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Vitamin D deficiency in children and adolescents: Epidemiology, impact and treatment

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Abstract Vitamin D deficiency is highly prevalent among children and adolescents worldwide. The high rates of vitamin D deficiency during childhood are of major public health relevance, given the growing evidence that vitamin D deficiency may play a key role in the pathophysiology of many chronic diseases beyond rickets, including autoimmune conditions, cardiovascular diseases, and cancer. Identification, treatment, and prevention of vitamin D deficiency in childhood may therefore have profound health effects throughout the life span. In this review, we discuss the definitions, epidemiology, clinical implications, and treatment of vitamin D deficiency in children and adolescents.

Keywords Vitamin D · Rickets · Epidemiology · Infants · Children · Adolescents

1 Introduction

Vitamin D deficiency is a highly prevalent condition among infants, children, and adolescents in the USA and around the world. In addition to rickets, growing evidence suggests that vitamin D deficiency may be a risk factor for the development of many chronic diseases throughout the life span, including autoimmune conditions, cardiovascular diseases, and cancer. Identification, treatment and prevention of vitamin D deficiency in childhood may, therefore, have profound future health effects. In this paper, we review the epidemiology and treatment of vitamin D deficiency in children and adolescents. We also outline the potential impact of early life vitamin D deficiency on the development of several diseases in children and adults.

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2 Sources of vitamin D

Vitamin D, a prohormone, is converted in the liver to 25-hydroxyvitamin D (25(OH)D), and then in the kidney to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the active metabolite involved in calcium and phosphorus homeostasis. The physiology of vitamin D production and metabolism has been recently reviewed in detail [1, 2].

The term "vitamin D" includes two different forms of vitamin, vitamin D2 and D3. Humans obtain vitamin D from dietary foods and supplements, or by endogenous synthesis. Dietary sources of vitamin D include fatty fish and foods fortified with vitamin D2 or D3, particularly fortified dairy products, infant formula, and breakfast cereals [3]. During the endogenous synthesis of vitamin D, the first crucial step involves the absorption of ultraviolet B radiation by 7-dehydrocholesterol in the skin to produce previtamin D3, which is rapidly converted to vitamin D3 [1]. This process is highly dependent on the penetration of ultraviolet B photons into the epidermis, which is greatly reduced in the presence of dark skin pigmentation, sunscreen, winter season, or high latitude [1, 4].

3 Vitamin D deficiency: Definitions

25(OH)D, the major circulating form of vitamin D, is the best summary measure of vitamin D status as it incorpo-

rates both endogenous and dietary sources of vitamin D [5]. Among infants and young children, both the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) have defined vitamin D deficiency as a serum 25 (OH)D level below 11 ng/mL (27.5 nmol/L) [6, 7]. Serum 25(OH)D levels of less than 11 to 15 ng/mL (27.5 to 37.5 nmol/L) have been observed among infants and children with skeletal abnormalities characteristic of vitamin D deficiency rickets [1, 8]. Among adults, the IOM defined the normal lower limit for serum 25(OH)D to range from 8 (20 nmol/L) to 15 ng/mL (37.5 nmol/L), derived from "the mean serum 25(OH)D±2 standard deviations (SD) from a group of healthy individuals," and varying by geographic location [6]. These data likely included individuals with subclinical vitamin D deficiency [4, 9].

Most vitamin D scientists now advocate the use of biomarkers (parathyroid hormone (PTH) concentrations, calcium absorption) or functional health outcomes to define adequacy of circulating vitamin D levels in adults [4, 10, 11]. 25(OH)D levels above 30 ng/mL (75 nmol/L) in adults are associated directly with increased calcium absorption and inversely with PTH levels [4]. Furthermore, levels of 25(OH)D ≥30 ng/mL (75 nmol/L) appear to be associated with optimal bone health, and prevention of colorectal cancer, among other health outcomes [11]. In children, some [1, 12], but not all [13], studies have shown that vitamin D deficiency is associated with higher PTH levels. In summary, a consensus is growing that vitamin D deficiency in adults be defined as a serum 25(OH)D level <20 ng/mL (50 nmol/L), and vitamin D insufficiency defined as 25(OH)D <30 ng/mL (75 nmol/L) [10, 14]. These definitions are being increasingly applied to children [15, 16].

