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Original Research Article

Vitamin D3 Dose Maintenance among Post-Menopausal Osteoporosis Diagnosed Indian Women

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Abstract:

Introduction: Limited research exists about the optimal dose of vitamin D3 (cholecalciferol) required to provide sufficient levels in women suffering from postmenopausal osteoporosis (PMO) in India. In this study we aimed to ascertain the optimal dosage of oral cholecalciferol needed to maintain a 25(OH)D concentration above 75 nmol/L in postmenopausal osteoporotic (PMO) Indian women. Our hypothesis was that those with a lighter complexion in the Indian community would need lower doses.

Methods: The study recruited 100 Indian women with first blood 25(OH)D levels over 40 nmol/L within a year at a tertiary care center in Bihar, India. Beforehand, the administration of vitamin D supplements was discontinued, and the patients were randomly assigned to receive either 15,000 IU/3-weekly (Group-A) or 60,000 IU/3-weekly (Group-B) of oral cholecalciferol for a duration of 15 weeks, with strict monitoring. Serum levels of 25(OH)D, PTH, and urine calcium were evaluated at the beginning (baseline), as well as at the seventh and fifteenth weeks.

Results: The severity of osteoporosis, amount of sun exposure (2 hours per week), and baseline features of serum 25(OH)D were similar across all treatment groups. The mean serum 25(OH)D values after 15 weeks were 108.0±20.3 and 114.6±18.3 SD nmol/L for the two groups. Among women who had adequate levels of 25(OH)D at the beginning, 91% remained sufficient on a dosage of 15,000 IU/3-weekly, while 97% stayed sufficient on a dosage of 60,000 IU/3-weekly (p=0.272). At the end of the experiment, 38% and 81% of the women in Groups A and B who initially had inadequate baseline levels, respectively, achieved adequacy. The statistical significance of this finding was p=0.056. There was no correlation seen between any dosage and the occurrence of toxicity or hyperparathyroidism.

Conclusion: Despite receiving vitamin D therapy before the experiment and having appropriate exposure to sunlight, 25.5% of women still had inadequate levels of vitamin D, indicating that sunlight alone is not sufficient. The majority of women, namely over 80%, may effectively maintain sufficient levels of vitamin D by consuming either 800 or 2700 IU of cholecalciferol daily.

Keywords: Postmenopausal osteoporosis, vitamin D, oral cholecalciferol, tropical, hyperparathyroidism.

Introduction

The ageing population in East and Southeast Asia is confronted with a significant public health issue regarding osteoporosis and its associated morbidity and mortality [1]. The greater frequency of hip fractures among Indian women over 50 provides evidence of the heightened susceptibility to osteoporosis among individuals of Indian descent [1]. Essential aspects of caring for postmenopausal osteoporosis (PMO) are using vitamin D supplements, antiresorptive medicine, and ensuring adequate calcium intake. Vitamin D is essential for calcium metabolism, maintaining bone health, and promoting muscular strength [2].

Supplementing with cholecalciferol reduces the occurrence of fractures and enhances the strength of the lower extremities. However, it has been scientifically shown that these benefits are influenced by the dosage. Approximately 80-90% of vitamin D is synthesised by the skin via sun exposure, while only 10-20% is obtained from food sources [3].

Hypovitaminosis D is a global problem that affects people living in both northern and southern latitudes, with a greater prevalence in the latter. Although the North American PMO women in a large cohort were taking severe osteoporosis therapy, 52% of them were found to have a vitamin

D insufficiency (75 nmol/L). There is emerging data indicating a widespread deficit of vitamin D in places with abundant sunlight, such as Hawaii, Saudi Arabia, and India [4]. Research has shown that women from China and South Korea/Japan (some of whom were previously taking vitamin D supplements) had a high prevalence of vitamin D insufficiency [5].

Women who have PMO are at a significantly increased risk of experiencing fractures. However, there have been relatively few research that specifically investigate the ideal dosage of vitamin D needed to maintain sufficient levels in these women [6, 7]. Women in India may need reduced supplementary vitamin D doses to sustain sufficient levels due to their higher sun exposure compared to women in northern Asia and Caucasians [8].

Nevertheless, cultural behaviours like avoiding sun exposure and the effects of ageing on the skin's ability to produce vitamin D may impede the ability of ageing women with PMO to maintain a serum 25(OH)D level over 75 nmol/L [9].

