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1

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CHAPTER 2

NUTRITION

2.1 Current Status of Vitamin D Deficiency and Its Management
Deepika Harit, Piyush Gupta

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2.1 CURRENT STATUS OF VITAMIN D DEFICIENCY AND ITS MANAGEMENT

Deepika Harit, Piyush Gupta

INTRODUCTION

Vitamin D is a prohormone which is essential for normal bone development in humans. Over the past two decades, substantial research has been published to ascertain its role in health and disease. Vitamin D serves a crucial role in maintaining the normal calcium metabolism and its deficiency causes altered chondrocyte differentiation. This results in poor mineralization of growth plate and abnormal osteoid mineralization. Since the discovery of vitamin D receptor (VDR) in various cells of our body (e.g. β cells of pancreas, mononuclear cells, osteoblasts and activated B and T lymphocytes), researchers have also explored the role of vitamin D in extraskeletal systemic disorders.

Deficiency of vitamin D and/or calcium causes nutritional rickets (NR), which remains the most common form of rickets in developing nations. Calcium deficiency is the main reason for development of rickets in Africa and some parts of tropical Asia. It is also being increasingly recognized in other parts of the world. Vitamin D deficiency rickets usually presents in the first 18 months of life, whereas calcium deficiency typically presents after weaning and often after the second year of life.[1] The overall incidence of nutritional rickets is high between 4 months and 18 months of age, though cases are not uncommon in older children. The incidence of rickets has decreased in developed nations due to fortification of dairy and other food products with vitamin D; however, the disease is highly prevalent in tropical countries.[2]

PROBLEM STATEMENT

Vitamin D deficiency is a global problem affecting all ages and ethnic groups. No country or ethnicity is devoid of vitamin D-deficient population. The prevalence of severe vitamin D deficiency is particularly high in women and girls in Middle East. Population representative data on vitamin D status is not available for many areas in Africa and Asia. Data on vitamin D levels in children and adolescents is also lacking from southern America and Africa. It is noteworthy that studies are not always directly comparable, since several different assays are used, and inter-laboratory variations can be considerable. More importantly, a vast difference occurs in the cut-off used to define vitamin D deficiency, based on serum levels of 25-hydroxyvitamin D [25(OH)D]. Areas with good sunlight throughout the year also have high prevalence of vitamin D deficiency.[2]

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GLOBAL OVERVIEW OF VITAMIN D STATUS

A recent systematic review, involving 95 reports from across the globe, evaluated serum 25(OH)D concentrations in maternal and newborn populations. The review included studies from Europe, Eastern Mediterranean region, Western Pacific, South East Asia, Africa, and Americas. The prevalence of 25(OH)D levels <50 nmol/L and <25 nmol/L in pregnant women was as follows—Western Pacific (83%, 13%), Europe (57%, 23%), Eastern Mediterranean region (46%, 79%), South-East Asia (87%, not available), and Americas (64%, 9%). The prevalence in newborns with same two cut-offs was as follows—Western Pacific area (54%, 14%), Europe (73%, 39%), Eastern Mediterranean region (60%, not available), South-East Asia (96%, 45%), and Americas (30%, 14%). Maternal and newborn 25(OH)D concentrations had strong correlation.[2]

In another population-based health survey of national representative population of >25 years age (n = 5034) in Australia, about 43% participants were classified as insufficient (45% men; 42% women) and 20% (19% men; 21% women) were classified as vitamin D deficient. Vitamin D deficiency and insufficiency were defined as serum 25(OH)D concentrations <50 nmol/L and 50–75 nmol/L, respectively.[3]

In a large-scale study (n = 1,814) on vitamin D status in China, optimal (50–125 nmol/L) 25(OH)D level was observed in only 47.6%. Serum 25(OH)D levels were significantly higher among the age group of 40–49 years (50.7 ± 17.99 nmol/L) than among ≥ 70 years (48.45 ± 14.49 nmol/L) or 18–29 years (47.81 ± 13.08 nmol/L) age groups.[4]

