Review: Vitamin D Deficiency in Children
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VITAMIN D DEFICIENCY IN CHILDREN

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Vitamin D Deficiency in Children

Introduction

Vitamin D deficiency (VDD) is one of the most common nutritional deficiencies with an estimate of 1 billion people worldwide. Vitamin D deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world (Balasubramanian, Dhanalakshmi et al. 2013).

In spite of majority of Indian population lives in areas receiving ample sunlight throughout the year, VDD is extremely common in all the age groups and both the sexes across the country. Although VDD is highly prevalent in Indian children, the data on the prevalence of vitamin D deficiency in children from India is limited. In 310 children and adolescents of pediatric hospital of Kolkata, deficiency was highest in adolescents (86.1%), followed by school children (61.0%), lowest in pre-school children (41.6%). 25(OH)D concentrations was lowest in winters and spring compared to summer (Basu, Gupta et al. 2015). Another study showed that as many as 95.7% neonates have serum 25 hydroxy vitamin D levels < 50 nmol/L (deficient) (Trilok Kumar, Chugh et al. 2015).

A recent study shows that countrywide studies have reported vitamin D deficiency in as high as 70%–100% of ostensibly healthy individuals. High prevalence of vitamin D deficiency was reported from northern to southern and western to eastern India, in ostensibly healthy children, adolescents, young adults and those ≥50 years old. All over India, vitamin D deficiency was highly prevalent in pregnant women and lactating mothers. Vitamin D status of these mothers correlated well with their neonates and their exclusively breastfed infants. Subjects from rural and urban areas presented a similar picture (G R and Gupta A 2014).

This review includes the information on vitamin D, vitamin D deficiency and preventive and treatment strategies for managing vitamin D deficiency in infants and children.

| TABLE 1. Prevalence of vitamin D deficiency in Kolkata and Chandigarh |
|-------------------------|-------------------------|
|                         | Kolkata (Basu, Gupta et al.2015) | Chandigarh (Angurana, Angurana et al. 2014) |
| Severe deficiency (<10 ng/ml) | 19.2 % | 40.24 % |
| Deficiency (<20 ng/ml) | 52.9 % | 25.44 % |
| Insufficiency (20-29 ng/ml) | 24.5 % | 34.32 % |
| Sufficiency (>30 ng/ml) | 22.6 % |  |
In another study at Chandigarh, in apparently healthy children between 3 months-12 years of age, from the upper socio-economical status, clinical signs of VDD were seen in only 8.53% of the children. The mean (±SD) levels of 25(OH)D were 27.48 (15.99) ng/mL. (Angurana, Angurana et al. 2014)

**Pharmacology of vitamin D**

The Vitamin D commonly refers to compounds vitamin D$_3$ (cholecalciferol) or vitamin D$_2$ (ergocalciferol). The main source of vitamin D$_3$ (cholecalciferol) is from direct synthesis in our skin (>90%). Upon exposure to sunlight the ultraviolet radiation, 7-dehydrocholesterol is in the epidermal cells converted to vitamin D$_3$. In the dietary sources vitamin D is available in either form, vitamin D3 or vitamin D2 (ergocalciferol). Both forms undergo hydroxylation in the liver to create the storage form of vitamin D, 25-hydroxy vitamin D (25[OH]-D, calcidiol, or calcifediol). Furthermore, in the kidneys, hydroxylation of calcidiol synthesizes the active metabolite, 1,25-dihydroxyvitamin D (1,25[OH]$_2$-D) (calcitriol). Calcitriol is responsible for increasing calcium absorption, bone resorption, and decreasing renal calcium and phosphate excretion to maintain bone health. The synthesis of calcitriol is mediated by parathyroid hormone (PTH), serum phosphate concentration, and growth hormone, and may occur in non-renal sites, such as alveolar macrophages and osteoblasts. Additionally, vitamin D has extra-skeletal responsibilities, with vitamin D receptors in the small intestine, colon, osteoblasts, activated T and B lymphocytes, beta islet cells, and major organs (brain, heart, skin, gonads, prostate, breast, and mononuclear cells). The immunologic effects of vitamin D have stimulated great interest, but studies in these areas are currently limited in pediatric patients. (Holick MF. 2007), (Adams JS, 2010)

The main source of circulating vitamin D is by synthesis from skin exposure to UVB radiation and less than 10% from other dietary sources. The highest and ideal time that provides UVB to produce vitamin D is between 10:00-15:00 hours in the spring, summer and fall. The disadvantage of UVR exposure for vitamin D generation is the risk of skin cancers, though in dark skinned individuals, the risk for melanoma is minimal. Children, particularly infants may require less sun exposure to produce vitamin D. (Joiner TA, 2000) Just about 30 min/week sunlight exposure to infants in diaper and 2 hour /week for fully clothed infants without hat (since infants’ scalp contributes a major part of body surface area) maintained vitamin D levels of >11ng/dL. In Asian children, three times the recommended amount of sun light exposure is required to maintain the vitamin D levels (because of dark skin colour). Fortunately, excess exposure to sunlight does not result in vitamin D toxicity.
Sun exposure alone ought to suffice to attain vitamin D sufficiency. However, even in tropical countries like India, despite abundant sunlight, vitamin D deficiency is as high as 70%–100% in ostensibly healthy individuals, due to several socioeconomic and cultural constraints. (G and Gupta 2014)

