Review

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Vitamin D deficiency in childhood: old lessons and current challenges

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Abstract: Hypovitaminosis D in childhood is a re-emerging public health problem in developed countries. New life style habits, current "epidemics" of obesity in children and adolescents worldwide, and other preventable risk factors may play a role in favoring the occurrence of vitamin D deficiency. In addition to skeletal consequences, hypovitaminosis D has been found to be involved in the development of serious health extra-skeletal problems in childhood, including atopy and autoimmunity. The increasing concerns about the global health impact of vitamin D deficiency make further research necessary to fill the gaps of knowledge in this field, and particularly to establish universally accepted "normal" serum 25(OH)D levels in the pediatric population, and to improve strategies for the screening, prevention and treatment of hypovitaminosis D. This review discusses the key points of hypovitaminosis D in childhood in the light of new knowledge, and highlights the limitations of current strategies to control this condition.

Keywords: children; extra-skeletal manifestations; hypovitaminosis D; newborns; rickets; screening; vitamin D.

Introduction

Sterols were discovered by Adolf Windaus who received the Nobel Prize in Chemistry in 1928 for his studies on the constitution of sterols and their connection with vitamins [1]. About a century ago, the sun's ultraviolet radiation was discovered to promote the conversion of cholesterol into vitamin D, thus preventing rickets. Vitamin D is a prohormone that plays a crucial role in the control of calcium and phosphorus metabolism, and is an essential determinant of bone health in childhood and adolescence. In recent years, emerging evidence suggests that vitamin D also has effects on extraskeletal tissues, as many cells throughout the body express the vitamin D receptor. In tissues including brain, heart, pancreas, stomach, gonads, prostate, lymphatics, and skin, vitamin D appears to play a role in improving immune function and reducing inflammation [2].

Vitamin D status in pediatric age has been greatly investigated around the world, particulary in US and in Europe. Available data on children and adolescents show that hypovitaminosis D is widespread and represents a re-emerging global health problem.

The deficiency of vitamin D is known to cause rickets in children and osteomalacia in adults. After the identification of vitamin D and the introduction of vitamin D supplementation of foods, nutritional rickets virtually disappeared from developed countries. However, in the past two decades, multiple factors have led to a resurgence of the disease, with an increasing number of cases particularly involving non-Caucasian children [3].

Current challenges in this field include the need to establish a universally accepted "normal" vitamin D status, and to improve strategies for the screening, prevention and treatment of hypovitaminosis D [4, 5].

This review discusses the key points of vitamin D deficiency in childhood in the light of new knowledge, and highlights the limitations of current strategies to control this condition.

Vitamin D: metabolism and biological activities

Calciferols are a group of fat-soluble secosteroids also known as the "D vitamins". Two forms of vitamin D are

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of practical importance: vitamin D_2 (ergocalciferol – plant-derived) and vitamin D_3 (cholecalciferol – animal-derived). Both can be ingested from different dietary sources; the latter can also be synthesized in the skin after exposure to ultraviolet B (UV-B) radiation [6].

Both cholecalciferol and ergocalciferol are biologically inactive, and their activation requires sequential hydroxylation reactions in the liver and kidney. In the liver, the two forms of vitamin D are converted to the 25-hydroxylated compound (25(OH)D), which is subsequently stored in the liver and in body fat. When required, it is then converted in the kidneys by the enzyme 1-alpha hydroxylase into the biologically active form of vitamin D ($1,25(OH)_2D$), under the control of the parathyroid glands. This form of vitamin D is also produced in other tissues such as bowel cells, vascular smooth muscle cells, B lymphocytes, monocytes and dendritic cells [7, 8].

The active form of vitamin D circulates in the blood mainly bound to an albumin superfamily protein named "vitamin D binding protein" (VDBP) [9]. Functioning as a hormone, $1,25(OH)_2D$ arrives at the target organs where it exerts its action through the cytosolic vitamin D receptor (VDR). The nearly ubiquitous expression of this receptor is able to explain the numerous mechanisms regulated by vitamin D. The active metabolite of vitamin D binds VDR, enters the cell nucleus and then activates gene expression [10]; up to 1250 genes are estimated to be regulated directly or indirectly by $1,25(OH)_2D$ [11].

A number of biological activities of $1,25(OH)_2D$ are well known. It is responsible for increasing intestinal absorption of calcium and phosphorus, bone resorption and for decreasing renal excretion of calcium and phosphorus, in order to maintain bone health. Together with parathyroid hormone (PTH) and calcitonin, $1,25(OH)_2D$ acts to maintain plasma calcium levels within the normal range. Moreover, it can influence the host's immune system through the modulation of both innate and adaptive immunity, and the regulation of the inflammatory cascade [12–30]. Most immune cells express VDRs, primarily after they have been stimulated [31]. Mechanisms of action and effects of vitamin D on immune system cells are summarized in Table 1.

