Review Article

Skeletal and Extra-Skeletal Effects of Vitamin D Deficiency in Children
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Abstract
Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis. It has skeletal growth and extra-skeletal effects in our body. Objective of this article is to update the information on skeletal and extra-skeletal effects of vitamin D deficiency in paediatric clinical disorders. In the paediatric population, vitamin D deficiency is associated with different clinical diseases such as rickets, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, anticonvulsant agents, extreme latitudes, low consumption, and little sun exposure. The recommendation is to prevent vitamin D deficiency and to maintain 25(OH) D serum levels >30ng/mL (>75 nmol/L).

Keywords: Vitamin D, Vitamin-D deficiency, Extra-skeletal manifestation.

INTRODUCTION
Vitamin D (VD) is a pro-hormone that is essential for absorption of calcium and phosphorus. Vitamin D deficiency (VDD) is associated with rickets in growing children and osteomalacia in adolescent. VD has role in skeletal health, apart from this it causes inhibition of cellular proliferation, angiogenesis and renin production, stimulating insulin production, and macrophage cathelicidin production.¹ There is high prevalence of VDD among children which is about 85% to 98%.²

CLASSIFICATION OF VITAMIN D DEFICIENCY
Optimum level of 25(OH) D is >30ng/ml (>75nmol/L) and hypercalcaemia is associated if the level is >150ng/mL (> 374nmol/L).³

Table I: Classification of VDD ³

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>ng/mL</th>
<th>nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficient</td>
<td>&lt;5</td>
<td>&lt;12.5</td>
</tr>
<tr>
<td>Deficient</td>
<td>&lt;20</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Insufficient</td>
<td>20-30</td>
<td>50-75</td>
</tr>
<tr>
<td>Sufficient</td>
<td>&gt;30</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Risk of Toxicity</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>Intoxication</td>
<td>&gt;150</td>
<td>&gt;374</td>
</tr>
</tbody>
</table>

Table II: Etiology of vitamin D Deficiency⁴

<table>
<thead>
<tr>
<th>Etiology of VD Deficiency</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased VD synthesis</td>
<td>Skin pigmentation, physical agents blocking ultraviolet ray exposure, clothing, latitude, season, air pollution, cloud cover, altitude, sedentary lifestyle and winter season</td>
</tr>
<tr>
<td>Decreased intake of VD</td>
<td>Strict vegetarian, high phytates diet</td>
</tr>
<tr>
<td>Age and physiology related</td>
<td>Prematurity, elderly, obese</td>
</tr>
<tr>
<td>Decreased maternal VD stores</td>
<td>Exclusive breast feeding</td>
</tr>
<tr>
<td>Mal-absorption</td>
<td>Celiac disease, pancreatic insufficiency, biliary obstruction</td>
</tr>
<tr>
<td>Decreased synthesis</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Increased degradation of 25 (OH) D</td>
<td>Drugs: rifampicin, isoniazid, anticonvulsants, glucocorticoids.</td>
</tr>
</tbody>
</table>

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VDD is associated with cardiovascular disease, hypertension, autoimmune diseases, and cancer.⁶⁷⁸⁹ The reasons of VDD in this subcontinent could be low dietary VD intake, high fiber and phytate intake, reduced exposure of skin to sun light because of cultural and traditional habits or pollution.¹⁰¹¹¹² Individuals with darker skin require a
longer time in the sunlight than those with lighter skin to produce the same amount of VD.\textsuperscript{13} Sunscreens reduces the ability of the skin to produce vitamin D by over 95% to 98%.\textsuperscript{14} Vitamin contents of food vary depending on cooking methods, fried fish loses 50% of VD.\textsuperscript{4}

VD has effect related to: 1) Nuclear and cytosolic characteristics of VD receptor (VDR) and the enzyme that metabolizes VD in multiple tissues e.g., adipose tissue, muscle, and pancreas. 2) Regulation of more than 200 genes. 3) The risk associated with VDD, and the presence of multiple diseases.\textsuperscript{15,16,17} Over 30 different types of tissues have been identified as having cells with a VDR.\textsuperscript{18} Neonate has 60–70% of maternal VD levels. In case of maternal deficiency, the neonate’s low reserves of VD can cause hypo-calcemic symptoms in the first six months of infant.\textsuperscript{19}

In countries where foods are not fortified, available option is to intake of fatty fish, which provides 5-13µg of VD/three ounces of fish, egg yolk contains 0.5 µg of VD and three ounces of beef liver contains 0.3µg of VD. It would be difficult to obtain the necessary 25µg of VD through these sources.\textsuperscript{20} When fortified foods are not available and exposure to sunlight is limited, supplementation is the only measure for attaining adequate VD status.\textsuperscript{21}

**MANIFESTATIONS OF VITAMIN D DEFICIENCY**

**Musculo-skeletal manifestation:** VDD is associated with nutritional rickets and osteomalacia which is characterized by bone deformations, hypocalcemic seizures, tetany, severe bone pain, muscle weakness and short stature.\textsuperscript{22} At infancy and adolescent there are increased growth velocity, the increased demand for calcium, and the children may present with hypocalcemia even before radiologic signs of rickets are observed.\textsuperscript{23} Severe vitamin VDD is associated with cardiomyopathy related to hypocalcemia.\textsuperscript{24}