4 Vitamin D deficiency: Prevalence and risk factors

Vitamin D deficiency appears to be a widespread global problem prevalent in all age groups. Estimates suggest that up to 1 billion people around the world may have vitamin D deficiency or insufficiency, if insufficiency is defined as a 25(OH)D level≤30 ng/mL [17]. Comparing study prevalence estimates can be challenging due to varying definitions of vitamin D deficiency and assay techniques. Many studies provide incomplete data regarding vitamin D deficiency risk factors, which include breastfeeding without supplementation, dark skin pigmentation or race, female gender, living at a northern latitude, lack of direct sun exposure, and winter season, when serum vitamin D concentrations are at a nadir [18]. In addition, the majority of studies have small numbers of participants that may not be nationally representative. These limitations must be considered in comparing study results.

In the USA, cases of nutritional rickets have been reported from at least 17 states, with 166 cases reported in the medical literature between 1986 and 2003 [19]. Relatively high rates of subclinical vitamin D deficiency have been reported in otherwise healthy infants [16, 20–22], children [23, 24] and adolescents [15, 25] in several American states. A high prevalence of vitamin D deficiency has also been reported in infants, children, and adolescents from diverse countries around the world, including the UK [26], France [27], Greece [28], Lebanon [29], Turkey [30], China [8, 31], Finland [32, 33], and Canada [34].

In a study of 84 breastfed infants in Iowa (latitude 41°N), 10% had 25(OH)D levels<11 ng/mL (27.5 nmol/L) at 280 days of age [21]. A study of 400 newborns in Pittsburgh (latitude 34°N) found that 25(OH)D levels were <15 ng/mL (37.5 nmol/L) in 10% of white newborns, and 46% in black newborns [35]. Using a cutoff of 25(OH)D≤20 ng/mL (50 nmol/L), we found that 12.1% of a sample of 365 infants and toddlers from the Boston area were vitamin D deficient, and 40% were below an accepted optimal threshold (≤ 30 ng/mL or 75 nmol/L) [16]. Surprisingly, serum 25 (OH)D levels in our study did not vary by skin pigmentation [16]. In a smaller study (n=40) of mostly black newborns from the Boston area, 65% were vitamin D deficient (<12 ng/mL or <30 nmol/L) [22].

Among adolescents, reported prevalence rates of vitamin D deficiency have ranged from 0 to 42%, with variation noted secondary to season, latitude, and participant race/ethnicity [36]. In our clinic population at Children's Hospital Boston (latitude 42°N), we found that 42% of healthy adolescents had 25(OH)D levels≤20 ng/mL (50 nmol/L), and the prevalence of vitamin D deficiency (25(OH)D levels≤ 15 ng/mL or 37.5 nmol/L) was six-fold higher among black compared with white adolescents [15]. In a Finnish study (latitude 61°N) of 14 to 16 year old girls conducted during the winter, 13.5% were vitamin D deficient, and 61.8% had vitamin D insufficiency [33]. A large US sample of 12–19 year olds from the Third National Health and Nutrition Examination Survey (NHANES III) found that vitamin D deficiency (25(OH)D<25 nmol/L) was uncommon, with prevalence rates <1% [25]. However, prevalence rates of insufficiency were common. Among a subpopulation (36% of whom were non-Hispanic black) living at a median latitude of 32°N with levels measured in the winter, 25(OH) D was <15 ng/mL (37.5 nmol/L) in 5% of males and 12% of females; 25(OH)D was <20 ng/mL (50 nmol/L) in 25% of males and 47% of females. These findings are noteworthy in light of the assumption that more favorable UVB radiation levels at lower latitudes during winter should protect against vitamin D deficiency.

