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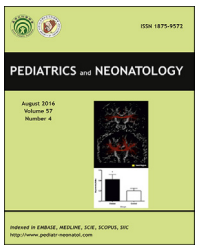

Review Article

Vitamin D and health - The missing vitamin in humans

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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. It was reported that 96% children with rickets were breastfed, since breast milk contains inadequate vitamin D. The American Academy of Pediatrics 2008 recommended infants who were exclusively or partially breastfed required 400 international units vitamin D daily from the first few days of life. Furthermore, since vitamin D receptors are present all over the body, insufficient vitamin D status may correlate with several extra-skeletal effects, such as pregnancy-related complications and 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.

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1. Discovery of vitamin D

Rickets, a condition with impaired mineralization of bone tissue and growth plates, may result in weak bones in infants and children. The word "rickets" was first used in 1634.[1] From reports of the Royal Infirmary in Manchester, cod liver oil was found to heal rickets.[1] In 1822, Sniadecki pointed out the relationship between sunlight and rickets.[2] At the end of World War I, when rickets was an untreatable major problem in Vienna, Harriet Chick led a group from the British Medical Research Council to study it.[3] They concluded both cod liver oil and sun exposure could heal rickets. In 1922, McCollum et al. coined the term "Vitamin D" in papers suggesting the existence of a vitamin which promotes calcium deposition.[4]

2. Metabolism and bioactivity of vitamin D

Vitamin D is a fat-soluble vitamin. Its processing flow diagram is shown in Fig. 1. Few foods naturally contain vitamin D (oily fish, such as sardines, herring, tuna, mackerel, salmon, and cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats), so dermal synthesis after ultraviolet-B (UVB) radiation remains the major route to obtain vitamin D, accounting for 90% of vitamin D replenishment.[5] Cholecalciferol (vitamin D3) is from animal sources and ergocalciferol (vitamin D2) is from plants.[6] 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 its active forms. First, 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 h. This process is driven by parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone.[7,8] 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 $1,25(OH)_2D$.[7,8] 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 $1,25(OH)_2D$ from circulating 25(OH)D. The elevation of $1,25(OH)_2D$ 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 sufficient circulating 25(OH)D is essential to maintain adequate $1,25(OH)_2D$ synthesis and plasma calcium level.[6] However, vitamin D deficiency may result in inadequate circulating 25(OH)D,

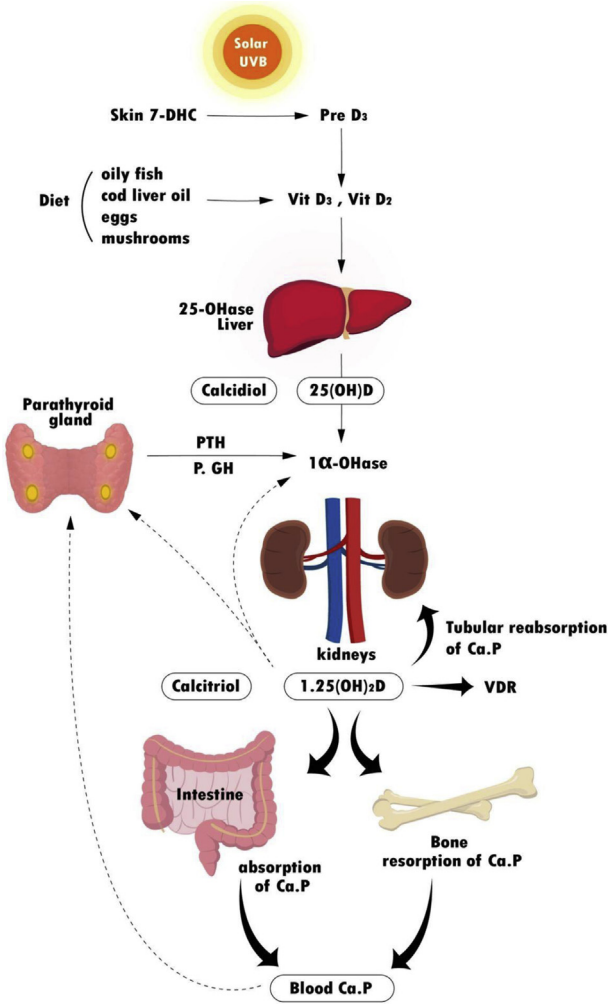

Figure 1 The metabolism and bioactivity of Vitamin D. Flow diagram of vitamin D's metabolism. Solid arrows demonstrate the direct effects of its products and dotted lines indicate the negative-feedback of plasma calcium or $1,25(OH)_2D$ (Ca: calcium; 7-DHC: 7-dehydrocholesterol; GH: growth hormone; 1α-OHase: 1-alpha-hydroxylase; 25-OHase: 25-hydroxylase; P: phosphate, PTH: parathyroid hormone; VDR: vitamin D receptor; Vit: vitamin)

which decreases $1,25(OH)_2D$ synthesis and calcium absorption, elevating PTH levels. It is reasonable that nutritionists should focus on plasma 25(OH)D 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,[8] coexisting extra-skeletal effects of vitamin D deficiency are to be expected. Table 1.

