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Efficacy and Safety of Cholecalciferol Supplementation in Vitamin D Deficient Subjects Based on Endocrine Society Clinical Practice Guidelines

Chittari Venkata Harinarayan[1]*, Leena Appicatlaa[2], Bangalore Arunachalam Nalini[3] and Shalini Joshi[3]

[1]*Chief Consultant Endocrinologist, Fortis Hospitals (opp IIM-B), Bannerughatta Road, Bangalore - 560 076, India*
[2]*Chief Biochemistry Services, Fortis Hospitals (opp IIM-B), Bannerughatta Road, Bangalore - 560 076, India*
[3]*Consultant Internal Medicine, Fortis Hospitals (opp IIM-B), Bannerughatta Road, Bangalore - 560 076, India*

Abstract

Background: Hypovitaminosis is widely prevalent in India with limited data on vitamin D supplementation regimens.

Objective: We studied efficacy and safety of vitamin D supplementation as per the Endocrine Society Clinical Practice Guidelines (ESCPG) in vitamin D deficient subjects.

Design: Fifty two healthy subjects had their serum albumin, creatinine, calcium, alkaline phosphatase, 25 OH vitamin D (25OH D) and ntact PTH estimated at baseline, two and five months of supplementation. They were supplemented with Cholecalciferol 9572 IU/day and elemental calcium 1 gm/day. At the end of the 2nd month, those who attained vitamin D sufficiency were supplemented Cholecalciferol 3000 IU/day, and those still did not attain vitamin D sufficiency with Cholecalciferol 5286 IU/day along with 1 gm elemental calcium and the later were reassessed after three months.

Results: The mean ± SD of serum calcium, phosphorous, alkaline phosphatase were in the normal range at baseline, 2 and 5 months of supplementation (P= NS). The baseline median (IQR-Interquartile range) of 25 OHD and PTH was 6 (4-11) ng/ml and 19.6 (33-62) pg/ml respectively. At 2nd month there was threefold increase in 25 OHD levels 19.6 (14.6-28.75) ng/ml and further 50% increase at 5th month of supplementation. PTH levels were suppressed by 38 % at 2nd month and remained stable at 5th month. At end of 5th month, 46% had attained vitamin D sufficiency and 27% of subjects were still vitamin D insufficient.

Conclusions: Vitamin D supplementation based on recent ESCPG even up to upper tolerable intake levels (UL) along with elemental calcium of 1gm/day is safe and does not lead to hypercalcemia.

Keywords: Vitamin D deficiency; Vitamin D supplementation; Endocrine society clinical practice guidelines; Cholecalciferol

Introduction

Vitamin D is synthesized in adequate amounts on casual exposure of skin to sunlight to a radiation waveband 290 - 315 nm in most humans [1,2]. The UVB photons are absorbed by the epidermal 7-dehydrocholesterol e(7-DHC) (provitamin D) which is rapidly converted to cholecalciferol (previtamin D_3) by a temperature dependent process. This previtamin D_3 enters into the circulation bound to vitamin D binding protein (DBP). Previtamin D_3 is converted into 25 hydroxy vitamin D (25 OH D) in the liver which is biologically inert and requires hydroxylation in the kidney on carbon 1 by the enzyme 1 hydroxylase. The biologically active form of vitamin D is responsible for regulation of calcium and phosphate metabolism and is essential for maintaining bone health from infant to adult health. Vitamin D_2 is from the dietary sources. Vitamin D_2 and D_3 (D represents D_2 and D_3) are fat soluble vitamins incorporated into chylomicrons and absorbed into the lymphatics. Serum 25 OH D levels are reliable indicator of vitamin D status of an individual. The optimal level of 25OH D to maintain skeletal health and maximal dietary absorption of calcium in the gut is accepted to be 30 ng/ml and is defined as vitamin D sufficiency [3-6]. A value of <20 ng/ml is defined as vitamin D deficiency and values between 20 to 30 ng/ml is defined as vitamin D insufficiency.

Indian subcontinent is situated between latitude 37.6°N and 8.4°N with plentiful sunlight throughout the year. Despite this fact, several studies from India have documented widespread prevalence of hypovitaminosis D across the length and breadth of the country in all age groups [7]. Studies in South India have shown that rural agricultural laborers' who have their torso exposed to sunlight for more than 5-6 hours during their agricultural profession have also hypovitaminosis D of varying degree [8,9]. Increased urbanization, avoidance of sunlight, clothing practices, and greater atmospheric pollution may aggravate this problem [10]. While severe vitamin D deficiency may present with radiological features of rickets/osteomalacia, subclinical vitamin D deficiency or insufficiency may have adverse consequences on the bone because of secondary hyperparathyroidism. Adequate supplementation with vitamin D may increase the bone mass and decrease the risk of fractures [11,12].

