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Original Research Article

Requirements for Maintenance Vitamin D3 Dosage in Indian Women with Postmenopausal Osteoporosis

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Abstract

Objective: There hasn't been much research on the vitamin D3 (cholecalciferol) dosage needed to maintain adequacy in women with postmenopausal osteoporosis (PMO) in India. While some recommendations call for 700–1100 IU of vitamin D per day, the Endocrine Society (US) recommends 1500–2000 IU per day to keep 25(OH)D concentrations at >75 nmol/L (1ng/ml = 2.5 nmol/L). We wanted to determine the oral cholecalciferol dose necessary to keep 25(OH)D concentration at >75 nmol/L in PMO Indian women, with the hypothesis that lower dose requirements would apply to those with a light complexion in Indian population.

Method: Within a year, 100 Indian women with baseline blood 25(OH)D concentrations more than 40 nmol/L were enrolled at Department of PMR, RNT Medical College, Udaipur. Prior vitamin D supplementation were stopped, and patients were randomized to receive either 15,000 IU/3-weekly (Group-A) or 60,000 IU/3-weekly (Group-B) oral cholecalciferol for 15 weeks while being closely monitored. At baseline, week seven, and week fifteen, serum 25(OH)D, PTH, and urine calcium levels were assessed.

Results: Osteoporosis severity, sun exposure (2 hours/week), and serum 25(OH)D baseline characteristics did not differ across treatment arms. With mean serum 25(OH)D values of 108.0±20.3 and 114.6±18.3 SD nmol/L, respectively, after 15 weeks, 91% of women who were sufficient at baseline remained sufficient on 15,000 IU/3-weekly compared to 97% on 60,000 IU/3-weekly (p=0.272). At the trial's conclusion, 38% and 81%, respectively, of the baseline-insufficient women in Groups A and B had acquired sufficiency (p=0.056). No dose was connected to toxicity or hyperparathyroidism.

Conclusion: Despite pre-trial vitamin D treatment and adequate sun exposure, 25.5% of women had insufficient levels of vitamin D, showing that in the, sunshine alone cannot provide enough. More than 80% of women can safely maintain vitamin D adequacy with cholecalciferol doses of either 800 or 2700 IU per day.

Keywords: Osteoporosis following menopause, vitamin D, oral cholecalciferol, tropical, hyperparathyroidism.

Introduction

The rapidly ageing population of East and Southeast Asia faces a serious public health concern with osteoporosis and its related morbidity and death [1]. The fact that hip fracture incidence is higher among Indian women over 50 is evidence that people of Indian heritage are particularly susceptible to osteoporosis [1]. The fundamentals of postmenopausal osteoporosis (PMO) care include vitamin D supplementation, antiresorptive medication, and appropriate calcium consumption. Vitamin-D is crucial for calcium metabolism, bone health, and muscle strength [Figure 1; 2]. Supplementing with cholecalciferol lowers the incidence of fracture and boosts lower extremity strength, but these effects have been proven to be dose dependent. 80–90% of vitamin-D is produced on the skin because of sun exposure, while just 10–20% comes from dietary sources [2].

