

Prevention and Treatment of Vitamin D Deficiency in India: An Expert Group Consensus

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Abstract

Vitamin D deficiency is highly prevalent in India, yet no standardized guidelines exist for classifying vitamin D status or its prevention and treatment. Even more, there is no consensus specific to vitamin D supplementation for the Indian population, and there are inconsistencies in the cut-off values for deficiency, severe deficiency, and insufficiency across various guidelines, which this evidence-based consensus seeks to resolve, thus guiding healthcare professionals in identifying, preventing, and managing vitamin D deficiency. An expert group of 41 endocrinologists from across India developed the consensus using the DELPHI method, achieving over 90% agreement on all recommendations. The consensus defines vitamin D deficiency, severe deficiency, and insufficiency, recommending supplementation strategies to maintain physiological 25(OH) D levels of 40–60 ng/mL (100–150 nmol/L). Tailored treatment regimens for neonates, infants, children, adolescents, adults, the elderly, pregnant and lactating women, and individuals with co-morbid conditions are provided to ensure optimal health for all age groups in India.

Keywords: 25-hydroxyvitamin D3, vitamin D, vitamin D deficiency, vitamin D sufficiency

INTRODUCTION

Vitamin D deficiency is reported worldwide, both in sunshine-deficient and sunshine-sufficient nations, yet it continues to be one of the most underdiagnosed and undertreated nutritional deficiencies.^[1] Findings of a systematic review and meta-analysis have shown that Vitamin D deficiency is highly prevalent among adults from South Asian countries.^[2] India

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is a heliophobic (sun-fearing) nation, with almost 490 million people deficient in vitamin D.^[3] In a multicenter study, more than half the Indian children or adolescents were reported to be vitamin D deficient or insufficient^[4]—a trend that also applies to Indian adults.^[5]

Sufficient serum levels of 25-hydroxyvitamin D (25[OH] D) are required to maintain the skeletal and extra-skeletal physiologic effects.^[1] Inadequate vitamin D status is prevalent worldwide, which, apart from the well-known skeletal effects, has also been related to autoimmune disorders, cardiovascular diseases, cancers, insulin resistance, inflammation, neurological disorders, poor pregnancy outcomes, and enhanced mortality risk.^[6]

There is a lack of standard, uniform guidelines followed all over the world for the classification of vitamin D status. Many studies use serum 25(OH) D level <20 ng/mL (50 nmol/L) as vitamin D deficiency, but other studies use other thresholds for defining vitamin D deficiency status.^[1] Vitamin D administration varies between governmental agencies and clinical practice guidelines from various medical societies owing to differences in the definitions of sufficiency, deficiency, and insufficiency based on serum 25(OH) D levels.^[6]

The two major bodies, i.e. The Institute of Medicine (IOM)^[7] and the Endocrine Society (ES)^[8], have different opinions regarding the thresholds for defining Vitamin D deficiency, which are <12.5 ng/mL (31.25 nmol/L) and <20 ng/mL (50 nmol/L), respectively.^[7,8] This discrepancy occurs due to the interpretation of data surrounding the PTH plateau threshold. PTH levels are inversely associated with 25(OH) D.^[8]

IOM strictly believes that PTH values decline to a plateau at levels between 15 and 50 ng/mL (37.5 and 125 nmol/L), depending on age, race, ethnicity, body composition, renal function, and geographic location.^[9] ES believes that PTH begins to plateau in adults who have serum 25-hydroxyvitamin D levels between 30 and 40 ng/mL (75 and 100 nmol/L).^[8] Hence the different cut-off values.

It is also worth considering that the calcium absorptive performance at 20 ng/mL (50 nmol/L) of 25(OH) D is much lower than 34.4 ng/mL (86 nmol/L).^[10] This suggests that lower serum 25(OH) D levels may not provide the full benefit of calcium intake.^[10]

Kalra *et al.*^[3] proposed a clinical approach to managing individuals with vitamin D insufficiency [Figure 1].

A key challenge in India regarding vitamin D supplementation is the widespread lack of knowledge and awareness about vitamin D deficiency.^[3] Many individuals with deficiency are unaware of natural and dietary sources of vitamin D.^[3] Additionally, since vitamin D deficiency can often be subclinical, it is frequently overlooked, making both diagnosis and appropriate supplementation more challenging.^[3]

The present article reviews the existing clinical evidence and guideline-based recommendations to develop a consensus on

definitions of vitamin D sufficiency and deficiency, as well as dosage and use in special populations.

METHODS

The consensus was developed by an expert group comprising 41 endocrinologists from all four zones of India. All working group members had given a declaration of their individual conflicts of interest as per the rules of the International Committee of Medical Journal Editors (ICMJE).

The methods were adopted from the methods on which the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines are developed. The topics covered in the consensus were decided after several rounds of discussion and alterations. The search was initiated to cover literature encompassing vitamin D classification status, standard vitamin D dosage, vitamin D dose in different patient populations, and conditions where higher or lower vitamin D dosage may be required. The literature was searched through several clinical questions regarding vitamin D, for which the answers, particular to the Indian scenario, were needed. The working process was supervised and monitored by the chairperson of the consensus development group. The draft and the literature were made accessible to all the members through a shared Google Drive.

The draft recommendations were sent to the consensus group via email as a Google form in the first DELPHI round from January to February 2024. We received a strong consensus (agreement of >90%) for 80% of the recommendations and a consensus (agreement of 80–90%) for 20% recommendations. Recommendations having an agreement lower than 90% were again deliberated in virtual meetings. The chairperson of the consensus development group guided the discussion and ensured that all the experts presented their opinions. In case of disagreements, the chairperson summarized the differing viewpoints and asked the members to clarify their reasoning. After the voting, all the selected recommendations were discussed, modifications were incorporated, and a consensus greater than 90% was reached. There was more than 80% agreement on all the proposals.

Before starting with the classical literature search, the relevant published guidelines were explored and identified. Following the first review, the main bibliographic databases, including PubMed and the Cochrane Library, were searched for systematic reviews, meta-analyses, clinical trials, clinical studies, and clinical guidelines and consensus statements that answered the clinical inquiries. To screen the literature, the abstract was initially read to shortlist the article. After this, the text was thoroughly scanned to include or exclude it. A literature search was carried out for the last 10 years until February 2024, although the working group was allowed to consult and include highly relevant older literature in developing the consensus.

