

# Review Article

## Management of Vitamin D Deficiency in Children: An Update

SURAIYA BEGUM<sup>1</sup>, KOHINOOR JAHAN SHYAMALY<sup>2</sup>, BARAKA BADRUDDUZA TITHI<sup>2</sup>, ROMANA OMANA AHKTER<sup>2</sup>, RUKHSANA PARVIN<sup>2</sup>, MUHAMMAD REJAUL KARIM<sup>2</sup>, ISMAT ARA JANNAT<sup>3</sup>

### Abstract

*Vitamin D is a steroid hormone that plays a major role in maintaining skeletal health and it also has a role in disorders other than bone metabolism. In the paediatric population, vitamin D deficiency has emerged as a significant public health problem throughout the world and majority of children has vitamin D deficiency in spite of wide availability of sunlight. Vitamin D deficiency status is defined as deficiency when 25(OH)D level is less than 30 ng/mL (75 nmol/L). The manifestations of deficiency may vary from hypocalcemic seizures and tetany in infancy, florid rickets in toddlers, and pain in adolescent. Vitamin D deficiency is associated with other different clinical diseases, such as, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is also associated with prematurity, obesity, malabsorption, extreme latitudes and little sunlight exposure. Routine supplementation of vitamin D starting from newborn period is endorsed by various international organizations. Prevention by adequate sunlight exposure, food fortification and routine supplementation are the currently available options for this nutritional deficiency. In conclusion, vitamin D deficiency is highly prevalent in the paediatric age group. Aim of this review article is to discuss the health benefits of vitamin D and to provide recommendations for the prevention and treatment of vitamin D deficiency.*

**Key words:** S. 25(OH)D, vitamin D deficiency, children, rickets

### Introduction:

Vitamin D is important for bone development in children.<sup>1</sup> It also has many non-calcemic functions, including immune, cardiovascular, endocrine, neuropsychological functions, neuromuscular performance, cellular differentiation, and anticancer actions.<sup>2,3</sup> Vitamin D deficiency causes rickets among children which represents only the tip of the vitamin D deficiency iceberg. Vitamin D deficiency was initially considered quite rare as most of the studies were based on serum calcium and alkaline phosphatase.<sup>4</sup> Currently its potential health implications are the subject of significant interest. There is a high prevalence of vitamin D deficiency among children which is up to 85 to 98% in several studies.<sup>5,6</sup> The

risk factors associated with vitamin D deficiency are inadequate exposure to sun, atmospheric pollution, darker skin pigmentation, low physical activity, indoor confinement of children and high rise buildings.<sup>7-10</sup> Over the last two decades, concept about vitamin D, its function and deficiency has changed remarkably. In this review, the current knowledge on diagnosis, screening, prevention and treatment of vitamin D deficiency is discussed.

### Physiology of vitamin D:

Vitamin D known as 'the sunshine vitamin' is a pro-hormone. Different forms of vitamin D are cholecalciferol, calcidiol (25-OHD), and calcitriol (1,25-OHD). Cholecalciferol has two physiologically active forms, vitamin D<sub>2</sub> (ergocalciferol), and vitamin D<sub>3</sub> (cholecalciferol).<sup>11</sup> Source of vitamin D<sub>2</sub> is food which is formed from ultraviolet (UV) radiation in plants and yeast, and vitamin D<sub>3</sub> is synthesized in the skin from 7-dehydrocholesterol. Vitamin D in animal origin is cholecalciferol (vitamin D<sub>3</sub>), sources

1. Professor, Department of Paediatrics, BSMMU, Dhaka.  
2. Paediatrician, Department of Paediatrics, BSMMU, Dhaka.  
3. Registrar, Paediatric Hematology and Oncology Department, National Institute of Cancer Research and Hospital  
**Correspondence:** Dr. Suraiya Begum, Professor, Department of Paediatrics, BSMMU, Room no. 231 B, Block-C, BSMMU, Dhaka. Cell no. 01715131535, e-mail: Suraiyadr07@yahoo.com