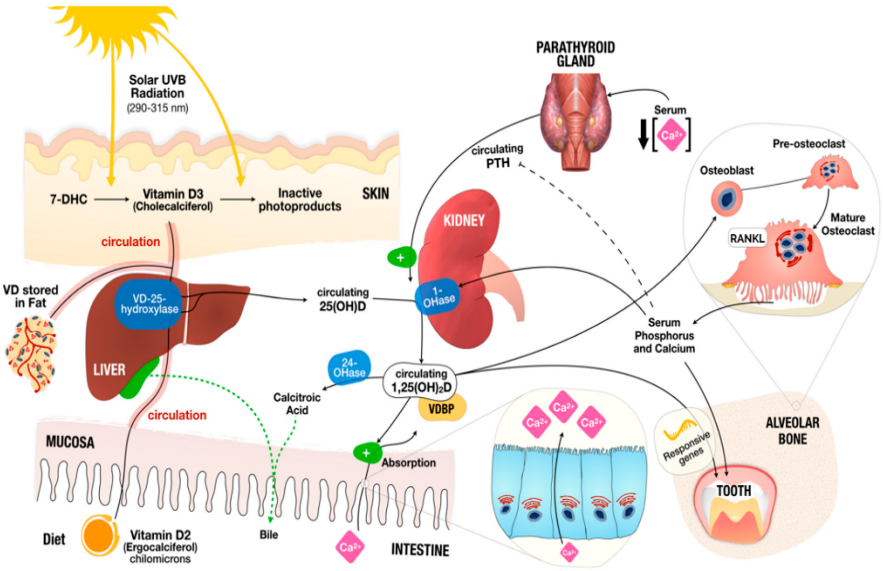

Figure 1: Association of Vitamin D Deficiency and Oral Health

A worldwide issue, hypovitaminosis D affects populations in both northern and even more southern latitudes. Despite receiving aggressive osteoporosis medication, vitamin D deficiency (75 nmol/L) was found in 52% of a large cohort of North American PMO women [3]. In recent years, there has also been evidence of widespread vitamin D deficiency in sun-rich regions including Hawaii, Saudi Arabia, and India [3]. Studies have also shown that China and South Korean/Japanese PMO women (some of whom were already using vitamin D supplements) have widespread vitamin-D deficiency [3].

Women with PMO at high risk of fracture, very few interventional studies focusing on the optimal dose of vitamin D required to maintain adequacy have been undertaken [4]. Women in India may need lower supplemental vitamin D dosages to maintain adequate levels because they are exposed to more sun than their counterparts in northern Asia and Caucasians [4]. However, cultural practises such as sun avoidance and the impact of ageing on the skin's capacity to synthesise vitamin D may hinder the ability of the ageing PMO woman to keep her serum 25(OH)D level over 75 nmol/L [4].

The aim of this study was to determine the maintenance dose of vitamin D supplementation in PMO women and other women at high risk of fracture.

Methods:

Study Design: This prospective study was carried out at Department of PMR, RNT

Medical College, Udaipur within one year of enrollment of patients.

Methodology: Following a baseline screening visit where the serum 25(OH)D level was measured, the subjects underwent initial randomization, a visit at three, seven, eleven, and fifteen weeks after randomization. Initial laboratory evaluations included measures of albumin, calcium, phosphorus, 25-(OH)D, intact PTH, and intact PTH as well as renal and liver function tests. Through an interview, physical exam, questionnaire, and review of medical records, all pertinent information was gathered. A validated sun exposure questionnaire was given to the patients, and the level of skin pigmentation was measured.

At the second visit, patients who were still eligible and had serum vitamin D levels greater than 40 nmol/L had their previous vitamin D supplements stopped. They were then randomly assigned to receive either 15,000 IU of oral cholecalciferol (vitamin D3) or 60,000 IU every three weeks for a total of 15 weeks. At 7, 11 and 15 weeks after randomization, serum 25(OH)D levels, calcium, phosphorus, intact PTH, albumin levels, and 25-hour urine calcium measures were reassessed. At the three-weekly appointments, any concurrent drugs or adverse events were noted.

Sample Size: 120 patients were originally enrolled in this study, however, only 100 patients were included based on inclusion criteria.

Inclusion criteria: Participants in the trial were postmenopausal osteoporotic women over the age of 50 who were patients at Department of PMR, RNT Medical College, Udaipur and had baseline blood vitamin D values more than 40 nmol/L. 100 women who matched the requirements for inclusion were chosen.

Exclusion criteria: Secondary osteoporosis (granulomatous disorders, thyrotoxicosis, glucocorticoid-induced osteoporosis, liver/renal illness), known metabolic condition other than PMO, and malabsorption (previous history of colectomy, Roux-en-Y gastric-bypass). Patients taking over-the-counter vitamin D supplements as well as those taking drugs (such as rifampicin, oestrogen, glucocorticoids, and anticonvulsants) that impact vitamin D metabolism were also eliminated.

