Original Communication

Vitamin D, an Essential Nutrient with Versatile Functions in Nearly all Organs

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Abstract: For decades, vitamin D has been known to be essential in the development, function, and maintenance of healthy bones through the regulation of calcium homeostasis throughout life. Sufficient vitamin D prevents the occurrence of rickets in children and osteomalacia in adults. The adequate nutritional intake of vitamin D and calcium are the basis for the prevention and management of osteoporosis, a disease producing brittle bones that are prone to fractures. Vitamin D has been implicated in the regulation of neuromuscular function and in reducing the risk of falls, a major cause of bone fractures. Thus vitamin D may be a central component of musculoskeletal health through its beneficial effects on muscle function and bone stability. The action of vitamin D by the active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], however, is not limited to its endocrine function in bone metabolism. The active metabolite behaves as a hormone and binds to the vitamin D receptor (VDR) present in nearly all tissues of the human body. In addition, the 1-alpha-hydroxylase enzyme is present not only in the kidney but also in many other organs. Both vitamin and enzyme exert their biological effects via paracrine/autocrine actions related to cardiovascular disease, diabetes, cancer, and the immune system. Thus vitamin D may show favorable effects in many organs and play a significant role in the maintenance of general health.

Key words: vitamin D, vitamin D deficiency, recommendations, fractures, falls, health benefits

Vitamin D sources

Vitamin D is a unique nutrient because it can come from two sources. It is part of the diet, but it can also be synthesized in the skin through the action of sunlight. Both sources complement each other to meet physiological requirements. In the absence of ultraviolet-B (UVB) sunlight exposure, dietary vitamin D becomes an essential nutrient. Vitamin D from the diet is provided as cholecalciferol (D3, from animal sources) or as ergocalciferol (D2, from plant sources). However, few food sources are rich in natural vitamin D, like fatty fish, herring, salmon, or eel. But the body has evolved an efficient method of synthesizing vitamin D in the skin following exposure to sunlight (UVB radiation) providing the major source of vitamin D. The endogenous dermal production of vitamin D, however, is limited by several factors. Vitamin D synthesis is reduced at latitudes greater than 37°, especially in the winter. It is also dependent on the time of day, and is restricted by air pollution and weather conditions. Dark-skinned individuals and people using

sunscreen synthesize less vitamin D on sunlight exposure [1, 2]. Furthermore, elderly and institutionalized people with limited sunlight exposure are vulnerable and synthesize inadequate vitamin D levels. Skin-covering clothes, indoor lifestyles, and even obesity can become further limiting factors [1, 3, 4]. It becomes crucial, then, to find a reasonable balance of sun exposure, i. e. a dose that provides the daily requirements for optimal human health, but avoids the excessive sun exposure associated with skin cancer. Since such optimal conditions cannot always be met, vitamin D supplementation or food fortification becomes an important health issue.

Vitamin D metabolism

Vitamin D is an essential nutrient and as such is biologically inert. After absorption and distribution via the circulation, vitamin D is converted in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite. This 25(OH)D metabolite is usually measured in serum and reflects the vitamin D status. The conversion of this compound into the classic endocrine functional metabolite occurs in the kidney. 25(OH)D is metabolized by the enzyme 1-alpha-hydroxylase (CYP27B1) to the active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], which is thought to be responsible for most of the biological functions [5]. $1,25(OH)_2D$ regulates serum calcium and phosphorus homeostasis by intestinal calcium and phosphate absorption and thus exerts a favorable effect on bone mineralization. The activation step of $1,25(OH)_2D$ at the kidney is tightly regulated by parathyroid hormone (PTH) in response to serum calcium and phosphorus level, and by the fibroblast growth factor-23 (FGF-23). Active vitamin D [$1,25(OH)_2D$] functions as a ligand for the vitamin D receptor, VDR. This receptor belongs to the nuclear receptor family and acts as a transcription factor upon ligand activation. The VDR interacts with the retinoid X receptor (RXR) to form a heterodimer that binds to the vitamin D-responsive element to initiate biological responses [6, 7]. The VDR is expressed in at least 38 types of tissue [8]. Beside the endocrine function, the active metabolite $1,25(OH)_2D$ also acts via a paracrine/autocrine function on the VDR. In addition to the kidney, many tissues in the body possess the 1-alpha-hydroxylation enzyme (CYP27B1) and thus convert 25(OH)D to the active $1,25(OH)_2D$, dependent upon local needs. This non-renal hydroxylation step is not under negative feedback control, but is regulated locally by cytokines and the substrate, the intermediate metabolite 25(OH)D [9–12]. An adequate vitamin D status is important for optimal function of many organs. The VDR functions either as a nuclear transcription factor activating specific genes, or by a non-genomic action, modulating rapid signal transduction pathways in plasma membranes [6, 13, 14]. Both affect various recently identified biological actions of $1,25(OH)_2D$ such as regulation of cell differentiation and proliferation, apoptosis, hormone secretion, and immune modulations. This could explain the molecular basis by which vitamin D benefits various tissues and organs; e. g., the muscles, the cardiovascular and immune systems, the brain, and others [8]. About 3 % of the human genome is regulated directly or indirectly by vitamin D metabolites [3, 15].

