Vitamin D deficiency in pediatric clinical practice

Gustavo Cediel, M.D., Ph.D.[a], Johanna Pacheco-Acosta, M.D.[b] and Carlos Castillo-Durán, M.D.[†b]

ABSTRACT

Vitamin D research suggests it has a role in disorders other than bone metabolism.

Objective: To update the information on vitamin D deficiency (VDD) in pediatric clinical disorders.

Methods: Search in virtual libraries, giving priority to clinical and longitudinal studies and meta-analyses on VDD in the pediatric age group published in the past 20 years. The terms "vitamin D deficiency", "children and adolescents" (both in Spanish and English) were used as search descriptors.

Results: In the pediatric population, VDD is associated with different clinical diseases, such as bone alterations, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. Besides, it is associated with prematurity, obesity, malabsorption, use of anticonvulsant agents, and lifestyle characteristics, such as clothing, extreme latitudes, low consumption, and little sun exposure.

Conclusions: According to the evidence, VDD is highly prevalent in several disorders and diseases in the pediatric age group. The recommendation is to prevent VDD in risk conditions and to maintain 25(OH)D serum levels > 75 nmol/L.

Key words: *vitamin D, deficiency, review, child.*

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a. Institute of Nutrition and Food Technology (Instituto de Nutrición y Tecnología de los Alimentos, INTA), Universidad de Chile.
b. Department of Pediatrics, Central Campus of the School of Medicine, Universidad de Chile.

E-mail address:
Gustavo Cediel, M.D.:
gcediel@inta.uchile.cl

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INTRODUCTION

Vitamin D (VD) research has played an increasingly growing role because of the following: 1) VD receptor characterization (nuclear and cytosolic) and the enzymatic machinery that metabolizes VD in multiple tissues (e.g., adipose tissue, muscle, and pancreas);[1] 2) the role related to the regulation of more than 200 genes,[2] and 3) the risk associated with the suboptimal range of 25-hydroxyvitamin D [25(OH)D] and the presence of multiple diseases.[3] As a result, in the field of pediatrics, it is very important to discuss VD's non-bone roles and consider the necessary measures to prevent VD deficiency (VDD).

The objective of this review was to update the information on VDD in some clinical disorders occurring in the pediatric age group. The search was done using the online libraries Pubmed and Scielo, and bibliographic references of other reviews. The terms "vitamin D deficiency", "children and adolescents" (both in Spanish and English) were used as search descriptors. Inclusion criteria were articles published in the past 20 years, giving priority to randomized controlled trials, case-control studies, and meta-analyses.

Vitamin D deficiency in children and adolescents

In the past decade, VDD rickets has re-emerged,[4] mainly in association with a low consumption of VD food sources and little exposure to the sun (winter, clothing and/or excessive sunscreen use).[5,6] Available studies conducted in the pediatric population show that 25(OH)D serum levels range between 24.5 nmol/L (Ushuaia, Argentina) and 116 nmol/L (Tehran, Iran).[7] The size of this problem in children and adolescents in Latin America is unknown; only Mexico has representative data at a national level that show a 54% and 28% prevalence of VD deficiency and insufficiency in preschoolers and school children, respectively.[8] Argentina has representative data available for the Patagonia region in children aged 6-23 months, who had a mean 25(OH)D serum level of 67.5 nmol/L (95% confidence interval [CI]: 65.3-69.8), with extreme values ranging from 10.5 to 177.5 nmol/L. As observed, values for the provinces assessed in the months closer to winter (Chubut, Neuquén, and Santa Cruz) are significantly lower than in those

assessed in November and December (Río Negro, Tierra del Fuego, and La Pampa).[9] Some countries have reported a VDD prevalence in children using non-representative samples, e.g., Colombia: 10-12% (< 50 nmol/L), Brazil: 9% (< 50 nmol/L)[8] and, more recently, Chile: 64% (< 50 nmol/L) among preschoolers from southern regions (> 45° 35′ S).[10] This evidence suggests a high prevalence of VD deficiency and insufficiency in children and adolescents, especially during the winter and at extreme latitudes.