Limitations of the DELPHI process: Some well-known limitations of the Delphi process include its time-consuming nature, which can lead to participant drop-outs, and the potential

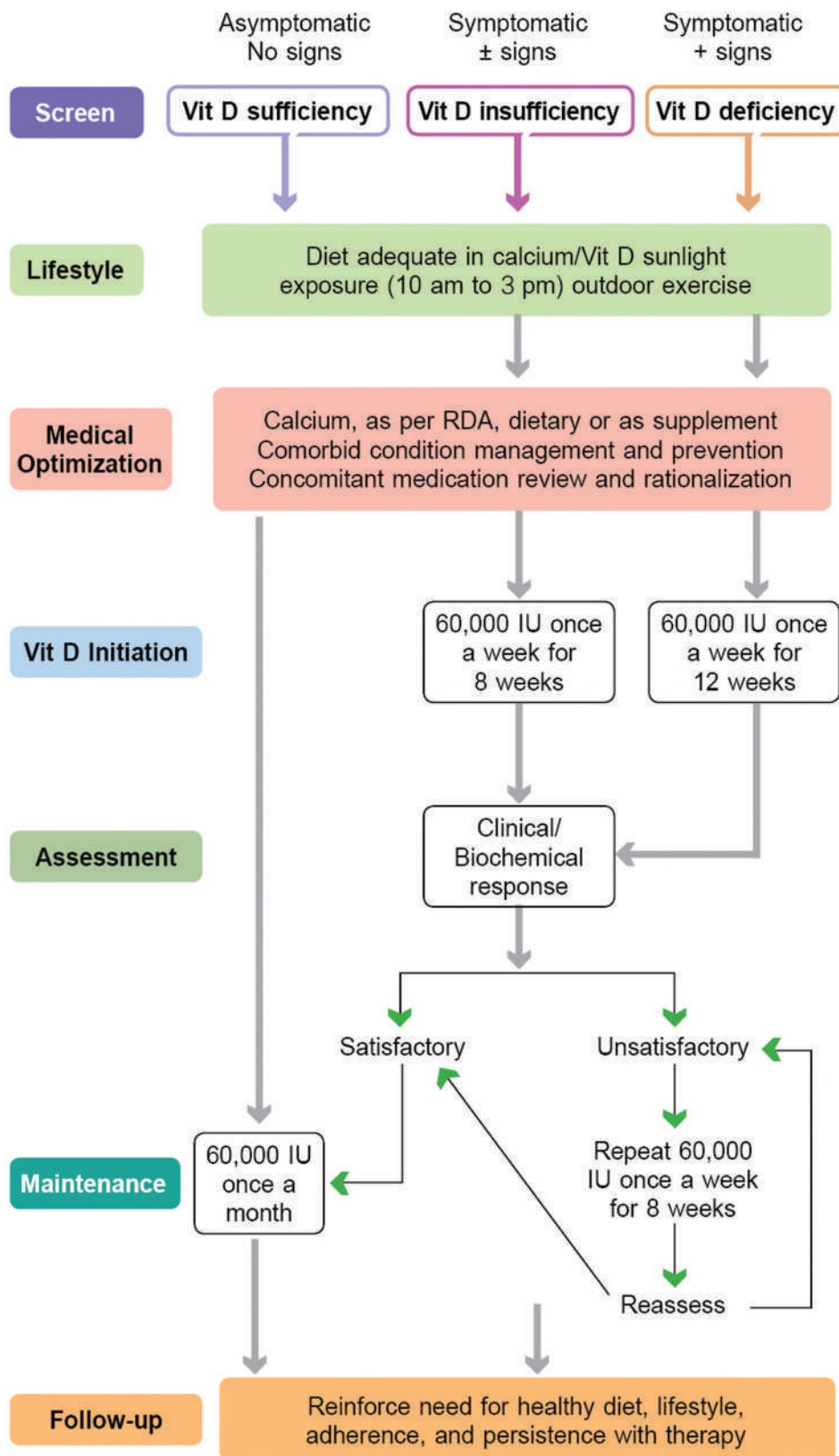


Figure 1: Algorithm for a clinical strategy to manage individuals with vitamin D insufficiency

for bias if monetary or moral incentives are used.^[11] While anonymity is a strength, it may reduce personal ownership of

ideas.^[11] The methodology faces challenges in generalizing results due to small sample sizes, limited expertise, or

regional biases.^[11] Expert interactions may also compromise independence, particularly when they are in contact outside of the process.^[11] Various strategies were employed to mitigate these limitations in this study. No drop-outs were observed, ensuring full participant retention, and there was no bias introduced by financial or moral incentives. While anonymity typically reduces ownership of ideas, the committee placed emphasis on the collective consensus and encouraged the valuable input of each participant. The panel consisted predominantly of endocrinologists from across India, but including experts from public health, nutrition, and epidemiology would have provided additional perspectives. Finally, to ensure the independence of expert responses, explicit requests were made for fair and unbiased opinions, reducing the risk of undue influence from participant interactions.

RESULTS

After the literature search and selection, reading, and evaluation of the manuscripts were completed, the consensus group held a meeting to discuss and deliberate on the suggested recommendations. Following their review and feedback, the final 29 recommendations were drafted.

The conversion factor for estimating serum 25(OH) D levels is 1 ng/mL = 2.5 nmol/L.

Recommendations and statements

Clinical question 1: What is the standard definition of vitamin D sufficiency and deficiency?

Recommendation 1: Vitamin D deficiency, severe deficiency, and insufficiency can be defined as

- Deficiency <20 ng/mL (50 nmol/L) of serum 25-hydroxyvitamin D
- Severe deficiency <10 ng/mL (25 nmol/L) of serum 25-hydroxyvitamin D
- Insufficiency: 20–30 ng/mL (50–75 nmol/L) of serum 25(OH) D levels.

Recommendation 2: Prevention of vitamin D deficiency in the general population is recommended irrespective of age, physical activity, and lifestyle.

Recommendation 3: The aim of vitamin D3 therapy should be to achieve a physiological 25(OH) D level (40–60 ng/mL or 100–150 nmol/L).

Recommendation 4: If disease-specific practice guidelines are unavailable, strategies for preventing vitamin D deficiency in high-risk groups should be similar to those for the general population.

Recommendation 5: The vitamin D supplement/replacement regimen in adults should be

- a. Vitamin D sufficiency – cholecalciferol 60,000IU, once a month
- b. Vitamin D insufficiency – cholecalciferol 60,000IU, once a week for 8 weeks (once sufficiency is achieved, transition to cholecalciferol 60,000 IU, once a month)

- c. Vitamin D deficiency: Cholecalciferol 60,000 IU, once a week for 12 weeks (once sufficiency is achieved, transition to cholecalciferol 60,000 IU, once a month).

