Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics (IAP) Guidelines

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From Indian Academy of Pediatrics 'Guideline for Vitamin D and Calcium in Children' Committee.

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Received: November 26, 2016; Initial review: January 10, 2017; Accepted: May 20, 2017.

Justification: Vitamin D deficiency (VDD) is being increasingly reported from India from all age-groups. Reports suggest that VDD affects all age groups, from neonates to adolescents. Further, habitually low calcium intakes are also reported in Indian children. Given the multiple guidelines, peculiarities of Indian circumstances, changing lifestyles, and lack of fortification, the Indian Academy of Pediatrics (IAP) felt the need for a Practice Guideline for Pediatricians for the prevention and treatment of vitamin D and calcium deficiency in children and adolescents.

Process: The 'Guideline for Vitamin D and Calcium in Children' committee was formed by the IAP in September 2016. A consultative committee meeting was held in November 2016 in Mumbai. Evidence from Indian and international studies and other previous published recommendations, which were pertinent to the Indian circumstances, were collated for the preparation of these guidelines.

Objectives: To present a practice guideline for pediatricians for the prevention and treatment of deficiency of vitamin D and calcium in the Indian context.

Recommendations: For the prevention of rickets in premature infants, 400 IU of vitamin D and 150-220 mg/kg of calcium, and in neonates, 400 IU of vitamin D and 200 mg of calcium are recommended daily. For prevention of rickets and hypocalcemia in infants (after neonatal period) upto 1 year of age, and from 1-18 years, 400 IU and 600 IU vitamin D/day and 250-500 mg/day and 600-800 mg/day of calcium, respectively, are recommended. For treatment of rickets in premature neonates, infants upto 1 year and from 1-18 years, 1000 IU, 2000 IU and 3000-6000 IU of vitamin D daily, respectively, and elemental calcium of 70-80 mg/kg/day in premature neonates and 500-800 mg daily for all children over that age are recommended. Larger doses of vitamin D may be given from 3 months to 18 years of age as 60,000 IU/week for 6 weeks.

Keywords: *Consensus statement, Hypovitaminosis D, Management, Rickets.*

Vitamin D deficiency is increasingly being recognized the world over as also in India [1-5]. Reports from various parts of India and in all age groups from neonates to adolescents as well as pregnant and lactating mothers have reported vitamin D deficiency to the tune of 30-90% [6-8]. Further, habitually low calcium intakes are reported in children and adolescents from several studies all over India, especially those from lower socio-economic classes [9,10]. Given that vitamin D and calcium are both critical for musculoskeletal health in growing years, addressing the issues of their deficiency in the pediatric and adolescent population is critical.

Deficiency of vitamin D (with or without calcium deficiency) may result in rickets in an infant or adolescent or osteomalacia (abnormal mineralization of bone matrix) and muscle weakness in an older child/adolescent [11]. 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 [12]. Rickets in a neonate resulting from maternal vitamin D deficiency may result in hypocalcemic seizures and rarely cardiomyopathy [13]. There is lack of consensus amongst clinicians and scientists on the role of vitamin D supplementation in relation to extraskeletalal effects particularly in pediatrics; this Guideline therefore, does not deal with these effects of vitamin D [14]. Rickets resulting from deficiency of vitamin D and/or calcium deficiency may be prevented and treated with adequate intake of vitamin D and calcium [15]. However, children with vitamin D deficiency, without raised Parathormone (PTH) or signs of rickets are not at an increased risk of fractures [16].

Less than 10% of vitamin D is derived from the diet while close to 90% is synthesized in the skin with sunlight exposure [17]. Socio-cultural practices, darker pigmentation, a diet low in calcium and high in phytates and oxalates which depletes vitamin D, absence of

fortification with vitamin D, genetic factors such as increased 25(OH)D-24-hydroxylase, which degrades 25(OH)D to inactive metabolites, geographical location of various places in the country (India extends from 8 to 38 degrees north latitude) and environmental pollution are some reasons proposed for vitamin D deficiency in Indian children [18-21]. Together with these factors, changing lifestyles with sedentary behavior in children with indoor lifestyle (avoiding optimal hours of sun exposure between 10 AM to 3 PM, the best time to form Vitamin D in the skin) further reduce the sunlight exposure and thus increase the tendency for vitamin D deficiency [21-23]. Further, very few Indian foods are fortified with vitamin D, and that too, with small amounts [23]. Premature babies and children with renal, hepatic disorders, malabsorptive states, *etc.* are at special risk for metabolic bone disease [24].

