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Vitamin D supplementation – still a subject of debate

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Abstract

Vitamin D is a standard vitamin supplementation for children in many countries, used mainly for preventing rickets. Many studies were published about the efficiency of vitamin D administration in children and adults for other pathologies besides rickets. Very often the results were contradictory, but nevertheless, more and more articles are published on this matter. There is no consensus for the effective vitamin D dosage nor for the vitamin D normal serum values. Both vitamin D deficiency and vitamin intoxication are dangerous for children. Recently some studies are showing controversial data that advise being more careful in prescribing vitamin D as a routine.

Keywords: vitamin D, rickets, deficiency, intoxication, consensus, controversies

INTRODUCTION

Vitamin D (VD) is a group of secosteroids that promotes the absorption of calcium (Ca) and phosphorus (P) within the intestinal tract and complements bone mineral metabolism. Vitamin D has a critical role in human health, however, vitamin D deficiency can be found in every child and adult. Without an optimal calcium-phosphorus ratio, collagen matrix mineralization is diminished and symptoms of rickets in children and osteomalacia in adults occur [1-5]. The benefits of breastfeeding the newborn and infant are undeniable as breast milk contains almost all important vitamins. Despite the many benefits of breast milk, some reviews have shown that prolonged or single breastfeeding is linked to certain dietary diseases, including vitamin D deficiency [6-7].

Low maternal vitamin D intake throughout pregnancy will increase the likelihood of vitamin D deficiency in young children [8].

Beyond its classical function as a regulator of calcium and phosphate metabolism, it plays a fundamental role in bone health regardless of age, and its deficiency is associated with several health problems. Typical effects of vitamin D deficiency in pregnancy and newborns have been late-onset hypocalcemia and nutritional rickets. However, recent studies link vitamin D to fertility and some clinical manifestations during pregnancy: pre-eclampsia, gestational diabetes, higher incidence of cesarean section and premature birth, low birth weight, low bone mass and possible association with the development of diseases such as bronchiolitis, asthma, type 1 diabetes, multiple sclerosis and autism. Vitamin D supplementation and achieving optimal lev-

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els support maternal fertility and reduce neonatal complications. Supplementing children with VD reduces the risk of respiratory infections, autoimmune diseases and autism [9].

Why are the recommendations for vitamin D supplementation so different?

Recommendations and consensus from different countries vary widely in their recommendations for daily vitamin D requirements for healthy children. The reasons behind these variations are as follows: a) the values defining VD deficiency continue to be intensely debated and vary widely; b) exposure to sunlight differs according to geographical location [10, 11]; c) nutritional habits, race, skin color, sunscreen use, air pollution, economic system and cultural influences are factors that may affect values [12]. Previous studies have shown that as altitude increases, VD synthesis with skin increases [13,14]. People with dark tone skin have a higher risk for VD deficiency than people with light skin. d) differences in dosing techniques, e) lack of dose-response studies about vitamin D administration in youth and adolescents has hindered the improvement of evidence-based guidelines.

Optimization of vitamin D intake in the body can be estimated by measuring serum 25(OH)D concentration. It is recommended that 25(OH)D is greater than 20 ng/mL (50 nmol/L) serum. A distinction must be made between the two forms of vitamin D, 25(OH)D2 and 25(OH)D3. The half-life for 25(OH)D3 is longer than that of 25(OH)D2, and the affinity of vitamin D binding protein for 25(OH)D3 is higher than that of 25(OH)D2 [15,16]. As a result, the opinion that VD2 and VD3 are equivalent should be treated with great caution and the results of dosing the two types of vitamin D cannot be compared.

Vitamin D administration in newborns

Vitamin D supplementation is a general recommendation for breastfed newborns. Breast milk does not contain vitamin D in sufficient amounts to meet the needs of infants [17]. The recommended daily dose of vitamin D for newborns is 400 IU/day according to the AAP [18]. Recommended daily doses of vitamin D range from 100 IU to 1000 IU [19,20]. In the past, the AAP [51] has indicated that 200 IU/day of vitamin D would be sufficient to prevent rickets. It has been observed that despite a daily intake of 400 IU of vitamin D, some newborns have a blood level of 25(OH)D <32 ng/ml in winter, even in countries where mothers have a vitamin D-enriched diet [21]. This has led to the routine administration of 400 IU/day of vitamin D and an even higher dose in northern regions, starting from the first days of life.

