

Effect of two different doses of oral cholecalciferol supplementation on serum 25-hydroxy-vitamin D levels in healthy Indian postmenopausal women: A randomized controlled trial

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ABSTRACT

Aim: To compare the effect of two different doses (500 and 1000 IU/day) of oral vitamin D3 (cholecalciferol) on serum 25-hydroxy vitamin D [25(OH)D] levels in apparently healthy postmenopausal Indian women. **Materials and Methods:** Serum 25(OH)D, calcium with albumin, phosphorus, and alkaline phosphatase were measured in 92 apparently healthy postmenopausal women. The subjects were randomly assigned to one of the three groups and received supplementation for 3 months each. Each group received 1000 mg calcium carbonate daily while groups B and C received 500 and 1000 IU of cholecalciferol in addition, respectively. The tests were repeated after 3 months. **Results:** At baseline, 83.7% subjects had vitamin D deficiency (≤ 20 ng/mL). The difference in the percentage change in mean serum 25(OH)D levels from baseline in group A ($-30.5 \pm 5.3\%$), group B ($+8.9 \pm 19.7\%$), and in group C ($+97.8 \pm 53.3\%$) was statistically significant ($P < 0.001$) between the three groups. Serum 25(OH)D level >20 ng/mL was achieved in 4.7% (1/21), 16% (4/25), and 66.67% (12/18) subjects in groups A, B, and C, respectively. No significant change was found in serum calcium, phosphorus, and alkaline phosphatase levels at 3 months in either of the groups from baseline. **Conclusions:** Standard dose of cholecalciferol available in "calcium tablets" (250 IU per 500 mg calcium carbonate) is not adequate for achieving optimum serum 25(OH)D levels in Indian postmenopausal women. Higher dose of vitamin D supplementation with 1000 IU/day (500 IU per 500 mg calcium carbonate) daily is superior to the standard dose therapy. For achievement of optimum serum 25(OH)D levels (>30 ng/mL) in Indian postmenopausal women, still higher doses of vitamin D are likely to be required.

Key words: 25-hydroxy vitamin D3 [25(OH)D], calcium carbonate, cholecalciferol, postmenopausal women

INTRODUCTION

Postmenopausal women suffer from increased risk of osteoporosis and fractures.^[1,2] It is seen that a large population of the healthy adult population has low or borderline low serum 25(OH)D levels which

further increases the risk of falls and fracture.^[3-7] Vitamin D plays a critical role in bone health.^[1,5,8-12] Optimization of vitamin D status is therefore an essential component of preventing and managing osteoporosis especially in vulnerable groups like postmenopausal women.^[13]

Definition of optimum levels of vitamin D for maintenance of bone health has been a matter of debate. However, the evolving consensus is to define vitamin D deficiency (VDD) as a serum 25(OH)D level of less than 20 ng/L (50 nmol/L) and insufficiency as a level of 25(OH)D of 21-29 ng/mL (525 to 725 nmol/L). Vitamin D intoxication is observed when serum levels of 25(OH)D are greater than 150 ng/mL (374 nmol/L).^[14]

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Vitamin D synthesis is affected by geographical location (latitude and altitude), atmospheric pollution, clothing, melanin pigmentation, and sunlight exposure. In addition, ageing is also associated with decreased vitamin D synthesis. Vitamin D deficiency is rampant. In India, it has been reported from all over the country (both rural and urban), in all age groups including toddlers, school children, adolescent girls, pregnant women,^[15-21] and postmenopausal women.^[1,17,22]

The Indian Council of Medical Research (ICMR) recommends daily intake of 600 mg of calcium in adults and 800 mg of calcium in postmenopausal age group. The typical Indian diet is deficient in calcium,^[23] which becomes more important in postmenopausal women where calcium requirement is more.^[17,19] The ICMR Recommended Daily Allowance data states that habitual Indian diet does not provide even 10% daily vitamin D requirement and sunlight is the main source of vitamin D. It continues to recommend 400 IU/day of oral vitamin D regardless of the special requirement.^[24] Considering these facts, in typical Indian clinical practice it is standard to recommend calcium tablets, each containing 500 mg of calcium and 250 IU of vitamin D₃, twice daily as supplementation in the postmenopausal women. The current study was planned to see the effect of two different daily doses (500 IU – the standard and 1000 IU) of vitamin D supplementation added to standard calcium dose (1000 mg/day), on vitamin D levels and parameters of calcium homeostasis (calcium, phosphorus, and ALP) in postmenopausal women. We hypothesized that 1000 IU vitamin D was superior in comparison to 500 IU, which is the commonly used daily dose, for achieving serum 25(OH)D level >20 ng/mL.