Sources of vitamin D

Diet

In nature, there are few dietary sources of vitamin D. Natural vitamin D sources include oily fish (sardines, herring, tuna, mackerel, salmon, etc.), cod liver oil, egg yolks, shitake mushrooms, and liver and organ meats. Only negligible amounts are found in vegetables, cereals and fruits. In the usual diet of infants, the vitamin D content is small. In human milk, it is low and influenced by maternal exposure to ultraviolet radiation, skin pigmentation, clothing, season, latitude and maternal diet [32]. Lactating women treated with 4000 IU of vitamin D_3 per day, not only showed an increase in 25(OH)D levels to more than 30 ng/mL, but were also found to transfer enough vitamin D_3 into their milk to meet an infant's requirement [33].

Infant formulas contain about 40–120 IU/100 kcal (400 IU/L) [34].

Unfortunately, most natural sources of vitamin D are not frequently consumed by children, therefore fortifying food with this vitamin may become important if there is inadequate sunlight exposure.

Sunlight exposure

The main source of vitamin D is sun exposure [35] as skin synthesis contributes 80–90% of an individual's serum 25-hydroxyvitamin D levels. Skin exposure to UV-B component of sunlight (wavelengths 290–315 nm) results in the photochemical isomerization of 7-dehydrocholesterol to previtamin D_3. The stratum basale and the stratum spinosum of the epidermis possess the greatest capability of previtamin D_3 synthesis. Once formed, previtamin D_3 isomerizes to vitamin D_3, which is then transported to the extracellular space and dermal capillaries.

Children, and particularly infants, need less sun exposure to produce sufficient amounts of vitamin D due to both greater surface area for size and greater ability to produce vitamin D, as compared to older people [36].

Skin pigmentation, sunscreen use, time of the day, season, altitude, latitude and clothing dramatically influence sun-induced skin synthesis of vitamin D_3. In people with darker skin, the high levels of melanin reduce the skin's ability to synthesize vitamin D after sunlight exposure [37]. Sunscreen absorbs UV-B and some UV-A radiation thus preventing it from reaching the skin. The use of sunscreens with a sun protection factor of 8 can reduce cutaneous vitamin D_3 synthetic capacity by 95% [38]. The exposure to sunlight before 10 a.m. or after 3 p.m., or to winter sunlight, results in little, if any, vitamin D_3 skin production [39]. People living in the Northern latitudes, women wearing long robes and head coverings, and housebound subjects may not obtain adequate vitamin D from sunlight.

Table 1: Immunological effects of vitamin D.

Target Cells	Mechanisms of action	Effects	References
Humoral components of innate immunity	Increased production of cathelicidin hCAP18 and defensin β2–4	Chemotatic action and toxic neutralization	Lemire et al. [12]
Monocyte/dendritic cell (DC)	Inhibition of p38 MAP kinase [13] Decreased NF-kB activation [14] Decreased expression of TLR 2 and 4 [15] Decreased production of TNFα, IL-6, IL-12 and IL-23 [16]	Decreased fuction, maturation and antigen presentation [16], with an overall anti-inflammatory effect [17]	Zhang et al. [13] Yu et al. [14] Sadeghi et al. [15] D'Ambrosio et al. [16] Wöbke et al. [17]
T lymphocyte			
Th1	Decreased DC function Decreased IL-12 [15], IL-2, IFN-γ production [18] Increase of IL-10 [19]	Inhibited development and function	Matheu et al. [18] Chang et al. [19]
Th17	Up-regulation of Smad3-VDR complex (hypothesis) Down-regulation of CCR6	Inhibited development and function	Chang et al. [19]
Th2	Uncertain	Both high and low 25(OH)D levels have been associated with increased aeroallergen sensitization and elevated IgE levels	Kerley et al. [20]
T-regulators	Increased IL-10 production [19] Up-regulation of ILT3 [21] Increased Foxp3 function [22]	Favored development and function of CD4 + Foxp3 + regulatory T cells [21,22] with anti-inflammatory effects	Chang et al. [19] Penna et al. [21] Morales-Tirado et al. [22]
B Lymphocyte	Up-regulation of p27 [23]	Inhibition of proliferation, differentiation to plasmacells and immunoglobulin production [23]. Increased IL-10 production [24]	Chen et al. [23] Heine et al. [24]
Airway smooth muscle (ASM)	Reduced growth [25] Reduced contractility [26] Decreased proinflammatory cytokine production (like RANTES) [27] Decreased MMP-9 and ADAM-33 production [28]	Influence on lower airways remodelling and inflammation	Damera et al. [25] Bosse et al. [26] Banerjee et al. [27] Song et al. [28]

MAP kinase, mitogen-activated protein kinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR, toll-like receptor; Smad3, small mother against decapentaplegic 3; CCR6, chemokine receptor 6; ILT3, immunoglobulin-like transcript 3 (ILT3); Foxp3, forkhead box P3; RANTES, regulated on activation normal T cell expressed and secreted; MMP-9, matrix metallopeptidase-9; ADAM-33, a disintegrin and metalloprotease domain-33.

