



Review Article

Update on perinatal and pediatric vitamin D

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ABSTRACT

Context: Vitamin D has emerged as a topic of great interest among researchers. Recent evidence indicates that today the world is facing vitamin D deficiency pandemic. Sensitizing pediatricians to widespread vitamin D deficiency in children and benefits accrued from its correction would go a long way as far as clinical practice and public health is concerned.

Evidence Acquisition: We performed a literature search using PubMed/medline, EMBASE and Science Direct databases indexed under the Medical Subject Heading (MeSH) terms; “Vitamin D OR Vitamin D deficiency” combined with the terms “children” OR “pediatric” OR “child health”. The literature search was limited to articles in last 35 years and written in the English language. All articles having direct relevance to the present review were searched. Reference lists of all articles were also reviewed. Emphasis was placed on pediatric literature, although sentinel adult studies relevant to this article have been included. Latest editions of standard texts were also searched.

Results: Vitamin D deficiency is highly prevalent throughout the world including India. Though some evidence suggests a role of hypovitaminosis D in pathophysiology of many clinical situations other than rickets and osteomalacia like autoimmune diseases, cardiovascular diseases, infections, cancers, fetal health, and exercise performance, some authorities feel there is a lack of unequivocal evidence in favour of nonskeletal health benefits of vitamin D.

Conclusions: Widespread subclinical and pre-rachitic vitamin D deficiency in children should be diagnosed by serum 25(OH)D levels and these levels should be maintained above 20 ng/mL to obtain optimal health benefits. There is a need for large randomized clinical trials to investigate the nonskeletal benefits of vitamin D deficiency.

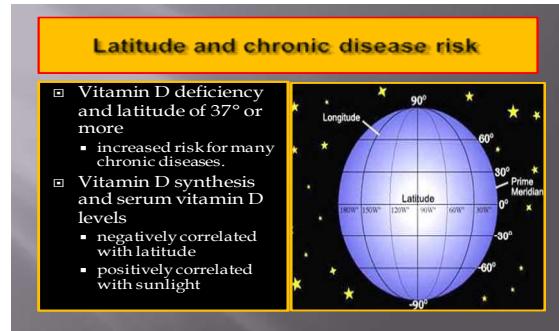
Key words: Vitamin D, Deficiency, Child health, Hypovitaminosis D, Rickets

Till few decades ago, vitamin D was thought of only in relation to bone health and calcium homeostasis. Now, medical and nonmedical fraternities across the world are getting increasingly curious and realizing the potential role vitamin D plays in health and disease. There had been a rise in the rate of publication of peer reviewed articles on vitamin D in PubMed from about 100 articles per year in 1975 to >1400 in 2007¹. Time magazine has reported vitamin D as one of the top 10 medical breakthroughs of 2007².

New York Times has claimed vitamin D as a potential new miracle drug³. It stands at the frontline of current scientific endeavors, being a topic of greatest interest to medical researchers all over the globe. A growing body of evidence, implicating hypovitaminosis D as a risk factor for many diseases right from conception throughout lifespan, implies that awareness and management of widespread vitamin D deficiency may fetch profound future health benefits.

Vitamin D is not a true vitamin, because individuals with adequate exposure to sunlight do not require any dietary supplements. It is a steroid hormone acting on specific cell receptor to regulate various tissue processes. Vitamin D₂ (ergocalciferol), obtained from influence of ultraviolet B radiations (UVR) on plants and yeast and vitamin D₃ (cholecalciferol), produced in skin by UVR (UV-B and not UV-A) are the two main forms of vitamin D. Both forms are metabolised similarly in the body, first by hepatic 25 hydroxylation into inactive but stable 25(OH)D (Calcidiol) and then by renal 1 hydroxylation into active but unstable 1,25(OH)₂D (Calcitriol). Calcitriol exerts its effects by binding to vitamin D receptor (VDR), which belongs to the family of nuclear hormone receptors. In vitamin D sufficient state, net intestinal calcium absorption is between 30-80%, which goes down to 10-15% in vitamin D deficient state⁴. Resultant Hypocalcemia stimulates parathyroid hormone (PTH) secretion leading to increased calcium reabsorption and phosphorus loss in renal tubules and increased synthesis of 1,25(OH)₂-D. Decreased calcium phosphorus product leads to reduced bone mineralisation causing rickets in growing bones and osteomalacia in mature bones. Vitamin D is measured in various units; 400 IU equals 10 µg or 26 nmol. Recent data indicates that vitamin D deficiency is pandemic, even the healthy and the young are not spared. High prevalence rates are reported in otherwise healthy infants, children and adolescents⁵⁻⁸, and also from diverse countries around the world including India^{9,10}.