**Sources of Vitamin D**

Very few foods have Vitamin D in them naturally. Some of the best dietary sources include fish liver oils and fatty fish like salmon, mackerel and tuna. Milk has only a small amount of Vitamin D unless it’s fortified, which is rare in India. Small amounts of the vitamin D is found in cheese and egg yolks.

Body also synthesizes Vitamin D when skin is exposed to ultraviolet B (UVB) rays from the sun. However, many things affect UVB exposure and ability to produce Vitamin D, including age, skin tone, area of skin covered by clothing, use of sunscreen, the season, and both the amount of time and what time of day spent outside.

**Definition of Vitamin D status**

The VDD is controversial and debated by clinicians and researcher alike especially in the paediatric population. Deficiency is generally measured by the calcidiol [25(OH)-D] concentration by the virtue of its long half-life of 2 to 3 weeks, relatively reliable robust circulating concentration, and resilience to changes in PTH concentrations.

The classification of normal and abnormal serum vitamin D concentrations is summarized in Table 1. Vitamin D insufficiency is defined as calcidiol (25-OH-D) concentrations 16 to <20 ng/mL in the pediatric population by American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM). (Misra M, 2008), (Ross AC, 2013)

It has been estimated the serum 25(OH)D levels of 20 ng/dL meet the needs of at least 97.5% of population across all age groups in developed countries. Hence, 25(OH)D levels >20ng/ dL indicates vitamin D sufficiency, 5-15 ng/dL are considered as mild to moderate deficiency and ≤ 5 ng/dL are considered as severe deficiency. (Misra M, 2008)
Prerachitic, Subclinical Vitamin D Deficiency

Vitamin D deficiency can be easily diagnosed in presence of clinical features of rickets. But rickets is an extreme form of vitamin D deficiency and represents the tip of vitamin D deficiency iceberg. Improved understanding of the detrimental effects of insufficient vitamin D before the appearance of rickets led to a growing interest in these lesser degrees of vitamin D deficiency and diagnosing this prerachitic, subclinical vitamin D deficiency is important for nonskeletal health benefits. Serum 25 (OH) D level is the best available biomarker for the diagnosis of vitamin D deficiency. (Rathi N, 2011)

It should be emphasised here that serum level of 1,25(OH)2D is not a good indicator of vitamin D deficiency because (i) subtle hypocalcemia causes PTH elevations leading to increased 1-α-hydroxylase activity resulting into normal or elevated 1,25(OH)2D in face of vitamin D deficiency, (ii) circulating concentrations of 1,25(OH)2D are 100 to 1000 fold less abundant than 25 (OH) D , (iii) half-life of 1,25(OH)2D is only 4 hours as against 3 to 4 weeks in case of 25 (OH) D and (iv) 25 (OH) D is the storage form of vitamin D. (Rathi N, 2011)

Aetiology of vitamin D deficiency

Vitamin D deficiency in children is related with sociodemographic and lifestyle factors. The prevalence of vitamin D deficiency is higher in winter than in summer suggesting inadequate body exposure to sunlight as main determinant of VDD. (Voortman, van den Hooven et al. 2015) Children exposed to sunlight, living in rural or less polluted areas have been reported to have a better vitamin D status, especially in summer months. (Trilok Kumar, Chugh et al. 2015)
The vitamin D deficiency is also attributed to low dietary calcium.

Vitamin D deficiency is common in infancy and childhood because of various reasons such as:
1. Decreased dietary intake: strict vegan diet
2. Decreased cutaneous synthesis: because of cultural and religious practices, seasonal variation, fear of cancer, and practice of not taking the child out, increase in pigmentation
3. Increasing rate of exclusive breast-feeding, and
4. Low maternal vitamin D
5. Increased degradation: drug interaction with rifampicin, isoniazid, anticonvulsants, glucocorticosteroids

**Vitamin D and Skeletal Health**

It is estimated that approximately 40%–60% of total skeletal mass at maturity is achieved during childhood and adolescence. Rickets results from inadequate mineralization of growing bone. Thus, it is a childhood disease and it is manifested as bone deformities, bone pain and weakness. Biochemical abnormalities consistently include hypophosphatemia, elevated alkaline phosphatase levels and serum 25(OH) D levels are usually below 5 ng/mL. (GR, 2014)

**Nutritional rickets**

Rickets is usually attributed to VDD. Some school of thought hypothesize that a deficiency of dietary calcium rather than vitamin D deficiency is responsible for rickets after infancy, evidenced by the fact that they have a better response to treatment with calcium alone or in combination with vitamin D compared to vitamin D alone. (Pettifor JM. 2004)

Studies from some tropical countries have postulated low dietary intake of calcium as the cause of nutritional rickets. Both vitamin D and dietary calcium deficiency are highly prevalent in India. Information on their relative contribution in the development of rickets in Indian children is limited.

