

Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D

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Hypovitaminosis D is common in Asian Indians. Physicians often prescribe 1500 µg (60 000 IU) cholecalciferol per week for 8 weeks for vitamin D deficiency in India. Its efficacy to increase serum 25-hydroxy vitamin D (25(OH)D) over short (2 months) and long (1 year) term is not known. We supplemented a group of twenty-eight apparently healthy Asian Indians detected to have low serum 25(OH)D (mean 13.5 (SD 3.0) nmol/l) on screening during January–March 2005. Serum parathyroid hormone (PTH) level was supranormal in 30 % of them. Oral supplementation included 1500 µg cholecalciferol per week and 1g elemental Ca daily for 8 weeks. Serum 25(OH)D, total Ca, inorganic P and intact (i) PTH were reassessed in twenty-three subjects (twelve females and eleven males) who had follow up at both 8 weeks and 1 year. At 8 weeks the mean 25(OH)D levels increased to 82.4 (SD 20.7) nmol/l and serum PTH normalized in all. Twenty-two of the twenty-three subjects had 25(OH)D levels > 49.9 nmol/l. At 1 year, though the mean 25(OH)D level of 24.7 (SD 10.9) nmol/l was significantly higher than the baseline, all subjects were 25(OH)D deficient. Five subjects with supranormal iPTH at baseline showed recurrence of biochemical hyperparathyroidism. Thus, with 8 weeks of cholecalciferol supplementation in Asian Indians with chronic hypovitaminosis D, mean serum 25(OH)D levels would be normalized and serum PTH value would be reduced to half. However, such quick supplementation would not maintain their 25(OH)D levels in the sufficient range for 1 year. For sustained improvement in 25(OH)D levels vitamin D supplementation has to be ongoing after the initial cholecalciferol loading.

Hypovitaminosis: Vitamin D supplementation: Asian Indians: Serum 25-hydroxy vitamin D: Cholecalciferol

Hypovitaminosis D is common in India despite its sunny environment^(1–3). More than 90 % of apparently healthy Indians residing in India have subnormal serum 25-hydroxy vitamin D (25(OH)D) levels with values almost undetectable during winter^(1–3). One fifth of them also have evidence of parathyroid hyperactivity reflected in serum parathyroid hormone (PTH) levels^(1,2). Poor exposure to sunshine and skin pigmentation are the main causes of their hypovitaminosis D⁽¹⁾. The usual dress sense practised in India gives scope for sunshine exposure to merely face and hands/forearm. Under these circumstances the prospect of achieving normal serum 25(OH)D by sunshine exposure seems a distant reality in urban Indians working indoors. Recently Malabanan and colleagues reported successful normalization of serum 25(OH)D levels at 8 weeks after giving orally 1250 µg (50 000 IU) cholecalciferol granules each week to hypovitaminotic elderly Caucasians⁽⁴⁾. Currently, it is a common practice by physicians in India to prescribe a cholecalciferol sachet of 1500 µg to be taken each week for 1–8 weeks for overt or occult vitamin D deficiency. However, its short- and long-term effects on serum 25(OH)D levels in Asian Indians have not been systematically studied. Here, we report on the efficacy of similar vitamin D supplementation in Asian Indians as reported by Malabanan and co-workers, in

Caucasian subjects in terms of serum 25(OH)D and PTH levels at 2 months and again after 1 year in the same group of individuals⁽⁴⁾.

Materials and methods

Subjects

Study subjects included twenty-eight apparently healthy Asian Indians who were found to have subnormal serum 25(OH)D levels on screening. Twenty-four of the twenty-eight subjects were from a cohort of 193 first-degree relatives of patients with nutritional osteomalacia or rickets who were investigated at our centre for assessing association of the disease with vitamin D receptor gene polymorphisms using a transmission disequilibrium test. None of these relatives had clinical signs and symptoms of overt metabolic bone disease such as bone pains, myopathy or fractures. Besides, four of the twenty-eight subjects were volunteers including three of the authors (R. G., D. R. and N. T.). The criteria for selection of the study subjects included: (1) age > 18 years; (2) residence in Delhi; (3) commitment for follow-up at 2 months and again after 1 year; (4) consent for 8 weeks of supplementation;

Abbreviations: 25(OH)D, 25-hydroxy vitamin D; PTH, parathyroid hormone; iPTH, intact PTH.

