Vitamin D in Toddlers, Preschool Children, and Adolescents

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Key Messages

- Vitamin D status is associated with avoidance of rickets and various autoimmune, infectious, and allergic diseases.
- Randomized, controlled trials of vitamin D supplementation for pediatric bone health are limited and equivocal in their results.
- The specific vitamin D supplementation to optimize toddler, child, and adolescent outcomes is unknown, but doses 10–50 µg/day are safe and may be beneficial.

Keywords

Vitamins · Pediatrics · Bone disease · Calcium homeostasis · Fractures · Vitamin D

Abstract

Background: Vitamin D supplementation is known to both prevent and treat rickets, a disease of hypomineralized bone. Childhood is a period of great bone development and, therefore, attention to the vitamin D needed to optimize bone health in childhood is imperative. **Summary:** Observational studies have pointed to a vitamin D status, as indicated by a 25-hydroxyvitamin D concentration, of 50 nmol/L to ensure

avoidance of rickets and of 75 nmol/L to optimize health. However, the benefits of achieving these levels of vitamin D status are less evident when pediatric randomized, controlled trials are performed. In fact, no specific pediatric vitamin D supplementation has been established by the existing evidence. Yet, study of vitamin D physiology continues to uncover further potential benefits to vitamin D sufficiency. This disconnection between vitamin D function and trials of supplementation has led to new paths of investigation, including establishment of the best method to measure vitamin D status, examination of genetic variation in vitamin D metabolism, and consideration that vitamin D status is a marker of another variable, such as physical activity, and its association with bone health. Nevertheless, vitamin D supplementation in the range of 10–50 µg/day appears to be safe for children and remains a promising intervention that may yet be supported by clinical trials as a method to optimize pediatric health. **Key Message:** Pediatric vitamin D status is associated with avoidance of rickets. Randomized, controlled trials of vitamin D supplementation for pediatric bone health are limited and equivocal in their results. Beyond bone, decreased risk for autoimmune, infectious, and allergic diseases has been associated with higher vitamin D status. The specific vitamin D supplementation to optimize toddler, child, and adolescent outcomes is unknown, but doses 10–50 µg/day are safe and may be beneficial.

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Introduction

Vitamin D deficiency rickets was a disease pervasive in children during the Industrial Revolution and prevented with one spoonful of cod liver oil. The disease dissipated in the pediatric population with improved living conditions, including sunlight exposure, and the addition of vitamin D fortification to food products. Through the 20th century, only a small number of studies investigated the vitamin D supplementation required to maintain health in general populations. Lack of attention to vitamin D health status is evident by the 1989 United States Institute of Medicine (IOM) report which recommended 5 µg/day (200 IU/day) for adults because this represented half the dose recommended to infants and was considered a “generous allowance” of supplementation [1]. The 10 µg/day dose recommended to infants was based on the amount of vitamin D in a spoonful of cod liver oil that prevented rickets and demonstrated how the scientific understanding of vitamin D physiology remained limited even in 1989.

However, in the 1990s, a resurgence in infant vitamin D deficiency rickets was described worldwide. These cases occurred in various populations but concentrated in those with less exposure to sunlight (i.e., high latitude especially in winter months), those with darker skin pigmentation, or those practicing complete covering of women and were often associated with breastfeeding. Despite this small but significant rise in prevalence, the IOM in 1997 decreased their recommendation of vitamin D supplementation from 10 to 5 µg/day due to studies demonstrating that this dose provided adequate vitamin D to achieve a 25-hydroxyvitamin D (25[OH]D) status of 27.5 nmol/L (11 ng/mL), which was thought to prevent rickets in “most” populations [1]. Remarkably, despite increasing reports of rickets, the American Academy of Pediatrics (AAP) chose to uphold the 1997 IOM recommendation and decreased their recommendation from 400 to 200 IU/day for all infants, children, and adolescents [2].