Hypovitaminosis D

Hypovitaminosis D may result from inadequate nutritional vitamin D intake, inadequate sunlight exposure, disorders reducing vitamin D absorption, and conditions that impair vitamin D conversion into active metabolites. Additionally, life style habits, ethnicity and genetic polymorphisms, in a variable combination, affect the vitamin D status and the risk of hypovitaminosis D in children.

Several studies have investigated vitamin D status and hypovitaminosis D in childhood, both in developed and developing countries [40–48]. Over the past two decades, the reappearance of nutritional rickets has been reported in North America, Europe and the UK, in various ethnic groups. In a Canadian study, the annual incidence of nutritional rickets was found to be 2.9 per 100,000 (0–18 years) [49]. A UK study by Callaghan et al. [50] reported an incidence of 7.5 per 100,000 per year among 0–5-year-old children, with the highest incidence in African children (95 per 100,000). In southern Denmark, Beck-Nielsen et al. [51] determined an incidence rate of 2.9 and 5.8 per 100,000 per year among 0–14.9 year old and 0–2.9 year old children, respectively. In Italy, migrant and adopted children have been found to be groups at high risk for rickets [52, 53]. Moreover, other Italian studies revealed a high prevalence of vitamin D deficiency in pediatric

age, with a significant proportion of newborns (46.3%) and children (6.2–20%) having serum 25(OH)D levels <10 ng/mL [48, 54–56].

Risk factors for hypovitaminosis D

Age related factors may play a role in increasing the risk of vitamin D deficiency.

At birth, the newborn vitamin D status depends mostly on the maternal vitamin D status. Low maternal vitamin D levels during pregnancy have been shown to be associated with adverse neonatal outcomes, including small for gestational age and preterm births [57, 58]. Preterm infants are more prone to be vitamin D deficient. In this group of infants, vitamin D stores at birth can be lower than those of full-term infants, but they seem to be mostly influenced by the vitamin D status of mother rather than the shortened gestation time [59, 60]. Additionally, preterm infants are unlikely to be significantly exposed to ultraviolet light (specifically UV-B) during hospitalization and after their hospital discharge, so they are substantially dependent on exogenously derived vitamin D.

During childhood and adolescence, hypovitaminosis D is mostly a consequence of a poor and unbalanced diet, even in developed countries. During the first years of life, exclusive breastfeeding without adequate sun exposure or vitamin D supplementation is an important risk factor for vitamin D deficiency [61], whereas, in adolescence, the frequent consumption of fast and junk food is a relevant risk factor.

Other risk factors include obesity, diseases interfering with vitamin D activation or fat absorption, life style and drugs.

There is evidence for the role of obesity as a risk factor for vitamin D deficiency. The sequestration of vitamin D into adipose tissue, or the increased adipose storage capacity of this vitamin, in obese children, can prevent appropriate release of vitamin D resulting in deficiency states [61, 62]. However, there is no evidence that vitamin D deficiency, in children with increased body fat mass, has negative effects on bone mineral density and bone health [63].

Diseases involving one of the steps of vitamin D metabolite activation such as severe liver or renal failure [64], and diseases interfering with fat absorption (celiac disease, cystic fibrosis, inflammatory bowel disease [IBD], short bowel syndrome, patients with percutaneous gastrostomy, food allergies) are known to increase the risk of developing vitamin D deficiency.

Another increasing risk factor is a sedentary lifestyle, due to the time spent in front of screens, including TV and computer games. Sedentary habits reduce time spent outdoor in sunlight, on the one hand, and on the other hand, increase the risk of obesity [65].

Also the chronic use of certain drugs (anticonvulsants including phenytoin and carbamazepine, systemic glucocorticosteroids and antifungals) can interfere with vitamin D pathways, leading to hypovitaminosis D [66, 67].

Finally, genetic factors may contribute to increasing the risk of hypovitaminosis D.

Several single nucleotide polymorphisms (SNPs) of vitamin-D related genes have been reported to be associated with hypovitaminosis D [68, 69]; this may explain the wide inter-individual variability in vitamin D sensitivity, which may affect disease risk.

The *VDR* gene, located on chromosome 12q13-14, exhibits several polymorphic regions [70]. Two common polymorphisms at the *VDBP* gene on chromosome 4q12-q13 also affect circulating 25(OH)D levels [71].

Pediatric groups at risk for developing hypovitaminosis D are summarized in Table 2 [62, 67].

Vitamin D status and clinical manifestations of hypovitaminosis D

Vitamin D status may have skeletal and extraskeletal effects, which are described in the following sections.

