

Low Vitamin D Status: Time to Recognize and Correct a Wisconsin Epidemic

Neil Binkley, MD; Diane Krueger, BS, CCRC, CDT; Marc K. Drezner, MD

ABSTRACT

As a result of low dietary intake and sun avoidance, low vitamin D status is endemic in Wisconsin. In a convenience sample of postmenopausal Wisconsin residents, 59% had suboptimal D status. Only recently, the medical community has begun to appreciate that low vitamin D status underlies multiple deleterious health consequences including skeletal fragility, muscle weakness, and a potential multitude of non-skeletal morbidities. At present, a routine recommendation indicates that at least 1000 IU of vitamin D₃ (cholecalciferol) daily is indicated, although the true requirement may be greater. This review details vitamin D physiology and the prevalence of low vitamin D status in Wisconsin and elsewhere, and provides approaches to optimizing vitamin D status.

VITAMIN D PHYSIOLOGY

Vitamin D is produced in the skin when 7-dehydrocholesterol is converted to vitamin D₃ (cholecalciferol) by ultraviolet B (UVB) radiation.¹ Additionally, dietary or supplement intake may contribute either vitamin D₃ or vitamin D₂ (ergocalciferol). Subsequently, vitamin D requires activation by hydroxylation at the 1 and 25 carbons in the liver and kidneys, respectively, to a compound that has historically been viewed as the active or hormonal form of the vitamin: 1, 25 dihydroxyvitamin D (1, 25, diOHD).² The 1, 25, diOHD is important for active calcium transport in the intestine. Vitamin D deficiency is classically viewed as causing decreased gastrointestinal calcium absorption and consequent impaired bone mineralization (rickets/osteomalacia). However, it is becoming increasingly recognized that local production of both 25-hydroxyvitamin D (25[OH]D) and 1, 25, diOHD is important for normal function of multiple tissues.³

DEFINITION OF LOW VITAMIN D STATUS

Since 1, 25, diOHD is the active form of vitamin D, it makes sense that measuring this analyte would provide an accurate assessment of an individual's vitamin D status. However, this is not the case. Low levels of vitamin D induce an elevation of parathyroid hormone (PTH), which increases 1-hydroxylase activity in the kidney, thereby converting available 25(OH)D to 1, 25, diOHD and artifactually maintaining the circulating 1, 25, diOHD concentration. Thus, 1, 25, diOHD measurement is inappropriate as a measure of vitamin D status; it is necessary to measure circulating 25(OH)D as well.

It is tempting to consider using PTH measurement as a surrogate marker of vitamin D status. However, as high calcium intake can provide adequate calcium absorption despite low vitamin D status, serum PTH may not be elevated even in the presence of low 25(OH)D levels.^{4,5} Consistent with this, normal PTH values do not assure optimal vitamin D status, as calcium absorption can be improved by increasing vitamin D intake in individuals with normal PTH levels.⁶ Therefore, the best functional measure of vitamin D status is circulating 25(OH)D concentration.⁷

However, clinical 25(OH)D measurements have been problematic in the recent past, and individual results have been highly laboratory dependent.^{8,9} But more recent evaluation suggests that clinical 25(OH)D measurement has substantially improved (Figure 1).¹⁰ Therefore, clinicians can have reasonable confidence in 25(OH)D measurements performed in laboratories using high-pressure liquid chromatography (HPLC), liquid chromatography tandem mass spectroscopy (LC-MS/MS), or the Diasorin radioimmunoassay (RIA).

A spectrum of vitamin D status has been proposed wherein individuals with a serum 25(OH)D value below approximately 10 ng/ml are identified as deficient and may sustain impaired bone mineralization (rickets/osteomalacia), while those below approximately 30 ng/ml are identified as insufficient (Figure 2) and may sustain long-term adverse health consequences such as osteo-

Author Affiliations: University of Wisconsin Osteoporosis Clinical Center and Research Program.

Corresponding Author: Neil Binkley, MD, University of Wisconsin Osteoporosis Research Program, 2870 University Ave, Ste 100, Madison, WI 53705; phone 608.265.6410; fax 608.265.6409.

porosis.¹¹ However, this apparently simple concept (and even the verbiage to describe low vitamin D status) is controversial. Specifically, a number of terms such as deficiency, insufficiency, inadequacy, and hypovitaminosis have been used, without consistent definitions, in various publications. To avoid this controversy, this review will primarily use the terminology “low vitamin D status.”