Children at particular risk for vitamin D deficiency include those with chronic medical conditions that impair the absorption or synthesis of vitamin D [17, 37]. In

patients with chronic gastrointestinal disease, multiple factors may contribute to risk of vitamin D deficiency, including reduced sun exposure, reduced vitamin D intake, impaired mucosal absorption, and increased gastrointestinal vitamin D losses [37, 38]. In a recent study of 130 subjects from Children's Hospital Boston with Crohn's disease aged 8 to 22 years, 34.6% had vitamin D levels ≤15 ng/mL [39]. Cystic fibrosis patients have high rates of vitamin D deficiency and fractures, even when supplemented daily with 400–800 IU of vitamin D [40–43]. Both human and animal data suggest that hepatic 25-hydroxylation of vitamin D tends to be preserved, even in the setting of cholestasis or cirrhosis [44]. Chronic renal impairment resulting in hyperphosphatemia or substantially reduced glomerular filtration rate can reduce renal 1-alpha hydroxylase activity or concentrations, resulting in deficiency of $1,25(OH)_2D$ [45].

5 Health effects of vitamin D deficiency

Increasing evidence suggests that optimal vitamin D status throughout the lifespan—even *in utero*—may be important not only in maintaining bone health, but also in protecting against many chronic conditions, including autoimmune diseases, diabetes, cardiovascular diseases, and cancer [46]. Many bodily tissues express the nuclear receptor for $1,25(OH)_2D$, including the stomach, pancreas, brain, skin, gonads, activated T and B lymphocytes, and activated macrophages [2, 5]. Several of these tissues are also capable of producing the 1-alpha hydroxylase enzyme, allowing for the local production of $1,25(OH)_2D$ [5]. $1,25(OH)_2D$ is involved in the regulation of genes controlling cell proliferation and differentiation, apoptosis, and angiogenesis [5]. The nonskeletal biologic actions of vitamin D thought to underlie disease associations were recently reviewed [5].

5.1 Rickets

Vitamin D deficiency is the most common cause of rickets. Nutritional rickets is often thought of as a "historical disease" given that up to 40 to 60% of children living in certain locations during the Industrial Revolution had the problem [18]. Cod liver oil, rich in vitamin D, and sunlight cured the condition. Subsequently, rickets largely vanished with fortification of infant formula and public education regarding adequate exposure to sunlight. However, in the 1960s, the problem began to reappear, especially among breastfed infants and in those infants whose mothers' dress included covering [47].

Many groups have noted an increased prevalence of rickets in the U.S. over the last decade [48–50]. Kreiter et al. [50] identified thirty cases of nutritional rickets in North Carolina between 1990 and June 1999, with over half of the cases occurring between 1998 and the first half of 1999. In contrast to earlier reports of rickets, all thirty children in that study of Southern infants were African-American, breastfed, and did not receive vitamin D supplementation [50]. A recent review identified 166 pediatric cases of rickets in the USA, published between 1986 and 2003 [19]. Among affected children, the majority were <30 months old at presentation, 83% were of black race/ethnicity, and 96% were breast-fed [19]. These findings were similar to a published review of 65 clinical cases of rickets reported in the USA between 1975 and 1985 [51].

Around the world, rickets remains a common disease. Among ethnic minorities in the UK, 1.6% (77% of whom were of Southeast Asian descent) were found to have rickets [52]. Examples of other rickets prevalence estimates in the last decade range from 27% in Yemen to 70% in Mongolia [52].

5.2 Osteoporosis

Emerging and still controversial data suggest that vitamin D status *in utero* and in early childhood may be associated with bone mass in later childhood. A retrospective cohort study found that vitamin D supplementation during the first year of life was associated with higher areal bone mineral density at age 7–9 years [53]. In a study of 216 British mother–child pairs, 25(OH)D levels in late pregnancy (mean 34 weeks gestation) were predictive of bone mass in offspring at 9 years of age [54]. Vitamin D insufficiency (<20 ng/mL) in late pregnancy was associated with reduced bone size and total bone mineral content, as measured by dual energy X-ray absorptiometry [54]. Vitamin D deficiency may prevent children from attaining their optimal peak bone mass, [5] which is a determinant of osteoporotic fracture risk in adulthood.

