Role of Vitamin D on Body Systems

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Abstract

Severe vitamin D deficiency may cause rickets in infants or children and osteomalacia in adults, though it is now uncommon in developed countries. However, subclinical vitamin D deficiency is more prevalent, and it is associated with osteoporosis and higher incidence of falls or fractures. Since vitamin D receptors are present all over the body, insufficient vitamin D status may correlate with several extra-skeletal effects, such as immune dysfunction. This paper discusses the researches regarding system-based vitamin D effects, the possible risk factors leading to vitamin D deficiency, and the recommendations of vitamin D requirements. It is well-known that vitamin D can be obtained by sun exposure or limited natural dietary sources. The American Academy of Dermatology declared ultraviolet radiation to be a known skin carcinogen, so it may not be safe or efficient to obtain vitamin D via sun exposure or other artificial sources. Therefore, many pediatricians and physicians recommend appropriate vitamin D supplementation to achieve optimal plasma concentration. Trials assessing the effects of vitamin D repletion and establishing its optimum serum level are ongoing. Medical advice for vitamin D supplementation should be individualized accordingly.

Key words: Vitamin D, bone health, metabolism, immune system, Vitamin D deficiency,

Introduction

Vitamin D is essential for calcium and bone homeostasis, especially in children because childhood and adolescence are the most critical periods for bone development. The role of Vitamin D is not limited to bone health as it also has important roles in many extra-skeletal targets throughout the body, such as the muscles, immune system, and the cardiovascular system(1,2). Severe vitamin D deficiency (VDD) is a well-established cause of disease, including hypocalcemia and skeletal abnormalities (e.g., rickets)(3-5). Although severe deficiency causing classic bone manifestations is now rare, many adults and children endure a subclinical VDD state that may predispose them to neurologic, cardiovascular, respiratory, and immune pathology (6-8).

Vitamin D metabolism

Vitamin D is a fat-soluble vitamin. The major route to obtain vitamin D is dermal synthesis after ultraviolet-B (UVB) radiation, accounting for 90% of vitamin D replenishment and only a few foods naturally contain vitamin D (oily fish, cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats)(9). Cholecalciferol (vitamin D3) is from animal sources and ergocalciferol (vitamin D2) is from plants(10) Cholesterol-like precursor (7-dehydrocholesterol) in skin epidermal cells can be converted after UVB radiation (wavelength 290-315 nm) into pre-vitamin D, which also isomerizes to vitamin D3. Both vitamin D3 and D2 are biologically inactive. They need further enzymatic conversion to their active forms. Firstly, it undergoes 25-hydroxylation in liver to 25(OH)D (calcidiol), the major circulating form of vitamin D, with a half-life of 2-3 weeks. Then it is converted in kidneys through 1-alpha-hydroxylation to its most active form, 1,25(OH)2D (calcitriol), with a half-life of 4-6 hours. This process is driven by parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone(11,12). The 1-alpha-hydroxylation also takes place in non-renal sites, such as alveolar macrophages, osteoblasts, lymph nodes, placenta, colon, breasts and keratinocytes, suggesting possible autocrine-paracrine role of calcitriol(11,12). It functions through a vitamin D receptor (VDR) that is universally expressed in nucleated cells. Its most important biological role is promoting enterocyte differentiation and intestinal calcium absorption, facilitating calcium homeostasis. At the time of hypocalcemia, the plasma level of ionized calcium falls and this is detected by parathyroid gland calcium receptors. PTH is secreted by parathyroid gland, which stimulates 1-alpha-hydroxylation in kidneys to make more calcitriol from circulating calcidiol. The elevation of calcitriol increases calcium transport within intestines, bones, and kidneys, and further regulates the osteoblast and osteoclast activity. As plasma calcium rises back to normal, further secretion of PTH decreases. This physiologic loop of vitamin D and calcium homeostasis demonstrates that enough circulating calcidiol is essential to maintain adequate calcitriol synthesis and plasma calcium level(10). However, vitamin D deficiency may result in inadequate circulating calcidiol, which decreases calcitriol synthesis and calcium absorption, elevating PTH levels. It is reasonable to focus on plasma calcidiol and PTH level to assess vitamin D clinically. Additionally, because VDRs are found not only in small intestine, but also in colon, osteoblasts, activated T and B lymphocytes, mononuclear cells, beta islet cells and major organs, such as brain, heart, skin, gonads, prostate and breasts(12), coexisting extra-skeletal effects of vitamin D deficiency are to be expected.