The optimal amount of vitamin D required for treatment of vitamin D has been a matter of debate until the recent publication of Endocrine Society Clinical Practice Guidelines (ESCPG) [13]. The ESCPG suggests that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 week or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH) D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/day. The upper tolerable limit of 10,000 IU/day for children and adults 19 yr and older may be needed to correct vitamin D deficiency. In India one study used 60,000 IU of Cholecalciferol once a month

***Corresponding author:** Prof C.V.Harinarayan, Fortis Hospitals (opp IIM-B), Bannerughatta Road, Bangalore - 560 076, India, E-mail: cvhari5endo@rediffmail.com

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(2000 IU/day) and later 120,000 IU per month (4000 IU/day) for three months without calcium supplementation [14]. This study concluded that monthly administration of 60,000 IU of cholecalciferol in healthy subjects with hypovitaminosis D may be sufficient in summer months but higher doses are required in winter months to maintain 25(OH) D levels in normal range. Another study has used 60,000 IU/week along with oral calcium supplementation 1 gram per day which also contains Cholecalciferol 500 IU/day (totaling to a dose of Cholecalciferol of 8642 IU/day) for a period of eight weeks [15]. Though this study has shown a loading dose of vitamin D raises the 25OH D levels to normal range the effect is not sustained over a period of one year [15]. The recent clinical practice guidelines by the endocrine society [13] give us the guidance to treat "Vitamin D deficiency" and the amount of supplementation dose required to *maintain* adequate vitamin D levels. We report our experience in a group of subjects with vitamin D deficiency treated based on recent endocrine society guidelines.

Materials and Methods

Fifty two consecutive subjects were recruited for the study. Most of them were asymptomatic volunteers; attenders of patients who accompanied them for other illnesses. None of them had clinical signs or symptoms of overt metabolic bone disease such as bone pains, myopathy or fractures.

Exclusion criteria included history of renal, liver, dermatological diseases, known cases of hypocalcemia or hyperparathyroidism, pregnant and lactating women, history of drug ingestion (steroids, antiepileptic drugs and rifampicin) and those with vitamin D intoxication and granulomatous diseases.

Study design and conduct

The study was conducted from July to November in 2011. All patients were given cholecalciferol supplementation administered orally 60,000 IU (1500 µg) (Calcirol, Cadila Pharmaceuticals) per week [equivalent to Cholecalciferol 8,572 IU/day; (214 µg/day)] along with supplementation of calcium tablets twice a day [each tablet contains 1,250 mg of calcium carbonate equivalent to elemental calcium of 500 mg along with Cholecalciferol 500 IU (12.5 µg)] ("Shelcal – HD" Elder pharmaceuticals) for eight weeks. In total, these patients received Cholecalciferol of 9572 IU/day (239 µg/day) [8572 from the sachets (calculated from the weekly dosage of Cholecalciferol) and 1000 IU/ day via the calcium tablets along with 1 gm of elemental calcium] as "supplementation therapy" (Figure 1). The tolerable upper intake level (UL) of Cholecalciferol given by Endocrine Society Clinical Practice Guidelines of is 10,000 IU/ day for adults who are vitamin D deficient for a period of eight weeks [13].

Follow-up, compliance and subjects analyzed

After two months of therapy, they were evaluated again for their vitamin D status and other biochemical parameters. Those who had achieved "vitamin D sufficiency (25 OH vitamin D levels >30 ng/ml)" were treated with cholecalciferol supplementation administered orally 60,000 IU once a month (equivalent to 2,000 IU/day – as suggested by the guidelines as maintenance dose to maintain the 25 OH vitamin D levels above 30 ng/ml) along with supplementation of calcium tablets twice a day. Hence in total, these patients received Cholecalciferol of 3,000 IU/day [2,000 IU from the sachets and 1,000 IU via calcium tablet supplementation along with 1 gm of elemental calcium per day).

