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Review Article

Vitamin D deficiency: a cause of clinical concern

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ABSTRACT

In India, the prevalence of vitamin D deficiency ranges from 35% to 99% despite the fact that India is a tropical country with plenty of sunshine. The prevalence of vitamin D deficiency is high in patients with comorbid conditions such as type 2 diabetes mellitus (T2DM) (84.2%), hypertension (82.6%), and hypothyroidism (76.9%). The effects of vitamin D deficiency are not just restricted to the musculoskeletal system. The presence of vitamin D receptors on the pancreatic beta cells, adipose tissues and skeletal muscle cells indicates the function of vitamin D in the glucose metabolism. Recent literature shows that altered vitamin D and calcium homeostasis may play a role in the development of T2DM. This review delves into recommendation shared by group of expert endocrinologists on skeletal and extra skeletal implications of vitamin D deficiency and the ways to manage patients of vitamin D deficiency. Experts shared that as per guidelines vitamin D deficiency be defined as a 25(OH)D below 20 ng/ml, insufficiency as a 25(OH)D of 21–29 ng/ml, and sufficiency as a 25(OH)D of ≥30 ng/ml. The experts opined that vitamin D levels should be maintained between 40-60 ng/ml for extra skeletal benefits. Vitamin D supplementation has demonstrated potential benefits on glycemic control. Thus, vitamin D supplementation can be added as an effective adjunctive intervention in diabetic and prediabetic patients. Recent advances in technology have enabled delivery of vitamin D through nanoparticle-based Vitamin D which ensure higher absorption and better serum vitamin 25(OH) levels. Experts shared that nano-particle based vitamin D3 appears to be better in achieving higher levels of serum 25(OH)D than that observed with other oral dosage formulations of vitamin D3.

Keywords: Vitamin D deficiency, T2DM, Diabetes, Vitamin D supplementation, Nanoformulation

INTRODUCTION

Vitamin D deficiency has recently been recognized as a widespread global disorder especially in metropolitan cities around the world and in India. It is estimated that 1 billion people globally have vitamin D deficiency or insufficiency.[1-4] In India, the prevalence of vitamin D deficiency ranges from 35% to 99%, despite the fact that India is a tropical country with plenty of sunshine.[2,3,5,6] This deficiency of vitamin D in Indians may be attributed to prolonged indoor working, sun –shy nature of Indians, clothing habits that reduce the exposure of skin to sunlight, skin pigmentation (Indians come under the skin category-type V), atmospheric pollution.[7,8] Research highlights a significant high prevalence of vitamin D deficiency across various regions in India; however, the lifestyle of people in different regions has an impact on vitamin D status. Surprisingly, the prevalence of vitamin D deficiency has been observed to be the highest in the age-group of ≥18 to ≤30 years (61.9%).[2] Furthermore, vitamin D status has been found comparable ($p>0.05$) between both genders, suggesting that sex does not play a role in determining vitamin D status within the Indian population. Vitamin D deficiency/insufficiency in Indians is prevalent across all the strata of Indian population, regardless of sex, age, and geographical location, underscoring the need for optimal public health action.[2]

The prevalence of vitamin D deficiency is high in patients with comorbid conditions such as type 2 diabetes mellitus (84.2%), hypertension (82.6%), type 2 diabetes and hypertension (84.5%), and hypothyroidism (76.9%).[9] Even though vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent with a prevalence close to 77% in general population, very little information exists about its clinical practice management among patients with T2DM.[2,9]

Vitamin D deficiency patients present with general musculoskeletal symptoms, such as bone pain, myalgias, and generalized weakness.[10] The effects of vitamin D deficiency are not just restricted to the musculoskeletal system. Vitamin D deficiency has been implicated in diabetes, lowered immunity, hypertension, and cardiovascular disease, and several more disorders. The presence of vitamin D receptors on the pancreatic beta cells, adipose tissues and skeletal muscle cells indicates the role of vitamin D in the glucose metabolism. Further, it has been proposed that disruptions in vitamin D and calcium homeostasis may play a crucial role in the development of T2DM.[9]