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital at New Delhi, India, after ethical clearance from the Institutional Review Board. Post-menopausal women volunteers (mainly attendants of patients who presented in the out-patient department or medical and paramedical staff and their relatives, representing a relatively high socioeconomic strata relative to the national average) who were not taking calcium or vitamin D supplementation for minimum 3 months and were permanent residents of the city for past 3 months were enrolled. At induction, a detailed history including dietary history and history of daily sun exposure was taken. Subjects on calcium or vitamin D replacement or any drugs affecting vitamin D status, chronic renal failure, chronic liver disease, chronic smokers, and chronic alcoholics were excluded. A total 92 subjects were enrolled from the months of September to November. At induction, morning fasting

samples were collected for serum calcium, phosphorus, alkaline phosphatase, albumin, and 25(OH)D after written informed consent.

The subjects were randomized in three groups by unrestricted sequential simple randomization. The enrolment and randomization were done by the same person. The study was an open label study. Each group received one tablet corresponding to their group twice daily for 3 months. The group A ($n = 30$) served as control and received only 1000 mg calcium carbonate daily in equally divided two doses, group B ($n = 31$) received 1000 mg of calcium carbonate and 500 IU of vitamin D (as a combination tablet containing 500 mg calcium carbonate and 250 IU vitamin D) daily in equally divided two doses, and group C ($n = 31$) received 1000 mg of calcium carbonate and 1000 IU of vitamin D (as a combination tablet containing 500 mg calcium carbonate and 500 IU vitamin D) daily in equally divided two doses. The tablets were procured from Eris Pharmaceuticals which were market preparations DeCal (a combination tablet containing 500 mg calcium carbonate and 250 IU vitamin D), D-500 Cal (a combination tablet containing 500 mg calcium carbonate and 500 IU vitamin D), while plain calcium tablets containing 500 mg calcium carbonate were manufactured for the study after appropriate approval.

Drugs were supplied every month, and compliance was ensured by weekly telephonic reinforcement. Compliance was considered as consumption of at least 80% of the supplied tablets. At the end of three months morning fasting samples were collected for measurement of serum calcium, phosphorus, alkaline phosphatase, albumin, and serum 25(OH)D levels in subjects who were considered to be compliant.

Serum albumin, calcium, phosphorus, and alkaline phosphatase estimation was performed on the auto-analyzer immediately. Serum 25(OH)D concentrations were estimated by radioimmunoassay after storage at -20°C (Diasorin, Stillwater, MN 55082-0285, USA; kit, normal range: 9.3-37.9 ng/mL). The sensitivity of this assay was 1.5 ng/mL, within-run coefficient of variation (CV) was 10.5%, and the total imprecision CV was 8.2% at 22.7 ng/mL. Primary outcome was the change in the mean serum 25(OH)D level from baseline in the group receiving 1000 IU of vitamin D per day as compared to the group receiving 500 IU of vitamin D per day and the group not receiving any vitamin D supplementation, at the end of three months of intervention. Secondary outcome was the change in mean serum calcium (corrected for serum albumin), phosphorus, and alkaline phosphatase level from baseline in the three groups at the end of 3 months of intervention.

Statistical methods

The data are presented in mean ± SD, and non-parametric test, Kruskal Wallis test, was used to assess the significance level of the percentage change in serum 25(OH)D, corrected calcium, phosphorus, and alkaline phosphatase within and between the groups.