In subjects whose 25 OHD levels did not reach a vitamin D sufficiency range they were supplemented again with Cholecalciferol. They were given Cholecalciferol supplementation administered orally 60,000 IU per fortnight (equivalent to Cholecalciferol 4,286 IU/day) along with supplementation of calcium tablets twice a day. Hence in total these patients received Cholecalciferol of 5,286 IU/day (132.5 µg/ day) [4,286 IU from the sachets (calculated from the weekly dosage of Cholecalciferol given once in a fortnight) and 1000 IU/ day via the calcium tablets] along with 1 gm of elemental calcium. After three months of therapy they were reassessed for their vitamin D status and other biochemical parameters. The second dose of supplementation was half the initial dose so that the patients may not go in to hypercalcemia with prolonged therapy (Figure 1).

All subjects were stressed the need of regularity and compliance of supplementation in study period to achieve normal 25(OH) D levels.

Biochemical estimations

After an overnight fast venous blood samples were collected in the fasting state without applying a tourniquet for estimation of baseline biochemical and hormonal parameters. Quantitative estimation of serum creatinine, albumin, calcium, phosphorous and alkaline phoshatase were determined by an automated analyser (Roche cobas c 501), using kits supplied by of Roche cobas. Serum albumin was estimated by BCG green (normal range 3.5 to 5.2 g/dl) (detectable limit: 0.2-6g/dl); serum creatinine by Jaffe, generation 2 (normal 0.5 -1.2 mg/dl),(detectable limit: 0.17 -24.9 mg/dl); serum calcium by O-cresolphthalein complexone,(normal range 8.4 -10.2 mg/dl), (detectable limit: 0.4 to 20 mg/dl); serum phosphorous by UV Molybdate method (normal range 2.7 -4.5 mg/dl; (detectable limit 0.31 to 20 mg/dl), serum alkaline phoshatase by IFCC Gen 2 (normal range Men: 40 -130 IU/L; Women: 35-105 IU/L), (detectable limit: 5-1200 IU/L). Serum Vitamin D_3 was estimated by electrochemiluminiscence ECLIA on Elecsys 2010, the assay employs a polyclonal antibody directed against 25-OH vitamin D_3. It is a competitive assay. (Traceability: The method has been standardized against LC-MS-MS) (Detectable range: 4-100 ng/ml). A value of 30 ng/ml is defined as vitamin D sufficiency. A value of < 20 ng/ml is defined as vitamin D deficiency and values between 20 to 30 ng/ml is defined as vitamin D insufficiency. Parathyroid Hormone (PTH) intact was estimated by electrochemiluminiscence ECLIA on Elecsys 2010 Roche cobas kit. (Normal range is 15-65 pg/ml), (detectable range 1.2 to 5000 pg/ml.

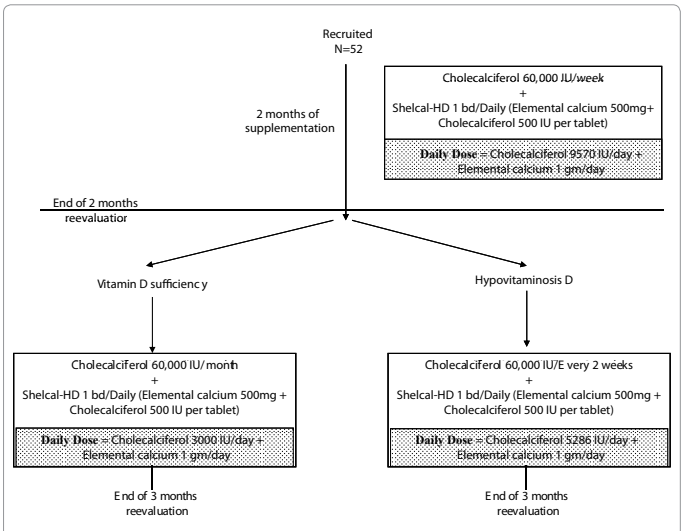

Figure 1:

Statistical analysis

Statistical analysis was performed with a statistical software SPSS (Version 11.5). Results are expressed as mean ± standard error of mean (SEM). Group means at different intervals of time of supplementation were compared using parametric (paired students *t* test) tests. ANOVA followed by Bonferroni correction test was used to compare various indices at three different intervals. With respect to 25 OHD and intact PTH variables because of the wide dispersion median and interquartile range (IQR) is calculated. For these two parameters to compare the changes in therapy with different intervals of time nonparametric test (Wilcoxon-signed ranks sign test) was used. P value of <0.05 was considered significant.

Results

The mean age of the study group was 48 ± 15 years (17 men and 35 women). The baseline biochemical and hormonal parameters are shown in Table 1.

