REVIEW ARTICLE

Vitamin D Deficiency in Childhood – A Review of Current Guidelines on Diagnosis and Management

S BALASUBRAMANIAN, K DHANALAKSHMI AND SUMANTH AMPERAYANI

From Kanchi Kamakoti CHILDS Trust Hospital, The CHILDS Trust Medical Research Foundation, 12-A, Nageswara Road, Nungambakkam, Chennai 600 034, Tamil Nadu, India.

Correspondence to: Dr S Balasubramanian, Kanchi Kamakoti CHILDS Trust Hospital, The CHILDS Trust Medical Research Foundation, 12-A, Nageswara Road, Nungambakkam, Chennai 600 034, Tamil Nadu, India. sbsped@gmail.com

Vitamin D deficiency has emerged as a significant public health problem throughout the world. Even in the Indian context,it has been reported to be present in majority of children in spite of wide availability of sunlight. Recent guidelines have defined vitamin D status as severe deficiency, deficiency, sufficiency and risk for toxicity as 25(OH)D levels <5, <15, >20 and >50ng/mL, respectively.The manifestations of deficiency may vary from hypocalcemic seizures, tetany in infancy and adolescence to florid rickets in toddlers. Treatment is necessary for all individuals with deficiency whether symptomatic or not and consists of vitamin D supplementation as Stoss therapy or daily or weekly oral regimens with equal efficacy and safety, combined with calcium supplements. Routine supplementation starting from newborn period is being increasingly endorsed by various international organizations. Prevention by sensible sunlight exposure, food fortification and routine supplementation are the currently available options for tackling this nutritional deficiency.

Key words: *Child, Hypocalcemia, Nutrition, Rickets, Sunlight, Supplementation, Vitamin D.*

Vitamin D deficiency is considered to be the most common nutritional deficiency [1] and also one of the most common undiagnosed medical conditions in the world. Vitamin D has evolved into a hormone that is active throughout the body not only to regulate calcium and bone metabolism but also to reduce the risk of chronic diseases including auto immune diseases, malignancies, cardiovascular and infectious diseases. It has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency [2]. Though majority of population in India lives in areas receiving ample sunlight throughout the year, vitamin D deficiency is very common in all the age groups and both the sexes across the country [3-5].

Over the last two decades, understanding of vitamin D synthesis and its function has changed remarkably. This led us to re-examine the traditional concepts and current recommendations for vitamin D supplementation, sun light exposure and revised management strategies for deficiency. In this review, we discuss the current knowledge on diagnosis, prevention and treatment of vitamin D deficiency.

Etiology of Vitamin D Deficiency

The prevalence of vitamin D deficiency is 50-90 % in the Indian subcontinent and is attributed to low dietary calcium along with skin color and changing lifestyle [3]. Some postulate that a deficiency of dietary calcium rather than vitamin D deficiency is responsible for rickets after infancy, supported by the fact that they have a better response to treatment with calcium alone or in combination with vitamin D rather than vitamin D alone [6]. Vitamin D deficiency is observed among breastfed infants at one end with dietary calcium deficiency in older children at the other end. 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 [7] (***Table* I**).

Vitamin D deficiency is common in infancy due to several factors such as – decreased dietary intake, 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), increasing rate of exclusive breast feeding, and low maternal vitamin D.

Definition of Vitamin D Status

Definitions of vitamin D status have been intensely debated by clinicians and researchers alike. Vitamin D deficiency is defined as serum levels of 25(OH)D less than 20 ng/dL whereas 21- 29 ng/dL is considered to be insufficient by US Endocrine Society. This has been done to utilize full advantage of all the health benefits of vitamin D [8] (***Table* II**). Chapuy, *et al.* [9] and Malabanan, *et al*. [10] concluded that those who had

TABLE I ETIOLOGY OF VITAMIN D DEFICIENCY [19]

Decreased vitamin D synthesis	Skin pigmentation, physical agents blocking UVR exposure, clothing, latitude, season, air pollution, cloud cover, altitude
Decreased nutritional intake of vitamin	Strict vegan diet
Age and physiology related	Elderly, obese and institutionalised
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.