Recommendation 6: Adjusting the dosing regimen to the patient's preference and supplementing weekly or monthly may positively impact adherence.

Recommendation 7: In the risk groups (Box 1), the evaluation of vitamin D status, based on a serum 25(OH) D assay, is strongly recommended.

Recommendation 8: A 25(OH) D value of ≤ 20 ng/mL (≤ 50 nmol/L) reflects a strong need to initiate vitamin D replacement.

Recommendation 9: A single-loading therapy using a cholecalciferol dose of 1,00,000 IU or higher is not recommended in India*.

*A loading dose of vitamin D should be used only under expert monitoring.

Recommendation 10: Cholecalciferol dosing for therapy of vitamin D deficiency should be based on serum 25(OH) D concentrations (if affordable and feasible) and previous prophylactic schemes.

Recommendation 11: A daily and cumulative (weekly, biweekly, monthly) dosing regimen of therapy with the use of cholecalciferol to attain and maintain optimal 25(OH) D concentrations is complementary, effective, and safe.

In a healthy Indian population, the reference range of 25-hydroxycholecalciferol is very low, and the lower threshold of normal is about 13.5 ng/mL (33.75 nmol/L). A study conducted among 20- to 50-year-old individuals indicated that vitamin D insufficiency starts at 25-hydroxycholecalciferol values of 13.5 ng/mL (33.75 nmol/L) and deficiency at 7 ng/mL (17.5 nmol/L).^[12]

Serum 25(OH) D levels <10 ng/mL are associated with numerous skeletal and extra-skeletal manifestations like increased risk of osteopenia, fractures, serum PTH levels,^[13] high levels of hepatitis B virus replication in patients with chronic hepatitis B,^[14] lower 5-year survival rate in patients with ovarian cancer,^[15] etc. Hence, it is justifiable to consider serum 25(OH) D levels <10 ng/mL (<25 nmol/L) as a severe deficiency.

In a study on 2,500 Indian children, the mean vitamin D concentration was 18.32 ± 9.56 ng/mL (45.8 ± 23.9 nmol/L),

Box 1: High-risk Conditions Needing Routine Vitamin D Supplementation

1. Conditions such as cerebral palsy, neuromuscular disorders
2. Chronic kidney disease
3. Chronic liver disease
4. Malabsorption syndromes
5. Chronic use of glucocorticoids, antiepileptic drugs, ketoconazole
6. Endocrine diseases such as hyperparathyroidism
7. Diseases with extensive cutaneous involvement

with younger age, female gender, overweight, and urban residence being major contributors to vitamin D deficiency.^[4]

Table 1 depicts the recommendations on the serum 25-hydroxyvitamin D levels given by various medical bodies across the globe.

While there is no clear consensus for the optimal level of 25(OH) D, serum levels >20 ng/mL (>50 nmol/L) seem adequate for bone health. Different clinical studies use different thresholds for defining vitamin D deficiencies.^[16] Furthermore, serum 25(OH) D has been regarded as the barometer of Vitamin D status; hence, it is used to determine Vitamin D deficiency, severe deficiency, and insufficiency before initiating Cholecalciferol therapy.^[17]

As seen in Table,^[16,18-20] there is a need for a consensual definition of vitamin D sufficiency and deficiency levels, considering the vitamin D deficiency epidemic.^[16]

The dose of vitamin D supplement varies depending on the deficiency, the patient's age, and the presence of risk factors. It

has been suggested that every 100 IU vitamin D supplement per day results in an increase of 0.7–1.0 ng/mL (0.28–2.5 nmol/L) in serum 25(OH) D. Vitamin D supplementation is safe up to a dose of 10,000 IU/day for 5 months without any signs of toxicity.^[21] Besides, there is a sync between the Indian, Brazilian, and Endocrine Society's guidelines.^[8,19,20] A Central and Eastern Europe expert consensus statement recommends a vitamin D supplement of 800 to 2,000 IU daily for adults to ensure vitamin D sufficiency. Similar doses are also recommended for the treatment of vitamin D deficiency; however, higher vitamin D doses (6,000 IU daily) may be used in the initial 4 to 12 weeks of treatment for rapid treatment of deficiency, followed up with a maintenance dose of 800–2,000 IU daily.^[22]

It is worth mentioning that the debate between daily and bolus vitamin D supplementation remains ongoing, as both regimens offer distinct benefits. However, it is important to note that adherence to daily dosing is often lower, which may be due to difficulties in swallowing combined vitamin D/calcium tablets, gastrointestinal side effects, polypharmacy, and patient reluctance toward regular supplementation.^[23] In contrast, bolus doses of Vitamin D can lead to sustained improvements in serum 25(OH) D and parathyroid hormone levels, likely due to its long half-life. After ingestion, vitamin D is either converted to 25(OH) D or stored in fat, which is slowly released over time. As a result, daily, weekly, or monthly dosing can achieve similar circulating concentrations of 25(OH) D over an equivalent period.^[23]

An oral loading dose of vitamin D can be considered in Vitamin D deficient patients like those with Colorectal Cancer,^[24] cardiovascular risk factors (Diabetes mellitus, insulin resistance, peripheral artery disease, and stroke history), autoimmune and inflammatory conditions (primary dysmenorrhea and rheumatologic patients), infectious or acquired conditions (alcoholic liver cirrhosis, cystic fibrosis, Tuberculosis, intensive care unit placement, and pregnancy).^[23]

Clinical question 2: What vitamin D dosage is recommended in neonates and infants?

Recommendation 12: For children aged 0–6 months, 400 IU/day (10 µg/day) of cholecalciferol should be taken from the first days of life, regardless of the feeding method.

Recommendation 13: For children aged 6–12 months, take 400–600 IU/day (10–15 µg/day) of cholecalciferol, depending on the daily amount of vitamin D consumed with meals.

