International Journal of Homoeopathic Sciences

E-ISSN: 2616-4493
P-ISSN: 2616-4485
Impact Factor (RJIF): 5.96
www.homoeopathicjournal.com
IJHS 2025; 9(4): 479-484
Received: 04-07-2025
Accepted: 11-08-2025

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Vitamin D deficiency in children: Biochemical insights and emerging clinical implications

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DOI: https://www.doi.org/10.33545/26164485.2025.v9.i4.H.1951

Abstract
In recent years, Vitamin D has emerged as a focal point of biomedical research owing to its proposed involvement in the pathogenesis of numerous conditions, including cancers, autoimmune diseases, hypertension, and infectious diseases. Insufficient awareness of the fact that controlled sunlight exposure is the primary source of endogenous Vitamin D production remains the leading cause of its deficiency. The assessment of Vitamin D status in clinical practice relies primarily on the measurement of serum 25-hydroxyvitamin D [25(OH)D], which is widely recognized as the most accurate and informative biomarker. Complementary laboratory findings, including hypocalcemia, hypophosphatemia, and elevated levels of alkaline phosphatase, can further support the diagnosis of Vitamin D deficiency, reflecting its impact on mineral metabolism and skeletal health. The widespread prevalence of Vitamin D deficiency, coupled with its involvement in the pathogenesis of numerous disorders, highlights the necessity for broad public health initiatives and educational programs directed at both healthcare providers and the general population.

Keywords: Vitamin D deficiency, children, biochemical mechanisms, immunity, metabolic syndrome, neurodevelopment

Introduction
Vitamin D, commonly referred to as the "sunshine vitamin," is a unique micronutrient because of its dual origin: endogenous synthesis in the skin through ultraviolet B (UVB) exposure and dietary intake from foods such as fortified milk, fish, and egg yolk [5]. Originally recognized for its role in preventing rickets, it is now understood as a steroid hormone that regulates the expression of more than 200 genes via the Vitamin D receptor (VDR) [6].

Despite abundant sunlight in many tropical regions, Vitamin D deficiency has emerged as a widespread problem among children. This phenomenon is largely driven by modern lifestyle changes, including decreased time spent outdoors, extensive use of sunscreen, air pollution limiting ultraviolet B (UVB) exposure, and inadequate dietary intake [7]. A combined prevalence of 58% for vitamin D deficiency and insufficiency has been reported among Indian children and adolescents aged 5 to 18 years, highlighting the substantial burden of this condition even in a sun - rich environment [8]. This high prevalence of Vitamin D deficiency can be attributed to a combination of factors. Limited sun exposure, dietary insufficiencies including low intake of Vitamin D and calcium, high consumption of phytates and phosphates, caffeine intake, and widespread lactose intolerance all contribute significantly [9, 10]. Other important determinants include higher levels of skin pigmentation, environmental pollution that diminishes UVB penetration, genetic polymorphisms affecting Vitamin D metabolism, and increased body fat, which may sequester Vitamin D and reduce its bioavailability [9, 10]. A thorough understanding of Vitamin D at the biochemical level is therefore essential, as it allows clinicians and researchers to correlate molecular mechanisms with clinical outcomes in the pediatric population.

Biochemical insights into vitamin d metabolism
Vitamin D a fat-soluble prohormone exists in two main forms: Vitamin D_3 (cholecalciferol), produced in the skin upon exposure to ultraviolet B (UVB) light or obtained from animal-derived foods, and Vitamin D_2 (ergocalciferol), which is found in certain plant sources and fortified foods [4]. Both forms are biologically inactive and require enzymatic conversion to achieve hormonal activity [4].

Cutaneous Synthesis of Vitamin D_3

Vitamin D_3 is produced in the skin through a non-enzymatic photochemical process that begins with 7-dehydrocholesterol (7-DHC). 7-DHC absorbs UVB radiation with a wavelength of 280-320 nm, leading to the cleavage of its B-ring and the formation of an intermediate, pre-vitamin D_3. Pre-vitamin D_3 then spontaneously undergoes a heat-dependent thermal isomerization to form vitamin D_3 (cholecalciferol) [11].