Skeletal effects

Vitamin D sufficiency and adequate intake of calcium are both required for bone health. In childhood, bone mineralization may be negatively affected by vitamin D deficiency or insufficiency. Moreover, vitamin D has been shown to have direct and indirect effects on muscle [72].

Vitamin D deficiency leads to a decreased intestinal absorption of calcium and phosphorus. The parathyroid glands recognize the low serum concentrations of calcium and release PTH in order to elevate the serum calcium back into a normal range. PTH increases the calcium reabsorption and the phosphorus excretion in the kidneys, while it stimulates bone resorption thus decreasing bone mineralization. In the short term, low levels of vitamin D may be tolerated in infants and children, therefore the

Table 2: Pediatric groups at-risk for vitamin D deficiency.

At-risk group	Mechanism of vitamin D deficiency
Newborns born to mothers with vitamin D deficiency	Insufficient stores
Preterm infants	Insufficient stores
Exclusively breastfed Infants	Decreased intake
Infants without vitamin D supplementation	Decreased intake
Children with darker skin	Decreased skin synthesis
Children living at higher latitudes during winter and spring season	Decreased skin synthesis
Children with restricted sunlight exposure	Decreased skin synthesis
Obese children	Increased sequestration in adipose tissue [62]
Children with severe liver failure	Decreased synthesis of 25(OH)D
Children with severe renal failure	Decreased synthesis of $1,25(OH)_2D$
Children with chronic diseases reducing fat absorption	Decreased intestinal absorption
Children with skin diseases	Decreased skin synthesis
Children under chronic treatment with systemic glucocorticoids	Enhanced inactivation of 25(OH)D by up-regulation of 24-hydroxylase activity [67]
Children under chronic treatment with anticonvulsants (CBZ, PHT, TOP and PB)	Increased hepatic vitamin D catabolism
Migrant children and adopted children	Multiple mechanisms

CBZ, carbamazepine; PHT, phenytoin; TOP, topiramate; PB, phenobarbitone.

majority of them show few or no symptoms. Conversely, when vitamin D deficiency continues for weeks to months, stunted growth and florid rickets may develop.

Rickets is primarily caused by a nutritional deficiency of vitamin D, but may also be due to calcium and phosphorus deficiency or, more rarely, to other causes (e.g. familial hypophosphatemic rickets, and mutations of vitamin D receptors). Recently, nutritional rickets has been defined as follows: "Nutritional rickets (NR), a disorder of defective chondrocyte differentiation and mineralization of the growth plate and defective osteoid mineralization, is caused by vitamin D deficiency and/or low calcium intake in children" [73].

Nutritional rickets may show a very variable clinical presentation. Children with rickets commonly present with symptoms of bony deformity (genu varum or genu valgum, anterior bowing of the femur, internal rotation at the ankle, swelling at the wrist, prominence of costochondral joints, and abnormal softening of the skull bone) and muscle weakness. Irritability and impaired growth may also be present. Severe vitamin D deficiency may give rise to hypocalcemic seizures or tetany, especially in the neonatal period and during the pubertal growth spurt. Cardiomyopathy and even heart failure may develop in rare cases of severe vitamin D deficiency. Finally, it has been suggested that rickets may be responsible for unexplained fractures [61].

Extra-skeletal effects

The deficiency of vitamin D has been related to common extra-skeletal disorders of childhood. The vitamin D receptor is present in a large variety of cell types (osteoblasts, small intestine, colon, β islet cells, activated T- and B-lymphocytes, mononuclear cells, etc.) and organs in the body (heart, brain, skin, breast, gonads, prostate, etc.). Vitamin D acts as a potent modulator of human immune responses, also through the local production of $1,25(OH)_2D$, playing a main role in B- and T-lymphocytes' functions (Table 1). Vitamin D deficiency impairs both Th1 and Th2 pathways, leading to atopy, autoimmunity and affecting the host immune response against infections [74].

Over the past two decades, epidemiological studies have suggested that vitamin D deficiency may play a role in a variety of extra-skeletal disorders, and these findings have increased the interest in this vitamin. The major vitamin-D related pediatric disorders are discussed in the following sections.

Asthma

An association between lower serum levels of 25(OH)D and increased asthma severity, decreased lung function, and poor asthma control has been reported [75]. Asthma is classically characterized by enhanced activity of Th2 cells, which induce IgE production and promote eosinophilic airway inflammation and airway hyperresponsiveness. Down-regulation of Th2 immune responses may ultimately explain a primary preventive effect of vitamin D against asthma. In vitro studies have shown that vitamin D may influence airway remodeling by a direct inhibitory effect on airway smooth muscle cells by affecting their growth and contractility and inhibiting fibroblast proliferation [76]. Moreover, Bosse et al. [26] have found that vitamin D enhances the bioavailability of glucocorticoids in bronchial smooth muscle cells, thus suggesting an additional beneficial role for vitamin D.