Vitamin D is necessary for calcium absorption in the cells through its active form, 1, 25-dihydroxy vitamin D. While the role of serum 25(OH) D as a vitamin D marker is extensively studied, currently, there are no recommendations regarding routine screening of 25(OH) D levels in healthy preterm or full-term infants. As indicated by the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP), the adequate serum level of 25(OH) D is at least 20 ng/mL (50 nmol/L) in preterm and full-term infants. Vitamin D-deficient rickets are

Table 1: Recommendations on Vitamin D serum levels from different medical bodies

Medical Body	Year of recommendation	Recommendation
The Endocrine Society ^[8]	2011	Defines Vitamin D deficiency as a 25(OH) D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH) D of 21–29 ng/ml (525–725 nmol/liter).
The US Institute of Medicine ^[9]	2015	A serum 25(OH) D level of at least 20 ng/mL (50 nmol/L) is sufficient to meet the bone health outcome requirements of almost 97.5% of the population.
Brazilian Endocrine Society ^[10]	2014	Serum 25(OH) D under 20 ng/mL (50 nmol/L) is defined as deficiency, levels from 20 to 29 ng/mL (50–72.5 nmol/L) as insufficiency and 30 to 100 ng/mL (75–250 nmol/L) as sufficiency. The guidelines define hypovitaminosis D as a serum 25(OH) D below 30 ng/mL (75 nmol/L).
Consensus group of 11 scientific organizations ^[12]	2016	Recommended the following serum 25(OH) D levels; sufficiency-25(OH) D>20 ng/mL (>50 nmol/L), insufficiency-25(OH) D between 12 and 20 ng/mL (30–50 nmol/L) and deficiency-25(OH) D<12 ng/mL (<30 nmol/L).
Endocrine Society of India ^[13]	2015	25(OH) D levels between 20 and 40 ng/mL (50–100 nmol/L) are considered to be adequate for the majority of the population.

Conversion factor: 1 ng/ml=2.5 nmol/L

seen in individuals with serum 25(OH) D levels below 12 ng/mL (30 nmol/L).^[25] Based on research evidence, it is suggested in IOM and AAP guidelines that 400 IU/day dose of vitamin D is adequate for almost all full-term infants.^[25]

It has also been seen in a study on full-term infants with low cord blood 25(OH) D levels that a daily vitamin D intake of 400 IU in the early months of life was sufficient to increase the serum 25(OH) D levels and promote the accrual of bone mineral content even when the initial levels of 25(OH) D was low.^[26] Several guidelines worldwide recommend the supplementation of 400 IU/day (10 µg) to prevent rickets and reduce vitamin D deficiency.^[27] The Indian Academy of Pediatrics (IAP) recommends 400 IU/day of vitamin D supplementation during infancy, with doses above 400 IU not offering any additional benefits for skeletal growth during childhood. Vitamin D toxicity in infants is defined as serum 25(OH) D >100 ng/mL (>250 nmol/L) with hypercalcemia and/or hypercalciuria.^[28] The guidelines provided by the Endocrine Society of India, comprising a group of 22 experts, recommend 400 IU of vitamin D daily for infants.^[16]

In a study on 100 preterm infants, it was seen that the majority of the preterm infants have biochemical vitamin D deficiency. The findings of this pilot trial showed that in extremely low gestational age newborns, initial higher doses of 800 IU/day for a small period of 1–2 weeks followed by a reduced dosage of 200 IU/day may be an ideal regimen. Generally, a standard total intake of 400 IU/day can help reach the serum 25(OH) D value over 20 ng/mL (50 nmol/L) in most infants and may be >30 ng/mL (>75 nmol/L) in many cases.^[28] Among different age groups, infants are considered to be at a higher risk of vitamin D deficiency as breast milk is a poor source of vitamin D, and complementary feeds for infants are not fortified or rich in vitamin D.^[29] In Turkey, the national vitamin D supplementation program provides 400 IU daily to children between 0 and 3 years old, which led to a gradual reduction in the prevalence of nutritional rickets.^[30] While a dose of 400 IU daily is beneficial in achieving serum 25(OH) D levels >20 ng/mL (>50 nmol/L) and preventing rickets in infants^[31–34]; however, the administration of doses over 400 IU did not bring about any significant benefits in bone mineral content or bone markers, and the risk of hypervitaminosis was seen with doses of 1,600 IU/day.^[33,34]

Clinical question 3: What vitamin D supplementation is needed in healthy children 1–10 years of age? What are the recommended doses and regimens of vitamin D in children with vitamin D deficiency?

Recommendation 14: In healthy children aged 1–3, 600 IU (15 µg)/day of cholecalciferol should be supplemented. Due to age-related restrictions on sunlight exposure, supplementation is recommended throughout the year.

Recommendation 15: In healthy children aged 4–10, cholecalciferol supplementation in doses 600–1,000 IU (15–25 µg)/day is recommended throughout the year, based on body weight and dietary vitamin D intake.

Recommendation 16: In children aged 3 years and above with confirmed vitamin D deficiency, 60,000 IU should be given once a week for 6 weeks.

Clinical question 4: What is the requirement of vitamin D in healthy and vitamin D-deficient adolescents?

Recommendation 17: In healthy adolescents, sunbathing with uncovered forearms and legs for 30–45 minutes between 10 am and 3 pm without sunscreen throughout the year is recommended. Routine vitamin D supplementation is not necessary, although it is safe and effective.

Recommendation 18: In adolescents aged 11–18 years with confirmed vitamin D deficiency, 60,000 IU should be given once a week for 6 weeks.

The IAP has given guidelines for using vitamin D in children. The proposed thresholds of vitamin D deficiency, insufficiency, and sufficiency are <12 ng/mL (<30 nmol/L), 12–20 ng/mL (30–50 nmol/L), and >20 ng/mL (>50 nmol/L), respectively. The recommended vitamin D supplementation during infancy is 400 IU/day; however, in older children and adolescents, the average requirement, 400–600 IU/day, respectively, should ideally be met from diet and natural sources like sunlight. Vitamin D deficiency should be treated with oral cholecalciferol in a recommended daily schedule of 2,000 IU for children under 1 year of age and 3,000 IU in older children for 12 weeks. In case there is a compliance issue, an intermittent dosing regimen is recommended for children over 6 months of age. A vitamin D level of >20 ng/mL (>50 nmol/L) should be maintained in children who have a high chance for vitamin deficiency, such as nephrotic syndrome, chronic liver disease, chronic renal failure, and administration of medicines like anticonvulsants or glucocorticoids.^[35]

In children under 5 years of age, vitamin D supplementation is linked to a mild betterment in the linear growth of the study participants. Adolescents are susceptible to manifest the effects of vitamin D and calcium deficiency.^[36] As per the Comprehensive National Nutrition Survey (CNNS) survey, the prevalence of vitamin D deficiency was higher in adolescents compared with other age groups.^[37] The IAP group recommends that the estimated average requirements of vitamin D and calcium during adolescence should be met with natural sources such as sunlight and dietary intake of vitamin D.^[35] Children at high risk in whom natural sources do not meet vitamin D adequacy should receive pharmacological supplementation (at least 400 IU/day) for the prevention of vitamin D deficiency. Hence, supplementation with vitamin D is effective for the prevention of vitamin D deficiency in infants and children at high risk.^[35] Box 1 provides conditions in children and adolescents who require daily vitamin D supplementation.