Clinical characteristics of vitamin D deficiency in children and adolescents

Multiple studies have established an association between low 25(OH)D serum levels and the presence of non-bone diseases in children.[3] Below we describe the evidence available on the association between different clinical diseases and VDD in the pediatric age group (*Table 1*).

Prematurity and VDD: The third trimester of gestation is the most relevant period in terms of bone mineral mass gain and, therefore, in this period there is an increase in bone alterations caused by VD deficiency.[11] A recent study assessed 100 children with a gestational age (GA) between 23 and 27 weeks and a mean weight of 770 g who received different VD doses. At 28 days of life, VDD was observed in 41% of infants from the placebo group, in 16% from the group dosed with 200 IU daily, and in 0% from the group dosed with 800 IU daily.[12] This is consistent with the recommendations made by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) to administer VD at 800-1000 IU/day estimated based on feeding and oral supplementation.[13]

Obesity and VDD: The evidence obtained from prepubertal children shows a reverse association between 25(OH)D serum levels and adiposity indicators,[14,15] and this is consistent with the hypothesis of VD sequestration in adipose tissue because of its lipid-soluble nature.[16] These findings are also consistent with a recent study that demonstrated that excess weight in children had an effect on VD supplementation and that these children achieved a lower 25(OH)D increase; therefore, children with excess weight may require higher VD doses than normal weight children to achieve the same 25(OH)D levels.[17] Considering the effect of adiposity on VD bioavailability, countries from central Europe have issued specific recommendations for obese children and adolescents: supplementation with 1200-2000 IU/day (30-50 μg/day) depending on obesity severity during the fall and winter; however, it is recommended all-year round if skin synthesis is not enough during the summer.[18]

The evidence suggests that the active form of VD [1,25(OH)2D] regulates gene transcription in adipogenesis, inflammation, and insulin

TABLE 1. *Recommendations for vitamin D supplementation in different diseases in the pediatric age group*

Disease	Recommendation
Obesity	Administer VD3 at 1200-2000 IU/day.[18]
Insulin resistance	Administer VD3 at 4000 IU/day for 6 months to obese children and adolescents with VDD.[20]
Metabolic syndrome	Studies are still required to clarify adequate VD dosing and duration and establish its effects.
Type 1 diabetes	Administer VD3 at 2000 IU/day.[38]
Cystic fibrosis	- Children < 1 year old: VD3 at 400-800 IU/day; if 25(OH)D < 75 nmol/L, increase to a dose between 800 IU and up to 2000 IU. - Children 1-10 years old: VD3 at 800-1000 IU/day, up to 4000 IU/day if 25(OH)D < 75 nmol/L. - Children > 10 years old: VD3 at 800-2000 IU/day, up to 10 000 IU/day if 25(OH)D < 75 nmol/L, until reaching values from 75 to 150 nmol/L.[37]
Celiac disease	Gluten-free diet. Administer VD3 at 400-600 IU/day and adhere to calcium requirements.[40]
Respiratory tract infections	Studies are still required to clarify adequate VD dosing and duration in relation to beneficial effects.
Asthma	There is no strong evidence to support VD3 supplementation at 500-1200 IU/day.[56]
Neurological diseases	Administer VD3 at 800-1000 IU/day.[41]

VD: vitamin D.