TABLE II VITAMIN D STATUS IN RELATION TO 25 (OH) D LEVELS

Vitamin D status	*Levels*
US IOM classification [17]	
Severe deficiency	<5 ng/mL
Deficiency	<15 ng/mL
Sufficiency	>20 ng/mL
Risk of toxicity	>50 ng/mL
US Endocrine Society classification [8]	
Deficiency	<20 ng/mL (50 nmol/L)
Insufficiency	21-29 ng/mL (52.5–72.5) nmol/liter
Sufficiency	>30 ng/mL
Toxicity	>150 ng/mL

1mcg = 40IU; 0.025 mcg is 1 IU

25(OH)D more than 20 ng/dL had no significant change in their PTH levels. Recently IOM (Institute of Medicine) remarked that available scientific evidence supports a key role of calcium and Vitamin D in skeletal health is consistent with cause and effect relationship whereas evidence supporting the role of vitamin D deficiency in extra skeletal health outcomes is inconsistent, inconclusive and insufficient to be considered more than "hypothesis of emerging interest" [11]. A variety of definitions exist in the literature [12-16].

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 [17]. Hence it has been concluded by IOM that 25(OH)D levels >20ng/dL indicates vitamin D sufficiency [18]. Levels of 25(OH)D 15 ng/dL or less are considered as deficiency and 5 ng/dL or less are considered as severe deficiency [19,20].

Sufficient data are not available to define the upper limits of normal or dose levels above which toxicity occurs. Previously it was thought that vitamin D intoxication does not occur until serum levels of 25(OH)D reach 150 to 200 ng/dL [21,22]. Recently the IOM concluded that the serum concentrations of 25(OH)D above 30 ng/dL are not consistently associated with increased benefits and risks have been identified at higher levels above 50 ng/dL [17]. There is an urgent need for consensus derived cut off points for serum levels of 25 (OH)D to define vitamin D status in order to avoid problems of both over-and under-treatment (***Table* II**).

Measurement of Vitamin D Levels

25(OH)D is the major circulating form of vitamin D with a half-life of 2-3 weeks and its levels are the best available indicators of vitamin D status. Although 1, 25 $(OH)_2D$ (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 because (*i*) vitamin D deficiency can cause PTH elevation that induces increased 1- alpha hydroxylase activity, which results in normal or increased levels of 1,25 $(OH)_2$ D; and (*ii*) it circulates at the concentration that is 100-1000 fold less than 25(OH)D [23].

The assays used to measure 25(OH)D levels should be capable of measuring both D2 (ergocalciferol) and D3 (cholecalciferol) derivatives. The total 25(OH) D [25(OH)D2 and 25(OH)D3] levels measured by high performance liquid chromatography (HPLC) or tandem mass spectrometry have been reported as the gold standard for vitamin D metabolite assay [19]. Other methods of measurement include radio-immune assays using monoclonal antibodies to 25(OH)D and chemiluminescent protein binding assay.

When to Treat?: 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 [19]. The three stages of

vitamin D deficiency are outlined in ***Table* III**.

Recommended Treatment Regimen

Several therapeutic regimens have been attempted for deficiency of vitamin D. Short term administration of vitamin D2 or D3 2000 units daily or vitamin D2 50,000 units weekly has yielded equivalent outcomes in the treatment of hypovitaminosis D in young children [24]. Common recommendations 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. The total dose of vitamin D has been reported to be more predictive of vitamin D sufficiency rather than the frequency of dosing (daily, weekly or monthly) [24]. Therefore, treatment regimens for a given patient can be individualized to ensure compliance, since no difference in the efficacy or safety was reported in these common treatment regimens [24].

Lack of compliance is an important cause for lack of response to therapy and an option to prevent this is to administer high dose of 1,00,000 to 6,00,000 IU over 1-5 days [25,26]. Doses of 10000 units /kg [27] instead of smaller doses over longer period followed by maintenance dose have also been reported to be effective. Shah and Finberg have successfully administered 1 lakh IU every 2 hours over 12 hours period [25]. 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* IV**).

Stoss therapy regimens with large oral or parenteral dose of vitamin D3 has been shown to cause increased and sustained higher levels of 25(OH)D levels, especially the regimen with 6 lakh IU. Stoss therapy is safe and can lead to hypercalcemia only at very high doses. Doses of 1,50,000 to 3,00,000 IU can be effective with less side effects [28].

