ORIGINAL PAPER

EVALUATION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND DEFICIENCY IN CHILDREN

OANA MARIA OPREA[1], RALUCA MARIA VLAD[1,2,*]

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Abstract. *Vitamin D is not just a fat-soluble vitamin with important roles in bone health and calcium homeostasis; key functions in regulating innate immune response and modulating intestinal inflammation or allergic reactions are evidence-based findings in the last decade. Attributing the term of deficiency or insufficiency is irrelevant, but correct prophylaxis and treatment for inadequate levels of vitamin D is essential to maintaining good bones, efficient immunity, and low risk of intestinal inflammation. However, the dosage for maintenance and therapeutic purposes should be tailored to individual needs, considering factors like age, severity of deficiency, and comorbid conditions. Addressing vitamin D deficiency through supplementation, food fortification, and sunlight exposure is key to improving public health.*

Keywords: *Vitamin D; deficiency; rickets; children.*

1. INTRODUCTION

Fat-soluble vitamin D is important to bone health due to its implication in calcium homeostasis [1]. Few foods contain vitamin D; it is predominantly found in fatty fish. In some parts of the world, cereals, infant formulas, or bread may be fortified with vitamin D. However, the most important natural source is dermal synthesis after exposure to ultraviolet radiation. It is subsequently metabolized twice to its hormonally active form, 1,2,5-dihydroxyvitamin D, and catabolized to 24,25-dihydroxyvitamin D [1,2]. Vitamin D metabolism is represented in Figure 1 [3].

Vitamin D is also necessary for the optimal functioning of many tissues unrelated to the calcium economy and is now proven to be involved in the autocrine signaling system by which various tissues control cell reproduction, differentiation, and apoptosis [4].

The role vitamin D also plays as a key regulator of innate immune responses to microbial threat is intensely discussed in the last decade. 25-hydroxyvitamin D 1α-hydroxylase is induced in immune cells (macrophages) by immune-specific inputs, leading to local production of 1,2,5-dihydroxyvitamin D at sites of infection. This process directly induces the expression of antimicrobial peptides encoding genes. Moreover, this locally produced hormonally active form of vitamin D stimulates autophagy, a critical control mechanism for intracellular pathogens like Mycobacterium tuberculosis [5]. Autophagy is an important facet of immune responses to intracellular infections and boosts microbial clearance [6]. Poor vitamin D status is associated with increased susceptibility to viral infections. Vitamin D administration during the COVID-19 pandemic was one of the therapeutic

[1] "Grigore Alexandrescu" Emergency Children's Hospital, 011742 Bucharest, Romania.
[2] "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania.
* *Corresponding author: raluca.vlad@umfcd.ro.*

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interventions that helped reduce disease severity, morbidity, and mortality and accelerate recovery [5]. While there were some conflicting results reported, the consensus is that vitamin D has immunomodulatory effects, which may have been beneficial in the context of SARS CoV-2, and that low levels of vitamin D have resulted in the dysfunction of antimicrobial effects, potentially contributing to poor prognosis of COVID-19 [7].

In Crohn's disease (CD), defective intestinal innate immunity is a proven fact, and vitamin D deficiency is commonly found in CD patients [8]. Several studies have been published stating that vitamin D supplementation may be beneficial for CD patients. A systematic review demonstrated that a low 25-hydroxyvitamin D status is associated with increased odds of inflammatory bowel disease activity, mucosal inflammation, subsequent clinical relapse, and low quality of life in CD [9]. Li et al. evaluated 18 randomized clinical trials and found decreased relapse rates in CD patients treated with vitamin D [10].

There is a lot of debate in the published literature on the link between vitamin D and allergies. The vitamin D to Prevent Severe Asthma Exacerbations (VDKA) Study did not find any significant improvement in time to a severe asthma exacerbation by supplementing vitamin D3 in children with persistent asthma and low vitamin D levels [11], but a cross-sectional study in Cyprus proved that the average vitamin D level of asthmatic children was lower, and the vitamin D level was negatively correlated with the severity of asthma [12], while Bener et al. compared the vitamin D levels of asthmatic versus healthy children in Qatar, and also considered vitamin D deficiency a major predictor of childhood asthma [13]. Willitis et al. did not identify a significant association between vitamin D status and food allergy [14], but Allen et al. showed that in infants who already have food sensitization, those who are vitamin D deficient have a 6-fold risk of developing food allergies rather than food tolerance [15]. Most studies support the negative correlation between vitamin D levels and atopic dermatitis: Germany [16], Egypt [17]. Furthermore, the more severe the vitamin D deficiency, the higher the atopic dermatitis scores in Korean [18] and Indonesian [19] studies. No correlation was demonstrated in Japan [20] and Norway [21].

