Boosting Pediatric Health: Oral Vitamin D for Growth and Immunity

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Introduction

Vitamin D is a fat-soluble vitamin synthesized in the skin during sun exposure, essential for calcium and phosphate regulation, and critical for maintaining bone and skeletal health. Optimizing bone mineral density in childhood and adolescence is crucial for lifelong skeletal strength.[1] Deficiency impairs bone health, with severe cases causing hypocalcemia, seizures, rickets, and osteomalacia.[2] Infants are born with limited stores transferred from the mother[3] and rely postnatally on supplementation, or cutaneous synthesis via UVB exposure, though production is limited beyond 37° latitude in late fall to early spring. Breast milk is a very poor source of Vitamin D (0.5–1.8 μg/L), making exclusively breastfed babies also prone to Vitamin D deficiency. Darker skin, sun avoidance in infants (with the risk of skin care in white-skinned races), and cultural practices restricting supplementation further reduce availability. Children are at the highest risk if exclusively breastfed without supplementation, have darker skin, low fortified food intake, or limited sun exposure due to an indoor lifestyle, polluted or cloudy climates. Additional risks include prematurity, obesity, sedentary habits, chronic illnesses (Chronic Kidney Disease, Cystic Fibrosis, asthma, sickle cell disease), medications affecting Vitamin D metabolism (glucocorticoids, anticonvulsants, cytochrome P450 inducers, antiretrovirals), and malabsorptive conditions such as Celiac disease or Crohn's disease.[1-5]

Vitamin D deficiency is common across all life stages, including infancy, childhood, adolescence, and pregnancy. Epidemiological studies in children report a prevalence of Vitamin D deficiency ranging from 50% to 94%, although many studies have limitations such as small sample sizes, urban bias, and varied diagnostic criteria. A nationally representative Indian survey showed high prevalence (1.1%–76.1%) across states, with risk factors including age, urban residence, winter season, vegetarian diet, female sex, high-income status, and low physical activity (<3 hours/week) in adolescents.[6]

Overview of the Molecular Basis for the Non-Classical Actions of Vitamin D In Immunity

Vitamin D, the "sunshine vitamin," is a fat-soluble nutrient synthesized in the skin during sun exposure, essential for calcium and phosphate regulation and musculoskeletal health.[1] It also influences cell growth, neuromuscular and cardiopulmonary function, immune modulation, inflammation, and recovery from injury. Skeletal health depends on maximizing bone mineral density during childhood and adolescence, as peak bone mass in early adulthood strongly predicts lifetime osteoporosis risk. Severe neonatal deficiency causes hypocalcemia and rickets—once treated with sunlight and cod-liver oil—but nutritional rickets persists worldwide and is under-reported. Beyond bone disease, rickets highlights the broader impact of Vitamin D deficiency, linking it to infections, impaired innate immunity, autoimmune disorders such as type 1 diabetes and multiple sclerosis, and allergic conditions including atopic dermatitis.[3]

Vitamin D Metabolism and Mechanism of Action

Vitamin D becomes biologically active through sequential hydroxylation: in the liver, CYP2R1 converts it to 25-hydroxyvitamin D [25(OH)D], the main circulating metabolite

and best status marker (half-life 2–3 weeks); in the kidney and peripheral tissues, CYP27B1 converts it to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D$_3$], the active form (half-life 4–6 hours, ~1,000-fold lower levels). Renal CYP27B1 is regulated by PTH and FGF23 to maintain calcium homeostasis by enhancing intestinal absorption. The active metabolite acts via the Vitamin D Receptor (VDR), a nuclear transcription factor influencing gene expression across multiple systems. Defining "normal" 25(OH)D levels remains difficult due to assay variability and lack of universal consensus.[1,3]

Vitamin D Supplementation

Vitamin D supplementation (calciferol) exists in two forms:

Vitamin D_2 (Ergocalciferol): Ergocalciferol is naturally produced in plants and fungi (like mushrooms and yeast) when they are exposed to Ultraviolet (UV) light, which converts the precursor molecule ergosterol into Vitamin D_2. Wild-growing or sun-dried mushrooms can contain significant amounts of it. Ergosterol is exposed to UV light in commercial man-made settings to manufacture Ergocalciferol. It has shorter half-life and lower affinity for binding proteins, hydroxylase enzymes, and receptors.