are fish, such as eel, salmon, herring and to a lesser extent - egg yolk, cheese and milk.<sup>12</sup> It is estimated that balanced diet covers 10-20% of the required daily vitamin D intake. The production of vitamin D is dependent on the amount of ultraviolet ray reaching the skin, and is therefore influenced by skin pigmentation, use of sunscreen, type of clothing, season of the year, and geographical latitude. Sun exposure cannot result in toxic vitamin D concentrations.<sup>7</sup> As skin synthesis is varied and balanced diet cannot provide the complete vitamin D requirement, so an appropriate vitamin D supplementation plays a crucial role in maintenance of the optimal health outcomes.<sup>12</sup> Prevention of vitamin D deficiency at the population level, a mandatory fortification of selected food products (milk, dairy products, cereals, orange juice, margarine and pasta) is provided in some countries.<sup>13</sup> Vitamin D is converted by 25-hydroxylase enzyme to 25(OH)D in liver and then converted to 1,25-dihydroxyvitamin D in kidneys by 1  $\alpha$ -hydroxylase enzyme.<sup>11</sup>

#### **Epidemiology of Vitamin D deficiency:**

Vitamin D deficiency is the most common nutritional deficiency.<sup>14</sup> It is one of the most common undiagnosed medical conditions in the world. It has been estimated that one billion people worldwide have vitamin D deficiency or insufficiency.<sup>15</sup> Though majority of population in this subcontinent receive sunlight throughout the year, vitamin D deficiency is very common in all the age groups and both the sexes.<sup>16</sup> One study found that about 80% of Bangladeshi children had vitamin D deficiency and there was no difference in relation to sex and socioeconomic condition.<sup>17</sup> Agarwal et al in their study showed that in exclusively breastfed infants, 55.67% at 10 weeks and 44.33% infants at 6 months had vitamin D deficiency and 16.49% infants developed rickets.<sup>18</sup> In Delhi of India, 93.7% children aged 6-17 years have shown to be deficient in vitamin D.<sup>19</sup> Prevalence of Vitamin D deficiency was noted to be almost similar in children from both upper (91.9%) and lower (89.6%) socio economic strata.<sup>6</sup>

#### **Pathophysiology of Vitamin D deficiency:**

Inadequate circulating 25(OH)D is associated with secondary hyperparathyroidism which may result in increased mobilization of calcium from the bone.<sup>20</sup> Vitamin D deficiency with or without calcium deficiency may result in rickets in infants/toddlers or osteomalacia, pain, and muscle weakness in older

children/adolescents.<sup>15</sup> Vitamin D deficiency may also have a negative impact on the peak bone mass resulting in low bone mineral density in childhood, which may subsequently result in osteoporosis in adulthood.<sup>21</sup> Maternal vitamin D deficiency may result in hypocalcemic seizures, rickets and rarely cardiomyopathy in neonate.<sup>22</sup> Vitamin D not only regulates calcium and bone metabolism but also reduces the risk of chronic diseases including autoimmune diseases, malignancies, cardiovascular and infectious diseases. Vitamin D binds to vitamin D receptors on various cells which participate in immune responses, and modulate activation and deactivation of the innate and adaptive responses by its effect on B-lymphocyte and T-lymphocyte function.<sup>23</sup> Vitamin D deficiency being associated with autoimmune diseases such as type 1 diabetes and multiple sclerosis.<sup>24,25</sup> Protective effects of vitamin D supplementation have been demonstrated against rheumatoid arthritis, autoimmune thyroiditis and inflammatory bowel disease.<sup>26,27</sup> Low levels of vitamin D level was associated with increased susceptibility of sepsis.<sup>28</sup> The biologically active form of vitamin D can modulate gene expression, inhibit the cellular proliferation, induction of differentiation, and apoptosis ultimately inhibiting the cell growth of cancer. An increased incidence of VDD was observed in children suffering from cancer (leukemia/lymphoma or solid tumors) as compared to the control and vitamin D supplementations reduced total cancer mortality.<sup>29,30</sup> In all the age groups, Vitamin D deficiency is related to bone pain and increased susceptibility to bone fractures.<sup>31</sup>