Therefore, the early 21st century marked a period of discord in vitamin D public health; as reports of disease escalated, public policy paradoxically decreased the recommended supplementation, and, finally, research in adult populations launched the identification of the vitamin D status, 25(OH)D status, associated with optimal health outcomes. These investigations into the vitamin D status needed to optimize vitamin D function were greatly needed because the previous recommended 25(OH)D concentration of 27.5 nmol/L (11 ng/mL) was based on an observational study of 25(OH)D status in 3 adult cohorts. The vitamin D status in a cohort of “healthy” adult volunteers was compared to status in a cohort of lifeguards (high sunlight exposure) and to status

in a cohort of subjects with biliary cirrhosis who were assumed to have difficulty with conversion of vitamin D to 25(OH)D in the liver. From these measurements, a bell curve of 25(OH)D status was developed with the status of lifeguards deemed the highest of “normal,” the healthy volunteers deemed “normal,” and the biliary cirrhosis patients deemed “low” [3]. This study and others ignored the potential issue that “healthy volunteers” were exhibiting insufficient or deficient vitamin D.

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In the early 21st century, several investigators challenged this existing definition of normal when they performed studies to identify the vitamin D status required to optimize intestinal calcium absorption, to appropriately lower parathyroid hormone (PTH) concentration, and to optimize bone mineralization [4–6]. In these studies of vitamin D function in the adult population, results pointed to 75–100 nmol/L as the lower limit of vitamin D sufficiency for adult calcium homeostasis and bone health. These studies and others led to new public health recommendations that include not only a definition of vitamin D deficiency but also a definition of vitamin D sufficiency (Table 1) [7–11]. In 2008, the AAP reevaluated its 2003 statement and chose to increase to a recommendation of at least 400 IU/day for all infants, children, and adolescents [9].

Additionally, in the early 21st century, there were reports of vitamin D’s potential role in disease processes not related to calcium homeostasis and bone health. Many organs have 25(OH)D receptors which bind 25(OH)D. Instead of relying on the renal production of 1,25-dihydroxyvitamin D (1,25[OH]₂D) from 25(OH)D, these organs form 1,25(OH)₂D locally in a paracrine fashion (Fig. 1). Therefore, these organs depend on the availability of vitamin D and its transformation to 25(OH)D by the liver to provide circulating 25(OH)D. Disease processes in adults found to have an association with vitamin D status include cancer, specifically breast, colon, and prostate; heart

Table 1. Public health recommendations for vitamin D status [7–11]

Organization	Deficiency, nmol/L 25(OH)D	Sufficiency, nmol/L 25(OH)D
Institute of Medicine [7]	<30	>50
American Academy of Pediatrics [9]	<50	
Endocrine Society [10]	<50	>75
European Society for Paediatric Gastroenterology, Hepatology and Nutrition [8]	<25 severe deficiency	>50
European Calcified Tissue Society [11]	<25 severe deficiency <50 deficiency	>50

disease; autoimmune disease, specifically diabetes, rheumatoid arthritis, and systemic lupus erythematosus; infectious disease, specifically influenza and tuberculosis; and allergic disease [12]. Not all associations have been substantiated by further investigation such as trials of vitamin D supplementation. However, they have led to exploration of similar associations in children and adolescents, which thereby are considerations in vitamin D supplementation to these age groups.

Specifically, for toddlers, children, and adolescents, the significance of vitamin D supplementation in bone health is of paramount importance during this critical time of skeletal development. Especially in lower-resource countries where calcium deficiency also is widespread, supplementation of both nutrients is required to avoid bone disease. Additionally, determining the evidence regarding the role of vitamin D in autoimmune, allergic, and infectious disease is critical to ensure disease risk is minimized for all children.

Prevalence of Vitamin D Deficiency and Insufficiency

Studies vary in reports of vitamin D deficiency and insufficiency worldwide. A snapshot of large population studies is provided in Table 2 to demonstrate the trends through the years, differences and similarities between countries, and variation between age groups. Studies performed in Asia demonstrate a higher prevalence of vitamin D deficiency compared to those in Europe, North America, and New Zealand [13–22]. However, one Western population observed to have a higher prevalence are adolescents in the Public Health England database where 20% of boys 11–18 years old and 24% of girls 11–18 years old demonstrated a 25(OH)D level <25 nmol/L [18]. In fact, though infants are at risk for disease such as vitamin D-associated rickets worldwide, many population studies in higher-resource countries demonstrate lower vitamin D

Fig. 1. Production of active vitamin D in humans.

status in adolescents compared to toddlers [15, 16, 18], while studies in lower-resource countries show the expected higher vitamin D deficiency prevalence for infants/toddlers especially when breastfeeding [21]. Dark skin color, measured by race, ethnicity, or skin pigmentation, is a risk factor for deficient vitamin D [13, 15, 19, 22]. In countries where milk and/or juice are fortified with vitamin D, lower or no intake of these products is associated with higher risk for deficiency, which supports fortification as a method to improve child vitamin D status [13, 15, 19].