Vitamin D_3 (Cholecalciferol): Produced in the skin during sun exposure and obtained from animal-based foods.

Most studies demonstrate that **Vitamin D_3 is more effective** than D in raising serum 25(OH)D concentrations, making it the preferred form for supplementation.[1,3]

Molecular Mechanisms in the Immune System

Beyond bone health, Vitamin D modulates immune function, with pediatric studies linking it to reduced autoimmune risk and stronger innate defenses.[2] VDR and Vitamin D–metabolizing enzymes are widely expressed in immune cells, and CYP27B1 is induced during pathogen detection, accounting for elevated 1,25(OH)$_2$D$_3$ in granulomatous diseases like sarcoidosis. In innate immunity, Vitamin D enhances microbial recognition (CD14, NOD2), induces antimicrobial peptides (cathelicidin, β-defensin 2), stimulates cytokines such as IL-1β and IL-8, and supplementation increases antimicrobial activity in airway fluid. In adaptive immunity, it shifts dendritic cells to less inflammatory states, suppresses T-cell inflammation, promotes regulatory T cells, and regulates numerous immune-related genes.[3]

Vitamin D and Pediatric Infectious Diseases

Widespread Vitamin D deficiency raises concerns for infection risk in children. European surveys of >1000 adolescents revealed 80% had insufficient 25OHD (<75 nmol/L), with 42% deficient or severely deficient. A meta-analysis across 55,844 Europeans found 40% below sufficiency (<50 nmol/LM), with greater deficiency in dark-skinned subgroups.[3] Deficiency is equally common in India, reaching >80% in school-aged children, and is predictive of infection risk.

Benefits of Supplementation:

- Japanese RCT: Supplementation reduced influenza A incidence in schoolchildren.[3]
- Mongolian RCT: Vitamin D-fortified milk (daily 300 IU vitamin D_3) halved acute respiratory infections.[3]
- Italian trial: 1,000 IU/day reduced acute otitis media episodes in otitis-prone children.[3]

Ineffective Strategies: Bolus dosing (100,000–300,000 IU) showed no pneumonia prevention benefit.[3]

Meta-analysis of 7434 pediatric ICU patients: 47% deficient (<50 nmol/L), 64% in sepsis, strongly linked to higher mortality.[3]

Vitamin D and Other Pediatric Immune Disorders

Vitamin D deficiency has been linked to multiple pediatric conditions. Maternal and infant deficiency increases early childhood dental caries, with a meta-analysis of 24 trials showing a 47–54% risk reduction with supplementation. In Crohn's disease, risk correlates with latitude and sunlight exposure, with VDR regulating susceptibility loci such as NOD2/IBD1. Autoimmune diseases also show strong associations: in type 1 diabetes, animal models demonstrate accelerated onset with deficiency, while human studies highlight VDR's protective role in T-cell regulation; higher sun exposure in childhood lowers multiple sclerosis risk, paralleling latitude-linked incidence; supplementation in systemic lupus erythematosus reduces disease activity and fatigue; and sun exposure may lower juvenile idiopathic arthritis risk. Deficiency is further associated with allergic diseases, with higher prevalence at northern latitudes. Vitamin D enhances keratinocyte defenses in atopic dermatitis, while deficiency increases risk of food allergies—tripling peanut and multi-food allergies in infants (Australian HealthNuts study)—and a meta-analysis confirmed sufficiency reduces aeroallergen sensitization and allergic rhinitis risk in children.[3]

