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Vitamin D: From Gestation to Adolescence in Health and Disease

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Editorial

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Vitamin D

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The editorial role for this issue of *Annales Nestlé* was initially assumed by Dr. Jatinder Bhatia. For unforeseen reasons, he was not able to complete this work. His friends at the Nestlé Nutrition Institute and the Institute's Faculty members would like to dedicate this issue to him. We look forward to his continued support and valuable contributions to the activities of the Nestlé Nutrition Institute.

In the mid-1600s, two authors independently published in Latin a description of rickets. In 1840, Sniadecki, a Polish physician, observed that cases of rickets occurred in children living in the industrial center of Warsaw, while they did not occur among those living in the country outside Warsaw. He hypothesized that lack of exposure to sunlight in the cramped city streets, with considerable pollution due to the burning of wood and coal, was the cause of the disease. However, the concept that the sun could have any useful benefit on the skeleton was not well accepted at that time. Since then, much has been learned about vitamin D. Undoubtedly, vitamin D plays a fundamental role in the development and maintenance of the musculoskeletal system. But its function goes well beyond hormone-like regulation, as it can also be generated by simple unicellular organisms.

Vitamin D is a prohormone absorbed from food sources or supplements and also synthesized in the skin following exposure to ultraviolet light. The prohormone subsequently is converted to the metabolically active form in the liver and then the kidneys. Few foods naturally contain vitamin D. The principal food sources of vitamin D are fish that are oil rich, such as salmon, mackerel, and herring, as well as organ meats, liver, and egg yolk. However, how much and how frequently do most children consume these natural dietary sources of vitamin D? In humans, dermal synthesis is the major natural source of the vitamin. Individuals who do not have sufficient sun exposure, especially infants, require supplemental vitamin D from fortified foods or supplements. Vitamin D deficiency is frequent in children and adults and leads to serious health problems worldwide. In recent years, vitamin D has notably attracted scholars' attention because of its influences on cell growth and differentiation, immune and cardiovascular function, as well as calcium and phosphate homeostasis [1].

In this issue, firstly, Carol L. Wagner and Bruce W. Hollis discuss the early-life effects of vitamin D in their article "Early-Life Effects of Vitamin D: A Focus on Pregnancy and Lactation." They describe that the active form of vitamin D – 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) – increases during pregnancy and remains elevated throughout, and unlike at other times during the lifecycle, it is directly affected by the circulating 25-hydroxyvitamin D (25[OH]D) concentration. When a mother is vitamin D deficient, her milk is deficient, which can be remedied by direct infant supplementation; however, this treats only the infant. A safe alternative during lactation to infant supplementation is direct maternal vitamin D supplementation at higher doses than usual (6,400 IU/day), improving the vitamin D status of the mother and the content

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of the milk and, consequently, the vitamin D status of the infant, effectively treating both mother and infant.

In the second article, Steven A. Abrams discusses vitamin D needs in premature and full-term infants. He states that vitamin D is necessary for the active (transcellular) absorption of calcium and for skeletal health. Inadequate vitamin D in infants leads to increased risks of poor bone mineralization and ultimately rickets. Rickets is uncommon in full-term infants with a much higher risk in very premature infants. However, the primary cause of rickets in premature infants is a deficiency of calcium and phosphorus, not vitamin D. The usual total dietary intake level should be approximately 400 IU daily in healthy infants.

In the last article, Sarah N. Taylor writes about vitamin D in toddlers, preschool children, and adolescents. Childhood is a period of significant bone development and, therefore, attention to the vitamin D needed to optimize bone health in childhood is imperative. Observational studies have pointed to a vitamin D status, as indicated by a 25(OH)D concentration of 50 nmol/L, to ensure avoidance of rickets, and of 75 nmol/L to optimize health. Ongoing research is directed to the 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.

Aspects not addressed in the above-mentioned contributions will now be briefly discussed.

Vitamin D Deficiency in Obese Children

Another aspect of vitamin D are the requirements of obese and chronically ill children. Excessive fat accumulation and vitamin D insufficiency have negative effects on each other as a result of excessive metabolic processes and enzymatic disorders in a situation of decreased activity of the key enzyme in the biotransformation of calciferol, α-hydroxylase, in a fat-infiltrated liver [2]. This results in an accumulation of inactive forms and decreased bioavailability of vitamin D [3]. Vitamin D affects insulin secretion, tissue sensitivity to insulin, and systemic inflammation in obesity. Insulin secretion and tissue insulin sensitivity are Ca^{2+}-dependent mechanisms, and vitamin D regulates intracellular concentrations of Ca^{2+} and its passage through membranes. In addition, vitamin D affects in a positive manner the expression of insulin receptors in peripheral cells and counteracts the systemic immune response by modulating the expression and activity of cytokines [4]. The influence of adipose tissue on the metabolism of vitamin D, on the one hand, and its pathogenic role in the obesity development mechanisms, on the other, are closely interrelated and represent mutually dependent processes [2]. A study conducted in 58 obese adolescents demonstrated that a 1% increase in fat weight was associated with a 1.15 $\pm$ 0.55 nmol/L reduction in serum calcifediol (25[OH]D_3) [5]. There are several theories regarding why calcifediol levels are decreased in obese individuals. The first and most accepted is that adipose tissue absorbs the fat-soluble vitamin D [6]. Another theory explains the low 25(OH)D concentrations by the fact that obese people lead a sedentary lifestyle and are less active physically, which entails a decrease in exposure to sunlight and in endogenous synthesis of vitamin D [7]. Also, vitamin D metabolism and 25(OH)D synthesis could be impaired as a result of hepatic steatosis developing in obesity [8]. The prevalence of vitamin D insufficiency in groups of overweight and obese children is very high (36–93%) [1]. There is no conventional dose universally recommended for the treatment of vitamin D insufficiency in overweight and obese children. The Committee on Nutrition of the French Society of Pediatrics recommends administration of vitamin D in 80,000-IU single doses and 100,000-IU single doses in the winter months for obese children aged 5–10 years or uninterrupted supplementation over the age interval of 1–10 years [1]. The United States Endocrine Society recommends a 2-fold increase in the therapeutic dose of cholecalciferol for overweight and obese patients and setting the calcifediol target at 75 nmol/L (30 ng/mL), with subsequent switching to a maintenance dose.

Vitamin D Deficiency in Children with Chronic Kidney Disease

Deficiency of vitamin D is prevalent and frequently severe in children and adults with chronic kidney disease (CKD). 25(OH)D deficiency is linked causally to rickets and fractures in healthy children and more so in those with CKD, a contributing factor to the CKD–mineral and bone disorder complex [9]. There are few studies to provide evidence for vitamin D therapy or guidelines for its use in CKD. It has been suggested to use native vitamin D supplements for the treatment of vitamin D deficiency in children with CKD stages 2–5 who have serum 25(OH)D concentrations below 75 nmol/L. In children with CKD stages 2–3, native vitamin D supplements may be used for the prevention or treatment of secondary hyperparathyroidism. It has been suggested to use either vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) treatment in children with CKD stages 2–5D to increase serum 25(OH)D levels to the target range. Mega-dose vitamin D therapy is not recommended.

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Vitamin D Deficiency in Children with Chronic Liver Disease

The liver produces 25(OH)D (calcidiol), which is the immediate precursor to the metabolically active $1,25(OH)_2D$ (calcitriol). 25(OH)D is measured to assess vitamin D deficiency [10]. Although in patients with liver failure levels of calcidiol can be low due to impaired synthesis, liver function has to be severely compromised for this impairment to occur. Liver disease could also lead to impaired absorption of vitamin D, likely related to impaired bile acid production or intestinal edema secondary to portal hypertension. Hypovitaminosis D and bone disease are well-recognized complications of "cholestatic" liver disease, which impairs production or bile flow. Vitamin D deficiency is frequent in biliary atresia patients [11]. In their study, Dong et al. [11] also found that despite bile flow restitution after surgery, vitamin D deficiency was confirmed in the majority of biliary atresia patients.

Vitamin D in Children with Inflammatory Bowel Disease

Vitamin D deficiency is highly prevalent in children with inflammatory bowel disease (IBD), which may contribute to an increased risk of poor bone health as well as affect the course of the illness. An optimal treatment strategy of vitamin D therapy in children with IBD, however, has not yet been established. A recent review article [12] identified that some pediatric trials have shown that vitamin D deficiency may in part contribute to an increased risk of poor bone health, but others have reached contrasting conclusions. Recent studies have also focused on the relationship between vitamin D deficiency and disease severity in children with IBD. While some limited data suggest an association of vitamin D deficiency with a more severe course of disease, other studies do not report such a relationship. The authors of the above-cited review identified 277 discrete articles, but only 10 met the requirements to be included in their review. The included trials featured diverse treatment regimens that were predominantly insufficient in correcting vitamin D deficiency or maintaining adequate levels in children with IBD. Better treatment regimens are required for the management of vitamin D deficiency in children with IBD. The Institute of Medicine sustains that serum 25(OH)D levels above 30 ng/mL do not provide additional benefit [13]. However, other studies suggest that a level of at least 32 ng/mL is required for optimal intestinal calcium absorption. However, a level of 30 ng/mL has been found to be sufficient to reduce parathormone activity [14]. Based on the above, the goal for the serum 25(OH)D level should be at least 30 ng/mL for children with IBD. In one of the included studies, 2,000 IU vitamin D_3 daily raised serum 25(OH)D above 30 ng/mL in 74% of the participants after 6 months of treatment [15]. Another study showed a similar response after weekly dosing of 50,000 IU vitamin D_3 for 6 weeks [16]. In a third study, 2,000 IU vitamin D_3 daily was able to achieve a mean serum 25(OH)D above 30 ng/mL in the study population throughout the course of treatment [17]. Both 5,000 IU/10 kg vitamin D_3 per week and 10,000 IU/10 kg vitamin D_3 per week for a period of 6 weeks were able to raise serum 25(OH)D above 30 ng/mL at week 8 in one of the trials; however, this effect was lost by week 12 [18]. We sincerely hope that Dr. Bhatia will be satisfied with this issue of the *Annals*.

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Focus

Vitamin D is a critical nutrient for bone health and needs to be provided to all infants whether via infant formula or as a supplement to breastfed infants or high-dose supplement to their mothers

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Vitamin D in Preterm and Full-Term Infants

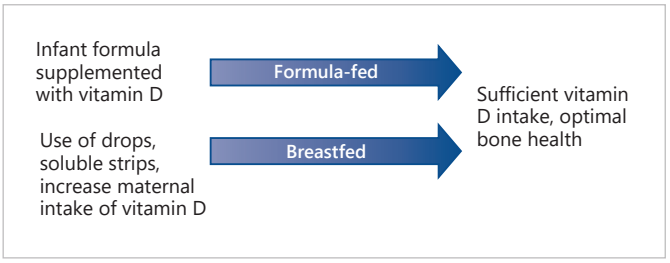
Steven A. Abrams

Key Insight

Vitamin D is essential for transcellular absorption of calcium and for skeletal health. Inadequate vitamin D in infants leads to poor bone mineralization and increased risk of rickets. Most guidelines recommend 400 IU daily of vitamin D to support bone health in preterm and full-term infants. Although cutaneous production of vitamin D occurs in infants, the use of sunblock and other factors limiting sun exposure make this an unreliable source. Therefore, recommendations for vitamin D intake are made assuming minimal or nonexistent cutaneous production of vitamin D. Not surprisingly, neonatal vitamin D status reflects maternal status. This knowledge has prompted current guidelines to recommend that vitamin D supplementation for infants is initiated as soon as possible.