After the completion of treatment, vitamin D has to be continued at 800-1000 IU/day till serum alkaline phosphatase returns to normal, followed by RDA for age [29]. Vitamin D supplements are available as both vitamin D2 and D3. Although traditionally D2 and D3 have been considered to be equipotent, studies have shown that D3 may be at least 3 times more potent than D2 [30]. Hence supplements containing D3 may be preferred.

Calcium supplementation: Even for children who are not frankly hypocalcemic, calcium supplements are important for avoiding subsequent hypocalcaemia from a decrease in bone demineralization and an increase in bone mineralization as PTH levels normalize (hungry

TABLE III BIOCHEMICAL MARKERS OF VITAMIN D DEFICIENCY

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

ALP: Alkaline phosphatase; PTH: Parathrmone; 25(OH)D: 25-hydroxy vitamin D; 1,25 (OH) D_3: 1,25-dihydroxy vitamin D_3.

TABLE IV TREATMENT REGIMENS FOR VITAMIN D DEFICIENCY

Group	*Daily regimen (8-12 weeks)*	*Weekly regimen (8-12 weeks)*	*Stoss therapy (oral or IM)*	*Maintenance*
< 1 mo old	1,000 IU	50,000 IU	-	400-1,000 IU
1-12 mo old	1,000-5000 IU	50,000 IU	1 lakh -6 lakhs units over 1-5 days (Preferably 3 lakh)	400- 1,000 IU
1-18 y old	5,000 IU	50,000 IU	3-6 lakh units over 1-5 days	600-1,000 IU
>18 y old	6,000 IU	50,000 IU	3-6 lakh units over 1-5 days	1,500-2,000 IU
Obese patients, patients with malabsorption syndrome, or on medications affecting vitamin D	6,000-10,000 IU/ day			3,000-6,000 IU

* *To convert (IU) to mcg of calciferol divide by 40.*

bone syndrome), particularly with Stoss therapy. Supplementation of elemental calcium in a dose of 30-75mg/kg/day in 3 divided doses is recommended. High doses of calcium are necessary early in the course of therapy, after which doses are reduced by half for next 1-2 weeks. Once vitamin D supplements have been decreased to 400 IU /day with normal PTH and 25(OH)D, calcium supplementation is usually not necessary [19]. Administration of parenteral calcium is essential for symptomatic hypocalcemia (10-20 mg of elemental calcium/kg IV slowly over 5-10 minutes) and is usually given as 1-2 mL/kg of calcium gluconate. This becomes necessary in case of manifest tetany or convulsions and repeat boluses may also be necessary on occasion. Calcium levels should thereafter be maintained with oral calcium supplements.

Calcium preparations: Calcium carbonate and citrate are the most common forms of calcium supplements. Calcium carbonate, the most effective form should be taken with a meal to ensure optimal absorption. Calcium citrate can be taken without food and is the supplement of choice for individuals with achlorhydria or who are taking histamine-2 blockers or Proton Pump Inhibitors since calcium carbonate needs acid environment for calcium absorption. Calcium lactate and gluconate are 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. Tolerable upper limit is 2500 mg/day for ages 1 year and above.

In addition to calcium supplements, 1, 25 $(OH)_2D$ may be necessary till calcium levels normalize (***Table* V**). Calcitriol is not used for Stoss therapy, since it has a short half-life, does not build up vitamin D stores, and is expensive. In higher doses it may cause hypercalcemia because of its rapid onset of action which limits the amount that can be administered.

Monitoring therapy: Estimation of serum calcium, phosphorus and serum alkaline phosphatase levels is recommended 1 month after initiation of therapy. With Stoss therapy biochemical response is usually evident in 1 or 2 weeks [19]. 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. Complete radiological healing takes longer than one month although evidence of healing is seen within 4 weeks.

After 3 months it is recommended to obtain 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. Subsequently 25(OH)D levels may be monitored yearly [19]. Considering the cost of performing laboratory tests, reserving investigations only for those not improving (based on clinical assessment) may be an appropriate practical option.

Screening for Vitamin D Deficiency

The US endocrine society guideline recommends screening only in population at risk, as no evidence currently exists to support screening at all population levels. The candidates for screening or those who are at risk for vitamin D deficiency include patients with few specific disorders (***Table* VI**) [8].