resistance in the adipose tissue of obese patients.[19] In addition, in muscle and pancreas, 1,25(OH)2D may improve insulin sensitivity through the regulation of calcium flow in these tissues, by controlling insulin secretion in pancreatic beta cells and increasing insulin receptor expression in peripheral tissues.[1] Recent results obtained from prepubertal children show a mild reverse association between 25(OH)D serum levels and insulin resistance indicators, even after adjusting them for adiposity. The 75 nmol/L cut-off point for 25(OH)D is the best predictor for these conditions.[14] A controlled clinical study conducted in obese children and adolescents aged 9-19 years found a significant reduction in the homeostatic model assessment of insulin resistance (HOMA-IR) in the active group versus the placebo group following the administration of 4000 IU/day of VD3 for 6 months (active group: -1.36 versus placebo group: +1.2).[20] In addition, knowledge on the active form of VD as a hormone with insulin-like actions in children started almost 20 years ago, and it has been observed that VD supplementation reduces the risk for type 1 diabetes.[21-25] The correlation to type 1 diabetes may be attributed to the systemic anti-inflammatory actions of VD as an immunomodulator, acting on dendritic cells, T cell differentiation, and the interference in cytokine generation and action.[26]

Metabolic syndrome and VDD: A cross-sectional analysis of the 2001-2004 National Health and Nutrition Examination Survey (United States) found that low VD levels in adolescents were strongly associated with metabolic syndrome, regardless of adiposity.[27] Another study conducted in Argentine indigenous schoolchildren (a group at a higher risk for dyslipidemia) showed a reduction in low density lipoproteins cholesterol (LDL-C) following VD supplementation (beta = -0.41, $p < 0.01$).[28-30] Although the biological mechanisms involved in these associations have not been completely elucidated yet, the evidence suggests that VD acts as a cardiovascular and renal protective factor by suppressing the renin-angiotensin-aldosterone system, which inhibits vascular calcification and plaque formation, and also has anti-inflammatory and immunomodulatory actions.[31-33]

Intestinal malabsorption syndromes and VDD: VDD prevalence in patients with intestinal malabsorption syndromes, including cystic fibrosis (CF), celiac disease (CD), short bowel syndrome, and inflammatory bowel disease, is higher than in the general population. VD decrease in these patients is the result of several factors, such as a reduced absorption of lipid-soluble vitamins, a greater inflammation-mediated extrarenal expression of CYP27B1, and hyperparathyroidism secondary to hypocalcemia in some patients; this leads to a greater 25(OH)D conversion into 1,25(OH)2D and, therefore, lower 25(OH)D levels.[34]

Cystic fibrosis and VDD: The prevalence of an inadequate VD status in patients with CF may be as high as 95%.[35] Ninety percent of the CF population have pancreatic insufficiency, which causes malabsorption of fat and, therefore, lipid-soluble vitamins, including VD. However, VDD has also been observed in up to 50% of patients with CF who have a normal pancreatic function.[36] In recent years, outcomes other than bone health in relation to VD have been assessed in children with CF; in this regard, recent studies have established an association between 25(OH) D levels and pulmonary function and bacterial colonization by *S. aureus* and *Pseudomonas sp*.[36] At present, the United States Cystic Fibrosis Foundation recommends measuring 25(OH) D every three months and adjusting the dose to achieve sufficient levels of 25(OH)D (> 75 nmol/L).[37]

Celiac disease and VDD: VD and calcium levels are reduced in most patients with untreated CD. This is because of several reasons: malabsorption caused by epithelial-intestinal damage, milk restriction due to the associated lactose intolerance and/or reduced calcium binding protein expression, which is regulated by VD. Also, studies have not found a relationship between healthy people and CD patients in terms of VD receptor polymorphisms. Tanpowpong and Camargo described the hypothesis that VDD led to a deregulated immune response, especially a disruption of the intestinal mucosal integrity in the antigen presentation (gluten) and microbial antigens (viral gastrointestinal infections), which promoted an unfavorable microbial environment among individuals who are genetically predisposed to developing CD. Thus, VDD during a critical period of life such as the first year may increase the risk of developing CD in the future.[39] The objective is to maintain 25(OH)D levels > 75 nmol/L and, to this end, the main treatment is a strict gluten-free diet, which has shown improvements in VD and calcium serum levels as well as in bone mineral density in children and adolescents.[40]