Statistical analysis: To conduct the statistical analysis, SPSS 15.0 for Windows was used. Mean±SD is the format used to report descriptive statistics. Depending on normality, the student's t test or the Mann-Whitney test was used to analyze baseline comparisons. To compare the effects of oral cholecalciferol supplementation, a one-way between-groups analysis of covariance (ANCOVA) was performed. Statistics were judged significant at $p < 0.04$.

Results:

Baseline Characteristics:

Table 1 summarises the initial characteristics of the study participants. In this study, 100 women with postmenopausal osteoporosis who live in communities were included. Prior to study enrollment, 82.1% of the women were taking vitamin D supplements in some form, which were stopped at the time of recruitment. At the beginning, 42.1% of the participants were taking 300 IU per day, while 31.0% were taking >700 IU per day. Alendronate was actively used to treat osteoporosis in 81% of the sample group. Each group of 50 patients was randomly assigned to receive either 15,000 IU (Group-A) or 60,000 IU (Group B) of oral cholecalciferol every three weeks.

Table 1: Baseline Characteristics

Criteria	Mean±SD	Total vitamin D concentration		P-Value
		<50 nmol/L	>50 nmol/L	
BMI, kg/m^2	Mean±SD	22.6±2.7	22.7±3.7	0.964
Age, years	Mean±SD	66.4±6.3	68.0±5.4	0.262
PTH, pmol/L	Mean±SD	4.91±2.11	4.52±1.66	0.394
Vitamin dose at baseline, IU	Mean±SD	360±325	538±374	0.045
Hours of sun exposure per week, hours	Median (IQR)	2.51 (1.24-4.32)	2.24 (1.16-4.51)	0.827
Fraction of BSA exposed, %	Median (IQR)	0.36 (0.20-0.44)	0.38 (0.25-0.44)	0.724
Sun Exposure Index (SEI)	Median (IQR)	0.92 (0.34-1.94)	0.78 (0.36-1.57)	0.830
Skin colour	Median (IQR)	26.1 (24.1-26.1)	26.1 (24.1-26.1)	0.707

Age, BMI, the length of menopause, the severity of osteoporosis, sun exposure, skin color, mean serum 25(OH)D, serum calcium, and 25-hour urine calcium levels did not significantly differ between the two groups at the beginning of the study. At baseline, 25.5% of the 100 participants had 25(OH)D values that were insufficient (50.0–74.8 nmol/L), while 74.3% had enough (>70 nmol/L).

Insufficient and sufficient participants had used vitamin D supplements before study enrollment in 82.5% and 82.0% of cases, respectively, at baseline. At baseline, the median vitamin D dose was considerably lower in the inadequate group than in the sufficient group. In the categories with low and sufficient levels at baseline, respectively, 12% and 37.2% of participants were taking more than 700 IU per day prior to study enrollment. With both subgroups spending a median of 2.4 and 2.24 hours per week in the sun, there was no discernible difference in sun exposure between the insufficient and sufficient subgroups at baseline. Between the insufficient and sufficient groupings, there were no appreciable variations in age, BMI, or sun exposure index. After receiving monthly cholecalciferol, both treatment groups' mean serum 25(OH)D concentrations significantly increased from baseline to 15 weeks: Group A: 90.1±23.0 to 96.1±24.0 SD nmol/L; Group B: 91.5±24.5 to 107.0±22.6 SD nmol/L.

It was also not clinically significant (p=0.272) that the vitamin-D sufficiency rate decreased from 100% at baseline to 90% and 96% in Groups A and B, respectively, after three months. In Group A (low dosage) and Group B (high dose), respectively, only 38% and 81% of individuals who were deficient at baseline achieved adequacy; these differences, however, only approached clinical significance (p=0.056). At 7 weeks, the mean serum 25(OH)D concentrations in the sample population as a whole did not differ significantly between the low dose and high dose therapy groups; however, at 16 weeks, the mean vitamin D concentration in patients receiving high dose monthly vitamin D was significantly higher (p=0.026).