How to Screen? Serum alkaline phosphatase has been reported to be useful as a screening test [29], which if elevated for age should be followed with measurements of 25(OH)D, calcium, phosphorus and PTH along with radiological examination of distal ends of radius and ulna or tibia and femur depending on the age [31]. 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 (levels of serum alkaline phosphatase vary with the method of estimation used). Some studies however, indicate that though all children with radiographic evidence of rickets have low vitamin D levels, not all have high serum alkaline phosphatase and the wrist radiography may be the most reliable test for

TABLE V MANAGEMENT OF HYPOCALCAEMIA DUE TO VITAMIN D DEFICIENCY

Symptomatic hypocalcaemia due to vitamin D deficiency	*Asymptomatic vitamin D deficiency*
IV calcium gluconate (1-2ml/kg) (up to a 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 X 1-2 weeks	Oral calcium 30-75mg/kg/day (up to a maximum of 1 – 2 g/ day) in 3 divided doses X 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.

TABLE VI WHOM TO SCREEN [8]

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.	Mal absorption syndromes.
	Cystic fibrosis
	Inflammatory bowel disease
	Crohn's disease
vii.	Hyper parathyroidism
viii.	Medications
	1. Anticonvulsants
	2. Glucocorticoids
	3. AIDS medications
	4. Antifungals (ketoconazole)
ix.	Obese children and adults (BMI > 30kg/m^2)
x.	Granuloma forming disorders
	1. Sarcoidosis
	2. Tuberculosis
	3. Histoplasmosis

detecting subclinical rickets [32-34]. 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 [34].

Guidelines for Vitamin D Intake

The recommended vitamin D intake is 400 IU/day in infants less than 1 year and 600 IU/day in children more than 1 year of age as suggested by US IOM [17,35,36].

The dietary reference intake for vitamin D is chosen with a margin of safety and "over shoot" that targeted serum values to ensure that the specified levels of intake achieve the desired 25(OH)D levels in almost all persons. It is assumed that there are no contributions to serum 25(OH)D levels from sun exposure and recommendations are applicable to people with dark skin or negligible sun exposure.

However, to keep the serum levels of 25(OH)D >30 ng/dL which is considered to be the optimal level, the US Endocrine committee has suggested 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].

Children at risk (on anticonvulsants, glucocorticoids, antifungals and medications for AIDS) need 2 to 3 times the requirement for their age.

The upper limit of vitamin D intake as maintenance therapy which is not to be exceeded without medical supervision is as follows : 1000 IU/ day for infants from 6 months-1 yr; 1500 IU/day for 1-3 years; 2500 IU/day for 4-8 years, 3000 IU/day for >8 years - 4000 IU/day.

Prevention

The most important factor determining the vitamin D status in infancy is the maternal vitamin D status [37]. Though practically difficult, all pregnant women should have their 25(OH) D levels checked during the first trimester of pregnancy. If they are deficient they should be treated with 3000-5000 IU until 25(OH)D is more than >20 ng/dL followed by 400 IU /daily [38].

Routine vitamin D supplementation to all the pregnant women is controversial [39]. Administration of high dose of vitamin D (400-6400 IU) daily to breast feeding mothers increases the anti-rachitic activity of breastmilk [40,41] without causing hypervitaminosis in the mother.

Preterm infants should be supplemented from birth with 400-800 IU/day because of inadequate transfer of maternal vitamin D stores and issues associated with prematurity such as poor feeding, gastrointestinal difficulties impairing absorption and sometimes liver and kidney impairment. Consideration for universal supplementation particularly in breastfed infants has been suggested [42].

The preparations available in India are; Vitamin D3 – as oral drops 400 IU/mL; Syrup 400 IU/5mL; and Tablets as 1000 and 2000 IU in blister packing and also as sachet in powder form with each sachet containing 60000 IU of vitamin D3.

Supplementation in newborn period: For infants who are exclusively breastfed a minimum daily intake of 400 IU/ day should be initiated within a few days after birth. Since most of the infant formulas contain 400 IU/L, infants who are on formula feeds also need supplementation unless they consume more than 1000 mL of formula per day.

