Pediatric Hypovitaminosis D: Molecular Perspectives and Clinical Implications

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Abstract
Vitamin D, a secosteroid, is essential for the development and maintenance of healthy bone in both the adult and pediatric populations. Low level of 25-hydroxy vitamin D (25-(OH)-D) is highly prevalent in children worldwide and has been linked to various adverse health outcomes including rickets, osteomalacia, osteomalacic myopathy, sarcopenia, and weakness, growth retardation, hypocalcemia, seizure and tetany, autism, cardiovascular diseases, diabetes mellitus, cancers (prostate, colon, breast), infectious diseases (viral, tuberculosis), and autoimmune diseases, such as multiple sclerosis and Hashimoto’s thyroiditis. Risk factors for hypovitaminosis D are people with darker skin pigmentation, use of sunscreen, insufficient ultraviolet B exposure, prematurity, living in northern latitudes, malnutrition, obesity, exclusive breastfeeding, low maternal vitamin D level, certain medications, drinking unfortified cow’s milk, liver failure, chronic renal insufficiency, cystic fibrosis, asthma, and sickle cell hemoglobinopathy. This review highlights and summarizes the molecular perspectives of vitamin D deficiency and its potential adverse health outcomes in pediatric age groups. The recommended treatment regimen is beyond the scope of this review.

Keywords
general pediatrics, endocrinology, medical education

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Introduction
Vitamin D deficiency is highly prevalent in children worldwide with a new resurgence as an important and significant global health issue. The prevalence and risk factors are highest in children with maternal vitamin D deficiency, darker skin pigmentation, insufficient sun exposure, living in northern latitudes, winter season, malnutrition, exclusive breastfeeding beyond 6 months of age (human milk contains vitamin D less than 40 IU/L), chronic use of medications (such as anticonvulsants, aluminum-containing antacids, rifampicin, isoniazid, antifungals, antiretrovirals, and glucocorticoids), malabsorption states, liver failure, biliary atresia, chronic renal insufficiency, obesity, cystic fibrosis, inflammatory bowel disease, asthma, sickle cell hemoglobinopathy, and prematurity.

An adequate level of vitamin D plays an important role in calcium and phosphorus homeostasis, normal mineralization of type I collagen matrix in the skeleton, bone metabolism, and muscles development in infants and children.

The American Academy of Pediatrics (AAP) Committee on Nutrition and Section on Breastfeeding in 2008 recommended a vitamin D intake of 400 IU per day (1 IU = 25 ng) as an adequate dietary intake for healthy infants and children; and the Institute of Medicine (IOM) of the National Academy of Sciences issued a recommended dietary allowance (RDA) of 600 units daily for healthy children 1 to 18 years of age. The United States Endocrine Task force in 2011 suggests, however, that infants up to 12 months of age require at least 400 IU per day of vitamin D and those over 12 months or older require at least 600 IU. The RDA of 400 IU of vitamin D per day will keep the 25-hydroxy vitamin D (25-(OH)-D) level above 50 nmol/L (20 ng/mL), which is the minimally acceptable level in pediatrics recommended by the AAP (in October 2008). This RDA of 400 IU is now a requirement for children from few days after birth until the adolescence period, although there is still no agreement on the serum 25-(OH)-D- considered appropriate.
Vitamin D Biophysiology and Metabolism

Vitamin D is a fat-soluble vitamin involved in mineral metabolism and bone growth. It is essential for the intestinal absorption of calcium and its homeostasis. Dietary sources of vitamin D (cholecalciferol) are few, mainly from deep sea oily fishes (eg, sockeye salmon), raw Atlantic herring, fish oils (eg, cod liver oil), egg yolks of chickens fed vitamin D, mushrooms, organ meats, beef livers, cheese, butter, margarine, vitamin D supplement, and vitamin D–fortified milk, cereals, and bread.