A few studies have shown that preterm infants born <32 weeks (and especially those <28 weeks) are more likely to be vitamin D deficient compared to term normotensive infants [22,23]. Approximately 10% to 20% of extremely low birth weight preterm infants have radiological evidence of rickets with metaphyseal changes, despite current feeding practices [24].

Rickets in premature infants is correlated with insufficient calcium and phosphorus intake. Phosphorus deficiency is at least as important as calcium deficiency in the etiology of this disease [25].

Vitamin D intoxication

Easy accessibility to vitamin D without a prescription and routine recommendation of vitamin D without prior investigation are risk factors for overdose and intoxication [26]. More recently, there has been increased interest in assessing vitamin D levels during pregnancy and the effects of vitamin D deficiency on the fetus [9]. However, vitamin D intoxication (VDI) is as important as vitamin D deficiency, as there is no consensus on when to start vitamin D supplementation, the optimal dose and duration of treatment, and the optimal vitamin D level during pregnancy [27].

Vitamin D intoxication usually sets in due to inappropriate use of high-dose vitamin D on the advice of doctors in cases suggesting vitamin D deficiency, such as delayed teething, or genu varus and delayed gait. Other causes of VDI include the prescription of vitamin D supplements by physicians prior to a paraclinical diagnosis of vitamin D deficiency [28]. Tolerable upper limits for vitamin D administration according to the AAP are 1000 IU/day for 0-1 year, 2500 IU/day for 1-3 years, 3000 IU/day for 4-8 years, and 4000 IU/day for age 9 years and older [29]. Patients with VDI usually present with symptoms of hypercalcemia such as polyuria and polydipsia, decreased appetite, weight loss, and gastrointestinal manifestations such as nausea, vomiting, and constipation; they may also present with dehydration and seizures in severe cases [27]. In VDI, high levels of either free 1,25(OH)2D or 25-hydroxyvitamin D lead to hypercalcemia through intestinal calcium absorption and bone resorption [30]. Hypercalcemia increases the burden in the kidneys due to calcium excretion in the distal tubules, causing hypercalciuria. It can also lead to nephrocalcinosis [26].

Vitamin D intoxication (VDI) is scarce but not uncommon, with a recent uprise in its reporting [28]. Overdose and intoxication can occur due to prescribing, manufacturing or formulation errors [31]. Patients and doctors should be more conscient about the potential effects of vitamin D overdose. According to the American Academy of Pediatrics (AAP), serum 25-hydroxyvitamin D (25(OH)D) levels above 250 nmol/L (100 ng/ml) are considered hypervitaminosis D. Conversely, serum 25(OH)D levels above 375 nmol/L (150 ng/ml) are associated with vitamin D intoxication (VDI) [32].

The role of vitamin D in immunity

Several studies have been published on a possible correlation between DV supplementation and reduced risk of autoimmune disease, along with type 1 diabetes [59-61] and inflammatory bowel disease [34], with conflicting results. Experimental data suggest that VD may modulate monocyte, macrophage and dendritic cell responses and interleukin production [35].

Published data suggest the involvement of VD in suppressing T lymphocyte proliferation and the adaptive immune machinery, causing a switch from a Th1 to a Th2 phenotype by inducing T cell regulatory function [36,37].

B lymphocytes also express VD receptors. When activated, they can inhibit differentiation into plasma cells and modulate immunoglobulin production [38]. These results could provide an explanation for the link between variable serum levels of VD and the likelihood of developing an autoimmune disease [39].

Vitamin D and respiratory distress syndrome

The effect of vitamin D on lung maturation and on lung disease early in life is a new area of research. Some data from laboratory animals shows that vitamin D deficiency is a risk factor for NRDS.