However, recent studies have implicated dietary calcium deficiency in its etiology. Information on relative efficacy of calcium, vitamin D or both together in healing of rickets is limited.

Vitamin D deficiency is seen in breastfed infants at one extreme with dietary calcium deficiency in older children at the other extreme. Between these two extremes, it is likely that vitamin D insufficiency and decreased calcium intake or high phytate intake combine to induce vitamin D deficiency and rickets, which may be the most frequent cause of rickets globally. (Holick M, 2011) Inadequate calcium and vitamin D intake, presumably because of low intake of milk after weaning, may have contributed to stunting in this
population. (van Stuijvenberg, Nel at al. 2015)

Rickets develops when low dietary calcium intake coexists with a low or borderline vitamin D nutrition status. (Aggarwal, Seth et al. 2012)

**Management of Vitamin D deficiency**

**Who should be screened for Vitamin D deficiency?**

As per the US endocrine society guideline, only population at risk should be screened. Currently, no evidence exists to support screening at all population levels. The children at risk for vitamin D deficiency who should be screened include those with:

1. Rickets
2. Hepatic failure
3. Chronic kidney disease
5. Dark skin living at higher altitude and vitamin D deficient mothers.
6. Malabsorption syndromes (Cystic fibrosis, Crohn’s disease, Inflammatory bowel disease)
7. Hyperparathyroidism
8. Medications (Anticonvulsants, AIDS medications, Glucocorticoids, Antifungals ketoconazole etc.)
9. Obesity
10. Granuloma forming disorders (Sarcoidosis, Tuberculosis, Histoplasmosis etc.)

Serum alkaline phosphatase is useful as a screening test, which if elevated for age should be followed with measurements of 25(OH) D, calcium, phosphorus and PTH. This should be accompanied by radiological examination of distal ends of radius and ulna or tibia and femur depending on the age. (Joiner TA, 2000), (Spence JT, 2004) Serum alkaline phosphatase levels are usually <500 IU/L in neonates and <1000 IU/L in children up to 9 years and decrease after puberty.

Caution must be exercised during interpretation of levels as they vary with the method of estimation used. (Balasubramanian, S, 2013) Moreover, all children with radiographic evidence of rickets have low vitamin D levels, but not all have elevated serum alkaline phosphatase. The x-ray wrist may be the most reliable test for detecting subclinical rickets. Recent reports suggest that serum alkaline phosphatase is a good screening test particularly for healthy infants and toddlers who have been breastfed for a prolonged period. (Taylor JA, 2010)
Prevention

Adequate vitamin D levels in the blood contribute to improved bone health and a reduced incidence of a range of chronic diseases and infections. Ultraviolet (UV) radiation exposure from the sun being the main source of vitamin D, regular weekly sun exposure may be beneficial for young children, especially in winter, to maintain healthy vitamin D levels in the blood. (Ramankutty, de Klerk et al. 2014)

Vitamin D supplements effects at early age benefits for motor development and later cognitive as evidenced from a recent meta-analysis (Filteau, Rehman et al. 2016)

Maternal vitamin D status is a critical determinant of vitamin D status in infancy. To have adequate 25(OH)D levels during pregnancy, pregnant women with deficient VDD should be treated with 3000-5000 IU until 25(OH)D is ≥ 20 ng/dL followed by 400 IU /daily. (Moy R, Shaw 2004)

Routine vitamin D supplementation to all the pregnant women is controversial. Thomson K, 2004) Supplementation of high dose of vitamin D (400-6400 IU) daily to breast feeding mothers led to anti-rachitic activity of breastmilk without causing hypervitaminosis in the mother. (Basile LA, 2006), (Wagner CL, 2004)

Inadequate transfer of maternal vitamin D to preterm infants and factors associated with prematurity such as poor feeding, gastrointestinal difficulties impairing absorption and sometimes liver and kidney impairment make them vulnerable to VDD. It is recommended that preterm infants should be supplemented from birth with 400-800 IU/day. Universal supplementation particularly in breastfed infants could be a good strategy to prevent VDD. (Balasubramanian S, 2008)

Infants who are exclusively breastfed should receive a minimum daily intake of vitamin D3 400 IU/ day and should be initiated within a few days after birth. Those on infant formulas also need supplementation unless the formula provide 400 IU of vitamin D per day.