The objective of this research was to ascertain the appropriate dosage of vitamin D supplementation for women with postmenopausal osteoporosis (PMO) and other women who are at a heightened risk of experiencing fractures.

Method

Study design: This prospective study was carried out at a tertiary care center in Bihar, India within one year of enrollment of patients.

Methodology: Following measuring the blood 25(OH)D level at a baseline screening visit, the individuals were randomly assigned and then had visits at three, seven, eleven, and fifteen weeks following the randomization. The first laboratory assessments included evaluations of albumin, calcium, phosphorus, 25-(OH)D, intact PTH, and intact PTH, in addition to renal and liver function tests. All relevant information was collected via an interview, physical examination, questionnaire, and review of medical records. The patients were given a validated questionnaire on sun exposure, and the measurement of skin pigmentation was conducted.

During the second visit, individuals who were still eligible and had blood vitamin D levels over 40 nmol/L had their prior vitamin D doses discontinued. Subsequently, the participants were randomised in a random manner to receive either 15,000 IU of oral cholecalciferol (vitamin D3) or 60,000 IU every three weeks for a cumulative duration of 15 weeks. Serum 25(OH)D levels, calcium, phosphorus, intact PTH, albumin levels, and 25-hour urine calcium measurements were reevaluated at 7, 11, and 15 weeks following randomization. During the sessions that occurred every three weeks, any medications being taken at the same time, or any negative effects experienced were recorded.

Participants

120 individuals were initially recruited in this research, however only 100 patients met the inclusion criteria and were included.

Inclusion criteria: The experiment included postmenopausal women with osteoporosis who were above the age of 50 and were patients at a tertiary care center in Bihar, India. These women had baseline blood vitamin D concentrations that were more than 40 nmol/L. A total of 100 ladies who met the specified criteria were selected.

Exclusion Criteria: Secondary osteoporosis caused by granulomatous diseases, thyrotoxicosis, glucocorticoid-induced osteoporosis, hepatic or renal sickness. Also, those with known metabolic conditions other than primary osteoporosis and those with a history of malabsorption due to prior colectomy or Roux-en-Y gastric-bypass are excluded. Patients who were using non-prescription vitamin D supplements, as well as those who were using medications (such as rifampicin, oestrogen, glucocorticoids, and anticonvulsants) that affect the way vitamin D is used in the body, were also excluded from the study.

Statistical Analysis: The statistical analysis was performed using SPSS 15.0 for Windows. The format often used to describe descriptive data is Mean ± SD. The choice between the student's t test or the Mann-Whitney test was determined based on the normality of the data, and these tests were employed to analyse the baseline comparisons. A one-way between-groups analysis of covariance (ANCOVA) was conducted to compare the impact of oral cholecalciferol supplementation. The statistical significance was determined at a p-value of less than 0.04.

Results

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 summarises the initial characteristics of the study participants.

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

At the start of the trial, there were no significant differences between the two groups in terms of age, BMI, duration of menopause, severity of osteoporosis, sun exposure, skin colour, mean serum 25(OH)D, serum calcium, and 25-hour urine calcium levels. Initially, 25.5% of the 100 individuals had 25(OH)D readings that fell below the recommended range of 50.0–74.8 nmol/L, whereas 74.3% had levels that were considered adequate, above 70 nmol/L.

82.5% of the insufficient individuals and 82.0% of the adequate participants had used vitamin D pills before the trial began. Initially, the median vitamin D dosage was significantly lower in the deficient group compared to the sufficient group. Within the groups characterised by low and adequate amounts at the beginning, 12% and 37.2% of individuals, respectively, were consuming more than 700 IU per day before joining the research. Both categories had a median sun exposure of 2.4 and 2.24 hours per week. There was no noticeable difference in sun exposure between the inadequate and sufficient subgroups at the beginning. Also, no differences were seen in age, BMI, or sun exposure index between the groups classified as inadequate and sufficient. Following the administration of monthly cholecalciferol, the average blood 25(OH)D levels in both treatment groups exhibited a considerable rise from the first measurement to the 15-week mark: Group A had an increase in their levels from 90.1±23.0 to 96.1±24.0 SD nmol/L. On the other hand, Group B revealed an increase in their levels from 91.5±24.5 to 107.0±22.6 SD nmol/L.