1.1. PHYSIOLOGY AND PHYSIOLOGICAL FUNCTIONS OF VITAMIN D

Vitamin D has several forms: cholecalciferol (D_3) - found in some particular food or supplements and also formed in skin by UV light action; ergocalciferol (D_2) - found mostly in supplements; Calcidiol (25-hydroxyvitamin D) – formed in the liver through 25-hydroxylation - it's serum concentration is used to evaluate the vitamin D level; Calcitriol (1,25-dihydroxyvitamin D – the active form of vitamin D) - formed in the kidney under the process of 1-alpha-hydroxylation controlled by parathyroid hormone (PTH) [1,22]. Ergocalciferol (vitamin D_2) is converted from ergosterol found in fungi or yeast on exposure to UVB light. Similarly, cholecalciferol (vitamin D_3) is converted from 7-dehydrocholesterol found in human skin on exposure to UVB light [23]. The vitamin D forms are schematically presented in Figure 1. Therefore, vitamin D deficiency may be caused by pathology of any of these different mechanisms: a diet poor in vitamin D, malasorbtion diseases or lack of sunlight, liver and renal pathologies that affect enzymatic processes or genetic disorders resulting in decreased enzyme activity at any level [24, 25].

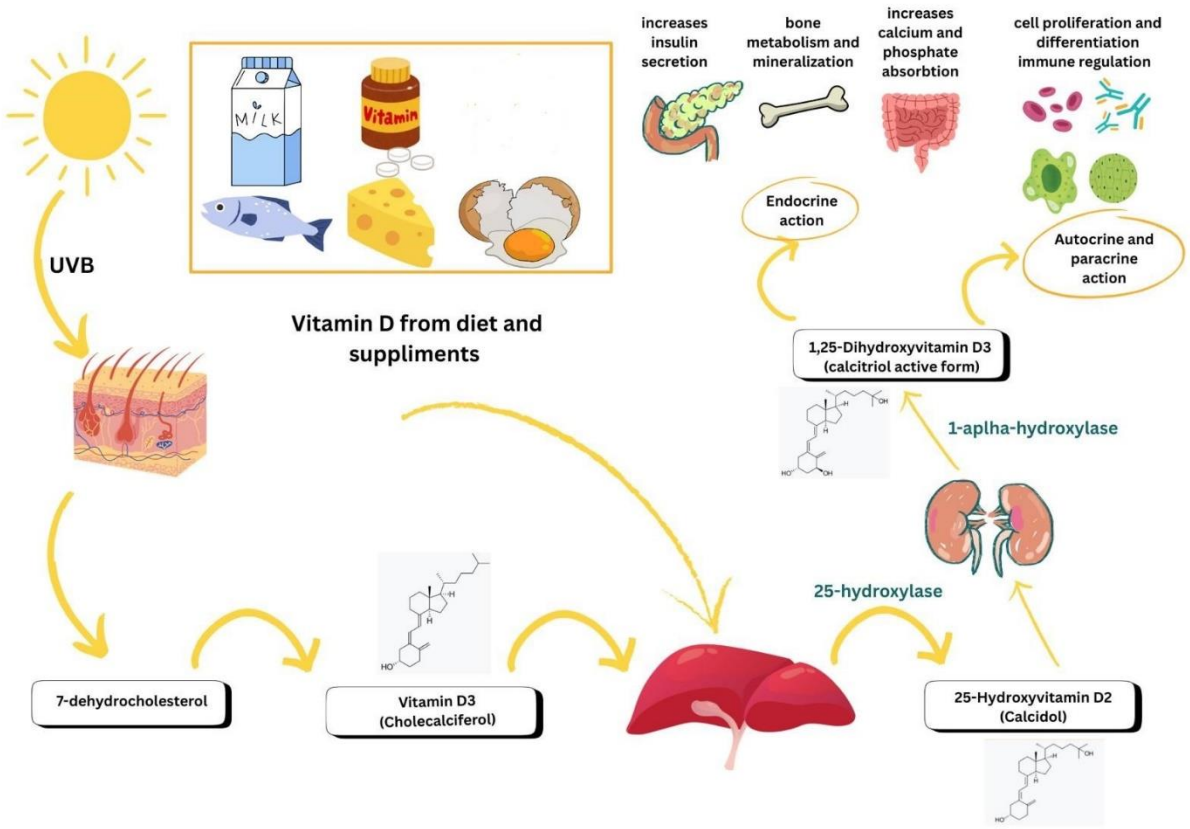

Figure 1. Schematic representation of vitamin D sources, metabolism, and physiological functions

Vitamin D plays an important role in bone growth by maintaining a balance between osteoblasts and osteoclasts. Low levels of vitamin D lead to impaired calcium intestinal absorption, which is translated as hypocalcemia. Hypocalcemia, in turn, stimulates the secretion of PTH. PTH tries to normalise serum calcium concentration by stimulating absorption, decreasing calcium renal excretion, and increasing phosphate renal excretion.