RESULTS

A total of 92 postmenopausal women were enrolled from the months of September to November and followed up for 3 months from the date of enrolment. The mean age of the subjects in the study population was 54.8 ± 6.7 years (range 40-73). Their mean daily calcium intake was 1076.43 ± 376.2 mg and median of daily sun exposure was 5 (range 0-38) min with exposure of about 20% body surface area. The mean daily calcium intake was relatively higher than the national average^[23] probably due to a higher socioeconomic status of the subjects included. 83.7% subjects (*n* = 77) had vitamin D deficiency (25(OH)D <20 ng/mL) and 8.7% (*n* = 8) subjects had vitamin D insufficiency (25(OH)D 20-30 ng/mL) and 7.6% subjects (*n* = 7) had normal vitamin D defined as 25(OH)D >30 ng/mL [Table 1].

Thirty (30) subjects were randomized to group A, while 31 subjects each were randomized to groups B and C. The baseline parameters were not significantly different in the three groups as assessed by the Kruskal Wallis test to evaluate the significance [Table 2].

At the end of follow up, 26 from group A, 29 from group B, and 23 from group C presented for second sampling. Four subjects from group A, two from group B, and six from group C withdrew consent during the course of the study and two subjects from group C were lost to follow up. Data for subjects with less than 80% compliance (five subjects from group A and C each and four from group B) were excluded. Data for 21 (70%), 25 (80.6%), and 18 (58.06%) subjects from groups A, B, and C, respectively, were finally analyzed [Figure 1].

At 3 months, the difference in percentage change in mean serum 25(OH)D level from baseline in between the

three groups was statistically significant (*P* < 0.05) with percentage change being maximum in group C (178.78%) and group A actually showing a decline [Table 3]. Figure 2 shows the comparison in mean serum 25(OH)D level at baseline and at 3 months in between the three groups.

Although not significantly different (*P* > 0.05), the mean serum calcium attained in group C was highest (8.67 mg/dL) from the average baseline corrected calcium of 8.49 mg/dL. The mean serum phosphorus and alkaline phosphatase in the three groups were not significantly different within or between the groups at the end of follow up [Table 2].

There were no reported serious adverse events. Twelve subjects (four in group A, three in group B, and five in group C) reported minor gastritis and abdominal discomfort but did not result in discontinuation of the supplementation.

DISCUSSION

This study evaluates the response of different doses (500 IU daily, 1000 IU daily or control) of vitamin D along with 1000 mg of calcium daily on the parameters of calcium homeostasis in healthy postmenopausal women. It was carried out in New Delhi (location -28.38°N, 77.12°E). This city experiences marked seasonal variation. The zenith angle is 84.5° in peak summer and 38.5° in peak winter. Subjects were recruited from September to November, prior to the onset of peak winter. Since the subjects were randomly divided into the three groups, any effect of season was equally distributed.

In the present study, 83.7% subjects (*n* = 77) had vitamin D deficiency (25(OH)D <20 ng/mL), 8.7% (*n* = 8) subjects had vitamin D insufficiency (25(OH)D 20-30 ng/mL), and 7.6% subjects (*n* = 7) had normal vitamin D defined as 25(OH)D >30 ng/mL. Our results are in accordance with other studies which have demonstrated high prevalence of vitamin D deficiency in India although limited data is available regarding postmenopausal women.

From a study conducted in Delhi, the authors reported VDD in 91.2% among older Indian adults (more than

Table 1: Baseline parameters (mean±SD) in three groups

Parameter	Group A	Group B	Group C	P value
Age (years)	56.30±7.71	53.84±5.12	54.19±7.09	0.37
Daily calcium intake (mg/d)	1003.50±407.07	1134.06±383.85	1089.39±336.02	0.51
Daily sun exposure (20% BSA, min/d)	41.50±83.140	11.50±17.79	10.91±17.61	0.173
BMI (kg/m ²)	27.12±4.42	28.87±6.33	28.34±4.90	0.57
Corrected calcium (mg/dL)	8.37±0.69	8.55±0.60	8.54±0.76	0.61
Phosphorus (mg/dL)	3.76±0.47	3.774±0.58	3.72±0.46	0.97
ALP (IU)	87.93±19.19	81.77±19.46	98.71±30.28	0.09
25(OH)D (ng/mL)	12.99±6.74	12.92±8.20	14.38±11.07	0.77