In a recent cross-sectional study from Ethiopia, serum 25(OH)D levels were estimated in rural and urban school children aged 11–18 years. Vitamin D deficiency defined as 25(OH)D <50 nmol/L was observed in 42% participants. Students in urban settings had higher prevalence of deficiency as compared to rural areas (61.8% vs. 21.2%).[5] In the USA NHANES 2011–12 study, 1,981 out of 4,962 (39.9%) participants were vitamin D deficient (considering serum levels <150 nmol/L).[6]

Vitamin D Status in India

People living closer to equator are believed to receive abundant sunshine and therefore expected to have better vitamin D status. Contrary to this belief, residents of tropical countries, including India, have a very high prevalence of vitamin D deficiency or insufficiency **(Table 2.1.1)**.[7-13] In a recent study by Mandlik et al., 71% of children aged 6–12 years in semirural settings were vitamin D insufficient with serum 25(OH)D concentrations between 50 nmol/L and 74.9 nmol/L, despite >2 hours of sun exposure.[14] Sahu et al. reported that prevalence of vitamin D deficiency (25(OH)D <50 nmol/L) in adolescent girls was 88.6%. 74% of pregnant women had vitamin D deficiency.[15]

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Table 2.1.1: Prevalence of vitamin D deficiency in Indian children.

Author	*Site of study*	*Sample size*	*Age group*	*Prevalence of vitamin D deficiency*
Bawaskar et al. 2017[7]	Maharashtra	640	No age preference	65.4%
Kapil et al. 2017[8]	Himachal Pradesh	626	6–18 years	93%
Chowdhary et al. 2017[9]	Delhi	960	6–30 months	34.5%
Basu et al. 2015[10]	Kolkata	310	1–16 years	52.9%
Angurana et al. 2014[11]	Chandigarh	338	3 months–12 years	40.2%
Khadagwat et al. 2012[12]	Delhi	62	6–17 years	99.8%
Marwaha et al. 2005[13]	Delhi	5137	10–18 years	84.9–92.6%

In a study by Jain et al., 66.7% of infants and 81.1% of mothers had vitamin D deficiency [25(OH)D <15 ng/mL]. An additional 19.8% infants and 11.6% mothers had vitamin D insufficiency [25(OH)D 15–20 ng/mL].[16] Aggarwal et al. observed vitamin D deficiency in 186 low birth weight (LBW) infants (87.3%) and 103 normal birth weight (NBW) infants (88.6%) at birth. The same newborns when reassessed at a median corrected age of 12 and 15 weeks (LBW and NBW, respectively) showed vitamin D deficiency in 77 (60.6%) of LBW and 55 (71.6%) of NBW infants. Vitamin D deficiency was near universal (93–97%) in all mothers.[17]

Comprehensive National Nutrition Survey (CNNS) is one of the largest nutrition surveys in the world, conducted from 2016–18, in 30 states of India with a multistage survey design, covering both urban and rural households.[18] The survey collected data from three target population groups; preschoolers (0–4 years), school-age children (5–9 years), and adolescents (10–19 years). Vitamin D was estimated by electrochemiluminescence assay and serum vitamin D level of <12 ng/mL (30 nmol/L) was considered as deficient in all three population groups. In this survey, overall prevalence of vitamin D deficiency was 14% in preschool children, 18% in school-age children, and 24% in adolescents. Vitamin D deficiency varied considerably over states. Highest prevalence was found in Punjab (52% in 1–4 year, 76% in 5–19 year, and 68% in 10–19 year age groups) and lowest prevalence was found in Assam (1.1% in 1–4 year, 4.0% in 5–19 year, and 7.1% in 10–19 year age groups). Other states with overall consistently high prevalence of vitamin D deficiency in all age groups were Uttarakhand, Delhi, Rajasthan, Haryana, Gujarat, Jammu & Kashmir, and Manipur. There were striking differences in vitamin D levels of the children according to the type of residence (rural/urban), type of diet (veg/veg with egg/non-veg), and wealth index (poorest/poor/middle/rich/richest) **(Table 2.1.2)**.