High levels of PTH also increase osteoclast activity and cause calcium to be released from bone. This combination of low serum phosphate levels due to renal excretion and increased osteoclast activity due to hyperparathyroidism results in bone demineralization [26].

1.2. INSUFFICIENCY AND DEFICIENCY OF VITAMIN D

Vitamin D replacement is indicated in patients with clinical signs of rickets or with low serum 25-hydroxi-Vitamin D (25(OH)D). Until recently, to define the need for vitamin D supplementation the level of 25(OH)D was used, thereby defining “deficient” status when serum 25(OH)D was lower than 20 ng/mL and “insufficient” status when serum 25(OH)D was 20 ng/mL to 29 ng/mL [27]. Relying on a single cutoff value to define vitamin D deficiency or insufficiency is problematic because of the wide individual variability of the functional effects of vitamin D and interaction with calcium intakes [28]. According to the Endocrine Society, in 2024, this practice was abandoned in healthy patients as no links were found between distinct serum levels and clinical outcomes [27].

Vitamin D deficiency remains widespread; Adolescents from nine European countries were evaluated in Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study for vitamin D levels, and 80% were below the threshold of sufficiency, more than 40% being

deficient/severely deficient [5,29]. This finding is to be expected as dietary intakes estimates from Europe are generally low in vitamin D, less than about 55% of the recommendations [30], vitamin D deficiency being evident throughout the European population at prevalence rates that are concerning and that require action from a public health perspective [31]. Even in more southern countries, such as India, poor vitamin D status is common [5,32].

2. CLINICAL FEATURES AND CASE STUDY

In terms of clinical manifestations, vitamin D deficiency can lead to rickets in children and osteomalacia in all age groups. The literature also describes muscle weakness or walking difficulties due to secondary hypophosphatemia and, occasionally, seizures or tetany [1].

The most common clinical signs of rickets are: craniotabes, macrocrania, sometimes delay in closing of the anterior fontanelle, generalised muscular hypotonia, deformities of the ribs and thus the chest wall resulting in the so-called rachitic rosary along the costochondral junctions (Figure 2), flaring over the diaphragm, which is known as Harrison groove. Knobby deformity is seen on radiography as cupping and flaring of long bones (Figure 3) [33].

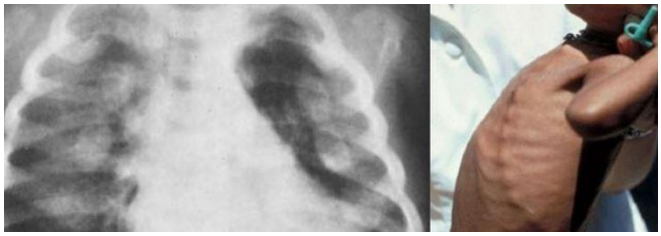

Figure 2. Rachitic Rosary - Wide sternal ends of the ribs at the costochondral junction.

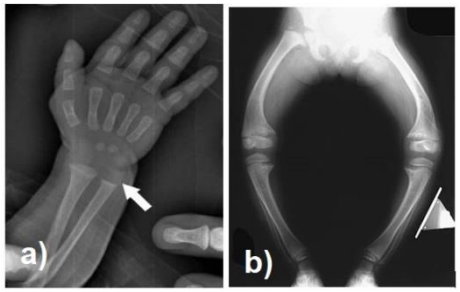

Figure 3. Radiological signs of rickets: a) Left hand-wrist radiograph: metaphyseal widening and irregularities in radius and ulna, decrease in bone density b) Fraying, splaying, and cupping of metaphysis with reduced density; bowing of bilateral tibia and femur

A 1 year 9 months old boy presented to the Pediatrics Department of “Grigore Alexandrescu” Emergency Children’s Hospital, Bucharest for failure to thrive. He was readily diagnosed with celiac disease. Among other clinical findings related to this disease, signs of severe malabsorption were present, and amidst other deficits, florid rickets. Macrocrania, with frontal and parietal bossing, flaired chest, with Harrison groove and rachitic bracelets were described upon physical examination. The blood tests confirmed the diagnosis: normal serum calcium but low serum phosphate with increased urinary phosphate excretion, increased alkaline fosfatase (x 2 normal value), and severely decreased 25-hydroxyvitamin D (5 ng/mL).