Current knowledge

In the first weeks of life, calcium absorption occurs mainly via paracellular mechanisms that are not dependent on vitamin D. In preterm infants, absorption of vitamin D may be affected by various disease states, including malabsorptive disorders, such as cystic fibrosis. Cholestasis is another common problem in high-risk neonates and is associated with long-term use of parenteral nutrition. These highlight the importance of identifying the populations of mothers and infants who are at risk in order to ensure adequate vitamin D intake. Caution should be taken to ensure that the appropriate dose is given and that accidental ingestion of high doses of vitamin D does not occur.



Ensuring adequate vitamin D intake is essential for all infants, regardless of whether they are formula fed or breastfed.

Practical implications

Currently, there is no clinical evidence to support the need for routine vitamin D supplementation for infants who are exclusively formula fed. In fully or partially breastfed infants, there are several methods for providing vitamin D. One is to administer the drops to the infant using a dropper. Vitamin D drops can also be placed directly on the breast or given as dissolvable film strips. Another approach is to have the lactating mother take a relatively high dose of vitamin D (6,400 IU daily) to ensure an adequate level of vitamin D in the breast milk. However, adherence to guidelines varies widely between countries, highlighting the need for education for healthcare providers and families on the importance of providing sufficient vitamin D to infants.

Recommended reading

Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: A roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018 Oct;1430(1):44–79.

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Vitamin D

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Vitamin D in Preterm and Full-Term Infants

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Key Messages

- Dietary vitamin D intake should be assured in all infants, preterm and full term, with emphasis on adequate supplementation of infants who are receiving human milk.
- Usual total dietary intake level should be approximately 400 IU daily in healthy infants.
- There are multiple methods for providing vitamin D to infants; these may be selected based on parental desires.

Keywords

Bone health · Calcium absorption · Vitamins

Abstract

Vitamin D is necessary for the active (transcellular) absorption of calcium and for skeletal health. Inadequate vitamin D in infants leads to increased risks of poor bone mineralization and ultimately rickets. Rickets is uncommon in full-term infants with a much higher risk in very premature infants. However, the primary cause of rickets in premature infants is a deficiency of calcium and phosphorus, not vitamin D. Available research, as well as most guidelines, recommend an intake of 400 IU daily of vitamin D as adequate for bone health in preterm and full-term infants. Higher doses have not been consistently shown to have specific clinical benefits for healthy infants. There are no strong data to support either routine testing of serum 25-hydroxyvitamin D or targeting high serum 25-hydroxyvitamin D levels (e.g., 30 ng/mL) in healthy preterm or full-term infants. Vitamin D is commonly provided to infants via drops for breastfed babies or via infant formula, although alternative dosing approaches exist for breastfed infants, which some families may prefer. These include the use of drops placed on the mother's breast, dissolvable doses, and high maternal doses (approximately 6,400 IU daily). Infant formula contains vitamin D, and most infants will reach an intake from formula of about 400 IU daily within the first 2 months of life if they are consuming routine cow milk-based formula. Although vitamin D toxicity is very uncommon, caution should be used to avoid extremely concentrated high doses found in some commercially available drops. Infants with liver or kidney disease may need special attention to vitamin D intake and status. Further research is needed to define the role of vitamin D in non-bone health outcomes of infants and to identify methods to enhance compliance with current recommendations for vitamin D intake in infants.

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Vitamin D Physiology and Bone Health in Infants

Vitamin D is an essential nutrient for bone health in all individuals, including infants regardless of size or gestational maturity. Although other roles for vitamin D in health and disease exist, this discussion will focus on bone health, especially bone health in infants who do not have underlying endocrine disorders or severe nutritional diseases.

Vitamin D is critical for the transcellular absorption of calcium, via its active form, 1,25 dihydroxyvitamin D. Dietary vitamin D or vitamin D formed via solar exposure is converted in the liver to the circulating and primary storage, 25-hydroxyvitamin D (25[OH]D). The 25(OH)D is then transferred to the kidney where it is converted to 1,25 dihydroxyvitamin D. These physiological processes function normally in preterm and full-term infants who are otherwise healthy. A detailed review of vitamin D-related physiology can be found elsewhere [1].

Serum 25(OH)D in Infants

The role of serum 25(OH)D as a marker of vitamin D status has been extensively reviewed and discussed in a 2011 Institute of Medicine (IOM) report [2]. There are no recommendations either in that report or in any official American Academy of Pediatrics (AAP) statement for routine screening of 25(OH)D level in healthy preterm or full-term infants [2–7]. It is critical to understand that 25(OH)D is not necessarily a marker of physiological vitamin D function as it is not the primary active form of vitamin D. Rather, its concentration in the serum is valuable as a means of assessing individual and population vitamin D status. Different values for serum 25(OH)D have been described as "inadequate" or "deficient" in the literature. However, the adequate serum level indicated by the IOM and subsequently affirmed by the AAP of at least 20 ng/mL is the value that may be used for infants, both preterm and full term [2–6], pending further information clearly documenting non-bone health-related benefits to higher minimum levels. There are no data reliably establishing a value of 25(OH)D that is toxic, especially in infants. Values of >100 ng/mL have been used to indicate toxicity without good clinical correlation of this or any specific toxic 25(OH)D level [7]. Nonetheless, uncommonly, vitamin D toxicity associated with hypercalcemia can exist in infants and may cause significant illness.

Values of serum 25(OH)D in the range often considered "inadequate" (12–20 ng/mL) are not generally associated with clinical evidence of vitamin D deficiency causing inadequate calcium absorption or rickets in infants. Vitamin D-deficient rickets is commonly seen with values of serum 25(OH)D below 12 ng/mL, although this is dependent on calcium intake as well as vitamin D status. In adults, data have suggested that values of 12–20 ng/mL are associated with normal efficiency of vitamin D-dependent calcium absorption, but data in infants are very limited as such studies are difficult to perform [2, 8]. In older children, values above about 12 ng/mL are associated with adequate calcium absorption, although there is a small, likely clinically insignificant, benefit to calcium absorption associated with increasing values [9].

In considering rickets, it is the relationship between vitamin D and calcium intake and status, as well as the status of other minerals, especially phosphorus and magnesium, which are crucial for the development of rickets. Because of this central role of mineral deficiency, rickets is not accurately described as being entirely a disease of vitamin D deficiency in any group of infants, especially preterm ones. Furthermore, some rare disease states in which vitamin D function is not present are relatively effectively treated with high doses of oral calcium [10].

It is the relationship between vitamin D and calcium intake and status, as well as the status of other minerals, especially phosphorus and magnesium, which are crucial for the development of rickets

Vitamin D Intake and Function

The relationship between dietary intake of vitamin D and serum 25(OH)D levels has been evaluated both in preterm and full-term infants for many years. There are far fewer data relating 25(OH)D levels and bone mineral content or density in preterm infants or even fracture rates in these infants. Some data suggest a possible benefit for higher 25(OH)D levels on bone mineralization but need confirmation in larger trials and correlation with clinical events and outcomes [11–13]. There are no data indicating that doses of vitamin D of 400 IU daily, or serum 25(OH)D achieved with those doses, are associated with an increased risk of rickets or fractures in any population of preterm or full-term infants.

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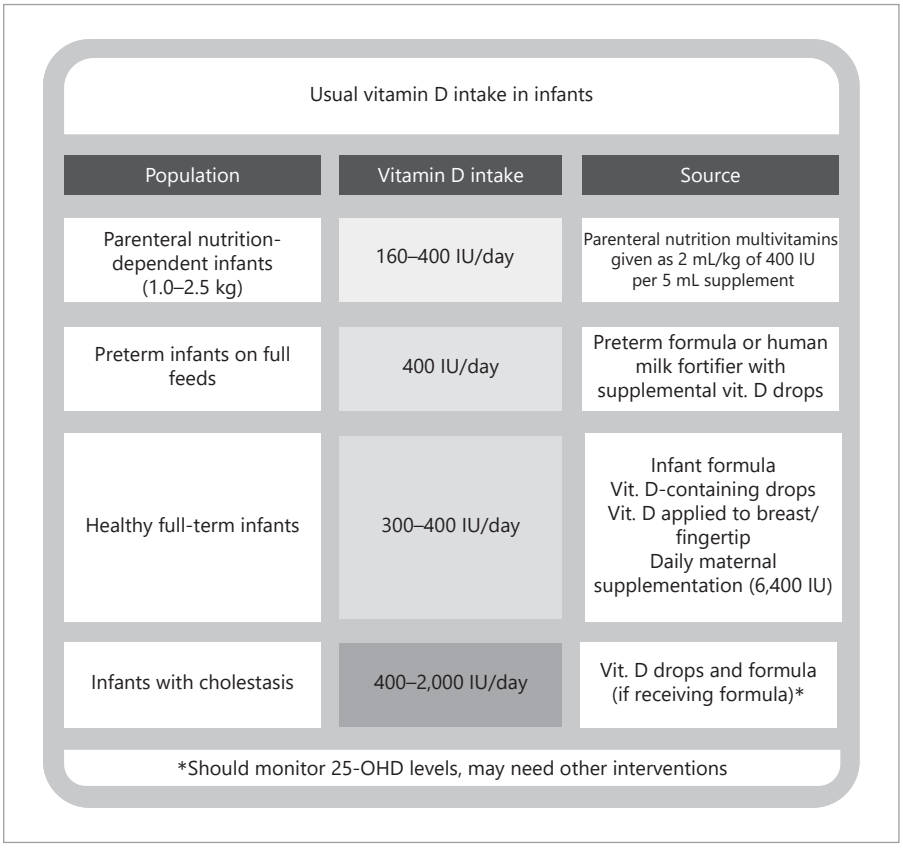

Fig. 1. Usual vitamin D intake in infants.

Most data in infants, both preterm and full term, do not specifically allow for an understanding of the relationship between body weight and dose-response of vitamin D intake. The IOM report considered these relationships related to age but not specifically for infants [2]. Although cutaneous production of vitamin D exists in infants, this too is generally minimally considered in most research as it is extremely hard to quantify, and the use of sunblock as well as other factors limiting sun exposure make this an unreliable source of vitamin D for infants. Recommendations for vitamin D intake, including those of the IOM [2], are generally done on the assumption that cutaneous conversion of pro-vitamin D to vitamin D in infants is minimal or nonexistent.

Calcium absorption in all populations is both by transcellular vitamin D-dependent and by paracellular vitamin D-independent mechanisms. There are very few data to indicate the timing and relative role of these 2 mechanisms in newborns, whether preterm or full term. Numerous studies in preterm infants have shown a high level of calcium absorption, about 50% (compared to adults of 10–25% typically), in preterm infants. This includes infants fed human milk with or without fortification and those fed preterm formula across a broad range of calcium intakes [14, 15]. It has been suggested that these data indicate the likelihood that calcium absorption is primarily paracellular, not vitamin D dependent, in the first weeks of life in both preterm and possibly in full-term infants [16]. Transition to a greater proportion of calcium absorption by vitamin D-dependent active absorption may not occur for 1–2 months, but there are no data clearly defining this timing. Such research is nearly impossible to conduct, and we may never have a definitive answer to the timing and relative proportion of active versus passive calcium absorption in small infants and its relationship to dietary intake.