When the skin is exposed to ultraviolet B (UVB) radiation from sunlight, 7-dehydrocholesterol in the skin is initially converted to previtamin D₃. However, only approximately 15% of the 7-dehydrocholesterol is converted to previtamin

D₃, with the remainder undergoing photoisomerization into lumisterol₃ and tachysterol₃, both of which lack any role in calcium metabolism. The rest all cause a photo-equilibrium resulting in previtamin D₃ conversion into lumisterol₃ and tachysterol₃ and back to 7-dehydrocholesterol or several toxisterols. Hence, even with prolonged sun exposure, the risk of vitamin D intoxication is mitigated, as excess previtamin D₃ and vitamin D₃ are degraded into inactive photo-products. 10 am to 3 pm is an ideal time because the sun's zenith angle is more oblique before and beyond that time, resulting in very little vitamin D₃ production in the skin.^[38]

Clinical question 5: What is the recommended vitamin D dosage and regimen for elderly patients (>65 years)?

Recommendation 19: Due to the decreased efficacy of the skin synthesis, supplementation based on cholecalciferol in a dose of 1,00,000 IU every 90 days or 4,000 IU/day may be given empirically*.

*Specific patients may require high doses.

Those who are underweight may need reduced dosing frequency. Obese individuals may require higher doses.

Vitamin D supplementation is the most convenient option to achieve vitamin D adequacy efficiently, particularly in the elderly and those living in service homes.^[39] A 2023 consensus resulting from the 5th International Conference on "Controversies in Vitamin D" held in Italy suggested that vitamin D supplementation should be combined with calcium to reduce fractures in the older population. In elderly individuals, the target to achieve sufficient vitamin D should be a serum level of 25(OH) D >20 ng/ml (>50 nmol/L). It has been seen that a daily low dose of vitamin D can lower the chances of falling, particularly in elderly individuals.^[40] There is a consensus amongst experts that serum 25(OH) D levels under 10–12 ng/mL (25–30 nmol/L) must be prevented and treated.^[41] The findings of the Vitamin D Assessment (ViDA) study have shown that 1,00,000 IU of vitamin D administered monthly did not lead to a rise in fractures or falls.^[42] While many studies testing different regimens of vitamin D have revealed a dose-dependent rise in serum 25(OH) D levels, there is humongous person-centric variance.^[40] A study by Alavi *et al.*^[43] concluded that the dose to prevent severe deficiency (defined as 10 ng/ml or 25 nmol/L) is 400 IU/day. However, 1,000 IU/day is required to reach the safe levels of 20 ng/ml (50 nmol/L). In an ideal scenario, a combination of fortified foods and vitamin D supplementation is needed to manage vitamin D deficiency and increase the serum 25(OH) D levels to 20 ng/ml (50 nmol/L).^[40] The 'Study to Understand Fall Reduction and Vitamin D in You' (STURDY) study showed that when compared to 200 IU/day, 4,000 IU/day had a reduced risk of frailty status. However, there was no significant link between vitamin D doses and frailty status.^[44] Studies have suggested that 700–1,000 IU daily vitamin D supplementation may bring the concentration of 25(OH) D in older adults up to 30–40 ng/ml (75–100 nmol/L). However, those with a lower

baseline level of vitamin D may require a higher vitamin D dose to attain the targeted levels, while those with a lower baseline value may need a lower vitamin D dose. Vitamin D levels are also associated with seasonal variance, and it is suggested that many elderly may not achieve optimal serum 25-hydroxyvitamin D levels during the summer months. On the other hand, some individuals may achieve the targeted levels in the summer months but may not sustain optimal vitamin D levels during the winter months. These seasonal fluctuations suggest that the supplementation of vitamin D in the elderly should be independent of the season.^[45] The treatment of vitamin D deficiency should be dependent on baseline 25(OH) D levels and previous prophylactic management. In addition, patients with clinical risk factors for developing vitamin D deficiency and those with bone diseases should be treated. Vitamin D dosing should be ensured to achieve a level of 25(OH) D above 30 ng/mL (75 nmol/L). A loading dose of vitamin D, approximately 3,00,000 IU, should be given in daily divided doses or weekly intermittent doses. It is important to achieve a rapid correction of vitamin D deficiency in osteo-sarcopenic patients who are starting therapy with a potent antiresorptive or anabolic agent. Divided daily doses with maintenance doses are required in these patients to achieve targeted vitamin D levels.^[46]

Endocrine Society recommends a daily dose of 1,500–2,000 IU vitamin D, with an upper tolerable limit of 10,000 IU. As per the Endocrine Society and the American Association of Clinical Endocrinologists (AACE), a daily dose of 800 IU can be given to achieve >30 ng/mL (>75 nmol/L).^[8,47] Individuals visiting clinics for osteoporosis falls and fragility fractures are recommended to achieve a serum 25(OH) D level of at least 30 ng/mL (>75 nmol/L).^[8] The IOM recommends the administration of ≥800 IU/day of vitamin D through supplementation. However, they warn against excessive intake of vitamin D, but it has been suggested that doses <4,000 IU/day can be considered safe.^[48] A consensus from the European Menopause and Andropause Society (EMAS) is that in elderly people, diet is inadequate in achieving desired vitamin D levels. EMAS group recommends a daily dose of 600 IU, which can be increased to 700 IU/day from age 71 years.^[49] Elderly over 65 years of age, with proven deficiency, should be treated with a cumulative dose of ~6,00,000 IU, administered in daily divided doses of 5,000–10,000 IU throughout 2–4 months.^[50] Supplementing vitamin D₃ 97,333 IU every four months for one year, along with 1 g of calcium daily, significantly raises serum 25(OH) D₃ concentration in the first, second, and third months but then declines after the third to fourth month.^[51] Hence, supplementing 1,00,000 IU every 90 days is a reasonable choice.

Clinical question 6: What is the recommended dose of vitamin D in women planning for pregnancy, during pregnancy, and lactation?