BMI: Body mass index, BSA: Body surface area, ALP: Alkaline phosphatase

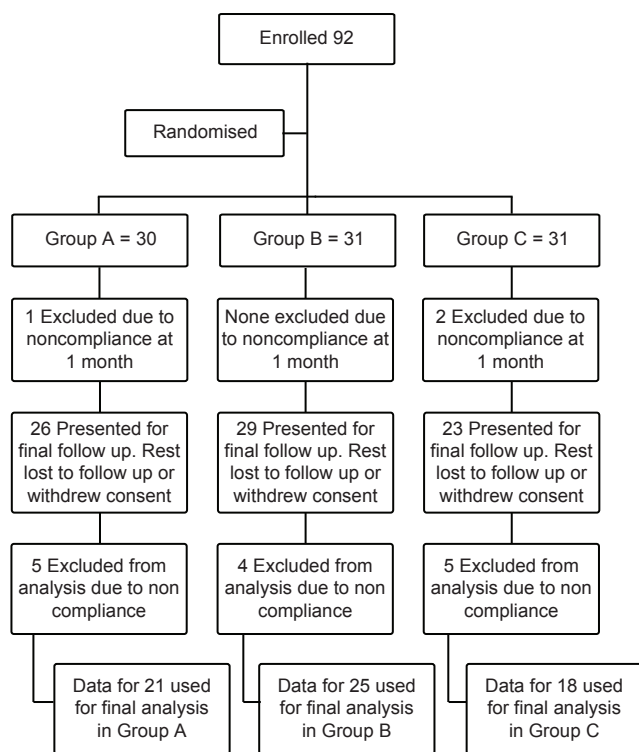


Figure 1: Participant flow

Table 2: Studied parameters at three months follow up (mean±SD)

	Group A	Group B	Group C
N	21	25	18
Calcium corrected (mg/dL)	8.59±0.69	8.53±0.74	8.67±0.75
Phosphorus (mg/dL)	3.91±0.53	3.93±0.46	3.72±0.43
ALP (IU/L)	89.71±21.06	80.64±15.78	94.67±22.21
25(OH)D (ng/mL)	8.07±5.28	13.34±9.52	23.71±11.71

ALP: Alkaline phosphatase

Table 3: Percentage change in various parameters at 3 months from baseline (mean±SD)

	Group A	Group B	Group C	P value
Calcium corrected (mg/dL)	2.69±10.84	1.23±11.48	3.86±10.40	0.786
Phosphorus (mg/dL)	2.10±13.57	4.68±14.18	-2.01±12.79	0.237
ALP (IU/L)	1.66±4.10	-1.51±14.39	-0.49±14.42	0.705
25(OH)D (ng/mL)	-29.22±24.16	32.34±98.59	178.78±225.96	0.000

ALP: Alkaline phosphatase

50 years age) of both sexes despite the fact that more than half the subjects studied were taking 200-400 IU of oral vitamin D daily.^[22] In a study from the southern part of the country, vitamin D deficiency (<20 ng/mL), insufficiency (20-30 ng/mL) and replete states (>30 ng/mL) were seen in 70%, 23%, and 7%, respectively, among postmenopausal women, similar to levels in reproductive

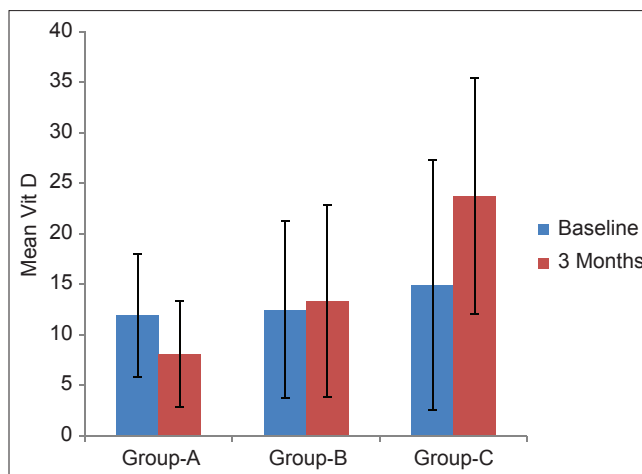


Figure 2: Mean levels of 25(OH)D at baseline and 3 months in the three groups

age women.^[25] Similarly, in another study conducted among postmenopausal south Indian women (n = 164), the author found that only 18% patients had “normal” 25(OH)D levels (>20 ng/mL), 52% had 25(OH)D “insufficiency” (10-20 ng/mL), and 30% had 25(OH)D “deficiency” (<10 ng/mL).^[17]