Children who are dark skinned, unexposed to adequate sun light or who have underlying medical condition should be administered 400 IU of vitamin D daily to prevent vitamin D deficiency.

Infants who are exclusively breastfed should receive a minimum daily intake of vitamin D3 400 IU/ day and should be initiated within a few days after birth.
Who should be treated?

Infants and children who present with clinical features of hypocalcaemia as a result of vitamin D deficiency or rickets and when vitamin D levels are in the deficient range even if asymptomatic should be treated with vitamin D supplementation. The three stages of vitamin D deficiency are depicted in Table 3.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Serum Calcium</th>
<th>Serum phosphorus</th>
<th>ALP</th>
<th>PTH</th>
<th>25(OH) D</th>
<th>1,25 (OH) D3</th>
<th>Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>N/↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Moderate</td>
<td>N/↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Rachitic change 1+</td>
</tr>
<tr>
<td>Severe</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>N↑↑</td>
<td>Rachitic change 2+</td>
</tr>
</tbody>
</table>

ALP: Alkaline Phosphatase, PTH: Parathyroid hormone, 25(OH) D: 25 hydroxy Vitamin D, 1,25 (OH) D:1,25 dihydroxy Vitamin D3

Treatment

Various dosage regimens have been evaluated for deficiency of vitamin D. Short term therapy of vitamin D2 or D3 2000 units daily or vitamin D2 50,000 units weekly has demonstrated equivalent results in the treatment of VDD in young children. (Gordon CM, 2008) Dosage regimen recommended include vitamin D 1000- 5000 units/day for several weeks or single IM injection of 6 lakh units (Stoss therapy) or 50,000U of vitamin D2 weekly for 8 weeks. It is the total dose of vitamin D that is more predictive of vitamin D sufficiency rather than the frequency of dosing (daily, weekly or monthly). As no difference in the efficacy or safety was reported in these common treatment regimens, therefore treatment regimens should be individualized to ensure compliance. (Gordon CM, 2008). Table 4 shows the summary of Vitamin D deficiency treatment regimen.

One of the important factors for treatment failure is lack of compliance. Stoss therapy which involves administration of high dose of 1,00,000 to 6,00,000 IU over 1-5 days an option to successful therapy. (Shah B, 1994), (Hochberg Z, 2002) In a randomized controlled trial on safety and efficacy of single intramuscular versus staggered oral dose of 600 000IU Vitamin D (60 000IU vitamin D orally once a week for 10 weeks) in treatment of nutritional rickets it was found that both are equally effective and safe in treatment of nutritional rickets. (Mondal, Seth et al. 2014)
Higher doses of 10000 units/kg compared to smaller doses over longer period followed by maintenance dose have also been demonstrated to be effective. (Soliman AT, 2010) Shah and Finberg have notice effective results with administration of 1 lakh IU every 2 hours over 12 hours period in a day. (Shah B, 1994). Another advantage of Stoss therapy is that vitamin D is efficiently stored in adipose tissue and muscle and is continuously converted into active form.

<table>
<thead>
<tr>
<th>Group</th>
<th>Daily regimen (8-12 weeks)</th>
<th>Weekly regimen (8-12 weeks)</th>
<th>Stoss therapy</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1mo old</td>
<td>1,000 IU</td>
<td>50,000 IU</td>
<td></td>
<td>400-1,000 IU</td>
</tr>
<tr>
<td>1-12 mo old</td>
<td>1,000-5,000 IU</td>
<td>50,000 IU</td>
<td>1-6 lakh units over 1-5 days</td>
<td>400-1,000 IU</td>
</tr>
<tr>
<td>1-18 y old</td>
<td>5,000 IU</td>
<td>50,000 IU</td>
<td>3-6 lakh units over 1-5 days</td>
<td>600-1,000 IU</td>
</tr>
<tr>
<td>&gt;8 y old</td>
<td>1,000-5,000 IU</td>
<td>50,000 IU</td>
<td>3-6 lakh units over 1-5 days</td>
<td>1,500-2,000 IU</td>
</tr>
<tr>
<td>Obese patients, patients with malabsorption syndrome, or on medication affecting vitamin D</td>
<td>6000-10,000 IU/day</td>
<td>50,000 IU</td>
<td>3-6 lakh units over 1-5 days</td>
<td>1,500-2,000 IU</td>
</tr>
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</table>

Large oral or parenteral (Stoss therapy) 1,50,000 to 3,00,000 IU dose of vitamin D3 have demonstrated to increase and maintain higher levels of 25(OH)D levels, especially the regimen with 6 lakh IU. It was found to be safe and may lead to hypercalcemia only at very high doses. (Sahay M, 2012)

Generally after the completion of treatment, vitamin D needs to be continued at 800-1000 IU/day till serum alkaline phosphatase returns to normal, followed by RDA for age. (Joiner TA, 2000) Vitamin D supplements are available as both vitamin D2 and D3. Studies have demonstrated that D3 may be at least 3 times more potent than D2. (Asmas LA, 2004).