DEFICIENCY OF 'SUNSHINE VITAMIN' IN SUNNY COUNTRIES



Adapted from Vitamin D and Health by, Heli J. Roy, PhD,
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Major source of vitamin D for our body is cutaneous synthesis through the effect of UVR on 7-dehydrocholesterol because dietary source through fatty fishes, organ meat, egg yolk, cod liver oil and milk products does not contribute significantly as these are not consumed in sufficient quantities by children. Thus fortifying foods with vitamin D remains the only alternative in case cutaneous synthesis is inadequate. It is surprising and disturbing to note that hypovitaminosis D is highly prevalent even in areas with adequate sunshine¹⁰⁻¹⁵. Sensitizing pediatricians and health policy makers to this fact has important implications on child health, as widely held notion that vitamin D supplementation is not necessary in sun replete areas is preventing policy makers from coming out with definite guidelines regarding vitamin D requirements. There are many factors which can explain this paradox of hypovitaminosis D inspite of abundant sunshine like duration and timing of sun exposure, amount of skin exposed, atmospheric pollution, skin pigmentation, sunscreen use, dietary and genetic factors^{4,11,16}. Modern day life style changes have significantly reduced the total duration of sun exposure in children. UV-B, having shorter wavelength, tend to scatter earlier or later in the day and hence cutaneous vitamin D synthesis is maximum between 10 AM to 3 PM, the time when most of the children are either in school or indoors. Exposure of only face, hands and arms due to clothing versus whole body is associated with marked differences in vitamin D synthesis¹⁷. Cloud cover, increasing water vapour and industrial pollution can reduce the amount of UV-B that reaches the earth's surface¹⁸. Epidermal melanin (a natural sunscreen) on one hand reduces the risk of skin cancer induced by UVR but on the other hand, reduces cutaneous vitamin D synthesis. An asian Indian would require 3 times the sun exposure than light-skinned person to produce equivalent amount of vitamin D¹⁷. It is interesting to note that women of all population have lighter skin than men, presumably because of increased vitamin D needs during pregnancy and lactation¹⁹. Sunscreens block UV-B more than UV-A and

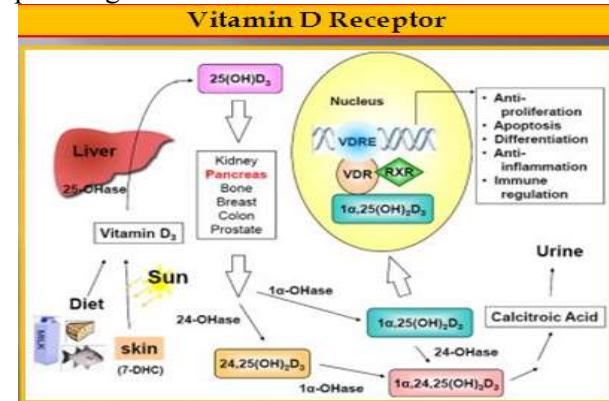
sunscreens with sun protection factor (SPF) of 8 and 15 will decrease vitamin D synthetic capacity by 95% and 98%, respectively²⁰. Dietary factors like very low calcium intake and high fibre diet may deplete vitamin D stores²¹. Genetic factors like increased 25(OH)D-24-hydroxylase (leading to degradation of vitamin D) activity in South Asians²¹ are also among the various explanations of hypovitaminosis D in sunny countries. Given the facts that vitamin D crosses the placenta and poor vitamin D content of breast milk even in vitamin D replete mothers, maternal vitamin D deficiency and exclusive breastfeeding without vitamin D supplements or adequate sunlight exposure are important risk factors for vitamin D deficiency in infants.