There are 2 forms of biologically inert vitamin D molecule: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is formed by the action of ultraviolet light on fungal steroid ergosterol (previtamin D3), present in mushrooms and the yeast cell membrane and is available mostly as vitamin D supplement. Majority of the body vitamin D (vitamin D3) is formed endogenously by exposure of the skin to solar ultraviolet B (UVB) radiation (280-320 nm wavelength) and from cutaneous synthesis through the photolysis on the stratum spinosum and stratum basale of the epidermal layer of the skin resulting in the conversion of 7-dehydrocholesterol (previtamin D3) to an unstable previtamin D3 (precalciferol), which then become isomerized (rearrangement of its double bonds) by a temperature-dependent process into vitamin D3 (3-cholecalciferol). Excess precalciferol and 3-cholecalciferol are destroyed (photoconversion) by sunlight to biologically inactive photoproducts (tachysterol and lumisterol).5-7

Vitamin D2 differs from D3 in having a double bond between C22 and C23 and a CH3 group at C24 in the doxin reductase, and cytochrome P-450 (CYP27B1). CYP27B1 comprises a ferredoxin, a ferredoxin reductase, and cytochrome P-450.10 DBP is a glycosylated α-globulin with 458 amino acids and is a key determinant of 1α,25(OH) vitamin D (calcitriol) levels in infants and toddlers. The 25(OH) vitamin D, although has low biological activity, is relatively inactive and very stable and it is the most abundant circulating form of vitamin D with its half-life (T1/2) at 2 to 3 weeks and is little regulated by serum calcium (Ca), phosphorus (P), and parathormone (PTH). Its level is used as a functional indicator or biomarker in monitoring vitamin D status, unlike the 1α,25(OH)2 vitamin D (calcitriol), which is the biologically active form of vitamin D in the body with a short half-life (of a few hours) and is tightly regulated by the serum PTH, calcium, and phosphorus and by circulating fibroblast growth factor-23 (FGF23) produced by osteocytes.11,12

Renal 25-hydroxy vitamin D-1α hydroxylase (CYP27B1) is regulated by direct negative feedback inhibition by 1,25(OH)2D, but is mostly and tightly regulated (although less precisely in infants) by hypocalcemia and 3 hormones: PTH, calcitriol, and FGF23. Hypocalcemia and PTH stimulate (upregulate), whereas FGF-23 and calcitriol inhibit (downregulate) CYP27B1.13,14 Fewer studies in pediatric age groups have evaluated the optimal or minimal 1α,25(OH)2 vitamin D levels that elicited or diminished PTH response and calcium absorption.15 It appears that bone disease is associated with a 25(OH) vitamin D level of 10 ng/mL (25 nmol/L), and at a level of 30 ng/mL (75 nmol/L) or less, there is a decreased intestinal calcium absorption and a decrease in serum calcium concentration that stimulates via the cAMP-dependent mechanism, the release of PTH via the “calcium-sensing receptor” CASR signal (from the parathyroid gland), which then triggers osteoclast differentiation (transformation of preosteoclasts to mature osteoclasts by stimulating the expression of receptor activator of NFkB ligand),6,17 enhances distal renal tubular reabsorption of calcium (decreasing calcium clearance), increases renal phosphate excretion and bone resorption (through the activation of PTH receptor in the bone), and the conversion of 25(OH) vitamin D to 1α,25(OH)2 vitamin D. The increased circulating levels of calcium and phosphate will not cause marked hypercalcemia or hyperphosphatemia due to the counter-effect of PTH. The 1α,25(OH)2 vitamin D, in turn, appears to have a mild inhibitory effect on the parathyroid gland.18

The activated calcitriol in the cytosol migrates and binds to a specific nuclear (genomic) receptor protein called vitamin D receptor (VDR) to influence gene transcription (slow genomic action). The VDR is a phosphoprotein (encoded by the VDR gene) with 2 overlapping ligand binding sites, VDR-GP (genomic pocket) and VDR-AP (alternative pocket), and in human, it consists
of 427 amino acids and at physiological concentration requires the presence of cofactor protein, 9-cis retinoic acid X receptors (RXRα, RXRβ, and RXRγ) to form VDR homodimers or VDR-RXR heterodimers that bind to specific sites on the DNA called vitamin D response elements (VDREs).\textsuperscript{13,19,20}

The VDR is present mostly in the intestine and bone and has high affinity for 1α,25(OH)\textsubscript{2} vitamin D and is also present in the nuclei of over 30 extraintestinal tissues (such as parathyroid gland, brain, stomach, pancreas, thymus, natural killer cells, activated T and B lymphocytes of the immune system, heart, skin, gonads), responsible for the noncalcemic functions of vitamin D.\textsuperscript{6,7,21}

The VDRE mediates the biological actions of calcitriol and functions as a transcription factor at multiple target gene sites, and especially in the nuclei of enterocytes, it leads to an increase in intestinal calcium, intracellular calcium flux, and phosphorus absorption (across the brush borders) via the expression and activation of multiple hormone-sensitive genes.