Other populations at increased risk for vitamin D deficiency include immigrant/refugee children moving to higher-latitude countries [23, 24], children with chronic disease that decreases fat absorption, children receiving anti-epileptic medications, and obese children [25–27]. For children with diseases with impaired fat absorption, such as cystic fibrosis, higher supplementation of this fat-soluble vitamin likely is required [25]. For children on anti-epileptic medications, these medications are known to upregulate enzymes involved in

Table 2. Prevalence and risk factors for vitamin D deficiency in pediatric (non-infant) populations worldwide

Study	Population	Vitamin D deficiency prevalence (25[OH]D)	Identified risk factors for deficiency
Gordon et al. [13], 2004	307 adolescents (11–18 years old) in Boston, MA, USA	≤20 nmol/L: 4.6% ≤37.5 nmol/L: 24.1% ≤50 nmol/L: 42%	Season, ethnicity, low milk and juice consumption, low body mass index, low physical activity
Marwaha et al. [14], 2005	5,137 10- to 18-year-olds in New Delhi, India	<22.5 nmol/L: 35.7%	Lower socioeconomic school, female
Kumar et al. [15], 2009	6,275 children 1–21 years old in USA, 2001–2004	<37.5 nmol/L: 9% <72.5 nmol/L: 70%	Older, female, non-Hispanic black, Mexican-American, obese, milk < once/week, >4 h screen time
Rabenberg et al. [16], 2018	10,015 children 1–17 years old in Germany, 2003–2006	<30 nmol/L: 12.5% in both boys and girls 30 to <50 nmol/L: 32.7% in boys and 33.5% in girls	Highest prevalence of deficiency in girls 11–13 years old (18.9%) and lowest prevalence of deficiency in boys 1–2 years old (4.9%)
Foo et al. [17], 2009	301 adolescents (15-year-old girls) in Beijing, China, 2004	<25 nmol/L: 31.2% ≤50 nmol/L: 57.8%	Not provided
Public Health England, National Diet and Nutrition Survey [18], 2014	902 children in the United Kingdom, 2008–2011	<25 nmol/L: 8% of children 1.5–3 years old, 12% of boys 4–10 years old, 16% of girls 4–10 years old, 20% of boys 11–18 years old, 24% of girls 11–18 years old	Not provided
Maguire et al. [19], 2013	1,898 children (1–5 years old) in Toronto, ON, Canada	<50 nmol/L: 6% <75 nmol/L: 35%	No vitamin D supplement, no cow's milk intake, winter season, dark skin pigmentation
Garg et al. [20], 2014	1,829 adolescents in New Delhi, India	<12.5 nmol/L: 28% <25 nmol/L: 71% <50 nmol/L: 97%	Not provided
Angurana et al. [21], 2014	388 children (3 months to 12 years) in Chandigarh, India	<50 nmol/L: 40% <75 nmol/L: 66%	Younger age, female, failure to thrive, exclusive breastfeeding, inadequate sun exposure, and no vitamin D supplements
Cairncross et al. [22], 2017	1,329 children (2 to <5 years) in New Zealand	<25 nmol/L: 7% <50 nmol/L: 48% <75 nmol/L: 89%	Female gender, other non-European ethnicities (not including Māori or Pacific), had olive-dark skin color, no vitamin D supplements, mothers with less than secondary school qualifications, and lived in more deprived households

25(OH)D, 25-hydroxyvitamin D.

vitamin D metabolite inactivation. Therefore, higher supplementation is also a consideration in this population [26].

For obese children, a significant inverse association between vitamin D status and overweight status was identified as early as 15–23 months of age [28]. Due to this association, increased vitamin D supplementation often is recommended in the presence of overweight or obesity. Also, an additional benefit for achieving vitamin D sufficiency may be improved carbohydrate and lipid metabolism [27].

