

Controversies in Vitamin D Recommendations and Its Possible Roles in Nonskeletal Health Issues

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Abstract

This article discusses one of the current most controversial nutrition topics. Recent vitamin D recommendations, as well as the serum 25-hydroxyvitamin D (25OHD) concentrations and implications on health status are reviewed. The various functions of vitamin D, starting from the cellular level, through autoimmune diseases, cancer, cardiovascular disease, and neuromuscular processes, to its role in obesity and metabolic syndrome, as well as in pregnancy outcomes, are also discussed. The most up-to-date literature published in peer-review scientific journals was reviewed. While the role of vitamin D in bone metabolism and the amount to support bone health is unequivocal, its benefits and/or roles in various other health conditions and the best way to achieve and maintain optimal levels are still controversial. Opinions vary on the recommended intake for vitamin D and what the desirable serum levels of vitamin D may be. Despite the numerous reports about its impact in autoimmune processes, several cancers, cardiovascular diseases, obesity, metabolic syndrome, and pregnancy complications, the evidence is not robust enough to draw definite conclusions or to establish a causal relationship. Only the role of vitamin D in neuromuscular functions and prevention of falls in frail elderly seems to be more substantiated. Reaching the current or even higher levels of consumption (e.g. 1500-2000 IU/day) seems improbable by food and sun exposure only and supplementation should be in place, particularly for individuals at risk, including breast-fed infants, children, pregnant/lactating women, elderly, obese and individuals with fat mal absorption.

Introduction

In the recent years, vitamin D has become one of the most studied and written-about nutrients regarding the wide variety of skeletal and nonskeletal health issues, the latter ranging from its role in the immune system [1], to various psychotic states subsequently developing later in children delivered by mothers having low vitamin D status during pregnancy [2]. The interest in vitamin D and concerns about its possible inadequate status in various populations were particularly heightened after the 2009 report from the National Health and Nutrition Examination Surveys (NHANES), collected from 1988 to 2004 in over 30,000 adults and teenagers [3]. According to these large observational surveys, 77% of screened population had serum concentration of 25-hydroxyvitamin D (25OHD), an indicator of vitamin D status, below the level considered adequate. Even of a higher concern was a finding that only 3% of African Americans surveyed were above this adequate level [3].

Despite the overwhelming evidence of the importance of vitamin D in various health conditions, and its apparently inadequate levels in most of the population segments, the report from the Food and Nutrition Board of the Institute of Medicine (IOM), released in November 2010, concluded that the evidence linking vitamin D (and calcium) deficiency to anything, but impaired bone health was inconclusive. Moreover, the IOM's report declared that most people in the US and Canada are getting enough of the vitamin through food or supplements. Although the IOM slightly raised the Recommended Dietary Allowances (RDA), as well as the Tolerable Upper Levels (TUL), for most of the population groups [4], this relatively small increase in recommendations caused a strong reaction among numerous researchers familiar with the topic. The assertion by Heaney and Holick [5], stating that "the IOM recommendations for vitamin D fail in a major way, on logic, on science, and on effective public health guidance," and that in general, these recommendations may lead the development of nutritional policies in the wrong direction, was probably the most out spoken. The issues surrounding the dietary recommendations of vitamin D, and the optimal serum levels of 25OHD are still contentious. The objective of

this paper is not to support nor contest the IOM recommendations, but to present some evidence of the possible roles of vitamin D in various health conditions, and expound why some universal dietary recommendations, and/or optimal serum levels might be harder to establish.

Dietary Recommendations for Vitamin D by IOM

The Food and Nutrition Board of the IOM was established in 1940 with the goal to provide recommendations for nutrient intakes, as well as other scientific-based views about nutritional influences on health and disease. A new system of defining optimal nutrient intakes for healthy populations in the United States and Canada has been developed in 1997, and is known as the Dietary Reference Intakes (DRI) [4]. Unlike the previous Recommended Dietary Allowances (RDA), where only one level of a nutrient was defined, the DRI delineates different levels of intakes, including the Estimated Average Requirement (EAR), the RDA, the Adequate Intake (AI), and the Tolerable Upper Intake Level (TUL). It needs to be noted that the updated recommendations for both vitamin D and calcium are not directly comparable to the previous sets that were established in 1997. The 1997 recommendations were based on AI rather than on the RDA, the latter one being more precise and derived from EAR. A somewhat simplified presentation and comparison between old and new recommendations are given in Table 1.