Anticonvulsant agents and VDD: VDD prevalence in children with epilepsy receiving anticonvulsant agents is above 50%.[41] Phenytoin, phenobarbital, and carbamazepine interfere with VD metabolism. These drugs act at the hepatic microsomal level by inducing the activity of cytochrome P450 hydroxylase enzymes, thus leading to an accelerated VD and metabolite catabolism and a reduced activity; however, such enzyme inducers are only one of the factors associated with VDD. Other associated factors include polypharmacy, anticonvulsant therapy duration (79% of VD deficiency and insufficiency cases have been observed with more than 2 years of treatment), prostration, nasogastric or gastrostomy tube feeding.[41] As a result, the recommendation is to administer VD supplementation at a dose of 800-1000 IU/day to children with neurological disease.[41]

Respiratory tract infections and VDD: During the first year of life, the risk for respiratory syncytial virus (RSV) bronchiolitis is higher if VD cord blood levels are < 50 nmol/L.[42] The studies conducted in Germany by Łuczyńska et al.[43] reported that the risk for acute lower respiratory tract infections (ALRTIs) practically doubled in infants with VD cord blood levels < 25 nmol/L. In addition, there is a seeming relationship between VDD and a more severe RSV bronchiolitis. Such reduction in the response against RSV may be associated with the Fok-I polymorphism of VD receptor and a VD-mediated lower inflammatory response of airway epithelial cells.[44] In addition, VD has been described as being effective to reduce the risk for influenza and to achieve an adequate vaccine response because it activates T cells.[45,46] Our search results showed no evidence that would support a beneficial effect of VD supplementation to prevent acute respiratory infections, reduce mortality or the rate of hospitalizations due to respiratory infections.[47]

Asthma and VDD: Several studies have established an association between VDD and asthma severity. Einisman et al.[48] found no differences in 25(OH)D levels between healthy and asthmatic children; however, the group of children with asthma showed a difference in the levels of sufficiency of 25(OH)D, which were higher among asthmatics according to the Global Initiative for Asthma (GINA) treatment step 4. Also in this group, the Fok-I C allele of the VD receptor was present in all children, unlike the other children with asthma. A recent meta-analysis assessed studies on VD supplementation (VD3 doses ranging from 500 to 1200 IU/day) and showed a significant reduction in the risk for asthma exacerbation (RR = 0.28, 95% CI: 0.12-0.64).[49] There is still no consensus on the doses and duration of VD in children with asthma; however, most of the evidence is in favor of using VD3 at a dose of 500-1200 IU/day together with the standard asthma treatment.

Other clinical disorders associated with VDD: Recent studies have established an association between VDD and other clinical disorders. For example, it is worth noting the association between VDD and menarche, which started 9 months earlier among girls with VDD compared to those with normal VD levels in Bogotá, Colombia.[50] A reverse association has been reported between 25(OH)D levels and systolic blood pressure in adolescents.[51] There are other studies that have been conducted in recent years and showed a potential association with some forms of cancer, both in adults and children.[2] Future studies will demonstrate if VDD management prevents any of these diseases.

Vitamin D deficiency prevention in children and adolescents

According to the evidence, exposure to ultraviolet rays in a small portion of the dorsal area of the body rapidly increases 25(OH)D plasma levels until reaching a plateau at 15 minutes.[52] This has prompted the recommendation that the population should be exposed to sunlight for 15 minutes at least 3 times a week to cover VD requirements; however, similar studies are required in children and adolescents to validate this suggestion. In case of no sun exposure (e.g., few activities outdoors, weather conditions, clothing or seasonality), intake becomes the main source of VD. Given that few foods contain enough VD to cover vitamin requirements (*Table 2*) and that food vitamin contents vary depending on cooking methods (e.g., fried fish loses 50% of VD),[53] strategies such as fortified food consumption and the administration of 400 IU/day during the first year of life have proven to be cost-effective.[15] Decades ago, oral doses of 600 000 IU were used worldwide to prevent VDD. However, subsequent studies found a higher probable effect on calcium metabolism, height involvement, and increased blood pressure.[54] Subsequent studies have found that a dose between 100 000 and 150 000 IU is enough to prevent VDD without known adverse effects.[55] *Table 3* includes some

recommendations to prevent VDD in the pediatric population.