<table>
<thead>
<tr>
<th>Serum 25 (OH) D (ng/mL)</th>
<th>Low dose Vitamin D therapy (IU/day)</th>
<th>High dose Vitamin D therapy (IU)</th>
<th>Total duration of therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>8000</td>
<td>50,000/week x 4weeks 50,000/fornight x 8 weeks</td>
<td>3</td>
</tr>
<tr>
<td>5-15</td>
<td>4000</td>
<td>50,000/fornight</td>
<td>3</td>
</tr>
<tr>
<td>16-30</td>
<td>2000</td>
<td>50,000/month</td>
<td>3</td>
</tr>
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</table>

Adapted from Holick [50].
Calcium supplementation: In Stoss therapy, calcium supplements are important for avoiding subsequent hypocalcaemia from a decrease in bone demineralization and an increase in bone mineralization.

Randomized controlled trial vitamin D (600 000 IU single intramuscular dose), calcium (75 mg/kg/day elemental calcium orally) or a combination of the above two for a period of 12 weeks have demonstrated radiological and biochemical evidence of healing rickets. The combined end point of normal serum alkaline phosphatase and complete radiological healing at 12 weeks was observed in 50% subjects on combination therapy as compared with 15.7% subjects on vitamin D alone and 11.7% on calcium alone. The best therapeutic response was seen with a combination of vitamin D and calcium than either of them given alone. (Sankar, Lotha et al. 2016)

It is recommended to administer elemental calcium in a dose of 30-75mg/kg/day in 3 divided doses. Initial calcium dose should be high, which can be reduced by half for next 1-2 weeks and it may not be required once vitamin D supplements have been decreased to 400 IU/day with normal PTH and 25(OH)D. (Misra M, 2008)

It is imperative to administer parenteral calcium for symptomatic hypocalcemia (10-20 mg of elemental calcium/kg IV slowly over 5-10 minutes) and is generally administered as 1-2 mL/kg of calcium gluconate. This is required in case of tetany or convulsions and repetition of boluses may required on case to case basis. Calcium levels should maintain with oral calcium supplements and additional 1, 25 (OH) 2D may be necessary till calcium levels normalize.

Calcitriol is not recommended for Stoss therapy because of its short half-life which does not build up vitamin D stores. Moreover, at higher doses it may cause hypercalcemia because of its rapid onset of action which limits the amount that can be administered. (Balasubramanian, S, 2013)

Monitoring therapy: After initiation of therapy with vitamin D, it is recommended to estimate serum calcium, phosphorus and serum alkaline phosphatase levels. The biochemical response is generally achieved by 1 or 2 weeks of Stoss therapy. It takes about 6-10 days for calcium and phosphorus levels to normalize within whereas PTH, 25(OH)D levels normalize within 1-2 months and serum alkaline phosphatase by 3-6 months. Although evidence of healing is seen within 4 weeks, complete radiological healing may take longer than one month. It is recommended to estimate serum levels of calcium, phosphorus, magnesium, serum alkaline phosphatase, 25(OH)D and PTH, and a repeat X-ray if there are bone changes initially after 3 months. As a follow-up 25(OH)D levels should be monitored on yearly basis. (Misra M, 2008)

Vitamin D Intake Guidelines

The Institute of Medicine and the US Endocrine Task Force recommend 400 IU vitamin D per day, for infants, and also in children both societies recommend 600 IU vitamin D per day.
The US Endocrine committee has suggested that to keep the serum levels of 25(OH)D >30 ng/dL which is considered to be the optimal level the intake of 400-1000 IU/day under 1 year of age and 600-1000 IU/day from 1 to 18 years of age [8]. (Holick MF, 2011)

The IOM also has increased the recommended dietary allowance of vitamin D to 600 units daily for healthy children 1 to 18 years of age, which has been endorsed by the Endocrine Society. (Ross AC, 2013; Holick MF, 2011)

The American Academy of Pediatrics (AAP) recommends all infants, children, and adolescents should be administrated a minimum 400 IU of vitamin D per day to prevent rickets and to maintain vitamin D concentrations at >20 ng/mL (50 nmol/L). (Misra M, 2008)

Term infants should be receive 400 to 800 IU daily to account for the insufficient transfer of maternal vitamin D stores and ensure calcidiol concentrations of >20 ng/mL (50 nmol/L). (Misra M, 2008)