Given the plethora of literature on vitamin D deficiency, multiple guidelines suggested by various international bodies, lack of consensus about the ranges for deficiency and sufficiency, peculiarities of the Indian circumstances, evidence from India suggesting high prevalence of vitamin D and calcium deficiency in the pediatric population [16,24-26], the practitioner may be confused regarding appropriate prevention and treatment of vitamin D and calcium deficiency. The Indian Academy of Pediatrics (IAP) therefore felt the need for a practice guideline for pediatricians for the prevention and treatment of vitamin D and calcium deficiency in children and adolescents. These guidelines do not include conditions causing non-nutritional rickets; *e.g.,* renal disorders, disorders of the parathyroid hormone axis.

METHODS

The 'Guideline for Vitamin D and Calcium in Children Committee' was formed by the IAP in September 2016. The consultative committee scrutinized the methodology, results and scientific content of the manuscript in November 2016 in Mumbai after data from an extensive search on prevalence of deficiency of vitamin D and calcium from India was performed. Guidelines on the deficiency of vitamin D and calcium with reference to deficiencies for children and adolescents published by various bodies in Indexed journals were identified through internet-based search engines *viz*. Google, PubMed and Embase [16,24-27]. Indian studies reporting the prevalence of vitamin D deficiency and intakes of calcium were also reviewed. Evidence from Indian studies and other previously published recommendations, which were pertinent to the Indian circumstances, were collated for preparation of these guidelines. For vitamin D, the guidelines are based on the assumption of minimal sun exposure [26].

Definitions

This is based on the serum concentrations of 25(OH)D. Although professional bodies recommend that the assessment should be performed by tandem mass spectrometry (TMS), most reports from India suggest that these are performed by enzyme-linked immunosorbent assay, chemiluminescence or radio-immuno assay. Very few centers have the facility for assessment of vitamin D with TMS. Although a fasting specimen is recommended, it is not required; further, diurnal variations are also not a major consideration [28,29]. Given the various methods and the variability in the values of vitamin D using different assays, reports for serum 25(OH)D should be interpreted with care, taking into account the laboratory and type of assay employed. Measurement of the active form of vitamin D, 1,25-dihydroxycholecalciferol for the assessment of vitamin D deficiency is not recommended [25]. Data suggest that 20 ng/mL (50 nmol/L) can be set as the serum 25(OH)D level that coincides with the level that would cover the needs of 97.5 percent of the population [16,26]; thus, vitamin D concentrations of >20 ng/mL (50 nmol/L) are considered as sufficient, between 12-20 ng/mL (30-50 nmol/L) as insufficient and <12 ng/mL (<30 nmol/L) as deficient [16].

Calcium deficiency is difficult to define as there is no specific biochemical marker for the reserves of calcium (like 25(OH)D for vitamin D); therefore, these guidelines refer to dietary calcium deficiency [30].

Although ensuring adequacy is important, there is also concern about excessive intake and administration of vitamin D, particularly on the basis of only low 25(OH)D concentrations. Toxicity is defined as vitamin D concentrations of 25(OH)D of >100 ng/mL (250 nmol/L) with hypercalcemia, hypercalciuria and suppressed PTH concentrations [31]. Following inadvertent high doses of vitamin D, testing for serum levels of calcium and vitamin D are recommended, especially in children with symptoms of hypercalcemia such as irritability, constipation and polyuria [32].

Hypercalcemia (that can result in vascular and soft tissue calcification, nephrocalcinosis, nephrolithiasis, *etc.*) occurs when serum calcium concentrations are above 10.5 mg/dL (reference to the laboratory values is also recommended) [33]. Preferably, serum ionized calcium may be assessed as 1 gm% reduction in serum albumin will reduce total serum calcium by 0.8 mg% [34].

Tolerable upper limit (*i.e*. the maximum level of total chronic daily intake of a nutrient from all sources judged to be unlikely to pose a risk of adverse health effects to humans) for intake of vitamin D and calcium during

neonatal period, 1-12 months, 1-18 years are 1000 IU/day, 1000-1500 IU/day, 3000-4000 IU/day and 1000 mg/day, 1000-1500 mg/day, and 2500-3000 mg/day, respectively (***Table* 1**) [16,25,33,35]. Larger doses may be required for treatment of rickets; however, tolerable upper limits are not to be exceeded without supervision.