Yu et al. [40] indicated that low serum vitamin D level at birth is an independent risk factor for NRDS. Dogan et al. [41] postulated that higher serum vitamin D levels in preterm infants may prevent NRDS.

In recent years, several laboratory animal studies have found that vitamin D deficiency is also implicated in the development of respiratory diseases in children [42-44]. NRDS is one of the most common respiratory diseases in newborns. In contrast, in the most recent prospective study, when the cut-off value used was 10 ng/ml, vitamin D status in preterm infants was not found to correlate with NRDS, which was opposed to the results of previous studies [45]. Therefore, their relevance is still highly controversial.

A meta-analysis was used to explore the correlation between vitamin D levels and risk of developing NRDS. A total of 9 high-quality studies were included. The results of the meta-analysis indicated that 25(OH)D levels of newborns in the NRDS group were lower than those in the non-NRDS group, suggesting that vitamin D deficiency is likely to be a risk factor for NRDS.

The mechanism of vitamin D involvement in the development of NRDS is unclear and could include these aspects: (1) Vitamin D is a steroid hormone, which can regulate fetal lung development and induce phosphatidylglycerol and phosphatidylcholine synthesis by binding with the corresponding receptors of alveolar epithelial type II cells to promote surfactant synthesis and secretion in alveolar epithelial cells. Vitamin D insufficiency or deficiency will to some extent affect fetal lung maturation.

Vitamin D deficiency may result in the down-regulation of airway proliferation protein expression, resulting in an inflammatory reaction, small airway spasms, reduced alveolar surface tension and alveolar collapse. (3) Vitamin D deficiency may induce oxidative stress and stimulate the production of large amounts of oxygen free radicals, which may result in lipid peroxidation damage in the respiratory tract and alveoli. (4) Other: some studies indicate that the occurrence of NRDS is related to vitamin D inhibition of PDGF-A mRNA and gene expression protein in lung tissue, and that low-level gene expression will inhibit lung development [46]. Other researchers believe that the occurrence of NRDS is related to polymorphism of vitamin D receptor genes (ApaI, BsmI, FokI and TaqI) [47].

Vitamin D deficiency is most probable a high-risk factor for NRDS, but the vitamin D mechanism involved in the development of NRDS is still unclear and further research is needed. In future research, the therapeutic effect of vitamin D on NRDS and its optimal dose and timing should be explored in a larger number of cases [47].

Vitamin D deficiencies and allergies

Food allergy and food allergy-related anaphylaxis have dramatically and inexplicably increased over the last two decades [48]. It has been hypothesized that low vitamin D levels may increase the risk of food allergy [49]. Plausible mechanisms for the association between vitamin D and food allergy include lack of induction of innate epithelial defenses (such as cathelicidins) by vitamin D or deregulation of tight junction proteins, [50] resulting in a compromised intestinal barrier.

Vitamin D-mediated alteration in the function or composition of the gastrointestinal microbiota is another possible mechanism for triggering allergy. The potential role of vitamin D in promoting food tolerance may also be explained by vitamin D's ability to induce the expression of regulatory T cells that secrete IL-10 [51,52].

According to recent work, vitamin D is more strongly associated with peanut allergy as well as multiple food allergies (peanut, egg or sesame allergy) [53].

Controversies about the use of vitamin D

Various studies on vitamin D supplementation during childhood have reported contrasting results. Greer et al, and Chandy et al. showed that anthropometric measurements at 3 months of age did not differ significantly between infants who received vitamin D supplementation at a dose of 400 IU/day and the control group [54,55]. However, Kumar and colleagues showed that weekly vitamin D supplementation at a dose of 1400 IU improved growth and prevented failure to thrive

in low birth weight infants at 6 months of age, but had a borderline negative effect on head circumference [56]. Some studies have evaluated different doses of vitamin D (200, 400, 800, 1200, 1200, and 1600 IU/day) among healthy breastfed infants. Higher doses of vitamin D increased plasma 25(OH)D concentration but had no effect on growth differences between groups [57,58]. Vitamin D promotes infant growth through Ca and P metabolism, parathyroid hormone expression, and regulation of insulin-like growth factorn [59]. Therefore, vitamin D supplementation may improve infant growth.

