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Review Article

Vitamin D: role of vitamin D in human health beyond skeleton

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ABSTRACT

Deficiency of vitamin D is now considered as epidemic in Indian subcontinent, with a prevalence of 70-94% in the general population. Like in US, Indian dairy products are rarely fortified with vitamin D. Socioreligious and cultural practices followed in India do not facilitate adequate sun exposure, thereby negating potential benefits of plentiful sunshine resulting in vitamin D deficiency. Deficiency is highly prevalent in both urban and rural settings. Vitamin D deficiency can lead to rickets, osteoporosis, cardiovascular diseases, diabetes, cancer and infections. In present review authors have revisited the details pertaining to vitamin D to increase the awareness on Vitamin D efficiency.

Keywords: Extra-skeletal benefits, Hypovitaminosis D, Measurement, Secosteroid, Vitamin D deficiency

INTRODUCTION

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. It plays a pivotal role in calcium homeostasis and skeletal metabolism throughout life.

Vitamin D appears to have an effect on numerous disease states and disorders, including diabetes (types 1 and 2), multiple sclerosis, cardiovascular disease, osteoporosis, and tuberculosis.

As per numerous studies and research, there is currently a worldwide vitamin D deficiency in various populations, including infants, pregnant and lactating women, the elderly, individuals living in latitudes far from the equator, persons who avoid the sun or ultraviolet radiation in the blue spectrum (UVB) and populations with dark skin pigmentation. Classical vitamin D deficiency causes rickets in children and osteomalacia in children and adults. Vitamin D is also important for the functioning of many other systems, such as the immune and cardiovascular systems.

Increasing evidence strongly supports the benefits of vitamin D supplementation and also reveals that present recommendations are inadequate. This review covers all the aspects related to the deficiency status of vitamin D in India, vitamin D biochemistry and patho-physiology and use as pharmacotherapy in different hypovitaminosis D related disease conditions.

REVIEW OF LITERATURE

Hypovitaminosis D status in Indian population

It has been estimated that 1 billion people worldwide have Vitamin D deficiency or insufficiency. There is widespread prevalence of 50-90% of Vitamin D deficiency with low dietary calcium intake in Indian population according to various studies published earlier. Apart from low dietary intake, people suffering from hepatic, renal, dermatological disorders, alcoholics and

inflammatory rheumatological conditions also have Vitamin D deficiency.[1]

Indian subcontinent is situated between latitude 37.6°N and 8.4°N with plentiful sunlight throughout the year. Despite this fact, several studies from India have documented widespread prevalence of hypovitaminosis D across the length and breadth of the country in all age groups. Studies in South India have shown that rural agricultural laborers' who have their torso exposed to sunlight for more than 5-6 hours during their agricultural profession have also hypovitaminosis D of varying degree.[1] (Table 1) shows the average level of vitamin D (ng/ml) among different study populations.

Table 1: Vitamin d health summary of various age groups and patient profile surveys in different cities of India.[2-5]

City	Study Population (number of subjects)	Vit. D levels
Delh[2,3]	School Girls (211)	6-16ng/ml
	School Boys (187)	10-25ng/ml
Tirupati[4]	Urban Male (134)	18ng/ml
	Urban Female (807)	15ng/ml
	Rural Male (109)	23ng/ml
	Rural Female (96)	19ng/ml
Lucknow[5]	Pregnant Women (Summer) (139)	14-28ng/ml
	Pregnant Women (Winter) (139)	4-18ng/ml

Vitamin D deficiency rickets and osteomalacia are widely prevalent in our country. On an average 25-30 cases of clinically overt patients with Vitamin D deficiency related osteomalacia in adolescent and adult age group are managed in indoor endocrine services every year. Most of them have undetectable serum 25(OH)D levels with serum parathyroid hormone values more than four folds above upper limit of normal. In such a scenario, anticonvulsant and anti-tuberculous therapy, fluoride excess, prolonged steroid therapy and bisphosphonates easily precipitate clinically overt rickets and osteomalacia in our population.[6]

CV Harinarayan et al, have studied 25(OH) D and BMD in women of reproductive age group and post-menopausal women in South India.[4] They have reported Vitamin D deficiency in 76% in women of reproductive age, 70% in post-menopausal women, insufficiency in 16.5% in women of reproductive age and 23% in post-menopausal women. Marwaha et al have reported Vitamin D deficiency in healthy Indians above 50 years from North India.[3]

Among the orthopaedic services, the highest rates of low serum vitamin-D levels were seen in the trauma and sports services, in which the rates of abnormal (insufficient and deficient) vitamin D levels were 66% and 52%, respectively.

Vitamin D

Although Vitamin D is commonly called a vitamin, it is not in the sense an essential dietary vitamin as it can be synthesized in adequate amounts by all mammals from sunlight. Vitamin D fits within the definition of vitamin as it is "an organic compound required as a vital nutrient in tiny amounts by an organism."

Vitamin D designates a group of calcitriols, fat soluble hormones of secosteroid nature (Figure 1). The term "Vitamin D" refers to several different forms of this vitamin. Two forms are important in humans: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3).

Vitamin D2 is synthesized by plants. Vitamin D3 is synthesized by humans in the skin when it is exposed to ultraviolet B (UVB) rays from sunlight. Foods may be fortified with vitamin D2 or D3. Vitamin D2 and D3 (D represents D2 and D3) are fat soluble vitamins incorporated into chylomicrons and absorbed into the lymphatics.

Serum 25 OH D levels are reliable indicator of Vitamin D status of an individual.

Vitamin D is a fat-soluble nutrient absorbed primarily in the duodenum. Individuals with malabsorption disorders of the small intestine, such as those with celiac disease, cystic fibrosis and Crohn's disease or people who have undergone gastric bypass surgery may be at increased risk for Vitamin D deficiency. Obesity is also a risk factor for deficiency due to the inability of fat tissue to sequester Vitamin D.

Vitamin D needs increase during pregnancy and lactation. Limited Vitamin D passes through the breast milk. As a result, many pregnant women and their offspring are Vitamin D deficient. The liver and kidneys play direct and indirect-roles in Vitamin D physiology;

therefore, diseases of either organ can adversely affect Vitamin D status.

The optimal level of 25OH D to maintain skeletal health and maximal dietary absorption of calcium in the gut is accepted to be 30 ng/ml.

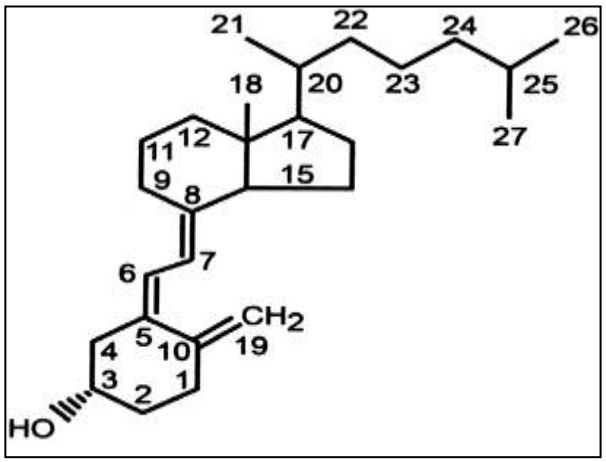

Figure 1: Structure of vitamin D.

Biosynthesis of vitamin D (figure 2)

Chemical structure of Vitamin D is almost identical to cholesterol, except Vitamin D has double bonds between C-7 and C-8, and C-10 and C-19, and an open B ring structure (Figure 1). The two forms of Vitamin D utilized in the human body, D2 and D3, begin with four intact rings. UVB, when at an adequate strength (18 mc/cm2) and particular wavelength (290-315 nm), can alter the cholesterol-based precursor 7-dehydrocholesterol in human skin by breaking the bond between C-9 and C-10 of the B ring. Consequently, a double bond is formed between C-10 and C-19, making pre-vitamin D3. With naturally occurring thermogenic isomerization, a more open configured molecule is formed, termed D3 (cholecalciferol). In a similar manner, lanolin is irradiated to form supplemental D3, while ergosterol from plant sterols or yeast can be irradiated to form supplemental D2 (ergocalciferol). Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation.[7]

The complex Vitamin D system includes regulation of Vitamin D serum concentrations, transcellular transport and intracellular metabolism, in addition to its target action. Vitamin D is taken up from food or synthesized in the skin [sun light with the photon energy wavelength of 290-315 nm causes photolysis of 7-dehydrocholesterol (7-DHC; provitamin D3) to pre-vitamin D3, the immediate precursor in the biosynthetic pathway to Vitamin D].[7]

In the circulation, all Vitamin D metabolites are bound to Vitamin D-binding protein (DBP). To become active, vitamin D3 is hydroxylated first in the liver (25-hydroxylases) and successively in the kidney (1a-hydroxylase) to its final form, 1α,25(OH)2D3. Macrophages and other cells are also capable of hydroxylating Vitamin D to 1α,25(OH)2D3, thereby facilitating locally regulated tissue concentrations.[8]

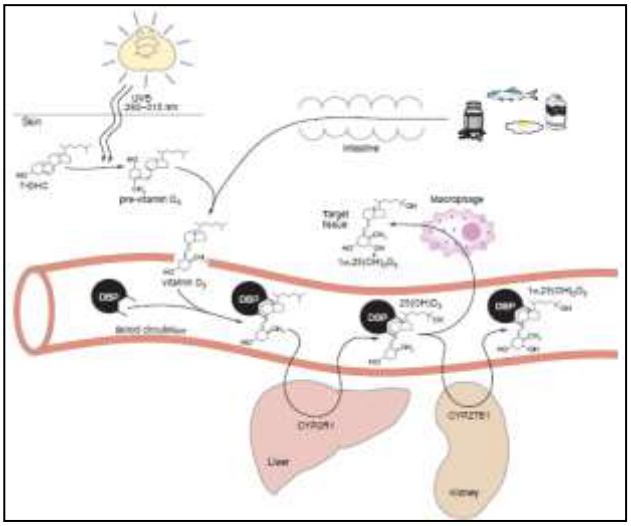

Figure 2: Biosynthesis of vitamin D.

Dietary calcium (Ca++) regulates the enzyme 1α-hydroxylase directly through changes in serum calcium and indirectly by altering parathyroid hormone (PTH) levels. Dietary PO4 restriction also has been shown to stimulate renal 1α-hydroxylase activity as well as its messenger (mRNA). This action of PO4 is independent of PTH. In organs and tissues other than kidney where 1α-hydroxylase activity related 1α,25 (OH)2D3 production is shown to occur, 1α,25(OH)2D3 synthesis and degradation are under control of local factors like cytokines and growth factors.[9]

Pharmacokinetics of vitamin D

Vitamin D is a lipophilic molecule, so it requires a protein carrier for solubility in plasma. Its mono-, di-, and tri-hydroxylated metabolites culminate in the water-soluble biliary form calcitroic acid.[10]

When absorbed from the gut, Vitamin D enters the circulation on chylomicrons first, and it is only slowly transferred to DBP. This chylomicron bound form of dietary Vitamin D is taken up by peripheral tissues, such as adipose tissue and muscle, due to the action of lipoprotein lipase. The liver takes up the Vitamin D left in the chylomicron remnant and quickly removes it from the bloodstream.

Physiologically relevant doses of Vitamin D show short plasma half-life of 4-6 h, whereas studies with radiolabeled Vitamin D have shown the whole-body half-life of 2 months.

The liver converts Vitamin D into 25(OH)D by a microsomal cytochrome P450 enzyme, CYP2R1, or the mitochondrial cytochrome P450 CYP27A1. 25(OH)D quickly enters the plasma pool that constitutes the predominant pool of Vitamin D in the body, with a capacity of ~4.5µmol/L. 25(OH)D3 has a strong affinity for DBP at 5 X10-8 mol/L, which is at least an order of magnitude higher than that of its vitamin precursors. As a consequence, 25(OH)D3 has a half-life of 15 d in the circulation.1α25(OH)2D3 has a half-life of 10-20 h.

Sources of vitamin D

Food

Very few foods in nature contain Vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of Vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D3 and its metabolite 25(OH)D3. Some mushrooms provide vitamin D2 in variable amounts. Mushrooms with enhanced levels of vitamin D2 from being exposed to ultraviolet light under controlled conditions are also available.

Sun exposure

Most people meet at least some of their Vitamin D needs through exposure to sunlight. Ultraviolet (UV) B radiation with a wavelength of 290-315 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to pre-vitamin D3, which in turn becomes vitamin D3.

Ultraviolet exposure beyond the minimal erythemal dose does not increase Vitamin D production further. The ultraviolet induced production of Vitamin D precursors is counterbalanced by degradation of Vitamin D and its precursors. The concentration of previtamin D in the skin reaches equilibrium in white skin within 20 min of ultraviolet exposure. Although it can take 3-6 times longer for pigmented skin to reach the equilibrium concentration of dermal previtamin D, skin pigmentation does not affect the amount of Vitamin D that can be obtained through sunshine exposure. However, aging does lower the amount of 7-dehydrocholesterol in the skin and lowers substantially the capacity for Vitamin D production.

Daily intake and levels of vitamin D

Daily intake

Many arguments favoring higher intakes of calcium and other nutrients have been based on evidence about the diets of prehistoric humans. Likewise, the circulating 25-hydroxyvitamin D [25(OH) D; calcidiol] concentrations of early humans were surely far higher than what is now regarded as normal. Humans evolved as naked apes in tropical Africa. The full body surface of this ancestors was exposed to the sun almost daily. In contrast, author modern humans usually cover all except about 5% of this skin surface and it is rare for us to spend time in unshielded sunlight. This evolution has effectively designed us to live in the presence of far more vitamin D than what most of us get now, yet there is no consensus about what vitamin D intakes are optimal or safe. Table 2 depicts the Recommended Dietary Allowances (RDAs) for Vitamin D in different age groups and gender.

The WHO Expert Committees recommended 100 Units (2.5 mcg) /d for adult males in 1988 and increased them later in 2005 to 200 Units (5 mcg)/d. This is obviously due to progressive decrease in the exposure to sunlight and the need to obtain the requirements from dietary and supplement sources.[13]

Table 2: Recommended Dietary Allowances (RDAs) for Vitamin D as per the office of dietary supplements "National Institute of Health."

Recommended Dietary Allowances (RDAs) for Vitamin D				
Age	**Male**	**Female**	**Pregnancy**	**Lactation**
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		
* Adequate Intake		100 IU = 2.5 mcg = 1ng/ml = 2.5 nmol/L		

Dietary sources of vitamin D are inadequate to meet daily requirements. Therefore, the majority of the world's population relies on unimpeded skin exposure to UVB radiation to allow for endogenous production of vitamin D or vitamin D supplementation. Any factor that impedes the endogenous or exogenous absorption,

formation, or transformation of this nutrient may contribute to deficiency.

In India Vitamin D deficiency is a common problem due to several factors

- Changing food fads and food habits contribute to low dietary calcium and Vitamin D intake.[1,2]
- High fiber diet containing phosphates and phytates which can deplete Vitamin D stores and increase calcium requirement.
- Genetic factors like having increased 25(OH)D-24-hydroxylase which degrades 25(OH)D to inactive metabolites
- It has been shown that increment in serum 25(OH)D in response to treatment depends on the heritability of Vitamin D binding protein.
- With modernization, the number of hours spent indoor have increased thereby preventing adequate sun exposure. This is particularly true in the urban Indians.
- Increased pollution can hamper the ultraviolet rays to adequately synthesize Vitamin D in the skin.
- Cultural and traditional habits prevalent in certain religions like "Burqa" and the "pardah" system in Muslims have been well known.
- Repeated and unplanned, unspaced pregnancies in dietary deficient patients can aggravate Vitamin D deficiency in the mother and the fetus.

Vitamin D deficiency is considered to be present when serum 25(OH)D levels are <20 ng/ml; insufficiency between 20-30ng/ml and sufficient when >30 ng/ml (Figure 3).[11]

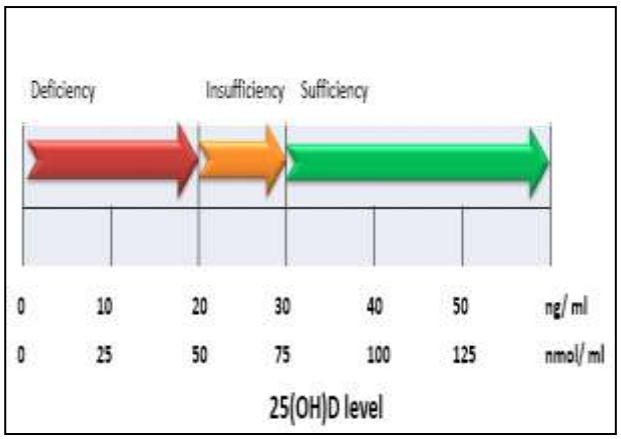

Figure 3: Cut off's for vitamin D deficiency, insufficiency and sufficiency.

Clinical role of vitamin D

Skeletal health

- The treatment of Vitamin D insufficiency can decrease the risk of hip and nonvertebral fractures.[12]
- Oral Vitamin D supplementation reduced the risk of hip fractures by 18% when Vitamin D and calcium taken together.[13]
- The minimum 25(OH)D level at which anti-fracture efficacy was observed was 30 ng/ml (74 nmol/L). Vitamin D offers dose-dependent fracture protection. Doses of more than 400 IU/day were found to reduce fractures by at least 20% in individuals aged 65 years or older, these effects were independent of calcium supplementation.[14,15]
- Vitamin D insufficiency contributes to osteoporosis by decreasing intestinal calcium absorption. Treatment of Vitamin D deficiency has been shown to improve bone mineral density.[16]
- Secondary Hyperparathyroidism consequent to inadequate dietary calcium intake and low 25(OH)D concentrations mobilizes mineral and matrix from the skeleton. This increases the risk of fractures, especially in postmenopausal women and elderly patients.
- TASOAC (The Tasmanian Older Adult Cohort) study clearly demonstrated that there is both cross-sectionally and longitudinally, positive association between sun exposure, serum 25(OH)D levels, and knee tibial cartilage volume in older people, particularly in women and those with radiographic osteoarthritis and knee pain, suggesting that Vitamin D is an important hormonal contributor to cartilage homeostasis. Also, the study confirms a positive association between Vitamin D insufficiency and moderate-to-severe joint space narrowing in older adults.[17]

Diabetes

Vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes, and receptors for its activated form-1alpha, 25-dihydroxyvitamin D3-have been identified in both beta cells and immune cells. Vitamin D deficiency has been shown to impair insulin synthesis and secretion in humans and in animal models of diabetes, suggesting a role in the development of type 2 diabetes. Furthermore, epidemiological studies suggest a link between Vitamin D deficiency in early life and the later onset of type1 diabetes.[18]

Vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and type 2 diabetes mellitus. Vitamin D replenishment improves glycaemia and insulin secretion in patients with type 2 diabetes with established hypovitaminosis D, thereby suggesting a role for Vitamin D in the pathogenesis of type 2 diabetes mellitus.[19]

Vitamin D deficiency leads to the impaired secretion of insulin but not other islet hormones in both animal models and humans, and induces glucose intolerance, while replenishment with Vitamin D rectifies the abnormalities. This impairment is primarily caused by the direct effect of Vitamin D deficiency on the beta cell,

but other effects of Vitamin D deficiency, such as impaired food intake and hypocalcaemia, may also play a role.[19] Another study found that an intake of 2,000 IU of Vitamin D during the first year of life diminished the risk of developing type 1diabetes, and showed that the incidence of childhood diabetes was three times higher in subjects with suspected rickets (Table 3).[19]

Table 3: List of studies in humans for role of Vitamin D in the etiology of type 2 diabetes.[18,19, 20]

Vitamin D administration	Type of subjects (age at study)	Results
Vitamin D 2,000 IU/day (50 mcg) for 1 month*	Vitamin D-deficient women (adult)	Improved glucose tolerance and beta cell function
Vitamin D 2,000 IU/day for 6 months#	Vitamin D-deficient subjects (adult)	Improved insulin secretion
Vitamin D single IM injection 100,000 IU#	Vitamin D-deficient subjects (adult)	Improved insulin and C-peptide responses
Vitamin D 0.5mcg/day for 21 days (or +500 mg Ca2+)#	Uraemic women (adult)	Improved first-phase insulin secretion and sensitivity
Vitamin D 1mcg/day for 4 days#	Type 2 diabetic women (adult)	Improved insulin and C-peptide responses to Sustacal (Mead Johnson, Evansville, IN, USA)
Hypovitaminosis D (<5 ng/ml)*	Type 2 diabetic women (adult)	Decreased 25(OH)D3 levels and beta cell function
Vitamin D 1,332 IU/day for 1 month#	Type 2 diabetic women (adult)	Improved first-phase insulin secretion
Vitamin D single IM injection 300,000 IU*	Type 2 diabetic men and women (adult)	Increased insulin resistance
Vitamin D supplementation for the first year of life#	Infancy (<5 years)	Reduced risk of childhood-onset Type 1 diabetes
	Childhood (5–9 years)	Reduced risk of childhood-onset Type 1 diabetes
	Childhood (10-14 years)	Reduced risk of childhood-onset Type 1 diabetes
Vitamin D (cod-liver oil) 10 mcg for >5×/week for first year of life#	Childhood (<15 years)	Reduced risk of childhood-onset Type 1 diabetes
Vitamin D > 2,000 IU/day during the first year of life#	Infancy till early adulthood (1-31 years)	Reduced risk of childhood-onset Type 1 diabetes
Rickets during the first year of life#	Infancy till early adulthood (1-31 years)	Increased risk of childhood-onset Type 1 diabetes
Vitamin D via food continuous variable IU during pregnancy#	Infancy (<5 years)	Reduced risk of insulin auto-antibodies in offspring

*Observational study, # Case control study

The inhibition of beta cell function (insulin synthesis and insulin secretion) induced by IL-1β or IFN-γ in vitro is prevented by Vitamin D. In addition to the alteration of the effects of cytokines on beta cell function, Vitamin D blocks the induction of surface markers by these cytokines.[21]

Cardiovascular disease

Geographic latitude, altitude, season, and the place of residence (urban or rural) are associated with CVD mortality, which is derived as per the epidemiological data. Interestingly, all these factors also have an influence on human UVB exposure and thus on Vitamin D status. Several mechanisms might be responsible for a protective role of Vitamin D in CVD. These mechanisms include the inhibition of vascular smooth muscle proliferation, the suppression of vascular calcification, the down regulation of pro-inflammatory cytokines, the up-regulation of anti-inflammatory cytokines, and the action of Vitamin D as a negative endocrine regulator of the renin-angiotensin system.[22]

Ten observational studies and nine randomized control trials concerned with the association between Vitamin D and blood pressure were identified and analyzed. Of these, eight observational studies and three randomized control trials supported an inverse association between Vitamin D and blood pressure. Current observational studies strongly support an inverse association between Vitamin D and blood pressure.[23] The antihypertensive effects of Vitamin D include suppression of renin and

parathyroid hormone levels and renoprotective, anti-inflammatory and vasculoprotective properties. Low 25-hydroxyvitamin D levels, which are used to classify the Vitamin D status, are an independent risk factor for incident arterial hypertension.[24]

Concentrations of 25(OH)D>80 nmol/L decreased the age-related increase in SBP by 20% compared with participants having 25(OH)D concentrations <50 nmol/L (P<0.001).[25]

Infection and immunity

Vitamin D enhances bactericidal activity of human macrophages against Mycobacterium tuberculosis, the causative agent of TB. stimulation of macrophage-bound Toll-like receptor 2/1 complex by M tuberculosis-derived antigens upregulates the expression of both VDR and CYP27b1, an enzyme that converts 25-hydroxyvitamin D to its active 1,25-dihydroxyvitamin D form. Intracellular 1,25-(OH)2D generated though action of CYP27b1 then interacts with the VDR and leads to induction of the antimicrobial peptide cathelicidin and killing of intracellular M tuberculosis. In the state of vitamin D deficiency, the infected macrophage is unable to produce sufficient 1,25-(OH)2D to upregulate production of cathelicidin. Although this antimicrobial mechanism of Vitamin D has been demonstrated only in macrophages infected with M tuberculosis, it is also well known that cathelicidin has broadspectrum activity against a wide variety of other pathogens, including gram-negative and grampositive bacteria, viruses, and fungi. Vitamin D is also known to regulate the expression of β-defensin, another antimicrobial peptide with multiple effector functions within the immune system.

Vitamin D modulates cytokine profiles in animal models of autoimmune disease through limiting excessive production of proinflammatory cytokines, such as tumor necrosis factor α and interleukin-12, and thus leading to suppression of inflammation.

In addition, it also has a major role in the immune defense of the respiratory system through direct inactivation of viral pathogens and increased recruitment of phagocytes. [26]

Vitamin D metabolism leads to activation of macrophages and restricts the intracellular growth of M tuberculosis. This effect may be influenced by polymorphisms at three sites in the Vitamin D receptor (VDR) gene.

In a trial conducted in Indonesia that used a Vitamin D in cumulative dose of 10,000 IU daily documented 100% sputum conversion in the Vitamin D group against 77% in the placebo group 6 weeks after initiation of anti-tuberculous therapy.[27]

Pregnancy

High prevalence of physiologically significant hypovitaminosis D among pregnant women and their newborns is observed. In a population that already has a high prevalence of Vitamin D deficiency and poor dietary calcium intake, the problem is likely to worsen during pregnancy because of the active transplacental transport of calcium to the developing fetus.

Hypovitaminosis D during pregnancy has important consequences for the newborn, including fetal hypovitaminosis D, neonatal rickets and tetany, and infantile rickets.

Table 4: Comparison of 25-hydroxyvitamin D3 levels before and after oral cholecalciferol in patients receiving cumulative dose of 100 000, 150 000, or 200 000 IU.

	1,00,000 IU		1,50,000 IU		2,00,000 IU	
	Before	**After**	**Before**	**After**	**Before**	**After**
25-hydroxyvitamin D3 (nmol/l)	19.0±7.4	48.3±13.0	20.4±9.7	63.6±27.5	20.7±8.4	89.7±26.9
Difference (nmol/l)	29.3±15.4		43.1±29.1		69.0±28.7	

Rickets during infancy has been associated with higher prevalence of lower respiratory tract infections, the largest cause of infant mortality in India (Table 4).

Neurological health

Vitamin D can cross the blood–brain barrier and bind to nuclear vitamin D receptors in the brain. Nuclear Vitamin D receptors have been found in brain neurons, glial cells, spinal cord, and the peripheral nervous system.

Membrane Vitamin D receptors have also been identified in the brain, which also contains enzymes of biosynthesis and metabolism of active forms of Vitamin D. So, Vitamin D can be considered as para and autocrine hormone neurosteroid playing an important role in the nervous system.[28]

The neuroprotective effects of Vitamin D

1. Reduction of Ca2+ level in the brain. Mechanisms involved in decrease in brain Ca2+:

a) Vitamin D stimulates expression of Ca2+ binding proteins- parvalbumin and calbindins D9k and D28k
b) It inhibits expression of Ltype Ca2+ channels in hippocampus

Both effects protect neurons against toxic damage by reducing cell calcium.

2. Inhibition of brain γ-glutamyl transpeptidase, the key enzyme of glutathione metabolism.

Increasing antioxidant defense by increasing brain glutathione, Vitamin D decreased hydrogen peroxide and exerted a neuroprotective effect during brain damage caused by iron and zinc ions.[28]

Supplementation

There are various options for the supplementation of Vitamin D deficiency exists in practice, from daily to weekly to monthly to yearly dosage forms. There is an emerging consensus that serum 25(OH)D levels of about 80 nmol/l are optimal for bone health and extra-skeletal effects. However, there is no consensus on how to achieve this target rapidly.

- In USA, ergocalciferol (Vitamin D2) is recommended at a dose of 50,000 IU/week for 8 weeks, irrespective of the degree of Vitamin D deficiency or body weight
- In Europe, cholecalciferol (Vitamin D3) is mainly used to treat Vitamin D deficiency. Usually, this is done with daily supplementation using tablets
- Lenneke van Groningen et al, conducted a trial on 208 Vitamin D-deficient subjects, aged 18-88 years. Subjects received either 25,000 IU every fortnight for 8 weeks (total dose 1,00,000 IU), 25,000 IU every week for 6 weeks (total dose 1,50, 000 IU), or 25,000 IU every week for 8 weeks (total dose 2,00, 000 IU). Different group showed the response as follows: [29]

The Endocrine Society Clinical Practice Guidelines (ESCPG) suggests:[30]

- All adults who are Vitamin D deficient be treated with 50,000 IU of Vitamin D2 or Vitamin D3 once a week for 8 week or its equivalent of 6,000 IU of Vitamin D2 or Vitamin D3 daily to achieve a blood level of 25(OH) D above 30 ng/ml, followed by maintenance therapy of 1,500-2,000 IU/day.
- The upper tolerable limit of 10,000 IU/day for children and adults 19 year and older may be needed to correct Vitamin D deficiency.[30]
- In India one study used 60,000 IU of Cholecalciferol once a month (2,000 IU/day) and later 1,20,000 IU per month (4,000 IU/day) for three months without calcium supplementation. Monthly administration of 60,000 IU of cholecalciferol in healthy subjects with hypovitaminosis D may be sufficient in summer months but higher doses are required in winter months to maintain 25(OH) D levels in normal range.[30]
- Marium Ilahi et al, demonstrated that 100 000 IU cholecalciferol is a safe, efficient, and cost-effective means to increase Vitamin D concentrations in the elderly. In their study they suggested that 100000 IU cholecalciferol dose every 2 months can be safely recommended in persons with moderate baseline vitamin D concentrations. However, in those persons with baseline Vitamin D concentrations <20 ng/mL, even this large dose will not adequately raise their Vitamin D concentrations.[31]
- 23 Asian Indians whose serum 25(OH)D was low (mean 13·5 (SD 3·0) nmol/l) were studied by supplementing 60,000 IU cholecalciferol/ week along with 1gm elemental calcium daily till 8 weeks, in a trial. Subjects enrolled were group of apparently healthy Asian Indians who had been in the chronic hypovitaminosis state for years. End point evaluation parameters were serum 25(OH)D and serum intact PTH level (Table 5). On follow up at 8 weeks and at 1year following noticeable results was found.

Table 5: Study comparing serum 25(OH)D and serum intact PTH level.

Serum level	Baseline	At 8 weeks	At 1 year
25(OH)D (in nmol/l)	13.5±3.0	82.4±20.7	24.7±10.9
Intact PTH (in ng/l)	54±40	29±20	72±32

These results signify the impact of weekly loading dose (60,000IU) of cholecalciferol. Increase in serum 25(OH)D was in the range currently considered adequate or sufficient for bone mineral homeostasis. Increase in the serum level is not sustained for long. Investigator of the trial concluded that to maintain serum 25(OH)D and intact PTH level in blood, short course treatment of weekly 60,000IU cholecalciferol is not adequate and it should be given for long.[1]

Details of Indian studies conducted

- Marwaha et al, have reported that in the study he conducted more than half of the subjects were taking calcium and Vitamin D supplements, but there was no difference in serum 25(OH)D levels between the two groups. Most of the subjects were taking between 200-400 IU of Vitamin D3 (cholecalciferol) which is insufficient to normalize serum 25(OH)D levels in a Vitamin D deficient population.[3]
- One study from North India reported requirement of 60,000-1,20,000 IU per month to achieve Vitamin D level >30 ng/ml. This is the level at which calcium absorption from the gut is maximum
- Goswami et al have reported correction of Vitamin D level to normal after 8 weeks of supplementation with weekly dose of 60,000 IU. Both these studies highlight the need of regular supplementation of at least 2,000 IU/day of Vitamin D supplementation to maintain normal Vitamin D levels.[32]

Looking at the high prevalence of diabetes and tuberculosis in Indians, which has proved to have very strong correlation with hypovitaminosis D status, it is very essential to take some solid steps for its management. This study indicates that cholecalciferol given every week for 8 weeks in patients with chronic hypovitaminosis D would correct the serum 25(OH)D levels to the vitamin D-sufficient range in short-term period of 2 months.

DISCUSSION

So, based on the evidences and study results along with the expert analysis, it is clear that Vitamin D is not just a vitamin for strengthening bone and is responsible for overall health and works as very important adjuvant medication for many systemic disease conditions. Also, the recommended daily intake is not sufficient for the Indians and there is a generalized need for the loading dose on weekly, monthly or yearly duration for better care and cure.

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