Screening for vitamin D deficiency: Routine screening of healthy children for vitamin D deficiency is not recommended [16,25]. However, screening may be performed for children, who are at risk of vitamin D deficiency, for determination of vitamin D concentrations and treatment [25]. Monitoring 25(OH)D levels in the population is not practical because of the need for drawing blood, high monetary cost of assessment, and also a low positive predictive value; and is thus reserved for high-risk groups.

Route of administration: Oral treatment is recommended; reports suggest that oral administration of vitamin D restores vitamin D concentrations more rapidly than by the intramuscular (IM) route [16]. This is especially important in the Indian context as injectable preparations of vitamin D are inadvertently used in very large doses for longer periods. The IM route with larger doses may only be considered when compliance or absorption from the gut is an issue. Further, vitamin D may be administered with a meal or on an empty stomach as absorption is independent of fed state [25].

RECOMMENDATIONS

The recommendations for prevention and treatment of vitamin D and calcium deficiency for various age groups and for at-risk groups are provided in ***Table* I**. Assessment of dietary intake of calcium to ensure that children are having adequate calcium for optimum bone health is required.

Prevention of Deficiency of Vitamin D and Deficiency of Calcium

Premature neonates: Calcium and phosphorus in breast milk do not meet the needs of rapidly growing premature infants who have missed some of the critical period of intrauterine bone growth; this puts them at a higher risk for metabolic bone disease [36]. Exposure to medications that alter mineral levels, immobilization, and long-term parenteral nutrition may further increase the risk of the premature baby for metabolic bone disease (MBD) [37,38]. Routine measurement of serum 25(OH)D levels in premature infants is not recommended; however, in the presence of a likely impairment of 25-hydroxylation, such as might be present in an infant with cholestasis, measurement of serum 25(OH)D level may be considered [26]. Enteral calcium intake of about 150 to 220 mg/kg per day, phosphorous intake of 75-140 mg/kg/day and vitamin D intake of 400 IU/day is recommended [37]. Backstrom, *et al.* have found that an intake of 200 IU/kg of vitamin D in

TABLE I RECOMMENDATIONS FOR VITAMIN D AND CALCIUM DEFICIENCY – PREVENTION AND TREATMENT

	Vitamin D				*Calcium*		
Age	*Prevention*	**Tolerable upper limit*	*Treatment*	*Treatment with large dose (oral route preferred)*	*Prevention*	**Tolerable upper limit*	*Treatment*
Premature neonates	400 IU/day	1000 IU/day	1000 IU/day	NA	Intake of 150 to 220 mg/kg per day	1000 mg/day	Maximum of 175–200 mg/kg/day
Neonates	400 IU/day	1000 IU/day	2000 IU/day[$]	NA	200 mg/day	1000 mg/day	500 mg/day
1-12 months	400 IU/day	1000-1500 IU/day	2000 IU/day[$]	60000 IU wkly for 6 weeks (over 3 mo of age)	250-500 mg/day	1000-1500 mg/day	500 mg/day
1-18 years	600 IU/day	3000 IU day till 9 years, 4000 IU/day from 9-18 years	3000/-6000 IU/day[$]	60000 IU wkly for 6 weeks	600-800 mg/day	2500 mg/day till 8 years and 3000 mg/day for 9-18 years	600-800 mg/day
At-risk groups	400-1000 IU/day	as per age group	as per age group	as per age group	as per age group	as per age group	as per age group

*[$]For a minimum of 3 months; after treatment, daily maintenance doses need to be given; *Tolerable Upper Limit - the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.*

premature infants in first 6 weeks after birth lead to mean 25(OH)D concentrations of around 50 nmol/L [38]. It is however critical to avoid excessive administration of vitamin D that can lead to hypervitaminosis, especially as various preparations with varying amount of vitamin D and calcium are available in India.

Neonates and infants upto 1 year of age: Although there is likelihood of a high prevalence of vitamin D deficiency in apparently healthy term neonates who are born to vitamin D deficient mothers, due to financial and logistic limitations in the Indian context, routine screening for vitamin D concentrations in this age group cannot be recommended. Breastmilk is not an adequate source of vitamin D [39]; 400 IU of vitamin D has been shown to maintain serum 25(OH)D concentrations at >50 nmol/L in breastfed infants [40]. Further, for formula-fed infants, the amount of formula milk to obtain 400 IU/day would be close to a liter, which a baby may not consume daily. Thus, for all newborns, 400 IU of vitamin D supplementation is recommended till one year of age; it is also recommended that supplementation be started in the first few days of life. It is critical to give careful instructions about the dosage and administration and to avoid excessive administration of vitamin D, which could lead to hypervitaminosis, particularly in infants.

