Annals of Medicine and Medical Sciences (AMMS)
Volume 04, 2025, *Page No.: 1025 to 1030*
Available at: *http://ammspub.com*

Original Article

OPEN ACCESS

Effectiveness and Safety of Vitamin D_3 Supplementation in Adults: Insights from an Indian Retrospective Analysis

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Abstract

Objective: To evaluate the efficacy and safety of vitamin D_3 supplementation in vitamin D-deficient Indian adults. ***Design:*** Retrospective, multi-center, observational study. ***Methods:*** Medical records of 8,685 patients were reviewed for demographics, comorbidities, baseline and post-supplementation serum vitamin D levels, perceived health improvement, and adverse events. Descriptive statistics and correlation analyses were performed. ***Results:*** Mean age was 53.7 years (SD = 12.3); common comorbidities included diabetes (14.6%) and hypertension (7.9%). Serum vitamin D increased significantly from 18.6 to 33.9 ng/mL ($p < 0.001$). All patients received 60,000 IU weekly for up to 12 weeks, followed by 1,000 IU daily maintenance. Significant improvements were seen only with ≥8 weeks of supplementation. Post-therapy, 32.1% reported excellent and 35.8% very good overall health. No adverse events occurred in 98.1%; mild, transient effects were reported in 1.6%. ***Conclusion:*** Vitamin D_3 supplementation significantly improved serum vitamin D levels with meaningful benefits observed only after at least 8 weeks of therapy, with a favourable short-term safety profile, supporting its use in managing vitamin D deficiency in Indian adults.

Keywords: ***Cholecalciferol, Real World Evidence, Serum vitamin D level, Vitamin D deficiency.***

Introduction

Vitamin D is a fat-soluble precursor molecule, produced by the body when it is exposed to ultraviolet B (UVB) present in sunlight [1]. Vitamin D deficiency is prevalent among the majority of the population globally, with approximately a billion patients deficient in Vitamin D belonging to diverse ethnicities and age groups [2]. Among the Indian population, Vitamin D deficiency is prevalent in approximately 490 million, with 31% of the affected patients comprising children and adolescents [3].

Adequate vitamin D within the body is critical for maintaining optimal serum levels of various minerals, which in turn facilitate normal bone mineralization, signal transmission, and muscular contraction [1]. Endogenous production of Vitamin D fulfils up to 90% of the body's vitamin D requirements, while minor vitamin D concentrations are derived from dietary intake, including fortified foods, supplementations, and certain fish oils [4]. Deficiency in vitamin D increases the susceptibility to developing rickets in pediatric population and osteomalacia in adult population. In addition, Vitamin D deficiency leads to increased chances of developing fractures, autoimmune conditions, infections, hypertension, and cardiovascular disorders [5].

Several risk factors contribute to vitamin D deficiency such as breastfeeding infants while lacking adequate vitamin D serum levels, pigmentation of the skin, obesity, old age, regional differences, insufficient consumption of vitamin D in the diet, and limited exposure to sunlight [6]. While India receives high sunlight throughout the year, it exhibits a large number of Vitamin D-deficient patients, attributable to the various underlying factors [7]. The common risk factors include inadequate exposure to sun and UVB, low consumption of calcium and vitamin, high consumption of phytates, phosphates, and caffeine, lactose intolerance, high levels of skin pigmentation, air pollution reducing UVB skin penetration, genetic factors, and obesity [4,8].

Diagnosis of vitamin D deficiency requires clinical assessment of 25-hydroxyvitamin D (25(OH)D) concentration in blood. It is a metabolite synthesized during vitamin D metabolism which serves as a clinically validated marker in vitamin D level assessment in patients. Vitamin D is biologically inert that becomes active when converted to 25(OH)D by hepatic enzymes. Therefore, the concentration of 25(OH)D acts as a marker for vitamin D status, such as serum levels and activity of the vitamin D [9]. Evidence reveals that, the recommended dietary allowance (RDA) of vitamin D is at least 400 IU to prevent the development of musculoskeletal disorders such as rickets in children [10]. The RDA for adults increases to 600 IU for adults, both men and women below 80 years, and 800 IU for the geriatric population over the age of 80 [11]. However, the benefits of vitamin D on skeletal and general health in

Received: July 23, 2025; **Revised:** September 04, 2025; **Accepted:** September 10, 2025

the adult and geriatric population are not well studied. Furthermore, the minimum therapeutic dose that must be administered in vitamin D-deficient patients varies across different international guidelines[12].