Vitamin D supplementation is recommended in patients of vitamin D deficiency/insufficiency to maximise bone health.[11] Studies report that approximately 50% of orally ingested vitamin D3 is absorbed. However, studies have showed that absorption of nanoformulation to be more than 90%. Nanoformulation was also reported to be convenient and widely accepted by the patients and doctors as well. Nanoformulation has been reported to be effective and well tolerated in managing patients of vitamin D deficiency.[10]

An advisory board meeting (ABM) was conducted in May 2024, with panel of nine experts qualified in endocrinology. At ABM, the experts discussed the impact of vitamin D deficiency on diabetes and the current management practices to manage vitamin D deficiency. A literature search across databases such as Pubmed, Cochrane, and Google Scholar was conducted for articles with keywords such as “vitamin D deficiency,” “T2DM,” “diabetes,” and “vitamin D supplementation,” and “nanoformulation”. The current literature for vitamin D were also critically reviewed, and a descriptive analysis of the literature and expert opinions are summarized below.

DEFINING NORMAL RANGE OF VITAMIN D STATUS

Serum 25-hydroxyvitamin D (25[OH]D) level is the major circulating form providing vitamin D status of an individual. Maintaining adequate serum levels of 25(OH)D is crucial for both skeletal and extraskeletal physiologic effects.[8] The clinical practice guidelines of the Endocrine Society Task Force on vitamin D have described a cut-off level of 20 ng/ml as vitamin D deficient, 21-29 ng/ml as vitamin D insufficiency, 30-100 ng/ml as sufficient.[12] The National and International Osteoporosis Foundation and the American Geriatric Society define vitamin D deficiency as the level of 25-hydroxyvitamin (25 OH D) of less than 30 ng/ml.[13] As per Indian Society of Bone Mineral Research recommendations (ISBMR), a level of 30–40 ng/ml is considered ideal.[14] Studies have shown that the desirable and safe levels of serum 25(OH)D levels should be 30-100 ng/ml, because, at the level of 30 ng/ml, the intestinal calcium absorption reaches its highest level and parathyroid hormone (PTH) levels are continually reduced until this level of 25(OH)D is reached.[12] The maximal desired vitamin D status, defined by estimated maximum PTH suppression, was at least 25OHD levels ≥40 ng/ml.[15]

Experts’ consensus

Vitamin D insufficient levels is ≥20 to <30 ng/ml. Vitamin D deficient levels is <20 ng/ml. The target level for vitamin D recommended by Indian experts is >40 ng/ml; as 40-60 ng/ml provides extra-skeletal benefits.[1,13]

ROLE OF VITAMIN D IN BONE HEALTH

Vitamin D is synthesized in the skin through adequate sunlight exposure.[2] Vitamin D deficiency affects the calcium, phosphorous and bone metabolism. Vitamin D deficiency leads to a decreased efficiency of intestinal absorption of calcium and phosphorous from the diet resulting in elevated PTH levels. The resulting secondary hyperparathyroidism (SHPT) maintains the serum calcium in the normal range by mobilising the calcium from the skeleton and increasing phosphate excretion from the kidneys. The PTH-mediated osteoclastic activity leads to weakening of the bones and decreases bone mineral density (BMD) resulting in osteopenia and osteoporosis. Vitamin D deficiency results in osteoporosis and fractures, mineralization defects, and muscle weakness, causing falls and fractures. A decrease in serum phosphate levels associated with increased levels of PTH plays a significant role in disruption of mineralization. This impairment in bone mineralization leads to bone defect, presenting as osteomalacia. In children, this manifests as condition called as rickets.[8]

Majority of vitamin D trials demonstrate to have a clear significant effect on BMD and consequently on fracture incidence. Studies have demonstrated that vitamin D supplementation can improve muscle strength which in turn contributes to a decrease in incidence of falls, thus leading to subsequent decrease in fracture risk.[12] Moreover, the immunoregulatory mechanisms of vitamin D may modulate the effect of pro-inflammatory cytokines on bone health in osteoporotic patients and subsequent fracture risk.[12]