3. INTAKE RECOMMENDATIONS

Exposure to sunlight is one of the major determinants of vitamin D status. The amount of sunlight necessary for optimal vitamin D status varies by individual factors (skin tone, adiposity, and age), season, latitude, and time of day. It is difficult to recommend increased exposure to sunlight as a public health strategy to improve vitamin D status because of concerns over skin cancer risk [23]. Therefore, there has been increased interest in improving vitamin D status by either recommending vitamin D supplement use or fortifying foods with vitamin D. Some foods such as meat, fish, and eggs contain vitamin D naturally as the hydroxylated vitamin D metabolite 25-hydroxyvitamin D. However, it is unknown whether 25(OH)D3 found in foods or supplements has the same impact on vitamin D status compared with vitamin D3 (cholecalciferol). The randomized controlled clinical trial by Cashman et al. evaluated the potency of oral supplementation with $25(OH)D_3$ compared to vitamin D_3 in raising total serum 25-hydroxyvitamin D in adults. They found that supplementation with $25(OH)D_3$ resulted in 4–5 times higher serum 25(OH)D concentrations compared with supplementation with vitamin D_3 [23,34]

Since vitamin D is found in few foods, supplementing and fortifying foods remains a valid solution. Most international guidelines recommend vitamin D prophylaxis during the first year of life. In terms of doses, for children born at term who are fed with milk formula, a dose of 400 UI/day is considered sufficient to prevent deficiency. On the other hand, the supplementation of the lactating mother's intake was considered for breastfed infants, but the excretion in the milk is too small. For this reason, prophylaxis is also applicable with the same doses. Regarding premature newborns, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), recommends prophylaxis with 800-1000 UI/day to prevent symptomatic deficiency, despite the United States recommendations of 400 UI/day. After 12 months of life, evidence about pediatric vitamin D supplementation needs are controversial [26, 35, 36].

Regarding vitamin D replacement therapy, the literature is rich in dosing schemes used in clinical practice. Infants (<1 year old) require treatment with 2000 IU/day for 6-12 weeks, then a 400 IU/day maintenance dose. Children older than one require 2000 IU/day for 6-12 weeks, followed by a maintenance dose of 600-1000 IU/day. A special situation applies to children with clinical rickets; they require higher doses of vitamin D, between 3000 and 6000 IU/day [1, 36].

Early clinical studies have suggested that cholecalciferol is superior to ergocalciferol in sustaining higher serum 25(OH)D concentrations, Vitamin D_2 potency being less than one third that of vitamin D_3 [37], but subsequently different authors report different efficacy of vitamin D_2 and vitamin D_3 in maintaining vitamin D status and normal serum concentrations: Holick et al found that a 1000 IU dose of vitamin D_2 daily was as effective as 1000 IU vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels [38], while Logan et al concluded that daily supplementation of vitamin D_3 was more effective than D_2 [39]. Tripkovic et al. conducted a systematic review and meta-analysis of 10 randomized controlled trials and found a significant mean difference in serum 25(OH)D in favor of cholecalciferol (i.e., vitamin D3) compared with ergocalciferol (i.e., vitamin D2) supplementation. These results suggest that cholecalciferol may be the preferred form of vitamin D for use in supplements or food fortification [40]. However, the functional consequence of various metabolic responses warrants further investigation; also, the effects across age, sex, and ethnicity may induce significant differences in responses [39,40].

Concomitant calcium supplementation should be considered for patients with hyperparathyroidism or clinical signs of rickets, along with vitamin D supplementation.

Vitamin D replacement and a normalization of PTH concentrations can precipitate hypocalcemia by suppressing bone resorption, also known as the "hungry bone" syndrome. To prevent hypocalcemia, calcium replacement should be given at doses of 30-75 mg/kg/day, administered in two to three doses, for 2-4 weeks or until vitamin D doses have been reduced to maintenance levels [1, 36]. In the case study, the patient received 2000 IU/day of Vitamin D3 with 50 mg/kg/day of oral calcium in the first two weeks of treatment.

4. MONITORING AND FOLLOW-UP

Depending on the severity of the vitamin D deficiency, these patients can be monitored in different ways. To begin with, the patients who only present low levels of 25-hydroxyvitamin D without biochemical changes or signs of rickets do not require sustained monitoring. They will be monitored for 25(OH)D after two or three months of treatment initiation, considering the patient's adherence to treatment. Secondly, those who have biochemical changes (PTH or alkaline phosphatase) but without signs of rickets require vitamin D dosing four to six weeks after the initiation of treatment and then monthly for several months. Finally, patients with signs of rickets require close follow-up to document radiographic healing and normalization of serum 25(OH)D, PTH, calcium, and phosphorus concentrations [1,41].