3. 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

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Table 1 Outlines of Vitamin D and health.

Discovery of vitamin D
Metabolism and bioactivity of vitamin D
Skeletal and extra-skeletal effects of vitamin D
Vitamin D and bone health
Can vitamin D prevent falls and fractures?
Vitamin D Need in Pregnancy and Lactation
Vitamin D and immune system
Vitamin D and other systemic effects
Vitamin D deficiency
Definition of vitamin D deficiency
Risk factors of vitamin D deficiency
Recommended vitamin D requirement
Vitamin D supplementation
Vitamin D intoxication and complications

be associated with osteoporosis and higher incidence of falls or fractures. Bone mineral deposition begins in pregnancy, especially during the third trimester.[9] Bone mass increases about 40 times from birth to adulthood, with 90% of peak bone mass achieved at the end of the second decade of life.[10] Childhood and adolescence are critical periods for bone mineral deposition.[11] A 2010 public health evaluation concluded that calcium supplementation of healthy children did not significantly decrease the incidence of fractures.[12] A healthy balanced diet that fulfilled the recommended calcium intake was superior to routine calcium supplementations.[11,12] 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 25(OH)D levels is not recommended, except for those with higher risk (as listed in Table 2), 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).[7,13,14]

Table 2 Risk factors of Vitamin D deficiency.

Inadequate cutaneous vitamin D synthesis
Dark skin
Age (infants, adolescents and elderly)
Obesity
Physical blocking of ultraviolet-B exposure (clothing, using of sun screens, ...)
Geographic-related factors (higher latitude, winter season, lower altitude, ...)
Inadequate dietary intake of vitamin D
Unbalanced diet
Vegetarians, eating disorders (anorexia nervosa, bulimia nervosa, ...)
Malabsorption syndrome
Intestinal malabsorption (Celiac disease, Crohn's disease, ulcerative colitis, ...)
Pancreatic insufficiency (Cystic fibrosis)
Cholestasis syndrome (Biliary atresia)
Following gut resection (short bowel syndrome)
Perinatal factors
Maternal vitamin D deficiency during pregnancy
Prematurity
Exclusively breastfed beyond three to six months of age
Genetic or endocrine disorders
Chronic liver/renal diseases
Hyperparathyroidism, growth hormone deficiency, diabetes mellitus
Hereditary resistance of vitamin D
Medications
Anticonvulsants (Carbamazepine, phenytoin, phenobarbital, topiramate)
Antiretroviral agents for treating human immunodeficiency virus
Azole antifungal agents (Ketoconazole)
Glucocorticoid

4. Can vitamin D prevent falls and fractures?

Since vitamin D is essential for calcium homeostasis and bone metabolism, discussion of vitamin D supplementation and prevention of falls and fractures is worthwhile. However, the evidence is contradictory. Several meta-analyses showed decreasing risks of falls in the elderly after vitamin D repletion with doses 700–1000 international units (IU) per day (relative risk (RR) about 20%), especially in those with underlying low vitamin D levels.[15] A meta-analysis in 2007 concluded that combination approach (800IU vitamin D plus 1200 mg calcium daily) was more effective in reducing hip fractures and mortality in institutionalized patients.[16] However, subsequent reviews stated that vitamin D alone or in combination with calcium did not significantly reduce the risk of falls and fractures in community-dwelling adults.[17] Furthermore, combination therapy with vitamin D and calcium might increase the incidence of renal stones.[17] Another large trial by Sanders et al. found an even higher risk of falls and fractures when using high-dose vitamin D (single high dose 500000IU annually, resulting in chronic serum 25(OH)D > 40 ng/mL), so intermittent high-dose regimen should be avoided.[18]

5. Vitamin D need in pregnancy and lactation

Several studies indicated the association between maternal vitamin D deficiency and an increasing risk of pre-eclampsia, gestational diabetes mellitus, preterm birth, small-for-gestational age infants, and impaired fetal bone formation.[19] A Cochrane systematic review in 2016 stated that daily or intermittent vitamin D supplementation in pregnant women could increase serum 25(OH)D concentration at term and reduce the incidence of pre-eclampsia, preterm birth and low birth weight, although the quality of the evidence was low to moderate.[20] However, combination therapy with vitamin D and calcium might increase the risk of preterm birth.[20] With limited evidence available to evaluate the benefits and harm of vitamin D supplementation during pregnancy, this intervention is not recommended by the World Health Organization as routine antenatal care.[21] However, Oxford University Hospital suggested the decision of maternal vitamin D supplementation should be discussed with all pregnant and