Data from other study populations suggests the universal presence of low vitamin D levels even though variable cut-offs were used. In the study conducted in Delhi, at the same institute where the present study was conducted, among 100 healthy volunteers from the hospital staff, the mean 25(OH)D was 4.7 ± 3.4 ng/mL. All the subjects had hypovitaminosis D (<20 ng/mL) and more than 90% subjects had 25(OH)D levels <10 ng/mL.^[26] In a study conducted among healthy hospital staff, in Lucknow, a city south east of Delhi, the authors found 66.3% of their subjects to be vitamin D deficient, using a cut-off value of 15 ng/mL. Of these, 20.6% had severe vitamin D deficiency (<5 ng/mL), 27.2% had moderate (5-9.9 ng/mL), while 18.5% had mild vitamin D deficiency (10-14.9 ng/mL). When a serum 25(OH)D level of 20 ng/mL was used as a cut-off value, 78.3% subjects were diagnosed to be vitamin D deficient/insufficient.^[8]

Similar data has been reported from other parts of the country. In a study among healthy adult native population, from Kashmir, 83% of the subjects studied had vitamin D deficiency (serum 25(OH)D concentration of <50 nmol/L equivalent to 20 ng/mL). 25%, 33%, and 25% had mild (25-50 nmol/L equivalent to 10-20 ng/mL), moderate (12.5-25 nmol/L equivalent to 5-10 ng/mL), and severe (<12.5 nmol/L equivalent to 5 ng/mL) deficiency, respectively. The prevalence of VDD ranged from 69.6% in the employed group to 100% in the household group with equal prevalence of VDD in subjects from rural and

urban areas.^[21] Similarly, high prevalence of vitamin D deficiency was reported among pregnant women and adolescent girls from a rural Indian community. Boys were found to be relatively protected. The age-adjusted community prevalence of vitamin D deficiency, defined as 25(OH)D <50 nmol/L (20 ng/mL) in adolescent girls was 88.6%.^[20]

A significant urban and rural difference is seen in the serum level of 25(OH)D but despite long hours of sun exposure, the rural population is also deficient. In a study conducted among residents of a North Indian village with 200 families, 70% were vitamin D deficient. Males had significantly higher 25(OH)D values than females. When compared to urban subjects, the mean serum 25(OH)D value of rural males and females was six- and threefolds higher, respectively. However, even with 5 hours of daily sunshine exposure only 31.5% had serum 25(OH)D levels \geq 50 nmol/L (20 ng/mL).^[15] In a study conducted among urban and rural population in Andhra Pradesh, they found that the 25(OH)D levels of rural adult subjects were significantly higher ($P < 0.001$) than that of urban adult subjects in both males and female groups. The 25(OH)D levels of both the urban and rural children were low.^[19]

The ICMR recommends daily intake of 600 mg of calcium in adults and 800 mg of calcium in postmenopausal age group. The typical Indian diet is deficient in calcium, which becomes more important in postmenopausal women where calcium requirement is more.^[17,19] The ICMR recommended daily allowance data states that habitual Indian diet does not provide even 10% daily vitamin D requirement and sunlight is the main source of vitamin D. It continues to recommend 400 IU per day of oral vitamin D regardless of the special requirement^[24] like in postmenopausal women. The IOF recommends that vitamin D intake may need to be adjusted upward to as much as 2000 IU/day in individuals who are obese, and in those with osteoporosis, limited sun exposure (institutionalized, homebound), and malabsorption, and in non-European populations known to be at high risk for vitamin D deficiency such as those in the Middle East and South Asia, or immigrants from such regions living in Europe.^[13]