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Table 2.1.2: Percentage of children with vitamin D deficiency in blood by selected background characteristics.[18]

	1–4 years	*5–9 years*	*10–19 years*
Residence			
Urban	19.1	27.8	33.2
Rural	12	15.2	20.6
Diet			
Vegetarian	17.4	24.9	27.8
Vegetarian with egg	16.6	22.9	28.1
Non-vegetarian	12.8	16.2	22.5
Wealth Index			
Poorest	14.1	13.3	18.9
Poor	13.1	13.2	18.8
Middle	9.6	14.8	19.8
Rich	4.4	20.4	28.7
Richest	13.8	30.2	32.9

PHYSIOLOGY OF VITAMIN D

Vitamin D is a secosteroid, which is produced in skin from 7-dehydrocholesterol by the action of ultraviolet B (UVB) rays (290–315 nm) from the sun. Most of the vitamin D (90%) in our body is synthesized in the skin. The diet contributes to only 10% of the vitamin D in the body. Vitamin D synthesis in the skin is affected by various factors, e.g. time of day, presence of clouds and/or smog, geographic latitude, time of year, melanin content in skin, and sunscreen application. The vitamin D formed in skin and the one ingested in diet, are then absorbed by the intestine, and carried to the liver via the bloodstream **(Fig. 2.1.1)**. In the liver, it is transformed into 25(OH)D (calcidiol), which is the primary circulating form of vitamin D. It is also the most commonly measured form of vitamin D in serum. It is later converted into 1,25 dihydroxyvitamin D (calcitriol) in the kidneys. The biologically active form of vitamin D is 1,25 dihydroxyvitamin D [1,25OH)2D]. When serum calcium falls below 8.8 mg/dL, it leads to a proportional increase in the secretion of parathyroid hormone (PTH). PTH increases the 25(OH)D–1α-hydroxylase production in the kidneys, which finally increases the production of 1,25(OH)2D. The increase in 1,25(OH)2D augments calcium absorption in the intestines to stimulate bone remodeling. Kidneys reduce the production of 1,25(OH)2D to a normal state after the phosphorus and bone genes levels signal a normal state of bone remodeling.

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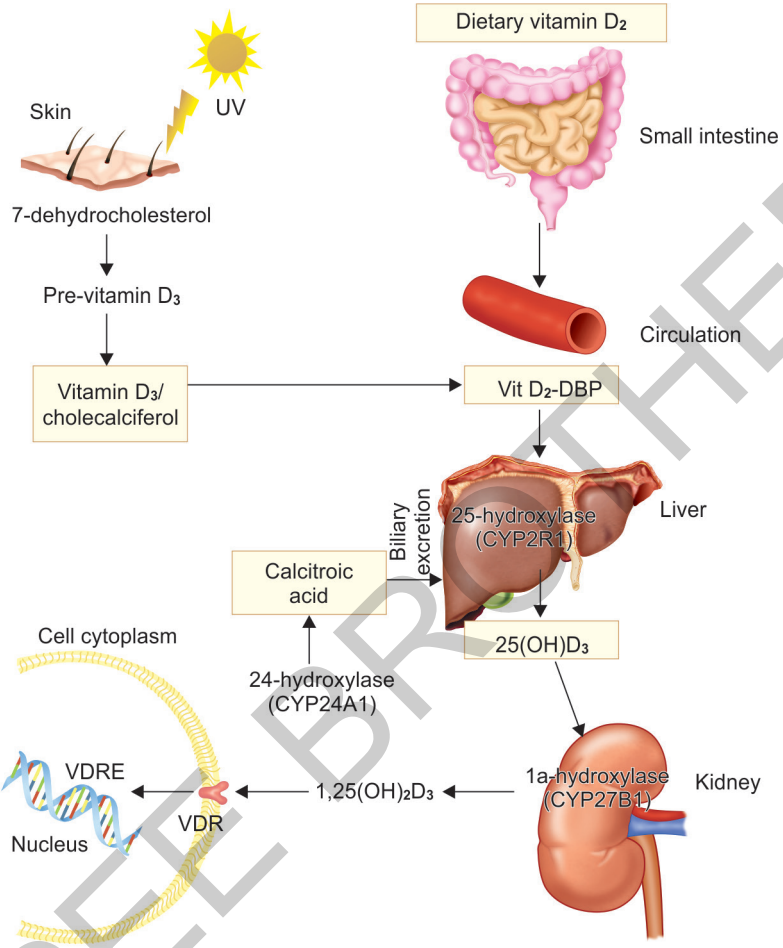