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(5) ability to recruit in the winter between January and March 2006. Blood samples were drawn at baseline for estimation of serum total Ca, inorganic P, alkaline phosphatase, serum 25(OH)D and intact (i) PTH.

All study subjects were provided with packets containing four sachets of cholecalciferol (each containing 1500 µg (60 000 IU) vitamin D₃; Cadila Pharmaceutical, India) and sixty tablets of CaCO₃ (each tablet containing 500 mg elemental Ca + 6.5 µg (250 IU) vitamin D₃; Elder Pharmaceutical, India). Subjects were counselled for daily intake of two tablets of CaCO₃ and weekly intake of a cholecalciferol sachet and follow-up at completion of 4 weeks. Similar packets were given after 4 weeks of follow-up. Drug compliance was assessed by counting the empty sachets. Blood samples were drawn at completion of 8 weeks of supplementation and again after 1 year for biochemical assessment.

Daily dietary intake of proximate principles including Ca and phytic acid was measured by semiquantitative FFQ and 24 h recall method using published data of nutritive value of Indian foods^(5,6).

None of the study subjects took Ca and vitamin D supplementation after 2 months. The study protocol including vitamin D-supplementation dose was approved by the Institutional ethics committee and written informed consent was obtained from all the subjects.

Follow up, compliance and actual number of subjects analyzed

Three of the twenty-eight subjects did not follow up at 2 months for unknown reasons and two of the remaining twenty-five subjects did not come for follow-up at 1 year because of migration to other states. Two of the twenty-five subjects who were followed up for 2 months admitted missing Ca supplementation during the third and fourth weeks of supplementation. These subjects gave their Ca tablets to their female siblings who were earlier treated by us for nutritional osteomalacia. However all the subjects confirmed weekly intake of cholecalciferol and returned the correct number of empty sachets to us on follow-up. None of the subjects complained of side effects including gastrointestinal disturbance after Ca intake either at 1 or 2 months of follow-up after the start of supplementation. Final analysis was performed only in twenty-three subjects (twelve females and eleven males), who had follow-up at both 8-weeks and 1-year interval.

Biochemical estimations

Blood samples after an overnight fast without venostasis were cold centrifuged at 800 g for 5 min at 8°C and serum was stored in multiple aliquots at -20°C. Serum total Ca, inorganic P and alkaline phosphatase assays were assayed in duplicate using commercial kits (Roche, Germany) and semiautomated analyzer (Hitachi 4020; Boehringer, Germany). Normal range and intra- and inter-assay CV for serum Ca was 2.0–2.6 mmol/l, 3.6% and 3.8%; for P, 0.80–1.45 mmol/l, 3.5% and 4.8%; and for alkaline phosphatase, < 840 IU/l up to age 18 years and < 280 IU/l for > 18 years of age, 5.2% and 4.1%, respectively. Serum iPTH was measured by an immunoradiometric assay (Diasorin, Stillwater, MN, USA; normal range 13–54 ng/l, intra- and inter-assay CV 4% and

8%, respectively). Serum 25(OH)D concentrations were estimated by radioimmunoassay (Diasorin; normal range 22.4–93.8 nmol/l). Vitamin D deficiency, insufficiency and sufficiency was defined based on serum 25(OH)D concentrations as < 49.9 nmol/l, 49.9–79.8 nmol/l, and > 79.8 nmol/l respectively^(7–9).

Statistical analysis

Data are shown as means and standard deviations. Analysis was performed using SPSS software (version 10.0). ANOVA followed by the Bonferroni correction test was used to compare various indices at three different intervals. A value of $P < 0.05$ was considered significant.