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Age group	Old AI IU(μg)/day	Old TUL IU/day	New RDA IU (μg)/day	New TUL (IU/day)
0-12 months	200 (5)	1000	400 (10)	1000-1500
1-50 years*	200 (5)	2000	600 (15)	2500-4000
50-70 years	400 (10)	2000	600 (15)	4000
>70 years	600 (15)	2000	800 (20)	4000

*Includes pregnant and lactating women; AI: Adequate Intakes; IU: International Units; RDA: Recommended Dietary Allowances; TUL: Tolerable Upper Levels.

Table 1: Comparison between old (1997) and new (2010) recommendations for vitamin D intake (adapted from reference [4]).

Vitamin D is not abundant in food--its main dietary sources are egg yolks, fatty fish, cod liver oil and whole milk, or fortified dairy products. Therefore, encouraging supplementation through diet and sunlight exposure presents an alternative option for receiving recommended amounts. However, sun exposure could be quite unpredictable and limited to many people. Moreover, current health recommendations discourage sun exposure due to possible risk of skin cancer. Therefore, there is a concern that the RDA of 600 IU/day [4], may not be easily reached with food only, especially if lower food consumption to reduce weight is in place. Four servings of fortified dairy products (100 IU/8 oz of vitamin D), or a serving of fatty fish (300-600 IU of vitamin D), or vitamin D supplement intakes of 400 IU were associated with serum 25 (OH) D increases of only about 4 to 8 nmol/L, depending on vitamin D status at starting point, and indicating that the relationship between dietary vitamin D and serum 25 OHD is not linear [6]. Therefore, reaching the current, or even higher levels of consumption (e.g. 1500-2000 IU/day), as recommended by some researchers [7], seems improbable by food and sun exposure only, and supplementation should be in place, particularly for individuals at risk, including breast-fed infants, children, pregnant/lactating women, elderly, obese and individuals with fat malabsorption.

Serum Levels of Vitamin D

The best objective measure of vitamin D status is circulating serum 25 OHD concentration [8], since it reflects both endogenous and exogenous sources, and has a longer half-life than the active vitamin D (1,25-dihydroxyvitamin D₃). Serum 25OHD is formed in the liver by the hydroxylation of precursors originating from skin and diet, and provides a substrate for production of active metabolite, 1,25-dihydroxyvitamin D₃, in kidney [9]. Therefore, besides a possible low intake, inadequate vitamin D status may be a consequence of decreased conversion of 7-dehydrocholesterol in the skin (due to indoor confinement, living in northern latitudes, clothing habits, and/or the use of sunscreen), but also a result of the impaired hydroxylation in the liver or kidney [9].

Although serum 25 OHD is considered as the best measure of vitamin D status, there is a wide variability of the different assays for its determination in different laboratories, despite the reference standards that were established in 2009 [4]. Additionally, there is also a lack of agreement, as to what level constitutes optimal concentrations for prevention/treatment of any of the conditions it is implicated in, and where the cutoff levels should be for different population groups [9]. Kim et al. [10] defined hypovitaminosis D as serum 25 OHD<75 nmol/L. Millen et al. [11] studying women aged 50-70 years, reported serum 25OHD concentrations<50 nmol/L presented deficiency, while concentrations ≥ 50 to <75 nmol/L presented insufficiency. According to Holick [9], the concentration of >75 nmol/L presents an optimal level of serum 25OHD; the concentrations between 50-75 nmol/L present insufficiency; and those <50 nmol/L present deficiency. These values

are based on bone health, and seem to be accepted by most researchers in that field [5], although they are in some discord with the newest IOM suggestions, which are presented in Table 2 [4].

Various Functions of Vitamin D

Vitamin D in bone metabolism

The role of vitamin D in the skeletal health has been known for a long time and widely investigated, therefore, it will not be discussed in detail here. Briefly, its deficiency is associated with rickets in children and osteomalacia, and/or osteoporosis in adults. Vitamin D plays a critical role in bone metabolism by maintaining serum calcium levels *via* several modalities; a) by inducing the synthesis of calcium binding protein, calbindin, involved in the intestinal calcium absorption, thereby preventing hypocalcemia and stimulating bone mineralization; b) in the absence of dietary calcium, vitamin D stimulates osteoclastogenesis and bone resorption, enabling the mobilization of calcium from bone reserves; c) in conjunction with parathyroid hormone, vitamin D promotes reabsorption of calcium filtrate in the renal tubule, decreasing its urinary excretion [9]. Therefore, from a clinical standpoint, vitamin D is undisputedly a crucial factor for bone health.