Some studies tried to use vitamin D-related biomarkers to review the response to treatment. Thus, it has been shown that for each 100 IU increment in vitamin D intake, serum 25(OH)D increases by 1.7 nmol/L (equivalent 0.68 mg/mL) [42].

The male toddler presented was closely monitored clinically and biochemically (serum calcium, phosphate, alkaline phosphatase, and 25 hydroxyvitamin D). Frontal and parietal bossing significantly decreased, and rachitic bracelets were no longer present. The serum 25(OH)D level evolution in clinical treatment from September 2024 until January 2025 is depicted in Table 1 and Figure 4.

Table 1. Evolution of total serum 25(OH)D over 4 months of oral supplementation in the toddlers diagnosed with celiac disease and florid rickets

Vitamin D oral dose	**Serum 25-hydroxyvitamin D [ng/mL]**		
	Initial	**After 1 month**	**After 4 months**
2000 IU/day	5.0	12.0	35.0
References values [ng/mL]	**Deficiency**	**Insufficient level**	**Optimal level**
	≤ 20.0	21.0-29.0	30.0-55.5

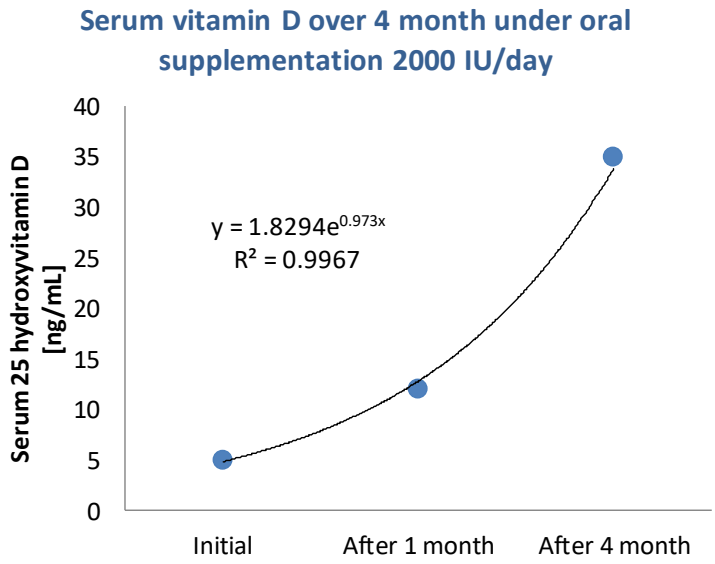

Figure 4. Serum vitamin D over 4 months under oral supplementation 2000 IU/day

Considering that vitamin D deficiency is very common in all age groups and few foods contain vitamin D, the Task Force recommended supplementation at the suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. Measurement of serum 25-hydroxyvitamin D level is recommended at initial diagnostic in patients at risk for deficiency. Treatment with either vitamin D_2 or vitamin D_3 is recommended for deficient patients. Currently, there is insufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the noncalcemic benefit of cardiovascular protection [43].

5. CONCLUSIONS

Vitamin D is not just a fat-soluble vitamin with important roles in bone health and calcium homeostasis; key functions in regulating innate immune response and modulating intestinal inflammation or allergic reactions are evidence-based findings in the last decade.

The relationship between vitamin D levels and clinical outcomes remains complex. While vitamin D supplementation is crucial for individuals with low levels or those at risk for deficiency, the optimal dosing remains a topic of debate. Current guidelines recommend vitamin D supplementation during the first year of life and for individuals with conditions like rickets or hyperparathyroidism. However, the dosage for maintenance and therapeutic purposes should be tailored to individual needs, considering factors like age, severity of deficiency, and comorbid conditions.

Defining vitamin D deficiency solely based on serum 25(OH)D levels is no longer sufficient, as individual responses to vitamin D and interactions with calcium intake vary significantly. Moreover, the effectiveness of different vitamin D forms, such as vitamin D_2 and D_3, in maintaining adequate serum levels warrants further investigation, particularly with respect to long-term outcomes. The growing evidence supporting the immunomodulatory effects of vitamin D underlines the need for a better understanding of its role in chronic diseases and infections.

Addressing vitamin D deficiency through dietary supplementation, food fortification, and controlled sunlight exposure remains a necessary public health strategy, particularly given its widespread prevalence and impact on health. Ongoing research into vitamin D's broader

physiological roles and optimal therapeutic approaches will be vital to improving health outcomes and informing future recommendations.

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