Assessment of vitamin D status and optimal serum levels

Circulating 25(OH)D is a sensitive marker to assess vitamin D status. Its levels reflect both dietary vitamin D intake and the endogenous dermal vitamin D production. There is a general agreement that serum 25(OH)D is the best indicator of vitamin D status [4]. It is widely accepted that 25(OH)D below 25 nmol/L is the lower threshold that defines deficiency [16]. However, no consensus has been reached on the definition of a required or adequate serum 25(OH) D level: Should it be higher than 50 nmol/L or even exceed 75 nmol/L? The Institute of Medicine (IOM) has recently stated that a serum level of 25(OH)D at or above 50 nmol/L is adequate for the general population for bone health. This opinion has been questioned by vitamin D experts [17–19]. They favor a 25(OH)D level of more than 75 nmol/L. It has been reported that parathyroid hormone (PTH) levels [20] and calcium absorption [21] are not optimal unless serum 25(OH) D levels reach 75–80 nmol/L [9]. In addition, clinical trials and epidemiologic studies suggest various health benefits of 25(OH)D levels above 75 nmol/L [18, 19, 22–25]. This has been summarized in a review on the risk-benefit assessment of vitamin D supplementation [26]. Data suggest that a mean serum 25(OH)D level of 75–110 nmol/L is positively associated with health benefits for various endpoints, including fall and fracture prevention. This observation has also been supported by epidemiologic data on cardiovascular health, colorectal cancer, incident hypertension, and general mortality [3, 27–30]. Vitamin D experts favor serum 25(OH)D levels above 75 nmol/L to optimize

health [18, 31–34]. However, further clinical trials are warranted to evaluate the beneficial effects of greater doses of vitamin D (above 1000 IU) on skeletal and non-skeletal health outcomes and on the 25(OH)D threshold level.

Vitamin D deficiency is a global concern

Vitamin D deficiency is widespread around the globe even in countries with long hours of sunshine. It is a re-emerging health problem. The risk for vitamin D deficiency increases with age, especially in institutionalized and geriatric people [35]. Furthermore vitamin D deficiency has become an epidemic in children, and rickets has again become a global health issue [1,36]. Non-Western immigrants, particularly from African Caribbean, Middle East, and South Asian origins immigrated to Northern European Countries show a high risk of vitamin D deficiency [1, 35, 37–39]. A recent review of the global vitamin D status found that serum 25(OH)D levels below 75 nmol/L are prevalent in every region of the world investigated [40]. Levels below 25 nmol/L, reflecting severe vitamin D deficiency, are most common in South Asia and the Middle East [38, 41]. In European countries, the prevalence of severe vitamin D deficiency, below 25 nmol/L, is between 2–30 % in adults, and is increased in the older population and in homebound and institutionalized people, to more than 80 % [35, 42]. Clinical symptoms such as bone disease and muscle weakness may occur when serum 25(OH)D levels fall below 25 nmol/L. In the USA and other developed countries, 25(OH)D levels have dropped significantly in the last decade [2]. The decline in vitamin D status appears to be contributed to by several environmental factors such as general increase in sun avoidance and in sun protection, changes in lifestyle, and an increase in obesity [2, 43]. Moreover, vitamin D deficiency has been associated with adverse health effects in many countries [44].