Several factors influence the efficiency of this process. The intensity of UVB radiation, which depends on latitude, season, and time of day, plays a major role-individuals living farther from the equator experience reduced vitamin D_3 synthesis during the winter months. Skin pigmentation also affects production, as melanin absorbs UVB rays and limits the conversion of 7-dehydrocholesterol (7-DHC) to vitamin D_3 [11]. In addition, clothing and sunscreen physically block UVB exposure, further reducing cutaneous vitamin D_3 synthesis [12].

Vitamin D_2 is generated by UVB irradiation of ergosterol in plants and fungi, including mushrooms. Structurally, it differs from D_3 by having a double bond between C22-C23 and a methyl group at C24 in its side chain [13, 14]. These differences result in:

- Lower affinity for Vitamin D Binding Protein (DBP) and faster clearance from circulation [14].
- Reduced conversion efficiency to 25-hydroxyvitamin D (25(OH)D) by certain hepatic 25-hydroxylases [14].
- Altered catabolism by 24-hydroxylase (CYP24A1) [14].

Consequently, vitamin D_2 supplementation typically results in lower circulating 25(OH)D levels than equivalent doses of vitamin D_3, unless it is administered on a daily basis.

Biochemical Pathway for Activation of Vitamin D [15]

Vitamin D metabolism involves three major enzymatic steps catalyzed by cytochrome P450 (CYP) mixed-function oxidases, which are localized either in the endoplasmic reticulum (ER) or the mitochondria, depending on the specific CYP enzyme.

1. 25-Hydroxylation [16]

This step takes place in the liver. The key enzymes catalyzing this reaction are:

- **CYP2R1 (Endoplasmic Reticulum):** The major hepatic 25-hydroxylase.
- **CYP27A1 (Mitochondria):** Initially identified as a sterol 27-hydroxylase involved in bile acid synthesis; it is widely distributed but does not hydroxylate vitamin D_2.

25-hydroxylation produces 25(OH)D, which is the main circulating form used to assess vitamin D status.

2. 1α-Hydroxylation

This step takes place in the kidney and is catalyzed by mitochondrial CYP27B1, the only enzyme with 25(OH)D 1α-hydroxylase activity. It converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] [17].

Renal CYP27B1 activity is tightly regulated by the following factors [18]:

- **Parathyroid hormone (PTH):** Stimulates enzyme activity.
- **Fibroblast growth factor 23 (FGF23):** Inhibits enzyme activity.
- **Calcitriol ($1,25(OH)_2D$):** Exerts negative feedback regulation.

In addition, elevated calcium levels suppress CYP27B1 activity indirectly by reducing PTH secretion, while increased phosphate levels inhibit CYP27B1 through FGF23.

3. 24-Hydroxylation

CYP24A1 serves as the only enzyme responsible for 24-hydroxylase activity in vitamin D metabolism. It catalyzes both 24- and 23-hydroxylation, with the ratio species-dependent.

- The 24-hydroxylase pathway produces biologically inactive calcitroic acid for excretion [19].
- The 23-hydroxylase pathway produces biologically active 1,25-26,23-lactone

These steps ensure vitamin D homeostasis and prevent toxicity [19].

Transport and Bioavailability of Vitamin D Metabolites

Vitamin D metabolites circulate in the bloodstream predominantly bound to vitamin D binding protein (DBP) and, to a lesser extent, albumin. Approximately 85-88% of these metabolites are bound to DBP, while 12-15% are associated with albumin. The typical plasma concentration of DBP ranges between 4-8 μM [20].

DBP has a strong binding affinity for vitamin D metabolites, leaving only a very small fraction circulating in the free or unbound form-approximately 0.03% for 25(OH)D and $24,25(OH)_2D$, and around 0.4% for $1,25(OH)_2D$ [21].

A decline in total serum concentrations of 25(OH)D and $1,25(OH)_2D$ can occur in conditions such as liver disease and nephrotic syndrome due to decreased circulating levels of DBP and albumin. However, these changes do not necessarily alter the physiologically active free fractions of these metabolites [21]. Similarly, during acute illness or following trauma, DBP concentrations may decrease, which can misrepresent total vitamin D status and make interpretation of total 25(OH)D levels more challenging [22].