Treatment with low-dose vitamin D (Group-A) produced a significant increase in serum 25(OH)D concentration only after 15 weeks of therapy, whereas treatment with high dose (Group B) produced significant increases at both 7 and 15 weeks among women with insufficient vitamin D concentrations at the start of the trial [serum 25(OH)D level: 40 -70 nmol/L]. Low dose therapy had no discernible effect on blood 25(OH)D levels in patients who had

adequate levels at baseline, whereas high dose cholecalciferol led to discernible rises at both time periods.

Suppression of PTH

At both the beginning and completion of the research, all patients had normocalcemia. In the low-dosage (Group-A) and high-dose (Group-B) groups, respectively, 15.5% and 8.8% of patients had secondary hyperparathyroidism at baseline. After 3 months of treatment, all subjects with secondary hyperparathyroidism achieved serum PTH levels that were within the normal range. Between the subgroups with insufficient vitamin D at baseline and those with sufficient vitamin D at baseline, the mean PTH levels were not statistically different (4.8±2.0 vs 4.4±1.6 pmol/L, p=0.394). With vitamin D therapy, PTH levels dramatically decreased in both treatment arms. At any time point, there was no discernible change in mean PTH levels between the two treatment arms.

Safety

Throughout the course of this trial, none of the participants experienced hypercalcemia or hypercalciuria. Between treatment groups, there were no discernible variations in urine calcium excretion or adjusted serum calcium.

Discussion

Unexpectedly, even though 70% of the women in our group with PMO used vitamin D supplements, a quarter of them had baseline indications of vitamin D insufficiency (40–70 nmol/L). On the other hand, only a tiny minority of those who were adequate at baseline (17.8%) did not use cholecalciferol supplements before enrolling in the study. Only 12% of the women in the insufficient cohort were taking more than 700 IU of vitamin D per day, compared to 37.0% of the women in the sufficient subgroup, who were taking more than 700 IU per day. Additionally, individuals who had insufficient sun exposure at baseline had a median of 2.4 hours of sun exposure each week, which did not differ substantially from those who had sufficient sun exposure at baseline. These results suggest that in this cohort of patients with high fracture risk, food and sun exposure alone are insufficient to maintain appropriate vitamin D concentrations. Given that numerous guidelines recommend a minimum vitamin-D dose of 700 IU/day as one of the pillars of osteoporosis therapy, ethical considerations prevented a placebo arm in our investigation [5,6].

The older PMO lady should take vitamin D supplements universally for a number of reasons: (1) Regardless of vitamin D level, vitamin D therapy reduces the risk of falls and fractures in the elderly. (2) Calcium and vitamin D supplements have been used in conjunction with active osteoporosis therapy in the majority of RCTs proving its effectiveness. (3) The notion that vitamin D deficiency is common in the elderly (supported by our cohort) [7, 8]. In fact, the fact that a sizable portion of our cohort had insufficient vitamin D levels at baseline despite taking supplements shows that the issue is whether or not vitamin D supplementation is necessary, but rather how much vitamin D is required for the diaspora in India to have optimal bone health.

Although mean serum 25(OH)D concentrations after 15 weeks of therapy were significantly higher in patients in the high dose arm in the overall study population, both dosing regimens produced average serum 25(OH)D concentrations that were either within the 80-200 nmol/L range, which has been linked to the best outcomes for bone health, such as reduced fracture risk, increased BMD, and improved lower extremity function [8,9]. Importantly, neither the low dosage nor the high dose groups had any patients with secondary hyperparathyroidism after 15 weeks of treatment. There were no instances of hypercalciuria, hypercalcemia,

or vitamin D intoxication in either arm for the low dose or high dose maintenance regimens.