There appears to be increasing consensus that circulating 25(OH)D values below ~30 ng/ml indicate less than optimal vitamin D status for bone health.¹² However, as with all diagnostic “cutpoints,” minimal deviations on either side of this value likely have little clinical significance. For example, whether an individual’s bone mineral density T-score is -2.4 or -2.6, the fracture risk would be virtually identical despite crossing the arbitrary diagnostic threshold from osteopenia to osteoporosis. Similarly, an individual’s vitamin D status is likely no different if the serum 25(OH)D is 29 or 31 ng/ml. When using 30 ng/ml as a cutpoint for definition of low vitamin D status, it is important to recognize that many clinical publications in the United States, and all clinical laboratories in this country, report 25(OH)D values in ng/ml, whereas the European literature uses nmol/l. Simply dividing the 25(OH)D nmol/l value by 2.5 gives a very close approximation of the value in ng/ml.

LOW VITAMIN D STATUS: PREVALENCE AND CONSEQUENCE

Low vitamin D status is extremely common due to low dietary intake and limited sun exposure.¹³⁻¹⁹ Widespread low dietary intake²⁰ combined with low sun exposure, use of sunscreen that effectively blocks cutaneous vitamin D production, and geographic limitations that preclude vitamin D skin synthesis by the sun from November through February above 42° north latitude (approximately the southern Wisconsin border) places all Wisconsin residents at risk for vitamin D deficiency,²¹ especially during the winter.²²⁻²⁵ Consistent with this, recent data from our group found 59% of community-dwelling older Wisconsin women (age [mean/SD] 76.0 ±4.7 years) to have low vitamin D status (Figure 3). Although these data are in postmenopausal women, low vitamin D status is common in both sexes.^{13,16,26}

Skeletal Effects

Low vitamin D status has long been recognized as contributing to the development of osteoporosis, osteomalacia, and rickets, most directly by impairing intestinal calcium absorption. This impairment of calcium absorption, if severe, limits the supply of calcium necessary to allow normal bone mineralization to occur and

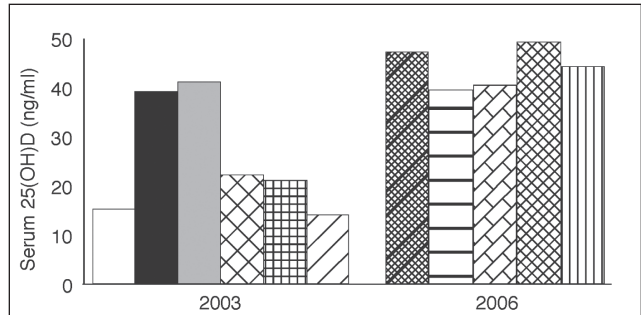


Figure 1. Serum 25(OH)D measurement. This figure illustrates the marked variability in 25(OH)D measurement that existed recently and the substantial improvement that has occurred over the past 3 years. In this example, aliquots of serum from 1 individual were sent to 6 laboratories for 25(OH)D measurement in 2003 and to 5 laboratories in 2006. Substantially improved agreement between laboratories in 2006 is apparent. Of the 5 laboratories in 2006, 2 each utilized high-pressure liquid chromatography (HPLC) and liquid chromatography tandem mass spectroscopy (LC/MS-MS) while 1 used a Diasorin radioimmunoassay (RIA).

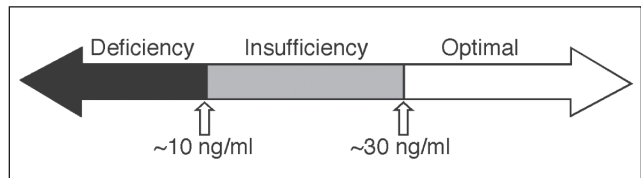


Figure 2. Continuum of vitamin D status. It is clinically useful to consider vitamin D status on a continuum, as illustrated here. Though these 25(OH)D “cutpoints” are not absolute, individuals with very low values, below approximately 10 ng/ml, may be considered as having vitamin D deficiency, while those with values between 10 and 30 ng/ml have vitamin D inadequacy or insufficiency. Adapted with author’s permission.¹¹

thus produces osteomalacia/rickets. If less severe impairment of calcium absorption occurs, the elevation of PTH necessary to maintain calcium homeostasis leads to elevated bone turnover and, consequently, to bone loss and osteoporosis.

Effects on Muscle Function

In addition to the skeletal effects noted, low vitamin D status adversely affects muscle performance. This is expected as vitamin D receptors are present in human muscle tissue²⁷ making a direct effect of vitamin D on muscle physiology probable.²⁸ Moreover, effects mediated via alterations of intracellular calcium status are plausible.²⁹ It is therefore not surprising that low vitamin D status has long been associated with reduced muscle strength.³⁰⁻³³ More recently, low vitamin D status has also been associated with loss of muscle mass.³⁴ As muscle weakness is a major risk factor for falls,³⁵ it is not surprising that low vitamin D status would be associated with an increased falls risk, an observation that was reported in a recent longitudinal study.³⁶ Moreover, a recent meta-analysis confirmed that vita-