Molecular Mechanism of Action of Vitamin D [23]

Vitamin D, traditionally recognized for its role in maintaining bone and mineral homeostasis, is now understood to function as a pleiotropic hormone with widespread physiological effects. Its biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], exerts its influence through both genomic mechanisms mediated by nuclear receptors and rapid non-genomic signaling pathways, thereby regulating diverse cellular and metabolic processes [23].

Genomic Actions of Vitamin D [24]

The genomic activity of vitamin D is mediated through the Vitamin D Receptor (VDR), a nuclear receptor that binds to the active form, $1,25(OH)_2D$. The VDR have two overlapping binding sites - a genomic pocket (VDR-GP) and an alternative pocket (VDR-AP). The genomic pocket of VDR binds ligands in a bowl-like conformation triggering gene transcription while alternative pocket binds ligands with a planar-like shape initiating rapid non-

genomic signaling [24]. Upon binding with 1,25(OH)$_2$D, the VDR undergoes a conformational change and forms a heterodimer with the Retinoid X Receptor (RXR). This heterodimer complex then binds to specific DNA sequences known as Vitamin D Response Elements (VDREs), located primarily within the promoter regions of target genes, where it recruits coactivators or corepressors to regulate gene transcription. The activated VDR thereby governs the synthesis of proteins essential for calcium and phosphate absorption, maintaining skeletal integrity and mineral balance [24].

The activated VDR-RXR complex modulates the expression of more than 200 genes involved in calcium homeostasis, immunity, and cell differentiation. Key targets include:

- Calbindin-D9k and TRPV6 - promote intestinal calcium absorption [25].
- Osteocalcin and RANKL - regulate bone formation and remodeling [25].
- CYP24A1 - Enzyme that mediates the feedback control of vitamin D metabolism by inactivating the active form of the vitamin [25].
- Cathelicidin (LL-37) - supports innate immune defense [26].

Non Genomic Actions of Vitamin D [27]

The non-genomic actions of 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] primarily involve the rapid activation of intracellular signaling pathways rather than gene regulation. These actions are mediated through signaling molecules such as phospholipase C (PLC), phospholipase A$_2$ (PLA$_2$), phosphatidylinositol-3 kinase (PI3K), and p21ras. Activation of these pathways triggers the production of second messengers, including calcium ions (Ca^{2+}), cyclic AMP (cAMP), fatty acids, and phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which in turn stimulate various protein kinases such as protein kinase A (PKA), Src kinase, mitogen-activated protein (MAP) kinases, protein kinase C (PKC), and Ca^{2+}/calmodulin-dependent kinase II (CaMKII). These kinases rapidly alter cellular processes and modulate ion channel activity, particularly Ca^{2+} and Cl^- channels, leading to changes in cellular excitability, secretion, and rapid physiological responses such as muscle contraction, hormone release, and immune cell activation [27].

Vitamin D deficiency in children: emerging clinical implications

Clinically, vitamin D deficiency is traditionally characterized by rickets, skeletal deformities, impaired growth, and muscle weakness [1]. In recent years, emerging evidence has linked vitamin D deficiency to an increased susceptibility to infections, autoimmune disorders, metabolic syndrome, and neurodevelopmental impairments, emphasizing its impact on pediatric health beyond skeletal manifestations [1].

Emerging Clinical Implications

Recent advances reveal vitamin D's pleiotropic effects extending beyond the skeletal system:

Vitamin D and Immune Function

Vitamin D and its downstream receptor signaling are crucial for macrophage and immune cell function, enhancing host antimicrobial defense and regulating immune and inflammatory responses. These effects are mediated in part through the induction of antimicrobial proteins (AMPs), including cathelicidins, defensins, hepcidins, and neutrophil peptides, which act as intrinsic antibiotics against diverse pathogens [28]. Cathelicidin (LL-37) facilitates the elimination of intracellular mycobacteria and modulates autophagy by promoting phagosome-autophagosome fusion. It also acts as a pleiotropic immunomodulator, displaying both pro- and anti-inflammatory effects depending on the cellular context. Vitamin D-induced LL-37 expression is therefore a central component of human innate immunity, linking nutrient status to effective host defense [28].

