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

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Abstract

Vitamin D is obtained from cutaneous production when 7-dehydrocholesterol is converted to vitamin D₃ (cholecalciferol) by ultraviolet B radiation or by oral intake of vitamin D₂ (ergocalciferol) and D₃. An individual's vitamin D status is best evaluated by measuring the circulating 25-hydroxyvitamin D [25(OH)D] concentration. Though controversy surrounds the definition of low vitamin D status, there is increasing agreement that the optimal circulating 25(OH)D level should be ~30-32 ng/ml or above. Using this definition, it has been estimated that approximately three quarters of all adults in the United States are low. Classically, low vitamin D status has skeletal consequences such as osteomalacia/rickets. More recently, associations between low vitamin D status and increased risk for various non-skeletal morbidities have been recognized; whether all of these associations are causally related to low vitamin D status remains to be determined. To achieve optimal vitamin D status, daily intakes of at least 1000 IU or more of vitamin D are required. The risk of toxicity with “high” amounts of vitamin D intake is low. Substantial between-individual variability exists in response to the same administered vitamin D dose. When to monitor 25(OH)D levels has received little attention. Supplementation with vitamin D₃ may be preferable to vitamin D₂.

Keywords

Vitamin D; 25-hydroxyvitamin D; supplementation; deficiency; insufficiency

Introduction

Vitamin D is obtained either by ingestion or cutaneous production. When skin is exposed to ultraviolet B radiation, 7-dehydrocholesterol is converted to vitamin D₃ (cholecalciferol). Dietary sources may provide either vitamin D₃ or vitamin D₂ (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 non-skeletal morbidities.^{7, 8}

This review will consider 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 D₂ or D₃) 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 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. Anecdotally, it is not rare to see healthcare 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 1-alpha 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 (nanogram/ml vs. picogram/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 volume. Suffice it to say that current evaluations find that clinical 25(OH)D measurement has improved¹³ allowing healthcare 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, healthcare 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 which 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 below approximately 10 ng/ml are classified as deficient and may sustain impaired bone mineralization (rickets/osteomalacia), while those below approximately 30 ng/ml are identified as insufficient (Figure 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 non-productive debate, the terminology “low vitamin D status” will be 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.”

Recognizing that controversy exists, there appears to be increasing consensus that circulating 25(OH)D values below ~30-32 ng/ml indicate less than ideal vitamin D status.¹⁶ These cutpoint values were suggested based upon 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 workers finding an apparent inflection point at ~20-30 ng/ml.^{16, 21} Moreover, some work demonstrates improved calcium absorption at 25(OH)D levels within what had previously been accepted at 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 others 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.²⁵ In this work, the authors found serum 25(OH)D to rapidly increase as circulating vitamin D₃ (cholecalciferol) increased. When circulating vitamin D₃ 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 30-32 ng/ml suggested by other endpoints 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 endpoints, i.e., the cutpoint for various non-classical targets of vitamin D might vary from that for bone.²⁶ Furthermore, it is possible/likely that the 25(OH)D value for “optimal” physiologic functioning might differ between individuals. Having a range of “normal” for virtually all clinically measured biological 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 our 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 (Figure 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 Figure 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 the above, 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 below approximately 30-32 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 52-77% of the studied cohorts as “low” using 30 ng/ml as a cutpoint.^{21, 36-38} Even the more restrictive cutpoint of < 20 ng/ml identifies 18-36% as “low” (Figure 3). It is not surprising that studies report a variable prevalence of low vitamin D status as the studied cohorts differ in age, sex, race, body mass index and dietary vitamin D intake. Though 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 over 32,000 subjects found no 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. Though measurement issues confound data interpretation, recent NHANES data report a decline in mean 25(OH)D concentration from the 1988-1994 data collection to that of 2000-2004.^{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 Additionally, 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/Falls

Both genomic and non-genomic 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 people.⁴⁹ Importantly, randomized prospective studies find vitamin D to reduce falls risk 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 falls risk.⁵² The 25(OH)D concentration needed to optimize leg function has been explored with various cutpoints (e.g. 16-24 ng/ml) suggested.^{35, 53} A recent review

finds 25(OH)D concentrations below ~16 ng/ml to be associated with substantially poorer leg function, but additionally finds values above ~36-40 ng/ml to be optimal.²⁶