Recommendation 20: Women planning pregnancy should receive adequate cholecalciferol supplementation, the same as

in the general adult population, if possible, under the control of serum 25(OH) D concentration.

Recommendation 21: When pregnancy is confirmed until the end of breastfeeding, cholecalciferol supplementation should be carried out under the control of 25(OH) D concentration to achieve and maintain optimal concentrations within the ranges of >30–50 ng/mL (>75–125 nmol/L).

Recommendation 22: If the assessment of serum 25(OH) D concentration is not accessible, it is recommended to use cholecalciferol at a dose of 2,000 IU/day (50 µg/day) throughout pregnancy and lactation.

In a prospective cohort study of vitamin D deficiency in pregnancy, it was seen that while more than half of the participants had vitamin D deficiency, supplementation at a dose of 100 IU had a small effect size and was not clinically significant. It has been seen that higher deficiency rates have higher chances of appearing in certain populations, particularly those with darker skin, those living in northern latitudes, and those with limited sun exposure.^[52] In a 2021 study by Kiely *et al.*^[53] India was one of the eight countries identified as a hot spot for exceptionally low vitamin D status.

A summary of clinical data on pregnancy outcomes revealed that early pregnancy is crucial and sensitive to deficiency of vitamin D or other micronutrients like folate or hormone deficiencies such as hypothyroidism.^[54] Subgroup analysis of a randomized controlled study has shown a reduction in mortality with vitamin D supplementation at a dose of ≤2,000 IU/day (risk ratio [RR]:0.35, 95% confidence interval [CI]:0.15–0.80); however, no significant doses more than 2,000 IU daily (RR: 0.95; 95% CI: 0.59–1.54). It has been demonstrated that a dose of vitamin D ≤2,000 IU/day during pregnancy can reduce the risk of small growth for gestational age, improve infant growth, and reduce the risk of fetal or neonatal mortality.^[55] In a study from Bangladesh comparing different doses of vitamin D in pregnant women from 17 to 24 weeks of gestation (weekly vitamin D doses of 4,200 IU, 16,800 IU, and 28,000 IU), it was seen that there were no safety concerns, and a significant rise in serum calcium and vitamin D ≥12 ng/mL (≥30 nmol/L).^[56] In a prospective cohort study among pregnant women assessing the impact of a 16-week daily vitamin D supplementation of 1,000 IU regimen, it was seen that a dose of 1,000 IU may not be adequate to address the issue of vitamin D deficiency.^[53] Wagner *et al.*^[57] suggested that breastfeeding mothers should receive supplementation of 6,400 IU vitamin D daily is safe in effectively increasing the maternal circulation of vitamin D in breast milk, thereby helping in achieving sufficient levels of vitamin D in breastfeeding infants.

There are varying guideline-based opinions about the recommendations of vitamin D in pregnant and lactating mothers. The World Health Organization (WHO) 2020 guidelines do not recommend using vitamin D supplementation in pregnant and lactating women with normal 25(OH) D levels. However, 200 IU of vitamin D supplementation is

recommended in pregnant women with suspected vitamin D deficiency.^[58] The American College of Obstetricians and Gynecologists (ACOG) does not recommend screening of vitamin D in pregnant and lactating women and suggests 1,000–2,000 IU as a safe dose.^[59] The National Health Service (NHS) England recommends using 400 IU units daily for pregnant women with normal vitamin D levels if they do not get adequate sun exposure. NHS also advises against prescribing a dose of more than 4,000 IU daily as it may be harmful. British Columbia guidelines, Canada, advises 400–600 IU for pregnant women and higher doses for those women who may be at a higher risk of deficiency. However, a maximum safe dose was not specified.^[60] A high prevalence of vitamin D deficiency (96%) has been reported in pregnant and lactating women in India. Pregnancy increases the requirement of 25(OH) D to support calcium absorption and the metabolism of calcium in the mother and fetus. Vitamin D deficiency during early pregnancy has long-lasting implications on health, including reduced bone mineral content and bone mineral density in offspring in later life. It may also lead to the development of rickets in infants. Vitamin D deficiency during pregnancy may also increase the chances of preeclampsia, the risk of preterm birth, and low birth weight neonates. Hence, ensuring adequate maternal vitamin D levels will lead to positive and beneficial pregnancy outcomes.^[61] Existing evidence has shown that the mother needs much higher doses of vitamin D (4,000 IU/day) to achieve adequate vitamin D levels in her breastfed infant.^[62] Two randomized controlled trials during pregnancy involving pregnant women less than 16 weeks of gestation showed that 4,000 IU vitamin D/day was superior to 400 or 2,000 IU/day by the second trimester in reaching adequate levels of at least 40 ng/mL (100 nmol/L) of 25(OH) D.^[63] Studies on pregnancy have shown that 400 IU/day vitamin D supplementation is completely inadequate. In the case of insufficient sun exposure, vitamin D supplementation of up to 4,000 IU/day is safe and effective in achieving the minimal level of 25(OH) D. Besides, women of darker pigmentation are at a much higher risk of being vitamin D deficient, and hence, careful vitamin D supplementation must be given to achieve vitamin D sufficiency in at-risk women.^[63]

Currently, no standard protocols are establishing the dose of vitamin D supplementation in pregnancy required to achieve the adequacy levels of circulating 25(OH) D of at least 40 ng/mL (100 nmol/L).^[64] As per the IOM of vitamin D during pregnancy and lactation, the recommended intake should be enough to manage blood levels of 25(OH) D >20 ng/mL (>50 nmol/L) in women with minimal sunlight exposure.^[7] The findings of a systematic review and meta-analysis suggested that supplementation of 4,000 IU daily is safe and effective in attaining the minimum required level of 25(OH) D.^[65] As recommended by the Federation of Obstetric and Gynaecological Societies of India (FOGSI), the recommended dose of vitamin D in pregnant and lactating women at risk of vitamin D deficiency is 1,500–2,000 IU/day. FOGSI has also recommended that

vitamin D status screening should be considered in early pregnancy and for those planning to get pregnant. A dose of 6,000 IU daily is considered safe and effective in maternal and nursing infants' vitamin D requirement.^[61]

Clinical question 7: How can a vitamin D deficiency be treated in individuals at risk of vitamin D deficiency? Do obese, immunocompromised, and those with metabolic disorders or cancer require different doses of vitamin D?