In vitamin D deficiency, a three-stage regulatory mechanism was described. Initially, a compensatory increase of parathormone (PTH) secretion to sustain normo-calcemia. A relative resistance to PTH may develop resulting in decreased calcium concentrations and increased phosphate concentrations. At this stage, symptoms of hypocalcemia, including tetanic convulsions, may occur. Osteopenia is visible on radiographs, without typical ricketic lesions. In the next stage, when vitamin D deficiency continues to progress, PTH resistance gets overcome leading to improved calcemia, hypophosphatemia and clinical and radiological manifestation of rickets, Alkaline phosphatase (ALP) increases and 1,25(OH)<sub>2</sub>D is normal or increased. When vitamin D deficiency becomes very severe and 1,25(OH)<sub>2</sub>D synthesis is markedly inhibited, the calcitriol concentration decreases, and absorption of both calcium and phosphorus is impaired, along with persistent elevation of PTH and increased ALP.<sup>20</sup>

**Classification of vitamin D deficiency<sup>32</sup>**

Vitamin D status is measured through assay of 25(OH) D. Twenty-five (OH)D is the major circulating form of vitamin D with a half-life of 2-3 weeks and its levels are the best indicators of vitamin D status. Although calcitriol is the active form, it has a half-life of only 4 hours and it is not a good indicator of vitamin D stores. Optimum level of 25(OH)D is more than 30pg/ml (> 75 nmol/L) and hypercalcaemia is associated with 25(OH) D when the level is more than 150 ng/mL (> 374 nmol/L).

**Etiology of vitamin D Deficiency:**

No age is immune for vitamin D deficiency and causes of vitamin d deficiency are decreased synthesis, intake, absorption and increased degradation of vitamin D.<sup>20</sup>

**Table-I**  
*Classification of vitamin D deficiency*

Vitamin D status	ng/mL	nmol/L
Severe deficient	<5	12.5
Deficient	<20	<50
Insufficient	20-30	50-75
Sufficient	>30	>75
Risk of Toxicity	100	250
Intoxication	>150	>374

**Table-II**  
*Etiology of vitamin D Deficiency*

Decreased vitamin D synthesis	Skin pigmentation, physical agents blocking UVR exposure, clothing, latitude, season, air pollution, cloud cover, altitude, sedentary lifestyle
Decreased nutritional intake of vitamin D	Strict vegetarian, high phytates and oxalates diet
Age and physiology related	Prematurity, Elderly, obese and institutionalized
Decreased maternal vitamin D stores	Exclusive breast feeding
Malabsorption	Celiac disease, pancreatic insufficiency (cystic fibrosis), biliary obstruction (biliary atresia)
Decreased synthesis	Chronic liver disease
Increased degradation of 25 (OH) D	Drugs such as rifampicin, isoniazid, anticonvulsants, glucocorticoids.

Vitamin D levels is low in breast milk which is on average 22 IU/L (15 -80 IU/L) in vitamin D sufficient mother.<sup>33</sup> The prevalence of Vitamin D deficiency in term breastfed infants without vitamin D supplementation was 40% at four months of age in the USA, and 83% at one month of age in Qatar<sup>34,35</sup> Vitamin D deficiency is common in infancy due to several factors such as – decreased dietary intake, decreased cutaneous synthesis, exclusive breast feeding, and low maternal vitamin D.<sup>36</sup> Individuals aged 11–18 years are among the groups of increased risk of vitamin D deficiency due to rapid and significant weight gain, an acceleration of skeletal growth, rapid bone turnover and modeling, redistribution of muscle-fat compartments, sedentary behavior and dietary habits. This is the target group of special concern

and highlighted a need to increase a recommended vitamin D daily dose.<sup>37</sup>

**Clinical features of vitamin D deficiency:**

Vitamin D deficiency is often a silent disease. By definition, rickets occurs in children whose growth plates have not fused.<sup>20</sup> These children often walk quite late or prefer to sit down for prolonged periods. In children with a severe vitamin D deficiency, bowing in the legs may be found. In adolescents and adults with a severe vitamin D deficiency, periosteal bone pain may be found. This is best-detected by using firm pressure on the sternal bone or tibia. Vitamin D deficiency is often associated with other clinical diseases, such as, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases.