Preterm infants are at increased risk to be vitamin D deficient as their trans-placental transfer from the mother was a shorter duration. Hospitalization of preterm infants leading to a negligible amount of UV-mediated vitamin D formation, and possibly lower vitamin D stores due to a lower fat mass also make them more vulnerable to VVD (Abrams SA; 2013). Thus, the AAP recommends 200 to 400 units per day of vitamin D supplementation in very low birth weight infants (<1500 g) and 400 units per day of vitamin D supplementation in infants weighing >1500 g. Since established upper tolerable intake for healthy full-term infants is 1000 units per day, it is rationale to consider increasing this dose to in >1500 g in them. In the preterm, the calcidiol concentration goal population remains the same as full-term infants (>20 ng/mL). (Abrams SA, 2013)

Children vulnerable to VVD (on anticonvulsants, glucocorticoids, antifungals and medications for AIDS) need 2 to 3 times the requirement for their age. The upper limit of vitamin D administration as maintenance therapy which is not to be exceeded without medical supervision is as follows: (Balasubramanian, S, 2013)

**Role of Vitamin D in various diseases in children**

**Bronchial asthma**

Bronchial Asthma is a common chronic inflammatory disorder of the airways in childhood. Vitamin-D deficiency is highly prevalent in asthmatic children and is associated with airway limitation. Vitamin-D is also a potent immune system regulator having a potential role in various allergic diseases. A cross-sectional study was undertaken to determine the difference in serum levels of Vitamin-D in asthmatic children and to determine the
association between vitamin-D and asthma in children. It was found that serum vitamin-D level was significantly lower in asthmatic children than in control group and in the asthmatic group, vitamin-D levels had a significant positive correlation with forced expiratory volume 1 (FEV1) % and FEV1/FVC%. Vitamin-D deficiency is highly prevalent in asthmatic children and is associated with airway limitation. (Somashekar, Prithvi et al. 2014), (Awasthi and Vikram 2014)

Low maternal vitamin D intake during pregnancy is associated with increased risk of children developing asthma in the first 10 years of life. These associations may have significant public health implications. (Allan, Prabhu et al. 2015)

Monthly doses of 60,000 IU vitamin D significantly reduced the number of exacerbations as compared to placebo (p = 0.011). Peak expiratory flow rate (PEFR) significantly increased in the treatment group (p = 0.000). Monthly doses of vitamin D significantly reduced the requirement of steroids (p = 0.013) and emergency visits (p = 0.015). Control of asthma was achieved earlier in patients who received monthly vitamin D. Vitamin D significantly reduced the level of severity of asthma patients over 6 month of treatment (p = 0.016). Study indicates that vitamin D has a definite role in the management of moderate to severe persistent bronchial asthma as an adjunct to standard treatment. (Yadav and Mittal 2014)

**Seasonal influenza A**

Vitamin D3 supplementation (1200 IU/d) during the winter appear to reduce the incidence of influenza A, especially in specific subgroups of schoolchildren (Urashima M et al 2010).

**Risk of acute respiratory infections**

In a double-blind clinical trial conducted by Camargo CA et al., it was found that vitamin D3 supplementation (300 IU/day for 3 months) significantly reduced the risk of acute respiratory infections during winter in children with vitamin D deficiency (Camargo CA Jr 2012).

**Tension-type headache and associated musculoskeletal pain**

Headache, musculoskeletal pain and VDD, with possible inter-relationship, are common in the general population. Three cases of premenarchal girls presenting with chronic tension-type headache and generalised body pain were reported. The patients did not show any response to conventional therapy for tension headache. Investigations showed a severe VDD and biochemical osteomalacia in all three patients. The headaches and musculoskeletal pain responded markedly to vitamin D therapy. It is suggested that musculoskeletal pain and headache together in a patient may be a part of a single symptom complex, with vitamin D deficiency being the possible cause. (Prakash, Makwana et al. 2016)
Nonspecific Lower-Extremity Pain

High prevalence of VDD or insufficiency in children with nonspecific lower-extremity pains was found in a clinical study, indicating a positive association between VDD and growing pains. It was found that Serum 25-(OH)D levels were <10 ng/mL in 5.7% of patients, 10 to <20 ng/mL in 51.4%, 20 to <30 ng/mL in 37.9%, and ≥30 ng/mL in only 5.0%. Most patients visited the hospital in the winter (41.4%) (summer, 12.9%), and serum 25-(OH)D levels were also lowest in the winter (17.2±5.5 ng/mL). (Park, Lee et al. 2015)

Atopic dermatitis

Vitamin D supplementation (1000 IU/day) improved winter-related atopic dermatitis (AD) among Mongolian children, a population likely to have VDD in winter. Vitamin D could be of help in children with allergic predisposition. (Camargo, Ganmaa et al. 2014)

Congenital Ichthyosis

Severe VDD and rickets are highly prevalent among children with congenital ichthyosis. A dramatic and excellent clinical response with regard to skin scaling and stiffness in children with congenital ichthyosis after short-term high-dose vitamin D supplementation (60 000 IU of oral cholecalciferol daily for 10 days under supervision. All children were subsequently put on recommended daily allowance of 400 to 600 IU of cholecalciferol) has been reported. (Sethuraman, Marwaha et al. 2016)