Results

The mean daily dietary Ca intake of the study group was 650 (SD 409) mg. The mean age and BMI of female (33.9 (SD 13.1) years and 22.1 (SD 3.0) kg/m²) and male (34 (SD 17) years and 20.6 (SD 4.0) kg/m²) subjects were comparable ($P = 0.95$ and 0.33 respectively). Change in serum 25(OH)D values in individual subjects and their mean values of biochemical estimations performed at baseline, at 8 weeks and at 1 year of follow-up after cholecalciferol and Ca supplementation are shown in Fig. 1 and Table 1 respectively.

Baseline

At baseline, all study subjects were vitamin D-deficient and serum PTH level was supranormal in 30% of them.

After 8 weeks of supplementation

After 8 weeks of supplementation, thirteen of twenty-three subjects were vitamin D-sufficient with serum 25(OH)D levels > 79.8 nmol/l, nine had serum 25(OH)D in the insufficient range and only one subject remained vitamin D-deficient (42.4 nmol/l, Fig. 1). None of the subjects had supranormal iPTH.

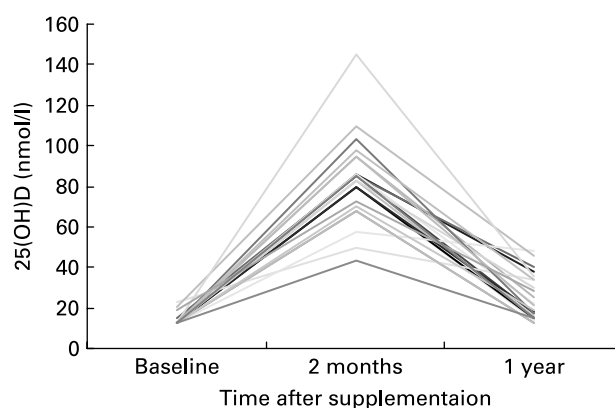


Fig. 1. Change in serum 25-hydroxy vitamin D (25(OH)D) values in same group of twenty-three subjects at 2 months and again after 1 year following 8 weeks of oral cholecalciferol (1500 µg (60 000 IU)/week) and Ca supplementation (1 g/d).

Table 1. Change in serum Ca, 25-hydroxy vitamin D (25(OH)D) and intact PTH (iPTH) after cholecalciferol (1500 µg (60 000 IU)/week) and Ca (1g/d) supplementation*

(Mean values and standard deviations)

Parameters	Baseline (pre-supplementation)		After 8 weeks of supplementation			
	Mean	SD	8 weeks		12 months	
			Mean	SD	Mean	SD
Serum total Ca (mmol/l)	2.27	0.22	2.22	0.17	2.34	0.17
Serum inorganic P (mg/dl)	1.32	0.13	1.42 ^a	0.13	1.29 ^b	0.13
Serum alkaline phosphatase (IU/l)	300	118	253	78	252	100
25(OH)D (nmol/l)	13.5 ^a	3.0	82.4 ^b	20.7	24.7 ^c	10.9
Serum iPTH (ng/l)	54 ^a	40	29 ^b	20	72 ^a	32
Supranormal PTH (n, %)	7 out of 23 (30.4%)		0 out of 23 (nil)		14 out of 23 (60.1%)	

^{abc} Values in the same row with different superscript are significantly different from each other.

* For details of subjects and procedures, see Materials and methods.

At 1 year of follow up

At 1 year, serum 25(OH)D levels were in the deficient range in all subjects. However, their mean 25(OH)D level was significantly higher as compared to the baseline. There was no significant difference in their mean PTH compared to baseline. Interestingly, five of the seven patients who had high serum iPTH at baseline again showed biochemical hyperparathyroidism with serum PTH > 54 ng/l. Serum inorganic P values were significantly lower at 1 year as compared to 2 months after supplementation.