A few studies in pre-pubertal children and adolescents have shown that 25(OH)D levels are associated with bone health. In a study of 14–16 year old females, serum 25(OH)D levels less than 16 ng/mL (40 nmol/L) were associated with lower mean forearm bone mineral density values at the radial and ulnar sites [33]. Similarly, a study of 10–12 year old girls found that 25(OH)D levels were directly associated with cortical bone mineral density at the radius and tibia shaft [12]. A study of 9–15 year old females followed prospectively for three years found that baseline 25(OH)D levels were directly associated with 3-year bone mineral density [55].

In adults, data suggest that high doses of vitamin D supplementation are associated with lower risk of fracture. A meta-analysis of vitamin D supplementation randomized controlled trials in adults found that vitamin D daily intake of ≥800 IU was associated with a 26% reduced risk of hip fracture, and a 23% reduced risk of any nonvertebral

fracture, compared with calcium or placebo [11]. In contrast, trials using doses of 400 IU did not show a protective effect [11].

5.3 Immune conditions: Asthma, type 1 diabetes, and multiple sclerosis

Low levels of serum 25(OH)D or vitamin D intake in pregnancy have been associated with higher risk of childhood wheezing illnesses [56, 57]. In a prospective Boston-area cohort, a 100 IU increase in vitamin D intake during pregnancy was associated with a 0.81 lower risk of recurrent wheezing in children at age 3 years [56]. Another large prospective cohort also found that the risk for persistent wheezing was lower for offspring of mothers in the highest quintile of maternal vitamin D intake, compared with the lowest quintile (OR 0.33, 95% CI 0.11, 0.98) [57].

Vitamin D supplementation during pregnancy and early childhood may reduce the risk of type 1 diabetes [58–60]. Among 233 children at increased risk for type 1 diabetes (determined by HLA-DR genotype or family history) followed prospectively from birth for an average of 4 years, maternal vitamin D intake from food was associated with a reduced risk of islet cell autoantibody formation [58]. However, no protective effect was seen from prenatal vitamin D supplements [58]. A population-based birth cohort study of 10,366 Finnish children followed for three decades found that children who regularly ingested 2,000 IU of vitamin D during the first year of life were 80% less likely to develop type 1 diabetes mellitus [60]. Not all studies have confirmed these findings. A Swedish birth cohort study of 11,081 children found that maternal use of supplements containing >5 mcg (200 IU) vitamin D during pregnancy was associated with reduced islet autoimmunity at age 1 year, but not at 2.5 years; vitamin D supplementation of 10 mcg (400 IU) per day during infancy was not associated with islet autoimmunity [59]. The discrepant findings may in part be explained by the different vitamin D doses used, and maternal serum 25(OH)D levels were not available for comparison. Differing assays used to measure 25(OH)D also make the comparison between studies more complex.

Vitamin D deficiency in early life may be a risk factor for the development of multiple sclerosis. Season of birth, a marker of vitamin D levels during pregnancy, has been associated with multiple sclerosis [61]. A case–control study showed that among white adults, those in the highest quintile of 25(OH)D pre-diagnosis had a lower risk of developing multiple sclerosis (OR 0.38, 95%CI 0.19 to 0.75) than those in the lowest quintile (<25.3 ng/mL or <63.3 nmol/L) [62]. The inverse relationship with multiple sclerosis risk was strongest if the 25(OH)D levels were measured before the age of 20 years [62].

5.4 Obesity, type 2 diabetes, and cardiovascular disease

Increasing data suggest that vitamin D deficiency may be a risk factor for the development of obesity, type 2 diabetes, and cardiovascular disease, but few studies exist in children. In addition to the limited data in children, studies in adults are also presented below because of their potential relevance to the growing epidemic of obesity, insulin resistance, and cardiovascular disease in children and adolescents.