CALCIOTROPIC TO PLEIOTROPIC ROLE

Calciotrophic effects of vitamin D on intestine, bone and kidney are known to medical science since ages. Recent and mounting evidence suggests that this secosteroid hormone plays pleiotropic role influencing numerous bodily processes in addition to calcium metabolism. Vitamin D pleiotropism concept has its origin in two discoveries^{22, 23}. The first is discovery of VDRs in non-osseous tissues. To date VDRs are found in more than 30 tissues including heart, intestine, liver, kidney, lungs, brain, muscle, skin, pancreas and various immune cells. The second is the discovery of enzyme CYP27B1 (capable of converting 25(OH)D into 1,25(OH)2D) in various tissues throughout the body. These findings suggest local autocrine

and paracrine role for vitamin D in addition to its role as an endocrine hormone²⁴. The nonskeletal autocrine effects of vitamin D are essentially different from its skeletal effects in that the former operate outside the tight feedback-controlled endocrine loop (independent of regulation by serum calcium, phosphorus and PTH levels)^{23,25} and are more substrate dependent²⁶. This observation gave birth to the concept of maintaining an adequate blood level of vitamin D for

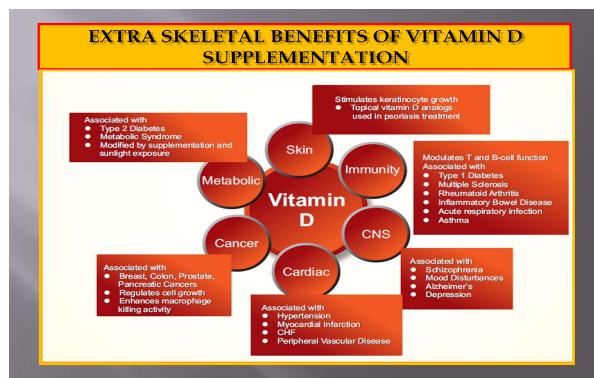
regulating its various nonosseous functions. This autocrine pathway of vitamin D, responsible for its nonskeletal effects, has three key features²²: (a) The bulk of the daily metabolic utilization of vitamin D is by way of the peripheral autocrine pathway; (b) autocrine action always results in expression of the 24-hydroxylase leading to degradation of locally synthesized calcitriol after its action is over, so that no calcitriol which is locally produced enters the circulation; and (c) local concentration of calcitriol required to support various tissue responses are higher than typical serum concentrations of calcitriol. When bound to the vitamin D receptor, calcitriol seems to be just the right key to open up the locked stores of DNA information, allowing cells to produce proteins needed for tissue specific responses²². As amount of calcitriol produced locally is substrate dependent, optimal serum level of 25(OH)D is crucial in maintaining ability of the cell to respond to pathological stimuli.



BEYOND BONES AND CALCIUM

Apart from its conventionally understood actions on bone health and calcium homeostasis, vitamin D is believed to have effect on body's endocrine system, immune system, cardiovascular system, neuropsychological functioning, neuromuscular performance and is also believed to act as a potent antioxidant protecting against free radical damage, as well as being an inducer of cellular differentiation, protecting against carcinogenesis^{20,24}. The term "vitamin D deficiency" does not