Preterm Infants

For preterm infants, it is generally found that a standard total intake of 400 IU daily will achieve a value of serum 25(OH)D above 20 ng/mL in most infants with averages well above 30 ng/mL [12] (Fig. 1). Some infants, especially those who have lower maternal vitamin D status at birth, may take longer to reach this value, but there are no suggestions of any clinical benefit to routinely giving higher doses [5]. A few infants receiving higher doses of vitamin D may have potentially toxic levels exceeding 100 ng/mL, but more information is needed

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Table 1. Common enteral sources of vitamin D[a]

	Vitamin D intake, IU/day	Comments
HM: mother on usual intake	<100	Maternal intake of 2,000 IU/day or less
HM: mother supplementing	300–400	Maternal intake approximately 6,400 IU/day
Fortified HM in preterm infants	280–380	<50 IU/day if all-HM-based fortifier without supplement
Routine formula	300–600	Dependent on formula content
Preterm formula	290–468	At full intake volume of formula (USA)
Transitional formula (22 kcal/oz)	125–200	Calculated at 1,500–2,000 g body weight

HM, human milk. [a] Assumes intake of approximately 120 kcal/kg/day in preterm infants.

to evaluate this risk or any clinical correlates of relatively high vitamin D status in preterm infants [12].

However, in this regard, there are differences in recommendations between those commonly given in the USA and in Europe for vitamin D in preterm infants. European authorities and authors have generally recommended a dose of 800–1,000 IU vitamin D daily, whereas in the USA, 400 IU daily remains the standard recommendation [17]. This distinction is due to the perspective in European reviewers, based on limited-balance studies, that a lower calcium intake can be used with a higher vitamin D intake to increase total calcium absorption to needed levels to support preterm infant bone mineralization. In the USA, it has been preferred to maintain a high calcium intake [4], and there are no current reasons to change recommendations or formulations of preterm infant products in the USA as there is no evidence of any harmful effects from calcium intake levels currently provided. Nonetheless, those who supplement preterm infants to a total intake of 800–1,000 IU daily may likely do so without serious concern for toxicity or need for close follow-up, given the long history of use of higher doses up to 1,000 IU daily in many countries in preterm infants.

Full-Term Infants

The requirements for vitamin D in full-term infants have been extensively investigated. Research has shown that the dose generally recommended for almost 100 years of 400 IU daily meets the needs of nearly all full-term infants, and it remains the recommendation for infants by the IOM and the AAP [2, 3] (Table 1). Even in populations in which values of 25(OH)D are low at birth, available data suggest that this dose will suffice for infants to adequately absorb calcium [18]. A recent study from Canada confirmed no effect on bone mineralization at 3 years of age of doses >400 IU/day for breastfed infants, although higher 25(OH)D levels were achieved with higher doses [19]. Of greater concern was the unexpected finding that doses of vitamin D >400 IU daily were associated with worse gross motor development at 6 months of age [20]. Caution needs to be used in overinterpreting single or small studies such as this, but without evidence of benefit, use of high-dose vitamin D cannot be routinely recommended in full-term infants.

Although vitamin D is generally safe with negligible risk of acute toxicity with recommended dosing, there have been reports of toxicity, such as severe hypercalcemia associated with very high doses [21]. This may occur when caregivers mistakenly give highly concentrated vitamin D drops to infants. Although most vitamin D drops designed for infants provide 400 IU per dropper (generally about 0.5–1.0 mL liquid), products exist in the marketplace that provide 400 IU or more of vitamin D in each drop. If given a full 1 mL or more of products containing for example 400–1,000 IU per drop of supplement for a period of days, toxic doses could easily be given. As such, it is imperative to advise families about avoiding high doses or highly concentrated sources of vitamin D [22].

Dietary Sources of Vitamin D and Timing of Introduction

Because neonatal vitamin D status is reflective of maternal status, it has been suggested that it is best to start supplementation as early as is possible [2]. As such, whereas earlier recommendations in full-term infants suggested waiting until up to 6 weeks to allow lactation to become well-established, more recently, it is recommended that vitamin D be started within the first few weeks if not the first days of life.

One important reason for this is that it is easier and more reliably performed to teach families to properly give the drops to their breastfed infant while still in the hospital as it is less likely to be missed if begun in the hospital. In some hospitals,

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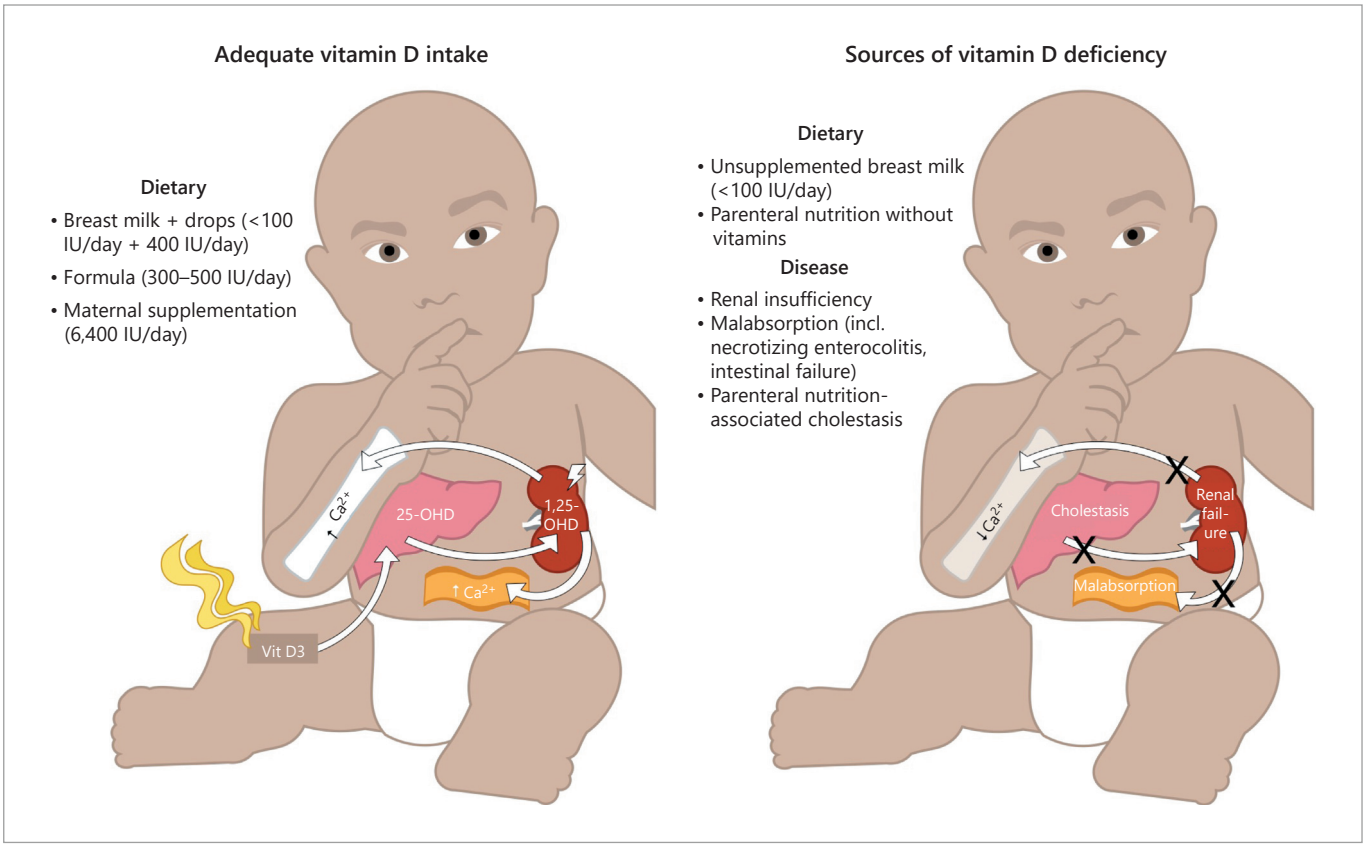

Fig. 2. Adequate and inadequate vitamin D metabolism in infants.

the first bottle of the drops may be sent home with the family. The opportunity to rapidly increase very low 25(OH)D levels in infants born to mothers with very low levels is also a reason to consider this. However, it should not be expected that there will be specific clinical benefits to beginning vitamin D in the first weeks of life, and if some families wish to delay giving drops for 4–6 weeks until lactation is well-established that should be considered as reasonable.

The situation for preterm infants is even less clear. Rickets in preterm infants is primarily a disease of inadequate calcium and phosphorus intake and absorption [5]. For those fed intravenously with parenteral nutrition, vitamin D is present in the multivitamins given with the parenteral nutrition with the standard intravenous multivitamin supplement containing 400 IU of vitamin D in 5 mL of the supplement. Typical dosing of 2 mL/kg daily of the supplement in parenteral nutrition would lead to doses from 160 to 400 IU daily for infants 1.0–2.5 kg. It is important to provide vitamin D to infants who are not taking enteral nutrition to prevent extremely low vitamin D levels which can increase bone resorption and cause failure to fully mineralize bone.

The timing of introduction of oral vitamin D in preterm infants has not been studied in terms of relative risks and benefits to any particular time point. The AAP recommended beginning after full feeds are achieved at about 1,500 g, but it was recognized that this specific time point is arbitrary and chosen primarily to ensure the tolerance of the drops [5]. Others might choose to begin supplementation somewhat earlier in very-low-birth-weight infants, but it is common to ensure a nontrophic volume of feeds are being well tolerated before doing so and waiting until after parenteral nutrition has been discontinued.

Other Issues with Vitamin D Dosing in Infants

Some families are resistant to providing drops of vitamin D to their breastfed infants or perceive them to be poorly tolerated, especially when given with iron-containing multivitamins. In these cases, there are several alternatives that may be considered (Fig. 2). The first is the use of vitamin D drops that can be placed directly on the breast or given as dissolvable filmstrips.

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Table 2. Regulatory guidance and common vitamin D content of routine cow milk-based infant formulas

	Concentration, IU per 100 kcal		Approximate intake, IU daily[a]	
	minimum	maximum	minimum	maximum
USA (FDA regulatory)	40	100	260	670
Europe (EFSA regulatory)	80	100	520	670
USA formulas (most common)	45	75	300	500

FDA, Food and Drug Administration; EFSA, European Food Safety Authority. [a] Based on 1,000 mL daily formula intake.

For some mothers, this is easier and more acceptable than giving a dropper of vitamins directly to the infant or mixed in their milk [23].

Another approach is to have the lactating mother take a relatively high dose of vitamin D. Studies have shown that a maternal dose of 6,400 IU daily will provide an infant with adequate vitamin D intake (usually about 300–400 IU daily) from the mother's milk if fully breastfed and if the mother takes the dose every day. Of note is that lower maternal doses, especially those of 400–2,000 IU daily, do not provide adequate vitamin D in breast milk. The dose of 6,400 IU daily is slightly above the IOM upper limit of 5,000 IU/day but is highly likely to be safe, and this should not be a concern in recommending this approach if desired by breastfeeding women [2, 24].

It is frequently asked whether vitamin D should be given to infants who are both breast and formula fed, and the general answer is "yes." An intake of 400 IU daily requires a full volume of formula intake, and whereas going slightly below the 400 IU/day level of intake is not problematic, the mixed-fed baby is best served by providing additional vitamin D as would be done for fully breastfed infants. There is no risk of toxicity with this approach, even if the infant switches entirely to infant formula prior to stopping the vitamin D supplementation.

Another common clinical question is whether vitamin D supplementation via drops is necessary for exclusively formula-fed infants. Some have indicated that vitamin D should be given until a volume of formula intake of 1,000 mL/day is reached [7]. This is because, based on the formula label and usual dilution of powdered infant formula, vitamin D was usually provided in infant formulas at 400 IU/L. Although there is no harm in this practice, it is questionable if needed and if it is best use of family and societal resources. The vitamin D requirement of 400 IU daily from the IOM is an average requirement in the first 6 months of life and as noted, there is little suggestion of a clinical concern with slightly lower doses until full feeding volume is achieved [2].

