

# What is the optimal vitamin D level for health?



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'The importance of maintaining relatively high 25(OH)D levels ... is established for bone health. An increasing body of evidence implicates vitamin D deficiency on other health outcomes, including infectious, autoimmune, cardiovascular and neoplastic diseases.'

Physicians are well aware of the traditional role of vitamin D on calcium and phosphorus homeostasis and bone health [1]. Vitamin D deficiency during the developmental years leads to rickets; later in life, its deficiency leads to osteomalacia, and probably contributes to osteoporosis [2]. In the elderly at least, deficient levels of vitamin D leads to reduced neuromuscular performance and an increased risk of falls. Through this increased risk of falls, and most likely by a reduction in bone mass, vitamin D deficiency increases the risk of fractures [3]. Fractures in the elderly could be catastrophic. Even in young, healthy military recruits, low vitamin D levels predict a higher occurrence of stress fractures, and supplementation with vitamin D and calcium reduced fractures in a randomized intervention study [4,5]. If consequences of vitamin D deficiency were limited to muscular-skeletal health, this would be important enough. However, in the past several decades, a large and ever-increasing number of studies has documented that inadequate vitamin D levels may contribute to a wide range of adverse health conditions.

All of the above raises the question: why should a single vitamin be so important? A brief evolutionary perspective may be informative. The human species evolved largely in tropical conditions, where abundant sunlight throughout the year and the warm climate requiring minimal clothing resulted in vitamin D levels that far exceed what most people experience today. The survival advantage conferred by light skin as our ancestors migrated to higher latitudes is generally believed to have resulted from the importance of maintaining adequate vitamin D levels

under conditions of reduced exposure to solar UV-B, which is required to make vitamin D (cholecalciferol). Vitamin D is converted in the liver to 25(OH)vitamin D (25[OH]D), the storage form of this vitamin and the proper indicator of nutritional vitamin D status. Most tissues in the body express vitamin D receptors and can convert 25(OH)D into the active form, 1,25(OH)<sub>2</sub>D. When 1,25(OH)<sub>2</sub>D binds to the vitamin D receptor, this complex acts as a transcriptional factor, which is an important regulator of gene expression. At least 200 genes have vitamin D response elements. Vitamin D is integrated into many cellular functions, and is utilized in numerous endocrine, autocrine and, perhaps, paracrine systems.

Compared with other hormonal systems, a unique aspect of the vitamin D axis is that the precursor molecule, cholecalciferol, is entirely dependent on sun exposure or dietary intake. This fact is remarkable; no other known hormonal system is similarly dependent on a lifestyle or dietary factor. For example, the synthesis of steroids requires cholesterol, but cholesterol is made endogenously and is not rate limiting in the production of steroid hormones. By contrast, a relative vitamin D deficiency that causes some physiologic and clinical consequences does occur commonly, as observed for bone and muscular-skeletal health.

The list of non-muscular skeletal effects of vitamin D continues to increase, but three general areas of health seem to be of particular importance, these are: effects on the immune system, cancer, and cardiovascular health. The level of evidence for these areas is generally considered to be less established than that for muscular-skeletal health, which is established in randomized clinical trials [2,5]. Nevertheless, the body of supportive *in vitro*, animal, clinical and epidemiologic evidence keeps growing at a remarkable pace. Our understanding of the mechanisms, although still rudimentary, suggests that the associations between vitamin D deficiency and various conditions may indeed be causal.

The immunologic aspects of vitamin D deficiency encompass increased susceptibility both to infections and to autoimmune diseases. Cell

types involved in both innate and adaptive immune responses, including macrophages, T cells, B cells and dendritic cells, produce 1,25(OH)<sub>2</sub>D from 25(OH)D and express the vitamin D receptor. The net effect of the vitamin D system on the immune response is complex, and involves both an enhancement of innate immunity and regulation of adaptive immune responses [6]. Vitamin D deficiency has been associated with risk of various autoimmune diseases, including multiple sclerosis [7] and Type 1 diabetes [8].

Adequate vitamin D is critical for innate immunity [9]. An elegant experiment demonstrated that the production of the endogenous antimicrobial peptide cathelicidin, which kills intracellular *Mycobacterium tuberculosis* in macrophages, is primarily dependent on 1,25(OH)<sub>2</sub>D upregulation; in addition, serum from African-American individuals, who have increased susceptibility to TB, is deficient in 25(OH)D and is inefficient in supporting cathelicidin mRNA induction [10]. Observational epidemiologic data indicate that vitamin D deficiency increases susceptibility to respiratory infections, including influenza [11]. A secondary analysis of a randomized, controlled trial found that supplementation with 2000 IU/day of vitamin D largely eliminated self-reported colds and influenza, especially those that occur during the winter months [12].

With regards to cardiovascular disease, vitamin D influences vascular smooth cell proliferation, inflammation, vascular calcification and the renin-angiotensin system and blood pressure [13]. Recently, studies have found individuals who are deficient in vitamin D to be at increased risk of myocardial infarction and cardiovascular disease [14-16] and stroke [17]. The higher risk in these studies was independent of established cardiovascular risk factors, including serum lipid levels. In a meta-analysis of 18 randomized trials of vitamin D intake, which were conducted for various end points but also reported results for total mortality, subjects who were randomized to vitamin D had a statistically significant 7% reduction in all-cause mortality [18]. Furthermore, the risk reduction was 8% for studies for which the intervention was at least 3 years, and also 8% for those studies with a placebo control group. The vitamin D intakes in these studies mostly ranged from 400 to 800 IU/day.

