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Special Article - Vitamin D Deficiency: Clinical Cases & Short Reports

Normal, Healthy, and Optimum Level of 25-Hydroxyvitamin D and Required Daily Intake of Vitamin D

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Abstract

There is controversy about the normal blood levels and daily requirement for vitamin D, an essential nutrient that functions like a hormone. The controversy stems from differences in views about the role of vitamin D in optimum health versus lack of disease, scope of tissues affected and processes affected by vitamin D, variations among ethnic groups, differences in exposure to sunlight, and lack of harmonization of analytical methods. The normal value for 25-hydroxyvitamin D, stated by different organizations, ranges from 10-60 ng/mL and the recommended daily intake varies from 400 IU to 4000 IU/day. We address the controversy about normal blood levels and suggest that the approach for establishing normal levels should focus on optimal health rather than lack of disease. We are inclined to recommend 30ng/mL as the lower limit of normal and desirable levels of 25-hydroxyvitamin D to be established as 50ng/mL.Levels consistently higher than 200ng/mLare associated with toxicity, however, given the current state of knowledge the upper limit of normal should be capped at 80ng/mL.Depending on the health status, sun exposure, intake of medications, we recommend that total daily intake of vitamin D should be about 1000 IU/day to prevent bone disease and about 2000 IU/day to promote optimal health. Special populations (e.g. nursing home residents, those with severe deficiency) may require higher doses. Daily supplements of 4000 IU are generally considered safe.

Keywords: 25-hydroxyvitamin D; Normal blood levels of 25-OH vitamin D; Recommended daily intake of vitamin D; Harmonization of tests for vitamin D; Ethnic variation in levels of vitamin D

Abbreviations

IOM: Institute of Medicine; PTH: Parathyroid Hormone; NHANES: National Health and Nutrition Examination Survey; ASG American Society of Geriatrics; ng: Nanogram; mL: Milliliter

Introduction

Vitamin D is one of thirteen essential nutrients and functions like a hormone. Deficiency of vitamin D is one of the common nutritional deficiencies, despite our capacity to synthesize vitamin D from cholesterol and sunlight. Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, it is added to some foods in some countries, and available as a dietary supplement. The richest dietary sources of vitamin D are fatty fish and to a lesser extent beef and eggs [1]. Foods are fortified with vitamin D in some countries, e.g. USA. Factors contributing to the high prevalence of vitamin D deficiency appear to be reduced intake of fortified milk or foods with naturally high vitamin D levels, and decreased exposure to sunlight [1-4]. Vitamin D, either taken orally or synthesized in skin from 7-dehydrocholesterol by sun-light, is converted to 25-hydroxyvitamin D (25-OH vitamin D) in the liver. 25-OH vitamin D is converted, mainly by kidney, into the biologically active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol. Vitamin D acts as a hormone, and along with parathyroid hormone (PTH), vitamin D is essential for calcium homeostasis, bone health and perhaps other functions [1,5]. The lack of supplementation of food stuffs with vitamin D, in many countries, contributes to the worldwide high prevalence of deficiency of vitamin D.

There is lack of consensus about normal levels of 25-OH vitamin D and this has led to multiple clinical guidelines [Institute of Medicine (IOM), Endocrine Society, American Society of Geriatrics (ASG)] and confusion about screening and treatment goals. It is timely and useful to review why 25-OH vitamin D is assayed and how "normal" values are established. 25-OH vitamin D has a long serum half-life (3 weeks), and its conversion from vitamin D in the liver is not tightly regulated, and has become the most common clinical measure of nutritional vitamin D status [6-8].

25-OH vitamin D circulates in the bloodstream primarily bound to proteins, with <1% in the free, unbound state. 85-90% of 25-OH vitamin D is bound to vitamin D-binding Protein (VDP), with the remaining 10-15% bound primarily to albumin. The commercially available clinical assays measure total 25-OH vitamin D (both bound and unbound), though the fraction bound to vitamin D-binding protein is biologically unavailable [9].

There are genetic variations in the VDP, with the form common in black Americans contributing to both lower levels of VDP and

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total 25-OH vitamin D [10]. Considering the effect of acute and chronic illness on protein status, including albumin, some of the associations with low vitamin D status and numerous acute and chronic diseases may be a reflection of the impact of these diseases on the vitamin D carrier proteins. The association between low vitamin D and chronic diseases (e.g., cardiovascular, metabolic, inflammatory, infectious, cancers, rheumatologic, etc.) may not be a cause and effect relationship, but reflect that the low measured total 25-OH vitamin D may be a marker for poor health, a situation akin to sick euthyroid syndrome [10,11]. This may partially explain why it has been difficult to demonstrate beneficial effects of vitamin D supplementation in chronic diseases [11,12].

There is universal agreement that vitamin D is essential for bone health and for prevention of rickets in children and osteomalacia in adults, and there is little controversy over the adverse effects of deficiency on bone and calcium metabolism [15-18]. There is a newer concept of "insufficiency," meaning levels that do not cause severe bone and calcium effects, but still cause secondary increases in parathyroid hormone and osteoporosis [6,8,19]. IOM defines "insufficiency" as levels <20 ng/mL, while the Endocrine Society defines it as 20-29 ng/mL. The ASG recommends a minimum target 25-OH vitamin D level of 30 ng/mL.