ROLE OF VITAMIN D BEYOND BONE HEALTH

Today, vitamin D is considered to be a hormone with effects beyond the skeletal system. The nidus for considering the extra skeletal benefits of vitamin D was the

finding that the enzyme that produces the active metabolite of vitamin D and ligand for vitamin D receptor (VDR), namely CYP27B1, likewise is widely expressed in a large number of cells and tissues not related to the classical target tissues for vitamin D. Secondly, several gene expression profiling studies have demonstrated that vitamin D regulates the expression of many genes unrelated to calcium homeostasis. Several molecular, genetic, cellular, and preclinical studies have proved that vitamin D signaling modulates many extra skeletal effects. These include regulation of immune function, inflammation, cell proliferation, and differentiation, skin differentiation, reproduction, vascular and metabolic functions.[2,16]

ROLE OF VITAMIN D IN DIABETES

Vitamin D deficiency has been reported in 84% of patients with T2DM and in 77% of those with prediabetes.[17] Vitamin D has been postulated to play a functional role in glucose tolerance through its effects on insulin secretion and insulin sensitivity. The hypothesis put forth to rationalize the role of vitamin D deficiency as a risk factor for diabetes is that both impaired pancreatic beta-cell function and insulin resistance are associated with low vitamin D levels.[18,19] β cells express both the vitamin D receptor transcript (VDR) and 1α-hydroxylase (CYP27B1), which catalyzes the activation of 25(OH)D into 1,25(OH)2D, consistent with the cell-intrinsic role for VDR. Furthermore, the presence of a vitamin D receptor element (VDRE) in the human insulin receptor gene promoter region suggests a potential role of vitamin D in influencing insulin action.[20]

Vitamin D has been shown to exert protective effects on diabetes through its effects on calcium and phosphorus metabolism and regulation of the insulin receptor gene. It seems that vitamin D enhances calcium levels in the cells, in turns leading to increased transport of glucose into the muscle. Vitamin D also regulates nuclear peroxisome proliferative activated receptor (PPAR) that has an important role in the insulin sensitivity. Vitamin D attenuates the expression of proinflammatory cytokines involved in insulin resistance such as interleukins, IL-1, IL-6, TNF-alfa and down regulates nuclear factor (NF-Kb) activity.[21]

Several observational studies have supported the association of low vitamin D and development of T2DM.[22] The amount of insulin secreted must be related to the increment in plasma glucose concentration, which provides the stimulus to β-cells.[23] As per Mitri study, vitamin D supplementation led to a 40% improvement in the disposition index, a measure of beta cell function.[24] Several other studies have also proved that vitamin D supplementation improves insulin sensitivity.[25,26] In a meta-analysis of 39 randomized trials involving 2982 patients, vitamin D supplementation was demonstrated to significantly reduce serum FBG, HbA1c, HOMA-IR and fasting insulin levels in T2DM patients. The effects were particularly significant when vitamin D was given to patients, who were overweight, or had an HbA1c of 8% or higher at baseline.[27] As per study by Talaei, the beneficial effects of vitamin D on insulin resistance were significant when vitamin D concentration were 40–60 ng/ml (100–150 nmol/l) and in lower and upper vitamin D concentration, it did not affect insulin resistance.[21] Thus, studies suggest that vitamin D supplementation could be an effective adjunctive intervention for glycaemic control in T2DM patients.[27]

