Original Article

A randomized controlled trial of cholecalciferol supplementation in patients on maintenance hemodialysis

Beena Bansal, Shyam Bihari Bansal[1], Ambrish Mithal[2], Vijay Kher[3], R. Marwaha[4], Padam Singh[5], Nasir Irfan[6]

Senior Consultant, Division of Endocrinology and Diabetes, [1]Senior Consultant, [3]Chairman, Kidney and Urology Institute, [2]Chairman, Division of Endocrinology and Diabetes, Medanta, The Medicity, Gurgaon, [4]Scientific Advisor, Institute of Life Sciences, [5]Chief Statistical Advisor, Medanta Institute of Education and Research, Gurgaon, Haryana, [6]Medical Officer, Chenab Hospital, Dulhasti Power Station, National Hydel Power Corporation Ltd., Kishtwar, Jammu and Kashmir, India

ABSTRACT

Background: Vitamin D deficiency is common in Indian patients with chronic kidney disease (CKD) on maintenance hemodialysis (MHD), but optimal dose of cholecalciferol is unclear. **Materials and Methods:** A total of 45 consenting patients were randomized to intervention and control groups. In the intervention group, patients (n = 35) with serum 25-hydroxy vitamin D (25(OH)D) <30 ng/mL (n = 33), received oral cholecalciferol 60,000 units/week for 6 weeks. The serum levels of 25(OH)D, calcium, phosphorus, albumin, and parathyroid hormone (PTH) were measured at 0, 6, and 12 weeks. In the control group (n = 10), these were estimated at 0 and 6 weeks. **Results:** In the intervention group, 25/35 patients completed the supplementation at 6 weeks and 20/35 were available at 12 weeks. The mean baseline level of 25(OH)D was 9.59 ± 7.59 ng/mL, and after 6 weeks 19.51 ± 4.27 ng/mL, mean increase being 9.99 ± 6.83 ng/mL, which was highly significant (P < 0.0001). After discontinuing supplementation at 6 weeks, serum 25(OH)D level dropped significantly from 6 to 12 weeks [–2.84 ± 6.25 ng/mL (P = 0.04)]. However, it was still significantly higher at 12 weeks (16.08 ± 8.27 ng/mL) as compared with the baseline. PTH and calcium did not change significantly with supplementation. The change in serum 25(OH)D level from baseline to 6 weeks in the intervention group was inversely related to baseline 25(OH)D levels and patient's weight. In the control group, change in 25(OH)D from baseline to 6 weeks was not significant. **Conclusion:** Supplementation with cholecalciferol 60,000 unit/week for 6 weeks was insufficient to achieve optimal levels of 25(OH)D in Indian patients with CKD on MHD.

Key words: Cholecalciferol, chronic kidney disease, hemodialysis, India, vitamin D hemodialysis

Introduction

Traditionally, bone and mineral disorders in patients with chronic kidney disease (CKD) are managed with active vitamin D, because renal 1-alpha hydroxylase activity is impaired.[1] There is, however, increasing evidence of the importance of nonrenal 1-alpha hydroxylase.[1-3] and growing consensus that 25-hydroxy vitamin D (25(OH)D) levels should be addressed in these patients.[1,4-7]

Studies report vitamin D deficiency in 70%-80% of CKD patients.[8-11] Vitamin D deficiency is prevalent in India.[12,13] and the two studies available in Indian patients with CKD, report vitamin D deficiency (25(OH)D less than 20 ng/mL) in 77%-88% patients.[14-16]

Despite accumulating evidence proving the safety and benefit of vitamin D supplementation in CKD,[4] 25(OH)D measurement or vitamin D (cholecalciferol or ergocalciferol) supplementation is not part of routine care for these patients. This may be due to lack of data on vitamin D supplementation in Indian CKD patients and sparse

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Corresponding Author: Dr. Beena Bansal, Division of Endocrinology and Diabetes, Medanta, the Medicity, Sector 39, Gurgaon - 122 001, Haryana, India. E-mail: beenabansal1975@yahoo.co.in

data on the optimum dose schedule of cholecalciferol or ergocalciferol in CKD patients.[17]

Aim

Our study was a randomized-controlled trial to document the effect of cholecalciferol supplementation on serum 25(OH)D levels in patients on maintenance hemodialysis (MHD) at Medanta, the Medicity, Gurgaon, India between July 2010 and December 2010.