There are no reports of full-term, vitamin D-replete infants developing calcium deficiency when exclusively fed human milk [41]. Also, calcium absorption is high in neonates to the tune of around 60% (facilitated by lactose from breast milk); hence, the adequate intake for calcium based on amounts of calcium in breast milk is 200 mg. In the first year of life, if dietary calcium intake is not adequate (250-500 mg), calcium supplementation is justified [42,43].

Maternal concentrations of vitamin D determine the status of vitamin D of her fetus and newborn [44]. Thus, the neonate of a mother who has vitamin D deficiency is also likely to be vitamin D deficient. Hence, it is recommended that pregnant mothers receive 600 IU of vitamin D daily [25]. This supplementation is also to be continued during lactation. Breastmilk contains very little vitamin D, which is inadequate for the newborn who requires around 400 IU/day [39]. However, to increase content of breast milk vitamin D, very large doses are required to be given to lactating mothers. Thus, it is recommended that infants be supplemented with 400 IU daily and mothers continue to take 600 IU daily for their own vitamin D needs. Maternal dietary intake of calcium is not associated with breast milk content; however, it is recommended that mothers take 1200 mg of calcium, as advised by the ICMR [17].

Children older than 1 year and adolescents: Vitamin D deficiency is likely to occur during rapid phases of growth as well as when there are physiological changes; Indian children are spending more and more time indoors and intake of milk and other calcium-containing foods is also low. As a result of this, as per reports, a very high percentage of children have vitamin D concentrations below 50 nmol/L. Hence, it is recommended that all children and adolescents be supplemented with 600 IU of vitamin D that is believed to maximize bone health [2,25]. Along with the vitamin D, it is recommended that adequate amounts of calcium *i.e.* 600-800 mg/day should also be supplemented/derived from dietary sources; this may be obtained from 2-3 servings of milk and milk products/day (as per recommendations from the Indian Council of Medical Research) [17].

At-risk groups: In cases where there is an increased risk of deficiency of vitamin D such as in children with fat malabsorption, liver disease or renal insufficiency, transplant recipients, those on anti-seizure medications, children on treatment for malignancy, restricted sun exposure such as in children with physical disabilities, history of rickets, children with predisposition to osteoporosis such as in hypogonadism or Cushing's syndrome, *etc*., higher doses of vitamin D may be required to ensure adequate concentrations of vitamin D [16,25,26]. Thus, for at-risk infants, 400-1000 IU/day and from 1 year onwards, 600-1000 IU/day may be required to maintain 25(OH)D concentrations above 50 nmol/L [25]. Screening for vitamin D concentrations may be performed in this group of children and treatment with vitamin D advised accordingly. Repeat measurements of vitamin D at 3-6 monthly intervals may be performed as clinically indicated, especially if follow up radiological assessments show poor/inadequate healing of rickets. Adequate calcium intake as per the age group (***Table* 1**) should also be ensured.

There is an inverse association of body fat with vitamin D concentrations; vitamin D being a fat soluble vitamin, is sequestrated in adipose tissue [45]. Thus, children who are obese may be given at least two to three times (between 400-1000 IU/day) more vitamin D for their age group to satisfy their body's vitamin D requirements [25].

Treatment of Deficiency of Vitamin D and Deficiency of Calcium

For preterm infants with rickets/metabolic bone disease who are able to tolerate oral/enteral feeding, calcium intake of upto a maximum of to a maximum of 70-80 mg/kg/day of elemental calcium and 40-50 mg/kg/day elemental phosphorus is indicated [37]. Preterm infants with rickets are also provided the tolerable upper intake of 1000 IU/day of vitamin D (target serum 25(OH)D concentration of >20 ng/mL (50 nmol/L) [27].

For the emergency treatment of hypocalcemia resulting in seizures in a neonate, calcium gluconate in a dose of 2 mL/kg as slow intravenous infusion and calcitriol ($1\text{-}25(OH)_2 D_3$) is recommended in a dose of 20-50 ng/kg/day. Also, vitamin D in a dose of 1000 IU/day is recommended [46].