Toddlers and adolescents: Children who are dark skinned, veiled, exposed to reduced sun light or who have underlying medical condition should receive 400 IU daily to prevent vitamin D deficiency.

Sources

Sunlight: Most of circulating vitamin D is provided by synthesis from skin exposure to UVB radiation and <10%

from dietary sources[43]. At solar noon the ratio of UVB – UVA light is the highest and the only time that enough UVB photons reach the earth's surface to produce vitamin D is between 1000-1500 hours in the spring, summer and fall. The disadvantage of UVR exposure for vitamin D generation is the induction of skin cancers, though in dark skinned individuals, the risk for melanoma is considerably less. Children, particularly infants may require less sun exposure to produce sufficient quantities of vitamin D because of greater capacity to produce vitamin D than older people [29].

Specker, *et al.* [43] reported that exposure to sunlight for 30 min/week for 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. Asian children require three times the recommended amount of sun light exposure to maintain the vitamin D levels (because of dark skin color). However, to maintain vitamin D level in the sufficiency range the duration of UVR exposure particularly in relation to time of the day, season or skin pigmentation, remains to be determined. Excessive exposure to sunlight dose not lead to vitamin D toxicity.

Dietary and supplemental sources of vitamin D: Oily fish such as salmon, mackerel and sardines, cod liver oil, and liver and organ meats are rich natural sources that are not commonly consumed by children.

Fortified foods are being recognised as an important source of vitamin D [44]. Fortification of milk has been found to be a safe, effective and acceptable method [45]. 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 [46]. 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.

Contributors: All the authors have contributed, designed and approved the review.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Holick MF. Vitamin D: extraskeletal health. Rheum Dis Clin North Am. 2012; 38:141-60.
2. Holick MF, Vitamin D deficiency. N Engl J Med. 2007;357:266-81.
3. Harinarayanan CV, Joshi SR. Vitamin D status in India – Its implications and remedial measures. J Assoc Physicians. 2009;57: 40-8.
4. Marwaha RK, Sripathy G. Vitamin D and Bone mineral density of healthy school children in northern India. Indian J Med Res. 2008;127:239-44.
5. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. Osteoporos Int. 2005;16:397-402.
6. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Reading JC, *et al*. A comparison of calcium, vitamin D or both for nutritional rickets in Nigerian children. N Engl J Med. 1999;34:563-8.
7. Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium or both? Am J Clin Nutr. 2004;80:17255-95.
8. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society. Practice guideline. J. Clin Endocrinol Metab. 2011;96:1911-30.
9. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, *et al*. Prevalence of vitamin D insufficiency in an adult normal population. Osteapor Int. 1997;7:439-43.
10. Malabanan AO, Turner AK, Holick MF. Severe generalized bone pain and osteoporosis in a premenopausal black female: effect of vitamin D replacement. J Clin Densitometr. 1998;1:201–4.
11. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine; 2011.
12. Hill TR, Flynn A, Kiely M, Cahsman KD. Prevalence of suboptimal vitamin D status in young, adult and elderly Irish subjects.Ir Med J. 2006;99:48-9.
13. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol. 2004;89-90:611-4.
14. Van der Meer IM, Karamali NS, Boeke AJP, Lips P, Middelkoop BJC, Verhoeven I, *et al*. High prevalence of vitamin D deficiency in pregnant non-Western women in the Hague, Netherlands. Am J Clin Nutr. 2006;84:350-3.
15. Laaksi IT, Ruohola J-PS, Ylikomi TJ, Auvinen RI, Haataja RI, Pihlajamaki HK, *et al*. Vitamin D fortification as public health policy: significant improvement in vitamin D status in young Finnish men. Eur J Clin Nutr. 2006;60:1035-8.
16. Vieth R, Carter G. Difficulties with vitamin D nutrition research: Objective targets of adequacy and assays for 25-hydroxyvitamin D. Eur J Clin Nutr. 2001;55:221-2.
17. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al*. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute Of Medicine: What clinicians need to know? J Clin Endocrinol Metab. 2011;96:53-8.
18. Gordon CM, De Peter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med. 2004;158:531-7.
19. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson

Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management. Review of current knowledge and Recommendations. Pediatrics. 2008;122;398.
20. Munns C, Zacharin MR, Rodda CP, Batch JA, Morley R, Cranswick NE, *et al*. Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement. Med J Aust. 2006;185:268-72.
21. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over the counter supplement. N Engl J. Med. 2001;345:66-7.
22. Adams JS, Lee G. Gains in bone mineral density with resolution of vitamin D intoxication. Annals Int Med. 1997;127:203-6.
23. Holick MF. Vitamin D status: measurement, interpretation and clinical application. Ann Epidemiol. 2009;19:73-8.
24. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, *et al*. Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab. 2008;93:2716-21
25. Shah B, Finberg L. Single day therapy for nutritional vitamin D deficiency rickets: a preferred method. J. Pediatr. 1994;125:487-90.
26. Hochberg Z, Bereket A, Davenport M, Delemarre-Van de Waal HA, De Schepper J, Levine MA, *et al*. Consensus development for the supplementation of vitamin D in childhood and adolescence. Horm Res. 2002;58:39-51.
27. Soliman AT, El-Dabbagh M, Adel A, Al Ali M, Aziz Bedair EM, Elalaily RK. Clinical responses to mega dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. J Trop Pediatr. 2010;56:19-26.
28. Sahay M, Sahay R. Rickets vitamin D deficiency and dependency. Indian J Endocrinol Metab. 2012;16:164-76.
29. Joiner TA, Foster C, Shope T. The many faces of vitamin D deficiency rickets. Pediatr Rev. 2000;21:296.
30. Asmas LA, Hollis BW, Haeney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J. Clin Endocrinol Metab.2004; 89: 5387-5391.
31. Spence JT, Serwint JR. Secondary prevention of vitamin D deficiency rickets. Pediatrics. 2004;113(1 Pt 1):e70-2.
32. Goel KM, Sweet EM, Logan RW, Warren JM, Arneil GC, Shanks RA. Florid and subclinical rickets among immigrant children in Glasgow. Lancet.1976;1:141-5.
33. Pettifor JM, Isdale JM, Sahakian J, Hansen JD. Diagnosis of subclinical rickets. Arch Dis Child. 1980;55:155-7.
34. Taylor JA, Richter M, Done S, Feldman KW. The utility of alkaline phosphatase measurement as a screening test for rickets in breast fed infants and toddlers. A study from pudget sound pediatric research network. Clinical Pediatr. 2010;49:1103-10.
35. Aloia JF. The 2011 report on dietary reference intake for vitamin D. Where do we go from here? J Clin Endocrinol Metab. 2011;96:2987-96.
36. Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. J Bone miner Res. 2011;26:455-67.
37. Moy R, Shaw N, Mather I. Vitamin D supplementation in pregnancy. Lancet. 2004; 363 (9408):574.
38. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust. 2005;182: 281-5.
39. Thomson K, Morley R, Grover SR, Zacharin MR. Postnatal evaluation of vitamin D and bone health in women who were vitamin –D deficient in pregnancy, and their infants. Med J Aust. 2004;181:486-8.
40. Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeed Med. 2006;1:27-36.
41. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High dose vitamin D3 supplementation in a cohort of breast feeding mothers and their infants: a 6 month follow-up pilot study. Breastfeed Med. 2006;1:59 -70.
42. Balasubramanian S, Ganesh R. Vitamin D deficiency in exclusively breast fed infants. Indian J Med Res. 2008;127:250-5.
43. Specker BL, Valanis B, Hertzberg V, Edwards N, Tsang RC. Sunshine exposure and serum 25- hydroxy vitamin D concentrations in exclusively breastfed infants. J. Pediatr. 1985;107:372-6.
44. Lamberg-Allardt C. Vitamin D in foods and as supplements. Prog Biophys Mol Biol. 2006;92:33-8.
45. Natri AM, Salo P, Vikstedt T, Palssa A, Huttunen M, Kärkkäinen MU, *et al*. Bread fortified with cholecalciferol increases the serum 25-hydroxyvitamin D concentration in women as effectively as a cholecalciferol supplement. J. Nutr. 2006;136:123-7.
46. Babu US, Calvo MS. Modern India and the vitamin D dilemma: evidence for the need of a national food fortification program. Mol Nutr Food Res. 2010;54: 1134-47.