Vitamin D and bone health

Severe vitamin D deficiency may cause rickets in infants or children and osteomalacia in adults, although these are uncommon diseases in most developed countries. However, subclinical vitamin D deficiency is more prevalent, and may be associated with osteoporosis and higher incidence of falls or fractures. A 2010 public health evaluation concluded that calcium supplementation of healthy children did not significantly decrease the incidence of fractures(14). A healthy balanced diet that fulfilled the recommended calcium intake was superior to routine calcium supplementations(13,14). However, due to limited natural dietary sources of vitamin D and insufficient sun exposure in most children and adolescents, vitamin D supplementation is necessary. Routine screening of calcidiol levels is not recommended, except for those with higher risk, or in children who present with poor growth, gross motor delay or unusual irritabilities; those who are hospitalized or institutionalized with limited sun exposure; or those with elevated serum alkaline phosphatase (ALP) levels (>500IU/L in neonates or >1000IU/L in children up to 9 years) (11,15,16).

Vitamin D and immune system

Functional VDR has been identified in almost all immune cells, including antigen-presenting cells (APCs) and T lymphocytes (17,18), thus providing an indirect evidence of vitamin D action on immune system. Vitamin D exerts its action on both innate and adaptive immune system through VDR (17,19,20). Overall, the immunomodulatory effects of vitamin D mostly depend upon the capacity of its biologically-active form calcitriol to regulate expression of several genes involved in cell proliferation, differentiation, and function (19,21,22). The relationships between vitamin D and these illnesses are discussed below.

Tuberculosis (TB)

There is an association between vitamin D deficiency and TB. It was reported in 2008 that UVB radiation had beneficial effects on TB therapy(23). However, Martineau et al. concluded that supplementation of vitamin D did not show significant improvement in clinical outcomes(24).

Respiratory tract infections

A prospective trial by Camargo found an inverse association between cord-blood calcidiol level and the risk of developing upper respiratory tract infection by 3 months and wheezing at 15 months of age(25). Newborns born with calcidiol < 20 ng/mL had six-fold higher risk of

respiratory syncytial virus-related bronchiolitis at 1 year old compared with those of calcidiol > 30 ng/ mL(26). A meta-analysis of 25 trials in 2017 showed reducing incidence of acute respiratory tract infection after vitamin D supplementation (OR 0.88, 95% CI 0.81e0.96), which is more significant in patients with severe vitamin D deficiency (< 10 ng/mL)(27).

Asthma

A cross-sectional study observed the calcidiol level between asthma and healthy groups(28). It showed that vitamin D concentration was directly correlated with forced expiratory volume/forced vital capacity (FEV1/FVC) ratio and predicted FEV1, meaning that lower calcidiol level was more significantly associated with asthmatic status. A Cochrane systematic review in 2016 documented that vitamin D supplementation had benefits on reducing risk of exacerbation requiring systemic glucocorticoids and risk of at least one exacerbation requiring emergency department visit or hospitalization or both (OR 0.39, 95% CI 0.19e0.78)(29). A recent review in 2019 that linked vitamin D and childhood asthma showed that there is evidence from clinical trials regarding the protective effects of vitamin D supplementation on the development of asthma and its beneficial effects in the management of asthma and recommended that because of its relatively low-cost and safety, supplementation with vitamin D to reverse deficiency and insufficiency in childhood asthmatics should be considered in the management of the disorder (30).

Coronavirus disease (COVID-19)

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has had a catastrophic impact worldwide(31). Recent observational studies have linked the population's relative vitamin D status to COVID-19 outcomes. Recently, a substantial body of evidence has clearly linked COVID-19 outcomes with low vitamin D status, but the results from those published to date are conflicting: two retrospective studies reported independent associations between low pre-pandemic calcidiol levels and the subsequent incidence and severity of COVID-19(32,33) while an analogous study in the UK did not support the potential link between calcidiol concentration and the risk of severe COVID19 infection and mortality (34).