Also problematic with this recommendation is the perception that 1,000 mL daily is the minimum volume of infant formula an infant *should* receive and infants taking below that need any supplements. The usual volume of breast milk intake is approximately 800 mL daily, and although formula intakes are somewhat variable, an intake of 1,000 mL of formula is higher than required for growth and development, and not all infants will ever take this volume nor should they be pushed to this volume [2]. Furthermore, although the label claim for vitamin D content was commonly 400 IU/L, when analyzed, many infant formula batches will have 10–20% over this amount so as to meet the label claim at the end of shelf life [25]. Overall, the IOM recommendation of 400 IU daily for infants should be understood as an average intake, not one needing to be met from label claim every day from birth [2].

Recently, many formulas have been marketed with vitamin D intakes over 400 IU/L as this is permitted by the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) [26]. Numerous routine cow milk-based and other formulas marketed currently contain approximately 400 IU in 800 mL as prepared, a daily intake volume similar to that ingested daily by many infants after the first 6–8 weeks of life (Table 2). Despite variations in the vitamin D content of infant formulas, there is no reason to specifically choose an infant formula based on vitamin D intake. Overall, there is no clinical evidence supporting routine supplementation of infants who are exclusively formula fed with vitamin D, and the emphasis should be on breastfed infants in this regard.

Common Disease-Oriented Issues in Infants

Hypocalcemia

Most cases of neonatal hypocalcemia with symptoms are not primarily due to vitamin D deficiency. Both early and late hypocalcemia are common in preterm and term infants, and in

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the USA, early hypocalcemia in preterm infants (first 2–3 days of life) is primarily related to hormonal factors [27, 28]. In full-term infants, hypocalcemia is commonly seen in infants of diabetic mothers or associated with severe birth depression and neonatal asphyxial disorders among other causes. In late hypocalcemic tetany (usually 4–7 days of age), vitamin D levels may be low, but the primary cause of hypocalcemia is the use of high phosphorus intakes associated with whole cow milk or use of infant formula [29, 30]. In late neonatal hypocalcemia, treatment with 1,25-dihydroxyvitamin D may shorten the time to resolution likely due to direct effects of vitamin D on the bone rather than a calcium absorptive effect [31].

An important situation in which vitamin D deficiency is more central to the etiology of hypocalcemia are cases commonly reported in full-term infants during the second week of life. Reports of this problem have primarily come from Middle Eastern countries and are associated with extremely low maternal and, thus, infant vitamin D levels [32, 33]. Although the etiology of the hypocalcemia is not clearly defined, likely it is due both to lack of effects of vitamin D at the bone and in the intestine. This highlights the importance of identifying at-risk maternal populations and providing them with adequate vitamin D intake during pregnancy.

Cholestasis

Common conditions related to the vitamin D requirement in preterm infants are those that affect either the enteral absorption of nutrients or those which affect the formation of 25(OH)D in the liver or 1,25-dihydroxyvitamin D in the kidneys. Absorption of fat-soluble vitamins, such as vitamin D, may be affected by a variety of disease states in preterm infants, including those with the loss of the terminal ileum surgically and malabsorptive diseases, such as cystic fibrosis. Management of these conditions is beyond the scope of this review, but these would be an indication for closely monitoring the serum 25(OH)D concentration and potentially providing higher doses of vitamin D or vitamin D metabolites as described below [34].

A second relatively common problem in high-risk neonates is cholestasis, especially secondary to long-term parenteral nutrition use. Although relatively little is known specifically about relating the level of conjugated bilirubin to 25(OH)D values or calcium absorption in infants, this may become a clinical problem in which it is difficult to maintain adequate vitamin D status using usual dietary approaches. In this case, if careful monitoring and higher vitamin D (e.g., 1,000–2,000 IU daily) intakes show a persistent level of serum 25(OH)D <20 ng/mL, then supplementation with very-high-dose vitamin D or use of vitamin D analogues, such as calcitriol, while continuing vitamin D may be considered [35]. This should generally be done in the context of consultation or management by a pediatric endocrinologist, nephrologist, or other expert in the use of vitamin D metabolites. Of note is that the enteral medication 25(OH)D, called calcidiol (also referred to as calcifediol), has recently become available in the USA but does not have a FDA-approved indication for use in infants and children.

Compliance with Vitamin D Intake Recommendations

As noted, many families of breastfed infants do not provide vitamin D supplements per recommendations. Recent data suggest that only about 20% of US infants who are breastfed are receiving vitamin D supplements to meet the recommendations [36]. Of note is that this is much lower than the rate in a study in Canada which found over 70% adherence, perhaps due to greater awareness of this issue in Canada among pediatricians and families [37]. Discharge from the hospital with vitamin D can markedly increase this rate as suggested in these preliminary results [38]. Education is needed for both providers and families related to the risks of rickets and the importance of providing vitamin D for infants. Providers should be prepared to answer concerns related to the use of drops in breastfed infants and provide alternatives as described above for those families unwilling to use drops. The option of delaying the drops for 6–8 weeks after birth can also be given, especially for families intending to offer a bottle of mother's milk at that time into which the drops could be added.

Future Research

Further studies are needed focusing on the risks associated with very low vitamin D status in infants, in particular, identifying the risks and best management approaches for infants who are at risk of hypocalcemia from extremely low maternal vitamin D status. Although this problem has not been identified commonly in the USA, it may not be identified when it occurs, and population studies of high-risk maternal infant pairs are needed.

Although vitamin D is largely safe, the increasing use of high-dose supplements in infants should be evaluated and practitioners encouraged to report cases to understand this problem and the clinical consequence of high-dose ingestion, whether intentional or accidental.

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Summary of Recommendations

Vitamin D is a critical nutrient for bone health and needs to be provided to all infants whether via infant formula or as a supplement to breastfed infants or high-dose supplement to their mothers. Solar conversion and cutaneous formation of vitamin D cannot be ensured in any population. In most healthy infants, preterm as well as full term, who are on full enteral nutrition and have a normal intestine and normal liver and renal function, provision of approximately 400 IU daily is necessary and sufficient for bone health, and routine monitoring of serum 25(OH)D levels is not needed. Caution should be used to ensure that the appropriate dose is provided and that accidental ingestion of high doses of vitamin D does not occur.

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Disclosure Statement

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Focus

The initiation of human life at the moment of conception involves a myriad of ancient signaling hormones, which include vitamin D

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Early- Life Effects of Vitamin D: A Focus on Pregnancy and Lactation

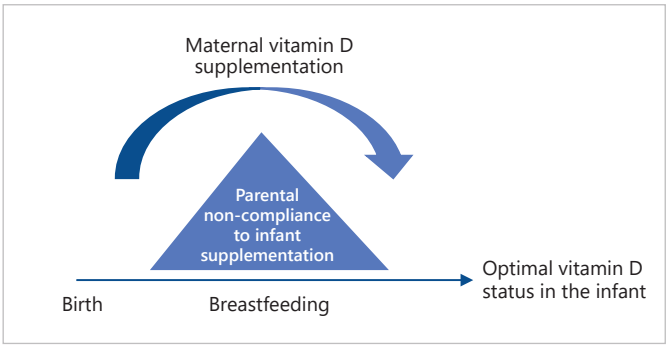
Carol L. Wagner and Bruce W. Hollis

Key Insight

Long known for its role as a preprohormone in calcium and bone homeostasis, our understanding of vitamin D now extends to its functions in regulating innate and adaptive immunity. From early in pregnancy, there is a rise in circulating levels of 1,25-dihydroxyvitamin D, but drop to prepregnancy levels after birth. A growing body of evidence indicates that vitamin D can affect gene expression, including genes associated with immune defense pathways. In turn, vitamin D metabolism during pregnancy is modulated by the individual's genetic background. In the future, this knowledge may enable us to fine-tune the dosing of vitamin D supplements during pregnancy, as well as identify subgroups of women who may be at greater risk of vitamin D deficiency.

Current knowledge

There are 2 forms of vitamin D: ergocalciferol (or vitamin D2, synthesized by plants and fungi) and cholecalciferol (or vitamin D3, synthesized in human skin and by animals). Humans are able to metabolize both forms of vitamin D. The initial step in metabolic activation of vitamin D is an enzyme-catalyzed insertion of an OH group at carbon 25, resulting in 25(OH)D, the most abundant form of vitamin D in the circulation. Parathyroid hormone (PTH) is an important mediator of vitamin D status. When vitamin D levels decrease, PTH increases, affecting intestinal absorption of vitamin D and skin conversion from its precursor. Thus, measurement of intact PTH levels also has been used as an indicator of vitamin D deficiency.



Maternal vitamin D supplementation from birth onwards ensures optimal vitamin D status in the mother and infant in case of lack of compliance of caregivers in administering vitamin D supplements to their infant.

Practical implications

When mother is vitamin D insufficient or deficient, breast milk has a relatively low vitamin D content. Consequently, all breastfed babies should receive a vitamin D supplement of 400 IU/day. Most infants in technologically dependent societies are not exposed to direct sunlight until after 6 months of age; therefore, endogenous synthesis is not a reliable source of vitamin D. Currently, a major challenge is lack of compliance among parents in giving vitamin D supplements to their breastfed infants. Where maternal compliance with taking a vitamin D supplement is greater than that of parental adherence to infant supplementation, maternal vitamin D supplementation remains a viable alternative that safely and effectively treats both the mother and her breastfeeding infant.

Recommended reading

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Annales Nestlé

Vitamin D

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Early-Life Effects of Vitamin D: A Focus on Pregnancy and Lactation

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Key Messages

- The active form of vitamin D – 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) – increases during pregnancy, remains elevated throughout, and, unlike at other times during the lifecycle, is directly affected by circulating 25-hydroxyvitamin D (25[OH]D) concentration with the optimal point of conversion of 25(OH)D to 1,25(OH)$_2$D at 100 nmol/L (40 ng/mL).
- Lactation has increased demands on the mother regarding nutrient intake delivered through her breast milk to her recipient infant: when a mother is vitamin D deficient, her milk is deficient, which can be remedied by direct infant supplementation; however, this treats only the infant.
- A safe alternative during lactation to infant supplementation is direct maternal vitamin D supplementation at higher doses than usual (6,400 IU/day), improving the vitamin D status of the mother, the content of the milk, and, consequently, the vitamin D status of the infant, effectively treating both the mother and the infant.