Objectives

The primary objective of the study was to evaluate the proportion of patients on MHD, with serum 25(OH)D <30 ng/mL who achieve optimal levels of 25(OH)D (i.e. >30 ng/mL) by the use of cholecalciferol 60,000 units once a week for 6 weeks.

The secondary objective was to evaluate the mean change in serum 25(OH)D, parathyroid hormone (PTH), calcium and phosphorus levels in patients on MHD, with serum 25(OH)D <30 ng/mL, after supplementation with 60,000 units cholecalciferol once a week for 6 weeks.

Study design

This was a randomized-controlled trial evaluating the effect of cholecalciferol 60,000 units once a week for 6 weeks versus no supplementation, in consenting patients on MHD, with low 25(OH)D (less than 30 ng/dL) at Medanta, Medicity, Gurgaon [Figure 1].

Patients with sufficient 25(OH)D, that is, level more than 30 ng/mL, hypercalcemia (corrected calcium more than 10.5 mg/dL), and those who had taken cholecalciferol supplementation within last 3 months were planned not to be supplemented with cholecalciferol.

Materials and Methods

The study was approved by the institutional review board and written informed consent was obtained by each patient.

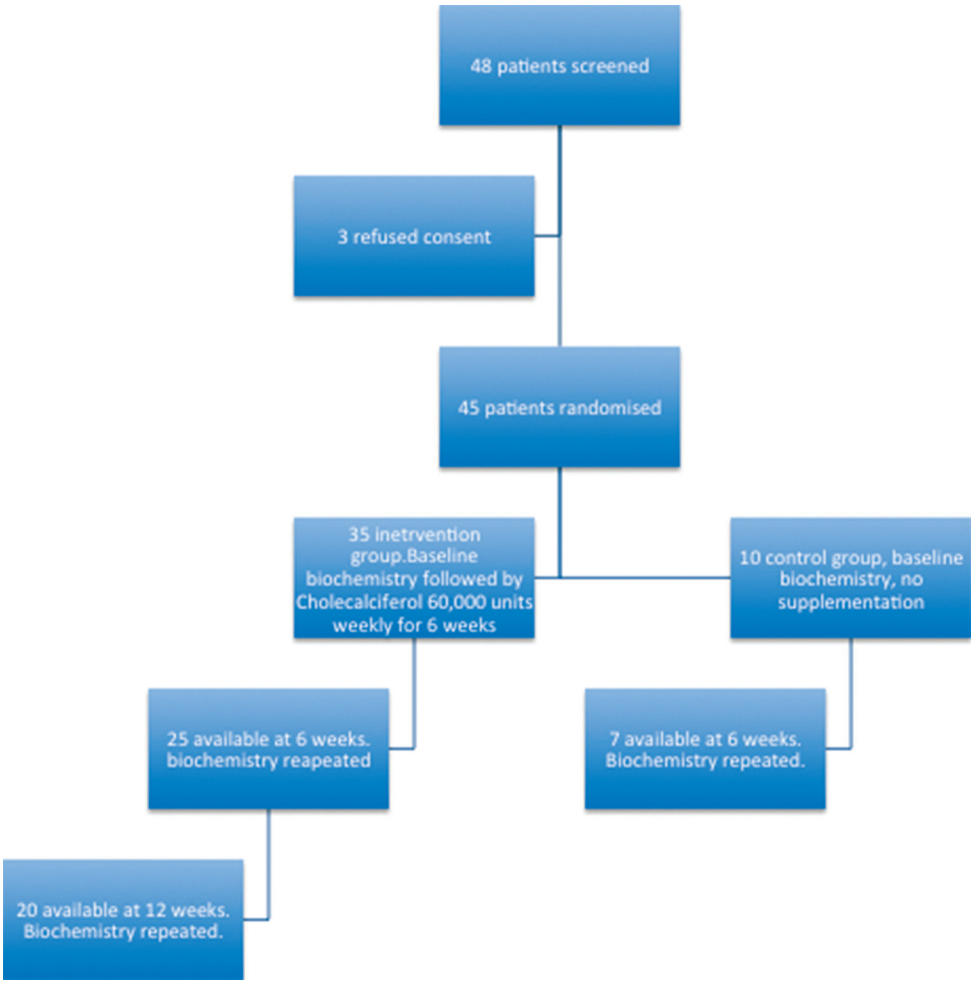

Figure 1: Study design. *Biochemistry included serum calcium, phosphuros, alkaline phosphatase, hemoglobin, albumin, 25-hydroxy vitamin D and intact PTH

A total of 48 patients on MHD for at least 1 month, at Medanta, Medicity were offered participation in the trial, three of which refused consent.

They were randomized to receive cholecalciferol 60,000 units versus no supplementation using a random number list generated by biostatistician, 35 in the intervention group and 10 in the control group.

A total of 10 mL of blood sample were collected during the start of their hemodialysis session from the vascular access.

- 5 mL was collected in plain tubes and sent for analysis of calcium, phosphorus, albumin and alkaline phosphatase to Medanta laboratory