In adults, an inverse association between serum 25(OH)D levels and total body fat, abdominal obesity, hypertriglyceridemia, or hyperglycemia has been noted in many [63–66], but not all [67], cross-sectional studies. Allelic variation in the vitamin D receptor (VDR) gene has been associated with susceptibility to higher body fat and weight in adults [68, 69], suggesting that vitamin D activity may be a risk factor for obesity development. Others have proposed that higher body fat leads to increased sequestration of vitamin D in adipose tissue, resulting in lower serum vitamin D levels, that lead to insulin resistance and metabolic syndrome [69]. We recently showed that the prevalence of vitamin D deficiency among underweight adolescent girls with anorexia nervosa was paradoxically low, supporting the fat sequestration hypothesis [70]. Low serum 25(OH)D levels in adults are associated with increased risk of type 2 diabetes [71, 72], impaired glucose tolerance [73], higher fasting plasma glucose levels [66], and insulin resistance and beta-cell dysfunction, even among healthy, glucose-tolerant adults [74]. Chiu et al. [74] speculated that an increase in plasma 25(OH)D from 10 to 30 ng/mL could improve insulin sensitivity by 60%. A recent systematic review noted that among Caucasians, the odds of type 2 diabetes prevalence was 0.36 (95% CI 0.16–0.80) for the highest vs. lowest quartiles of 25(OH)D levels [75]. Concomitant vitamin D and calcium supplements have been associated with lower risk of type 2 diabetes [76] and impaired glucose tolerance [77].

In adults, higher 25(OH)D levels have been associated with lower risk of hypertension [78, 79] and related complications, including myocardial infarction [79], and risk of diabetic retinopathy [80]. In a large prospective study, subjects with 25(OH)D<15 ng/mL (37.5 nmol/L) had a three-fold higher risk of incident hypertension over 4 years, compared to those with 25(OH)D>30 ng/mL (75 nmol/L) [78]. Hypertensive patients exposed to intermittent ultraviolet B radiation exhibited a 180% increase in 25(OH)D levels, and a 6 mmHg reduction in both systolic and diastolic blood pressure [81]. These associations remain controversial, as not all studies have confirmed these findings [82, 83].

In children, few studies have examined whether perinatal or childhood vitamin D status is associated with adiposity, insulin resistance, or blood pressure. A longitudinal study published in 2007 reported that maternal 25(OH)D levels in

late pregnancy were not associated with offspring weight, body fat, or blood pressure at age 9 years [84]. Some cross-sectional studies have shown that vitamin D deficiency is prevalent among obese children; one study of obese adolescents showed that vitamin D levels increased after a 1 year weight loss intervention [85]. In a recent retrospective chart review of 217 obese children, 55.2% of patients were vitamin D deficient (25(OH)D<20 ng/mL or <50 nmol/L) [86]. Compared with the vitamin D sufficient group, the vitamin D deficient group had a higher mean BMI and systolic blood pressure [86]. Serum 25(OH)D levels correlated negatively with BMI and positively with HDL-C [86]. Observational studies [87–89] and clinical trials examining the relationship between dairy intake and adiposity have found conflicting results. Given the provocative data outlined above, further pediatric data are needed to assess whether prenatal and childhood vitamin D status can affect the risk of child obesity or related metabolic conditions.

5.5 Cancer

A latitudinal gradient exists for several malignancies in adults, including Hodgkin's lymphoma, colon, pancreatic, prostate, ovarian, and breast cancer [5]. Several large cohort studies have now shown that 25(OH)D levels<20 ng/mL (50 nmol/L) are associated with a 30 to 50% higher risk of colon, prostate, and breast cancer. A recent review of vitamin D in the prevention of colorectal cancer concluded that 25(OH)D level of 36 ng/mL (90 nmol/L) provided optimal protection against the development of colorectal neoplasia [11]. In children, studies show that increased exposure to sunlight is associated with a reduced risk of non-Hodgkin's lymphoma, and reduced mortality risk from malignant melanoma [90, 91].

5.6 Effects on maternal health and fetal growth during pregnancy

Vitamin D deficiency in pregnancy is associated with lower birth weight in some, but not all studies [92, 93]. Data also show that season of birth is related to birth weight [94]. In trials of third trimester vitamin D supplementation among women of Asian descent, women in the placebo group—who were profoundly vitamin D deficient—had a greater incidence of small-for-gestational age infants [95], and their infants gained less weight in the first year of life [96]. Morley et al. [97] found that low third trimester 25(OH)D was associated with reduced intrauterine long bone growth and slightly shorter gestation, but not with birth weight.