A total of 72 infants were successfully evaluated using DXA. However, BMD and BMC were not different between the VD-400 and placebo groups at 4 months of age. Greer and his colleagues revealed that vitamin D3 supplementation at a dose of 400 IU/day increased BMC at 12 weeks in breastfed infants [60]. However, a subsequent study found no significant difference in BMC among breastfed infants who received vitamin D supplementation at 3 and 6 years of age. Months [54]. A Korean study showed that daily vitamin D3 supplementation at a dose of 200 IU did not increase BMD and BMC at 6 months of age [61]. Gallo et al. and Ziegler et al. found no effect of vitamin D on bone mineralization, regardless of dose. They postulated that bone mineral accumulation in breastfed infants is less affected by vitamin D supplementation unless there is a proven deficiency paraclinical [57,58]. In the study published by Lin et al.in 2022 the severe vitamin D deficient group had high levels of iPTH and relatively low BMC. Thus, severe vitamin D deficiency may be a risk factor for rickets and further studies should be performed to validate this result [62].

The paper published by Steven R. Cummings et al. in 2022 indicated that there is no justification for measuring 25-hydroxyvitamin D in the general population or treating it to a target serum level. A 25-hydroxyvitamin D level may be a useful diagnostic test for some patients with conditions that may be causing or may cause severe deficiency. For example, people living in residential environments with reduced sunlight or with malabsorption or those receiving treatments for osteoporosis that could cause hypocalcemia may benefit from vitamin D supplementation.

The VITAL study advances the controversy over the benefits of routine supplementation with vit D. The lack of vitamin D effect on fractures should dispel any suggestion of an important benefit of vitamin D alone to prevent fractures in the larger population. Adding these findings to previous reports and other studies showing a lack of effect for preventing numerous pathologies suggests that doctors should not routinely screen for 25-hydroxyvitamin D levels or recommend vitamin D supplements, and people should not take vitamin D supplements to prevent major conditions or life extension [63].

DISCUSSION

There is no consensus on the dose of vitamin D supplementation needed for a term or preterm infants. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition has recommended higher vitamin D intakes of 800-1000 IU/day for preterm infants [70,71] Although this vitamin D intake is probably safe for administration, data are not available for infants with birth weight <1000 g to assess the safety of providing these vitamin D intakes. A recent report from the AAP nutrition committee recommended that breastfed preterm infants receive 400 IU/day of vitamin D after discharge [72] Formula-fed preterm infants receiving formulas designed for term infants or transition formulas would generally not achieve an intake of 400 IU/day of vitamin D. Administration of 200-400 IU/day of vitamin D may be considered, but there are no data to indicate any clinical benefit for this practice. The amount of vitamin D in the formula will be adequate when the weight of a preterm infant reaches about 5 kg and consumes 800-1000 ml/day of formula. Routine assessment of bone mineral status by monitoring serum alkaline phosphatase (APA), calcium and phosphorus activity is indicated for infants with birth weight <1500 g at 4 weeks after birth and followed every 2 weeks until discharge. Infants with APA >500 IU/L at discharge will need laboratory monitoring every 2-4 weeks until normalization [25].

CONCLUSION

New dietary habits favoring the use of "more natural" forms of vitamin D supplements without the need for a prescription increase the risk of intoxication and abuse. To prevent rickets and support bone health, adequate nutritional intake of calcium and phosphorus should be encouraged and physical activity should be encouraged. VD supplementation should be reviewed according to different situations, offering multiple options for families, or assessing the best choice on a case-by-case basis, especially for less compliant subjects.

Moreover, given the great variability in the causes that might lead to this poor adherence in culturally and economically different settings and countries, specific strategies that might help increase adherence rates to vitamin D supplementation are not easy to identify. In the long term, it remains to be demonstrated whether vitamin D supplementation in children also has beneficial extraskeletal effects. Further studies are needed to establish safe limits for the recommended daily dose and a reassessment of service levels of vitamin D for deficiency and intoxication.

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