The vitamin D and T2DM trial evaluated the effect of vitamin D supplementation in adults with prediabetes. This randomized, double-blind, placebo-controlled clinical trial studied the safety and efficacy of oral administration of vitamin D3 (cholecalciferol; 4000 IU per day) for diabetes prevention. The vitamin D and T2DM study demonstrated a 12% reduction in the risk of new-onset diabetes in the vitamin D treated patients as compared with placebo. Trial participants who were assigned to daily vitamin D supplementation and maintained high intra-trial 25(OH)D levels (100–124 and ≥125 nmol/l) had substantial relative reductions in risk of diabetes (52% and 71%, respectively) compared with those who maintained an intra-trial 25(OH)D level of 50–74 nmol/l.[28] Daily vitamin D supplementation to maintain a serum 25(OH)D level ≥100 nmol/l is a promising approach to reducing the risk of diabetes in adults with prediabetes.[28] Another study concluded that for every 10 nmol/l increment in 25(OH)D levels, there was a 4% lower risk of developing T2DM.[22] Endocrine society clinical practice guideline' 2024, recommends empiric vitamin D supplementation for adults with high-risk prediabetes, in addition to lifestyle modification, to reduce the risk of progression to diabetes.[29]

Experts' consensus

Vitamin D deficiency may impair insulin secretion and contribute to the insulin resistance, resulting impact on pathogenesis of T2DM. Increasing vitamin D serum levels could lead to reduction in the risk of developing T2DM. Experts shared that first line of treatment in diabetes and prediabetes is lifestyle changes including nutrition and dietary changes where vitamin D supplementation can be added as a part of nutrition optimization.[28,29]

MANAGEMENT OF VITAMIN D DEFICIENCY

Option 1: Weekly dose followed by maintenance

60,000 IU weekly dose of vitamin D3 for 8 weeks followed by maintenance therapy of 60,000 IU once a month OR 1500-2000 IU/day.[30]

Option 2: Continuous monthly therapy: 60,000 IU/month

Healthy individuals with vitamin D deficiency can be given monthly doses of 60,000.[30]

Option 3: Daily continuous therapy: daily supplementation of up to 2000 IU

Recommended in maintenance therapy and in elderly in combination with calcium.[30] Endocrine Society has given a safe upper level for vitamin D supplementation as 10,000 IU, while the Institute of Medicine (IOM) and the European Food and Safety Authority recommend a value under 4,000 IU per day (100 µg). Most countries have recommended the upper level as 2,000 IU per day (50 µg) for adults. Moreover, vitamin D supplementation of 2000 IU is sufficient to achieve a level at least 30 ng/mL.[12,30]

Option 4: Parenteral mega dose: 300000-600,000 injections

The parenteral route has been shown to be effective in patients with hypovitaminosis D caused by severe intestinal malabsorption. Intramuscular vitamin D is the preferred treatment for malabsorption disorders like intestinal bowel disorders, pancreatic insufficiency, short-bowel syndrome, gluten enteropathy, post bariatric surgery and patients with poor compliance to oral therapy.[12,30]

VITAMIN D SUPPLEMENTATION BASED ON 25(OH)D CONCENTRATION

25(OH)D levels 0–20 ng/ml

The therapeutic dose of vitamin D should be supplemented, and treatment carried out until the 25(OH)D concentrations of >30 ng/ml is reached. The recommended dose of all adults with vitamin D deficiency is 6,000 IU/day.[11] Alternatively, adults and elderly can be given 60,000 IU/weekly for 8 weeks to achieve 25(OH)D concentrations of >30 ng/ml and followed by maintenance dose.[8]

25(OH)D levels 20–30 ng/ml

To confirm whether the patient was already on appropriate vitamin D supplementation schedule considering the regularity of dose, intake, type of preparation. If vitamin D was not supplemented previously, consider starting vitamin D intake.[8]

25 OH levels >30 ng/ml

When the patient is on desired vitamin D levels and on supplementation, it is advisable to continue the previous management. In those not on supplementation to consider starting vitamin D intake as recommended for the general population.[8]

Experts' consensus

Experts recommend that desired serum level of vitamin D more than 30 ng/ml should be achieved with the help of a loading dose of 60,000 IU vitamin D followed by maintenance therapy. Once 30 ng/ml levels are achieved, experts recommend a 60,000 IU monthly or daily 2000 IU maintenance therapy. Figure 1 provides algorithm proposed by experts giving a step-by-step approach to manage vitamin D deficiency.[8,30]