The effect of calcitriol on target tissues (aside of slow genomic action via the VDR) can also occur via a rapid, nongenomic activation of voltage-dependent calcium channels. The absorbed Ca is bound to Calbindins (D9K and D28K), a vitamin D–dependent calcium binding protein (and then transferred into the endoplasmic reticulum).\textsuperscript{17}

In summary, the main function of 1α,25(OH)\textsubscript{2} vitamin D is in the maintenance of calcium homeostasis in the plasma. Vitamin D alters the gene expression and protein synthesis of numerous matrix proteins and facilitate the expression of mature chondrocyte and mature osteoblast activity. The osteoblast response varies in response to the stage of osteoblast development.

Inactivation of 1α,25(OH)\textsubscript{2} vitamin D to the biologically inactive water-soluble metabolite 1α-hydroxy-23-carboxy-24,25,26,27 tetranorvitamin D\textsubscript{3} (calcitriol) is via CYP24A1, a highly upregulated gene that is most abundant in the endoplasmic reticulum.\textsuperscript{17}

Table 1. Vitamin D Status Based on 25(OH) Vitamin D Concentrations*.

| Vitamin D Status | Calcidiol Level (ng/mL) AAP 2008/IOM | Calcidiol Level (nmol/L) |
|------------------|--------------------------------------|-------------------------|
| Severe deficiency | <5                                   | <12.5                   |
| Mild to moderate deficiency | 5-15                               | 12.5-37.5               |
| Insufficiency    | 16-20                                | 40-50                   |
| Sufficiency      | 21-100                               | 52.5-250                |
| Excess           | 101-149                              | 252.5-372.5             |
| Intoxication     | >150                                 | >375                    |

*AAP: American Academy of Pediatrics, IOM: Institute of Medicine.

Clinical Outcomes of Vitamin D Deficiency

The exact definition for vitamin D sufficiency, insufficiency, or deficiency in the pediatric population is still debatable with divergence of opinion, and it is still not clear if any absolute level of 25-hydroxy vitamin D (25(OH)-D) exists, below which rickets can be diagnosed clinically. National data on vitamin D deficiency in children are not yet available even in the most developed nations. Most of the available data have been abstracted from studies that primarily focused on the adult population.

The current and well-documented definition in children was based on AAP and IOM reports, as a serum concentration of 25(OH) vitamin D level below 20 ng/mL (50 nmol/L) for deficiency and a level above 20 ng/mL (50 nmol/L) classified as sufficiency. This definition, however, is in variance with what many experts had recommended.\textsuperscript{14,15}

The United States Endocrine Society published a recent clinical practice guidelines reddefining deficiency as a level below 20 ng/mL (50 nmol/L), insufficiency as a level between 21 and 29 ng/mL (52.5-72.5 nmol/L), sufficiency at a level above 30 ng/mL (>75 nmol/L), and toxicity at a level above 150 ng/mL (375 nmol/L). The recommended target calcidiol levels for infants, children, and adolescents was published by the AAP in a review article in 2008 (Table 1).

Biochemically, vitamin D deficiency results in a reduction in intestinal calcium absorption and a decreased serum calcium concentration, and later, a decreased serum phosphate concentration (due to reduction in renal phosphate reabsorption causing a phosphate diuresis) and an elevated alkaline phosphatase with an increased serum PTH concentration to counteract and restore the low serum calcium concentration; however, with progressive reduction in 25(OH) vitamin D there is secondary hyperparathyroidism with worsening of the hypocalcemia and hypophosphatemia resulting in the impairment of mineralization of the organic matrix (osteoid). The level of 1α,25(OH)\textsubscript{2} vitamin D may be low, normal, or high and is usually of no value in making the diagnosis of vitamin D deficiency.
Regardless of the definition, the clinical syndromes associated with vitamin D deficiency in children include hypocalcemia, seizure and tetany, rickets, osteomalacia/osteomalacic myopathy, growth retardation, type 1 diabetes mellitus, infectious diseases, and autism.