- 5 mL was collected in tubes kept in ice, centrifuged immediately, 2 aliquots made and stored at −80 cold storage. These samples were sent for analysis of 25(OH)D and intact PTH to Institute of Nuclear Medicine and Allied Sciences, New Delhi ensuring a cold chain.

The intervention group was supplemented with cholecalciferol granules 60,000 units, once a week, orally, mixed with water, immediately after their hemodialysis session, under supervision by study staff. The supplementation phase was from 0 to 6 weeks and no supplementation, that is, maintenance phase from 6 to 12 weeks. Blood samples were collected for analysis as described below after 6 weeks (±4 days) and 12 weeks (±7 days).

The control group did not receive any supplementation for 0 to 6 weeks, and samples were collected as described after 6 weeks.

Both groups received usual care in the form of active vitamin D and phosphate binders if needed.

Calcium levels were checked once in 2 weeks (±2 days) in these patients.

Analytical methods

Measurement of calcium was done with aresanzo dye, phosphorus by phoshomolybdate reduction, alkaline phosphatase by 4-nitrophenyl phosphate method, hemoglobin by cyan-methemoglobin, and albumin by bromocresol green dye. Corrected calcium level was calculated when the albumin was abnormal. This was to make up for the change in total calcium due to the change in albumin-bound calcium.

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

The assays were performed on Johnson and Johnson instruments (vitros 5600 and 5.1). PTH was measured using electrochemiluminiscence immunoassay (ECLIA, Roche diagnostics, Mannheim, Germany). Serum 25(OH)D was measured by Radioimmunoassay (RIA) using a commercial kit (Diasorin, Stillwater, MN, USA). The normal range for 25(OH)D was 22.5-92.5 nmol/l (9-37 ng/mL), with analytical sensitivity being 3.75 nmol/L (1.5 ng/mL). The normal range for PTH assay was 9-65 pg/mL with an analytical sensitivity of 1.20 pg/mL (0.127 pmol/L).

In this study, we defined vitamin D deficiency as serum 25(OH)D ≤20 ng/mL and vitamin D insufficiency as serum 25(OH)D >20 and <30 ng/mL.