Low maternal 25(OH)D levels have been associated with an increased risk of preeclampsia [98] and insulin resistance during pregnancy [99]. Vitamin D supplementation of infants may reduce their risk of preeclampsia as adults [100].

5.7 Other diseases

Data in animals and humans suggest that vitamin D status may play an important role in the development of many other diseases, including periodontal disease [11], schizophrenia [46], and rheumatoid arthritis [101], among other illnesses [5].

6 Prevention of vitamin D deficiency

The optimal vitamin D intake needed to prevent skeletal and nonskeletal health problems associated with vitamin D deficiency is unclear. In 1963, the AAP Committee on Nutrition recommended 400 IU per day (the amount in one teaspoon of cod liver oil) for infants, children, and adolescents [102]. In 2003, the AAP Committee on Nutrition and Section on Breastfeeding issued recommendations consistent with the 1997 IOM report, defining adequate daily vitamin D intake in children of all ages as 200 IU per day, an amount deemed sufficient to prevent rickets [6, 7]. Many pediatric experts contend that the recommended quantity of vitamin D should be higher than the amount shown to prevent only the worst outcome, rickets. The US Food and Drug Administration recommends 400 IU per day for children and adults of all ages.

Infants ingesting >500 mL of formula will consume at least 200 IU of vitamin D, because infant formulas sold in the USA typically have a vitamin D concentration of 400 IU/L. However, both underfortification and overfortification have been reported [103]. Exclusively breastfed infants without adequate sunlight exposure or supplement use are unlikely to meet these recommendations, because human breastmilk may contain as little as 20–70 IU/L [104]. Because human milk vitamin D content is highly correlated with maternal vitamin D status [104], these low levels may result in part from chronic vitamin D insufficiency among pregnant women, as in all adults. A 3-month supplementation trial in lactating women using daily doses of 2,000 or 4,000 IU was associated with large increases in both antirachitic activity of milk and infant serum 25(OH)D levels [105]. Older children can meet the IOM requirements through fortified foods or supplements, but cross-sectional data in adolescents show that meeting these intakes does not prevent vitamin D insufficiency as measured by 25(OH)D levels [3].

Despite the publication of national guidelines on vitamin D intake, many breastfed infants are likely not receiving supplementation, and many children have inadequate intakes. In one small study of 84 Iowa infants, less than 10% of the exclusively breastfed infants received any vitamin D supplementation [21]. In a population-based US study, 31% of Mexican American, 41% of Non-Hispanic White, and 52% of Non-Hispanic black children aged 1 to 8 years did not

meet adequate intake levels for vitamin D from food [106]. Adolescent females reported the lowest intakes of vitamin D from food [107]. Few studies have examined the determinants of vitamin D intake, and it is unclear whether physicians follow the AAP guidelines. In a 1999 survey of 417 pediatricians, only 44.6% recommended vitamin D supplementation for all breastfed infants [108]. Eighty-three percent of pediatricians who did not recommend vitamin D for breastfed infants believed that breastmilk had sufficient vitamin D [108].

The low vitamin D intakes across all ages are concerning, in light of debate over whether recommended adequate intake thresholds should be raised. Many vitamin D scientists are calling for new recommended vitamin D intakes in adults of 800 to 1,000 IU per day, to achieve a serum 25(OH)D of≥30 ng/mL (75 nmol/L) [4, 10, 14]. In children, the ideal 25(OH)D serum levels to prevent short- and long-term health complications are unknown, but limited existing data suggest a similar threshold of ≥30 ng/mL (75 nmol/L) [1]. Supplementation trials in preterm and term infants, and children have shown that 25 (OH)D levels plateau around 30 ng/mL (75 nmol/L) [1, 109, 110]. To achieve this serum level, infants need vitamin D supplements of 400–1,000 IU per day depending on their vitamin D stores at birth [1]. Daily doses as high as 3,000 IU of vitamin D2 in premature infants [110], and 4,000 IU in older children [109], have been used to achieve 25(OH)D levels of 30 to 33 ng/mL (75 to 83.5 nmol/L) without adverse effects.