All 52 subjects recruited for the study, returned for follow up at the end of two months of vitamin D *supplementation* therapy. The results at the end of 2nd and 5th month of supplementation were as follows (Figure 2): 1)Twenty three percent (23%) of subjects (n=12) had 25 OH D levels in vitamin D sufficiency range. These subjects were given *maintenance* therapy as outlined. At the end of three months of maintenance therapy, they did not return for follow up. All of them were individually contacted over telephone and requested for review. These subjects claimed their well being was good and were not inclined to reevaluate again. 2) Twenty three percent (23%) of subjects (n=12) had 25 OHD levels in the vitamin D in insufficiency range. They were given second course of supplementation as outlined above to be reviewed after 3 months (Figure 2). Fifty percent of the subjects (n=6) returned for 2nd review at end of 5th month (i.e. after 3 months of 2nd supplementation). All of them had their 25 OHD levels in vitamin D sufficiency range. Remaining six of them was lost in follow up. 3) Fifty four percent of the subjects (n=28) had 25 OHD levels in vitamin D deficiency range (25 OHD levels < 20 ng/ml). This group of patients were given 2nd course of supplementation for three months and reviewed. At the end of three months, 22% (n=6) of subjects achieved vitamin D sufficiency; 29% (n=8) of subjects were still vitamin D insufficient; 22% (n=6) of subjects were vitamin D deficient and 8 subjects were lost on follow up (Figure 2 and Table 2).

All subjects had normal serum albumin, creatinine, calcium, phosphorous and alkaline phosphatase at baseline before initiation of supplementation. The median and IQR (in brackets) of 25 OH D and ntact PTH levels were 6 (4-11) ng/ml and 46 (33 – 62) pg/ml respectively at baseline. At the end of two months of supplementation, the 25OH D levels reached 19.6 (14.6 – 28.75) ng/ml and intact PTH

Parameter	Baseline	2 Mths of trt	5 Mths of trt
AGE (Yrs)	49.67 ± 2		
S.CR (mg/dl)	0.77 ± 0.2	0.77 ± 0.2	0.78 ± 0.3
S.ALB (gm/dl)	4.25 ± 0.6	4.28 ± 0.5	4.22 ± 0.9
S.CAL (mg/dl)	9.15 ± 0.06	9.17 ± 0.06	9.25 ±0.11
S.PHOS *(mg/dl)*	3.62 ± 0.06	3.61 ±0.07	3.55 ± 0.09
SAP (IU/l)	92.54 ± 6.33	82.37 ± 5.92	87.75 ± 8.48
25 OHD *(ng/ml)*	6 (4-11)	19.6* (14.6-28.75)	27.4* (19.4-41.5)
Ntact PTH *(pg/ml)*	46 (33-62)	28.7* (22.5-36)	28 (24-37)

All values are mean ± SEM
25 OH D and N tact PTH: median and Inter quartile range (IQR) in brackets
*P<0.001
MTHS- Months

Table 1: Biochemical Parameters of the study group at Baseline, 2nd and 5th month of cholecalciferol supplementation.

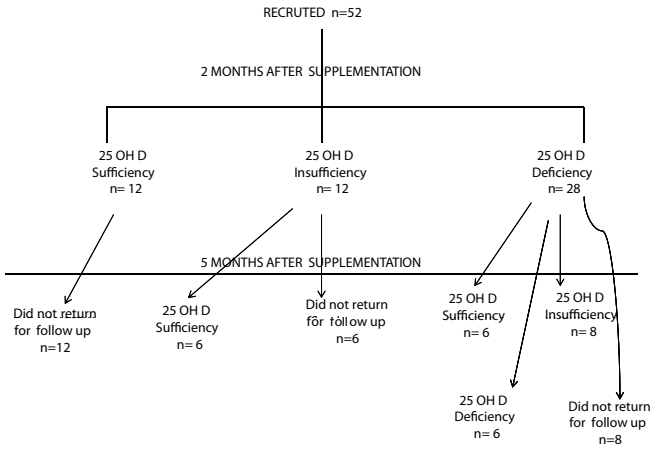

Figure 2:

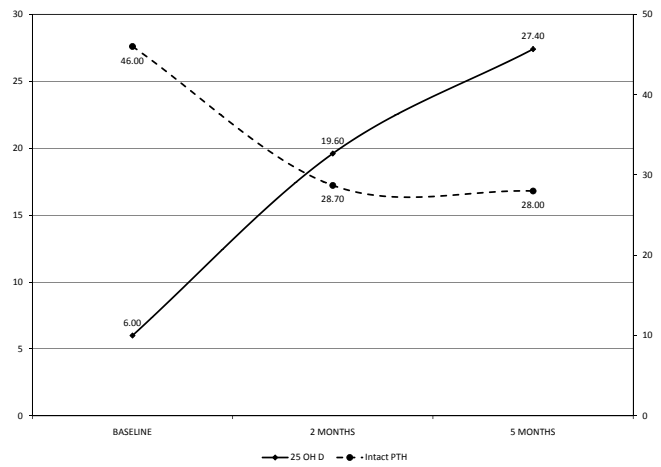

Figure 3:

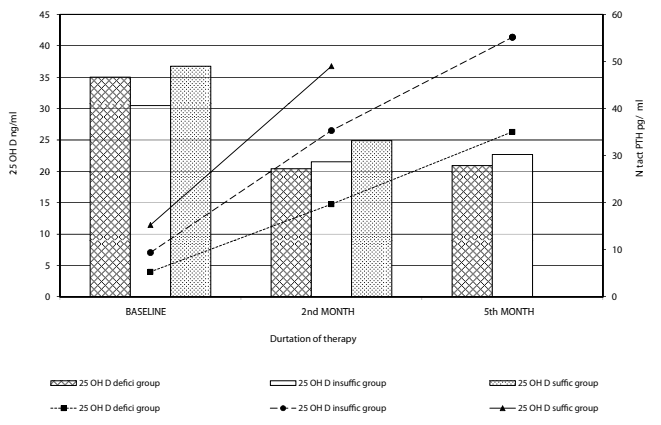

Figure 4:

Group	Baseline		2 Mths of supplem		5 Mths of supplem	
Whole group	25 OHD 6 [52] 4 – 11	N tact PTH 46 33 – 62	25 OHD 19.6* [52] 14.6 – 28.75	N tact PTH 28.7* 22.5 – 36	25 OHD 27.4* [26] 19.4 - 41.5	N tact PTH 28 24 - 37
Sub groups						
25 OHD Deficiency	4.00 [28] (4 - 9.55)	46.7 (31 - 66)	14.76 [28] (9.61 - 17.5)	27.23 (23 - 38)	26.30 [20] (18.62 - 33)	27.90 (24 - 39)
25 OHD Insufficiency	7.05 [12] (4 -11.5)	40.65 (29 - 61)	26.50 [12] (23.4 - 27.8)	28.71 (21.5 -37)	41.38 [6] (39.5 -52.8)	30.26 (19.6 - 53)
25 OHD Sufficiency	11.45 [12] (5.4 - 16.2)	49.00 (39.5 - 57.7)	36.75 [12] (32.9 - 47)	33.20 (19.2 - 34.7)		

Categorization of 25 OHD subgroups is based on their response after 2 months of supplementation
25 OH D *(ng/ml)* and N tact PTH *(pg/ml)*: median and Inter quartile range (IQR)
Values in square brackets in 25OHD columns denote the number.
*P<0.001

Table 2: Biochemical characterization of the study group based on subjects who responded at initial supplementation of cholecalciferol at the end of 2nd month and their follow up till 5th month.

fell to 28.7 (22.5-36) pg/ml which was statistically significant (P <0.001). The 25 OH D and ntact PTH correlated negatively (r = - 0.28; P < 0.05). The 25 OH D levels were elevated three times compared to baseline in the 2nd month and by 50% at 5th month of supplementation (compare to 2nd month) which was statistically significant (P<0.001). The ntact PTH levels were suppressed by 38% from the baseline at the 2nd month which was statistically significant P<0.001). With follow up, there was no significant suppression of PTH levels in the 5th month of supplementation (Figure 3).

There was no statistically significant difference in other biochemical parameters such as serum albumin, creatinine, calcium, phosphorous and alkaline phosphatase between baselines, 2nd and 5th months of supplementation.

Discussion

Following the increased awareness of widespread vitamin D deficiency in India [7] there has been much debate regarding corrective measures and adequate intake of vitamin D to correct vitamin D deficiency state. In India, apart from vitamin D deficiency, dietary calcium deficiency co-exists. Adequate levels of 25 OH D are required for maximal absorption of calcium from gut [3,4].