As the risk factors and treatment strategies for vitamin D deficiency differ across populations with various risk factors, it is important to determine effective therapeutic approaches to maintain optimal Vitamin D3 levels in populations. Previous studies provide evidence for using vitamin D supplementation to reduce the risk of all-cause mortality, cardiovascular mortality, and respiratory infections [13,14]. However, recent literature assessing the efficacy and safety profile of vitamin D3 supplementation specific to the Indian population is absent. Therefore, the present study aims to evaluate the safety and efficacy of vitamin D3 supplementation in vitamin D-deficient patients within the Indian population. The clinical endpoints include serum vitamin D levels, symptom improvement, clinical outcomes, and safety profile following vitamin D3 administration in adults.

Methods

Study design

The present study is a retrospective multi-center observational study design was employed for the present study. This design allowed for the retrospective collection of data from existing medical records focusing on clinical outcomes assessed post-vitamin D supplementation.

Study population

The study included adult patients (>18 years) who had completed at least two months of vitamin D_3 treatment, had documented vitamin D deficiency or symptoms suggestive of deficiency, and received vitamin D_3 supplements during the study period. Patients were excluded if they had underlying medical conditions affecting vitamin D metabolism or if their medical records were incomplete or had missing data.

Data collection

Screening medical records to identify patients with vitamin D deficiency or suggestive symptoms was performed. The patient medical records from Indian healthcare settings were used as the primary data source. Data were extracted by physicians using a standard reporting system. The extracted data included demographic information (age, gender, height, and weight), clinical data (serum Vitamin D levels, duration of treatment, and symptom relief), co-morbidities, and adverse events. Data cleaning and processing were managed through the electronic data capture and data management system. Patient records with missing data in any of these fields were not used for data analysis.

Data analysis

Both descriptive and inferential statistics were applied. Descriptive statistics were applied to assess self-reported overall health and calculated as percentage changes with mean and SD. Continuous variables such as age, height, weight, and serum 25(OH) vitamin D levels were reported as means and standard deviations (SD). The categorical variables were represented as frequencies and percentages. The efficacy of vitamin D supplementation was assessed by comparing baseline and endpoint measurements of vitamin D levels using paired t-test. Statistical Package for the Social Sciences [SPSS], Version 26 was used for carrying out the statistical analyses, with a significance threshold set at 5%.

Additionally, correlation analysis was performed to assess the relationship between endpoint vitamin D levels and Visual Analog Scale (VAS) scores, evaluating the strength and direction of the association using Pearson's correlation coefficient (R). A correlation coefficient close to ±1 indicated a strong linear relationship and statistical significance was determined by p-values (<0.05). The safety profile of the supplementation was analyzed descriptively, with adverse events reported as frequencies and percentages.

Ethical Considerations

The study ensured ethical conduct by complying with the ethical principles outlined in the Declaration of Helsinki and Indian Council of Medical Research guideline, prioritizing the rights, well-being, and confidentiality of participants. Approval from the local institutional ethics committee was taken before initiating the study for all sites. All collected data was anonymized to protect patient confidentiality. Stringent measures were implemented to safeguard the confidentiality and integrity of patient data throughout the research process. Informed consent was not obtained as the study does not include patient identifiers.

Results

Demographic data

The population demographic data is outlined in Table 1. The study cohort comprised 8,685 individuals with a mean age of 53.73 years (SD = 12.28). The cohort was predominantly male, constituting 63.74% (n = 5,536) of the participants, with females representing 36.10% (n = 3,135). The mean height of the cohort was 161.02 cm (SD = 7.43), and the mean weight was 68.49 kg (SD = 19.16) (**Table 1**).

Participants exhibited a range of comorbidities in less than 25% of the patient population. The most prevalent comorbidity was diabetes mellitus, present in 14.63% of individuals, and hypertension reported in 7.93% of the cohort. Dyslipidemia was identified in 1.70% (n = 148) of participants, while thyroid disorders (1.07%), osteoporosis (1.02%), and autoimmune disorders (0.53%) were less frequently observed (**Table 1**).

Effectiveness of Vitamin D3 Supplementation

Vitamin D levels were assessed both at baseline and after vitamin D3 supplementation. The mean baseline vitamin D level was 18.57 ng/mL (SD = 5.83), reflecting an overall deficiency in the cohort. Following supplementation, the mean vitamin D level significantly increased to 32.86 ng/mL (SD = 7.34), indicating a robust response to intervention (**Figure 1**). The increase in vitamin D levels was statistically significant ($p < 0.001$), as determined by a paired t-test with a 95% CI.