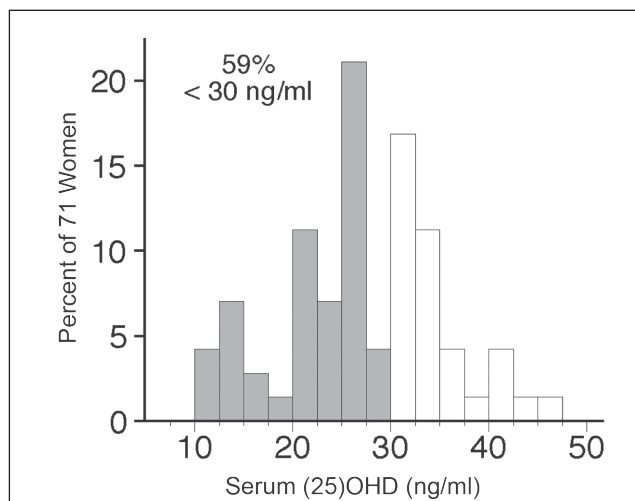


Figure 3. High prevalence of low vitamin D status in Wisconsin. In this convenience sample of 71 women over age 70 who volunteered for participation in a research study in Madison, Wis during the winter of 2005 to spring 2006, 59% were found to have low vitamin D status. For this study, 25(OH)D was measured by high-pressure liquid chromatography (HPLC).

min D treatment reduces falls risk by approximately 20% in older adults.³⁷ It is probable that much of the reported effect of vitamin D to reduce osteoporotic fracture risk^{38,39} reflects improved muscle performance and lower falls risk.³⁷

Falls in Wisconsin

Falls and fractures have immense personal and societal consequence; approximately 1.5 million osteoporotic fractures occur annually⁴⁰ in the United States at a cost exceeding \$17 billion.⁴¹ Importantly, Wisconsin has the highest crude death rate due to falls in the United States as of 2002 and the second highest age-adjusted fall-related death rate.⁴² Since low vitamin D status increases falls risk, and supplementation reduces falling,^{37,43,44} it is likely that vitamin D supplementation is an inexpensive way to reduce falls and fractures in Wisconsin and elsewhere.

Non-Musculoskeletal Effects

Moreover, non-musculoskeletal effects of vitamin D have been increasingly recognized.³ For example, low vitamin D status is associated with infection^{45,46} and immune dysfunction.⁴⁷ Importantly, a recent study found that daily supplementation with 1100 IU of vitamin D₃ reduces overall cancer incidence in postmenopausal women.⁴⁸ This prospective study provides strong support for the wealth of epidemiologic evidence relating low vitamin D status and/or low UV exposure to increased cancer risk.^{49,50} Multiple potential mechanisms by which vitamin D might reduce cancer risk have been

proposed, including inhibition of tumor angiogenesis.⁵¹ Additionally, low vitamin D status is epidemiologically linked to increased risk of multiple sclerosis, hypertension, and diabetes mellitus.^{47,52-55} Finally, it has recently been proposed that low vitamin D status may contribute to multiple morbidities that were felt to be simply “age-related”.⁵⁶

To summarize, though additional research is required to define the spectrum of morbidities associated with low vitamin D status, based on available data it is clear that widespread increased vitamin D intake is indicated to reduce the risk and consequences of musculoskeletal and other diseases.

HOW MUCH VITAMIN D IS NEEDED?

Given the long history of vitamin D research, it is possible to assume the recommended D intake (400 IU/day), established by the Food and Nutrition Board in the 1990s,⁷ is adequate and that low vitamin D status is no longer a public health concern. However, a wealth of recent data establish that daily vitamin D intakes much greater than 400 IU are required to achieve optimal vitamin D status.^{5,6,12,17-19,48,55,57-63} As such, current consensus recommendations suggest that approximately 1000 IU D daily is required.¹² Though this amount is 2.5 times the current recommended intake, it may still be conservative and suboptimal. In fact, internationally recognized vitamin D expert, Dr R. Heaney has recently suggested that 2600 IU daily is required.⁶⁴

Age and Ethnicity Considerations in Vitamin D Dosing

It is probable that individuals of varying age and ethnicity require differing amounts of vitamin D to assure optimal status. Specifically, since melanin decreases skin production of vitamin D on a per UV exposure basis,⁶⁵ it has been suggested that people with darker skin require higher vitamin D intakes.⁶⁶ Similar to different requirements based on ethnicity, it is likely that older individuals require higher vitamin D intakes to achieve optimal status. Clarification of different requirements based on age is essential as it is estimated that the number of older (age 65+) Wisconsinites will increase dramatically, from about 720,000 in 2005 to 1,022,000 in 2020.⁶⁷ Advancing age has long been associated with low vitamin D status, presumably due to less skin production.^{68,69} However, the impact of age on vitamin D status following oral ingestion is far less clear in that some, but not all, studies find poorer response to supplementation with advancing age.⁷⁰ Measurement of circulating 25(OH)D seems appropriate for all older individuals with low bone mass, or those with muscle weakness or falls, and for additional high risk groups including home-bound

older adults. The routine recommendation of ingesting at least 1000 IU of vitamin D₃ for older adults seems similarly prudent.