Rickets

The function of vitamin D is to increase the serum phosphorus and serum calcium levels needed for osteoid mineralization. Rickets is attributable to extreme hypovitaminosis D. It is a generalized skeletal disorder in children characterized by stunted growth and bone deformity due to defective mineralization of cartilage at the growth plate before epiphyseal closure as a result of inadequate supplies of calcium and phosphorus (as hydroxyapatite) sequel to vitamin D deficiency. Apart from dietary vitamin D disorders (privational or nutritional rickets), other forms of rickets include24 the following:

1. Pseudovitamin D deficiency rickets (vitamin D-dependent rickets type I-PDDR)—a rare autosomal recessive condition with anomalies in the gene encoding the cytochrome P450 of the renal 25(OH) vitamin D3-1-α hydroxylase
2. Vitamin D–resistant rickets (vitamin D–dependent rickets type II)—due to mutations in the vitamin D receptor gene (VDR; 12q13-14) resulting in a defective interaction of calcitriol and vitamin D receptor (nonfunctional receptor)
3. Vitamin D–dependent rickets types III and autosomal dominant or X-linked dominant hypophosphatemic rickets

Rickets can also develop as a result of dietary calcium deficiency, phosphorus deficiency, and chronic renal diseases. Most cases of nutritional rickets occur in children at the periods of rapid growth in early infancy (and early puberty), especially in infants who have dark skin and are exclusively breastfed with little or no vitamin D supplementation.

Clinical features consist of both skeletal and nonskeletal manifestations. The osseous changes are characterized by growth plate widening and enlargement at the wrists and ankles due to thickening of the unmineralized matrix, disorganization in the maturation of chondrocytes, and absence of endochondral calcification in the epiphyseal plates. Rachitic rosy is characterized by beading at the costochondral junction (lateral to the nipple line). The increased risks of greenstick fracture are due to softening and bending of long bones.25

Other skeletal features of classical rickets include craniofibrosis (softening of the cranial bones), Harrison’s sulci (due to in-drawing or flaring of the softened ribs by the diaphragm during inspiration), pectus excavatum, pectus carinatum, frontal and parietal skull bossing, craniosynostosis, delayed closure of anterior fontanel, bone pain, osteitis fibrosa cystica (Brown tumor) with secondary hyperparathyroidism, lateral and anterior bowing of tibia and femur, lordosis, scoliosis, and kyphosis.

VDR gene polymorphisms (DNA sequence variations) may be related to genetic susceptibility to hypovitaminosis D rickets in certain population but the influence on the VDR protein function and signaling are unknown.26

The nonskeletal manifestations include restlessness, lack of sleep, delayed motor milestones, dental enamel hypoplasia, delayed tooth eruption and growth retardation, pseudotumor cerebri, secondary myelofibrosis, short stature, and failure to thrive. Early diagnosis is crucial in order to minimize the morbidity of rickets. The diagnosis is based on clinical findings and classical radiographic abnormalities, which are beyond the scope of this review.

Osteomalacia and Osteomalacic Myopathy

Osteomalacia is an extreme manifestation of severe vitamin D deficiency. It is mostly an adult disease but may coexist with nutritional rickets in children. It is due to softening of bone as a result of impaired mineralization of the newly formed organic collagen matrix (osteoid) after the closure of growth plates at sites of bone modeling and remodeling.