Recommendation 23 (a): Obese patients with malabsorption syndromes and those on medications affecting vitamin D metabolism, including anticonvulsant medications, glucocorticoids, and antifungals such as ketoconazole, and those taking medications for acquired immunodeficiency syndrome (AIDS) should be given at least 2–3 times more vitamin D for their age group to achieve an optimal concentration of >30–50 ng/mL (>75–125 nmol/L).

Recommendation 23 (b): These patients should receive a higher dose of 6,000–10,000 IU/day.

Recommendation 24: If the assessment of serum 25(OH) D3 concentration is not possible in the risk groups, cholecalciferol dosing should be carried out according to the guidelines for the general population at the maximal doses for a given age group.

Recommendation 25: In patients with extrarenal production of 1,25(OH)₂D, regular monitoring of 25(OH) D levels and serum calcium is recommended during treatment with vitamin D to prevent hypercalcemia.

Recommendation 26: For patients with primary hyperparathyroidism and vitamin D deficiency, we recommend treatment with vitamin D as needed. Serum calcium levels should also be monitored.

Recommendation 27: In immunocompromised patients, empirical supplementation of vitamin D 60,000 IU every 30 days (monthly) should be considered.

Recommendation 28: In patients with cardiometabolic disease, diabetes mellitus, cancer, and infectious diseases, it is recommended to monitor vitamin D supplementation to ensure a physiological range between 40 and 60 ng/mL (100–150 nmol/L).

Recommendation 29: In patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², a physiological level of 25(OH) D3 > 40 ng/mL (>100 nmol/L) should be maintained, and they should be regularly monitored.

Critically ill patients have a high occurrence of vitamin D deficiency, and reduced vitamin D levels are linked to increased severity, morbidity, and mortality in adults and patients in medical and surgical intensive care units.^[66] Along with cardiovascular disease and diabetes, obesity is also related to an increased risk of other noncommunicable diseases like musculoskeletal disorders and even cancer. Vitamin D is important in bone health and calcium homeostasis and may also have an 'anti-obesity' effect.^[67] A bidirectional relationship

exists between obesity and the metabolism and storage of vitamin D.^[68]

In a randomized cohort study, vitamin D supplementation led to an increase in serum 25-hydroxyvitamin D biomarkers, but obese or overweight patients showed a dull response. In this study, 2,000 IU vitamin D given daily increased the total 25(OH) D levels as novel markers of vitamin D status. The study findings indicated that body mass index (BMI) may change the result of the vitamin D supplementation with a lower response and achieve desired vitamin D levels at higher BMIs.^[69] In a systematic review by Pereda and Nishishinya, it was concluded that vitamin D requirements are higher in patients with obesity compared to lean patients. Hence, to achieve the desired optimal vitamin D levels, patients taking cholecalciferol may need 3 times the actual recommended vitamin D doses.^[70] The results of a meta-analysis showed that vitamin D supplementation in obese but healthy populations, particularly from Asia region following intervention ≥ 6 months, had a significantly beneficial decrease in BMI and waist circumference and a significant increase in serum 25(OH) D levels.^[71] A study conducted on vitamin D deficient overweight/obese Asian Indian women showed that a vitamin D supplementation for 78 weeks led to a significant reduction in fasting blood glucose, 2-hour glucose post-oral glucose tolerance test, glycated hemoglobin (HbA1c), and truncal subcutaneous fat and reversal to normal glycemic levels.^[72] A study has reported that hypovitaminosis D is highly prevalent in patients awaiting bariatric surgery and that the postoperative weight and the quantity of weight loss at 6 months after surgery were linked with postoperative serum level of vitamin D.^[73] Chakhtoura *et al.* have reported that a high dose of vitamin D supplementation (1,100–7,100 IU) is needed for obese patients to achieve a desired level of vitamin D above 20 ng/mL (50 nmol/L) after surgery.^[74,75]

The American Society for Metabolic and Bariatric Surgery (ASMBS) guidelines, 2013 recommend that physicians should consider adequate levels of 25(OH) D as > 30 ng/mL (>75 nmol/L).^[76] The AACE, the Obesity Society (TOS), the ASMBS, and the Endocrine Society guidelines recommend a high dose of vitamin D (3,000 IU daily to 5,000 IU 1–3 times weekly) supplementation in patients undergoing bariatric surgery.^[77] Alsareii *et al.*,^[76] in their article, have said that as per the Clinical Practice Guidelines on vitamin D supplementation in bariatric surgery, a high dose of vitamin D supplementation (3,000 IU daily to 50,000 IU 1–3 times weekly) is recommended.

Several conditions, diseases, or medications can negatively affect the metabolism of vitamin D, thereby raising the requirement for this vitamin. There are several other conditions where low vitamin D status does not have a cause-effect relationship, but it accompanies certain diseases or conditions.^[78] It is of utmost importance to identify these risk factors so that these can be rectified or prevented to prevent and treat low vitamin D. Patients who have one or many risk factors for serum

25-hydroxyvitamin D levels should be screened for low serum 25(OH) D levels. Table 2 provides all the risk factors and associated diseases and conditions for low vitamin D status.^[79]

In individuals at risk of vitamin D deficiency, especially obese individuals or those having >90 kg and individuals with malabsorption syndromes, a 2–3 times higher dose of vitamin D may be necessary.^[6,21,41,80-84] In most patients, vitamin D doses of up to 10,000 IU daily are considered to be safe.^[85]

In a few cases, lower doses of vitamin D may also be needed. In patients who have or are at a high risk of hypercalcemia, like those with granulomatous disease, vitamin D dose should be adjusted for the individual patients depending on the calcemia, calciuria, 25(OH) D, parathormone, and 1,25-dihydroxy vitamin D levels.^[80] In such patients, small vitamin D doses are recommended to ensure serum 25(OH) D levels under 30 ng/ml (75 nmol/L).^[8]