Statistical analysis plan

Baseline values of age, weight, duration of dialysis, blood hemoglobin, and serum levels of 25 (OH)D, PTH, corrected calcium, albumin, and phosphorus were compared between the intervention and control group using *t* test.

Paired *t* test was used to compare changes in 25(OH)D, PTH and calcium between baseline to 6 weeks, 6 weeks to 12 weeks, and baseline to 12 weeks. This was done separately for intervention and control groups.

Change in the level of serum 25(OH)D from baseline to 6 weeks was compared between intervention and control groups using unpaired *t* test.

Multivariate regression analysis was done to see the effect of baseline 25(OH)D, age, sex, duration of dialysis, weight, and baseline calcium levels on change in serum 25(OH)D level from baseline to 6 weeks.

Sample size calculation: Vitamin D insufficiency was reduced by at least 15% in intervention group versus 0.5% in control group in various studies. To demonstrate noninferiority of cholecalciferol with 80% power and 5% level of significance, we need a sample size of 35 patients. Considering a 'lost to follow-up' rate of 10%, we recruited 40 patients for this study.

Results

Baseline data

The intervention and control groups were similar with regards to age, weight, duration of dialysis, baseline blood hemoglobin, serum levels of 25(OH)D, PTH, corrected calcium, albumin, and phosphorus Table 1.

Overall, mean 25(OH)D level was 10.14 ± 8.7 ng/mL. At baseline, only two (4.4%) patients were vitamin D

sufficient and three (6.7%) were vitamin D insufficient. The remaining 40 (88.9%) were vitamin D deficient. Of these, 29 (64.4%) had severe vitamin D deficiency with 25(OH)D less than 10 ng/mL. There was a weak correlation between baseline 25(OH)D levels and weight, sex, hemoglobin, albumin, alkaline phosphatase, and presence of diabetes. There was, however, no correlation of 25(OH)D with duration of dialysis or PTH levels.

Overall, 23 (51%) patients had diabetic nephropathy and 33 (74%) patients were on thrice a week hemodialysis. A total of 23 patients were on calcitriol and 17 on sevelemar.

Effect of supplementation

In the supplementation group, 25/35 patients completed the supplementation at 6 weeks and 20/35 remained at 12 weeks. The reasons for loss to follow up were: 1 patient had 25(OH)D >30 ng/mL, patients opting for another centre for hemodialysis (two subjects), renal transplantation (9 subjects-4 of these within 6 weeks and another 5 subjects between 6 and 12 weeks), continuous ambulatory peritoneal dialysis (CAPD) initiation (1 patient), death (1 patient), and irregular hemodialysis (1 patient).

At baseline 27/35 (77.1%) were vitamin D deficient and 7/35 (20%) had insufficient levels of 25(OH)D Figure 2. Only one patient had sufficient levels of 25(OH)D. The mean baseline level of 25(OH)D was 9.59 ± 7.59 ng/mL, which increased significantly after 6 weeks of supplementation to 19.51 ± 4.27 ng/mL [Table 2]. The mean change in serum 25(OH)D level from baseline to 6 weeks was 9.99 ± 6.83 ng/mL, which was highly significant ($P < 0.0001$). After stopping supplementation at 6 weeks, serum 25(OH)D level dropped significantly, change from 6 to 12 weeks being −2.84 ± 6.25 ng/mL ($P = 0.04$). However, it was still significantly higher at 12 weeks (16.08 ± 8.27 ng/mL) as compared with baseline; change from baseline to 12 weeks being 6.38 ± 8.49 ng/mL ($P < 0.01$).

The change in serum 25(OH)D level from baseline to 6 weeks in the intervention group was inversely related to baseline 25(OH)D levels and weight of the patient Table 3, Figure 3. This change was, however, independent of baseline calcium, phosphorus, age, or duration of dialysis.