Vitamin D Toxicity

Some might raise concern that these “high” doses of D are “toxic”; this fear appears unwarranted. Vitamin D toxicity requires ingestion of over 10,000 IU/day.^{71,72} In fact, a recent review of human clinical trials suggested that the tolerable upper intake level for vitamin D should be increased to 10,000 IU/day.⁷³ As such, a wide safety margin exists with daily intakes in the 1000-2600 IU range. Moreover, available data^{59,74,75} indicate that on average, for each 100 IU of vitamin D added daily, serum 25(OH)D should increase by ~1 ng/ml. Thus, for example, addition of 2600 IU daily as referred to above would be expected to increase serum 25(OH)D by ~26 ng/ml; an increment without toxicity.

APPROACHES TO CORRECTING LOW VITAMIN D STATUS

It is intuitive that increasing sun exposure would be an effective and inexpensive approach to improving vitamin D status. Unfortunately, several circumstances make widespread sun exposure an implausible approach. Most importantly, the message that sun exposure promotes skin cancer⁷⁶ and should be avoided, has been widely promulgated, leading to sun avoidance campaigns⁷⁷⁻⁸⁰ and widespread use of sunscreen.^{51,77,81,82} These measures are designed to reduce skin exposure to ultraviolet radiation, but consequently also reduce skin vitamin D production.^{1,83} 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 to be a clinically viable and inexpensive approach. However, given 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. Moreover, some individuals, even with chronic sun exposure, fail to achieve adequate concentrations of 25(OH)D.⁸⁴⁻⁸⁶ It is possible that this reflects genetic differences in vitamin D hydroxylation and/or degradation. Finally, age-related skin changes reduce vitamin D production from the sun.⁶⁸ Given the above, advocating sun exposure to correct endemic low vitamin D status seems unlikely to succeed. Therefore, oral vitamin D supplementation is indicated.

Widespread vitamin D supplementation is an

attractive approach from a public health standpoint as it is very inexpensive (approximately \$1 per month). Unfortunately, existing data suggests that daily vitamin D supplementation is less effective at increasing serum 25(OH)D status than expected because people simply did not reliably take the supplements.^{87,88} This is not surprising, since people often do not adhere to their prescribed therapies.⁸⁹ However, based on the increasing calcium intake of the US population over time,⁹⁰ which may be related to widespread educational programs, it seems feasible that similar approaches to informing the public about health benefits of vitamin D supplementation, beginning in the clinician’s office, could reduce widespread low vitamin D status.

Vitamin D₂ and D₃

Approaches to optimization of vitamin D status have received only limited evaluation. In this regard, though still officially seen as equal and interchangeable, available data suggest that vitamin D₂ (ergocalciferol) is less “potent” at maintaining serum 25(OH)D than vitamin D₃ (cholecalciferol).^{91,92} It is possible that this reflects lower affinity of vitamin D₂ for vitamin D binding protein in circulation, leading to more rapid clearance. Therefore, use of supplements containing vitamin D₃, rather than vitamin D₂, seems appropriate and is recommended.⁹³ It is unfortunate that the only high-dose prescription vitamin D preparation in the United States exclusively contains vitamin D₂. Despite the lower potency, use of high-dose vitamin D₂ does increase circulating 25(OH)D. For example, 50,000 IU of D₂ weekly for 8 weeks increases the mean 25(OH)D concentration to >30 ng/ml.⁹⁴ A more aggressive approach, 50,000 IU of D₂ 3 times per week for 1 month, increases serum 25(OH)D by >40 ng/ml without hypercalcemia in nursing home residents.⁹⁵ Thus, these short-term, high-dose approaches can rapidly correct low vitamin D status. However, long-term vitamin D supplementation will subsequently be required for many individuals. In this regard, a reasonable clinical “rule of thumb” is the addition of 100 IU of D₃ daily may be expected to increase circulating 25(OH)D by approximately 1 ng/ml.^{74, 75}

CONCLUSION

In summary, low vitamin D status is extremely common in Wisconsin due to low dietary intake and low skin production. Suboptimal vitamin D status contributes to many conditions, including but not limited to, osteoporosis, falls, and fractures. At least 1000 IU of D₃ daily is needed; it is probable that higher amounts, perhaps as high as 2600 IU daily are required to maintain the serum 25(OH)D >30 ng/ml. Measurement of cir-

culating 25(OH)D in older adults with low bone mass and falls risk, as well as homebound elders, 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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