7 Treatment of vitamin D deficiency

Vitamin D deficiency can be managed by either oral or intramuscular provision of vitamin D, together with adequate elemental calcium to prevent hypocalcemia that may be associated with remineralization of the bone matrix ("hungry bone syndrome") [111]. Recently, intramuscular vitamin D has been difficult to obtain in the USA. The three oral forms of vitamin D that are available are ergocalciferol (25-hydroxyvitamin D2 or vitamin D2), cholecalciferol (25-hydroxyvitamin D3 or vitamin D3), and calcitriol (1,25 $(OH)_2D$). Vitamin D2 and D3 are available in a concentrated syrup formulation useful for infants and young children. Calcitriol is not a first line treatment for vitamin D deficiency, because its direct renal effects increase the risk of cholelithiasis and hypercalcemia. While both vitamin D2 and D3 have been used to treat vitamin D deficiency rickets in infants and children [109, 112–115], their potency and duration of action differ. Some data in adults suggest that vitamin D3 raises serum 25(OH)D concentrations three-fold higher than vitamin D2 [116, 117], although this point is still under debate [118].

The optimal regimen, route, and duration of vitamin D therapy for vitamin D deficiency in infants and children remain controversial, with data from small studies driving current clinical practice [109, 112–115]. A commonly recommended regimen is vitamin D2 or D3 for 12 weeks at a dose of 1,000–2,000 IU daily in infants, and up to 4,000 IU daily in children older than 1 year, to achieve a total cumulative dose of 200,000 to 600,000 IU [1, 109]. Alternative regimens include a monthly intramuscular injection of 10,000 to 50,000 IU for 3 to 6 months, or the administration of a single oral dose of 300,000–600,000 IU [112, 115]. In older children and adults, Holick and colleagues have suggested that a cost-effective method to treat vitamin D deficiency is to provide an oral dose of 50,000 IU of vitamin D2 once weekly for 8 weeks, followed by a maintenance regimen of 50,000 IU every 2 to 4 weeks [17]. Some authors have advocated for provision of 400 IU of vitamin D for 6 months to 1 year to maintain 25(OH)D concentrations after treatment for vitamin D deficiency [115].

Children and adults with malabsorption or other risk factors for vitamin D deficiency may require higher chronic oral doses of vitamin D to maintain optimal levels [40, 119]. In one recent retrospective study of adult cystic fibrosis patients, 82% of patients who underwent counseling regarding vitamin D supplementation were able to achieve serum 25(OH)D levels >20 ng/mL (>50 nmol/L), with a mean supplementation dose of 1,405 IU of vitamin D3 [119].

Toxicity due to excess vitamin D intake is rare, but has been reported, generally with doses exceeding 10,000 IU daily [120, 121]. Published cases of vitamin D toxicity with hypercalcemia involved daily doses exceeding 40,000 IU [120–122] or single vitamin D doses greater than 300,000 IU [112]. It has been estimated that circulating levels of 25(OH)D>100–150 ng/mL (>250–375 nmol/L) are necessary to manifest signs and symptoms of hypercalcemia [104], which can include weakness, headache, somnolence, nausea, constipation, bone pain, and a metallic taste. There is no evidence of adverse effects in healthy individuals consuming daily vitamin D doses up to 10,000 IU [104, 122], and daily intakes exceeding this amount for several months would be required to maintain a vitamin D level of >100 ng/mL (250 nmol/L) [104].

8 Conclusions

Growing evidence supports a physiologic role for vitamin D in many chronic diseases, in addition to known effects on bone. In adults, many vitamin D experts are advocating vitamin D intakes of 800 to 1,000 IU per day, to achieve a serum 25(OH)D of >30 ng/mL (75 nmol/L). In children, further studies are needed to determine the optimal circulating concentration of 25(OH)D, and the effects of a

given 25(OH)D concentration on calcium absorption and PTH secretion. Additional clinical trials are required to compare the efficacy and cost-effectiveness of supplementation regimens designed to prevent and treat vitamin D deficiency in infants, children and adolescents. Knowledge gaps also exist regarding the potential physiologic impact of vitamin D deficiency in childhood on health outcomes throughout the lifespan. Given the high worldwide prevalence of vitamin D deficiency, well-designed outcomes studies in children are urgently needed to address these research priorities.

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