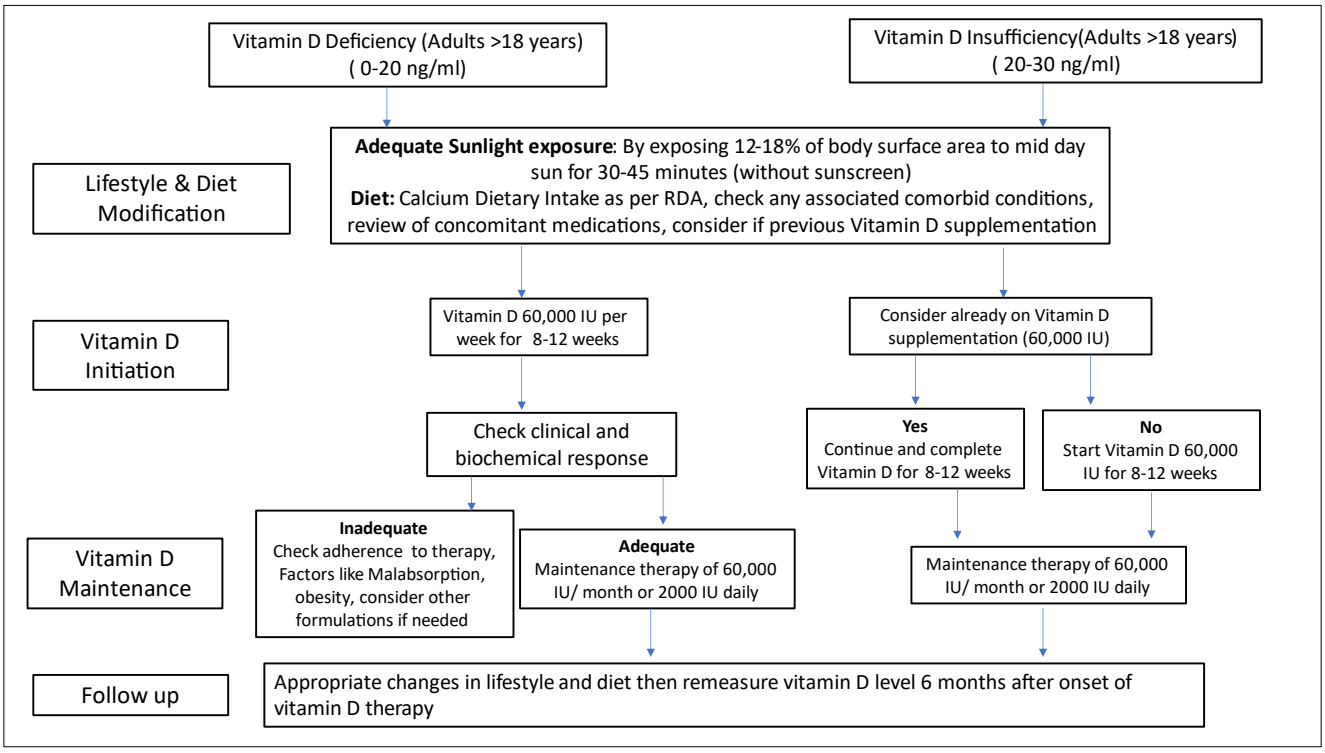

Figure 1: Proposed algorithm for management of vitamin D deficiency.[8,12]