Ichthyosiform erythroderma

Ichthyosiform erythroderma due to keratinizing disorders may suppress cutaneous vitamin D synthesis, leading to vitamin D deficiency and rickets. In a cross-sectional study in 45 children and adolescents with ichthyosiform erythroderma due to keratinizing disorders, it was found that the mean serum 25(OH)D levels of the disease group was significantly lower in ichthyosiform erythroderma group. The prevalence of VDD and frequency of hyperparathyroidism) was also significantly higher in them. (Chouhan, Sethuraman et al. 2012)

Inflammatory bowel disease

Vitamin D promotes bone health and regulates the immune system; both are important actions for pediatric patients with inflammatory bowel disease (IBD). In randomized controlled trial children with IBD, it was found daily oral vitamin D2 doses up to 2000 IU were inadequate to maintain optimal 25OHD but were well tolerated. However, the finding of lower incidence of elevated inflammatory markers and cytokines among participants receiving higher vitamin D2 doses merits further study.(Pappa, Mitchell et al. 2014)

Sickle cell disease

Vitamin D is increasingly recognized for its roles in non-skeletal disorders. Patients with sickle cell disease (SCD) have a high prevalence of vitamin D deficiency. In a clinical study it was observed that 91 % of children with sickle cell anaemia had 25-OHD levels <20 μg/L.
Correcting low vitamin D may offer a simple, low-cost intervention to help reduce acute vaso-occlusive complications. (Lee, Licursi et al. 2015)

**Tuberculosis**

Deficiency of vitamin D, an immunomodulator agent, is associated with increased susceptibility to tuberculosis in adults, but only limited studies are available in the paediatric age group, especially regarding association of vitamin D with type and outcome of tuberculosis. Majority of Indian children with newly diagnosed intrathoracic tuberculosis were deficient in vitamin D. Type of disease or outcome was not affected by 25-hydroxy vitamin D levels in these children. However, children who did not demonstrate sputum conversion after intensive phase of antitubercular therapy had lower baseline 25-hydroxy vitamin D levels as compared to those who did. (Khandelwal, Gupta et al. 2014)

**Critical illness**

Data on the prevalence of VDD in critically ill children with sepsis and its association with illness severity and outcome are limited. Prevalence of VDD [25(OH)D level < 50 nmol/L] was higher among critically ill children with sepsis compared to healthy controls (50.8% vs 40.2%, P = 0.04). (Ponnarmeni, Kumar Angurana et al. 2016)

**Renal diseases**

**Nephritic syndrome:** Short-term, high-dose glucocorticoid therapy decreases the bone mineral content (BMC) of the lumbar spine in steroid-naïve children with nephrotic syndrome. Vitamin D and calcium co-administration (D 1,000 IU/day and elemental calcium 500 mg/day) not only prevents this decline, but also enhances BMC of the lumbar spine. (Chowdhary, Agarwal et al. 2014)

Vitamin D stores may remain low for 3 months after nephritic syndrome relapse but showed an increase with longer remission time to control levels. (Banerjee, Basu et al. 2013)

**Chronic kidney disease:** Vitamin D insufficiency is common in patients with chronic kidney disease stages 2-4 and may contribute to mineral bone disease. High-dose cholecalciferol (600,000 IU) is safe and effective in correcting vitamin D insufficiency and results in a significant reduction in PTH levels in vitamin D-insufficient children. (Hari, Gupta et al 2010)

A recent study shows that in children with chronic kidney disease, vitamin D levels ≥50 nmol/L was associated with greater preservation of renal function. Renal survival increased 8.2% per 10 nmol/L increase in vitamin D levels (Shroff R et al 2015).

**Epilepsy**

A high proportion of children on antiepileptic drugs have hypovitaminosis D. There is a significant decrease in vitamin D levels after the start of antiepileptic drugs. Polytherapy and longer duration of antiepileptic drugs, tube feeding, and overweight are independently associated with longitudinally significant decrease of 25-hydroxy vitamin D. (Lee, Park et al. 2015)
Type 1 diabetes

Children with Type 1 diabetes (T1D) had lower 25OHD levels than their counterparts without diabetes. (Cadario, Prodam et al. 2015), (Borkar, Verma et al. 2010)

Severe ketoacidosis, as judged by bicarbonate but not pH, may transiently lower 25-hydroxyvitamin D3 levels in children with new onset Type 1 diabetes. Persistence of low 25-hydroxyvitamin D3 levels after resolution of ketoacidosis suggests a state of permanent vitamin D deficiency in this patient population. (Kumar, Sachdev et al. 2011), (Singh, Sachdeva et al. 2013)