The IOM report focused on bone health in populations; the Endocrine Society focused on recommendations for clinicians caring for individuals; and the ASG is targeted toward prevention of falls and fractures in elderly populations. In its focus on bone health, the IOM evaluated evidence of absence of skeletal disease in setting the "normal" level at 20 ng/mL. There is good evidence for a threshold of 20 ng/mL for bone effects as evidenced by increases in markers of bone turnover, such as urinary levels of pyridinoline and dexoxypyridinoline, serume levels of osteocalcin, and serum levels of alkaline phosphatase [23,24]. PTH increases in response to low vitamin D status, but there is variability in PTH response to given levels of 25-OH vitamin D, with no clear cut point across studies [20-22]. Threshold values for PTH increases range from 6-50ng/mL across studies [21]. The physiology of vitamin D and calcium absorption is complex, and depends on age, sunlight exposure, renal function, calcium intake, phosphorus intake, magnesium status, and other factors. Since most of the recommendations on "normal" 25-OH vitamin D are based on absence of disease rather than optimum health, these may thus underestimate the "normal" values for healthy populations [25].

Nearly all cells have receptors for vitamin D and this nutrient/hormone has been variously cited for affecting overall mortality, falls and fractures in the elderly, control of infections in general and tuberculosis and influenza in particular; prevention of some cancers, cardiovascular disease, multiple sclerosis and other neuropsychiatric disorders. There is generally a lack of controlled trials supporting most of these claims [1,14]. The lack of effect of vitamin D on the outcomes of treatment, especially prevention of fractures, may be due to inadequate dose of the supplement. For example, in a meta-analysis of vitamin D supplementation for prevention of fractures, the average and median doses were 1060 and 800 units respectively. Only one of the 40 trials used a dose higher than 2000 units [26]. At the same time it has been shown that it takes about 5000 IU/day of vitamin D to observe a consistent effect in correcting deficiency, therefore lack of positive outcome in trials using inadequate supplementation is questionable [27].

The controversy about normal levels of vitamin D and many other analytes stems from the difficulty in establishing normal levels. The animal and plant sources of vitamin D, namely D3 and D2, respectively add to the controversy and confusion. However, there is increasing recognition that vitamin D2, usually used as a supplement derived from irradiated ergosterol, is not stored as effectively as vitamin D3 and supplementation with vitamin D3 is preferred. Of the two forms of vitamin D added to foods and available as supplements, Vitamin D_2 is manufactured by the UV irradiation of ergosterol in yeast, and vitamin D_3 is manufactured by the irradiation of 7-dehydrocholesterol from lanolin. The two forms are generally equivalent, but at high doses vitamin D_2 is less potent [1,4]. Most methods in use in clinical laboratories measure the total amount of 25-OH vitamin D, though mass spectrometric analysis allows quantification of each type separately. We address the various issues and methods for determining normal levels of an analyte in general and 25-OH vitamin D in particular.

General approaches/methods to determine the normal blood levels of a substance/analyte:

1. Test "normal" individuals: The usual way to determine the normal level or reference range of a given substance or analyte, is to measure the substance in a healthy group of individuals and use the central 95% of the range as the reference range. At a minimum, 120 individuals of a given age, gender, and ethnic group need to be tested to determine the reference range for that population [28]. It is often difficult, if not impossible to select 120 healthy individuals with a given set of properties. In addition to the variation by age, gender, and ethnicity, different testing methods add additional uncertainty to the reference range. One way to overcome the differences in results from different methods is by harmonizing the testing methods to yield comparable results [29]. There is expected to be considerable variation in the serum levels of 25-OH vitamin D in apparently healthy individuals based on the amount of exposure to sunlight and skin pigmentation [30].

2. Expert opinion for "healthy" levels: Normal level or reference range for serum cholesterol is not based on the findings in "healthy" individuals but determined by "experts". The correlation of serum cholesterol with cardiovascular disease was used to develop desirable levels of serum cholesterol. The desirable levels further vary by the health status of the individual, e.g., people with diabetes have lower recommended level of serum cholesterol than non-diabetics [31]. Expert opinions have not coalesced to recommend normal serum levels for 25-OH vitamin D.

3. Use of surrogate markers for determination of normal levels: Deficiency of the essential nutrients often results in disease states or abnormal laboratory test results and these markers have been used to establish reference ranges. For example the lower limit of normal serum folate level varies from 2.0 to 13.0ng/mL depending on the surrogate marker being absence of megaloblastic anemia, normal level of homocysteine or optimum prevention of fetal neural tube defects [32,33]. A consensus surrogate marker for 25-OH vitamin D has not been established.

Specific approaches/methods to determine normal, healthy, and optimum blood levels of 25-OH vitamin D:

1. Levels of 25-OH vitamin D in apparently healthy sun exposed individuals: Measurement of serum 25-OH vitamin D in young healthy life guards exposed to sunlight as part of their duty could be used to establish normal healthy levels. 25-OH Vitamin D levels in sun exposed individuals have been noted to be above 60ng/mL without any evidence of toxicity. Similarly prevalent levels of 25-OH vitamin D in African tribal men are about 50ng/mL [34]. Serum levels of 25-OH vitamin D are higher in Hawaii residents than in the continental US and average levels being higher than 30 ng/mL [35].