At the end of follow up, the mean 25(OH)D level was highest in group C at 23.71 ng/mL. In group A it was 8.07 ng/mL, in group B it was 13.34 ng/mL, while at baseline the average 25(OH)D level was 13.43 ng/mL. The percentage change in mean serum 25(OH)D level from baseline was significantly different in between the three groups ($P = 0.000$) with percentage change being maximum in group C (178.78%) and group A actually

showing a decline. The decline probably reflects the effect of season as the follow-up period was winters. Whatever the effect of season, it was presumed that it would be uniform in the three groups. Our results suggest that 1000 IU vitamin D is better as compared to the currently prescribed doses of 500 IU daily. However, even this dose is not sufficient to optimize the levels in a severely deficient population.

The number of subjects who attained serum 25(OH)D level \geq 30 ng/mL was four (22.2%) in group C, one (4%) in group B, and none in the control group. The percentage of subjects who attained serum 25(OH)D level of 20-30 ng/mL in the three groups was 38.9% ($N = 7$), 12% ($N = 3$), and 4.7% ($n = 1$), respectively.

There percentage change in the blood levels of corrected serum calcium, phosphorus and total alkaline phosphatase from baseline was not different between the three groups.

Our results are in line with the results of previous studies. In a study conducted among older adults, it was seen that there was no difference in the prevalence of vitamin D deficiency among subjects who were and those who were not receiving vitamin D supplementation in dose ranging from 200 to 400 IU/day.^[22] In a previously conducted study from Delhi in healthy adults, the authors concluded that monthly oral administration of 60,000 IU cholecalciferol (\sim 2000 IU/day or 50 μ g/day) is effective in raising serum 25(OH)D to desired levels ($>$ 30 ng/mL) during summer. However, higher doses of cholecalciferol—120,000 IU/month administered orally (\sim 4000 IU/day or 100 μ g/day)—may be more appropriate during winter.^[26] From their study among ambulatory elderly in Finland, the authors concluded that 10 μ g/d (400 IU) is not enough to maintain 25(OH)D above 40 nmol/L in winter.^[27] An optimal daily dose of 115 μ g/d (4600 IU) was predicted statistically, to obtain 25(OH)D levels within the range of 75-220 nmol/L in the African- American population.^[28]

Our study suggests that even 1000 IU daily for 3 months may not be enough to attain optimum levels of serum 25(OH)D; and probably a higher dose is required to attain optimum levels. In our study, the mean 25(OH)D level in group C after 3 months of supplementation was less than 30 ng/mL (23.71 ng/mL) suggesting that even 1000 IU may not be sufficient to attain normal levels of 25(OH)D and a higher dose as much as 2000 IU/day may be required in special populations as postmenopausal women especially in the Indian subcontinent. As previously seen,^[29,30] the effects of calcium and vitamin D are not sustained and levels decline after some time. Thus, sustained duration of intake is desired.

There are some limitations to the present study. The subjects included in the study were based on convenience sampling and not population based sampling. Our study was a non-blinded and the subjects knew the nature of supplementation they were receiving. It sometimes could have affected compliance as the subjects were given the background information related to the study. The laboratory conducting the tests was however blinded. The number of subjects for final analysis after excluding the dropouts and subjects with less than 80% compliance was relatively small.

CONCLUSION

Standard dose of vitamin D available in calcium tablets (250 IU per 500 mg calcium carbonate) is not adequate for achieving optimum serum 25(OH)D levels. Higher dose of vitamin D supplementation with 1000 IU/day (500 IU per 500 mg calcium carbonate) daily was superior to the standard dose therapy and resulted in serum 25(OH)D values >20 ng/mL in postmenopausal women in our study. For achievement of optimum serum 25(OH)D levels (>30 ng/mL), still higher doses of vitamin D are likely to be required.

It is possible that the standard recommended dose may be adequate for maintenance in a “vitamin D sufficient” population. However, in the Indian population which is severely deficient, even 1000 IU daily cholecalciferol supplementation is not adequate. At this point therefore, it is recommended to make the population sufficient by giving therapeutic doses of vitamin D to the diagnosed cases. Further studies are required to evaluate higher doses in Indian postmenopausal women which will achieve and maintain optimal vitamin D levels without risk of toxicity.

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