REVIEW ARTICLE

Treatment of Vitamin D Deficiency and Comorbidities: A Review

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Abstract

Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis, skeletal growth and various other metabolic processes. The prevalence of vitamin D deficiency in India is 50-90% in various studies. Factors such as low sunlight exposure, age-related decrease in cutaneous synthesis, and low dietary intake of vitamin D contribute to the high prevalence of vitamin D inadequacy which has emerged as a highly pervasive condition. Bone diseases such as rickets in children, osteomalacia and osteoporosis in adults are related with vitamin D insufficiency. Literature evidences show that low vitamin D levels are also related with increased risk of falls, fractures, muscle pain, muscle weakness, cardiovascular risk, diabetes mellitus, polycystic ovary syndrome (PCOS), infections, and autoimmune disorders also. Adequate intake of vitamin D is necessary for all individuals of any age group. Sunlight exposure, food fortification and routine supplementation can only fulfill the deficiency of vitamin D.

This review article emphasizes on the prevalence of vitamin D deficiency, potential implications, and effect of supplementation on cardiovascular disease, diabetes mellitus, polycystic ovary syndrome (PCOS), autoimmune disorders, sleep disturbance and pain. In addition, the present review discusses the screening, treatment, and prevention strategies for vitamin D deficiency.

Introduction

Vitamin D has an established role in skeletal health, apart from this it also causes, inhibition of cellular proliferation, angiogenesis and renin production, stimulating insulin production, and macrophage cathelicidin production etc.[1,2] As per the Endocrine Society Clinical Practice Guideline, infants require at least 400 IU/d, children who are ≥1 year require at least 600 IU/d, adults between 19–70 years require at least 600 IU/d, and elders ≥70 years of age require at least 800 IU/d of vitamin D to maximize bone health and muscle function.[2] Vitamin D status is measured through assay of 25-hydroxy vitamin D [25(OH) D], its major circulating form. Its deficiency occurs when 25(OH) D level falls below 20 ng/mL (50 nmol/L) in serum. On the other hand, vitamin D insufficiency is defined as 25(OH)D level of 21–29 ng/mL.[2]

Vitamin D deficiency is one of the most common nutritional deficiencies worldwide. Globally, an estimated one billion individuals had vitamin D deficiency/ insufficiency across all ethnicities and age groups as estimated in 2007.[3] Approximately, 50-90% population in India is vitamin D deficient. According to a report released by the International Osteoporosis Foundation in 2009, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of pregnant women in North India were diagnosed with hypovitaminosis D.[4] Causes of vitamin D deficiency include inadequate exposure to sunlight, obesity, fat malabsorption syndrome, nephrotic syndrome, and certain medications like anticonvulsants etc. Patients with chronic granuloma-forming disorders, lymphomas, and primary hyperparathyroidism are also at high risk of developing vitamin D deficiency.[2] Individuals with vitamin D deficiency experience bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults. Additionally, it results in skeletal mineralization defects, bone deformities, short stature leading to increased risk of falls and fractures, muscle pain, muscle weakness, increased cardiovascular risk, diabetes mellitus, polycystic ovary syndrome (PCOS), infections, autoimmune disorders, sleep disturbance, and pain.[5]

According to a meta-analysis conducted by the Endocrine Society, vitamin D supplementation was associated with a statistically significant (p=0.01) reduction in risk of falls (odds ratio [OR] for the risk