2. Levels of 25-OH vitamin D in individuals supplemented under controlled circumstances: Administration of vitamin D3 in doses exceeding 5000 IU/day resulted in serum levels of 25-OH vitamin D to about 80ng/mL without evidence of toxicity. Toxicity is seen at serum 25-OHvitamin D levels consistently >200ng/mL [36].

3. Epidemiologic studies correlating the serum levels of 25-OH vitamin D and disease susceptibility: Garland et al noted that 25-OH vitamin D levels of 60-80ng/mL may be needed to reduce the risk of cancer. Using NHANES data on 25-OH vitamin D levels and favorable outcomes of influenza infection Ginde et al favor pegging the normal levels of the vitamin at 60 ng/mL [37].

4. Using parathyroid hormone as a surrogate marker: Deficiency of vitamin D impairs calcium absorption from the intestine and results in elevated levels of PTH in an attempt to maintain normal blood levels of calcium. When the concentrations of these two analytes were determined in the same samples, PTH levels were always elevated in samples with 25-OH vitamin D levels below 10ng/mL and were near-normal in samples with 25-OH vitamin D concentration > 18 ng/mL [22]. Therefore it could be suggested that the lower limit of normal 25-OH vitamin D level is about 20 ng/mL. However, prevention of elevated PTH levels may not be the optimum state of health. This situation may be similar to folic acid levels of >3.0ng/mL being sufficient to prevent megaloblastic anemia but being grossly inadequate for prevention of neural tube defects [32,33].

5. Prospective controlled trials evaluating prevention or amelioration of diseases associated with vitamin D: Observational studies often have non-reducible errors and in many instances are not validated by the current gold standard of controlled trials. Given the large number of diseases attributed to vitamin D deficiency, it would be a daunting task to perform controlled trials assessing all of these diseases. The available data indicate reduction in fractures with serum 25-OH levels of about 25 ng/mL [36]. However, the level at which maximum reduction in the fractures occurs needs to be determined and is likely to be higher than 25 ng/mL.

The data on naturally occurring levels of 25-OH vitamin D in sun exposed individuals and those receiving supplementation without any evidence of toxicity suggest that serum level of30-32 ng/mL of 25-OH vitamin D is the appropriate lower limit of normal and optimum levels is likely in the range of 50 ng/mL. With the present state of knowledge, it would be prudent to not exceed serum levels of 25-OH vitamin D of 80ng/mL.

Optimum daily intake of vitamin D: The Recommended Dietary Allowances (RDA), is the daily dietary intake level of a nutrient considered sufficient by the Food and Nutrition Board of the Institute of Medicine (IOM) to meet the requirements of 97.5% of healthy individuals in each life-stage and sex group. For vitamin D the IOM-recommended daily intake ranges from 400 to 800 IU/day [1-6]. Intake levels for older age groups have been revised upward from 400 IU to first 600 and then 800 IU/day. In general RDA is aimed at preventing disease rather than attaining optimal levels of the nutrient. Determination of the optimum serum levels of 25-OH vitamin D is a pre-requisite for ascertaining the optimum daily intake and the former has yet to be established. Empirical observations, especially in patients, have shown such a doses of 400 IU to 800 IU/day to be grossly inadequate for maintaining normal levels when normal is considered to be 30 ng/mL [27].

The WHO definition of health is worth stating in this context, "*Health* is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [39]. In determining normal or better yet, optimal levels of essential nutrients, one should aim for "health" rather than lack of disease as may be the case with current state of normal vitamin levels.

The relationship between vitamin D supplementation and reducing disease and optimizing health is complex and should continue to be clarified as clinical trials continue to be reported. There are currently 373 clinical trials of vitamin D and vitamin D deficiency listed on the National Institutes of Health clinical trials website [40]. However, based on current knowledge, we are inclined to recommend 30ng/mL as the lower limit of normal and desirable levels of 25-hydroxyvitamin D as 50ng/mL. Levels consistently higher than 200ng/mL are associated with toxicity, and, given the current state of knowledge the upper limit of normal should be capped at 80ng/mL. Doses of vitamin D of 400 IU – 800 IU/day may be sufficient to achieve 25-hydroxyvitamin D levels of 20 ng/mL (IOM recommendation) [5]. However, to achieve 25-hydroxyvitamin D levels of 30 ng/mLor higher, and depending on the health status, sun exposure, intake of medications, we recommend that total daily intake of vitamin D should be about 1000 IU/day to prevent bone disease and about 2000 IU/day to promote optimal health. Special populations (e.g. nursing home residents, those with severe deficiency) may require higher doses [27]. Daily supplements of 4000 IU are generally considered safe [4]. Recommendations of optimal vitamin D supplementation will continue to evolve as measures of vitamin D status are refined and studies of impact of vitamin D supplementation on health and disease continue to be reported.

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