Osteomalacia may manifest with pathologic fracture, bone discomfort and pain (due to stretching of the peristeam because of increasing water contents of the demineralized osteoid), myalgia, hyperreflexia, and painful proximal muscle weakness (with positive Gower’s sign) with waddling gait (hypovitaminosis D myopathy or osteomalacic myopathy).27,28 Hypovitaminosis D myopathy is often misdiagnosed due to its nonspecific symptoms at presentation. Vitamin D concentration of <10 ng/mL is associated with poorest muscle function compared to a level higher than 20 ng/mL (which is associated with improved muscle strength).29

Risk factors for osteomalacia are the same as in classical rickets. Etiology includes abnormal metabolism of vitamin D (from deficient intake or absorption, defective hydroxylation of cholecalciferol, loss of vitamin D binding protein, and defective 1α,25-hydroxylation), mineralization defects (from the abnormal matrix, enzyme deficiency, and inhibitors of mineralization), and phosphate deficiency (due to a decreased intake and impaired renal absorption).
**Susceptibility to Infections/Immune Functions**

Through the receptors on immune cells, vitamin D is recognized for its various immune functions: it induces immune tolerance; it can also control the adaptive and innate immune responses by inducing monocyte proliferation, expression of cathelicidin and interleukin-1 (IL-1), suppresses B-cell differentiation/proliferation and immunoglobulin production, suppresses IL-12 production, suppresses CD40-L induced IL-12 production in day 7 GM-CSF/IL-4 derived dendritic cells, and decreases the production of interferon-γ, IL-17, and IL-2. Immunomodulatory effects of vitamin D act through modulation of T-helper cell function, IL-10, and through induction of CD4+CD25 regulatory T-cells.\(^{30,31}\)

Maternal hypovitaminosis D during pregnancy has been linked to an increased risk of recurrent wheezing during early childhood.\(^{32}\)

Vitamin D deficiency increases susceptibility to severe infections, and recent epidemiological studies have shown the association between hypovitaminosis D and respiratory infection among children, especially tuberculosis. Low cord blood levels of 25(OH) vitamin D have been associated with respiratory infections and respiratory syncytial virus (RSV) bronchiolitis, especially in children with ff genotype of VDR gene polymorphisms.\(^{33}\) The ff genotype reduces the ability of immunocytes to utilize vitamin D for its immunomodulatory effects.\(^{23,33}\)

Serum level of vitamin D has been shown to be significantly lower in children with acute otitis media compared to healthy controls.\(^{34}\)

**Tetany and Hypocalcemic Seizure**

Maternal hypovitaminosis D increases the risks of neonatal vitamin D deficiency, hypocalcemia, and hypocalcemic seizures (which is the most serious sequelae of vitamin D deficiency). The symptoms of severe hypocalcemia due to vitamin D deficiency occur during the periods of rapid growth and include paresthesia, numbness, laryngospasm, muscle cramps, Chvostek’s and Trousseau’s signs, tetany, and seizure.

**Type 1 Diabetes Mellitus (T1DM)**

T1DM is related to autoimmune destruction (by pro-inflammatory cytokines) of pancreatic β-cells resulting in absolute insulin deficiency. Vitamin D modulates insulin receptor gene expression, pancreatic RAS activities, and insulin synthesis (conversion of proinsulin to insulin) and secretions.\(^{25,35}\) Genomic variations of vitamin D metabolism and target cell action predisposes to T1DM, and the association of vitamin D deficiency with insulin resistance has been published in scientific journals.

The presence of VDR in the islet cells of the pancreas and the nuclear presence of 1,25(OH)\(_2\) vitamin D is now well acknowledged, and the relationship between vitamin D deficiency and diabetes mellitus is also well known, and this was well supported by epidemiological studies, but the role of hypovitaminosis D in the disease progression is still uncertain.

Sufficient vitamin D level is important in the prevention of islet cell death, and a low level of vitamin D has been shown to increase the incidence of autoimmune disease and have a negative effect on pancreatic β-cell function in children with multiple islet autoantibodies and T1DM than in autoantibodies negative children. Meta-analysis of data from 5 different studies found that T1DM risk was significantly reduced (by nearly 33%) in children who had been given supplements of vitamin D in infancy and early childhood compared with nonsupplemented children.\(^{35,36}\) Moreover, vitamin D supplementation during pregnancy and early childhood reduces the risk of developing T1DM and islet cell autoimmunity at 1 year of age.\(^{37}\)