The down-regulation of glucocorticoid pathways results in the need for higher doses of steroids; conversely, the supplementation of vitamin D might potentiate the anti-inflammatory actions allowing to reduce steroid doses in asthmatic children but not in adults [77, 78]. In a recent meta-analysis of randomized, controlled trials, vitamin D supplementation was found to reduce asthma exacerbations, even if the quality of evidence was low [79]. All together, these findings suggest that hypovitaminosis D can worsen asthma severity. On the other hand, a meta-analysis of seven studies, three of which were conducted in children and four in adults, could not show a beneficial effect of vitamin D on the prevention of asthma exacerbations, fractional exhaled nitric oxide concentration, forced expiratory volume in 1 s (FEV1%) or asthma symptoms [80]. Very recently, a systematic Cochrane review by Martineau et al. [81], including nine randomized clinical trials, has evaluated the effect of vitamin D supplementation in preventing asthma attacks or improving disease control, as compared to placebo or no intervention. The results have revealed that vitamin D presents benefits in terms of risk of exacerbations requiring systemic corticosteroids, and risk of experiencing at least one exacerbation that requires an emergency department visit or hospitalization or both. However, no difference was found between the intervention groups for predicted percentage of FEV1%, asthma control test scores and risk of serious adverse events. The clinical relevance of these findings needs to be assessed, before any recommendation for practice is made.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic, inflammatory skin condition that affects many children worldwide. It is generally caused by a disruption of the epidermal barrier and an abnormal immune response. A recent meta-analysis has documented that serum vitamin D level is lower in patients with AD [82]. Small randomized clinical trials have found that vitamin D supplementation has a therapeutic benefit in children with winter-related AD [83]. However, some results conflicting with those above mentioned have also been reported. The systematic review by Bath-Hextall et al. [84] evaluated dietary supplements, including vitamin D, for the treatment of AD. This review found no benefit from vitamin D supplementation for primary efficacy outcomes (pruritus or sleep loss, or decrease in the number of flares or need for other therapies) or secondary efficacy outcomes (overall severity, quality of life or adverse events).

Type 1 diabetes mellitus

Hypovitaminosis D has been associated with several autoimmune diseases including type 1 diabetes mellitus (T1DM). The association of vitamin D deficiency and T1DM, however, is still debated as conflicting reports have been published. Serum vitamin D level was found to be lower in children with T1DM than in controls [85]. A recent cross-sectional study has documented a generalized 25OHD deficiency impacting metabolic status and glycemic homeostasis, in children with T1DM; additionally, vitamin D supplementation has been found to improve glycemic control [86]. Observational studies have demonstrated that an improved vitamin D status reduces the risk for T1DM. The association between vitamin D intake during early life and a reduced risk of developing T1DM has recently been confirmed [87]. Conversely, other studies conducted on large series of children have found no association between serum 25(OH)D concentration and the development of T1DM [88, 89].

Studies on genetic variants and currently ongoing pediatric clinical trials will help to clarify the effects of vitamin D supplementation and doses in children with T1DM [90, 91].

Inflammatory bowel disease

The two most common forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). These autoimmune conditions are characterized by chronic inflammation of the gastrointestinal tract, and recurrent periods of remission and exacerbation.

Ananthakrishnan et al. [92] showed that higher serum 25(OH)D levels significantly reduced the risk for CD while higher levels non-significantly reduced the risk for UC, suggesting that vitamin D may play a role as a mediator in the pathogenesis of IBD. The retrospective cohort study by Ulitsky et al. [93], including 504 IBD patients (403 CD and 101 UC), showed that 49.8% of them were vitamin D deficient. Vitamin D deficiency was found to be associated with older age, older age at diagnosis, lower health-related quality of life in CD but not UC, and increased disease activity in CD. In the study by Sadeghian et al. [94], patients with CD were shown to have lower circulating 25(OH)D levels compared with controls; an inverse correlation between serum 25(OH)D levels and severity of CD was also found. In contrast, Veit et al. [95] found no difference in serum 25(OH)D levels between children with IBD and controls, while, interestingly, IBD subjects with elevated ESR had significantly lower serum 25(OH)D than controls.

Other vitamin D-related disorders

In addition to the previously discussed disorders, other pediatric diseases have been investigated regarding their association with vitamin D deficiency. Selected recent studies assessing the association between vitamin D status and various extra-skeletal disorders in childhood are reported in Table 3 [96–107].

Deficiency or insufficiency of vitamin D has been shown to result in higher risks of elevated blood glucose levels, hypertension and metabolic syndrome, which are also increasing health issues in children and adolescents. Low levels of vitamin D are also associated with the obesity-related non-alcoholic fatty liver disease, which represents the hepatic manifestation of metabolic syndrome [108, 109]. Adequate levels of vitamin D in pregnancy have been associated with a decreased risk of schizophrenia, while low sunlight exposure has been shown to be associated with mood disturbances and seasonal affective disorder. In addition, vitamin D sufficiency in the mother and infant appear to reduce the risk of developing bipolar disorder [110].