Fig. 2.1.1: Vitamin D metabolism.
(Vit D_2 DBP: vitamin D_2 binding protein; VDR: vitamin D receptor; VDRE: vitamin D response element)

Vitamin D has an established role in bone metabolism and calcium homeostasis. Pleiotropic effects of vitamin D are now being increasingly recognized and are currently a key research area. Vitamin D plays a role in immunomodulation by regulating both innate and adaptive immune system.

The physiological actions of vitamin D are exerted by its binding to and regulation of nuclear VDR. Essentially every organ and cell in the body has a VDR. Over 900 genes are expressed throughout the genome by VDR, which is a ligand-induced nuclear receptor. It affects gene transcription by forming vitamin 1,25(OH)2D–VDR complexes. This complex translocates from the cytosol to the nucleus on successful entry into the cells. There it combines

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with retinoid X receptor (RXR). This RXR–1,25(OH)2D–VDR complex binds to vitamin D response elements (VDRE), which are the promoter regions of target genes. VDR is commonly expressed in immune system cells, e.g. neutrophils, T lymphocytes, macrophages, and dendritic cells. VDRs are present abundantly in cells of colon, lungs, neurons, cardiomyocytes, and kidneys. VDR gene lies on chromosome 12 and >60 VDR polymorphisms have been identified. These polymorphisms can alter the transcription activity, which leads to modulation of cellular responsiveness to 1,25(OH)2D. These VDRs control the cellular proliferation, differentiation, apoptosis, and angiogenesis. 1,25(OH)2D is increasingly recognized as a potent inhibitor of cellular proliferation.

When an infective agent like *Mycobacterium tuberculosis* or its liposaccharides encounter a monocyte/macrophage through toll-like receptor (TLR), it stimulates VDR expression and increases the production of cathelicidin. Cathelicidin is a peptide, which promotes innate immunity and causes destruction of several infective agents. 1,25(OH)2D also induces autophagy in human monocytes via cathelicidin and causes localization of mycobacterial phagosomes with autophagosomes in human macrophages in a cathelicidin-dependent manner.[19]

RECOMMENDED DAILY ALLOWANCE AND SOURCES

Vitamin D, unlike other vitamins, is not abundantly available in foodstuffs. Dietary consumption usually accounts for only 5–10% of the total vitamin D. The amount in vegetable sources is negligible **(Table 2.1.3)**. This fat-soluble vitamin is found in fish (oily fish, e.g. salmon, mackerel, herring, sardine, trout, anchovy, and tuna), cod liver oil and other fish oils, egg yolk (20 IU/yolk), mushrooms, supplemented cereals, and fortified foods including formulas, milk, bread, and margarine. Human milk has a low vitamin D content, approximately 12–60 IU/L, and it is considered insufficient to prevent vitamin D deficiency in exclusively breastfed babies. Supplementation of 400 IU of

Table 2.1.3: Vitamin D content of food items.