The drop in the vitamin-D sufficiency rate from 100% at baseline to 90% and 96% in Groups A and B, respectively, after three months was not clinically significant (p=0.272). In the low dosage group (Group A) and high dosage group (Group B), only 38% and 81% of persons who had a deficiency at the beginning of the study, respectively, reached a state of sufficiency. However, these differences only approached clinical significance with a p-value of 0.056. At 7 weeks, there was no significant difference in the average serum 25(OH)D levels between the low dose and high dose therapy groups in the overall sample population. However, at 16 weeks, the average vitamin D levels in patients who received high dose monthly vitamin D were significantly higher (p=0.026).

Administration of a low dosage of vitamin D (Group A) resulted in a notable rise in serum 25(OH)D levels only after 15 weeks of treatment. Conversely, treatment with a high dosage (Group B) led to significant increases in serum 25(OH)D levels at both 7 and 15 weeks for women with insufficient vitamin D levels at the beginning of the study [serum 25(OH)D level: 40 -70 nmol/L]. Administration of a low dosage of treatment did not have any noticeable impact on the levels of 25(OH)D in patients.

Inhibition of Parathyroid Hormone (PTH)

At the initiation and conclusion of the study, all patients had normocalcemia. At baseline, 15.5% of patients in the low-dosage group (Group-A) and 8.8% of patients in the high-dose group (Group-B) developed secondary hyperparathyroidism. Following a 3-month therapy period, all individuals with secondary hyperparathyroidism successfully attained blood PTH levels that fell within the established normal range.

The mean parathyroid hormone (PTH) levels were not significantly different between the subgroups with inadequate vitamin D levels at the beginning and those with adequate vitamin D levels at the beginning (4.8±2.0 vs 4.4±1.6 pmol/L, p=0.394). Vitamin D therapy resulted in a significant reduction in PTH levels in both treatment groups. There was no noticeable difference in the average PTH levels between the two treatment groups at any given period.

Safety

During the study, none of the subjects exhibited hypercalcemia or hypercalciuria. There were no noticeable differences in urine calcium excretion or adjusted serum calcium levels between the treatment groups.

Discussion

Despite 70% of the women in our sample with PMO used vitamin D supplements, 25% of them still showed signs of vitamin D deficiency in the

beginning (40-70 nmol/L). In contrast, a minor fraction of those who had sufficient levels initially (17.8%) refrained from taking cholecalciferol supplements before participating in the research. Out of the women in the inadequate cohort, just 12% were consuming more than 700 IU of vitamin D daily. In contrast, 37.0% of the women in the sufficient subgroup were taking more than 700 IU per day. In addition, participants with inadequate sun exposure at the beginning of the study had a median of 2.4 hours of sun exposure per week, which was not significantly different from those with sufficient sun exposure at the beginning of the study. These findings indicate that among this group of individuals who are at a high risk of fractures, relying just on diet and sun exposure is inadequate for maintaining adequate levels of vitamin D. Due to ethical constraints, we were unable to include a placebo group in our experiment, even though several recommendations suggest a minimum daily intake of 700 IU of vitamin D as a crucial part of osteoporosis treatment.

The elderly woman in the PMO position should uniformly include vitamin D tablets throughout her routine for several reasons:

(1) Irrespective of the individual's vitamin D level, administering vitamin D treatment effectively decreases the likelihood of falls and fractures in older adults.
(2) Calcium and vitamin D supplements have been used with active osteoporosis treatment in most randomised controlled trials, demonstrating their efficacy.
(3) Our cohort supports the idea that vitamin D insufficiency is prevalent among the elderly. Indeed, the fact that a significant proportion of our group had inadequate levels of vitamin D initially, despite consuming supplements, indicates that the question is not whether vitamin D supplementation is needed, but rather the amount of vitamin D required for the Indian diaspora to achieve optimal bone health.

After 15 weeks of therapy, patients in the high dose arm had significantly higher mean serum 25(OH)D concentrations compared to the overall study population. However, both dosing regimens resulted in average serum 25(OH)D concentrations within the range of 80-200 nmol/L. This range has been associated with positive outcomes for bone health, including reduced fracture risk, increased bone mineral density (BMD), and improved lower extremity function [10-13].

Crucially, both the low dosage and high dosage groups did not have any patients with secondary hyperparathyroidism after 15 weeks of therapy. No cases of hypercalciuria or hypercalcemia were found. To ensure adequate levels of vitamin D in women and promote bone health, a daily maintenance dose of 800 IU is recommended. This dosage has been demonstrated to be effective in reducing the risk of fractures and preventing falls, based on robust evidence from Western populations. It is important to note that the threshold levels for fracture risk reduction and fall prevention are 300 IU and 600-1100 IU, respectively.