The presence of VDR in vascular smooth muscle and cardiomyocytes, and the potent inhibitory effect of $1,25(OH)_2D$ on renin may contribute to explain why vitamin D deficiency is associated with an increased risk of hypertension, stroke, myocardial infarction and cardiac mortality [111]. Vitamin D deficiency has also been found to be related to prostate, breast and colon cancer [112, 113].

A more detailed discussion of extra-skeletal disorders related to hypovitaminosis D is beyond the scope of this paper.

Assessment of vitamin D status

Total body vitamin D status is usually assessed by measuring serum concentration of 25(OH)D, because of its long half-life (2–3 weeks), relatively abundant circulating levels and resilience to fluctuations in PTH levels [114].

Normal and abnormal serum concentrations of 25(OH)D have been classified by various scientific societies and institutions. The American Academy of Pediatrics (AAP) has classified vitamin D status in the pediatric population using the following 25(OH)D concentrations: severe deficiency for values <5 ng/mL; deficiency for values between 5 and 15 ng/mL; insufficiency for values between 16 and 20 ng/mL; sufficiency for values between 21 and 100 ng/mL; excess for values between 101 and 150 ng/mL; intoxication for values >150 ng/mL [61].

In 2011, after a careful review of available data, the Institute of Medicine (IOM) Committee stated that serum 25(OH)D levels of 16 ng/mL cover the requirements of about half the population, and levels of 20 ng/mL meet the requirements in almost 100% of the population. On the other hand, serum 25(OH)D levels above 50 ng/mL should raise concerns about potential adverse effects [115].

More recently, the "Global Consensus Recommendations on Prevention and Management of Nutritional Rickets" has classified vitamin D status as follows: sufficiency, serum 25(OH)D >20 ng/mL; insufficiency, serum 25(OH)D 12–20 ng/mL; deficiency, serum 25(OH)D <12 ng/mL. Furthermore, according to this consensus, toxicity has been defined as serum 25(OH)D >100 ng/mL and hypercalcemia, with hypercalciuria and suppressed PTH [73].

In contrast, other scientific societies have set the cutoff level for vitamin D sufficiency at ≥30 ng/mL [64, 116].

Screening of hypovitaminosis D

Currently, universal screening of 25(OH)D levels is not recommended, while pediatric groups at higher risk for insufficiency or deficiency should be screened, and supplemented where appropriate. In particular, screening for vitamin D deficiency should be carried out mostly (a) in the presence of nonspecific symptomatology (gross motor delay, unusual irritability and poor growth), (b) in dark-skinned infants living in higher latitudes during winter and spring, (c) in children under chronic treatment with anticonvulsants or glucocorticoids, and (d) in children affected by chronic diseases associated with malabsorption or maldigestion. Screening for vitamin D deficiency should be also considered in children with frequent fractures and evidence of low bone mineral density [61, 64].

Prevention of vitamin D deficiency

In order to prevent vitamin D deficiency there are a few measures we can take. Basically, it is necessary correct the risk factors by means of:

- increasing sunlight exposure;
- fortification of the habitual food supply;
- vitamin D supplementation.

Table 3: Selected recent studies investigating the association between vitamin D status and various extra-skeletal disorders in childhood.