Food items	*Vitamin D content*
Cow's milk	3–40 IU/L
Fortified infant formula	400 IU/L
Egg yolk	20–25 IU/yolk
Butter	35 IU/100 g
Cheese	12–44 IU/100 g
Cod liver oil	175 IU/g
Yogurt	89 IU/100 g
Fish	44–624 IU/100 g

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Table 2.1.4: Recommended dietary allowance for calcium and vitamin D.[20-23]

	Calcium (mg)	*Vitamin D (IU)*		
	NIH (20)	*ICMR (21)*	*NIH (20)*	*ICMR(21)*
Infants: 0–6 months	200	500	400*	400
6–12 months	260	500	400*	400
Children (1–3 years)	700	600	600	400
(4–8 years)	1,000	600	600	400
(9–18 years)	1,300	800#	600	400
Adults (19–70 years)	1,000	600	600	400
71+ years	1,200	600	600	400
Pregnancy	1,000	1,200	600	400
Lactation	1,000	1,200	600	400

*Adequate intake
#*10–17 years age*
Source: National Institute of Health (NIH) USA 2010 and Indian Council of Medical Research (ICMR) Dietary guidelines for Indians–NIN 2011.

vitamin D helps in maintaining serum 25(OH)D concentrations at >50 nmol/L in breastfed infants. Though formula milk has vitamin D, infants needs to consume 1 liter of milk to get 400 IU/day vitamin D, which is not possible in neonates. *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.* Both Indian Academy of Pediatrics (IAP) and Global Consensus Recommendations advocate this endorsement.[22,23] Recommended daily allowance for calcium and vitamin D are given in **Table 2.1.4**.[20-23]

CLINICAL MANIFESTATIONS OF VITAMIN D DEFICIENCY

We will not discuss the details of clinical manifestations, as they are well-described elsewhere.[24] Rickets is identified as the well-known clinical presentation of vitamin D deficiency. The spectrum of extraskeletal manifestations of vitamin D deficiency varies from nonspecific complaints of irritability, body ache, bone pain, failure to thrive, and gross motor developmental delay to hypocalcemic seizures, tetany, life-threatening apneic spells, stridor, and cardiomyopathy. Hypocalcemic seizure and tetany due to vitamin D deficiency are more frequently seen in infancy and adolescence. There is rapid growth of the body during these phases of growth. This growing demand for calcium cannot be met with the body calcium stores and thus the patient may present with hypocalcemia even before the signs of rickets are observed.[25]

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Directly or indirectly, vitamin D may affect every organ of the body either by the expression of VDR or by regulating other gene expressions. The extraskeletal effects of vitamin D have been a hot topic of debate and several studies (both observational and interventional) have been conducted with conflicting results. Data in children are limited. Most studies were designed to determine the beneficial effect of vitamin D supplementation on severity of various diseases, e.g. metabolic syndrome, diabetes mellitus, rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), multiple sclerosis, asthma, food allergies, cancers, respiratory infections, and chronic hepatitis.[26]

Interventional studies in children with obesity, prediabetes, and type 2 diabetes show conflicting results. Obese adolescents have shown improved homeostatic model assessment of Insulin Resistance (HOMA-IR), quantitative insulin-sensitivity check index (QUICKI), and improved apo-B and low-density lipoprotein-C (LDL-C) following vitamin D administration.[25,26] Other studies have failed to demonstrate any beneficial effect.[27-30]

Meta-analyses to determine the effect of vitamin D supplementation on bronchial asthma have demonstrated improvement in exacerbation, but no effect on the severity of asthma.[31] A subsequent meta-analysis on 435 children (seven trials) and 658 adults (two trials) concluded that people receiving vitamin D supplementation had a reduction in asthma exacerbations requiring systemic corticosteroids. It also reduced the risk for exacerbation requiring an emergency department visit or hospitalization, but it had no effect on the measures of severity (percentage of predicted forced expiratory volume in one second or Asthma Control test Scores).[32] Another meta-analysis (2017) showed that asthmatic children had lower 25(OH)D levels as compared to nonasthmatic children, but the correlations between 25(OH)D and asthma incidence, asthma control, and lung functions were varied.[33]