Keywords

1,25-dihydroxyvitamin D · 25-hydroxyvitamin D · Cholecalciferol · Calcidiol · Clinical nutrition · Human nutrition · Infancy and childhood · Lactation · Pregnancy

Abstract

Vitamin D is an endocrine regulator of calcium and bone metabolism. Yet, its effects include other systems, such as innate and adaptive immunity. Unique to pregnancy, circulating 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) increases early on to concentrations that are 2–3 times prepregnant values. At no other time during the lifecycle is the conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25(OH)$_2$D directly related and optimized at ≥100 nmol/L. Vitamin D deficiency appears to affect pregnancy outcomes, yet randomized controlled trials of vitamin D supplementation achieve mixed results depending on when supplementation is initiated during pregnancy, the dose and dosing interval, and the degree of deficiency at the onset of pregnancy. Analysis of trials on an intention-to-treat basis as opposed to the use of 25(OH)D as the intermediary biomarker of vitamin D metabolism yields differing results, with treatment effects often noted only in the most deficient women. Immediately after delivery, maternal circulating 1,25(OH)$_2$D concentrations return to prepregnancy baseline, at a time when a breastfeeding woman has increased demands of calcium, beyond what was needed during the last trimester of pregnancy, making one question why 1,25(OH)$_2$D increases so significantly during pregnancy. Is it to serve as an immune modulator? The vitamin D content of mother's milk is directly related to maternal vitamin D status, and if a woman was deficient during pregnancy, her milk will be deficient unless she is taking higher doses of vitamin D. Because of this relative "deficiency," there is a recommendation that all breastfed infants receive 400 IU vitamin D$_3$/day starting a few days after birth. The alternative – maternal supplementation with 6,400 IU vitamin D$_3$/day, effective in safely raising maternal circulating vitamin D, that of her breast milk, and effective in achieving sufficiency in her recipient

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breastfeeding infant – remains a viable option. Additional research is needed to understand vitamin D's influence on pregnancy health and the effect of maternal supplementation on breast milk's immune signaling.

Conception Onward

From the moment of conception, there are tremendous changes that must occur for growth and shaping of a single-cell organism to billions of cells as the construct of diverse systems, which function in concert to form a living human being. It is in the context of this timing, this concert of matter and energy transfer across cells, that we can appreciate what is happening surrounding conception. Conception does not occur in a hostile or nonnurturing environment, yet the very invasion of extravillous cytotrophoblasts into the uterine wall is an invasive and inflammatory process [1–3]. Pregnancy is a state of change and flux that must balance between negentropy—organization of tissue—and cellular death and apoptosis – necessary for refinement of tissue and organ structure. The very event of conception is dependent upon a functional neuroendocrine system in both the mother and father, a functioning uterus with a rich lining to allow for invasion of the extravillous cytotrophoblasts into the uterine wall, and a dynamic synchrony of cell division and cell death. The initiation of human life at the moment of conception involves a myriad of ancient signaling hormones, which include vitamin D [4, 5].

Vitamin D as Preprohormone

Long known as an endocrine facilitator in its role as a preprohormone affecting calcium and bone metabolism and homeostasis, vitamin D is something more as well. Our understanding of vitamin D has expanded in the decades since its discovery in the early 20th century. There are provocative experimental models in animals that extend to observational and some clinical trials in humans, which suggest that vitamin D plays a role in both innate and adaptive immunity, affecting our ability to survive infectious insults as well as long-latency diseases, such as autoimmune diseases and cancers, all of which depend on a balanced and functional immune system [6].

There are 2 forms of vitamin D: ergocalciferol (or vitamin D_2, which is synthesized by plants and fungi) and cholecalciferol (or vitamin D_3, which is synthesized in the skin of humans and animals). Humans can metabolize both forms of vitamin D. Pre-vitamin D_3 is synthesized in the epidermal layer of the skin by keratinocytes mainly in the stratum basale and stratum spinosum when 7-dehyrocholesterol is exposed to ultraviolet B light in the wavelength of 290–320 nm [7]. Through this photolytic energy transfer, pre-vitamin D is formed, and with further thermally induced isomerization in the skin, the parent compound vitamin D_3 is produced. Vitamin D_3 is carried into the bloodstream bound to vitamin D-binding protein (VDBP) or, less frequently, to albumin. Once vitamin D (either form D_2 or D_3) enters the circulation, either through epidermal transfer or intestinal absorption, it associates with VDBP, a 58-kD globular protein that binds vitamin D and its metabolites with various affinities based on the number and position of polar functional groups and/or methyl groups [8]. The initial step in the metabolic activation of vitamin D is the enzyme-catalyzed insertion of an OH group at carbon 25; this oxidation process is primarily a hepatic microsomal function mostly by CYP2R1, a 25-hydroxylase [9], producing 25-hydroxyvitamin D (25[OH]D), the most abundant circulating form of vitamin D [10].

Vitamin D plays a role in both innate and adaptive immunity, affecting our ability to survive infectious insults as well as long-latency diseases

As shown in Figure 1 (from Hollis and Wagner [11], with permission), following formation in the liver, 25(OH)D appears in the circulation – bound primarily to VDBP. The half-life of the parent compound is 12–24 h, while that of its first metabolite 25(OH)D is 2–3 weeks. The conversion of 25(OH)D to the active hormone 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) through the CYP27B1 enzyme mainly occurs in the proximal tubules of the kidney, and then it is carried throughout the body also bound to VDBP.

Unlike 25(OH)D, $1,25(OH)_2D$ has a much shorter half-life of 4–8 h. VDBP preferentially binds 25(OH)D with higher affinity than $1,25(OH)_2D$ or the parent compound [12]. The high affinity of VDBP for the vitamin D and its metabolites, coupled with the excessive binding capacity, keeps "free" or unbound concentrations of vitamin D and its metabolites at quite low relative concentrations [13, 14]. This is important because only the "free" concentrations of the vitamin and its metabolites have transmembrane diffusion capabilities, thus exerting their

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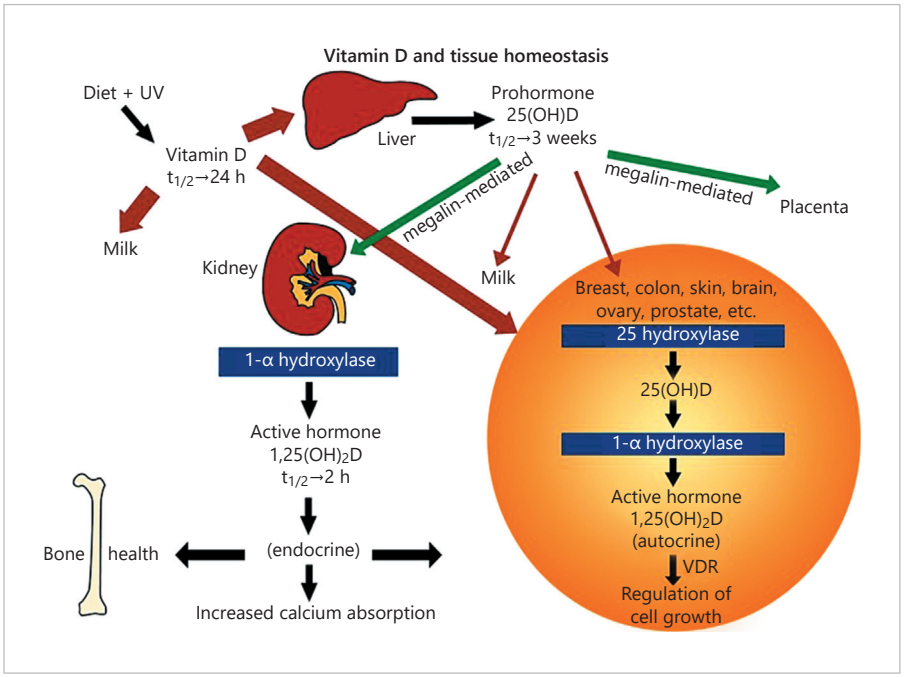

Fig. 1. Diagram of the metabolic processes providing vitamin D and its metabolites to various tissues of the body. Tissue distribution of vitamin D and 25(OH)D based on simple diffusion (red arrows) or endocytosis (green arrows). Endocytosis requires the tissue-specific megalin-cubilin system, whereas simple diffusion is primarily controlled by the dissociation constant of the vitamin D compound for VDBP. Bolder red lines indicate greater diffusion rates due to a higher dissociation constant. $t_{1/2}$, half-life. (Hollis and Wagner [11], 2013, with permission.)

biologic function. What influences vitamin D status throughout the lifecycle is parathyroid hormone (PTH). When circulating $1,25(OH)_2D$ concentrations decrease, PTH increases, affecting intestinal absorption of vitamin D and conversion of vitamin D from its precursor in the skin. The measurement of intact PTH (iPTH) has long been considered an indicator of vitamin D deficiency and is used as a marker [15].

All vitamin D moieties are capable of binding to the vitamin D receptor (VDR). As shown in Figure 1, the conversion of vitamin D to 25(OH)D and of 25(OH)D to $1,25(OH)_2D$ in the nuclear membrane of the cell is not limited to the liver and kidneys, respectively; keratinocytes and many cells throughout the body, including monocytes, macrophages, and prostate and breast cells, can convert vitamin D_3 to 25(OH)D and then to the active form $1,25(OH)_2D$ [16, 17]. $1,25(OH)_2D$'s endocrine effects include the following classic triad of action: (1) increase in intestinal calcium (as Ca_2+ ions) absorption through the actions of calbindin; (2) increase in urinary calcium reabsorption; and (3) regulation of PTH in a negative feedback loop that allows calcium to be absorbed from the gastrointestinal tract, reabsorbed from urine, and metabolized from bone in order to maintain calcium homeostasis within the body. Because calcium is essential to all tissues and organs, particularly the heart, skeletal muscle, and brain, the body will claim calcium, if necessary, from the skeleton. In individuals with vitamin D deficiency, only trace amounts of vitamin D will be found in the body because whatever comes into the circulation is quickly converted to 25(OH)D and then to $1,25(OH)_2D$ to maintain calcium homeostasis [18]. For this reason, $1,25(OH)_2D$ is not the indicator of vitamin D status and why 25(OH)D with its longer half-life should be used.

Another important factor influencing the conversion rate of 25(OH)D to $1,25(OH)_2D$ is the tissue transport mechanism for these secosteroids referred to as the megalin-cubilin system. The megalin-cubilin endocytic system [19] serves as an essential delivery system of 25(OH)D to the 25(OH)D-1-α-hydroxylase in the kidney, necessary in the conversion of 25(OH)D to $1,25(OH)_2D$ [19]. This system also exists in the parathyroid glands and, therefore, plays an important role in the endocrine function of vitamin D to maintain calcium homeostasis. Interestingly, the megalin-cubilin system also functions in the placenta and likely orchestrates maternal-fetal calcium homeostasis [20]. For those tissues that lack this endocytic transport system, free circulating concentrations of vitamin D moieties reach target cells through passive diffusion. For additional information, there are excellent reviews available that detail vitamin D metabolism in the nonpregnant individual [17, 21–23].

Also of importance is that $1,25(OH)_2D$ itself is responsible for reducing $1,25(OH)_2D$ concentrations in cells primarily by stimulating its catabolism through the induction of 24-hydroxylase, 24CYP24A1. This enzyme hydroxylates both 25(OH)D and $1,25(OH)_2D$ in the 24 position to form $24,25(OH)_2D$ and $1,24,25(OH)_3D$ [24]. As is discussed next, during pregnancy, there is increased $1,25(OH)_2D$ concentration presumed to be due to decreased catabolism.

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Differences in Vitamin D Metabolism during Pregnancy

From early on in pregnancy, circulating $1,25(OH)_2D$ concentrations increase without the predicted surge in PTH that causes a rise in calcitriol in nonpregnant individuals. While calcitriol is synthesized by the placenta, during pregnancy it is mainly synthesized by the kidneys [25]. There appears to be a slower rate of catabolism of $1,25(OH)_2D$ to $24,25(OH)_2D$ [26]. What purpose does this early and sustained rise in $1,25(OH)_2D$ serve? There has been much speculation about this. It has been theorized for decades that this increase during pregnancy was due to increased fetal calcium requirements, most notable during the last trimester [27]. Elevated circulating $1,25(OH)_2D$ was also thought to continue during lactation [28], but later, with more sensitive assay methodology surrounding the measurement of $1,25(OH)_2D$, this was shown not to be the case [29, 30]. The return to prepregnancy circulating concentrations of $1,25(OH)_2D$ during lactation is poorly understood and suggests that the role of $1,25(OH)_2D$ during pregnancy may be for reasons that extend beyond calcium metabolism and which surround vitamin D's role in immune function [25]. The above occurs in the presence of a continued high calcium requirement of the breastfeeding infant of at least 200–350 mg/day for growth that is comparable to fetal requirements during the last trimester of pregnancy.