For neonates and infants till 1 year of age, daily 2000 IU of vitamin D with 500 mg of calcium for a 3-month period is recommended. At the end of 3 months, response to treatment should be reassessed and treatment continued, if required [16]. Response to treatment may be assessed on clinical biochemical and radiological parameters. If larger doses of vitamin D are to be given, then, 60,000 IU of vitamin D weekly for 6 weeks is recommended (only in infants older than 3 months of age) [16]. After completion of this therapy with weekly doses, maintenance doses of 400 IU of vitamin D daily and 250-500 mg of calcium are necessary.

From one year onwards till 18 years of age, 3000-6000 IU/day of vitamin D along with calcium intake of 600-800 mg/day is recommended for a minimum of 3 months. For larger doses (oral preferred) 60,000 IU of vitamin D weekly for 6 weeks may be administered [25]. The maintenance doses of 600 IU/day of vitamin D and 600-800 mg of calcium need to be continued post therapy. Complete healing at 12 weeks has been observed in higher percentage of children with rickets who received combined therapy with vitamin D and calcium [47]. Calcitriol, the active form of vitamin D, should not be used for vitamin D deficiency rickets. Minimum treatment for vitamin D and calcium deficiency is advised for 3 months. If there are no radiological and biochemical signs of healing after 3 months, the patient may need to be investigated for non-nutritional rickets [48].

Available Preparations

Vitamin D3 (cholecalciferol) has been reported to have greater efficacy in raising 25(OH)D concentrations, most supplements available thus contain D3. Reports suggest that there is variability in cholecalciferol content of commercial preparations available in the Indian pharmaceutical market; thus caution should be used when prescribing preparations of vitamin D [49].

Most calcium supplements contain calcium carbonate, though preparations with gluconate and citrate are also available. Calcium carbonate contains the highest amount of elemental calcium (40%) compared to other preparations (gluconate, citrate). Thus, given the lower price and higher amount of elemental calcium, it should be the first choice [50]. Supplements containing calcium citrate may be taken with or without food. However, if the preparation contains calcium carbonate or any other form of calcium, it should be taken with food. All forms of calcium work better if taken in divided doses; however, compliance also needs to be considered. Very few preparations containing only calcium salts (without vitamin D) are available.

CONCLUSIONS

Considering the increased prevalence of vitamin D deficiency and the confusion about supplementation and treatment of vitamin D deficiency for various age groups, the IAP has put forth recommendations for prevention and treatment of vitamin D and calcium deficiency. The recommendations are in line with other international organizations. As a long term policy, fortifying everyday staple foods, which will be consumed by the at-risk segments of the population, with calcium and vitamin D is the solution to the problem. Till the time this can be implemented, supplementation of infants with 400 IU, and children and adolescents with 600 IU daily and higher doses for at-risk groups, with adequate calcium intake for prevention of deficiency is necessary. Adequate intake of calcium and continuing maintenance doses of vitamin D after treatment of rickets is warranted.

Disclaimer: The present guidelines are developed for the assistance of pediatricians in accordance with current scientific evidence and guidelines presented by major international bodies for preserving and promoting musculoskeletal health in children; however, many areas are still not clearly defined. Vitamin D has been reported to have many other important health benefits and when rigorous proof is available, guidelines will be suitably modified. These guidelines cannot establish a standard of care, and decisions about treatment should be based on the judgement of the pediatrician on a case-to-case basis.

Contributors: AK, VK: helped in conceptualizing and designing the guideline; AK,VK,JC,NR,RK,SB: contributed to the review of literature and helped with the manuscript writing; AK: will act as the corresponding author.

Funding: The cost of travel for the Consultative meeting of the 'Guideline for Vitamin D and Calcium in Children Committee' was borne by Cadila Pharmaceutical Pvt. Ltd. India.

Competing interests: None stated.

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ANNEXURE

Committee Members for Guideline for Vitamin D and Calcium in Children Committee

Chairperson: Pramod Jog, President Indian Academy of Pediatrics, 2016; *Co-Convener*: Anuradha Khadilkar and Vaman Khadilkar; *Committee Participants*: Jagdish Chinnappa, Narendra Rathi, Rajesh Khadgawat, S Balasubramanian, Bakul Parekh.

All members except BP participated in the meeting by either being there personally or through a conference call. All members satisfy the authorship criteria.