Role of vitamin D in respiratory infections is also under scrutiny. A meta-analysis showed that vitamin D reduced the risk of overall acute respiratory infections in 0–95 years old. This benefit was maximum in people with low 25(OH)D levels (<10 ng/mL) and those receiving daily or weekly vitamin D supplementation as compared to bolus doses. In children aged 1–5 years, these effects were not so robust.[34,35] Cochrane systematic review on vitamin D supplementation (2016) for preventing infections in children under five years of age concluded that evidence from one large trial did not demonstrate benefit of vitamin D supplementation on the incidence of pneumonia or diarrhea in children under five years.[36] We conducted a randomized control trial (RCT) for evaluating the efficacy of single oral mega-dose of vitamin D3 for treatment and prevention of pneumonia in under-five children. There was no significant difference in the risk of recurrence of pneumonia over next 6 months in both the groups. Median (95% CI) time for resolution of severe pneumonia was 30 hours in the vitamin D group, as compared to 31 hours in the placebo group

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(p = 0.005). Serum immunoglobulin A (IgA), cathelicidin, and immunoglobulin G (IgG) concentrations were also comparable. We did not find any significant difference in the duration for complete recovery, hospital stay duration, and fever clearance time.[37]

Vitamin D supplementation exerts a protective effect against IBD. VDR genes (TaqI and ApaI) polymorphism affects the development of IBD. One recent meta-analysis found that patients of Crohn's disease and ulcerative colitis had lower levels of vitamin D than controls. They also reported an increased severity of Crohn's disease in those with vitamin D deficiency.[38] Another randomized controlled trial on vitamin D supplementation (400 vs 2,000 IU) in children and adolescents with IBD showed that a higher dose of vitamin D results in lower levels of proinflammatory markers.[39] More robust studies in children are required to determine the efficacy of vitamin D in reducing the severity of IBD.

A recent meta-analysis suggests that vitamin D levels in children with overt and latent tuberculosis (TB) infection are significantly lower than in controls. TB may contribute to vitamin D deficiency in children. Therefore, vitamin D deficiency may be associated with TB in children.[40]

In a cross sectional follow-up study on LBW term infants, 912 children aged 5 years who had participated in an earlier trial of vitamin D for term LBW infants in the first 6 months of life were assessed for gross motor development, using the Ages and Stages Questionnaire (ASQ), gross motor scale, and several measures of motor performance. Interestingly, children with poorer vitamin D status were able to perform more stands and squats. Greater handgrip strength was associated with lower tibia ultrasound Z score. The current height age Z score and arm muscle area showed the strongest associations with gross motor outcomes.[41] Authors concluded that this needs further research.

DIAGNOSIS

Diagnosis of nutritional rickets is based on the clinical features, biochemical findings, and characteristic radiological features. Since vitamin D and calcium deficiencies often coexist, performing only biochemical testing is not a good tool to diagnose and differentiate the primary cause of nutritional rickets as vitamin D and/or dietary calcium deficiency. The most readily available biochemical laboratory tests for nutritional rickets are serum calcium, phosphorus, and alkaline phosphatase (ALP). Serum calcium is usually normal but in severe cases it may be low. Serum phosphorus is usually low and a level <4 mg/dL is more specific than serum calcium values in making a diagnosis of rickets. ALP is generally raised (>500 IU/L in neonates and >1,000 IU/L in children up to 9 years).

The classical laboratory findings in nutritional rickets are decreased serum levels of 25(OH)D, phosphorus, calcium, and low urinary calcium. Alkaline

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Table 2.1.5: Serum vitamin D status according to serum 25(OH)D levels.

Vitamin D Status	*Serum Vitamin D (25 hydroxyvitamin D) levels*	
	nmol/L	*mg/dL*
Sufficient	>50	>20
Insufficient	30–50	12–20
Deficient	<30	<12