A potential risk factor for vitamin D deficiency that is often associated with obesity and requires further study is low physical activity [13]. Since physical activity in children commonly occurs with sunlight exposure, physical activity may be a surrogate for sunlight exposure and, therefore, indirectly associated with vitamin D status. On the other hand, physical activity may confound studies of vitamin D sufficiency due to physical activity's positive association with bone health. In this scenario, increased physical activity would be associated with

increased sun exposure and, thereby, increased vitamin D status. This raises the theory that vitamin D status may serve as a marker of physical activity instead of serving as a cause of improved bone health. With persistent questions regarding the vitamin D supplementation that provides optimal bone health, these potential causal relationships warrant contemplation and investigation [29–32].

Vitamin D in Pediatric Bone Health

The primary function of vitamin D is to maintain calcium homeostasis and bone health. The most severe form of vitamin D-associated bone disease is rickets. Rickets occurs when hypocalcemia and/or hypophosphatemia affect development of the epiphyseal growth plate and is most common in infancy. Signs and symptoms associated with rickets include skeletal findings of leg bowing, knock knees, rachitic rosary, and nonskeletal findings, such as muscle weakness, seizures, tetany, and cardiomyopathy. These signs and symptoms, especially the radiographic finding of cupping, fraying, and splaying of metaphyses near the epiphyseal growth plate, are diagnostic of rickets.

Muscle weakness or muscular pain often are described in relation to vitamin D deficiency-associated bone disease [11, 29, 30]. In fact, perhaps rickets and osteomalacia should be described as musculoskeletal rather than only skeletal diseases. Osteomalacia is a disease of hypomineralization that may or may not have the pathognomonic cupping of the metaphyses. Osteomalacia occurs when the osteoblasts develop the osteoid but with inadequate mineral deposition due to deficiency in calcium and/or phosphorus. If this disease of demineralized bone does not affect the epiphyseal growth plate either due to lower severity or to the phase of bone growth, then rickets is not diagnosed by radiograph. However, significant skeletal disease may have occurred. This is of special concern in childhood because of the high rate of bone growth. Ninety percent of adult bone mineralization is accrued by the end of adolescence. Furthermore, vitamin D status in adolescence may be paramount because 40% of adult bone mineralization occurs within this time of peak bone growth velocity [29, 33].

Therefore, with the relatively high prevalence of vitamin D deficiency described in the pediatric population and the known importance of calcium in bone mineralization during this critical time of growth, evaluation of bone outcomes with vitamin D supplementation is of paramount importance. Randomized, controlled trials of vitamin D supplementation to optimize bone health have been performed in adolescents and mostly in females (Table 3) [34–42]. Two meta-analyses

of 6 of the randomized, controlled trials were published in 2010 and 2011 by the same authors in 2 different journals [43, 44]. Both meta-analyses concluded that vitamin D supplementation demonstrated no significant effect on total body bone mineral content (BMC) or bone mineral density of the hip or forearm [43, 44]. The 4 randomized, controlled trials in children, published after the meta-analyses were performed, demonstrate a range of results. The results of one study showed no significant effect of vitamin D supplementation [42]. In a second study, total body and lumbar spine BMC were improved with vitamin D supplementation in a subgroup of girls who were <2 years past menarche [40]. In a third study, girls exhibited significantly improved bone density especially in measures of bone parameters in the hip, but boys did not [39]. In a fourth study, whole body BMC and density were increased not in the whole group but in a subgroup of children expressing the FF vitamin D receptor genotype [41]. These studies raise the importance of the need for a further understanding of vitamin D physiology so that vitamin D supplementation trials are performed in the populations of greatest need either due to baseline vitamin D deficiency, sex, age, and stage of bone development or genetic predisposition to higher vitamin D needs for healthy bone development. Of the studies showing benefit of supplementation, the supplementation was given as either 5–10 µg/day or 35–350 µg/week of vitamin D₃. With the low risk of toxicity with these vitamin D doses, at least these amounts of supplementation may be of benefit and have very low risk of harm. However, despite conduction of 10 randomized, controlled trials in adolescent girls, the definitive amount of vitamin D supplementation associated with optimal bone mineralization remains unknown, and less is known regarding boys' needs.