Iron deficiency anaemia

Vitamin D deficiency is associated with increased risk of anaemia, especially iron deficiency anaemia, in healthy female children and adolescents. However, the association is attenuated after adjustment for iron deficiency. Further studies are needed to determine whether vitamin D deficiency is the cause of anaemia, or bystander of nutritional deficiency which cause iron deficiency. (Lee, Park et al. 2015)

Extensive data from animal and human studies indicate a role of vitamin D in erythropoiesis. Iron and vitamin D deficiencies are implicated with adverse health effects in children even if they are asymptomatic. The potential relationship between the two remains poorly understood. A cross-sectional study in children, anaemia was present in 66% of 25(OH) D deficient subjects compared with 35% in vitamin D sufficient individuals (p < 0.0001). The association of breast-feeding and development of VDD was also significant (p < 0.05). Serum levels of 25(OH) D were found lower in female sex and if the analysis was performed in the winter/spring season. Physicians should therefore assess vitamin D levels in all anaemic children and ensure adequate supplementation to prevent deficiencies. (Sharma, Jain et al. 2015)

Association between Vitamin D and Circulating Lipids

A recent study showing that vitamin D exposure in early life (children aged 1 to 5 years) may be an early modifiable risk factor for cardiovascular disease. Each 10 nmol/L increase in 25(OH) D was associated with a decrease in non-HDL cholesterol concentration of, total cholesterol of, and triglycerides. 25(OH)D concentrations were inversely associated with circulating lipids in early childhood. 1,961 children were examined in the study (Birken CS 2015).

Fortification of foods with vitamin D

Fortification of widely consumed staple foods offers one of the simplest and most practical methods to combat micronutrient deficiencies for both poor and wealthy societies. Vitamin D was added to milk in the United States in 1930s to help prevent rickets in children. Fortified foods are being recognised as an important source of vitamin D and is found to be a safe, effective and acceptable method of supplementation. However, in a setting like India, where the per capita milk consumption is very low, consideration for other methods of
fortification such as fortification of oil, cereal powders and even salt needs consideration. The need for a national food fortification program for vitamin D has been highlighted in an earlier review. Since adequate sunlight exposure at solar noon is difficult to achieve because of modernisation and existing cultural practices, supplementation and fortification may help in preventing vitamin D deficiency and such public health interventions need serious consideration in the Indian context.

The supplementation strategy certainly has greater specificity of intervention and allows better dose adjustment.

Fortification of staple foods with vitamin D offers a viable solution to address the vitamin D deficiency epidemic in India. The Indian diet is amenable to fortification with vitamin D. India has the scientific expertise to examine and implement fortification of food with vitamin D, either commercially or at the level of the local community or in an individual home. The aim of this article is to provide seminal information to encourage, examine and implement population-based strategies for the fortification of foods with vitamin D.

The quantity of foods consumed by children is much smaller compared to adults. Therefore, children need energy-dense and micronutrient-dense foods to meet their daily nutritional requirements. Targeted food fortification programs are needed to meet the special needs of children. Sattu, a protein rich Indian food has the potential to be a valuable vehicle for vitamin D fortification in India.

Fortification of foods with vitamin D, specifically targeted towards the nutritional requirements of infants and children, is a viable strategy in the Indian scenario. Government programs targeting the nutritional needs of children in India, especially via midday meal programs in schools, should incorporate indigenous ready-to-eat foods fortified with micronutrients including vitamin D. These foods would need to have longer shelf life, require minimal preparation, and have economic and technological feasibility. Sattu, comprised of roasted flour made from cereals and legumes, has immense potential to serve as an economically and technologically feasible fortification vehicle for vitamin D fortification strategies. (G and Gupta 2015)

Supplementing 60,000 IU of vitamin D3 per week for 4-8 weeks, followed by 600 IU daily through fortified milk, is an effective strategy for achieving vitamin D sufficiency in Indian adolescents. (Garg, Marwaha et al. 2013) Fortification of milk with vitamin D is an effective and safe strategy in improving S.25(OH)D levels in children aged 10-14 years. (Khadgawat, Marwaha et al. 2013)

References


PC04-07.


Dear Doctor,

It is indeed a pleasure to present to you this QMR issue by Dr. L. S. Deshmukh, a renowned Paediatrician & Neonatologist.

In this issue, Dr. L. S. Deshmukh is enlightening us on ‘Vitamin D Deficiency in Children’.

This booklet is presented to you by Raptakos, Brett & Co. Ltd.

We would very much like to have your valuable suggestions and comments to make our future issues more meaningful to you.

We will appreciate if you could spend a few minutes to fill in your comments and mail the same to us. You can also view the QMR on our website: www.raptakos.com and e-mail your feedback to following E-mail id: medical@raptakos.com

Thanking you

Dr. Balaji More
Vice President - Medical

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Feedback form: October - December 2016
Vitamin D deficiency in children

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