A recent meta-analysis conducted by Liu et al., 2021 was based on studies that assessed the impact of vitamin D deficiency or insufficiency on COVID-19 outcomes. They found that low vitamin D levels are associated with an increased risk of COVID-19 infection. Their findings also suggest that COVID-19 infected individuals have lower vitamin D levels than those who are not infected; their results confirm the link between outcomes of COVID-19 with low vitamin D status. They concluded that low serum vitamin D status may be related to the increased risk of COVID-19 and that individuals with vitamin D deficiency should receive special attention, and future research should focus on the benefits of vitamin D supplementation (35).

Atopic dermatitis (AD) A meta-analysis demonstrated that serum calcidiol level was lower in patients with AD(36). A small randomized clinical trial also found beneficial effects of vitamin D supplementation in children with winter-related AD(37). On the contrary, another systematic review in 2012 did not show a significant benefit in clinical outcomes (including pruritus, sleep loss, number of flares, or need of further therapies) after vitamin D intervention(38).

Calcitriol also functions as an inhibitor of dendritic cell maturation, which reduces the activation of acquired immunity and may increase the risk of autoimmune disease(39) such as type I diabetes, multiple sclerosis, and inflammatory bowel disease(9) However, because reports conflict on the association between vitamin D status and these diseases, supplementation is not recommended at present (40).

Vitamin D and other systemic effects

Observational studies demonstrated the association between vitamin D deficiency and the risk of hypertension or cardiovascular events, higher incidence of cancers, more musculoskeletal pain or migraine, and neuropsychiatric disorders such as schizophrenia, dementia or depression(16). However, current evidence for vitamin D intervention in treating or preventing these diseases is lacking.

Vitamin D deficiency

The best indicator of the human body's vitamin D status is the concentration of serum calcidiol(41). The optimal calcidiol level for either skeletal or extra-skeletal health varies for different populations. In adults, the essential level of vitamin D is determined through studies of calcium homeostasis, bone mineralization and PTH levels. Adult PTH has negative correlation with serum calcidiol level, though this relationship is weak in children. The Institute of Medicine (IOM) concluded a serum level of 20 ng/mL was optimal for skeletal health(41), whereas other experts, including the Endocrine Society (ENDO), the International Osteoporosis Foundation (IOF), the National Osteoporosis Foundation (NOF) and the American Geriatrics Society (AGS) stated that at least 30 ng/mL was needed for disease prevention(15,16,42-44). In children, optimal vitamin D status is based upon clinical evidence for rickets or bone turnover, such as elevation of serum ALP. The consensus for adequate calcidiol concentration in children has not yet been established because of inconsistent evidence. In 2008, the American Academy of Pediatrics (AAP) classified calcidiol > 20 ng/mL as sufficiency(11), whereas the Pediatric Endocrine Society used a higher threshold in 2011, regarding calcidiol < 30 ng/mL as insufficiency(45). In 2016, the Global Consensus also defined calcidiol > 20 ng/ mL as sufficiency but adjusted other criteria (46).