There is historical information as early as the 1940s with halibut liver oil – rich in both vitamins A and D and other vitamins – given as a supplement to pregnant women that showed benefit

Specific to pregnancy, there are changes in states of inflammation: early in pregnancy, there is inflammation – to allow the conceptus to invade the uterine milieu and for a network of channels between maternal and embryo to develop that give rise to the placenta, following a time of relative quiescence of those inflammatory processes that facilitate fetal growth beginning in the middle of the first trimester toward the end of pregnancy, with a return to a relatively inflammatory state with the onset of labor and the expulsion of the placenta [3]. Pregnancy represents tremendous change in numerous systems with most notable increases in estrogen, progesterone, human placental growth factor, the interleukins, as well as $1,25(OH)_2D$. Each has its purpose, but with any system, various growth factors and cytokines do not operate in isolation, but there is much interaction.

There is evidence that maternal vitamin D deficiency – however this is defined – affects maternal and fetal outcomes. Although scientific inquiry on the topic with published observational and clinical vitamin D supplementation trials did not consistently appear in the literature until the late 1970s/early 1980s [31], there is historical information as early as the 1940s with halibut liver oil – rich in both vitamins A and D and other vitamins – given as a supplement to pregnant women that showed benefit [32]. Specifically, a study conducted by the People's League of Health in 1938–1939 involving over 5,000 pregnant women who were randomized to receive a cocktail of vitamins and halibut liver oil (a source of both vitamins A and D) or placebo was rediscovered by Olsen and Secher [32] and the results published in 1990. This nutritional supplement was superior compared to control in achieving reductions in preterm birth and preeclampsia. Since that time, studies that have focused on one nutrient instead of a combined nutritional supplement, with the exception of higher-dose vitamin D studies in the most deficient women, and more recently in systematic reviews and meta-analyses, have failed to demonstrate this effect. Much research has occurred with far more studies published each year on the topic. With those trials, there have been mixed results, with some studies showing a positive effect and others showing a minimal or no effect. There are, however, indisputable findings surrounding gene expression on the basis of maternal vitamin D status.

Focusing on vitamin D, the metabolism of this important preprohormone during pregnancy is vastly different when compared to the nonpregnant state. As noted earlier, $1,25(OH)_2D$ increases 2- to 3-fold within days of conception, while 25(OH)D remains relatively stable within a certain range [33–35]. It is 25(OH)D which crosses the placenta to the fetus and, thus, is the main pool of vitamin D in the fetus, not $1,25(OH)_2D$; the fetus must synthesize $1,25(OH)_2D$ from that pool. While the main source of the increased $1,25(OH)_2D$ during pregnancy comes from the kidney, its other source is the placenta, with VDR and regulatory metabolic enzymes synthesized in the placenta and decidua. This is considered a potential critical point in the immunomodulation at the maternal-fetal interface and raises the question if maternal hypovitaminosis D during pregnancy leads to pregnancy-related disorders [36, 37].

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Genetic Studies and Vitamin D Status

There is an increasing number of genetic studies to evaluate vitamin D's effect on gene expression. One of the first was a study by Al-Garawi et al. [38] who, in their post hoc analysis of a randomized clinical trial of maternal vitamin D supplementation in women who themselves or of whom a first-degree relative had allergy or asthma, sought to explore vitamin D's effect on genomic changes during pregnancy, which is one of the first reports of its kind. Women were randomized at 10–18 weeks of gestation to 400 and 4,400 IU vitamin D_3/day [39] with the primary outcome wheezing in the offspring at 3 and 6 years. An analysis of a subset of blood samples for RNA gene expression changes between the first and third trimesters was conducted. Using significance of analysis of microarrays (SAM) and clustered weighted gene co-expression network analysis (WGCNA) to identify major biological transcriptional profiles between those time points, 5,839 significantly differentially expressed genes were studied. Transcripts from these genes clustered into 14 co-expression modules, of which 2 (associated with immune defense pathways, extracellular matrix reorganization, and Notch signaling and transcription factor networks) showed significant correlation with maternal 25(OH)D concentrations. The findings show that maternal gene expression changes during pregnancy are affected by maternal vitamin D status, which, in turn, is a direct reflection of maternal vitamin D supplementation.

Additional evidence of vitamin D's effect on gene expression comes from Baca et al. [40] and another from Barchitta et al. [41] in their focus on vitamin D-related genes. Baca et al. [40] conducted a meta-analysis of 2 large cohorts – the Epidemiology of Vitamin D Study (EVITA) and the Collaborative Perinatal Project (CPP) – where the combined analysis of more than 4,000 randomly selected samples showed that the maternal genotypes of 7 SNPs in VDR, 3 SNPs in GC (VDBP), and 1 SNP in the flanking regions of Cyp27B1 were associated with maternal vitamin D status as expressed as the log25(OH)D concentration. Adjusting for multiple comparisons, 1 SNP in VDR and 2 SNPs in GC remained significant. The investigators theorized that SNPs in VDR may influence circulating 25(OH)D by changing the rate at which 25(OH)D is hydroxylated either directly or indirectly through a negative feedback loop. The 2 SNPs in GC are likely related to the response of an individual to vitamin D supplementation, with certain GC polymorphisms associated with an attenuated or refractory response to supplementation compared to other genotypes, such as 1S or 2 [42].

Barchitta et al. [41] conducted a study to examine the association of VDR polymorphisms and preterm birth and neonatal anthropometric measures. Utilizing the Italian "Mamma and Bambino" cohort (n = 187), they studied the most common polymorphisms – BsmI, ApaI, FokI and TaqI. The investigators found that for the FokI polymorphism, gestational duration (age) and birth weight (that are clearly linked) were statistically significantly lower with increasing number of the A allele. In addition, when compared to mothers with the GG or GA genotype, those mothers who carried the AA genotype had a higher risk of preterm birth (OR 12.049, 95% CI 2.606–55.709, p = 0.001). Further, the BsmI polymorphism appeared to be protective against preterm birth, both allelic (A vs. G: OR 0.74, 95% CI 0.59–0.93) and recessive (AA vs. GG + AG: OR 0.62, 95% CI 0.43–0.89, p = 0.0001). Mothers with the AA genotype exhibited a 12-fold increased risk of preterm birth that was independent of sociodemographic characteristics, lifestyle, vitamin D intake/use of supplements, type of delivery, and parity. The results of this study were combined with earlier reported studies, which strengthened the robustness of these findings.

Maternal gene expression changes during pregnancy are affected by maternal vitamin D status, which, in turn, is a direct reflection of maternal vitamin D supplementation

These genetic studies collectively suggest that genotyping of common allelic variants and polymorphisms may play an important role in vitamin D metabolism during pregnancy. The findings further suggest that certain functional genetic variants may contribute to vulnerability or risk of vitamin D deficiency. The findings suggest that there may be subgroups of women based on their genotype profile for relevant vitamin D-related genes who would benefit from certain dosing regimens while others would not. The changes in gene expression from the first trimester compared to the third may also suggest that the prescription of one vitamin D supplement dose throughout pregnancy does not meet the physiological needs of the pregnant woman and might be based more on convenience than what is needed for optimal vitamin D status.

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Table 1. Systematic Reviews and Meta-Analyses of Various Clinical Studies Reporting the Effect of Maternal Vitamin D Status on Pregnancy Health Outcomes, 2018–2019

First author [ref.], year	Topic: Effect of Vitamin D on …	No. of studies included in analysis	No. of pooled participants	Findings
Amraei [65], 2018	Risk of gestational diabetes	26: 8 cross-sectional 6 prospective, nested case-control 7 retrospective case-control 5 prospective cohort studies	*n* = 5,464 GDM *n* = 15,039 without GDM	Risk of GDM, OR 1.18, 95% CI 1.01–1.35, $p < 0.0001$; 25(OH)D concentration lower in those with GDM, OR −0.26, 95% CI −0.39 to −0.14, $p < 0.0001$ No world regional differences Stated limitations: differences between studies in definition of low 25(OH)D and criteria for GDM; potential impact of other confounders, such as pregnancy wt gain, SES, and skin color could not be explored
Baca [40], 2018	Expression of VDR SNPs and association with log25(OH)D concentration during pregnancy	2 cohorts: Epidemiology of Vitamin D Study (EVITA) and Collaborative Perinatal Project (CPP)	EVITA: *n* = 1,958 randomly selected/analyzed CPP: *n* = 4,285 randomly selected/analyzed	Higher rates of vitD deficiency in black mothers Maternal genotypes of 7 SNPs in VDR, 3 SNPs in GC/VDBP, and 1 SNP in flanking regions of CYP27B1 were associated with difference in log25(OH)D concentration during pregnancy Adjusting for multiple comparisons, 1 SNP in VDR and 2 SNPs in GC/VDBP remained significant
Barchitta [41], 2018	Evaluation of VDR polymorphisms and their association with neonatal anthropometric measures and PTB	"Mamma and Bambino" cohort 11 observational clinical studies 3 case-control plus Mamma and Bambino included in meta-analysis	*n* = 187 Unclear total *N* *n* = 763	For FokI polymorphism, gestational duration and BW were decreased with an increase in the No. of A allele(s) Compared with GG and GA genotypes, mothers who carried the AA genotype exhibited higher PTB risk (OR 12.049, 95% CI 2.606 to 55.709, $p = 0.001$) Protective effect of BsmI polymorphism against PTB under the allelic (A vs G: OR 0.74, 95% CI 0.59–0.93) and recessive (AA vs GG+AG: OR 0.62, 95% CI 0.43–0.89) models
Bi [66], 2018	Infant/offspring growth, morbidity and mortality	24 RCTs	*n* = 5,405	VitD supplemented during pregnancy associated with lower risk of SGA (RR 0.72, 95% CI 0.52 to 0.99; RD −5.6%, 95% CI −0.86 to −10.34%), without risk of fetal or neonatal mortality or congenital anomaly Neonates of supplemented mothers: at birth, higher circulating 25(OH)D, serum calcium levels, and wt, carried through to 3, 6, 9, and 12 months after delivery Lower rates of fetal/neonatal mortality of mothers receiving 2,000 IU vitD/day and risk not reduced above that dose (RR 0.35, 95% CI 0.59 to 0.80)
Fang [67], 2019	Association of maternal vitD deficiency (<20 ng/mL/<50 nmol/L) during pregnancy with LBW	16 cohort or case-control	*n* = 8,403 from 8 studies analyzed for LBW risk *n* = 11,867 from 10 studies analyzed for BW differences	Maternal vitD deficiency associated with LBW (OR 2.39, 95% CI 1.25 to 4.57, $p = 0.008$) Total mean BW decreased by 0.08 kg or 80 g (OR −0.08 kg, 95% CI −0.10 to −0.06, $p < 0.001$)
Fogacci [68], 2019	Effect of maternal vitD-S on risk of preeclampsia	27 RCTs Low degree of heterogeneity 3 studies excluded that included multivitamins with vitD	*n* = 4,777 total VitD treatment group *n* = 2,487 Control group *n* = 2,290	Decreased risk of preeclampsia with higher maternal 25(OH)D (OR 0.37, 95% CI 0.26 to 0.52) If vitD-S initiated before 20 wks' gestation, lower risk of maternal preeclampsia (OR 0.35, 95% CI 0.26 to 0.52, $p < 0.001$) Increased vitD dosage inversely associated with preeclampsia risk (slope of log OR −1.1, 95% CI −1.73 to −0.46, $p < 0.001$ corresponding to OR 0.33, 95% CI 0.18 to 0.63, $p < 0.001$) Risk not associated with maternal age
Gallo [69], 2019	Risk of vitD deficiency in mother and neonate Risk of abnormal maternal homeostatic model assessment of insulin resistance Effect on BW Risk of preeclampsia, cesarean section, gestational age and neonatal length	20 RCTs qualitative analysis 17 RCTs quantitative analysis Significant heterogeneity between studies	*n* = 2,844	Good evidence to support maternal vitD-S, increased both maternal (13 studies, MD 14.1 ng/mL [35.2 nmol/L]; 95% CI 9.6 to 18.6 ng/mL [24.0 to 46.4 nmol/L]) and neonatal (cord blood) 25(OH)D (9 studies, MD 9.7, 5.2, 14.2 ng/mL [24.2, 12.9, 35.5 nmol/L]) Fair evidence that vitD-S was associated with decreased maternal HOMA-IR and increased BW in offspring Null effect seen for preeclampsia, mode of delivery, infant gestational age, or birth length