A maintenance dose of 800 IU daily may be assumed to not only maintain sufficiency in women but also improve bone-health related clinical endpoints [10–13] based on strong evidence in Western populations that the threshold levels for fracture risk reduction and fall prevention are 300 IU and 600–1100 IU, respectively. But it's vital to keep in mind that sunscreen use was not permitted for our study participants. Consequently, it is feasible that women who use sunscreen may need dosages greater than 800 IU per day to maintain sufficiency. Compared to 81% in the high-dose treatment group, only 37% of the women who were inadequate at baseline achieved sufficiency (>70 nmol/L) after 15 weeks of low-dose therapy. These variations in vitamin D sufficiency rates were statistically significant (p=0.036) and may have been clinically significant (p=0.056) if the sample size had been bigger. However, given that serum 25(OH)D continued to rise even in the second half of this 15-week study, it is possible that a longer course of treatment with low dose vitamin-D3 800 IU/day extending up to perhaps 5 months could have achieved 25(OH)D concentrations above 20 ng/ml in these women. Others have discovered that baseline serum 25(OH)D levels have an impact on vitamin D concentrations during treatment, and that lower maintenance doses are sufficient in people with greater baseline levels. According to a review a, participants who received 700–800 IU/day with mean baseline concentrations between 43.9–76.9 nmol/L experienced excellent fracture prevention in trials with mean reached levels of 100 nmol/L [14].

On the other hand, a review found that in a subgroup of 142 subjects whose serum vitamin D was measured, 800 IU daily increased serum 25(OH)D from a baseline 50 nmol/L to levels of 100 nmol/L at 6 months, maintaining concentrations at 105 nmol/L at 12 and 18 months, respectively. This landmark RCT included 3,270 healthy ambulant elderly postmenopausal women (mean age: 84 years) who lived in These mixed findings from randomized placebo-controlled trials in older Caucasian women in northern latitudes suggest that 800 IU/day is a sufficient amount to maintain vitamin D sufficiency in ambulant subjects who may also benefit from sun exposure, but is ineffective in institutionalised subject [15]. It is entirely plausible that our cohort of light skinned PMO women living close to the equator, with baseline vitamin D concentrations of >70 nmol/L, require a lower maintenance dose of vitamin D because baseline vitamin D is known to be influenced by latitude/sun exposure among other factors [16]. Our study's design had the advantage that patient compliance was guaranteed because all vitamin D administration took place in the hospital under close supervision.

These findings suggest that ethnic, geographic, and cultural variables should be taken into account when designing vitamin D therapy because of how these factors affect food and sun exposure. It is not unexpected that light-skinned women in India with year-round plentiful sun exposure need lower dosages of vitamin D than those who live in northern latitudes and are vulnerable to seasonal variations in UVB radiation [17]. These results, however, were not a guarantee given that skin production of vitamin D upon sun exposure is impaired in the elderly.

Additionally, Asian culture tends to value fair-skinned women, which may have required higher doses of supplemental vitamin D as a result of sun avoidance behaviors in our study sample. Contrarily, other studies appear to show that dark-skinned Asian Indians and African Americans need greater than usual dosages of vitamin D to treat vitamin D insufficiency because UVB sunlight doesn't penetrate as well into their skin as it does in

lighter-skinned people due of enhanced melanin pigmentation [18].

Limitation

Lack of precise food history about intake of fish, mushrooms, and eggs—important natural sources of dietary vitamin D—limits our study. However, since fatty fish like sardines, tuna, and salmon—which are fortified with vitamin D—are not commonly available or consumed**.**

Conclusion

In conclusion, 25.5% of PMO women had insufficient vitamin D levels despite vitamin D treatment and appropriate sun exposure, highlighting the necessity for cholecalciferol dose titration studies in this high fracture-risk population. Our findings that both 800 IU/day and 1700 IU/day Vitamin-D3 can safely maintain serum 25(OH)D above 70 nmol/L and suppress PTH in more than 80% of postmenopausal osteoporotic women who had vitamin D concentrations above 70 nmol/L at baseline have significant public health ramifications in India . These findings emphasize the necessity of ethnic location-specific dosage studies in the age of patient-centered treatment strategies. It is a need to conduct more research on the impact of vitamin D supplementation over time on fractures and falls.

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