Even fewer studies of high-level evidence have been performed in the toddler and younger child populations. Instead of supplementation trials, evaluation of the vitamin D status associated with bone health provides the available evidence. For example, in a large study in Korea, 429 boys 10–14 years of age demonstrated a significant association between vitamin D status and bone mineralization at the femoral neck, hip, and lumbar spine. Girls aged 10–13 years only demonstrated a significant association at the lumbar spine. In the larger population of this study, including older adolescents and adults up to 29 years, bone mineralization appeared to have a non-linear association with vitamin D status with optimal bone outcomes with 25(OH)D >53 nmol/L [45].

Other studies have evaluated PTH concentrations as a direct marker of body calcium homeostasis and as an indirect marker of bone health. In observational studies, a linear correlation between 25(OH)D and PTH often is significant and with a correlation coefficient of –0.2 to –0.3 [13, 14]. When

Table 3. Randomized controlled trials of vitamin D supplementation to adolescents

Study	Population	Intervention	Bone outcome measurements
Andersen et al. [34], 2008	26 female Pakistani immigrants to Denmark at 10.1–14.7 years old	Vitamin D ₃ 10 or 20 µg/day for 12 months compared to placebo	DXA measurements of the whole body and lumbar spine
Cheng et al. [35], 2005	195 girls 10–12 years old in Finland with <900 mg daily calcium intake	Calcium and 5 µg/day vitamin D ₃ or calcium or cheese or placebo for 2 years	Whole body DXA with indexes at the hip, spine, and peripheral quantitative computed tomography of the radius and tibia
Du et al. [36], 2004	757 girls at 10 years of age in Beijing, China	Calcium-fortified milk and 5 µg/day vitamin D ₃ or calcium-fortified milk and 8 µg/day vitamin D or placebo	DXA of the distal and proximal forearm of the nondominant arm and the whole body
El-Hajj Fuleihan et al. [37], 2006	179 girls at 10–17 years old in Beirut, Lebanon	Vitamin D ₃ 35 or 350 µg/week or placebo for 1 year	DXA of lumbar spine, hip, forearm, and total body
Viljakainen et al. [38], 2006	228 adolescent girls with adequate calcium intake in Helsinki, Finland	Vitamin D ₃ 5 or 10 µg/day or placebo for 1 year	DXA of lumbar spine and femur
Al-Shaar et al. [39], 2013	167 girls at a mean of 13.1 years and 171 boys at a mean of 12.7 years in Beirut, Lebanon	Vitamin D ₃ 35 or 350 µg/week or placebo for 1 year	DXA of full body and hip images with hip structural analysis (HSA) software
Khadilkar et al. [40], 2010	50 postmenarchal girls at 14–15 years old in Pune, India	Vitamin D ₂ 7,500 µg 4 times/year (quarterly) or placebo for 1 year	DXA of full body and lumbar spine
Mølgaard et al. [41], 2010	221 girls 11–12 years old in Denmark	Vitamin D ₃ 5 or 10 µg/day or placebo	DXA of full body and lumbar spine
Ward et al. [42], 2010	73 postmenarchal girls 12–14 years old	Vitamin D ₂ 3,750 µg 4 times/year (quarterly) or placebo	DXA of lumbar spine and peripheral quantitative computed tomography of nondominant radius and tibia
One µg vitamin D is 40 IU vitamin D. DXA, dual energy X-ray absorptiometry.			

examining 25(OH)D status and PTH status with nonlinear or multi-linear statistical approaches, an inflection point, a 25(OH)D value below which PTH decreases with increasing 25(OH)D concentration and above which PTH plateaus despite rising 25(OH)D, may be identified. This inflection point is hypothesized to be the 25(OH)D limit associated with PTH stability and, therefore, calcium homeostasis. In a sample of children aged 6–10 years, a 25(OH)D status above 75 nmol/L was associated with a plateau in PTH concentration, and a 25(OH)D status below 50 nmol/L was associated with a significant rise in PTH [46]. A study of children aged 12–22 months identified an inflection point of 60–65 nmol/L 25(OH)D [47]. In an evaluation of 214 children of whom 17 were diagnosed with rickets, an inflection point was evident at 34 nmol/L [48]. Yet, this inverse association or identification of an inflection point is not universally found in studies comparing 25(OH)D and PTH status. Consequently, further investigation is needed. Similarly, studies of an association between vitamin

D status and other markers of calcium homeostasis and/or bone health have yielded equivocal results. Researchers in this area are working to identify a compilation of serum measurements that would predict the development of osteomalacia, but these tests require validation [49].