**Obesity:** VD sequestration occurs in adipose tissue because of its lipid-soluble nature.\textsuperscript{25} The active form of VD regulates gene transcription in adipogenesis, inflammation, and insulin resistance in the adipose tissue.\textsuperscript{26} In muscle and pancreas, 1,25(OH)2D may improve insulin sensitivity, controlling insulin secretion in pancreatic beta cells and increasing insulin receptor expression in peripheral tissues.\textsuperscript{4} Higher circulating 25(OH)D3 level was associated with low body fat, and lower number of metabolic disturbances.\textsuperscript{27}

**Insulin Resistance:** There is reverse association between vitamin D and insulin resistance and VD supplementation reduces the risk for type 1 diabetes.\textsuperscript{28}

**Metabolic syndrome:** Low VD levels in adolescents were strongly associated with metabolic syndrome, regardless of adiposity.\textsuperscript{29} There is reduction in low density lipoproteins cholesterol (LDL-C) following VD supplementation.\textsuperscript{30} There is increased risk of hypertension with VDD.\textsuperscript{31}

**Intestinal malabsorption syndromes:** VDD in malabsorption syndromes due to reduced absorption of lipid soluble vitamins, and hyperparathyroidism secondary to hypocalcemia. This leads to a greater 25(OH) D conversion into 1,25 (OH)2D and lower 25(OH)D levels.\textsuperscript{32} The prevalence of VDD in Cystic fibrosis is 95%.\textsuperscript{33}

**Anticonvulsant agents:** Prevalence of VDD is 50% in children with epilepsy receiving anticonvulsant agents such as phenytoin, phenobarbital, and carbamazepine. These drugs inducing the activity of cytochrome- P450-hydroxylase enzymes, thus leading to an accelerated VD catabolism.\textsuperscript{34}

**Respiratory tract infections:** There is increased risk for wheezing in children of women who had VDD during pregnancy.\textsuperscript{35} Cord blood VDD is associated with respiratory syncytial virus bronchiolitis.\textsuperscript{36} VD reduces the risk for influenza and achieve an adequate vaccine response because it activates T cells.\textsuperscript{37} There is an association between VDD and asthma severity and significant reduction of asthma exacerbation with VD supplementation.\textsuperscript{38}

**Cardiovascular diseases:** Low VD are associated with secondary elevation of parathyroid hormone, increased arterial resistance, and endothelial dysfunction leading to hypertension.\textsuperscript{39} VD acts as a cardiovascular and renal protective factor by suppressing the renin-angiotensin-aldosterone system, which inhibits vascular calcification and plaque formation, and has anti-inflammatory and immunomodulatory actions.\textsuperscript{40}

**Diabetes mellitus:** VD supplementation was associated with significant reduction in the progression of diabetes and higher reversal to normoglycemia. It acts on
pancreatic β-cells by binding VDR to produce insulin synthesis and on the muscle and fat cells to reduce insulin resistance. \(^{41}\)

**Muscle Strength:** VDD causes muscle weakness and repeated fall. Infants and children with severe VDD and rickets may present with delayed motor development, muscle hypotonia, and weakness. \(^{42}\)

**Immune Effects:** VD binds to VDR on various cells and modulate activation and deactivation of the innate and adaptive responses. VD modulates B-lymphocyte and T-lymphocyte function. \(^{43}\) VDD is associated with autoimmune diseases such as type 1 diabetes and multiple sclerosis. \(^{44,45}\) Protective effects of VD supplementation have been demonstrated against rheumatoid arthritis and inflammatory bowel disease. \(^{46,47}\) VD supplementation showed a positive impact on autoimmunity by significantly reducing the fall in thyroid peroxidase antibody in autoimmune thyroiditis. \(^{48}\)

**Infectious Disorders:** VD supplementation modulates T-cell function in human immunodeficiency virus (HIV) infected patients, and a useful adjunct to antiretroviral therapy. \(^{49}\) VDD was associated with increased susceptibility of sepsis. \(^{50}\) Systematic review was indicated that low vitamin D status might be associated with an increased risk of COVID-19 infection. \(^{51}\)

**Cancer:** The biologically active form of VD 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 as compared to the control. \(^{52}\) VD supplementations reduced total cancer mortality. \(^{53}\)

**Sleep and Pain:** VD plays an important role in sleep and pain. Supplementation of VD with chronic pain improved the pain score, sleep latency, sleep duration and body pain. \(^{54}\)

**Skin:** Keratinocytes express the VDR, and when these cells are exposed to VD, their growth is inhibited and they are stimulated to differentiate. This has led to the use of topical VD analog to treat psoriasis. \(^{55}\)

**Psychiatric Conditions:** VDD has been linked to an increased incidence of schizophrenia, bipolar disorder and depression. \(^{56,57}\) Maintaining VD sufficiency in utero and during early life is important for VD receptor transcriptional activity in the brain, brain development and maintenance of mental function later in life. \(^{58}\)