**Table-III**  
*Symptoms and signs of vitamin D deficiency in children<sup>20</sup>*

<b>Infants</b>	Seizures, tetany and cardiomyopathy
<b>Children</b>	Aches and pains; myopathy causing delayed walking; rickets with bowed legs, knock knees, poor growth and muscle weakness
<b>Adolescents</b>	Aches and pains, muscle weakness, bone changes of rickets or osteomalacia

**Severe vitamin D deficiency:**

Advanced stages of nutritional rickets and osteomalacia are characterized by bone deformities, hypocalcemic seizures, tetany, severe bone pain, significant muscle weakness, hypocalcemic cardiomyopathy, circulatory failure, disorders of psychomotor and physical development, and short stature.<sup>38-40</sup>

**Screening of vitamin D**

Indian Academy of Pediatrics (IAP) Guidelines on vitamin D deficiency do not recommend routine screening of healthy children. The screening is done in people who are at risk of Vitamin D deficiency.<sup>31</sup>

**Biochemical change and radiography:**

**Table-IV**  
*Biochemical Markers and radiography of vitamin D deficiency in children<sup>41</sup>*

Stages	Serum calcium	Serum phosphorus	ALP	PTH	25(OH)D	1,25 (OH)D3	Radiography
Early	N /↓	↓/N	↑	↑	↓	N	Osteopenia
Moderate	N /↓	↓	↑↑	↑↑	↓↓	↑	Rachitic changes 1+
Severe	↓↓	↓/N	↑↑↑	↑↑↑	↓↓↓	↑/N /↓	Rachitic changes 2+

**Table-V**  
*Indications of screening of vitamin D deficiency<sup>32</sup>*

- i. Dark skinned infants who live at higher altitude and infants born to Vitamin D deficient mothers.
- ii. In the presence of nonspecific symptoms like poor growth, gross motor developmental delay and unusual irritability.
- iii. Children with suspected rickets, those with osteoporosis.
- iv. Chronic kidney disease
- v. Hepatic failure
- vi. Malabsorption syndromes:
  1. Cystic fibrosis
  2. Inflammatory bowel disease
  3. Crohn’s disease
- vii. Hyperparathyroidism
- viii. On medications:
  1. Anticonvulsants
  2. Glucocorticoids
  3. AIDS medications
  4. Antifungals (ketoconazole)
- ix. Obese children and adults (BMI > 30kg/m<sup>2</sup>)
- x. Granuloma forming disorders:
  1. Sarcoidosis
  2. Tuberculosis
  3. Histoplasmosis
- XI. Children with non-traumatic fall

**Table-VI***Prevention and treatment of vitamin D deficiency (Indian Academy of Pediatrics (IAP) guideline<sup>31</sup>*

Age	Prevention	Treatment	Treatment with large dose (oral route preferred)
Premature Neonates	400 IU/day	1000 IU/day	NA
Neonates	400 IU/day	2000 IU/day	NA
1-12 months	400IU/day	2000IU/day	60,000IU weekly (over 3 months of age)
1-18 years	600IU/Day	3000-6000 IU/day	60000 IU weekly
At risk groups	400-1000IU/day	As per age group	As per age group

**Treatment of vitamin D deficiency:**

Vitamin D therapy is necessary for infants and children who manifest clinical features of hypocalcemia as a result of vitamin D deficiency or rickets and when vitamin D levels are in the deficient range even if asymptomatic.<sup>20</sup> For infants, daily vitamin D intake should be initiated by one month of life. Duration of treatment is for a minimum of 3 months; after treatment, daily maintenance doses should be given.

Studies have shown that vitamin D3 is at least 3 times more potent than vitamin D2.<sup>42</sup> Hence supplements containing D3 may be preferred. Loading load is justified when everyday regular supplementation of vitamin D is not possible because of socioeconomic reasons or limitations of the health care system.