Diagnosis and Measurement of Vitamin D Deficiency

Vitamin D deficiency is diagnosed by serum 25-hydroxyvitamin D [25(OH)D], with <20 ng/mL (50 nmol/L) considered deficient, 21–29 ng/mL (52–72 nmol/L)

insufficient, and >30 ng/mL (75 nmol/L) sufficient.[7] 25(OH)D is the preferred marker due to its 2–3-week half-life, whereas 1,25-dihydroxyvitamin D is unreliable because of its short half-life and potential elevation from secondary hyperparathyroidism. High-Performance Liquid Chromatography (HPLC) or tandem mass spectrometry, which measure both D_2 and D_3, are the gold standards. Elevated Alkaline Phosphatase (ALP) may indicate deficiency, warranting further tests (25(OH)D, calcium, phosphorus, PTH, radiographs), though ALP can be normal in rickets, where wrist radiographs are more sensitive for subclinical cases.[8]

International Recommendations

Most international guidelines recommend Vitamin D supplementation for all infants during the first year (400 IU/day), as natural intake is inadequate; Preterm infants need higher doses (400–700 IU/kg/day for preterm infants, with a maximum dose of 1000 IU/day, ESPGHAN). Since breast milk is low in Vitamin D and maternal intake of 600 IU/day does not raise levels sufficiently, the AAP advises supplementation for all breastfed and partially breastfed infants. Less effective alternatives include high-dose maternal regimens (up to 6,400 IU/day) or monthly infant doses (50,000 IU). Beyond infancy, requirements are less defined, but supplementation is recommended in children and adolescents with low sun exposure, rapid growth, or risk factors, while fortified foods such as Vitamin D–enriched milk (ages 2–6) which is not routinely available in developing countries like India. The Endocrine Society and IOM suggest 600–1,000 IU/day for ages 1–18, whereas WHO emphasizes latitude and sun exposure. Routine screening is not recommended except in at-risk groups (NICE). Excess intake (>150 ng/mL) can cause toxicity with hypercalcemia, hypercalciuria, and soft tissue calcification. Vitamin D status is shaped by UVB exposure, season, skin pigmentation, maternal levels, breastfeeding, socioeconomic factors, obesity, and genetics.[9]

Treatment Regimens

Multiple regimens are effective, with the total cumulative dose being more important than frequency (Table-1). In IAP guidelines, preterm babies' maintenance dose mentioned is 400 IU/day, which is also recommended by AAP but ESPGHAN recommends 400-700 IU/kg with a maximum of 1000 IU/day, which is more commonly followed by most neonatologists in India. Daily doses are more physiological and show more benefits compared to monthly or fortnightly doses which are more convenient to use but have lesser benefits.[8,10]

After treatment, maintenance therapy (400–1,000 IU/day for children, 1,500–2,000 IU/day for adults) should continue until ALP normalizes, followed by age-appropriate preventive dosing. Vitamin D_3 is preferred over D_2 due to greater potency.[8]

Table-1: Vitamin D_3 dosing regimen

Age Group	Prevention (Daily Dose)	Alternative Intermittent Treatment Regimen	Maintenance Dose (Daily)
Preterm Babies	400 IU/day; 800 IU/day may achieve desired levels faster	Not applicable	400 IU/day
<6 months	400 IU/day	Not applicable	400 IU/day
6-12 months	400 IU/day	Equivalent of 2000 IU/day (e.g., 60,000 IU monthly)	400 IU/day
>12 months	400-600 IU/day	60,000 IU fortnightly (every 2 weeks) x 5 doses	600 IU/day

Nanotechnology in Vitamin D_3 Delivery

Nanotechnology has advanced the delivery of lipophilic nutrients, with nanoemulsions (<200 nm) outperforming conventional emulsions (>200 nm). Their smaller droplet size enhances physicochemical stability, prevents aggregation, improves digestion, and increases absorption of hydrophobic compounds like Vitamin D_3. This results in higher bioavailability and homogeneity, as demonstrated in both clinical and animal studies. In Non-Alcoholic Fatty Liver Disease (NAFLD) models, Vitamin D_3 nanoemulsions showed superior hepatoprotective, anti-inflammatory, and antioxidant effects.[11]

Advantages Over Conventional Formulations

Conventional Vitamin D preparations are fat soluble and needs to be given after breast feeding or a fatty meal while advanced nano Vitamin D can be given empty stomach or after a meal without any difference in absorption. Vitamin D_3 nanoemulsions hence improve compliance through easier administration and greater efficacy, and also enhance absorption in malabsorption syndromes such as IBD, celiac disease, pancreatic insufficiency, hepatobiliary disorders, short bowel syndrome, and post-bariatric surgery, and demonstrate superior hepatoprotective effects in NAFLD compared to conventional formulations.[11]