Possible Roles of Vitamin D in Nonskeletal Tissues: From Cellular to Whole-Body Levels

On the cellular level

Vitamin D is involved in modulation of cell growth, as several genes encoding for proteins that control cell proliferation, differentiation and apoptosis are regulated, at least in part by vitamin D. Some researchers estimate Vitamin D regulates approximately 5% of the total human genome [12]. Additionally, the cells of almost every tissue in human body have vitamin D receptors, and some are able to convert 25 OHD into active 1,25-dihydroxyvitamin D₃ [13,14]. Despite the expression of vitamin D receptors in cells of virtually all tissues, their role in some tissues has not been completely elucidated.

In autoimmune diseases

Several epidemiological studies reported the association between vitamin D deficiency, and an increased risk for developing multiple sclerosis (MS). Results from the study that followed almost 200,000 MS patients for up to 20 years showed an inverse relationship between vitamin D levels and the incidence of MS, with the prevalence of MS being 40% lower in women with adequate vitamin D levels. However, this association was only found in white patients, and not in other ethnicities, e.g. among black or Hispanic patients, who typically have lower serum levels of vitamin D [15]. The circumstantial evidence supporting connection between vitamin D and MS is that MS is not present in the equatorial regions, and that the prevalence increases with the increasing latitude, as well as that the outbreaks of MS typically occur during winter and spring, the periods corresponding to the

nmol/L*	ng/mL	Health status
<30	<12	Deficiency, leading to rickets in infants/children and osteomalacia in adults
30–50	12–20	Inadequate for bone and overall health in healthy individuals
≥ 50	≥ 20	Adequate for bone and overall health in healthy individuals
>125	>50	Potential toxicity and adverse effects, particularly >150 nmol/L

*1 nmol/L=0.4 ng/mL

Adapted from Institute of Medicine [4].

Table 2: Serum 25-hydroxyvitamin D (25OHD) concentrations and implications in health status.

months with the lowest levels of UV radiation, and, consequently, with lower serum levels of vitamin D [16]. Interestingly, optimizing vitamin D levels has been shown to prevent a second demyelinating attack, after a diagnosis of clinically isolated syndrome (CIS) or optic neuritis, which is an initial warning sign for MS [17]. Other research showed that a dose of 20,000 IU of vitamin D3 once per week, alongside interferon beta-1b treatment, resulted in significantly fewer lesions on brain MRI, reduced disability scales and improved ability to walk, compared to controls. In this particular study, the subjects' mean 25 (OH) D levels increased from 22 ng/mL to 44 ng/mL in one year [18].

Seasonal peaks observed in the onset of diabetes mellitus have also been associated with periodic oscillations in vitamin D levels. A large 4-year prospective multicenter study in 51 regions worldwide revealed an inverse relationship between sun exposure in each area and the incidence of type 1 diabetes mellitus [19]. Vitamin D supplementation, at least during childhood, appears to have some value in preventing this disease, and it has been shown after a follow-up period of up to 30 years that the administration of 2000 IU of vitamin D daily, significantly reduced children's risk of developing insulin-dependent diabetes mellitus [20]. With type 2 diabetes, meta-analysis of 21 independent prospective studies confirms that low vitamin D status is associated with an increased risk of developing type 2 diabetes [21]. However, there is currently insufficient evidence to support the therapeutic usefulness of vitamin D supplementation in managing or preventing diabetes mellitus.

The results of experiments with animal models of arthritis suggest that treatment with 1,25(OH)₂D3 in the early stages of rheumatoid arthritis may prevent disease progression [22]. Additionally, several epidemiological studies, one lasting 11 years, showed the inverse relationship between vitamin D status and severity or risk of developing rheumatoid arthritis [23]. It has been shown that patients with *systemic lupus erythematosus* have low levels of 25 OHD compared to healthy controls [24]. The factors that might contribute to these low levels of vitamin D include the pathophysiological mechanisms of the disease itself, the fact that some patients with the disease develop anti-vitamin D antibodies, and the photoprotective measures dictated by the disease. However, studies also show that patients with low vitamin D have higher risk of developing the disease; therefore, the cause-and-effect in this case is unknown. Vitamin D supplementation would therefore appear to be advisable in the patients with lupus.