Some of the genes targeted by vitamin D are important in the regulation of cell proliferation and differentiation; thus, deficiencies could con-

tribute to enhanced cancer risk. Epidemiologic studies indicate that individuals with low vitamin D levels may be at increased risk for various cancers [19]. The evidence appears strongest for colorectal cancer, for which a meta-analysis demonstrated a 50% lower risk associated with a serum 25(OH)D level of 33 ng/ml or higher compared with a level of 12 ng/ml or lower [20]. A small randomized trial using 1100 IU/day of vitamin D observed a reduction in total cancer in postmenopausal women [21], although a larger trial using only 400 IU/day did not show a reduction [22]. Interestingly, recent evidence suggests that patients with higher levels of vitamin D around the time of diagnosis and treatment have improved survival from various cancer types [23-25].

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Given our current knowledge, what should be the targeted level of 25(OH)D? A straightforward answer is not possible at this time, as the numerous potential benefits are not fully established, and the optimal level would not necessarily be similar for each of these. Nonetheless, based on the entire literature, various experts have concluded that the current levels of vitamin D are inadequate for optimal health in many, if not most, people [26-28]. Although the optimal level of 25(OH)D is not established, based on multiple end points, including risk of fracture, 30-40 ng/ml is a reasonable target for adequacy [3]. For many end points studied in epidemiologic studies (including fractures, bone mass density, falls, colorectal cancer, cardiovascular disease and multiple sclerosis), risk was lowest within this range. Whether higher levels would confer greater benefits is not known, largely because currently too few people attain higher levels that can be examined in population-based studies. Regarding concerns for toxicity, natural levels of 25(OH)D in humans who work in the sun are approximately 50-70 ng/ml. Not a single case of toxicity from sun exposure has ever been documented and, in fact, toxicity has not been seen at levels below 150 ng/ml [29].

What is the optimal way that individuals attain this level of 25(OH)D? The potential ways to increase 25(OH)D levels are through sun exposure, artificial UV-B sources (e.g., sun lamps) and intake. Any recommendation to increase vitamin D levels through sun exposure

will be controversial because of documented adverse effects of excessive sun exposure, especially for lighter-skinned individuals. Nonetheless, it is critical to appreciate that sun exposure is remarkably efficient for vitamin D production – an individual can make 20,000 IU equivalent of vitamin D in a day from sun exposure [26]. In fact, a light-skinned person sunbathing can make this amount in approximately 20–30 min; the darker the skin, the longer the time required for synthesis, but similar amounts can be attained. In the general population, most vitamin D comes from sun exposure. Thus, risk factors for vitamin D deficiency typically relate to a lack of sun exposure. These risk factors include darker skin, which inhibits synthesis, and behaviors (e.g., clothing customs) or living situations (e.g., nursing homes) that limit sun exposure. At higher latitudes, vitamin D deficiency is rampant during the winter months. In addition, probably through a sequestering effect, greater levels of adiposity lower vitamin D concentrations.

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Dietary and supplemental vitamin D could compensate for the lack of sun exposure experienced by the majority of the population, but the dose–response between vitamin D intake and serum levels needs to be understood. As a general rule, 100 IU of intake of vitamin D<sub>3</sub> (cholecalciferol) is required to increase 25(OH)D levels by 1 ng/ml [30]. Thus, in an individual with no sun exposure, 3000–4000 IU/day are required to maintain 25(OH)D levels in the range of 30–40 ng/ml. Intakes at this level may appear to be high by current standards, but no evidence demonstrates toxicity at intakes below at least 10,000 IU/day [29]. These findings are consistent with the observation that toxicity does not occur

at levels of 25(OH)D below 150 ng/ml. Since most individuals get some degree of sun exposure, recommended intakes of 1000–2000 IU/day may be sufficient for many individuals to achieve a circulating 25(OH)D level of approximately 30 ng/ml, although those at higher risk of deficiency owing to low sun exposure would typically require more. Fatty fish is the only natural source of vitamin D typically consumed by humans. A 3.5 oz serving of cooked salmon has approximately 360 IU of vitamin D, 3 oz of canned tuna has 200 IU and 3/4 oz of canned sardines has 250 IU. A glass of fortified milk (fortified in the USA, but not in most other countries) contains approximately 50–100 IU of vitamin D. Given the low amounts of vitamin D in foods, supplemental vitamin D, preferably as D<sub>3</sub> (cholecalciferol), which is more efficient in elevating 25(OH)D than D<sub>2</sub> (ergocalciferol), would generally be required to achieve the targeted 25(OH)D level.

In summary, vitamin D remains a fascinating area of research. The importance of maintaining relatively high 25(OH)D levels, in the range of 30–40 ng/ml, is established for bone health. An increasing body of evidence implicates vitamin D deficiency on other health outcomes, including infectious, autoimmune, cardiovascular and neoplastic diseases. A similar range of 25(OH)D may be required for lowering the risk of these conditions. Higher intakes of vitamin D, in the range of 1000–2000 IU/day or higher, are required for most individuals to achieve these levels.

#### Financial & competing interests disclosure

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