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Table 1 (continued)

First author [ref.], year	Topic: Effect of Vitamin D on …	No. of studies included in analysis	No. of pooled participants	Findings
Li [70], 2019	VitD-S during pregnancy and the risk of wheezing in offspring	4 prospective cohorts 3 RCTs	*n* = 6,068 mother/child pairs	Inverse relationship between maternal vitD intake during pregnancy and occurrence of wheezing in offspring (pooled OR 0.68, 95% CI 0.55 to 0.83, $p < 0.01$) Inverse relationship between maternal vitD intake during pregnancy and eczema but not significant (pooled OR 0.95, 95% CI 0.75 to 1.21, $p = 0.66$) Reported U-shaped dose curve between maternal vitD intake and risk of wheezing in offspring, with lowest risk in 800-IU group but were not able to control for timing of dose, maternal asthma, parental smoking, and other potential confounders
Maugeri [71], 2019	Effects of vitD-S on birth size	13 RCTs 17 comparison groups		Maternal vitD-S associated with BW (12 RCTs; MD 103.17 g, 95% CI 62.29 to 144.04), length (6 RCTs; MD 0.22 cm, 95% CI 0.11 to 0.33), and head circumference (6 RCTs; MD 0.19 cm, 95% CI 0.13 to 0.24) Also associated with reduced risk of LBW (3 RCTs; RR 0.40, 95% CI 0.22 to 0.74) and SGA (5 RCTS; RR 0.69, 95% CI 0.51 to 0.92)
Ojo [72], 2019	Effect of vitD-S on glycemic control in women with GDM	5 RCTs	*n* = 173	Compared to controls, vitD-S associated with decrease in fasting blood glucose (mean 0.46 mmol/L, 95% CI −0.68, −0.25, $p < 0.001$), glycated hemoglobin (mean 0.37%, 95% CI −0.65, −0.08, $p < 0.01$), and serum insulin concentration (mean 4.10 μIU/mL, 95% −5.50, −2.71, $p < 0.001$)
Pacheco-González [73], 2018	Prenatal vitD status and later offspring respiratory and allergy outcomes	34 observational 26 separate study populations 25 longitudinal and 1 case-control 16 countries represented	*n* not listed	Risk of RTIs: comparing highest with lowest 25(OH)D category, pooled OR 0.64 (95% CI 0.47, 0.87) Positive borderline association with lung function at school age (FEV_1 *z*-score coefficient 0.07, 95% CI −0.01, 0.15) No associations found for wheeze, asthma, atopic eczema, allergic rhinitis, and allergic sensitization
Santamaria [74], 2018	Prenatal vitD status and offspring growth, adiposity, and metabolic health	30 observational	*n* = 35,032 mother/offspring pairs	Low prenatal vitD associated with lower BW (g) (MD −100.69, 95% CI −162.25, −39.13), increased risk of SGA (OR 1.55, 95% CI 1.16, 2.07), and an elevated wt (g) in infants at the age of 9 months (MD 119.75, 95% CI 32.97, 206.52) No associations between prenatal vitD status and other growth parameters at birth, age 1 year, 4–6 yrs, or 9 yrs, or with diabetes type 1
Shen [75], 2018	Effect of maternal or neonatal (cord blood) vitD status on later risk of wheezing 5 yrs of age and >5 yrs	3 RCTs 33 cohort studies	*n* = 1,619	No statistically significant association between maternal or cord blood 25(OH)D or intake early in life and asthma either at 5 or >5 yrs
Shi [76], 2019	Maternal vitD intake during pregnancy and later risk of asthma and wheeze in offspring	10 observational, with 14 independent reports	2,073 incident cases of asthma 1,875 cases of wheeze Total 23,030 mother/child pairs	Compared to offspring of nonsupplemented mothers, offspring of vitD-S mothers with reduced risk of asthma or wheeze in infants Combined OR infant wheeze 0.65 (95% CI 0.54 to 0.79) and asthma 0.78 (95% CI 0.69 to 0.89)
Tous [77],2019	Association of low prenatal 25(OH)D (using 3 different threshold levels), PTB, and anthropometric and neurodevelop-mental outcomes in offspring	54 observational	*n* = 67,484	Mothers with 25(OHD threshold value of <30 nmol/L, at greater risk of offspring with: – lower BW (MD −87.82 g, 95% CI −119.73 to −55.919) – lower head circumference (MD −0.19 cm, 95% CI −0.32 to −0.06) – increased risk of SGA and PTB (OR 1.59, 95% CI 1.24 to 2.03) With threshold of <50 nmol/L, offspring with: – increased risk for SGA (OR 1.43, 95% CI 1.08 to 1.91) – increased risk for PTB (OR 1.38, 95% CI 1.08 to 1.52 When maternal 25(OH)D 75 nmol/L, *not* associated with BW, SGA status, or PTB Offspring of vitD insufficient/deficient mothers had lower scores on mental index (OR −1.12, 95% CI −1.82 to 0.42) and language (OR −0.35, 95% CI −1.00 to 0.31, but not statistically significant)

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Table 1 (continued)

First author [ref.], year	Topic: Effect of Vitamin D on …	No. of studies included in analysis	No. of pooled participants	Findings
Yuan [78], 2019	Association of maternal 25(OH)D and risk of preeclampsia	1 nested case-control 20 additional clinical studies	*n* = 122 women with preeclampsia *n* = 480 controls *n* = 39,031 participants: 3,305 with preeclampsia, various ethnicities	65.6% with preeclampsia had 25(OH)D <50.0 nmol/L vs. 55.3% of controls 25(OH)D was significantly lower in women with preeclampsia than in controls (median [IQR] 43.3 [35.5, 55.2] vs. 47.5 [37.6, 60.4] nmol/L, $p = 0.014$) Women with 25(OH)D <50.0 nmol/L with 65% increase in preeclampsia risk (95% CI 1.02 to 2.69) compared with women with 25(OH)D 50.0 to 74.9 nmol/L Meta-analysis showed that low 25(OH)D concentrations were associated with significantly increased risk of preeclampsia by 62% (pooled OR 1.62, 95% CI 1.36 to 1.94), and risk effect of low 25(OH)D concentrations existed in most subgroups
Zhang [79], 2018	Effect of maternal vitD status on risk of GDM	87 observational and 25 RCTs	*n* = 55,859 in observational studies *n* = 2,445 in RCTs	Low 25(OH)D associated with increased GDM (OR 1.850, 95% CI 1.471 to 2.328) 25(OH)D associated with fasting glucose and HOMA-IR index

BW, birth weight; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model assessment of insulin resistance; LBW, low BW; MD, mean difference; OR, odds ratio; PTB, preterm birth; RTCs, randomized clinical trials; SNPs, single nucleotide polymorphisms; SGA, small for gestational age; SES, socioeconomic status; vitD, vitamin D; vitD-S; vitamin D supplementation; VDR, vitamin D receptor; wt, weight; wks, weeks; yrs, years.

Vitamin D Clinical Trials during Pregnancy

The issue with nutrient studies is that they often are designed more like a drug study, where the starting concentration of the "drug" is zero, compared with a nutrient study, such as vitamin D, where there is some vitamin D concentration in everyone, and, thus, baseline 25(OH)D concentration is variable and not zero. Heaney [43] described the qualities that should define a nutrient study:

1 basal nutrient status must be measured, used as an inclusion criterion for entry into the study, and recorded in the report of the trial;
2 the intervention must be large enough to change nutrient status and must be quantified by suitable analysis;
3 the change in nutrient status produced in those enrolled in the report of the trial must be measured and reported;
4 the hypothesis to be tested must be that a change in nutrient status produces the sought-after effect; and
5 the status of other nutrients must be optimized to guarantee that the nutrient being studied is the only nutrition-related limiting factor in the response.

One might add another stipulation to the list – that the nutrient being investigated has to follow an appropriate dosing schedule to match what happens naturally. In the case of vitamin D, there is a plethora of data that show substantial physiological differences between daily, weekly, and monthly vitamin D dosing regimens [11].

In reviewing past clinical trials of vitamin D, most lack all 5 of the Heaney criteria and often the 6th dosing criterion. While systematic reviews and meta-analyses provide larger combined sample sizes, the analyses of several limited studies only compound the problem. More recently, the rigor of clinical trials with increased sample sizes has improved the consistency of pooled/aggregate data, and some compelling evidence from these clinical trials suggests that vitamin D sufficiency during pregnancy enhances maternal and fetal health. The "translation" of the laboratory data to the clinic and bedside supports this emerging concept that vitamin D plays a role not only in calcium homeostasis and bone function but also in immune function. Beyond the scope of this review for an exhaustive summary, below are some of the highlights of those systematic reviews and meta-analyses to date, with an emphasis on the salient findings, and their strengths and weaknesses.

As mentioned in the attributes of a well-designed nutrient study as outlined by Heaney [43], part of the issue is that these supplementation trials have varied by the onset of supplementation during pregnancy, the dosing and timing of that dose, the degree of vitamin D deficiency at the onset of the trial, and different methodology used in measuring 25(OH)D. There have been numerous systematic reviews and meta-analyses on the topic, also with mixed findings. Restricting systematic reviews and meta-analyses to the 2 recent years 2018–2019, there are over 30 publications on the topic of vitamin D and pregnancy outcomes. The analyses cover such topics as gestational age, infant birth weight, gestational diabetes and insulin resistance, small-for-gestational age, preeclampsia, and maternal and neonatal vitamin D status at de-

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livery. Compared to analyses performed in earlier years when there were few published randomized controlled trials that were often plagued with small sample sizes, the more recent reviews consistently have shown benefit of maternal vitamin D supplementation during pregnancy. The highlights of some of the larger systemic reviews and meta-analyses published in the past 2 years (2018–2019) are summarized in Table 1. With each review, there is evidence that there are still limitations to the clinical studies and there is a need for continued research, especially with genetic and epigenetic considerations in place and design of nutrient studies that take into account the Heaney criteria [43].

Association during Pregnancy: Linkage of 25(OH)D to 1,25(OH)$_2$D and a Unique Evolutionary Advantage?