In cancer

Several studies, in both animals and humans, have provided evidence that vitamin D may have a beneficial effect in some cancers, in terms of reducing the incidence, and/or improving the outcomes. The mechanism is probably linked to the regulatory effects of vitamin D on cell growth, differentiation, and apoptosis. Furthermore, several studies examined the link between blood levels of 25 OHD and the incidence of various cancers. The blood values of 25 OHD between 30 to 35 ng/mL (75 to 87.5 nmol/L) were found to be optimal for obtaining the maximal beneficial effects of vitamin D [25]. Recently, several meta-analyses have reported conclusive evidence regarding the protective effect of adequate levels of vitamin D against breast and colorectal cancer [26,27], but not against prostate cancer and melanoma. The beneficial effect persisted even after adjusting for factors that might influence vitamin D levels, such as obesity or age. In general, while some studies are convincingly showing the beneficial effects of higher vitamin D on some cancers, the scientific community is not ready to give official recommendations, and the issue is still widely open for more interventional clinical trials.

In cardiovascular diseases

Observational and epidemiological studies point into the inverse relationship between vitamin D status and various cardiovascular risk factors, including hypertension and arterial calcification, as well as into cardiovascular diseases themselves, like stroke and myocardial infarction. Several mechanisms were proposed, including endothelial dysfunction, inflammation and impaired renin angiotensin system, all possibly associated with low vitamin D levels [28]. However, despite this relatively convincing evidence from the observational studies, the results from the clinical trials with vitamin D supplementation were not that conclusive. Based on the meta-analysis conducted recently by the Endocrine Society Task Force and including 51 interventional studies, there was no significant effect of vitamin D on any of the outcome measures, including stroke, myocardial infarction and death [29]. There was also no effect of vitamin D on secondary outcomes, like lipid profile, serum glucose or blood pressure [30]. Additionally, an original study in postmenopausal women by Truesdell et al. [31] showed that there was no association between serum 25OHD and cardiovascular risk factors assessed by Framingham Cardiovascular Risk Score. The Task Force conclusion was that the evidence connecting vitamin D with the improvement of cardiovascular disease of any kind is weak or non-existent, and that more high-quality interventional studies need to be conducted to affirm vitamin's D role in any of the various types of cardiovascular diseases or risk factors.

In neuromuscular function

Many studies support the hypothesis that various levels of vitamin D insufficiency contribute to muscle weakness, which subsequently responds well to vitamin D treatment. The effect is linked to the presence of vitamin D receptors in muscle cells. When vitamin D binds to its receptors, it triggers a protein synthesis and muscle cell proliferation and differentiation [32]. Specifically, atrophic type II muscle fibers (recruited first to prevent a potential fall), have been found in muscle biopsies of patients with a decreased serum 25 OHD [32]. Furthermore, vitamin D deficient patients have been found to have decreased proximal hip muscle strength that affects gait stability, and can predispose them to falls [33]. However, analysis in the most recent Agency for Healthcare Research and Quality (AHRQ) systematic review identified a significant inconsistency across studies, including population heterogeneity, serum 25 OHD measurements and outcome measures, which all add more paucity into the issue [34].

Nevertheless, vitamin D supplementation is associated with a reduction in falls in individuals who have low baseline levels (less than 50 nmol/L or 20 ng/mL), by improving muscle strength and lower-extremity function. A meta-analysis performed by O'Donnell et al. [35] found a 34% decreased risk for falling in the vitamin D treated group compared to placebo. A recent 3-year randomized controlled trial showed an even more protective effect of vitamin D and calcium supplementation in fall prevention. Two hundred forty-six women >65 years were randomly assigned to receive 700 IU vitamin D and 500 mg calcium or placebo. The risk of falling in women who received supplementation was reduced by 46%. The fall reduction was even more apparent in women whose physical activity was below the median level at baseline [36]. This effect of vitamin D supplementation may lead to a substantial decrease in fall, and subsequent morbidity and mortality in the elderly population. However, the absolute threshold level of serum 25 OHD needed to prevent falls in an elderly population is not known, in part, because of the lack of true dose-ranging studies. Importantly, recommendations for vitamin D intake in any given individual must

also be considered within the context of optimal calcium intake (the mineral affecting both nerve and muscle functions). Notwithstanding, the effect of vitamin D supplementation on falls could have important public health implications, considering the morbidity associated with falls, particularly in the frail elderly. Selecting patients at risk for falls and defining the appropriate dose remain in need of further research.