**Prevention of vitamin D deficiency**

Balanced diet covers up to 10% of the required daily vitamin D intake.<sup>43</sup> When an additional source such as skin synthesis is scarce, only balanced diet can not provide the complete vitamin D requirement, so vitamin D supplementation is needed for maintenance of the optimal health. For preventing of vitamin D deficiency at the population level, mandatory fortification of selected food products is provided in some countries.<sup>44</sup> The most important factor determining the vitamin D status in infancy is the maternal vitamin D status.<sup>45</sup> Preterm infants should be supplemented from birth because of inadequate transfer of maternal vitamin D, poor feeding and impaired absorption.<sup>36</sup> For infants, daily

vitamin D intake should be initiated within few days after birth

**Sources of Vitamin D**

**Sunlight:** Most of the circulating vitamin D is provided by synthesis from skin exposure to ultraviolet radiation.<sup>42</sup> At solar noon between 10.00 – 15.00 hours, the ratio of UVB – UVA light is the highest.<sup>46</sup> Exposure to sunlight about 18% of the body surface area including face, uncovered forearms, hand and lower limbs for 10-30 minutes depending on time of day, season, latitude, and skin pigmentation, at least 3 times a week is adequate.<sup>47</sup> But it is difficult to achieve because of modernization and cultural practices so supplementation and fortification is needed. Asian children require three times the recommended amount of sun light exposure to maintain the vitamin D levels because of dark skin color. Fortified foods and supplementation are important source of vitamin D.<sup>48</sup>

**Dietary vitamin D:**

Dietary sources of vitamin D are scarce and include mainly fatty fish and egg yolk.<sup>49</sup> In some European countries, certain foods are fortified with vitamin D. These include milk, dairy products, margarine, breakfast cereals, and fruit juices.

**Calcium supplementation:**

While managing vitamin D deficiency, calcium supplementation is very important for avoiding subsequent hypocalcaemia from an increase bone mineralization as PTH levels normalize due to hungry bone syndrome.



**Table-VII**  
*Management of Hypocalcaemia Due to Vitamin D deficiency<sup>32</sup>*

Symptomatic hypocalcaemia due to vitamin D deficiency	Asymptomatic vitamin D deficiency
IV calcium gluconate (1-2ml/kg) (up to maximum of 20 ml/ dose) 1-2 doses (till symptoms subside). Then oral calcium 30-75mg/kg/day (up to a maximum of 1-2 g/ day) in 3 divided doses for 1-2 weeks	Oral calcium 30-75mg/kg/day (up to a maximum of 1 – 2 g/ day) in 3 divided doses for 1-2 weeks
Reduce the dose by half and continue till PTH and vitamin D becomes normal. Calcitriol 0.05 mcg/kg/ day (up to a maximum of 0.5 mcg/ day) may be needed till calcium levels normalize.	Reduce the dose by half and continue till PTH and vitamin D becomes normal. Calcitriol 0.05 mcg/kg/ day (up to a maximum of 0.5 mcg/ day) may be needed till calcium levels normalize.

Calcium preparations: Calcium carbonate is the most common form of calcium supplements. Calcium gluconate is less concentrated form of calcium and are not practical oral supplements. The maximal dose of elemental calcium that should be taken at a time is 500 mg.<sup>36</sup>

**Monitoring therapy in rickets:**

Estimation of serum calcium, phosphorus and PTH levels are recommended 1 month after initiation of therapy. Usually calcium and phosphorus levels become normal within 6-10 days whereas PTH, 25(OH)D levels normalize within 1-2 months and serum alkaline phosphatase by 3-6 months. Evidence of healing is evident within one month and complete healing takes longer time. After 3 months it is recommended to obtain serum levels of calcium, phosphorus, serum ALP, 25(OH)D, PTH, and a repeat X-ray if there are bone changes present initially. Subsequently 25(OH)D levels may be monitored yearly.<sup>20</sup>

**Conclusion**

Vitamin D deficiency is a global public health problem even in tropical regions where the risk of deficiency assumed to be low due to sunlight. The prevalence of vitamin D deficiency is very high and alarming in children. Only small percentage of patients are presented with rickets. Vitamin D deficiency is also associated with extra-skeletal problems. Four hundred IU of vitamin D supplementation should be started as universal coverage in all infants and fortification of food for all age group to be initiated for prevention of vitamin D deficiency disorders. Screening is needed in high risk groups and treatment

should be given in vitamin D deficiency appropriately for prevention of health-related consequences. National authorities should adopt policies aimed at improving vitamin D status by using measures such as dietary recommendations, food fortification, and vitamin D supplementation.

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