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breastfeeding women.[22] Higher dosage of vitamin D (started from 1000IU per day) in combination with calcium-replete diet (at least 1000 mg calcium daily) is indicated in high-risk non-Caucasian women with BMI >30 kg/m^2, living in higher latitude, or delivering during the period November to March.[22] More recently, a meta-analysis also demonstrated that vitamin D supplementation during pregnancy could reduce the risk of small-for-gestational-age infants and improve infant growth after birth.[23] Two thousand IU supplement daily did not increase the risk of fetal and neonatal death or incidence of congenital malformations.[23] Further guidelines and recommendations for optimal serum 25(OH)D level in pregnancy, timing of vitamin D supplementation, and dosing safety and efficacy should be established. As for breastfeeding women, a report in 2006 showed that higher maternal vitamin D intake (4000—6400IU per day) might achieve sufficient vitamin D concentration in breast milk for exclusively breastfed infants.[24] Elsewhere, it was found to be more efficient to give at least 400IU daily for exclusively breastfed infants.[7]

6. Vitamin D and immune system

As mentioned above, VDRs are present all over the body including antigen-presenting cells, with known direct effects on innate and adaptive immunity. 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.[25] However, Martineau et al. concluded that supplementation of vitamin D did not show significant improvement in clinical outcomes.[26]

Respiratory tract infections — A prospective trial by Camargo found an inverse association between cord-blood 25(OH)D level and the risk of developing upper respiratory tract infection by 3 months and wheezing at 15 months of age.[27] Newborns born with 25(OH)D < 20 ng/mL had six-fold higher risk of respiratory syncytial virus-related bronchiolitis at 1 year old compared with those of 25(OH)D > 30 ng/mL.[28] A recent meta-analysis of 25 trials in 2017 showed reducing incidence of acute respiratory tract infection after vitamin D supplementation (OR 0.88, 95% CI 0.81—0.96), which is more significant in patients with severe vitamin D deficiency (<10 ng/mL).[29]

Asthma — Maternal vitamin D intake during pregnancy may be associated with children's risk of developing wheezing episodes thereafter.[27] A cross-sectional study observed the 25(OH)D level between asthma and healthy groups.[30] It showed that vitamin D concentration was directly correlated with forced exploratory volume/forced vital capacity (FEV1/FVC) ratio and predicted FEV1, meaning that lower 25(OH)D 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 (RR 0.63, 95% CI 0.45—0.88) and risk of at least one exacerbation requiring emergency department visit or hospitalization or both (OR 0.39, 95% CI 0.19—0.78).[31]

Atopic dermatitis (AD) — A meta-analysis by Kim demonstrated that serum 25(OH)D level was lower in patients with AD.[32] A small randomized clinical trial also found beneficial effects of vitamin D supplementation in children with winter-related AD.[33] 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.[34]

1,25(OH)$_2$D also functions as an inhibitor of dendritic cell maturation, which reduces the activation of acquired immunity and may increase the risk of autoimmune disease,[35] such as type I diabetes, multiple sclerosis, and inflammatory bowel disease.[5] However, because reports conflict on the association between vitamin D status and these diseases, supplementation is not recommended at present.

7. 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.[14] However, current evidence for vitamin D intervention in treating or preventing these diseases is lacking.

8. Definition of vitamin D deficiency

The best indicator of human body's vitamin D status is the concentration of serum 25(OH)D.[36] The optimal 25(OH)D 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 25(OH)D 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,[36] 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.[13,14,37—39]

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 25(OH)D concentration in children has not yet been established because of inconsistent evidence. The definitions for vitamin D status are summarized in Table 3. In 2008, the American Academy of Pediatrics (AAP) classified 25(OH)D > 20 ng/mL as sufficiency,[7] whereas the Pediatric Endocrine Society used a higher threshold in 2011, regarding 25(OH)D < 30 ng/mL as insufficiency.[40] More recently in 2016, the Global Consensus also defined 25(OH)D > 20 ng/mL as sufficiency but adjusted other criteria.[41]

9. Risk factors of vitamin D deficiency

Possible causes relating to vitamin D deficiency are summarized in Table 2. UVB is more prevalent during the hours

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Table 3 Definitions of Vitamin D deficiency in children.