The present study is based on current Endocrine Society Clinical Practice Guideline [13]. Previous studies from India have used either 3000 or 4000 IU/day of Cholecalciferol without calcium supplementation [14,16] or 8642 IU/day of Cholecalciferol supplementation along with 1 gm of elemental calcium [15]. There is no mention of those who did not respond to therapy and their further follow up. This study addresses these issues. The present study has emphasized on *"supplementation therapy"* for achieving vitamin D sufficiency and later *"maintenance therapy"* to be followed as a preventive strategy for up keeping bone health based on guideline recommendations [14]. The present study also addresses the non responders follow up.

In the present study, only 23% of subjects attained vitamin D sufficiency at the end of 2 months of supplementation with threefold rise in serum 25OH D levels. We had used 9572 IU/day of Cholecalciferol which is the near upper tolerable intake level (UL) as per the guidelines [13]. In our study, 23% of subjects attained vitamin D sufficiency as compared to 54% of subjects who attained normalcy in other study from India [15] which has used similar dosage schedule. The probable reason could be that the present study was conducted beginning in July and the supplementation schedule followed through winter till December. The other study in India [15], the patients were recruited in March and followed through summer till May/June. Increased sunlight exposure could be the possible explanation for these differences. This explanation is substantiated by another study from India in the same location [14] which showed 2000 IU/day (50 μ/day) of Cholecalciferol provided different incremental response in serum 25 OH D levels of a group of patients supplemented in summer and winter. The incremental response of 25 OH D was higher in summer compared to winter [14].

There is no documented study from this country on the follow up of subjects who did not respond to initial 2 months of *"supplementation therapy"* (on supplementing with Cholecalciferol along with calcium). In the present study, only 23% of subjects attained vitamin D sufficiency at the end of 2 months of supplementation. Of the remaining 77% who did not achieve vitamin D sufficiency; 23% were in the vitamin D insufficiency range and 54 % in vitamin D deficiency range at the end of 2 months of supplementation. We used half the UL of Cholecalciferol recommended by the guidelines keeping in view the patient shouldn't go into hypercalcemia during 3 months of second supplementation (Figure 2).

At the end of five months of supplementation, 46% of the recruited subjects (n=52) had achieved vitamin D sufficiency and 27 % were still in vitamin D insufficiency range. None of them presented with hypercalcemia despite the dose of Cholecalciferol in the UL of the recommendation along with elemental calcium supplementation of 1 gm per day. About 27% of subjects were still vitamin D deficient at the end of 5th month of vitamin D supplementation. We postulate that these subjects should be evaluated for malabsorption of the gut. Other studies from India have also shown that only 56% to 47% of their study group had attained vitamin D sufficient range [14,15]. Other group has used 25 OH D levels of 20 ng/ml as their normal range and hence could not be compared [16]. The ntact PTH levels dropped by 38% from the baseline and were stable at the 5th month of therapy (Figure 3).

The potential implications of vitamin D deficiency in Indians are wide ranging. Apart from the low bone mass, it might involve association with type 2 diabetes mellitus and pulmonary tuberculosis. From the results of the present study, following conclusions can be drawn. 1) calcium supplementation should form an integral part of therapy for treatment of hypovitaminosis D, 2) Vitamin D used in upper ceiling does of 10,000 IU/day as recommended by the Endocrine society clinical practice guidelines does not produce hypercalcemia (despite elemental calcium supplementation of 1g/day) as observed in this study and other studies [17,18] also, 3) Evaluation of vitamin D status may be required at the end of 2 months of (Figure 4) supplementation to assess the need for further supplementation or maintenance therapy as a part of preventive strategy, 4) patients in

vitamin D insufficiency at baseline may reach vitamin D sufficiency after 2 months of supplementation, and 5) Patient with severe vitamin D deficiency at baseline (25 OH D <4ng/ml, which is also the lowest detectable limit of the assay – hence we may not be aware of the actual deficiency) may require a 2nd supplementation therapy (the dose and duration needs to be ascertained by further studies) (Figure 4). There are limitations in the study with respect to number of subjects studied and duration of the study. In a country like of India financial constraints are to screen, evaluate and follow up (mainly cost of investigation and medicines). More studies with larger number from different parts of India might help arrive at consensus especially with respect to duration of therapy and the need for second supplementation for non responders. Still this short duration study of five to six months gives us an idea of supplementations and problems one is likely to face in supplementation of vitamin D in a country like India.

Acknowledgement

CVH designed the study, followed up the patients, did analysis of data, involved in writing the manuscript, LA did the laboratory analysis and was in involved in writing the manuscript, BAN and SJ co ordinate in follow up of the patients and interacting with them. There is no conflict of interest among the authors.

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