NANOFORMULATIONS OF VITAMIN D

The vitamin D3 being a fat-soluble vitamin in conventional oral formulations is absorbed via lipid digestion and absorption pathway. Bile from liver and lipases/co-lipases from pancreas convert orally consumed vitamin D3 into nanosized micelles. These nanoparticles being water miscible cross the unstirred water layer covering the enterocytes and facilitate vitamin D3 absorption. Similar, to the body mechanism, nanoformulations traps solubilized vitamin D3 in a nano-lipid system. This system has a distinct stable hydrophilic surface that protects the breakdown of nanoparticles in presence of high concentration bile and lipases during its passage through the GIT. It delivers vitamin D3 directly at the site of absorption without depending on lipid digestion process like the traditional system.[31] Oral dosage forms like tablet, capsule, and oral solutions have different absorption rates. The efficiency of oral absorption of conventional vitamin D3 is approximately 50%.[32,33] The predicted human absorption of nanoformulation may be more than 90%. The bioavailability for absorption of drug was also found to be higher in oral solutions when compared to capsules in bioequivalent study conducted in healthy volunteers, it was found that relative bioavailability of nanoformulation was significantly higher than capsule by 36% based on $AUC_{(0\text{-}120\ hours)}$.[31] In another study by Krishnakumar et al, vitamin D3 oral solution formulated with nanotechnology was found to be bioequivalent to vitamin D3 tablet and capsule.[32] However, the oral solution of vitamin D3 demonstrated higher C_{max} and AUC when compared to tablet and capsule formulations.[32]

Other benefits of nanoparticle formulations of vitamin D are: they are stable at different PH reflecting stability of formulation in gastrointestinal tract; stable in different bile concentrations suggesting formulation is not affected by high or low bile concentrations which represents fed and fasting state respectively; uniform absorption across the duodenum, jejnum, and ileum; and higher absorption (90%).[33] Another advantage of nanoformulation is better compliance as it does not require consumption of milk or fatty meal for absorption.[31]

In a prospective, open label, single arm, non-comparative, dose response post-marketing efficacy study, in adults with deficiency or insufficiency of vitamin D (<30 ng/ml), the efficacy of 60,000 IU of nanoparticle-based vitamin D, once weekly, for 8 weeks orally was evaluated.[10] At baseline, the mean serum 25[OH] D levels were 15.90. After treatment with nanoparticle-based vitamin D a significant increase in the serum vitamin D levels was observed at 4 weeks (41.03) and 8 weeks (31.38) ($p<0.0001$). 84.2% of patients who received treatment for at least 4 weeks' period (n=38), had an improvement in serum 25[OH] D of >30 ng/ml.[10] In a multi-centre, parallel group, active-controlled study, the safety and efficacy of vitamin D3 nanoparticle-based vitamin D formulation was compared to that of tablet and capsule. All the patients with vitamin D deficiency in three groups were treated with 60,000 IU of vitamin D for 8 weeks. The serum 25(OH)D levels with nanoparticle-based vitamin D were elevated more than three times compared to baseline in the 8th week. This increase in 25(OH)D levels was significant as compared to the tablet and capsule group from the baseline to the 8th week. The iPTH levels in vitamin D3 oral solution were suppressed significantly by 63.53% as compared to tablet and capsule group from the baseline to the 8th week.[32] Vitamin D insufficiency is defined by hyperparthyrodism and vitamin D sufficiency by maximum PTH suppression.[15] Serum iPTH level showed better improvement in nanoparticle-based vitamin D when compared to tablets and capsules.[32]

Experts' consensus

Nanoparticle based vitamin D3 appears to be better in achieving higher levels of serum 25(OH)D than that observed with a similar dose of other oral dosage formulations of vitamin D3. Moreover, nanoparticle-based vitamin D provides better bioavailability and doesn't require consumption of fatty meal for better absorption.[32]

CONCLUSION

The prevalence of vitamin D deficiency in patients with comorbid conditions is reported as high as 84% in T2DM, 77% in prediabetes patients. Vitamin D deficiency may impair insulin secretion and impair the insulin resistance, resulting impact on pathogenesis of T2DM. Research indicates that vitamin D supplementation to maintain a serum 25(OH)D level 40 ng/ml is a promising approach to reducing the risk of diabetes in adults. The target level for vitamin D was reaffirmed by group of Indian experts as >40 ng/ml. Loading dose of vitamin D followed by maintenance therapy is recommended to manage vitamin D deficiency. Nanoparticle based vitamin D achieves better serum vitamin D levels owing to improved bioavailability. Considering high prevalence of vitamin D deficiency across comorbid conditions, there is a clear need to educate the public and health care professionals about the management of deficiency through adequate vitamin D supplementation followed by maintenance therapy.

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