25(OH)D (ng/mL)	American Academy of Pediatrics (2008)	Pediatric Endocrine Society (2011)	Global Consensus (2016)
Severe deficiency	<5		
Deficiency	5–15	<20	<12
Insufficiency	16–20	<30	12–20
Sufficiency	21–100		>20
Excess	101–150		
Intoxication	>150		>100

of 10am to 3pm. During spring, summer and autumn, 10–15 min 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.[7] 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.[42]

Infants and adolescents are populations at risk because of rapid skeletal growth after birth and during puberty.[6] Weisberg showed that 96% of cases of rickets occurred in breastfed children.[43] Because breast milk is known to contain very little vitamin D even in vitamin D-replete mothers (15–50 IU/L),[7,44] 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[9] and negligible sun exposure in postpartum hospital.[45] 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.[6,46] 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.[47] However, obese people still have higher risk due to sequestration of vitamin D in adipose tissue.[7,48]

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%.[49] Residents, beyond latitude of 33° 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 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 25(OH)D and $1,25(OH)_2D$, while Ketoconazole may further block 1-hydroxylation.[50] Patients with chronic high-dose glucocorticoids require more vitamin D due to inhibition of intestinal vitamin D-dependent calcium absorption.

10. 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 (Table 4).[51] 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.[9] However, even infants born to vitamin D-replete mothers may become vitamin D deficient after 8 weeks of life if unsupplemented during early infancy.[52] It is reported that infants can get adequate quantities of vitamin D by sunlight exposure of 30 min per week wearing only a diaper or 2 h per week when fully-clothed without a hat.[43] 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,[53] 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.[7,13,40] 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.[7] As for obese children or those on chronic medications, requirements may be 2–4 times more.[11]

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.[54] 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 >1500 g.[55] This lower dosage is adjusted according to smaller size of preterm babies and relatively lower need of vitamin D to achieve adequate 25(OH)D levels.[55] This advice is supported by a 1992 study revealing calcium absorption in low-birth-weight infants, especially during first few months of life, was in proportion to their daily

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Table 4 Dietary reference intake for calcium and Vitamin D by Institute of Medicine.

Age group	Calcium		Vitamin D	
	Recommended dietary allowance (mg/day)	Upper intake level (mg/day)	Recommended dietary allowance (IU/day)	Upper intake level (IU/day)
0–6 months	200	1000	400	1000
6–12 months	260	1500	400	1500
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
9–18 years	1300	3000	600	4000
19–50 years	1000	2500	600	4000
51–70 years (males)	1000	2000	600	4000
51–70 years (females)	1200	2000	600	4000
>70 years	1200	2000	800	4000
14–18 years (pregnant/lactating)	1300	3000	600	4000
19–50 years (pregnant/lactating)	1000	2500	600	4000

calcium intake, but independent of vitamin D.[56] However, in certain instances, the requirement may increase to 1000IU per day in infants >1500 g to achieve the goal of serum 25(OH)D > 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.[51] Since vitamin D intake is usually low in 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.[37] As for women during pregnancy or lactation, the RDA from the IOM is 600IU per day, the same as the basic requirement for other adults.[51] There is no consensus on optimal 25(OH)D concentration during pregnancy, with 20 ng/mL regarded as minimally acceptable.[36] For non-Caucasian women living at higher latitudes or pregnant during winter, higher vitamin D supplementation (1000IU daily) may be necessary.

11. Vitamin D supplementation

The guideline for vitamin D supplementation in children with nutritional rickets from ENDO and the Global Consensus is listed in Table 5.[13,41] Although radiologic bone healing is evident 2–4 weeks after treatment, this high-dose strategy should be continued for a further 2–3 months.[7] After achieving the optimal 25(OH)D 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.[7] Stoss therapy should not be administered for young infants, since they are much more likely to develop hypercalcemia. Recently, there is increasing evidence to support the combination use of calcium (500 mg daily) with vitamin D.[41] 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.[57] Serum calcium, phosphorus, ALP, 25(OH)D, PTH levels, and urine calcium to creatinine ratios with radiography should be monitored after treatment.[7]

Adult vitamin D repletion depends on baseline serum 25(OH)D concentration and effective absorptive capacity. In patients with normal absorptive ability, serum 25(OH)D 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 25(OH)D levels and declines above 40 ng/mL.[58] The treatment strategies for vitamin D supplementation in adults are summarized in Table 6. Serum 25(OH)D 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.[13]

12. Vitamin D intoxication and complications

Vitamin D intoxication generally occurs after inappropriate supplementation of vitamin D, especially with serum

Table 5 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 6–12 weeks, then maintain with 600–1000IU daily
Selected high-risk groups[a]	6000IU per day, then maintain with a higher dosage

[a] Selected high-risk groups indicate the populations listed in Table 2.

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Table 6 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[a]
10–20 ng/mL	800–1000IU per day[a]
20–30 ng/mL	600–800IU per day[a]
Underlying malabsorption syndrome	10000–50000IU per day[a]

[a] 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.

25(OH)D above 100–150 ng/mL.[14] Prolonged sunlight exposure does not produce excessive vitamin D3 due to photo-conversion of previtamin D3 and vitamin D3 to its inactive metabolites.[59] 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.

13. 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,[60] 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 25(OH)D are ongoing. Further recommendations for vitamin D supplementation should be individualized accordingly.

Conflict of interest

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