The findings of a cross-sectional study by Utmani *et al.*^[86] showed that significantly lower mean serum 25(OH) D levels were seen in a metabolic syndrome compared to those without the syndrome. Studies have shown that reduced vitamin D is linked to reduced insulin sensitivity, enhanced insulin resistance, and high fasting blood glucose levels.^[87] A meta-analysis by Taheriniya *et al.*^[88] has demonstrated a significant correlation between reduced 25(OH) D levels and autoimmune thyroid diseases, Hashimoto's thyroiditis, and hypothyroidism. Vitamin D deficiency is highly prevalent in endocrine disorders, and its supplementation may have several benefits.^[89] In a large randomized controlled trial on patients with prediabetes at an enhanced risk of disease progression to type 2 diabetes, supplementation with 4,000 IU/day of vitamin D led to a gradual progression to type 2 diabetes compared to a

placebo. In non-obese patients with severe vitamin D deficiency at the start, adherence to vitamin D treatment significantly decreased the progression to type 2 diabetes.^[90] Patients with endocrine conditions, such as primary hyperparathyroidism, can be given up to 2,800 IU/day safely, and it is linked to a decrease in parathyroid hormone without affecting calcium or creatinine concentration levels.^[91] Individuals who have malabsorption disorders such as inflammatory bowel diseases, pancreatic insufficiency, celiac disease, cystic fibrosis, cholestatic liver disease, and short bowel syndrome are highly susceptible to vitamin D deficiency.^[92,93]

Vitamin D deficiency is commonly seen and even worsens during chronic kidney disease and its progression. It was seen in a study that more than 80% of pre-dialysis patients had 25(OH) D concentrations <20 ng/mL (<50 nmol/L), and their decreased kidney function affected the anabolic and catabolic phases of the vitamin D metabolism.^[94] In a comparative study by Oksa *et al.*,^[95] comparing low-dose (5,000 IU/week) and high-dose (20,000 IU/week) cholecalciferol supplementation showed that the high-dose group demonstrated a statistically high increase in 25(OH) D concentrations compared to the low-dose treatment group. Plasma parathyroid hormone levels were significantly reduced in both cases; however, it was demonstrated that the high-dose supplementation was more effective in increasing 25(OH) D concentrations. The commonly prescribed monthly oral dose of vitamin D is 1,00,000 IU, leading to an optimal level of serum 25(OH) D value in over 85% of cases in France.^[96] In Belgium, another study reported that the recommended targets (>30 ng/mL or >75 nmol/L) could be achieved following 12 months of oral vitamin D supplementation in a dose of 25,000 IU every 14 days.^[97]

It has also been seen that vitamin D deficiency is highly prevalent in cancer patients, where a particular study showed that 72% of individuals diagnosed with cancer had an insufficient vitamin D status.^[98] It has also been seen that early vitamin D deficiency (<20 ng/mL or <50 nmol/L) and inadequate feeding may be linked to a poorer prognosis in patients with metastatic melanoma.^[99] The findings of the VITAL study have revealed a significant difference of about 12 ng/mL (30 nmol/L) in 25(OH) D levels between the intervention (daily dose of 2,000 IU vitamin D) and the placebo-controlled group. The study also showed time-dependent benefits, as the relative mortality risk was reduced to 0.75 after 2 years of intervention.^[100] If 25(OH) D levels of about 21–54 ng/mL (52.5–135 nmol/L) are achieved, it may lead to a reduction in cancer-associated mortality and an increase in vitamin D levels above 30 ng/mL (75 nmol/L). For this, a dose of at least 1,500–2,000 IU/day is needed in adults.^[8]

Results of observational studies have shown that a high rate of vitamin D deficiency is seen in immunocompromised patients, such as those living with human immunodeficiency virus (HIV). Daily supplementation of 7,000 IU in HIV patients, monitored over a year, was safe and efficacious in improving vitamin D status. Supplementation of 7,000 IU administered

Table 2: Risk factors for Vitamin D status requiring higher Vitamin D supplementation^[70]

Group of risk factors	Conditions needing higher vitamin D supplementation
Musculoskeletal disorders	Rickets, osteoporosis, osteopenia
Systemic connective tissue diseases	Rheumatoid arthritis, fibromyalgia, chronic musculoskeletal pain
Glucocorticoid induced osteoporosis	
Endocrine and metabolic conditions	Diabetes mellitus (type 1 and 2), metabolic syndrome, hypo- and hyperparathyroidism, obesity
Malabsorption syndromes	Inflammatory bowel disease, Crohn's disease, cystic fibrosis, ulcerative colitis, celiac disease
Kidney disorder	Chronic kidney disease, dialysis patients
Cancer	Breast cancer, colorectal cancer, prostate cancer, hematological malignancies
Immunocompromised	Caused by HIV infection
Central nervous system disease	Multiple sclerosis, epilepsy, dementia, Alzheimer's disease, Parkinson's disease

daily has been effective in improving vitamin D status.^[101] A review of studies, including vitamin D doses ranging from 400 to 14,000 IU given daily, assessed the potentially protective role of vitamin D supplementation in immunocompromised patients. The results showed that 7,000 IU daily was the most effective dose, restoring vitamin D sufficiency to >30 ng/mL in 80% of patients, with higher vitamin D levels seen after 12 months of treatment.^[102] The results of a meta-analysis have also shown that vitamin D supplementation has clear advantages in acute respiratory infection when a daily or weekly dose of vitamin D is administered; however, the same result is not obtained with longer dosing intervals.^[103]

These recommendations are made specifically for the Indian population. It should be remembered that overdosing by prescriptions or taking high doses of vitamin D that exceed suggested recommendations may risk toxication. Serum 25(OH) D >150 ng/mL (375 nmol/L) are regarded as toxic. It may be elevated in hypercalcemia or hypercalciuria and lowered PTH. Toxicity shows clinical symptoms of lethargy, vomiting, polyuria, polydipsia, changed sensorium, weight loss, nausea, constipation, renal dysfunction or calculi, muscle weakness, hypertension, neuropsychiatric disturbances, cardiac arrhythmias, or even death.^[104]

Limitations

The limitation of this study was the experts were only from endocrinology, but not from public health, nutrition, and epidemiology, who would have provided broader insights; secondly, the urban and rural geographic variation in the vitamin D levels and the influence of different food habits in the different parts of India, which might influence the dietary intake of Vitamin D and hence the serum levels of Vitamin D were not taken into account.

Also, implementing these recommendations in rural or resource-limited settings in India has some challenges. One key issue is the need for better education among both healthcare professionals and the general public to reduce the overuse of high-dose vitamin D supplements in individuals who do not require them while addressing the underuse in those who do.^[41] However, the lack of educational resources in rural areas makes this difficult. Additionally, individuals from low socioeconomic backgrounds, particularly in rural regions, may use vitamin D supplements infrequently. Ensuring adequate supplementation in such settings will largely depend on comprehensive public health initiatives.^[41]

Further research should be carried out to overcome these limitations.

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Dr. Sanjay Kalra conceived the idea and prepared the first draft. All authors contributed equally to the refinement of the manuscript.

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Conflicts of interest

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