It is crucial to note that the individuals in our research were not allowed to wear sunscreen. Therefore, it is possible that women who use sunscreen may need doses above 800 IU per day in order to maintain sufficient levels. After 15 weeks of low-dose therapy, only 37% of the women who had insufficient levels of a certain substance at the beginning were able to reach a sufficient level (>70 nmol/L). In contrast, 81% of the women in the high-dose treatment group attained adequacy. The differences in rates of vitamin D sufficiency were statistically significant (p=0.036) and potentially clinically meaningful (p=0.056) with a larger sample size. Nevertheless, considering that blood 25(OH)D levels continued to increase during the latter half of this 15-week investigation, it is plausible that a more extended regimen of low-dose vitamin-D3 therapy at 800 IU/day, lasting up to about 5 months, may have resulted in 25(OH)D concentrations surpassing 20 ng/ml in these female participants. It has been shown that the initial levels of 25(OH)D in the blood have an effect on the levels of vitamin D throughout therapy. People with higher initial levels need lower maintenance doses.

Based on a study, individuals who were given a daily dosage of 700-800 IU and had initial concentrations ranging from 43.9-76.9 nmol/L had effective fracture prevention in trials where the average achieved levels were 100 nmol/L [14]. However, a study discovered that in a specific sample of 142 participants whose blood levels of vitamin D were examined, a daily intake of 800 IU raised the levels of 25(OH)D in the blood from an initial level of 50 nmol/L to 100 nmol/L after 6 months. These levels were maintained at 105 nmol/L after 12 and 18 months, respectively [15].

A pivotal randomised controlled trial (RCT) included a cohort of 3,270 robust and mobile postmenopausal women of advanced age (mean age: 84 years) [16]. The results from this study conducted on older Caucasian women in northern latitudes present a combination of findings [16]. These findings indicate that a daily intake of 800 IU of vitamin D is enough to maintain sufficient levels of the vitamin in ambulant subjects who may also receive benefits from sun exposure. However, this dosage is not effective in institutionalised subjects. It is highly likely that our group of fair skinned PMO women who live near the equator

and have baseline vitamin D levels above 70 nmol/L may need a lower amount of vitamin D for maintenance. This is because baseline vitamin D levels are known to be affected by factors such as latitude and sun exposure [16].

The design of our trial had the benefit of ensuring patient compliance since all vitamin D deliveries occurred in the hospital under constant monitoring. These data indicate that when planning vitamin D treatment, it is important to include ethnic, regional, and cultural characteristics due to their impact on diet and sun exposure. Light-skinned women in India, who are exposed to abundant sunlight throughout the year, need fewer amounts of vitamin D compared to individuals living in northern latitudes who see seasonal fluctuations in UVB radiation. These findings, however, were not certain because of the diminished ability of aged individuals to produce vitamin D in their skin when exposed to sunlight.

In our research population, it is possible that the greater dosages of supplementary vitamin D were necessary for fair-skinned women due to their sun avoidance behaviours, which are valued in Asian culture. In contrast, other research indicates that those with dark complexion, such as Asian Indians and African Americans, need higher doses of vitamin D to address vitamin D deficiency [17, 18]. This is due to the fact that UVB radiation does not penetrate their skin as well as it does in lighter-skinned individuals.

Limitation

The absence of accurate food history about the use of fish, mushrooms, and eggs, which are significant natural sources of dietary vitamin D, restricts our research. Nevertheless, due to the limited availability and consumption of fatty fish such as sardines, tuna, and salmon, which are enriched in vitamin D.

Conclusions

To summarise, 25.5% of women with primary ovarian insufficiency (PMO) had inadequate levels of vitamin D despite receiving vitamin D medication and acceptable sun exposure. This emphasises the need for more investigations to determine the optimal dosage of cholecalciferol in this group, which is at a high risk for fractures. The results of our study indicate that both daily doses of 800 IU and 1700 IU of Vitamin-D3 can effectively maintain serum 25(OH)D levels above 70 nmol/L and reduce PTH levels in over 80% of postmenopausal women with osteoporosis who already have vitamin D levels above 70 nmol/L at the beginning of the study. These findings have important implications for public health in India. These results highlight the need of conducting dose studies that are particular to the ethnic location of patients in the era of patient-centered treatment approaches. Further investigation is necessary to examine the long-term effects of vitamin D supplementation on fractures and falls.

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