At 6 weeks, despite high dose of cholecalciferol supplementation, none of the patients achieved optimal 25(OH)D levels. Of these 25 subjects, 15 were still in the vitamin D deficient group and 10 were insufficient Figure 2. At 12 weeks, the number of subjects with deficient, insufficient, and sufficient values was 15, 3, and 1, respectively.

The levels of PTH and phosphorus did not change significantly after supplementation. The calcium levels increased significantly from baseline at 12 weeks ($P < 0.05$), but no patient developed hypercalcemia Table 2.

Control group

In the control group, 7/10 patients were available for follow up at 6 weeks. One patient had serum 25(OH)D > 30 ng/mL, while two patients underwent renal transplantation. Mean baseline 25(OH)D level was 11.51 ± 11.49 ng/mL and at 6 weeks 10.28 ± 9.81 ng/mL. The change in serum 25(OH)D level from baseline to 6 weeks was 2.51 ± 5.73 ng/mL, which was not significant Table 4.

Comparison of the change in serum 25(OH)D level from baseline to 6 weeks between intervention and control groups was found to be statistically different ($P = 0.008$) Table 5.

Discussion

Majority of CKD patients on MHD in this study were vitamin D deficient (88.9%). Studies in CKD patients report 70%-80% prevalence of vitamin D deficiency.[7]

Table 1: Comparison of baseline data between intervention group and control group

Parameters	Intervention group (*n*=32)		Control group (*n*=13)		*T* value	*P* value
	Mean	SD	Mean	SD		
Age (years)	55.72	13.69	53.85	12.96	0.42	0.6744
Duration of dialysis (Months)	15.55	19.61	5.35	4.44	1.85	0.0644
Weight (kg)	62.35	12.66	61.91	16.22	0.08	0.9362
Hemoglobin (g/dL)	9.71	1.69	9.88	1.86	0.28	0.7794
Calcium (g/dL)	8.02	0.71	8.72	1.15	2.42*	0.0156*
Corrected calcium* (g/dL)	8.60	0.63	8.38	1.15	0.79	0.4296
Serum phosphorus	5.35	2.34	4.93	0.85	0.60	0.5486
Serum albumin in g/dL	3.30	0.55	3.29	0.52	0.05	0.9602
Serum alkaline phosphatase (IU/L)	217.52	213.62	157.42	72.61	0.95	0.3422
PTH (pg/mL)	268.88	220.61	237.84	213.30	0.41	0.6818
25(OH)D# (ng/mL)	9.59	7.59	11.51	11.49	0.65	0.5156

*Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0-serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL. #25(OH)D=25-hydroxy vitamin D. PTH: Parathyroid hormone, SD: Standard deviation

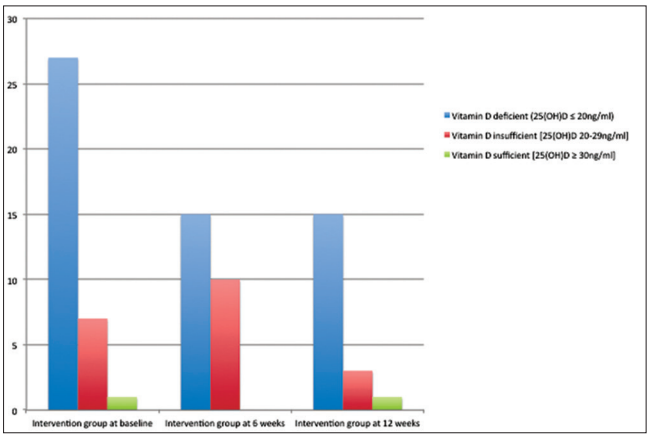

Figure 2: Number of patients who were vitamin D deficient, insufficient and sufficient at baseline, 6 weeks and 12 weeks in the intervention group

Table 2: Change in serum 25-hydroxy vitamin D (25-hydroxy vitamin D) and parathyroid hormone after cholecalciferol supplementation from baseline to 6 weeks, 6-12 weeks and from baseline to 12 weeks