Risk factors of Vitamin D deficiency

UVB is more prevalent during the hours of 10am to 3pm. During spring, summer and autumn, 10-15 minutes of sun exposure (over arms and face, or arms and legs/hands) from 10am to 3pm can produce adequate vitamin D in light-skinned populations(11). However, epidermal melanin of darker skinned individuals means more exposure is needed for cutaneous vitamin D synthesis. It is estimated that Asians from the Indian subcontinent require 3 times as much sun exposure as Caucasians, whereas Africans may need 6-10 times more(47). Infants and adolescents are populations at risk because of rapid skeletal growth after birth and during puberty(10). Weisberg showed that 96% of cases of rickets occurred in breastfed children(48). Because breast milk is known to contain very little vitamin D even in vitamin D-replete mothers(11,49) exclusively breastfed infants, especially those born to vitamin D-deficient mothers, are more at risk for rickets. Preterm infants are even more prone to vitamin D deficiency due to lack of transplacental transfer of vitamin D during the third trimester(50) and negligible sun exposure in postpartum hospital(50). Age-related declines in dermal synthesis of vitamin D, diminishing rate of hydroxylation, and poorer response of target tissues further explain the elevated risk for vitamin D deficiency in the elderly(10,52). Studies showed that children, particularly infants, may require less sun exposure than adults to produce adequate quantities of vitamin D because of their greater surface area to volume ratio and better capacity to produce vitamin D(53). However, obese people still have higher risk due to sequestration of vitamin D in adipose tissue(11,54). Cutaneous vitamin D synthesis depends on surface of skin exposed and duration of sun exposure. Extent of clothing due to cultural or religious factors and using topical sunscreen may block effective dermal synthesis. A sunblock of SPF 30 can reduce vitamin D production by 95%(55). Residents, beyond latitude of 33 degrees can receive little UVB due to the oblique angle and longer path of sunlight through the atmosphere. Air pollution and cloud-shading may further limit sun exposure. The amount of UVB is higher at greater altitudes and sunny areas. Individuals such as vegetarians or those with eating disorders are more likely to be vitamin D deficient due to an unbalanced diet. Chronic diseases involving intestinal malabsorption, or liver and renal insufficiencies may also reduce vitamin D production. Some anticonvulsants or antiretroviral agents can precipitate vitamin D deficiency by enhancing catabolism of calcidiol and calcitriol, while Ketoconazole may further block 1-hydroxylation(56). Patients with chronic high-dose glucocorticoids require more vitamin D due to inhibition of intestinal vitamin D-dependent calcium absorption.

Recommended Vitamin D requirement

In 2010, the IOM committee assumed only minimal sun exposure when establishing daily dietary intake requirements for calcium and vitamin D(57). Upper limits of intake indicate the level above which vitamin D may be risky for toxic or adverse events. The Recommended Dietary Allowance (RDA) of vitamin D for infants up to 12 months is 400IU daily, and 600IU for children of 1-18 years. Transplacental maternal vitamin D can build up the fetal store(50). However, even infants born to vitamin D-replete mothers may become vitamin D deficient after 8 weeks of life if unsupplemented during early infancy(58). It is reported that infants can get adequate quantities of vitamin D by sunlight exposure of 30 minutes per week wearing only a diaper or 2 hours per week when fully-clothed without a hat(48). Due to concern for possible risk of skin cancer later in life, the AAP suggest that infants younger than 6 months should be kept away from direct sunlight exposure(59), with natural food or vitamin D supplementation being preferable. Therefore, AAP and Lawson Wilkins Pediatric Endocrine Society recommend infants who are exclusively or partially breastfed require 400IU vitamin D daily beginning within first few days of life(11,15,45). This supplementation should be continued until infants are feeding on more than 1000 ml per day of vitamin D-fortified formula. Since most infant formulas contain at least 400IU/ L of vitamin D, formula-fed infants may also need vitamin D supplementation unless they consume beyond 1000 mL daily(11). As for obese children or those on chronic medications, requirements may be 2-4 times more(13). In 2010, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition updated a guideline for preterm infants, suggesting 800-1000IU of vitamin D, 110-130 mg of calcium and 55-80 mg of phosphorus per day, as essential for preterm bone health(60). Later in 2013, an expert report from the AAP recommended 200-400IU vitamin D daily in very-low-birth-weight preterms (<1500 g) and 400IU in babies weighing >1500g(61). This lower dosage is adjusted according to smaller size of preterm babies and relatively lower need of vitamin D to achieve adequate calcidiol levels(61). This advice is supported by a 1992 study revealing calcium absorption in low-birth-weight infants, especially during the first few months of life, was in proportion to their daily calcium intake, but independent of vitamin D(62). However, in certain instances, the requirement may increase to 1000IU per day in infants >1500 g to achieve the goal of serum calcidiol > 20 ng/mL, since this is the intake upper limit for full-term babies. The RDA of vitamin D for adults through to 70 years is 600IU daily, and 800IU if they are older than 71 years(57). Since vitamin D intake is usually low in the elderly, coupled with lower sun exposure, it is reasonable to advise older people to supplement at least 600-800IU daily. The AGS and NOF suggest an even higher dosage (800-1000IU per day) for adults >65 years to prevent falls and fractures (42).