**Type 2 Diabetes Mellitus (T2DM) and Metabolic Syndrome (MetSyn)**

Although there is a lack of consistent criteria in diagnosing MetSyn in the pediatric population, long-term hypovitaminosis D has been linked to MetSyn, including T2DM in children, and a higher plasma vitamin D level is related to a lower risk of developing T2DM. T2DM involves impaired β-cell function, inflammation, altered insulin secretion, and insulin resistance. Vitamin D with its immune modulating properties can downregulate the production of pro-inflammatory cytokines (IL-6) and is involved in glucose homeostasis and metabolism; hence, mild to moderate vitamin D insufficiency has been linked to a higher serum level of IL-6 and an impaired glycemic control in patients with T2DM and it is a risk factor for developing T2DM.\(^{35}\) Calbindin-D28K (a vitamin D–dependent calcium-binding protein) reduces the risk of T2DM by protecting the pancreatic β-cells from cytokine-mediated cell death.\(^{38}\)

**Hashimoto’s Thyroiditis**

A study by Mazokopakis et al indicated that there may be a link between vitamin D deficiency and the development of Hashimoto thyroiditis.\(^{39}\) Low level of vitamin D has been shown to correlate with an elevated anti-thyroid peroxidase (anti-TPO) in patients with Hashimoto’s disease and a high level of thyrotropin receptor antibody
titers in patients with Graves’ disease. The severity of hypovitaminosis D correlated well with thyroid volume and the duration of Hashimoto’s disease.40

**Autism**

Autism spectrum disorder, which is characterized by pervasive social behavior and deficit in verbal and non-verbal communication is a neurodevelopmental disorder caused by an etiology that is predominantly genetic but with a complex interplay of environmental factors. Vitamin D is an environmental factor that has a role in brain homeostasis and neurodevelopment and a higher level of which has been suggested to have an impact on the risk of autism.

Vitamin D also plays an important role in repairing DNA damage; thus, its deficiency would result in impaired DNA repair and higher de novo genetic mutation rates linked to an increased risk of autism. There is evidence that vitamin D influences fetal brain growth and neuronal differentiation, and there is an inverse correlation between the serum level of calcidiol concentration and autism rating scale, and a higher level of calcidiol may reduce the risk of autism.41

An infant’s vitamin D status is a direct reflection of maternal level; hence, vitamin D deficiency in mother during pregnancy has been linked to an increased risk of autism in preterm babies, and low maternal (prenatal) vitamin D during pregnancy may act as a risk factor for preterm delivery, which may possibly cause abnormal brain development in a developing child and an increased risk of impaired language development in the offspring.42,43

The rate of autism in the United States is highest in regions with lowest ultraviolet B (UVB) doses and impaired UVB production (especially areas with high air pollution). Recent reports from Minnesota (in the United States) and Sweden showed an increase in the prevalence of autism among offspring of Somali immigrant mothers with vitamin D deficiency living in those countries, presumably due to both covered Islamic clothing (veiled) and dark skin pigmentation. Also, there is a small Swedish study that linked vitamin D deficiency at birth in a group of children (compared to their unaffected siblings) with autism.44

There are now specifications that problematic social behaviors in autistic children may also be linked to vitamin D deficiency and abnormal level of serotonin. Higher levels of serotonin have been linked to a gene activated by vitamin D, which in turn produces an enzyme, tryptophan hydroxylase 2 (TPH-2), that converts tryptophan to 5-hydroxytryptamine (serotonin) that leads to a higher level of serotonin production, and another gene that makes the enzyme tryptophan hydroxylase 1 (TPH-1) to be inhibited by vitamin D to halt serotonin production.45 Further research on the link between vitamin D deficiency and autism is clearly warranted.

**Conclusions**

Vitamin D deficiency can result from inadequate intake of vitamin D or inadequate exposure to ultraviolet B radiation of the sunlight. Its prevalence is highest in children with darker skin pigmentation and those living in Northern latitude. In the recent past, numerous researches and studies have enhanced our understanding of the hormone called vitamin D. This is also evidenced by thousands of journal articles published each year. Vitamin D supplementation is a safe alternative to preventing its insufficiency or deficiency.

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