Author (year)	References	Study design	Patients' age	Type of disorder	Main findings
Onwuneme et al. (2015)	[96]	Case control study	<12 years	Sepsis	Children with suspected sepsis had lower serum 25(OH)D than controls, and deficient 25(OH)D status was found to be associated with confirmed sepsis and poor outcomes
Grant et al. (2013)	[97]	Ecological study	6–17 years	Autism	The prevalence of autism was found to be inversely correlated with solar UVB doses, suggesting that vitamin D deficiency is an important risk factor for autism
Modan-Moses et al. (2012)	[98]	Cohort study	Mean age 12.1 ± 5.8 years	Malignant disease	In pediatric patients with a history of malignant disease, a high prevalence of vitamin D deficiency and insufficiency was found, whereas calcium intake was low. Therefore, optimizing their vitamin D status and calcium intake could be advantageous
Lima et al. (2016)	[99]	Randomized controlled trial	18–25 years (onset <16 years)	Systemic lupus erythematosus (SLE)	Vitamin D replacement may improve immune modulation in patients with juvenile-onset SLE and is effective in decreasing disease activity and improving fatigue
Cediel et al. (2016)	[100]	Longitudinal follow-up study	6–8 years	Obesity	Serum 25(OH)D declined with puberty onset, probably because of adiposity increase. The combination of central obesity and suboptimal serum 25(OH)D before puberty onset increased pubertal insulin resistance
Stagi et al. (2014)	[101]	Case-control study	mean age 16.2 ± 7.4 years	Juvenile idiopathic arthritis (JIA)	Patients with JIA showed significantly reduced serum 25(OH)D and higher PTH levels compared to controls. Patients with active disease and/or frequent flares had significantly reduced serum 25(OH)D compared to those with no active disease and no frequent relapses
Sonmez et al. (2015)	[102]	Case-control study	5–16 years	Epilepsy	The level of 25(OH)D3 in newly diagnosed idiopathic epilepsy patients was significantly lower than controls, also when evaluation was made on a seasonal basis
Moreno-Solís et al. (2015)	[103]	Cross-sectional study	1–11 months	Bronchiolitis	The prevalence of hypovitaminosis D was remarkably greater in infants with bronchiolitis than in controls. An inverse correlation was found between serum 25(OH)D levels and disease severity
Vanstone et al. (2015)	[104]	Retrospective chart review	5–22 years	Cystic fibrosis	The number of pulmonary exacerbations (Pex) was significantly associated with 25(OH)D levels. Maintaining vitamin D sufficiency may lead to decreased incidence of Pex and hospitalizations requiring antibiotic therapy
Venturini et al. (2014)	[105]	Multicenter observational study	<18 years	Tuberculosis (TB)	A high prevalence of hypovitaminosis D was documented in children screened for TB. An increased risk of hypovitaminosis D was found in children with active and latent TB compared to controls
Dudding et al. (2015)	[106]	Mendelian randomization study	7–13.5 years	Dental caries	Vitamin D exposure in early life may play a role in caries prevention. Low evidence to support an inverse causal effect of 25(OH)D on dental caries
Bergman et al. (2013)	[107]	Meta-analysis of randomized, controlled trials	6 months–75 years	Respiratory tract infection (RTI)	Vitamin D had a protective effect against RTI, and dosing once-daily appears to be most effective compared to bolus doses

Sunlight exposure

Sunlight exposure reduces the risk of vitamin D deficiency. However, the concern about the role of sunlight exposure in increasing the risk of skin cancer [117, 118] has led to the recommendation of keeping children younger than 6 months out of direct sunlight to prevent skin cancer [119]. Further studies will have to determine the threshold of satisfactory UVB exposure for ensuring a sufficient vitamin D synthesis in infancy without increasing skin cancer risk [73].

Fortification of the habitual food supply

Food fortification practices vary widely throughout the world, mostly depending on both geographical and cultural lifestyle habits. In Canada, vitamin D fortification is mandatory for foods like milk and margarine [120]. Conversely, in the US, the fortification of vitamin D is optional for foods like milk, fruit juices and breakfast cereals [121]. In some European countries, dairy products, fruit juices and cereals are fortified with vitamin D [74]. The vitamin D content of milk and orange juice after fortification should be 400 IU/L.

Current food-fortification strategies may not be sufficient to avoid vitamin D deficiency, particularly in children with darker skin pigmentation, during winter and at higher latitudes. Therefore, a tailored strategy for food-fortification would be necessary, based on skin pigmentation, geography and cultural norms. Until this strategy is available, the vitamin D supplementation remains the main measure to prevent hypovitaminosis D.

Vitamin D supplementation

In efforts to prevent rickets, and to achieve and maintain the target 25(OH)D concentrations, recommendations have been made based on the existing literature. AAP guidelines published in 2008 stated that “breastfed and partially breastfed infants should be supplemented with 400 IU/day of vitamin D beginning in the first few days of life”, and that “supplementation should be continued unless the infant is weaned to at least 1 L/day or 1 qt/day of vitamin D-fortified formula or whole milk”. It was also stated that “All non-breastfed infants, as well as older children who are ingesting less than 1000 mL/day of vitamin D-fortified formula or milk, should receive a vitamin D supplement of 400 IU/day” [32]. In 2011, the IOM proposed a recommended dietary allowance of 400 and 600 IU/day of vitamin D for healthy infants younger than 1 year and for children from 1 to 18 years, respectively [115].

Literature data show that a daily vitamin D supplement of 400 IU is warranted to prevent rickets without adverse effects [122, 123]. Whether this or a larger dose is required to provide infants with the extra-skeletal beneficial effects of vitamin D is unclear. The exact duration of supplementation with vitamin D has not been established. A recent expert position statement has recommended vitamin D supplementation in all children during the first 2 years of life, when growth velocity is particularly high; in older children, supplementation should be tailored according to the sunlight exposure and the presence of risk factors for vitamin D deficiency [74].