Vitamin D supplementation

The guideline for vitamin D supplementation in children with nutritional rickets is available from ENDO and the Global Consensus (table 1)(15,46). Although radiologic bone healing is evident 2-4 weeks after treatment, this high dose strategy should be continued for a further 2-3 months(11). After achieving the optimal calcidiol level, a maintenance dosage is suggested. To combat poor daily compliance, an alternative single high dose regimen “stoss

therapy" was introduced in patients over 1 month old. It is administered as oral vitamin D 100000-600000IU once, then followed with maintenance dosage(11). Stoss therapy should not be administered for young infants, since they are much more likely to develop hypercalcemia. Recently, there has been increasing evidence to support the combination use of calcium (500 mg daily) with vitamin D(46). Vitamin D3 is preferable to vitamin D2 as a supplement because of its longer half-life and stronger potency, leading to 2-3 times greater storage after administration(63). Serum calcium, phosphorus, ALP, 25(OH)D, PTH levels, and urine calcium to creatinine ratios with radiography should be monitored after treatment(11). Adult vitamin D repletion depends on baseline serum calcidiol concentration and effective absorptive capacity. In patients with normal absorptive ability, serum calcidiol may increase by 0.7-1.0 ng/mL for every 100IU of vitamin D3. The increment seems to be larger in patients with lower baseline calcidiol levels and declines above 40 ng/mL(64). The treatment strategies for vitamin D supplementation in adults are summarized in Table 2. Serum calcidiol should be followed 3 months after treatment, and higher dosage may be required if goal serum level is not achieved. However, the safety of supplementation in vitamin D-depleted pregnant women (50000IU per week for 6-8 weeks) has not been established. Some experts prefer slow replenishment of vitamin D of 600-800IU daily. ENDO stated that it is safe to give pregnant women 1000-2000IU per day (15).

Vitamin D intoxication and complications

Vitamin D intoxication generally occurs after inappropriate supplementation of vitamin D, especially with serum calcidiol above 100-150 ng/mL(16). Prolonged sunlight exposure does not produce excessive vitamin D3 due to photo-conversion of previtamin D3 and vitamin D3 to its inactive metabolites(65). Acute vitamin D intoxication is mostly due to hypercalciuria and hypercalcemia, with symptoms of confusion, polydipsia, polyuria, anorexia, vomiting and muscle weakness. Chronic vitamin D intoxication may lead to nephrocalcinosis, bony demineralization and even pain.

Conclusion

Vitamin D is an essential nutrient not only important in bone health but also beneficial to many other systems. The American Academy of Dermatology declared UV radiation from sun or artificial sources to be a known carcinogen(66), so it may not be safe or efficient to obtain vitamin D via sun exposure. Therefore, physicians should provide information to patients who are at higher risk for vitamin D deficiency on how to get sufficient dietary or supplemental vitamin D. Trials assessing the effects of vitamin D supplementation and establishing the optimal serum level of calcidiol are ongoing. Further recommendations for vitamin D supplementation should be individualized accordingly.

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Table 1: Strategies of Vitamin D supplementation in nutritional rickets

Age or underlying condition	Vitamin D supplementation
0-12 months	2000IU per day for 6-12 weeks, then maintain with 400IU daily
>12 months	2000IU per day for 612 weeks, then maintain with 600-1000IU daily
Selected high-risk groups	6000IU per day, then maintain with a higher dosage

Table 2: Strategies of Vitamin D supplementation in adults

Baseline 25(OH)D level or underlying condition	Vitamin D supplementation
<10 ng/mL	50000IU once per week for 6-8 weeks, then maintain with 800IU daily.
10-20 ng/mL	800-1000IU per day*
20-30 ng/mL	600-800IU per day*
Underlying malabsorption syndrome	10000e50000IU per day*
*Serum 25(OH)D level should be followed 3 months after treatment, and higher dosage may be required if goal serum level is not achieved.	

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