Cancer

Vitamin D has anti-proliferative and pro-differentiating 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 endpoint 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 D₃ (1,100 IU daily) to reduce overall cancer risk by ~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 anti-tuberculous therapy.^{62, 63} More recently, it has become appreciated in 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 towards 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 Additionally, inflammation is increasingly being recognized in 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 Additionally, 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 the multiple adverse health outcomes, e.g., cardiovascular disease, diabetes, hypertension, etc., 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 of people include those with osteoporosis, a history of falls or high falls risk, malabsorption (e.g., celiac disease, radiation enteritis, bariatric surgery, etc.), individuals with liver disease and those requiring medications known to alter vitamin D status, e.g., 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. While 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 800-1000 IU daily⁹³ while some vitamin D experts suggests values over 2000 IU.⁹⁴ Moreover, as discussed below, vitamins D₂ and D₃ appear to not be equally potent in maintaining 25(OH)D.^{95, 96} As such, daily intake of 1,000 IU of vitamin D₂ may well not be equal to 1,000 IU of vitamin D₃. Additionally, vitamin D dosing may differ by age in that older adults likely require higher vitamin D intakes due 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 (Figure 4). Thus, if a healthcare 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 widespread sun-avoidance campaigns¹⁰⁰⁻¹⁰³ 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, e.g., 50,000 IU three times weekly, weekly or monthly have been evaluated.¹⁰⁸⁻¹¹¹ A recent evaluation of clinical approaches found vitamin D₂ regimens using >600,000 IU administered over an average time of two months achieved 25(OH)D values above 30 ng/ml in 64% of patients with the highest value being 100 ng/ml.¹⁰⁸ An additional clinical report of “high-dose” vitamin D₂ (50,000 IU once weekly for up to three years) achieved a 25(OH)D level above 30 ng/ml in 23/24 patients with the highest reported value being 100 ng/ml.¹¹²

Maintenance of vitamin D status with daily doses from 1,000-4,000 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 1,000 IU of vitamin D₃ daily can be expected to increase circulating 25(OH)D by approximately 10 ng/ml.

Though daily vitamin D supplementation is very inexpensive (approximately one dollar per month), available data finds 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 is hardly surprising in that suboptimal adherence to prescribed therapies for a variety of conditions is well known to clinicians.¹¹⁷ However, based upon the increasing calcium intake of the US 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 four to six months after initiating treatment in those at high risk (e.g., patients with osteomalacia, fragility fractures or high falls risk) seems reasonable. Repeat evaluation at earlier timepoints seems inappropriate as it takes 3-6 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 above will lead to toxicity. Clearly, huge doses of vitamin D do lead to hypercalcemia and hypercalciuria. However, there is no clear-cut definition of which serum 25(OH)D

should be considered “toxic.” This has led to variability in the clinical reporting of 25(OH)D results, with some laboratories reporting possibly toxic levels as being >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 > 88 ng/ml.¹²⁰

Regarding what constitutes a “high” 25(OH)D values, it seems reasonable that highly sun exposed individuals could be utilized 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 70-80 ng/ml range.^{30, 31} Thus, the current approach of reporting 80-100 ng/ml as the upper limit of normal seems appropriate.

Does the Effect of Vitamin D₂ Differ From That of Vitamin D₃?

Two chemically distinct forms of vitamin D exist; vitamin D₃ (cholecalciferol) is a 27 carbon molecule whereas vitamin D₂ (ergocalciferol) contains 28 carbons and differs from vitamin D₃ by the presence of an additional methyl group and a double bond between carbons 22 and 23. While clear chemical differences exist, whether vitamin D₂ and vitamin D₃ are equally effective at increasing 25(OH)D and/or have equivalent physiologic effects remains unclear. Currently, these two forms are regarded as equal and interchangeable. However, some data suggest that vitamin D₂ is less “potent” at maintaining serum 25(OH)D than is vitamin D₃.^{95, 96, 121} While a recent report challenges this¹¹³ and found D₂ and D₃ to be equally effective, the vast majority of studies find vitamin D₃ to be somewhat more potent. It seems probable that this reflects lower affinity of vitamin D₂ for vitamin D binding protein in the circulation leading to more rapid clearance. As such, use of supplements containing vitamin D₃, rather than vitamin D₂, seems appropriate.¹²² It is unfortunate that vitamin D₂ is the only high-dose prescription vitamin D preparation in the United States and some other countries. Despite the lower potency, use of high-dose vitamin D₂ does increase circulating 25(OH)D concentration.

Conclusion

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/likely that low vitamin D status increases risk for a multitude of other conditions. Though consensus does not exist, it appears that circulating 25(OH)D concentrations above 30-32 ng/ml are needed for optimal health. To achieve this, daily intakes of at least 1,000 IU of D₃ 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 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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Figure 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 below) 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 appears to be increasing agreement that values above approximately 30-32 ng/ml are associated with optimal physiologic function.

Figure 2. Distribution of Serum 25(OH)D in Highly Sun-exposed Adults

In these two 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. Data adapted from Binkley, et. al.,³⁰ and Barger-Lux, et. al.³¹ Note that the Barger-Lux, et. al., study utilized a 25(OH)D assay that measures approximately 10% higher than the HPLC assay used in the Binkley, et. al., report.

Figure 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 below 20 ng/ml or below 30 ng/ml is extremely common. Data adapted from various sources.^{21, 36-38}

Figure 4. Variable Response to Daily Vitamin D₃

In these seven 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 1,600 IU vitamin D₃ is apparent.⁹⁶