necessarily connote clinically explicit disease, rather it means an increase in risk for certain diseases and that also explains the seeming paradox that individuals who are ostensibly healthy today may nevertheless be “deficient”²². As these diseases are multifactorial, vitamin D deficiency, rather than being directly causal, acts by hampering the ability of tissues to deal adequately with physiological and pathological stimuli and though these diseases will continue to occur in presence of optimum vitamin D status, their risk will be lowered²². Though some studies suggest the potential role of vitamin D in immunological diseases (Type I diabetes, asthma, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases) through reduced activation of acquired immune system²⁷⁻³², various cancers through antiproliferative and prodifferentiating actions^{26,33,34}, infectious diseases through enhancement of the innate immune system and production of antimicrobial peptide cathelicidin or LL-37^{23,35-40}, fetal health^{16,41} and cardiovascular diseases, type II diabetes, obesity and hypertension^{24,42}; large, randomized, controlled trials are needed to establish nonskeletal role of vitamin D unequivocally.



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 iceberg²⁵. 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 deficiency⁴³ 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. 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(4), (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.

CHANGING DEFINITIONS OF VITAMIN D STATUS

Based on the study of biomarkers like PTH and intestinal calcium absorption and functional health outcomes, there has been a dramatic change in the definition of vitamin D deficiency over last few years. Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) in 1997 defined vitamin D deficiency in infants and children as a serum 25(OH)D level below 11 ng/mL^{44,45} but level below 20 ng/mL are now considered insufficient⁴. Table-1 shows the classification of vitamin D status based on serum 25(OH)D level⁴. IOM recently published a review⁴⁶ on dietary reference intakes for calcium and vitamin D. This review expressed that, as studies regarding nonskeletal health benefits provided mixed and inconclusive results, as yet there is insufficient evidence to recommend higher levels of serum 25(OH)D. It feels that benefits for most in the population is associated with levels of approximately 20 ng/mL and use of higher cutoffs would artificially increase the estimates of prevalence of vitamin D deficiency. This review has taken skeletal health as the basis for Dietary Reference Intakes (DRI). There is an urgent need to follow these current definitions of vitamin D status, as pediatricians (and obstetricians) are blamed for being a little

slow to address the suboptimal vitamin D status of their patients⁴⁷.

Table 1: Vitamin D Status in Relation to 25(OH) Level

Vitamin D status Serum	25(OH)D level (ng/mL)
Severe deficiency	≤5
Deficiency	≤15
Insufficiency	15-20
Sufficiency	20-100
Excess	>100
Intoxication	>150

Adapted from Misra, et al.[4]

and 600 IU/day respectively, while tolerable upper level of intake are 1000 IU/day for infants <6 months old, 1500 IU/day for 6-12 months old, 2500 IU/day for 1-3 years old, 3000 IU/day for 4-8 years old and 4000 IU/day for 9 years and above including pregnant and lactating mothers. The RDA estimates here have been made considering the minimal skin synthesis of vitamin D.

THERAPEUTICS OF VITAMIN D DEFICIENCY

Either D2 or D3 can be used for the treatment of hypovitaminosis D but D2 is not available in India. 1 mcg of either provides 40 IU,

Table 2: Vitamin D doses based on serum 25(OH)D levels

Serum 25(OH)D (ng/mL)	Low dose Vitamin D therapy (IU/day)	High dose Vitamin D therapy (IU)	Total duration of therapy (months)
< 5	8000	50,000/week × 4 weeks 50,000/fortnight × 8 weeks	3
5-15	4000	50,000/fortnight	3
16-30	2000	50,000/month	3

Adapted from Holick [50].

REVISED GUIDELINES FOR VITAMIN D RDA

There appears to be a discrepancy between vitamin D RDA (Recommended Dietary Allowance) based on recent research and current practice⁴⁸. In 2003, the AAP Committee on Nutrition and section on Breastfeeding advocated 200 IU per day of vitamin D intake for children of all ages^{49,50} but this amount was deemed to prevent the worst outcome of vitamin D deficiency i.e. rickets. But now the recommendation is 400 IU per day for all infants, children and adolescents^{4,49} till they are not getting this amount from alternative sources. It is likely that higher doses may be needed for dark skinned and preterm infants⁴. Supplementation trials in infants and children have shown that 400-1000 IU per day are needed to achieve serum level of 30 ng/mL⁵⁰. For children and adolescents (1 to 18 years of age), IOM⁴⁶ has specified estimated average requirements (EARs) and RDAs on the basis of serum 25(OH)D levels of 16 and 20 ng/mL, respectively. EAR and RDA for vitamin D, as per IOM review, are 400 IU/day

although D3 raises serum 25(OH)D levels upto three-fold higher than D2⁵¹. It is important to note that 1-alpha calcidiol should not be used for the treatment of vitamin D deficiency⁴⁷. Vitamin D given in daily doses of 1000-10,000 IU (depending on the age of the child) for a period of 3 months will normalise serum 25(OH)D and replenish stores⁴. Doses recommended are 1000 IU/day for neonates, 1000- 5000 IU/day for infants (1-12 months old) and >5000 IU/day for children >1 year old^{4,52}. If noncompliance is an issue, administration of high doses 1,00,000-6,00,000 IU over 1-5 days is an alternative for >1 month old⁵³. In teenagers and adults, 50,000 IU orally once a week for 8 weeks has been successfully used²⁵. Vitamin D doses, based on serum 25(OH)D levels, are used in case of children with kidney diseases or other chronic diseases as shown in Table 2⁵¹. It is estimated that each 100 IU of additional daily oral vitamin D intake produces an elevation of serum 25(OH)D of approximately 1 ng/mL and hence a patient having 10 ng/mL would need approximately 2000 IU/day to bring serum level of 25(OH)D up to 30 ng/mL⁵⁴, though it should be remembered that

individual response to standard doses varies widely. Toxicity due to excess vitamin D is rare, but has been reported, generally with doses exceeding 10,000 IU/day or single doses greater than 300,000 IU or with serum 25(OH)D levels of more than 100-150 ng/mL⁹. There is enough margin of safety between doses levels and those associated with toxicity. Calcium supplementation is necessary with vitamin D therapy to prevent hypocalcemia of 'hungry bone syndrome' associated with remineralisation of bone matrix. Calcium is used in the dose of 30-75 mg/kg/day of elemental calcium. Elemental calcium content of various calcium preparations are 9 mg/mL of calcium gluconate, 27 mg/mL of calcium chloride, 40% of calcium carbonate, 6% of calcium gluconate and 39% of tribasic calcium phosphate. After correction of deficiency, maintenance dose of 400-1000 IU/day of vitamin D or high dose every 3 months is needed. Vitamin D supplementation (at least 400 IU and perhaps as high as 800-1000 IU/day) is appropriate throughout life if sunlight exposure is limited⁵⁵. Calcium supplements are not necessary after serum 25(OH)D levels are normalized.

CONCLUSION

The world is currently facing an unrecognized and untreated pandemic of vitamin D deficiency. Sensitising pediatricians to recognise and treat this pandemic would have great impact on child health in the 21st century. Vitamin D deficiency is common even in countries with abundant sunshine. As a part of its autocrine function, vitamin D has multiple non-skeletal effects and these depend solely on its optimal circulating levels. Though observational studies suggest that correction of vitamin D deficiency lowers the risk of many long latency diseases like cancers, autoimmune diseases and cardiovascular diseases, and it also decreases the risk of infectious diseases and improves fetal health, muscle function and exercise performance; we need large, randomized, controlled trials before any recommendation for its use is made in these diseases. Measurement of serum 25(OH)D level is the only way to diagnose subclinical, prarachitic

vitamin D deficiency and recent evidence suggests maintaining it above 20 ng/mL for maximizing health benefits. Optimum doses of vitamin D should be used for prevention and treatment of vitamin D deficiency. We suggest ICMR should come out with definite guidelines regarding vitamin D RDA and health policy makers should take serious steps regarding food fortification with vitamin D.

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