Another area of potential consequence of hypovitaminosis D in pediatric bone health is the risk for fracture. One cross-sectional study and 2 case-controls have examined this potential association of vitamin D deficiency and increased risk for fracture in children [50–52]. In a cross-sectional study of 10- to 16-year-old children, those with upper limb fracture, lower limb fracture, and no fracture demonstrated no significant difference in 25(OH)D status [50]. In a case-control study of 5- to 9-year-old African American children, compared to the 74 controls, the 76 cases exhibited 3.64 (95% CI 1.09–10.94) higher odds of vitamin D deficiency [51]. However, in a second case-control study in Canada of children <6 years of age, compared to the 343 controls, the 206 cases had no dif-

ferences in vitamin D status or intake of cow's milk. Yet, use of vitamin D supplementation was associated with decreased odds of fracture (adjusted odds ratio of 0.42 [95% CI 0.25–0.69]) [52].

Another approach to evaluate the relationship between vitamin D deficiency and fractures was published recently. In this study of children under 2 years of age who were admitted with fractures, 11 of 79 demonstrated hypomineralization on skeletal survey. For every 10-point increase in vitamin D status, the adjusted odds of hypomineralization were reduced 0.3 (95% CI 0.17–0.82) [53]. This limited data of the association of vitamin D, osteomalacia, and fracture risk requires further exploration especially for populations at higher risk for vitamin D deficiency.

Expedient exploration of this relationship is crucial due to considerable debate in the literature as to whether fractures due to osteomalacia/rickets can be differentiated from fractures due to nonaccidental trauma by X-ray or laboratory markers [54–57]. Currently, published literature points to the consideration of bone biopsy as a method to detect hypomineralization disease versus child abuse. Further investigation to reliably differentiate the cause of fractures will provide further knowledge regarding osteomalacia and how this disease affects bone strength and development.

Vitamin D in Non-Bone-Related Disease

As in the adult population, in children, vitamin D has actions in health beyond calcium homeostasis and bone development. Greater detail regarding non-bone-related effects of vitamin D is provided in a separate article in this issue, but these potential effects are important to mention as they do affect recommendations for vitamin D supplementation. The role of vitamin D in both protection from development of type I diabetes mellitus and in improved glucose tolerance has been described with meta-analyses of vitamin D supplementation of observational trials [58]. Further randomized, controlled trials and investigation as to whether vitamin D improves β -cell function directly or through its beneficial effect on immune function are warranted. Children with allergic disease, especially asthma and atopic dermatitis, experience decreased exacerbations with vitamin D supplementation [31, 59, 60]. Infectious diseases with high incidence in childhood, such as otitis media, urinary tract infection, pneumonia, influenza, and other acute respiratory infections, all have a number of investigations demonstrating decreased incidence with higher vitamin D status [12]. Several randomized, controlled trials of vitamin D supplementation to prevent infections have been performed with equivocal results [12, 61, 62]. Therefore,

these roles of vitamin D in health promotion warrant consideration but require further study before definitive supplementation recommendations.

Children with allergic disease, especially asthma and atopic dermatitis, experience decreased exacerbations with vitamin D supplementation

Recommendations for Vitamin D Status

Several international and national guidelines for categorization of vitamin D status are presented in Table 1. Of note, only 2 recommendations are specifically for children. Circulating 25(OH)D is the best indicator of nutritional vitamin D status due to its half-life of 2–3 weeks and to its mechanism of action in numerous organ systems. Nonetheless, 25(OH)D status does not consistently increase as expected with vitamin D dosing, which has raised the question as to what further considerations should be taken in the identification of healthy or unhealthy vitamin D status. For example, antibody-based methods of 25(OH)D that are readily available for use in various settings demonstrate less reproducibility when compared to liquid chromatography-mass spectroscopy (LCMS). On the other hand, LCMS is not universally available, and excellent antibody-based methods do exist [63]. Other issues in the analysis of 25(OH)D status include the potential that free 25(OH)D is a more important measurement than total 25(OH)D due to population variation in vitamin D-binding protein affinities. Lastly, individual variation in response to vitamin D supplementation may be due to genetic differences in the vitamin D receptor [64]. Until these issues are elucidated, the interpretation of vitamin D study results remains with some uncertainty. In fact, the European Calcified Tissue Society has called for standardization of testing for all research of vitamin D status to improve consistency [11]. In the clinical setting, no guidelines are available to recommend specific vitamin D status screening in routine pediatric care partly because of this ambiguity in 25(OH)D test results [7, 65, 66]. Therefore, emphasis should be placed on providing the vitamin D supplementation to optimize health and to avoid toxicity for all children without the need for individual screening.