Source: Global Consensus Recommendations on Prevention and Management of Nutritional Rickets.[23]

phosphatase, serum PTH, and urinary phosphorus levels are elevated. Normal levels and cut-offs for vitamin D status (as recommended by Global Consensus Recommendations on treating nutritional rickets) are depicted in **Table 2.1.5**.[23] The aim of all these guidelines is to achieve and maintain optimal vitamin D level with minimal risk for toxicity and adverse effects. These cut-off values have been based partly on the studies done in children for assessing relationship of PTH and vitamin D. Evidence suggest that decrease in 25(OH)D levels below 34 nmol/L cause an increase in PTH secretion. A level of 30–34 nmol/L of 25(OH)D may be a critical cut-off, below which there is a high likelihood of developing NR. These recommended cut-off values are aimed to prevent NR in population at large. However, it is noteworthy that NR has been reported in children with 25(OH)D concentrations >30 nmol/L and on the other hand, NR may not develop in people with very low 25(OH)D concentrations. NR is more likely to occur when there is prolonged deficiency over a long duration. Many patients with very low 25(OH)D may not have increased PTH production, and conversely, PTH suppression may not occur even if 25(OH)D levels are >30 ng/mL.[42] Most children with vitamin D deficiency or insufficiency according to these cut-offs are asymptomatic and have no evidence of any other marker of poor health or disease. Thus, the clinical relevance of these cut-offs can be ascertained only by global, population-based, and long-term prospective studies and correlating them with functional, rather than biochemical outcomes.

Vitamin D Assay

Commercially available vitamin D assays can measure 25(OH)D2, 25(OH)D3, and total 25(OH)D. Total 25(OH)D is recommended to evaluate vitamin D status, if both 25(OH)D2 and 25(OH)D3 are biologically equivalent. The accuracy of various tests varies widely between different tests and different laboratories. Various laboratory methods include enzyme-linked immunosorbent assays (ELISA), radioimmunoassay, chemiluminescent assays, high performance liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry. Currently standard reference measurement procedure by

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National Institute of Standards and Technology (NIST) and Ghent University is established for minimizing the inter-laboratory variations that recommend liquid chromatography tandem mass spectrometry method.

Radiological Changes

Apart from the biochemical and hormonal investigations, radiological findings readily help in confirming the diagnosis of rickets. The classical X-ray changes occur at open growth plate. The distal end of ulna is involved first, as the distal ulnar growth plate grows more rapidly than the distal radius. Thus, changes in ulna are a more sensitive indicator at wrist joint. Widening of the growth plate due to increase in the cartilaginous cell mass is the earliest finding. Disorganized spongy bone growth leads to irregular, indistinct metaphyseal margins (fraying). Later the protrusion of bulky mass of the cartilaginous cells in the poorly mineralized metaphysis leads to widening and cupping of metaphysis. The poor mineralization coupled with loss of mineral content manifests as rarefaction of the shaft bones and thinned cortex. As the child starts walking, radiological changes become appreciable in knee and ankle joints also. Some patients may develop greenstick fractures.

■ TREATMENT OF NUTRITIONAL RICKETS

Various regimens have been used for the treatment of vitamin D deficient rickets. Traditionally, Stoss therapy has been the standard mode of treating rickets, wherein mega doses of vitamin D (100,000–600,000 IU) are administered over 1–5 days or 60,000 IU weekly for 6–8 weeks. Stoss therapy is preferred for ensuring good compliance. A study in 56 Turkish children aged 3–36 months with NR, compared three single dose oral regimes (150,000 IU vs 300,000 IU vs 600,000 IU) and found them to be comparable.[43]

We compared a single mega-dose of 300,000 IU vs 600,000 IU and found them to be equally effective. The study also observed hypercalcemia in five children (2 in 300,000 and 3 in 600,000 group).[44] Mondal et al. found no difference in 25(OH)D, bone profile, and side effects in the two groups when single intramuscular (IM) dose of 600,000 IU vitamin D3 was compared to a weekly oral dose of 60,000 IU D3 for 10 weeks.[45]

Appropriate Route of Administration and Duration of Therapy

Rickets used to be treated with mega doses of intramuscular injection of vitamin D. For past two decades, treatment with oral doses has been in use. Currently, oral treatment is recommended over parenteral route, as it restores 25(OH)D levels much more rapidly than IM treatment.[23] Both vitamin D2 and D3 are equally effective for daily treatment. In single large dose therapy, D3 is preferable to D2 because the D3 has a longer half-life.

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