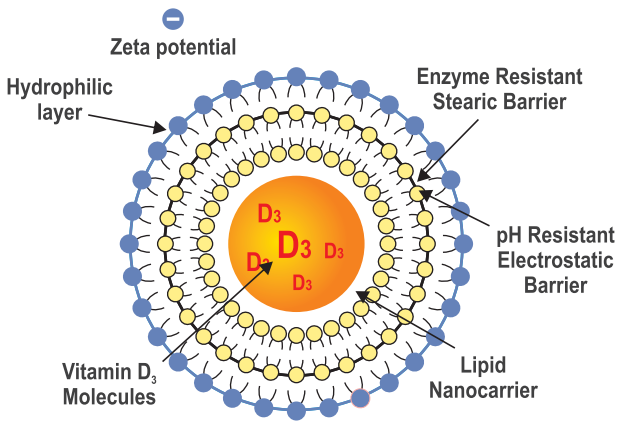
Nano-Carrier Entrapped Vitamin D_3 (Aqueol® Nanotechnology)

This patented platform produces stable nanoparticles (<150 nm) that are water-miscible, pH-resistant, and enzymatically stable. The hydrophilic surface enables direct intestinal absorption without reliance on fat digestion, providing clear advantages over granules, soft gels, or micellar syrups.[11]

Clinical Features of Nano-Carrier Entrapped Vitamin D_3-Oral Solution

Trials in Indian patients showed superior bioavailability (achieving higher serum Vitamin D_3 than standard

Nano-carrier entrapped Vitamin D_3-oral solution powered by Aqueol® Nanotechnology



formulations) and fat-independent absorption of Vitamin D_3, achieving levels above 40 ng/mL even in malabsorption states. Serum levels increased fourfold within 8 weeks across age, gender, and BMI, with excellent safety and no signs of toxicity or hypervitaminosis.[11]

Nano-Carrier Entrapped Vitamin D_3-Oral Solution powered by Aqueol® Nanotechnology represents a major advance-ment in supplementation, offering superior efficacy, fat-independent absorption, and hepatoprotective benefits. It is especially valuable for patients with malabsorption syndromes or chronic liver disease, setting a new benchmark in safe and effective Vitamin D_3 therapy.[11]

Clinical Evidence

Multiple clinical studies highlight the role of vitamin D in pediatric respiratory and allergic diseases. A meta-analysis confirmed that daily or weekly high-dose Vitamin D (>1,000 IU) lowered rates of influenza, cold, cough, and fever, with the strongest benefit in deficient children.[12] A Danish case-cohort study reported that children with higher birth 25(OH)D had a lower asthma risk between ages 3 and 9 (HR 0.51, 95% CI 0.35–0.75). In dermatology, a meta-analysis of 5 trials found that 1,000–2,000 IU daily for 1–3 months improved atopic dermatitis, reducing SCORAD scores by 11–21 points.[13] NHANES data showed an inverse relationship between 25(OH)D and aero-/food allergen sensitization in children but not adults. Finally, a trial of maternal and infant Vitamin D supplementation demonstrated that higher doses (2,000 IU/day in mothers and 800 IU/day in infants) significantly reduced house dust mite sensitization (RR 0.34, 95% CI 0.12–0.94) and lowered asthma-related healthcare visits compared to placebo.[3]

Conclusion

Vitamin D is essential for skeletal health and immune function, yet deficiency remains highly prevalent globally and more so in India. Though deficiency is prevalent in all age groups, it is most common in children, leading to hypocalcemic seizures, rickets, infections, and immune disorders. While conventional supplementation is effective, nanoformulations—such as Vitamin D_3 nanoemulsions—represent a significant advancement. These offer superior bioavailability, fat-independent absorption, and enhanced efficacy, especially in malabsorptive conditions. Their improved safety and rapid response profile make them a transformative option for addressing deficiency efficiently and effectively, marking a new era in targeted nutrient delivery.

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