Discussion

The current study for the first time evaluates serum 25(OH)D and PTH response at 2-months and again at 1-year interval after 8 weeks of quick supplementation with oral cholecalciferol in a group of apparently healthy Asian Indian subjects who had been in the chronic hypovitaminotic state for years. The results showed that after 8 weeks of oral supplementation with 1500 µg cholecalciferol per week, mean serum 25(OH)D levels were in the range currently considered adequate or sufficient for bone mineral homeostasis. The fact that the serum 25(OH)D level normalized in most study subjects also indicates that impaired 25-hydroxylation is not involved in the etiopathogenesis of subnormal 25(OH)D levels in Asian Indians. The pattern of rise in serum 25(OH)D at 8 weeks of supplementation with cholecalciferol and Ca supplementation and associated normalization of serum PTH levels observed in the current study is akin to that observed earlier in Caucasian subjects⁽⁴⁾.

The recommended intake for vitamin D was 10 µg (400 IU)/d until 1997⁽¹⁰⁾. Based on the belief that adequate vitamin D can be obtained through exposure to sunshine, the Indian Council of Medical Research made no recommendation for dietary vitamin D in 1989⁽⁶⁾. However, following increasing awareness about wide prevalence of vitamin D deficiency in Asian Indians, there has been debate in India regarding corrective measures and adequate intake to correct hypovitaminosis D⁽¹¹⁻¹³⁾. Similar debate is already on world-wide and there has been rethinking on adequate dietary intake for vitamin D which would maintain serum 25(OH)D in the vitamin D-sufficient range of > 79.8 nmol/l⁽⁷⁻⁹⁾. Recommended daily dietary intake for

vitamin D as suggested by various authors has varied from 25 to 250 µg (1000 to 10 000 IU)^(14,15).

In the current study, a dose of 1500 µg cholecalciferol per week in addition to 12.5 µg (500 IU) provided daily along with elemental Ca is equivalent to a dose of 216 µg (8642 IU)/d. The observations of the current study and that of Malabanan *et al.* indicate that on an average, daily intake of 200 µg (8000 IU) vitamin D would bring serum 25(OH)D levels to the vitamin D-sufficient range in most of the subjects at 2 months⁽⁴⁾. The daily oral dose of cholecalciferol which would maintain serum 25(OH)D levels in the vitamin D-sufficient range cannot be answered in the current study.

There has been no study to date for comparison of serum 25(OH)D and PTH response at 1 year after quick supplementation with oral 8-week cholecalciferol therapy. Serum 25(OH)D levels observed at baseline in the current study as well as those reported in our previous study have indicated that serum 25(OH)D levels are almost undetectable in Asian Indians during winter⁽¹⁾. The results of the current study indicate that with 8 weeks of cholecalciferol given at a dose of 1500 µg per week, serum 25(OH)D level increased twofold in winter at 1 year. However, despite efficacy of such a quick supplementation schedule, at 2 months normal 25(OH)D and PTH homeostasis could not be maintained for a period of 1 year. This was indicated by the fact that (1) serum PTH levels reverted to supranormal values at 1 year in those subjects who had high serum PTH at baseline and (2) serum 25(OH)D levels could not be maintained in the vitamin D insufficient to sufficient range.

There is a need for consensus to undertake corrective measures for hypovitaminosis D in Asian Indians. The potential implications of 25(OH)D deficiency are wide ranging. Specifically for Asian Indians it might involve association of vitamin D deficiency with type 2 diabetes and pulmonary tuberculosis^(16,17). These two disorders have an unusually high prevalence in Asian Indians^(18,19).

The results of the current study indicate that cholecalciferol given every week for 8 weeks in Asian Indians with chronic hypovitaminosis D would correct their serum 25(OH)D levels to the vitamin D-sufficient range and lower the serum PTH value to half the existing levels at a short-term period of 2 months. However, such quick supplementation would not maintain their 25(OH)D levels in the sufficient range

for 1 year. For sustained improvement in 25(OH)D levels vitamin D supplementation has to be ongoing after the 8 weeks of vitamin D-loading schedule in Asian Indians. Whether it should involve perennial fortification of common foods such as milk with vitamin D or change in lifestyle including exposure to sunshine needs to be investigated further.

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