Emerging evidence highlights that vitamin D deficiency impairs AMP induction, weakening host defense and increasing susceptibility to infections, autoimmune disorders, and inflammatory diseases [29].

Vitamin D and Metabolic Health

Previous studies have indicated a strong association between vitamin D deficiency and metabolic syndrome, as well as obesity-related comorbidities [30, 31]. Independent of age or ethnicity, vitamin D appears to influence glucose homeostasis, insulin sensitivity, and inflammatory processes, evidenced by positive correlations with leptin and adiponectin levels and inverse correlations with homeostatic model assessment insulin resistance score (HOMA-IR) and waist circumference [32]. Furthermore, by affecting adipokine balance, low vitamin D status may contribute to the development of cardiovascular disease, highlighting its role in metabolic and cardiometabolic health [33].

Vitamin D and Neurodevelopment

In children, vitamin D deficiency has been increasingly linked to neuropsychiatric disorders, with the strongest evidence supporting its association with autism spectrum disorder (ASD). Evidence suggests that vitamin D might be involved in the synthesis of neurotransmitters such as serotonin and dopamine, a key neurotransmitter involved in mood, social behavior, and cognition. However, a causal mechanism has yet to be established [34]. Several studies have reported that lower serum 25-hydroxyvitamin D [25(OH)D] levels are associated with a higher risk of developing ASD in children and adolescents [35]. Maternal vitamin D status during pregnancy plays a crucial role in fetal neurodevelopment. Vitamin D deficiency has been associated with an increased risk of autism spectrum disorder (ASD) in offspring. Studies have shown that vitamin D supplementation during pregnancy, particularly in mothers who already have a child with ASD, may reduce the risk of ASD in subsequent pregnancies [36]. Furthermore, growing evidence indicates that prenatal and early-life vitamin D deficiency may contribute to a higher susceptibility to other neurological and behavioral disorders, including schizophrenia, depression, multiple sclerosis, and general behavioral impairments [37].

Anti - inflammatory effect of Vitamin D on Cardiomyocytes

Vitamin D suppresses the production of inflammatory mediators, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thereby downregulating inflammatory responses. It also influences the expression of cyclooxygenase (COX), nuclear factor kappa B (NF-κB), and signaling cascades such as mitogen-activated protein kinase (MAPK), which play crucial roles in the

inflammatory pathway [38]. Various studies on Vitamin D and VDR suggest the crucial role of Vitamin D in regulating the synthesis of nitric oxide (NO) and maintaining endothelial function. Being a vasoactive compound, NO has a potent vasodilatory effect, which provides protection against vascular lesions and arterial inflammation [39].

Interrelationship Between Vitamin D, Lipid Metabolism, and Bone Health in Children [40]

Vitamin D plays a vital role in bone formation and maintenance, and adequate bone mineral accumulation during childhood and adolescence is essential for sustaining skeletal health throughout life. Deficiency of vitamin D is recognized as a major contributing factor to osteoporosis and bone fractures, particularly during the growth phase in children. Emerging research indicates that insufficient vitamin D levels may alter bone development by disrupting lipid metabolism; however, the precise mechanism underlying this interaction is not yet fully understood. Evidence from existing literature suggests that lipid metabolism could modulate the influence of vitamin D on bone formation by affecting adipocyte differentiation and activity. Therefore, maintaining appropriate levels of both vitamin D and lipids is important for healthy bone growth and overall skeletal function. Nonetheless, the exact role of vitamin D in regulating bone development via lipid metabolism in children remains to be clarified [40].

Serum 25-hydroxyvitamin D [25(OH)D] as a Biochemical Marker of Vitamin D Status

D [25(OH)D] is the primary metabolite used to assess vitamin D status and to classify individuals as deficient, sufficient, or intoxicated. It serves as the major circulating form of vitamin D in the body, with an approximate half-life of two to three weeks. The concentration of 25(OH)D in the blood reflects the combined contribution of vitamin D obtained through dietary sources and that synthesized in the skin upon exposure to sunlight [41].

Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health [42]

nmol/L*	ng/mL*	Health Status
< 30	< 12	Associated with vitamin D deficiency, which can lead to rickets in infants and children and osteomalacia in adults
30 - <50	12 - <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Linked to potential adverse effects, particularly at >150 nmol/L (>60 ng/mL)
*Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). One nmol/L = 0.4 ng/mL, and 1 ng/mL = 2.5 nmol/L.		

Prevention and Management Strategies for Vitamin D Deficiency in Children

1. Preventive Strategies

Adequate Sunlight Exposure

There are several factors that determine the extent of sunlight exposure necessary for adequate vitamin D synthesis. These factors include skin tone, time of day, season, and geographical latitude. A study conducted in India revealed a positive association between sunlight exposure and serum vitamin D levels in breastfed infants. This study concluded that those who were exposed to sunlight between 10:00 AM and 3:00 PM over 40% of the body area for at least 16 weeks could achieve sufficient vitamin D levels by 6 months of age [44]. It has also been reported that approximately 90% of the infants remained vitamin D deficient despite sun exposure and therefore required vitamin D supplementation [45].

Dietary Approaches

Dietary sources that help to maintain adequate vitamin D levels in the body include both natural and fortified foods such as liver, eggs, butter, cheese, fish liver oil, fortified foods, milk, and margarine [46]. Fortifying commonly consumed staple foods with vitamin D presents an effective and practical strategy to combat the widespread prevalence of vitamin D deficiency in India [47].

Maternal & Infant Nutrition

Hypovitaminosis D has emerged as a major public health concern, particularly among pregnant women who are at greater risk of deficiency. Numerous studies emphasize the vital role of vitamin D in supporting maternal and fetal health during both prenatal and postnatal periods and in minimizing adverse pregnancy outcomes. Adequate maternal vitamin D levels during pregnancy could have a positive influence on neonatal health parameters, including respiratory function, birth weight, and neurological development [48].

Lifestyle and Awareness

Many children continue to experience vitamin D insufficiency even after adequate sunlight exposure and consumption of natural vitamin D-rich foods. This might be due to various lifestyle, environmental, and dietary factors. Early detection, effective preventive measures, and enhanced awareness among parents and educators are crucial for addressing this growing concern. Promoting outdoor physical activities, enhancing dietary practices, and implementing regular health check-ups can play a significant role in reducing the prevalence of vitamin D deficiency. Maintaining adequate vitamin D levels during childhood is vital for ensuring optimal growth, bone health, and the prevention of long-term health complications [49].

2. Management Strategies

Vitamin D Supplementation

For infants, a daily intake of 400 IU of vitamin D is recommended, while children over one year of age and adolescents should receive 600 IU per day. In addition to vitamin D, adequate calcium intake-approximately 600-800 mg per day-is essential, preferably obtained through 2-3 servings of milk and other dairy products. Pregnant women are advised to consume 600 IU of vitamin D daily, and this supplementation should be continued throughout lactation to ensure optimal maternal and infant health [50].

Conclusion

Vitamin D is essential for bone mineralization, calcium balance, and immune regulation during childhood. However, deficiency remains widespread due to inadequate

sunlight exposure, poor diet, and lifestyle factors. Serum 25-hydroxyvitamin D [25(OH)D] is considered the most reliable biochemical indicator for evaluating vitamin D status. In children, deficiency has been associated not only with rickets and impaired bone development but also with immune dysregulation, metabolic disturbances, and neurodevelopmental disorders. Preventive measures such as adequate sun exposure, dietary modification, and routine supplementation are critical to maintaining optimal levels. Strengthening public awareness and implementing food fortification programs can further reduce deficiency prevalence. Continued research is necessary to elucidate vitamin D's broader physiological roles and long-term impact on pediatric health. Ensuring sufficient vitamin D during early life is vital for promoting healthy growth and overall well-being.

Conflict of Interest
Not available.

Financial Support
Not available.

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How to Cite This Article
Vasudevan A. Vitamin D deficiency in children: Biochemical insights and emerging clinical implications. International Journal of Homoeopathic Sciences. 2025;9(4):479-484.