] A recent evaluation of clinical approaches found vitamin D_2 regimens using more than 600,000 IU administered over an average time of 2 months achieved 25(OH)D values greater than 30 ng/mL in 64% of patients, with the highest value being 100 ng/mL.[108] An additional clinical report of ''high-dose'' vitamin D_2 (50,000 IU once weekly for up to 3 years) achieved a 25(OH)D level above 30 ng/mL in 23 of 24 patients, with the highest reported value being 100 ng/mL.[112]

Maintenance of vitamin D status with daily doses from 1000 to 4000 IU have been studied.[96,113,114] As noted above, between-individual variability exists. However, a reasonable clinical ''rule of thumb'' is that the addition of 1000 IU of vitamin D_3 daily can be expected to increase circulating 25(OH)D by approximately 10 ng/mL.

Although daily vitamin D supplementation is very inexpensive (approximately $1 per month), available data find daily vitamin D supplementation to be less effective than expected at increasing serum 25(OH)D status, simply due to failure to reliably take the supplements.[115,116] This finding is hardly surprising in that suboptimal adherence to prescribed therapies for a variety of conditions is well known to clinicians.[117] However, based on the increasing calcium intake of the United States population over time[118] (perhaps related to widespread educational programs), it seems feasible that similar approaches to informing the public about health benefits of vitamin D supplementation could improve endemic low vitamin D status. An alternative, and highly viable, approach is increased availability of vitamin D fortified foods coupled with higher amounts of vitamin D per serving in such food.

How best to monitor 25(OH)D status in individuals receiving vitamin D therapy has not been systematically evaluated. However, as compliance/adherence with many daily therapies (including vitamins) is often poor, monitoring 25(OH)D status 4 to 6 months after initiating treatment in those at high risk (eg, patients with osteomalacia, fragility fractures, or high risk of falls) seems reasonable. Repeat evaluation at earlier time points seems inappropriate, as it takes 3 to 6 months for serum 25(OH)D to plateau following initiation of supplementation.

WHAT IS VITAMIN D TOXICITY?

Both clinicians and patients may express concern that the ''high'' amounts of vitamin D noted here will lead to toxicity. It is clear that huge doses of vitamin D do lead to hypercalcemia and hypercalciuria. However, there is no clear-cut definition of which level of serum 25(OH)D should be considered ''toxic.'' This doubt has led to variability in the clinical reporting of 25(OH)D results, with some laboratories reporting possibly

toxic levels as being above 80 ng/mL while others include up to 100 ng/mL as being within the reference range. Such variability is not surprising, as recent expert opinion suggests "the serum 25(OH)D concentration that is the threshold for vitamin D toxicity has not been established."[119] However, a review of the published vitamin D toxicity cases finds all reports of hypercalcemia due to vitamin D intoxication to be associated with 25(OH)D concentrations greater than 88 ng/mL.[120]

Regarding what constitutes "high" 25(OH)D values, it seems reasonable that highly sun-exposed individuals could be used to assist in the determination of "normal" vitamin D status.[33] When such individuals are evaluated, it appears that the highest attainable 25(OH)D values from cutaneous production are in the 70 to 80 ng/mL range.[30,31] Thus, the current approach of reporting 80 to 100 ng/mL as the upper limit of normal seems appropriate.

DOES THE EFFECT OF VITAMIN D_2 DIFFER FROM THAT OF VITAMIN D_3?

Two chemically distinct forms of vitamin D exist: vitamin D_3 (cholecalciferol) is a 27-carbon molecule, whereas vitamin D_2 (ergocalciferol) contains 28 carbons and differs from vitamin D_3 by the presence of an additional methyl group and a double bond between carbons 22 and 23. Although clear chemical differences exist, whether vitamin D_2 and vitamin D_3 are equally effective at increasing 25(OH)D and have equivalent physiologic effects remains unclear. At present, these 2 forms are regarded as equal and interchangeable. However, some data suggest that vitamin D_2 is less "potent" at maintaining serum 25(OH)D than is vitamin D_3.[95,96,121] Although a recent report challenges this[113] and found D_2 and D_3 to be equally effective, the vast majority of studies find vitamin D_3 to be somewhat more potent. It seems possible that this reflects lower affinity of vitamin D_2 for vitamin D binding protein in the circulation, leading to more rapid clearance. As such, use of supplements containing vitamin D_3, rather than vitamin D_2, seems appropriate.[122] It is unfortunate that vitamin D_2 is the only high-dose prescription vitamin D preparation in the United States and some other countries. Despite its lower potency, use of high-dose vitamin D_2 does increase circulating 25(OH)D concentration.

SUMMARY

Low vitamin D status is extremely common worldwide due to low dietary intake and low skin production. Suboptimal vitamin D status contributes to many conditions, including osteomalacia/rickets, osteoporosis, falls, and fractures. It is possible or even likely that low vitamin D status increases risk for a multitude of other conditions. Although consensus does not exist, it appears that circulating 25(OH)D concentrations greater than 30 to 32 ng/mL are needed for optimal health. To achieve this, daily intakes of at least 1000 IU of D_3 daily are required, and it is probable that substantially higher amounts are required to achieve such values on a population basis. It seems premature to recommend widespread screening for 25(OH)D measurement. Targeted measurement in those at increased risk for vitamin D deficiency and those most likely to have a prompt positive response to supplementation is appropriate. Widespread optimization of vitamin D status likely will lead to prevention of many diseases with attendant reduction of morbidity, mortality, and expense.

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