Taken together, there is evidence to suggest that vitamin D deficiency increases the risk of adverse pregnancy outcomes in both the mother and her developing fetus. The question at the heart of the matter is what 25(OH)D concentration should be the target for pregnant women? What this target might be is suggested by this kinetic reaction saturation graph (Fig. 2) of 25(OH)D and 1,25(OH)$_2$D, which shows that 25(OH)D has direct influence on 1,25(OH)$_2$D concentrations throughout pregnancy, an event which does not occur during any other time during the human lifecycle. As is noted in our study reporting these results, as lower concentrations of 1,25(OH)$_2$D increase, first-order kinetics becomes zero-order kinetics, with a plateauing of the graph and an inflection point at 40 ng/mL (100 nmol/L) 25(OH)D – the level required to optimize 1,25(OH)$_2$D production during pregnancy [34].

If this inflection point of 40 ng/mL (100 nmol/L) represents where there is optimal conversion of 25(OH)D to 1,25(OH$_2$D, one would predict that attaining this level during pregnancy would be critical for both maternal and fetal well-being. In our post hoc analysis using multivariable log-binomial regression of maternal 25(OH)D status during pregnancy, McDonnell et al. [44] reported that in women who attained a maternal 25(OH)D concentration ≥40 ng/mL (100 nmol/L) compared to those who remained with a concentration ≤20 ng/mL (50 nmol/L), adjusted for covariates, their risk of preterm birth was reduced by 59%. Based on cellular, animal studies and genetic analyses, it appears that early vitamin D status may have greater bearing on pregnancy outcomes than later status [45, 46], but dissecting the factors that influence these early processes has been a challenge [47, 48]. At the very least, a woman who is considering becoming pregnant or who becomes pregnant should be vitamin D sufficient as defined by the kinetics curve of Figure 2, attaining at least a circulating 25(OH)D concentration of 40 ng/mL (100 nmol/L) as early as possible during pregnancy.

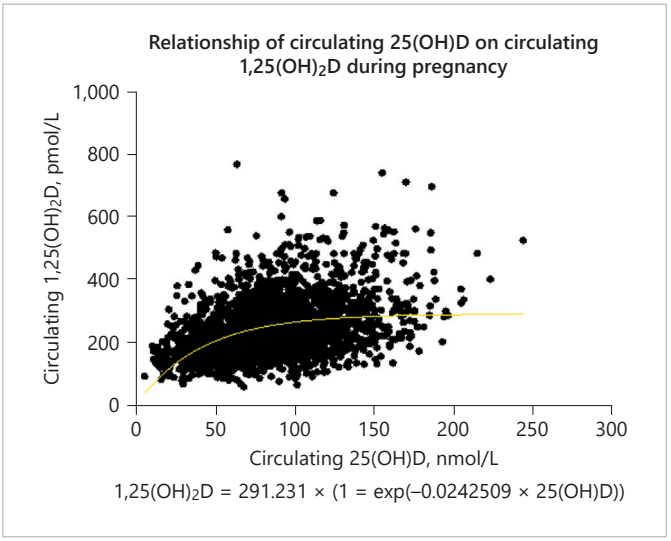

Fig. 2. The relationship of circulating 25(OH)D to control the production of 1,25(OH)$_2$D during pregnancy. All data points for all subjects in all groups were included in this analysis. (Hollis et al. [34], 2011, with permission.)

From Birth into Infancy – Achieving Vitamin D Sufficiency during Lactation in Both Mother and Infant

In numerous articles published during the last 3 decades, it is stated that breast milk has a relatively low vitamin D concentration and, as a result, all babies who are breastfed should receive a vitamin D supplement of 400 IU/day to prevent vitamin D deficiency that can lead to osteopenia and rickets in the exclusively breastfed infant [49–51]. This recommendation is based on the observations since the 1930s and beyond that infants and children who received one teaspoon of cod liver oil (which contains about 400 IU/teaspoon) had minimal risk of developing rickets. It does not address how we evolved as a species with such low concentrations of vitamin D. Most young infants today in technologically dependent societies are not exposed to direct sunlight until well after 6 months, and so their ability to use ultraviolet light to synthesize vitamin D endogenously is thwarted. If we look at groups throughout the world who live in sun-rich environments, we see a pattern that differs from those who live at higher latitudes – maternal vitamin D status is better if the mother is exposed to the sun [52], and, therefore, her milk anti-rachitic activity – the total

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amount of vitamin D moieties in human milk – is better. It is critical to understand that human milk is deficient in vitamin D only when the mother herself is deficient [53]. We know that during pregnancy, maternal vitamin D status is closely linked with fetal and neonatal vitamin D status. That connection and relationship continues during lactation.

That if a mother had an improved vitamin D status, then her milk anti-rachitic activity would be improved and that of her recipient infant, obviating the need for infant vitamin D supplementation

It was hypothesized by Hollis and Wagner [54] more than 2 decades ago that if a mother had an improved vitamin D status, then her milk anti-rachitic activity would be improved and that of her recipient infant, obviating the need for infant vitamin D supplementation. Maternal vitamin D supplementation would effectively treat both the mother and her breastfeeding infant. This was studied in 2 pilot studies by our group [54, 55] and then in a larger trial sponsored by the National Institutes of Health [56] that has since been repeated by Dawodu et al. [57] in another region of the world – the Middle East – where there is profound vitamin D deficiency. In the various trials, mothers at 1 month postpartum were randomized to receive 1 of 3 treatments: 400, 2,400, or 6,400 IU vitamin D/day. Infants of mothers in the 400-IU group received the standard of care of 400 IU/day, while infants of mothers in the 2,400- and 6,400-IU group received 0 IU/day (placebo). Maternal supplementation with 2,400 IU vitamin D/day with infants on placebo resulted in higher rates of infant insufficiency and that arm of the study was stopped early-on in the study. Mothers in the 6,400-IU group had improved vitamin D status, milk anti-rachitic activity, and their infants had circulating 25(OH)D concentrations that were comparable to infants receiving 400 IU/day direct supplementation [55, 56]. There were no safety issues noted in these studies except with the 2,400 IU arm and the higher rates of infant deficiency, but no issues with toxicity from vitamin D. Similar results were reported by Dawodu et al. [57].

Oberhelman et al. [58] studied 40 exclusively breastfeeding mothers and infants who were randomized to receive either daily maternal vitamin D supplementation of 5,000 IU/day versus a single large bolus of 150,000 IU once as a higher bolus vitamin D, with the primary outcome at 28 days being maternal and infant vitamin D status. The daily versus single bolus were comparable at 28 days; however, the mother and infant pair who received the single bolus had a large increase in their circulating 25(OH)D that rapidly declined but was still improved compared to baseline.

A systematic review and meta-analysis by O'Callaghan et al. [59], reviewing relevant studies on the topic of alternatives to daily infant vitamin D supplementation through September 2018, identified 28 relevant papers of which 5 were randomized clinical trials that met inclusion criteria for the analysis. The meta-analysis suggests that the results are promising, with the need for larger studies in diverse groups of women necessary to be carried out before policy changes can be made [59].

While application of alternatives to infant supplementation are being discussed, a major issue complicating recommendations is that compliance by parents to give their breastfeeding infants daily vitamin D drops is low in many regions of the world [60, 61]. In the USA, reports of compliance with the recommendation of infant vitamin D supplementation range from 9 to 20%, leaving most breastfeeding infants in the USA deficient, dependent on their mothers who are often themselves deficient [62–64]. These are less than satisfying statistics. At the end of the day, where maternal compliance with taking a vitamin D supplement is much greater than that of parental adherence with infant supplementation, maternal vitamin D supplementation alone remains as a viable alternative to infant vitamin D supplementation that safely and effectively treats both the mother and her breastfeeding infant.

Conflict of Interest Statement

The writing of this article was supported by Nestlé Nutrition Institute, and the author declares no other conflicts of interest.

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Focus

For toddlers and children, not only are the recommendations varied, but so are vitamin D intake and parental knowledge regarding child vitamin D needs

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Vitamin D in Toddlers, Preschool Children, and Adolescents

Sarah N. Taylor

Key Insight

Our knowledge of vitamin D has greatly expanded over the past decades, partly due to our efforts to address the persistent deficiency in global populations and its association with a wide range of diseases. Aside from its established role in bone health and calcium homeostasis, vitamin D is now known to have far-reaching effects on many organ systems. Sufficient vitamin D status has been shown to confer a protective effect on the incidence of type I diabetes mellitus, allergic diseases such as asthma and atopic dermatitis, as well as infectious diseases. In spite of the inconclusive findings from many supplementation trials, it is clear that there is a need to maintain minimal levels of this key vitamin to support optimal growth and organ function.

Public health organization	Deficiency	Sufficiency
American Academy of Pediatrics (AAP)	<50 nmol/L of 25(OH)D	
European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)	<25 nmol/L of 25(OH)D (severe deficiency)	>50 nmol/L of 25(OH)D

General recommendation for children:
Vitamin D supplements of 10–50 µg/day

25(OH)D, 25-hydroxyvitamin D

Current thresholds for vitamin D deficiency and sufficiency and recommended daily supplementation in children.

Current knowledge

The late 1990s witnessed a small but significant resurgence in infant vitamin D deficiency rickets. This led to a period of intense debate and research on the optimal vitamin D levels in adults and children. Much effort was directed towards identifying the vitamin D levels required to facilitate intestinal calcium absorption, to lower parathyroid hormone concentrations, and to optimize bone mineralization. The results of these studies pointed towards 75–100 nmol/L as the lower limit of vitamin D sufficiency in adults. These findings led to a revision of the recommended levels of daily vitamin D for adults as well as for infants and children.

Practical implications

The best indicator of nutritional vitamin D status is the level of circulating 25-hydroxyvitamin D (25[OH]D), mainly due to its 2- to 3-week half-life and its importance for numerous organ systems. There is still a lack of clarity in defining the specific doses needed for children of different ages, from birth to adolescence. Instead, the upper limits of recommended intake are used as a guide (i.e., the European Food Safety Authority's upper limit of 25 µg/day for infants, 50 µg/day for children aged 1–10 years, and 100 µg/day for children aged 11–17 years). Toddlers and young children are at especially high risk of vitamin D deficiency, particularly those from low-income or immigrant populations and those with underlying diseases (i.e., obesity, cystic fibrosis). Current data indicate that vitamin D supplementation in the range of 10–50 µg/day is safe for use in children.

Recommended reading

Marino R, Misra M. Extra-skeletal effects of vitamin D. Nutrients. 2019 Jun;11(7):E1460.

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Annales Nestlé

Vitamin D

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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$[OH]_2$D) from 25(OH)D, these organs form 1,25$(OH)_2$D 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

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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.

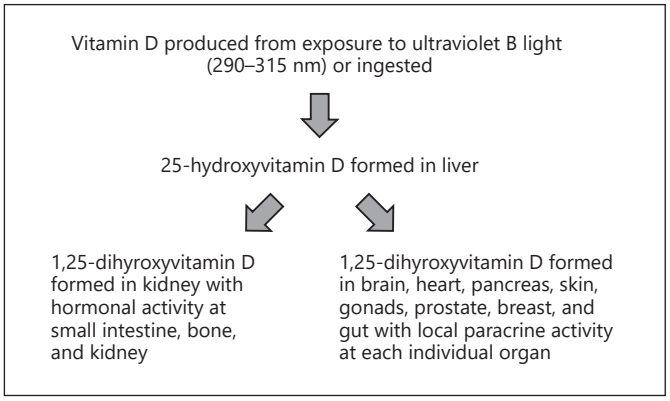

Fig. 1. Production of active vitamin D in humans.

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 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

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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

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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 D_3. 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 nonlinear 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

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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-

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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.

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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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