**Other effects:** In VDD, menarche is started 9 months earlier. \(^{59}\) It was found that the BMI, body fat, and testosterone were higher in polycystic ovarian syndrome with VDD. VD supplementation has provided improvement of hyperinsulinism, fertility and hyper-androgenism in PCOS. \(^{60}\)

**Table III: Screening of vitamin D deficiency**

| i. | Dark skinned infants who live at higher altitude and infants born to VDD mothers |
| ii. | Nonspecific symptoms like poor growth, gross motor developmental delay |
| iii. | Suspected rickets, osteoporosis |
| iv. | Chronic kidney disease |
| v. | Hepatic failure |
| vi. | Malabsorption syndromes: Cystic fibrosis, Inflammatory bowel disease |
| vii. | Hyperparathyroidism |
| viii. | Medications: Anticonvulsants, Glucocorticoids, AIDS medications, Ketoconazole |
| ix. | Obese children and adults |
| x. | Granuloma forming disorders: Sarcoidosis, Tuberculosis, Histoplasmosis |
| xi. | Children with non-traumatic fall |

**TREATMENT**

As per the Endocrine Society Clinical Practice Guideline, infants require 400IU/d, children ≥1 year require 600IU/d, adults between 19–70 years require 600IU/d, and elders ≥70 years of age require at least 800IU/d of VD to maximize bone health and muscle function. \(^{4}\)

VD therapy is necessary for infants and children who manifest clinical features of hypocalcemia due to VDD or rickets and when VD levels are in the deficient range even if asymptomatic. \(^{4}\)
Table IV: Prevention and treatment of VDD Indian Academy of Pediatrics guideline.\(^61\)

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevention</th>
<th>Treatment</th>
<th>Treatment with large dose (oral route preferred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature baby</td>
<td>400IU/day</td>
<td>1000IU/day</td>
<td>NA</td>
</tr>
<tr>
<td>Neonates</td>
<td>400IU/day</td>
<td>2000IU/day</td>
<td>NA</td>
</tr>
<tr>
<td>1-12 months</td>
<td>400IU/day</td>
<td>2000IU/day</td>
<td>60,000IU weekly (&gt; 3 months of age)</td>
</tr>
<tr>
<td>1-18 years</td>
<td>600IU/Day</td>
<td>3000-6000 IU/day</td>
<td>60000IU weekly</td>
</tr>
<tr>
<td>At risk groups</td>
<td>400-1000IU/day</td>
<td>As per age group</td>
<td>As per age group</td>
</tr>
</tbody>
</table>

Treatment should be continued for a minimum of 3 months, after that daily maintenance doses to be given.

Table V: Recommendations for VD supplementation in different diseases in the pediatric age group

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>1200-2000IU/day(^62)</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>4000IU/day for 6 months to obese children and adolescents with VDD(^63)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>2000IU/day(^64)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Children &lt;1 year old: 400-800IU/day; if VDD: 800IU to 2000IU/day Children 1-10 years old: 800-1000IU/day; if VDD up to 4000IU/day(^65)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>400-600IU/day(^66)</td>
</tr>
<tr>
<td>Asthma</td>
<td>500-1200IU/day(^67)</td>
</tr>
<tr>
<td>Neurological diseases</td>
<td>800-1000IU/day(^68)</td>
</tr>
</tbody>
</table>

Lactating women given 4000IU of vitamin D3 per day were able to transfer enough vitamin D3 into their milk to satisfy an infant’s requirement.\(^69\)

The following recommendations have been made to prevent VDD in the pediatric population:\(^70\)

- Adequate sun exposure to the face, hands or legs (at least 3 times a week for 15 minutes). In extreme latitudes and during the winter, ensure an adequate consumption of food sources.
- For infants, administer VD3 at 400 IU/day until 1 year old – due to the low VD content in breast milk.
- Prevent overweight and obesity.
- Assess VD status who are at risk for deficiency and administer according to recommendations.

**Calcium supplementation:** In VDD, 50-75mg/kg calcium supplementation are important for avoiding subsequent hypocalcaemia from an increase bone mineralization as PTH levels normalize due to hungry bone syndrome. The maximal dose of elemental calcium that should be taken at a time is 500mg.\(^71\)

**CONCLUSIONS**

VDD is associated with different clinical diseases such as bone alterations, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, use of anticonvulsant agents, and lifestyle characteristics, such as clothing, extreme latitudes, low consumption, and little sun exposure. Inadequate vitamin D levels may be responsible for the progression of cardiovascular disorders, diabetes mellitus, autoimmune disorders, sleep disturbance and pain to a considerable extent. Therefore, awareness is needed to combat the increasing prevalence of VDD through all age groups. Screening and treatment strategies are required for VDD. Adequate intake of VD through supplementation is essential for daily requirement as VDD has impact on various comorbidities.
Undiagnosed VDD is not uncommon. It is very difficult to obtain that much vitamin D3 on a daily basis from dietary sources. Thus, sensible sun exposure and the use of supplements are needed to fulfill the body's VD requirement.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

REFERENCES


43. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral