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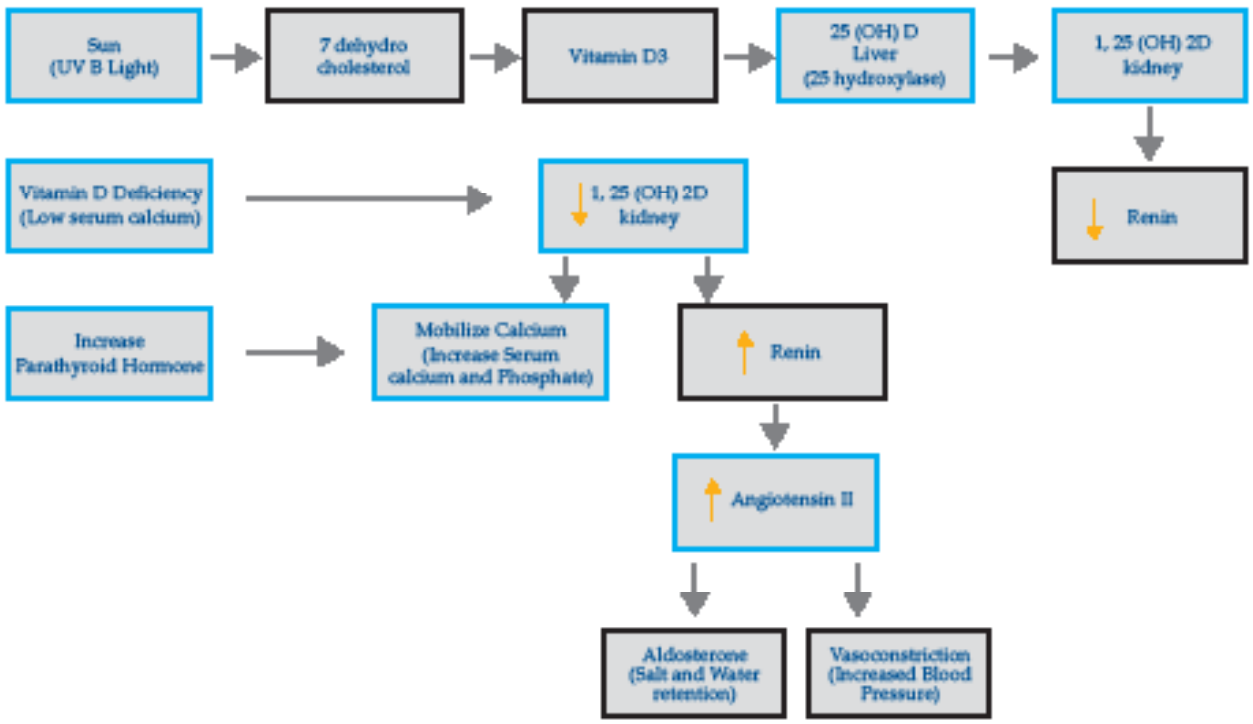

Fig. 1: Effect of vitamin D deficiency on parathyroid hormone and renin-angiotensin-aldosterone system

of experiencing at least one fall: 0.86; 95% confidence interval [CI] 0.77–0.96; 26 trials).[6] Similarly Ceglia *et al*, in a randomized, double-blind, placebo-controlled study including 21 elderly, mobility-limited, vitamin D-insufficient women (aged ≥65 years) demonstrated that vitamin D_3 supplementation increased intramyonuclear vitamin D receptor concentration by 30% and muscle fiber size by 10%.[7]

To highlight the importance of vitamin D and associated comorbidities, the present review article discusses vitamin D deficiency and its comorbidities in detail. The review further discusses treatment and prevention strategies for vitamin D deficiency.

Vitamin D Deficiency and Cardiovascular Risk

Vitamin D deficiency may be associated with an increased prevalence of cardiovascular disease. A cross-sectional case control study done in north India which included 201 adults reported that 90.2% patients with essential hypertension had deficient or insufficient levels of vitamin D.[8] Hypertension occurs due to an imbalance between vasoconstriction and vasodilation, which is controlled by the interaction of genetic and epigenetic factors. Vitamin D deficiency may disturb these epigenetic factors.[10] One of the mechanism is the disturbance of renin-angiotensin-aldosterone system (RAAS).[12] Low vitamin D levels are also associated with secondary elevation of parathyroid hormone, increased arterial resistance, and endothelial dysfunction leading to hypertension as shown in Figure 1.[12] It is also believed to increase the risk of cardiovascular diseases as it promotes vascular stiffness and calcification.[13] Another studies demonstrated that vitamin D is a potent endocrine inhibitor of renin synthesis which is one of the regulator of Renin Angiotensin Aldosterone system.[9] An interventional study included 33 patients with essential hypertension and hypovitaminosis D. All the patients treated with cholecalciferol 50 000 IU/week orally for a period of eight weeks in the study demonstrated normalized plasma 25(OH)D values with reduction in levels of plasma renin activity (1.17 ± 0.3 vs. 1.51 ± 0.4 ng/ml/h, p=0.02), renin (13.4 ± 1.7 vs. 19.2 ± 2.9 pg/ml, $p < 0.001$), angiotensin II (11.6 ± 1.6 vs. 15.8 ± 2.7 pg/ml, p=0.02) at the end of the study.[11]

Although global studies evaluating the prevalence of cardiovascular disorders in patients with vitamin D deficiency are scarce, multiple studies have been conducted across different parts of the world to evaluate this prevalence. A prospective case-control study which included 100 chronic stable angina patients and 100 matched controls showed a high prevalence of vitamin D deficiency in 75 angina patients (75%) as compared to 10 (10%) in controls.[18] Further, among 100 Indian patients undergoing coronary angiography, 80% of the patients were having vitamin D deficiency and had significantly higher prevalence of double- or triple-vessel coronary artery disease (53% vs. 38%), diffuse coronary artery disease (56% vs. 34%), and impaired flow-mediated dilation (FMD) (50.6% vs. 7%).[19]

Supplementation with vitamin D might play an important role in improving the condition of the patients with cardiovascular disorders. However; there are very few studies supporting this hypothesis. An interventional study in obese individuals with hypertension and vitamin D insufficiency showed that vitamin D_3 therapy for a period of one month (15,000 IU/d) increased 25(OH)D levels (18 to 52 ng/mL) and basal renal plasma flow (+5%), and lowered supine mean arterial pressure (-3%) (p<0.01 each).[14] Similarly Larsen T *et al*, investigated the effect of 75 µg (3,000 IU) cholecalciferol per day in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients. Supplementation with cholecalciferol effectively increased vitamin D levels resulting in decreased central systolic blood pressure to a significant extent (7/2 mm Hg, p=0.007/0.15) as compared with placebo.[15] In addition Rahimi-Ardabili *et al* investigated the effect of cholecalciferol (3 oral capsules of 50,000 IU vitamin D_3 every 20 days for 2 months) on cardiovascular disease risk factors in PCOS women with vitamin D deficiency and concluded that vitamin D_3 therapy increased serum vitamin D (7.00 ± 2.80 to 22.9 ± 6.14 ng/mL), and led to significant decrease (p<0.05) in cardiovascular risk factors like serum total cholesterol (196.6±32.8 to 179.1±34.1 mg/dL), triglycerides (156.8±73.0 to 130.5±56.5 mg/dL), and very low density lipoprotein (31.4±14.6 to 26.1±11.3 mg/dL).[16] However, a meta-analysis of 46 trials with 4541 participants showed no effect of vitamin D supplementation on systolic blood pressure (p=0.97) or diastolic blood pressure (p=0.84).[17] On the other hand, no significant relationship was found between vitamin D levels and endothelial dependent vasodilation (EDV, β±SE: 0.70±1.0; p=0 .48), flow mediated vasodilaion (FMD, β±SE, 0.12±0.33; p=0.70), and refractive Index (RI, β±SE, -0.02±0.05; p=0.57) in older individuals but a positive association was found in women between vitamin D and endothelium independent vasodilation (EIDV, β±SE: 1.41±0.54; p=0.001).[20] Also, no improvement was observed in endothelial dependent vasodilation (6.3±3.6% at baseline to 6.1±4.6% at 8 weeks; p=0.78) after repletion of vitamin D in non-hypertensive, non-diabetic overweight, or obese individuals with vitamin D deficiency.[21]

Vitamin D Deficiency and Diabetes Mellitus

Vitamin D may improve pancreatic β-cell function, decrease insulin resistance, and improve systemic inflammation. It directly acts on pancreatic β-cells by binding β-cell vitamin D receptor to produce insulin and on the muscle and fat cells to improve insulin action by reducing insulin resistance. Further, it indirectly improves insulin production and its action by increasing the level of calcium inside the cells, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscles and adipose tissues. Vitamin D also increases insulin sensitivity and β-cell survival by modulating the generation and effects of cytokines which play an important role in β-cell dysfunction by triggering β-cell apoptosis.[22]

Evidences from clinical studies also show a correlation between vitamin D deficiency and diabetes mellitus. A retrospective study (n=4628) in South India showed 3304 (71.4%) of the diabetic patients to be vitamin D deficient and 694 (15%) patients to be vitamin D insufficient, suggesting that vitamin D deficiency is highly prevalent among diabetic patients.[23] In another study which was conducted to establish a correlation between vitamin D deficiency and diabetes reported that of the 100 diabetic patients included in the study, 68% of the patients were vitamin D deficient.[24] Further, a prospective case control study in North India showed that 91.1% of the patients with youth-onset diabetes were vitamin D deficient as compared to 58.5% of the healthy controls, suggesting vitamin D deficiency is common in individuals with youth onset diabetes.[25] Another study showed an inverse association between serum 25(OH) D levels and A1C levels (r = −0.116, p=0.003) in 715 patients with type 2 diabetes mellitus (T2DM).[26] A study evaluating the incidence of T2DM in children (n=50) between the age of 6 to 12 years showed that 29 (58%) of the children with T2DM were also vitamin D deficient as compare to control. (20.02 ± 10.63 ng/mL vs. 26.16 ± 12.28 ng/mL, p=0.009).[27] Further, a meta-analysis of 20 observational studies including 9209 pregnant women showed a consistent association between vitamin D deficiency and an increased risk of gestational diabetes mellitus (odds ratio [OR] = 1.53; 95% CI: 1.33-1.75).[28]

Zhou *et al*, demonstrated that oral vitamin D supplementation (oral calcitriol 0.5 µg/d) in patients with T2DM led to significant improvement in body mass index (-0.7±1.7 kg/m^2 and 0.4±1.4 kg/m^2, p<0.05), fasting plasma glucose (-1.2± 2.3 mmol/L and -0.6±2.8 mmol/L, p<0.05), fasting insulin (-1.6±2.2 µU/mL and -0.32±1.49 µU/mL, p<0.05), and hemoglobin A1c (-0.1±0.6% and-0.03±0.94%, p<0.05).[29] An Indian study showed that vitamin-D supplementation (60,000 U) was associated with significant reduction in the progression of diabetes (6/55 vs. 13/49; p=0.04), higher reversal to normoglycemia (23/55 vs. 10/49; p=0.02).[30]

Vitamin D Deficiency and Polycystic Ovary Syndrome

Vitamin D deficiency is commonly found in women with

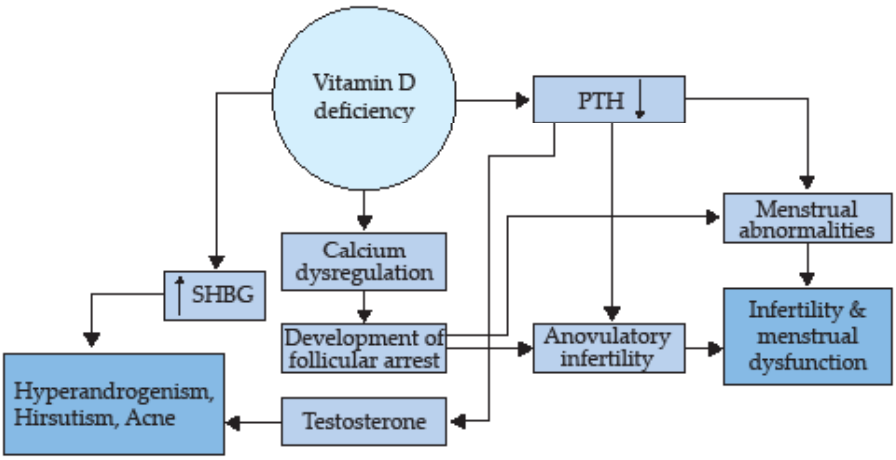

Fig. 2: Association of vitamin D deficiency with metabolic disturbances in PCOS[33]

PCOS as approximately 67-85% of PCOS women are having serum concentrations of 25-hydroxy vitamin D less than 20 ng/mL.[31] Low vitamin D levels are believed to be associated with increase in para thyroid hormone and sex hormone binding globulin (SHBG) which may cause metabolic disturbances in PCOS, including ovulation, menstrual irregularities, infertility, hyperandrogenism, increased testosterone, obesity, insulin resistance, and increased risk of cardiovascular diseases.[32,33] The role of vitamin D deficiency in the pathology of PCOS is illustrated in Figure 2.[33]

In a case-control study, 100 infertile PCOS women were evaluated to assess the efficacy of calcium and vitamin D supplementation (calcium 1000 mg/day and vitamin D 100000 IU/month for 6 months). While 83% of women showed vitamin D deficiency, 35% were severely deficient. Calcium and vitamin D supplementation regulate follicle maturation (28% vs. 22%, p=0.698), menstrual abnormalities (70% vs. 58%, p=0.211), and hyperandrogenism (18% vs. 12%, p=0.401) to a considerable but not significant extent among infertile women with PCOS.[34] However, another study showed that administration of vitamin D improved endometrial proliferation in PCOS women during Intra Uterine Insemination (IUI) cycle as compared to the placebo group (p=0.003).[35] In an Indian study, vitamin D levels were significantly lower in PCOS cases (p<0.05) as compared to healthy controls (15.31±2.11 ng/mL vs. 28.3±3.5 ng/mL, n=44) and was related to metabolic and hormonal disorders in PCOS.[36]

Vitamin D Deficiency and Other Comorbidities

Autoimmune Disorders

Vitamin D binds to vitamin D receptors on various cells which participate in immune responses, and modulate both activation and deactivation of the innate and adaptive responses. Vitamin D may induce innate tolerance by promoting tolerogenic dendritic cells as well as induce a robust macrophage response to infections.[37]

A cohort study in patients with rheumatoid arthritis (n=44), showed that the level of vitamin D was significantly low (15.26±1.07 ng/mL) as compared with the healthy control group (25.8±1.6 ng/mL, p<0.001), and suggested that vitamin D supplementation might be needed in patients with rheumatoid arthritis.[38] Further, 102 newly diagnosed autoimmune thyroid disorder patients were evaluated for the effect of cholecalciferol 60,000 IU weekly and calcium 500 mg/day for 8 weeks. Vitamin D supplementation showed a positive impact on autoimmunity by significantly reducing the fall in thyroid peroxidase antibody (p=0.028).[39] Vitamin D supplementation is also believed to modulate T-cell function in human immunodeficiency virus (HIV)-infected patients, and may represent a useful adjunct to highly active antiretroviral therapy.[40]

Infectious Disorders

Several studies conducted previously have indicated an association of low levels of vitamin D levels with increased susceptibility of sepsis.[41] A meta-analysis of 10 observational studies has shown a pooled OR of sepsis to be 1.78 (95% CI: 1.55-2.03, p<0.01) in patients with vitamin D deficiency.[41] Another meta-analysis evaluated the association between 25-hydroxyvitamin D and sustained virological response (SVR) in hepatitis C virus (HCV) infected patients and showed that 71% of HCV infected patients had low vitamin D levels (n=1575). Further, it was suggested that vitamin D supplementation improved SVR in HCV infected individuals (OR = 4.59; 95% CI: 1.67-12.63).[42] Another study indicated that vitamin D supplementation 50,000 IU twice weekly for 5 weeks, then 8000 IU twice weekly to 63 vitamin D insufficient HIV+ adults for 24 weeks improved cluster of differentiation 4 (CD4) recovery (r = 0.44, p = 0.01) and 83% vitamin D repletion (95% CI: 71–90%) showing improvement on immunologic recovery during HIV treatment.[43]

Respiratory Diseases

Vitamin D deficiency may be associated with chronic lung diseases such as asthma, cystic fibrosis, chronic obstructive lung disease and interstitial pneumonia as it may influence various cytokines, cellular elements, oxidative stress and protease/antiprotease levels and affect

Table 1: Levels of vitamin D as per the US Endocrine Society classification

Vitamin D status	Vitamin D levels
Deficiency	<20 ng/ml
Insufficiency	21-29 ng/ml
Sufficiency	>30 ng/ml
Toxicity	>150 ng/ml

lung fibroproliferation and its functions.[44]

A meta-analysis of 10 studies showed high prevalence of vitamin D deficiency among asthmatic patients as compared to control (relative risk [RR]=1.59, 95% CI: 1.07-2.36; prevalence 60% vs. 32%).[45] Further, a meta-analysis of five studies which included 48 participants suggested a reduction (RR 0.41, CI: 0.27-0.63) in asthma exacerbation with vitamin D therapy (2000 IU/day).[46] Manousaki *et al*, a Mendelian randomized study including 33,996 individuals showed no association of genetic 2(OH)D alleles with asthma (OR: 1.03; 95% CI: 0.90-1.19, p=0.63), childhood-onset asthma (OR: 0.95; 95% CI: 0.69-1.31, p=0.76), and atopic dermatitis (OR: 1.12; 95% CI: 0.92-1.37, p=0.27).[47]

Cancer

The biologically active form of vitamin D hormone, $1\alpha,25(OH)_2D_3$ can modulate gene expression, inhibit the cellular proliferation, induction of differentiation, and apoptosis ultimately inhibiting the cell growth of cancer. When prostate, colon, breast, lung and melanoma cancer cell lines are exposed to vitamin D_3, growth inhibition takes place.[48] An increased incidence of vitamin D insufficiency (80.4%) was observed in children of less than 18 years suffering from cancer (leukemia/lymphoma or solid tumors) as compared to the control (50.1%).[49] In another study, vitamin D supplementations (400-833 IU/day) reduced total cancer mortality (RR=0.88, 95% CI=0.78-0.98).[50] In a cohort study of 492 patients, the association of pre-transplant Vitamin D deficiency with higher relapse rate was observed to a significant extent (HR, 2.55; p=0.014) in myeloid patients. Pre-transplant vitamin D deficiency was associated with a higher risk of relapse in patients allografted for myeloid malignancies.[51]

Vitamin D Deficiency, Sleep and Pain

Vitamin D plays an important role in sleep and pain.[52] A case series of 28 veterans with multiple areas of chronic pain showed that supplementation with 1200 IU/ day cholecalciferol in an insufficient serum 25(OH)D and 50,000 IU/ weekly in deficient serum 25(OH) D significantly improved the pain score (p<0.001), sleep latency (p=0.019), sleep duration (p=0.012), body pain (p=0.014), and general health (p=0.006).[53]

Prevention and Treatment Strategies

Screening

As per the Endocrine Society, screening of vitamin D deficiency is recommended in individuals with rickets, osteomalacia, osteoporosis, chronic kidney disease, hepatic failure, malabsorption syndromes, cystic fibrosis, inflammatory bowel disease, Crohn's disease, bariatric surgery, radiation enteritis, and hyperparathyroidism. Further, it is recommended for African-American and Hispanic children and adults, pregnant and lactating women, older adults with history of falls, older adults with history of non-traumatic fractures, obese children and adults, and people who are suffering from granuloma.[2] Recommendations of the Endocrine Society of India are in line with the international guidelines. Universal screening is not recommended by the Endocrine Society of India and target screening in at-risk population is advised.[54] Competitive protein binding, immunoassay, high-performance liquid chromatography, combined high-performance liquid chromatography, and mass spectrometry are currently available screening methods used in routine testing of 25 hydroxy vitamin D in clinical laboratories.[55] Different levels of vitamin D deficiency in blood are shown in Table 1 as per the US Endocrine Society classification.[3]

Recommended Dietary Allowance and Treatment of Vitamin D Deficiency

Indian Council of Medical research (ICMR) committee had recommended outdoor physical activity to achieve adequate vitamin D as the young growing children and adults in India mainly in the urban areas are physically less active and are not being exposed outdoors which reduces the chances of vitamin D formation. The committee has not made any specific suggestions on the intake of vitamin D in different groups of people. A daily supplement of 400 IU (10 µg) is specifically recommended in case of minimal exposure to sunlight.[56] According to Institute of Medicine (IOM), adults of age 19 to 70 need a daily supplement of at least 400 IU of vitamin D, and recommended dietary allowance of at least 600 IU as shown in Table 2.[2,3] Obese adults need at least two to three times more vitamin D to treat and prevent vitamin D deficiency.

The vitamin D deficiency often remains undiagnosed or is undertreated due lack of recommended age-dependent adequate intake and the dearth of vitamin D toxicity.[57] Endocrine Society of India recommends vitamin D supplementation to combat high prevalence of vitamin D deficiency.[58] The guideline recommendations for the treatment of vitamin D deficiency as per the Endocrine Society Clinical Practice Guidelines recommend treatment of vitamin D deficiency with varying daily/weekly vitamin D_2 or vitamin D_3 for a period of six weeks

Table 2: Daily intake recommendation of vitamin D as per IOM and the endocrine practice guidelines committee

Life stage group	IOM recommendations		Committee recommendations for patients at risk of vitamin D deficiency
	EAR (IU)	RDA (IU)	Daily requirement (IU)
Infants (0-12 mo)	400	600	400-1000
Children (1-8 yr)	400	600	600-1000
Adolescents (9-18 yr)	400	600	600-1000
Adults (19-70 yr)	400	600	1500-2000
Elderly (>70 yr)	400	800	1500-2000
Pregnancy and lactation	400	600	1500-2000

EAR: Estimated Average Requirement; RDA: Recommended Dietary Allowance; IOM: Institute of Medicine

Table 3: Treatment regimens for the vitamin D deficiency[2,3]

Age group	Holick et al (Therapy duration: 6 weeks)			Balasubramanian et al (Therapy duration: 8-12 weeks)		
	Daily dose (IU)	Weekly dose (IU)	Maintenance (IU)	Daily dose (IU)	Weekly dose (IU)	Maintenance (IU)
≤1 mo	2000	50,000	400-1000	1,000	50,000	400-1000
1-12 mo	2000	50,000	400-1000	1000-5000	50,000	400-1000
1-18 yr	5000	50,000	600-1000	5000	50,000	600-1000
>18 yr	6000	50,000	1500-2000	6000	50,000	1500-2000
Special Cases*	6000-10000		3000-6000	6000-10000		3000-6000

*Obese patients, patients with malabsorption syndromes, patients on medications which affect vitamin metabolism

for different age groups.[2] Keeping the international clinical practice guidelines in consideration, Balasubramanyam *et al*, reviewed the current guidelines available for the treatment of vitamin D deficiency. The article reported that varying daily/weekly doses of vitamin D_2 or vitamin D_3 for a period of 8-12 weeks for different age groups are required for the treatment of vitamin D deficiency.[3] Indian physicians often prescribe 60,000 IU (1500 µg) cholecalciferol per week for 8 weeks for vitamin D deficiency.[59] In a meta-analysis which included randomized controlled trials (RCTs, n=1016), the effectiveness of vitamin D_3 (cholecalciferol) was significant (p=0.0002) in increasing serum 25-hydroxyvitamin D concentration as compared to vitamin D2 (ergocalciferol) (p=0.001). We have also shown that, regardless of whether supplementation with vitamin D was in small daily doses or in larger and more infrequent bolus dosages, the favoring toward cholecalciferol was still evident. Reason for this would be metabolism of different forms of vitamin D as suggested by evidence. Once the 2-step 25-hydroxylation process has been completed and 1,25-dihydroxyvitamin D has been formed, an additional step occurs that involves 24-hydroxylation at the kidney to form 1,24,25(OH)3D [1,24,25-trihydroxyvitamin D; 25(OH)D can also be converted to 24,25-dihydroxyvitamin D at this point] It is this 24-hydroxylation step that truly demarcates the impact of ergocalciferol compared with that of cholecalciferol. This differentiation between ergocalciferol and cholecalciferol is due to the fact that once 1,24,25(OH)3D2 has been formed, ergocalciferol has been deactivated and, therefore, is irretrievable. In contrast, cholecalciferol [now 1,24,25(OH)3D3] retains its capacity to bind to the VDR and still requires an additional side-chain oxidation to become deactivated. Thus, this additional step gives a vast advantage and potential for cholecalciferol to remain biologically active and, thus, maintain vitamin D status, which only strengthen the hypothesis that cholecalciferol is the preferred substrate compared with ergocalciferol.[60] The detailed treatment strategies are presented in Table 3.[2,3]

Indian Academy of Pediatrics Recommendation for Vitamin D

The Indian Academy of Pediatrics (IAP) observed the need for a practice guideline which can be used by pediatricians for the prevention and treatment of vitamin D in children and adolescents (Table 4).[61] In a prospective multiethnic population-based cohort study including 9901 pregnant women, severe maternal 25 hydroxy vitamin D deficiency (<25nmol/L) was associated with higher offspring bone mineral content (BMC, 4·71 g, 95% CI: 1.09-8·33; p=0·011) and larger bone area (7·54 cm^2, 95% CI: 2·99-12·11; p=0·001) at age 6 years, as compared with maternal 25 hydroxy vitamin D sufficiency (>=50 nmol/L) during mid pregnancy. However, in a subgroup of children with available data on 25(OH)D concentrations at 6 years (n=3034), such associations for BMC (4·67 g, −0·05 to 9·39; p=0·052) and bone area (5·25 cm^2, −0·41 to 10·91; p=0·069) were no longer significant after adjustment for the child's own 25(OH)D concentrations. No associations were seen between maternal 25(OH)D concentrations in mid-pregnancy and offspring bone mineral density (1·07 mg/cm^2, −1·84 to 3·99; p=0·47) or area-adjusted BMC (−1·58 g, −4·72 to 1·61; p=0·32), and the association with skeletal parameters at 6 years did not differ by maternal BMI, maternal calcium intake, child sex, or weight status. Similar associations were seen with fetal 25(OH)D concentrations at birth. Study found inverse associations between 25(OH) D concentrations during fetal life with BMC and bone area in childhood, but these associations were no longer significant after adjustment for childhood 25(OH)

Table 4: Prevention and treatment in vitamin D deficiency[61]

Age	Prevention	Tolerable* Upper Limit	Treatment	Treatment with large dose (oral route preferred)
Premature Neonates	400 IU/day	1000 IU/day	1000 IU/day	NA
Neonates	400 IU/day	1000 IU/day**	2000 IU/day	NA
1-12 months	400 IU/day	1000-1500 IU/day**	2000 IU/day	60000 IU weekly for 6 weeks (over 3 months of age)
1-18 years	600 IU/day	3000 IU/day till 9 years, 4000 IU/day from 9-12 years.[2]	3000-6000 IU/day	60000 IU weekly for 6 weeks
At risk groups	400-1000 IU/day	As per age group	As per age group	As per age group

*Tolerable Upper Limit - the maximum level of total chronic daily intake of a nutrient (from all sources).** For a minimum of 3 months; after treatment, daily maintenance doses need to be given.

D status. This suggest that 25(OH)D concentrations during childhood might be more relevant for bone outcomes than 25(OH) D concentrations during fetal life.[62] In another randomized, double blind, placebo-controlled clinical trial including 51 pregnant women, supplementation with 4400 IU of vitamin D_3 enhanced broad-spectrum proinflammatory cytokine response of cord blood mononuclear cells to a significant extent (p=0.0009). Study concluded by saying vitamin D exposure during fetal development influences the immune system of the neonate, which can contribute to protection from asthma-related, including infectious, outcomes in early life.[63]

Conclusion

In conclusion, the role of vitamin D has been established in several interventional, case control, retrospective, and observational studies. Inadequate vitamin D levels may be responsible for the progression of cardiovascular disorders, diabetes mellitus, PCOS, autoimmune disorders, sleep disturbance and pain to a considerable extent. Therefore, more awareness is needed to combat the increasing prevalence of vitamin D inadequacy through all age groups. Aggressive screening and treatment strategies are required for vitamin D inadequacy. Adequate intake of vitamin D through supplementation can only be achieved when one is educated appropriately regarding vitamin D deficiency and its impact on various comorbidities adequately.

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