All patients were initiated on a standard regimen of vitamin D_3, receiving 60,000 IU weekly for up to 12 weeks, followed by a maintenance dose of 1,000 IU. The duration of supplementation varied among participants: majority (80.63%) received it for 12 weeks, while smaller proportions continued for 52 weeks (5.68%), 8 weeks (5.23%), and 2 weeks (2.88%). Additionally, supplementation durations of 24 weeks (2.54%) and 16 weeks (1.22%) were also observed. A significant increase in vitamin D levels was noted with supplementation lasting 8, 12, 16, 24, or 52 weeks, but not with 2 or 4 weeks of therapy (**Table 2**). These findings suggest that a minimum of 8 weeks of vitamin D supplementation is required to achieve a meaningful rise in serum vitamin D levels.

Symptom relief and overall health Outcomes

Post-supplementation, participants reported notable improvements in their overall health. In general, patient health after vitamin D3 supplementation was reported as very good (35.79%) and excellent

(32.08%) by the majority of the patients. On the other hand, 17.55% demonstrated good health, while 8.07% and 6.52% were rated as fair and poor respectively.

The mean overall health score was 66.4 (SD = 21.0), and the Visual Analog Scale (VAS) score for symptom relief was 62.8 (SD = 24.2). A correlation analysis demonstrated a significant positive relationship between endpoint Vitamin D level and VAS scores, with a Pearson correlation coefficient (R) of 0.643 (p = 0.001).

Safety and adverse events

The safety profile of vitamin D_3 supplementation in the study cohort appeared favorable; however, this observation is limited to the short term, as most patients received therapy for 12 weeks. The vast majority of participants (98.08%) reported no adverse events. A small proportion of the cohort (1.59%, n = 138) experienced mild adverse effects, including constipation, nausea/vomiting, and headaches. These events were self-limiting and did not require discontinuation of supplementation.

Table 1: Patient demographics and comorbidities

	Mean	**SD**
Age (years)	53.73	12.28
Gender	**n**	**%**
Male	5536	63.74%
Female	3135	36.10%
	Mean	**SD**
Height (cm)	161.02	7.43
Weight (kg)	68.49	19.16
Comorbidities	**n**	**%**
Diabetes	1271	14.63%
Hypertension	689	7.93%
Dyslipidemia	148	1.70%
Thyroid disorders	93	1.07%
Osteoporosis	89	1.02%
Autoimmune disorders	46	0.53%
Asthma	10	0.12%
Ankylosing spondylitis	9	0.10%

Table 2: Changes in vitamin D levels at various vitamin D3 supplementation duration

Duration (in weeks)	**Total dose of Vit D received (IU)** #	**N**	**%**	**Vitamin D3 levels (Pre)**		**Vitamin D3 levels (Post)**		**p-value**
				Mean	**SD**	**Mean**	**SD**	
2	120,000	250	2.88%	16.2	1.4	19.1	1.7	0.1983
4	2,40,000	68	0.78%	16.25	1.2	18.6	2.6	0.1464
8	4,80,000	454	5.23%	20.7	8.1	35.8	10.1	0.0002*
10	6,00,000	28	0.32%	18.5	8.9	33.8	7.8	0.001*
12	7,20,000	7003	80.63%	18.1	7.1	40.2	9.6	0.0001*
16	7,48,000	106	1.22%	24.1	6.2	40.1	7.7	0.0001*
24	8,04,000	221	2.54%	17.3	7.6	36.0	9.0	0.0001*
52	10,00,000	493	5.68%	17.4	6.1	39.3	10.2	0.0001*

** Statistically significant*

 # All patients were administered 60,000 IU of vitamin D_3 for a maximum of 12 weeks, after which a maintenance dose of 1,000 IU was given daily.