Recommended Vitamin D Intake for Toddlers, Children, and Adolescents

In 2008, in response to the growing evidence of vitamin D deficiency in children, the AAP recommended at least 10 µg/day vitamin D for all children [9]. In 2010, the IOM recommended at least 15 µg/day for children over 1 year of age [7]. In Europe, ESPGHAN recommended 10 µg/day for infants but chose not to provide recommendations for older children. Instead, they endorsed the European Food Safety Authority's upper limit of recommended intake of 25 µg/day for infants, 50 µg/day for children 1–10 years, and 100 µg/day for children 11–17 years [8]. Recently, new recommendations in Europe, and specifically in Germany, have continued to emphasize the need for vitamin D supplementation to infants, have added recommendations for pregnant women, but have decreased the recommendations for older children and adolescents due to the equivocal results of randomized, controlled trials of vitamin D supplementation and due to the difficulties in interpretation of vitamin D status [11, 31]. Of note, the higher risk for vitamin D deficiency in non-Western or immigrant populations of Europe remains a concern with recommendation to consider 10 µg/day supplementation [11].

Recommendation for supplementation to children aged 1–3 years is quite varied in these new recommendations. These children, especially if not receiving fortified food products, remain at risk for inadequate bone mineralization. They also are a population found to have persistently low vitamin D intake despite existing recommendations. In France, in children who received vitamin D from food sources and supplementation, 10% of infants 30–35 months of age still received less than the recommended intake [67]. In the USA, despite attention to vitamin D supplementation in the last 2 decades, a greater number of children 0–47.9 months of age received less than the recommended supplementation in 2016 compared to 2002 [68]. In the United Kingdom, just over half of parents reported receiving information regarding vitamin D supplementation for their infant and 80% described that they found the information lacking adequate details [69]. Therefore, for toddlers and children, not only are the recommendations varied, but so are vitamin D intake and parental knowledge regarding child vitamin D needs.

When contemplating the appropriate intake of vitamin D, the potential for toxicity must be considered. Though the 25(OH)D concentration at which harm occurs is likely well above the therapeutic range, intoxication due to misadministration or accidental ingestion is reported to occur with doses of 6,000–112,500 µg and result in severe hypercalcemia. The literature contains one case report of vitamin D intoxication

in a 7-month-old receiving 35–40 µg/day [70]. Therefore, overdose is a rare but potential risk. Parental education regarding safe administration is required.

Conclusion

As the amount of research investigating the vitamin D needs of toddlers, children, and adolescents has grown, unfortunately, the answer has become less clear. Vitamin D-deficient rickets is a disease with severe morbidity that responds well to vitamin D repletion. This disease is most common in infants but can be observed in children especially in resource-limited countries. Osteomalacia, or bone hypomineralization not of the magnitude of rickets, is more difficult to diagnose and, therefore, study of its response to vitamin D supplementation is challenging. Observational studies in pediatrics point to at least 10 µg/day vitamin D supplementation to achieve optimal bone health, but results of randomized, controlled trials have been ambiguous. Vitamin D has been found to play a significant role in immune function and especially in autoimmune, infectious, and allergic disease, but again trials of vitamin D supplementation have been equivocal. Due to these study results and other issues, national and international guidelines are being modified to reflect this uncertainty and provide less directive regarding vitamin D supplementation after infancy. Attention to standard 25(OH)D concentration measurement and investigation of genetic or other individual variations in vitamin D metabolism hopefully will identify the cause of these discrepancies in research results. Until then, with the potential benefits and low risk of vitamin D supplementation of 10–50 µg/day for children, some physicians and public health leaders may elect to recommend these doses until further information is known.

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Author Contributions

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