Dietary Recommendations for vitamin D

National recommendations for dietary vitamin D are not harmonized across the European Union and vary from 200 to 400 IU [16, 45]. Even a recommended intake of 400 IU has been shown to be insufficient to prevent falls and bone fracture [46]. Higher recommendations for dietary vitamin D intake are increasingly being suggested in government documents, position statements, and clinical practice guidelines for bone health. In 2008, the U.S. Food and Drug Administration updated the health claim for the prevention of osteoporosis by adding vitamin D to the consumption of calcium [47]. In 2008 the American Academy of Pediatrics (AAP) also reacted and issued an update of their guidelines for vitamin D intake and rickets prevention. They doubled the recommended dose of vitamin D for children to 400 IU per day, beginning in the first few days of life and continuing throughout adolescence [48]. In 2010, the Institute of Medicine (IOM) released the revised Dietary Reference Intakes (DRIs) for calcium and vitamin D and tripled the recommendations for vitamin D intakes to 600 IU per day for children and all adults up to age 69 years. They also increased it to 800 IU per day for those 70 years and older. The IOM has set the recommendation for the general population based primarily on the need for bone health and concluded that a serum 25(OH)D above 50 nmol/L will cover the requirements of 97.5 % of the population to maintain healthy bones [4]. The IOM stated that there was insufficient evidence to make recommendations for non-skeletal benefits. In January 2012 the German, Austrian, and Swiss Nutrition Societies raised the recommended vitamin D intake to 800 IU per day, in the case of absent UVB exposure, for all age groups starting from one year of age [49]. Furthermore, key opinion leaders are increasingly recommending higher daily intakes for vitamin D, between 800–1000 IU or even higher for people at risk or older adults. The recent statement by the International Osteoporosis Foundation (IOF) [50] and the guidelines by the U.S. Endocrine Society [51, 52] suggest that higher vitamin D doses would be needed to achieve the desirable 25(OH)D serum level of 75 nmol/L, for people at risk or for older individuals. In contrast to the IOM, the IOF and the U.S. Endocrine Society recommend vitamin D for the prevention of falls for the elderly as do the American Geriatric Society and British Geriatric Society in their 2010 Clinical Practical Guidelines for fall prevention for the elderly [53].

However, the 25(OH)D response to vitamin D supplementation is highly variable and thus it becomes difficult to select the "optimal" vitamin D dose needed for a beneficial effect. No consensus exists currently about optimal 25(OH)D threshold levels. Several large-scale randomized controlled trials on higher vitamin D doses are in progress, which may clarify the scientific evidence for vitamin D [54].

Vitamin D has a dual role in preventing fractures

Vitamin D is essential to maintaining bone health, but is also thought to be important for muscle function and balance. Thus vitamin D may play a dual role in preventing fractures: it directly increases bone density, and it improves muscle strength [55] and balance [56]. Both effects reduce the risk of falling [57, 58]. Results from NHANES III which included younger and older individuals from different ethnic groups, reported a positive association between higher 25(OH)D serum levels and higher bone mineral density [59]. There is biological plausibility that vitamin D has a direct favorable effects on muscle function [9, 15]. Several observational studies have pointed to a beneficial association between increased 25(OH)D serum levels and muscle strength or improved lower extremity function [60–62]. Clinical intervention studies have reported that vitamin D reduces the risk of falls and fractures only at higher vitamin D intakes (800–1000 IU) or at higher achieved serum 25(OH)D levels. These randomized controlled trials (RCTs) have been summarized in systematic reviews reporting a significant reduction in the risk of fall prevention [58, 61, 63]. However, there is still conflicting interpretation of the clinical evidence on vitamin D and falls. The IOF [50] and the U.S. Endocrine Society [51, 52] recommend vitamin D for the prevention of falls for the elderly in contrast to the IOM, stating that there is insufficient evidence to make recommendations for fall prevention [4]. The main discrepancy was in the interpretation of data, inclusion of RCTs, and the dose and regimen [63–65].

A 25(OH)D level between 50 and 75 nmol/L is positively associated with an improvement in bone health, but for optimal functionality data suggests a 25(OH)D threshold of 75 nmol/L for fracture prevention among the elderly [66]. The higher threshold has been addressed in a risk-benefit analysis and is further supported by meta-analysis [46, 58, 67].

On the basis of these data the European Food Safety Authorities (EFSA) have recently issued a positive opinion on health claim Article 14 on the use of vitamin D to reduce the risk of falls and fractures in the elderly [68].

Vitamin D deficiency has multiple consequences beyond bone health

Vitamin D exerts biological functions beyond calcium homeostasis and bone metabolism through paracrine/autocrine actions, and through the presence of the VDR in virtually all cells of the body. $1,25(OH)_2D$ can be made locally to initiate biological responses to affect many organs and organ systems.

Available promising observational studies supported by plausible biological mechanisms and prospective studies suggest largely, but not consistently, a significant role for vitamin D in multiple health outcomes. Many of these beneficial associations are quite well established. Causation however needs still to be proven by large-scale, long-term randomized clinical trials [14, 69].