Preterm infants are at risk for developing vitamin D deficiency, and may require a vitamin D supplementation dosage different from that used in full-term infants. Based on literature data, a clinical report by the AAP has recommended a vitamin D intake of 200–400 IU/day in enterally fed preterm infants [124]. On the other hand, a recent position statement recommends a vitamin D intake of 400–800 IU per day in preterm infants [74]. In view of the widely different recommendations on vitamin D intake, it seems advisable to monitor 25(OH)D levels of preterm infants to ensure adequate vitamin D status [124].

Treatment of nutritional rickets

Treatment is aimed at replenishing the stores of 25(OH)D, and should be restricted to children with symptomatic hypovitaminosis D, due to the potential for vitamin D toxicity.

Current guidelines advocate various vitamin D regimens. The AAP recommends a 2- to 3-month dosing regimen of vitamin D therapy of 1000 IU/day in neonates, 1000–5000 IU/day in infants 1–12 months old, and 5000 IU/day in children over 12 months old. This course of high-dose therapy should be followed by a maintenance dose of 400 IU/day of vitamin D in all age groups. Larger maintenance doses (800 IU/day) may be considered in at-risk populations (preterm infants, dark-skinned infants and children, obese children, children living at higher latitudes, etc.). In patients where compliance is a concern, an alternative option, after 1 month of age, is to administer a single high dose (100,000–600,000 IU) of oral vitamin D, followed by maintenance dosing [61].

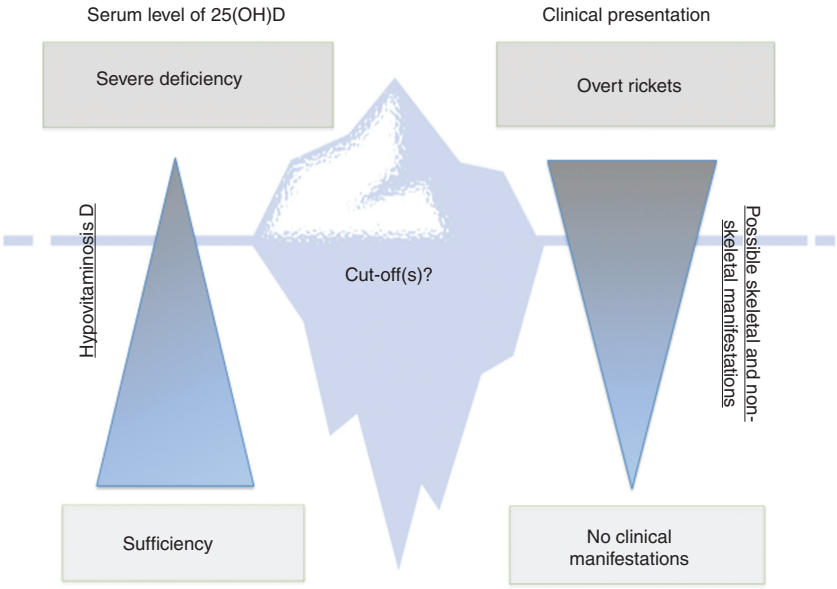

Figure 1: The "vitamin D iceberg" and spectrum of hypovitaminosis D.

On the other hand, the UK guidelines advocate a dosing regimen for 2–3 months with 3000 IU daily in children <6 months, 6000 IU daily in children 6 months to 12 years old and 10,000 IU daily in children 12–18 years old [125].

Increasing evidence supports the combined use of calcium and vitamin D in the treatment of rickets; oral calcium (500 mg/day) should be given either as supplements or by increasing dietary intake [73].

The patient's response to treatment should be monitored closely. One month after starting therapy, calcium, phosphorus and alkaline phosphatase (ALP) levels should be obtained. At 3 months, the levels of calcium, phosphorus, magnesium, ALP, 25(OH)D, PTH, and possibly urine calcium/creatinine ratio, should be determined and a radiograph should be performed. Subsequently, the levels of 25(OH)D should be monitored yearly [61].

Conclusions

Vitamin D status is a major determinant of bone health in infants, children and adolescents, but increasing evidence is accumulating that this vitamin has also important extra-skeletal effects. More RCTs related to the extra-skeletal effects of vitamin D deficiency should be undertaken, and appropriate biomarkers for non-skeletal disease need to be investigated.

The recognition of vitamin D deficiency is often difficult on a clinical basis, as silent forms are by far the most common. Figure 1 illustrates the "vitamin D iceberg" and clinical spectrum of hypovitaminosis D.

One of the current challenges is to achieve and sustain the optimal serum 25(OH)D levels that benefit all body tissues with no adverse effects. However, no consensus exists on the "normal" serum levels of 25(OH)D in the general pediatric population and in children with special medical conditions, and therefore conflicting recommendations for vitamin D supplementation and treatment have been provided [126].

Future research should focus on defining the optimal cut-off levels of 25(OH)D for children, determining the short- and long-term global health impact of hypovitaminosis D, and identifying the best strategies for tailored prevention.

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