In obesity and metabolic syndrome

Both obesity and metabolic syndrome have been associated with low serum levels of 25 OHD in numerous observational studies, with several explanations for possible mechanisms. The most frequently cited one is that vitamin D is stored in and sequestered by adipose tissue, and thus less available in circulation [9,37]. However, the precise connection between vitamin D and adiposity is not clear; neither is it known, what is the cause-and-effect relationship, at both the cellular and physiological levels. Similarly, the inverse relationship was found between vitamin D and metabolic syndrome in various types of studies, the latest one in Australian cohort study that followed participants for 5 years [38]. Since metabolic syndrome develops in individuals with any three of the following risk factors: obesity, diabetes, inflammation, hypertension and dyslipidemia, it is not clear which of these factors contributes to the hypovitaminosis D, or whether the latter is the cause for some or all of these comorbidities. A recent study showed that low vitamin D existed in individuals with metabolic syndrome, independently of the degree of obesity [39]. At present, the available evidence does not validate the use of vitamin D supplementation to curb obesity or metabolic syndromes.

In pregnancy

Meta-analysis of maternal vitamin D status and adverse pregnancy outcomes revealed that pregnant women who had 25 (OH) D levels below 20 ng/mL had an increased risk of preeclampsia, gestational diabetes, preterm birth and small-for-gestational age outcomes [40]. Bone pathology in sudden infant death syndrome (SIDS) was investigated by British researchers, who found that 87% of the SIDS babies less than one year of age showed histopathological evidence of rickets. However, none of the SIDS children over the age of one year displayed evidence of rickets, suggesting that SIDS is indeed multifactorial [41]. The American Academy of Pediatrics (AAP) released new guidelines for vitamin D recommendations in preterm and very low birth weight infants, as the IOM makes recommendations for the general population only, and preterm infants are considered a special population. AAP recommends 400 IU of vitamin D per day for babies born prior to 37 gestational weeks, with a maximum of 1,000 IU per day considered safe. Additionally, the AAP recommends that full-term infants placed on formula receive 400 IU per day.

Some research has indicated that vitamin D supplementation of 4,000 IU per day for pregnant women is safe and most effective in achieving vitamin D sufficiency in all women and their neonates, regardless of race [42]. A previous study showed a maternal intake of 400 IU/day was not able to sustain maternal 25 (OH) D levels, and supplied extremely limited amounts of vitamin D (between 40-50 IU/L) to the infant *via* breast milk. The same group of researchers from the University of South Carolina found that mothers who took a supplement of 6,400 IU every day provided their infants between 500-800 IU of vitamin D per liter of breast milk, without any adverse effects [43].

Conclusions

The benefits of vitamin D, and the best way to achieve and maintain

optimal levels are controversial, and still not elucidated issues, with potentially important implications for human health. There are different opinions on the recommended intake for vitamin D, and what the desirable serum levels of vitamin D may be. While in the previous few years, the serum 25 OHD level of 30 ng/mL (75 nmol/L) was considered to be optimal, the most recent IOM's recommendations indicate that levels of 20 ng/mL (50 nmol/L) appear to be sufficient and achievable for the general population, even under conditions of minimal sunlight exposure. If these figures are reliable, the apparent pandemic of vitamin D deficiency reported in past years may have been overstated. However, we still need a better understanding of the relationship between the maintenance of vitamin D levels through exposure to sunlight, and through diet and supplementation, and how the two sources interact.

The role of vitamin D in bone metabolism, and the amount to support bone health is unequivocal. However, despite the numerous reports about its impact in autoimmune processes, several cancers, cardio-vascular diseases, obesity, metabolic syndrome, pregnancy complications and SIDS, the evidence is not robust enough to draw definite conclusions, or to establish a causal relationship. The role of vitamin D in neuromuscular functions and prevention of falls in frail elderly seems to be more substantiated. Notwithstanding, more long-term population studies and randomized clinical trials are needed to shed light on the subject, and provide evidence that can be used to avoid the problems associated with both deficiency and excess of vitamin D, as well as to possibly improve other health conditions.

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