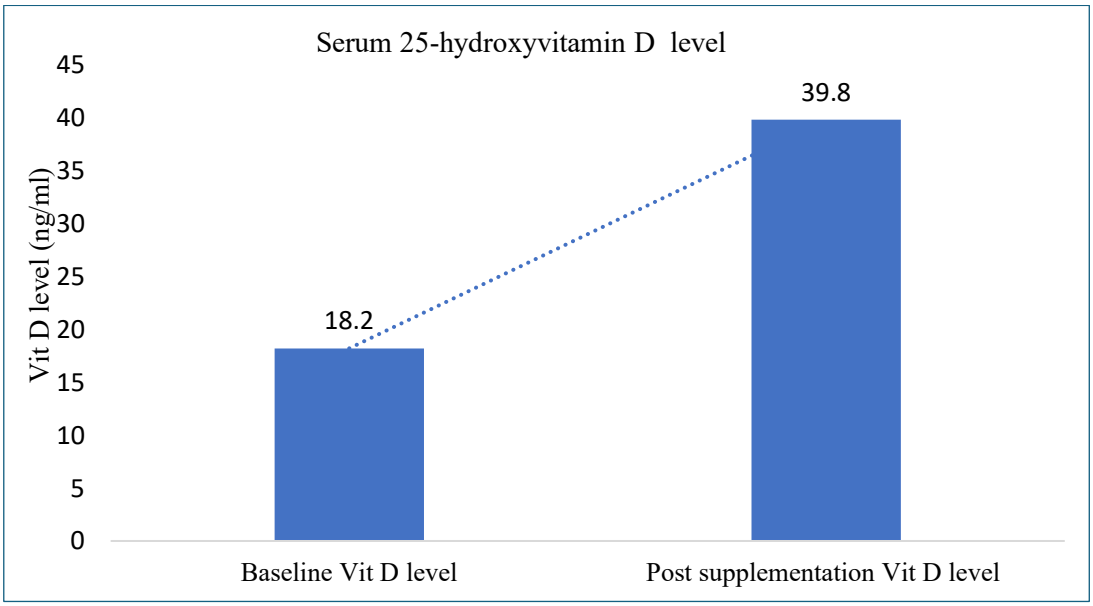

Figure 1: Serum Vit D level after vitamin D3 supplementation (overall)

Discussion

The present study shows that Vitamin D_3 supplementation was associated with improved mean serum vitamin D levels in deficient patients, with minimal short-term adverse events. Supplementation was also linked to better patient-reported outcomes, as indicated by a positive correlation between VAS scores and vitamin D levels. Adverse events were rare and mild, suggesting short-term tolerability. These findings highlight the association between Vitamin D_3 supplementation and improved vitamin D status in the Indian adult population, while emphasizing the need for further studies to confirm long-term safety and optimal dosing strategies.

The most prevalent comorbidity present in the study population is diabetes. Diabetes causes metabolic aberrations, including elevated excretion of vitamin D-binding protein through kidneys in comparison with the loss occurring in non-diabetic individuals, potentially causing the deficiency [15]. However, vitamin D deficiency causes elevated insulin resistance, leading to the hypothesis that low 25(OH)D levels potentially increase the incidence of type 2 diabetes mellitus (T2DM) in vitamin D-deficient population [16]. Despite the known correlation of vitamin D levels with diabetes, previous clinical studies have reported that vitamin D supplement therapy is not effective in reducing the risk of T2DM onset [17].

The primary finding of the study was the increased serum levels of vitamin D post-supplementation which is in alignment with other studies. Martineau *et al*. (2019) observed a 2.8 nmol/L elevation of vitamin D from baseline after 4-month vitamin D3 supplementation [18]. Another study by Qari (2013) reported the prevention of vitamin D deficiency in 98% of the patients using vitamin D supplements [19]. Hammami *et al*. (2017) reported a significant increment in serum 25(OH)D levels of 28.6(16.3) nmol/L in patients receiving vitamin D supplements in comparison with a mere increase of 3.3 nmol/L in the placebo group [20]. A recent study reported that consuming 20 g of vitamin D3 daily through the oral route for 12 weeks effectively improved vitamin D levels, with 94% of participants reaching 50 nmol/L or higher [21].

Our findings demonstrate that vitamin D supplementation must be continued for at least 8 weeks to achieve a significant improvement in serum levels, while shorter regimens of 2-4 weeks are inadequate. This reinforces the widely accepted strategy of an 8-12 week loading phase with high-dose therapy, followed by maintenance dosing to ensure long-term stabilization. The observed regimen is consistent with expert consensus, including Kalra *et al*., who recommend 60,000 IU weekly for 8-12 weeks to correct deficiency, followed by a lower maintenance dose to sustain adequate vitamin D levels [22]. It is important to note that there are no clear-cut guidelines on the optimal dose, duration, or frequency of vitamin D therapy for deficiency management, highlighting the need for individualized treatment decisions. Furthermore, high doses of vitamin D3 with a once-a-week administration have proven efficacy in improving the vitamin D status in Vitamin D deficient patients. Singh *et al*. (2019) reported an increase of 28.33 ng/mL vitamin D levels in patients receiving 60,000 units for 10 weeks [23]. However, the study observed a lack of association between the duration of vitamin D supplementation, and the clinical response in patients. Therefore, the efficacy of vitamin D supplementation can be predicted by the total administered dosage rather than the frequency of administration [23,24].