Evidence from large population studies suggests a strong inverse correlation mainly between vitamin D deficiency and higher risk of cardiovascular outcomes [3] such as increased risk of myocardial infarction [70], stroke, and heart failure [71–73]. The association between vitamin D deficiency and hypertension has been reported in epidemiologic studies supported by small intervention studies and physiological explanations [74, 75]. All these observations favor the hypothesis that vitamin D may play an important role in the pathogenesis of cardiovascular diseases, causation however, has still to be proven. Vitamin D has also been recognized to strengthen the immune system affecting both the innate and adaptive immune response [76–78]. Vitamin D may prevent or delay auto-immune diseases, such as diabetes mellitus Type 1 [79–80] and multiple sclerosis [81, 82]. In population studies the rate of auto-immune disease and cancer is increased at higher latitudes, and is significantly more prevalent at northern latitudes of Europe, the U.S., and the southern part of Australia, correlating well with the increased prevalence of vitamin D deficiency at higher latitudes [3, 38, 83]. Additionally, vitamin D influences adequate immune response and has effects on the defense against respiratory tract infections [84, 85] and tuberculosis [86]. Experimental data suggest that vitamin D inhibits bacterial growth [87] and decreases pro-inflammatory cytokines [88]. Moreover, in the pre-antibiotic area very high doses of vitamin D were used to treat tuberculosis [89]. Epidemiologic data have indicated an association between vitamin D deficiency and increased rate of mortality [28, 32, 90, 91], supported by a meta-analysis of 9 randomized controlled trials [27]. However, the findings from observational studies are not consistent [28, 92]. Newer data from epidemiologic studies suggest that vitamin D deficiency may have consequences on various chronic diseases, classified as non-communicable diseases (NCDs), especially in the elderly [44, 93]. These chronic diseases are the leading cause of disability and morbidity in seniors.

Vitamin D Safety

The main adverse outcome of excessive vitamin D intake is associated with hypercalcemia and hypercalciuria and related clinical symptoms. Renal stones, nephrocalcinosis, and renal function impairment can occur. Vitamin D toxicity is rare. Only a few cases of 25(OH)D levels above 500 nmol/L have been described, affecting individuals after accidental intake of high doses of vitamin D [94, 95]. To reach such high serum levels of 25(OH)D, healthy adults must consume at least 30,000 to 50,000 IU of vitamin D per day for an extended period of time [94, 96]. It must be noted that the IOM considers a circulating 25(OH)D above 125 nmol/L as potentially harmful [4]. A review on a risk assessment of vitamin D that re-analyzed controlled clinical trials concluded that a daily intake of 10,000 IU vitamin D can be considered as safe [97]. In a review of a risk-benefit assessment on vitamin D supplementation, a safe upper intake level of 10,000 IU of vitamin D per day has been suggested [26], which is further supported by a recent evaluation on the safety of oral vitamin D, concluding that long-term daily intakes of up to 10,000 IU of vitamin D are safe [96]. Additionally, no adverse effects were noted by the IOM at intakes up to 10,000 IU/day [4]. This is far more than the current vitamin D recommendations for adults, which range globally between 400 to 800 IU vitamin D per day. Furthermore in 2010, the Institute of Medicine (IOM) has set the upper safe limit (UL) at 4000 IU per day. This is double the amount previously recommended. In 2012 the European Food Safety Authority (EFSA) released the updated Tolerable Intake Levels (ULs) of vitamin D as 4000 IU for adults and for ages 11–17 year; a UL of 2000 IU has been proposed for children aged 1–10 years [98].

Conclusions

Several epidemiological studies have reported an association between vitamin D deficiency and increased risk of heart disease, hypertension, autoimmunity disorders, cancer, and even mortality. However, a causal relationship still needs to be proven. Findings from intervention studies demonstrate that vitamin D is important and support its beneficial role in reducing the risk of fractures and falls, at levels of vitamin D intake between 700 and 1000 IU. Several large-scale randomized controlled trials on higher vitamin D doses are ongoing, which may clarify the scientific evidence for vitamin D on health outcomes. Consensus on the optimal 25(OH)D threshold level is, however, not yet reached. The IOM recommends a 25(OH)D serum level above 50 nmol/L as sufficient, whereas key opinion leaders and guidelines by the IOF and the U.S. Endocrine Society suggest a threshold of 75 nmol/L as desirable for fracture prevention and optimal health. To achieve sufficient levels requires a significant increase of the current recommended daily intakes for adults in all countries to ensure adequate vitamin D nutrition. To address this need, the IOM as well as the European Nutrition Societies have issued updates of their guidelines and increased the recommended daily dose for all age groups: i. e. between 600 IU and 800 IU of vitamin D for adults. Even with a balanced diet, 800 IU of vitamin D per day is difficult to achieve in the absence of sunlight, which would mean consuming 2 portions of oily fish or 40 eggs per day. Vitamin D deficiency is a major public health burden in many parts of the world. There is an urgent need to take action and improve the vitamin D status of the public. This situation points to a need for supplementation or fortification of foods for maintaining a sufficient vitamin D status for the general population.

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