Vitamin D deficiency management

The evidence suggests that VD supplementation in clinical disorders at risk for VDD mentioned in this review to maintain 25(OH)D serum levels > 75 nmol/L, the current cut-off point for sufficient levels, with potential modifications (*Table 1*). In most cases, VD3 doses between 400 and 1000 IU may be enough to maintain these values; however, if that is not the case, the dose should be adjusted whenever possible and 25(OH)D levels should be checked until reaching optimal levels. It has been suggested that children with 25(OH)D levels < 25 nmol/L should be referred to a specialized team for their assessment and management.

CONCLUSIONS

Available studies suggest that VD deficiency and insufficiency in the pediatric population is high. Several body functions may be affected by VD deficiency: bone, glucose, and acute immune metabolism, autoimmunity, etc.; VD nuclear receptors may also be involved. Certain clinical disorders associated with VDD include obesity, prematurity, breastfeeding, intestinal malabsorption syndromes, and use of anticonvulsant agents, together with lifestyle conditions, body-covering clothing, living at extreme latitudes, low consumption of food sources, and little exposure to the sun.

More and more clinical disorders are now associated with VDD, so future studies are required to clarify VD's role in non-bone parameters in children and adolescents. The recommendation is to prevent and detect VDD in an early manner in the case of risk conditions and to maintain 25(OH)D serum levels > 75 nmol/L.

Homage

This manuscript is published in memory of Carlos Castillo-Durán, M.D.[†]

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TABLE 2. *Selected food contents of vitamin D*

Food*	Content (IU/100 g or mL)	Serving measured at home (g or mL)	Content (IU/serving)	% of adequacy for ≤ 1 year old (400 IU)	% of adequacy for > 1 year old (600 IU)
Salmon	522	Fillet (124 g)	647	161.8	107.8
Horse mackerel	292	3 oz fillet (85 g)	248	62	41.3
Tuna	82	3 oz fillet (85 g)	70	17.5	11.7
Liver	49	Slice (68 g)	33	8.3	5.5
Cheese (cheddar-like)	24	1 oz slice (28 g)	7	2	1.2
Egg (yolk)	530	Unit (17 g)	37	9.3	6.2
Mushrooms	18	Unit (19 g)	3	1	0.5
Milk (fortified)	49	Cup (250 mL)	120	30	20

* Data from the United States Department of Agriculture (USDA) per 100 g or mL and per serving.
IU = international units = 0.025 μg. Adequate percentage of vitamin D for children ≤ 12 months old, adults > 71 years old and other groups according to the American Institute of Medicine: vitamin D requirements for term infants up to 12 months old are 400 IU, for adults older than 71 years, 800 IU, and for other groups, 600 IU.[57]

TABLE 3. *Vitamin D deficiency prevention in children and adolescents*

The following recommendations have been made to prevent vitamin D deficiency in the pediatric population:

- Adequate sun exposure to the face, hands or legs (at least 3 times a week for 15 minutes).
- In extreme latitudes and during the winter, ensure an adequate consumption of food sources (*Table 1).*
- For infants, administer VD3 at 400 IU/day until 1 year old –due to the low VD content in breast milk, 22 IU/L (15-50 IU/L)–[53] and in extreme latitudes, analyze the possibility of a higher dose and extend it to other pediatric age groups. Consider the possibility of substituting daily doses with high single doses (100 000 IU of VD) 2-3 times a year in case of problems with administration throughout the year.[58]
- Prevent overweight and obesity.
- Assess VD nutritional status in clinical diseases at risk for deficiency and administer according to recommendations *(Table 1).*

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