Physicians tend to prefer bolus administration (large doses at intervals) of vitamin D supplementation over daily doses. This is in alignment with the results of Fassio *et al*. (2020), that noted that bolus dosing is favored for its ease of adherence [25]. While vitamin D supplements are often expressed in terms of daily dosages, they are commonly administered once a week or once a month. The rationale for bolus dosing is based on the fact that vitamin D3, being fat-soluble, is quickly stored in adipose tissue, providing a sustained release over time [26]. Emerging studies suggest that the choice between bolus dosing and more frequent intake can influence the overall effectiveness of vitamin D supplementation [27].

Recent studies and meta-analyses have shown more favourable outcomes with frequent supplementation regimens, benefiting both skeletal and extraskeletal health [26,28]. Therefore, while the majority of the patients receiving bolus formulation showed improved vitamin D status, the use of frequent supplementation can potentially increase the serum vitamin D levels even higher.

The major outcome of the present study was the excellent short term safety profile of vitamin D3 supplements across patients from diverse demographics. Although mild side effects, such as headache and nausea, were reported by a small percentage of patients, uncontrolled or unmonitored intake can result in vitamin D toxicity, also known as hypervitaminosis. The presence of vitamin D supplements as easily available drugs without prescription in India increases the risk of vitamin D toxicity, which causes hypercalciuria and eventually hypercalcemia [29]. While incidences of vitamin D overdose are rarely reported, 25(OH)D levels in blood exceeding 375 nmol/L are typically observed in overdose cases, with high dietary calcium intake further increasing the likelihood of hypercalcemia [30]. Endogenous factors, including excessive generation of 1,25(OH)2D in granulomatous diseases or lymphomas, can also contribute to vitamin D toxicity [31]. As the half-life of vitamin D in tissues is longer, excessive intake may result in prolonged accumulation, persisting for up to 18 months, potentially inducing chronic toxicity, including nephrocalcinosis, secondary to sustained hypercalcemia and hypercalciuria [31,32]. Therefore, administration of vitamin D3 should be tailored to each individual and continuously monitored for toxicity.

While the RDA for vitamin D is established, the optimal vitamin D supplementation regimen (bolus or frequent) lacks standardization with heterogeneous recommendations across various guidelines and studies [12]. With an absence of defined dosage, treatment frequency, administration schedule, and treatment duration of Vitamin D3 supplementation, the current investigation sheds light on the most recent real-world data about its impact on clinical symptom improvement. A strength of the study lies in its data collection method, which involved gathering first-hand information from healthcare institutions across India on the management of vitamin D deficiency. Additionally, it is the largest real-world study assessing the clinical response of vitamin D3 in Indian patients. The study offers a thorough insight into administration patterns, underlying comorbidities, and safety profiles of patients, ensuring the findings are generalizable to the Indian population.

Supplementation was associated with better patient-reported outcomes, as indicated by a positive correlation between VAS scores and vitamin D levels; however, this association does not confirm causality and may be influenced by confounding factors such as comorbidities, diet, and sunlight exposure.

Certain limitations of the study must be addressed. Firstly, the study does not include a comparator arm. The absence of a comparator arm limits the ability to compare the efficacy against a control group or alternative treatment. Secondly, data on patient adherence to the supplements was not available, which may have led to the exclusion of severe adverse events or underestimation of the changes in clinical endpoints. Nonetheless, the large dataset reported

that the majority of the patients demonstrated improved vitamin D serum levels without side effects.

In conclusion

Vitamin D_3 supplementation improved serum vitamin D levels after at least 8 weeks of therapy, with good short-term safety in Indian adults. Although the present study indicates that vitamin D_3 supplementation is associated with improved levels and short-term tolerability in the Indian vitamin D-deficient population, further research is needed to evaluate optimal dosing frequency, treatment duration, the role of sun exposure, and regimen strategies for sustained vitamin D improvement. These insights will support evidence-based management of vitamin D deficiency.

Declarations

Conflict of interest

None

Funding/ financial support

Nil

Contributors

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Ethical Clearance

Approved

Trial details

A retrospective, multicentre, observational real-world evidence study

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