Parameters	*N*	Mean	SD	SE	*T* value	*P* value
Δ 25(OH)D (6-0)	25	9.99	6.83	1.37	7.32	<0.001
Δ 25(OH)D (12-6)	20	−2.84	6.25	1.40	−2.04	0.0414
Δ 25(OH)D (12-0)	20	6.38	8.49	1.90	3.36	<0.01
Δ PTH (6-0)	25	−38.43	201.40	41.11	−0.93	0.3524
Δ PTH (12-6)	20	24.04	119.83	26.15	0.92	0.3576
Δ PTH (12-0)	20	4.21	119.74	26.13	0.16	0.8728

Δ 25(OH)D (6-0) = Change in serum levels of 25(OH)D from baseline to 6 weeks; Δ 25(OH)D (12-6) = Change in serum levels of 25(OH)D from 6 weeks to 12 weeks; Δ 25(OH)D (12-0) = Change in serum levels of 25(OH)D from baseline to 12 weeks; D PTH (6-0) = Change in serum levels of PTH from baseline to 6 weeks; Δ PTH (12-6) = Change in serum levels of PTH from 6 weeks to 12 weeks; D PTH (12-0) = Change in serum levels of PTH from baseline to 12 weeks. 25(OH)D: 25-hydroxy vitamin D, PTH: Parathyroid hormone, SD: standard deviation, SE: Standard error of the mean

Table 4: Change in serum 25-hydroxy vitamin D in control group from baseline to 6 weeks

Parameters	*N*	Mean	SD	SE	*T* value	*P* value
Δ25(OH)D (6-0)	7	2.51	5.73	2.17	1.16	0.2460

Δ 25(OH)D (6-0) = Change in serum levels of 25(OH)D from baseline to 6 weeks. 25(OH)D: 25-hydroxy vitamin D, SD: Standard deviation, SE: Standard error of the mean

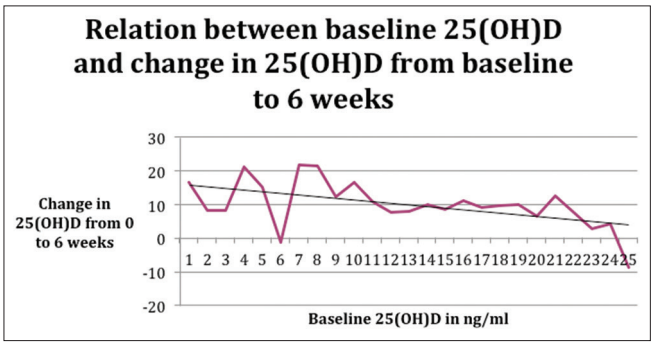

Figure 3: Correlation between baseline 25-hydroxy vitamin D and change in 25(OH) vitamin D after cholecalciferol supplementation 60,000 units weekly from baseline to 6 weeks

Table 3: Correlation of change in 25-hydroxy vitamin D levels from baseline to 6 weeks in the intervention group with various parameters

Parameter	Change in 25-hydroxy vitamin D levels from baseline to 6 weeks	
	"*r*" correlation coefficient	Significance
Baseline hemoglobin	−0.35	0.0702
Baseline corrected calcium	0.13	0.5156
Baseline calcium	0.08	0.6966
Baseline phosphorus	−0.26	0.2006
Baseline albumin	−0.08	0.6818
Baseline alkaline phosphatase	0.21	0.3078
Baseline PTH	0.30	0.1336
Baseline 25(OH)D	−0.67	<0.01*
Age	−0.37	0.0614 (NS)
Duration of dialysis	0.12	0.5824 (NS)
Weight	−0.50	0.0066*

25(OH)D: 25-hydroxy vitamin D, PTH: Parathyroid hormone, NS: Not significant

Table 5: Comparison of intervention and control group with respect to change in the 25-hydroxy vitamin D from baseline to 6 weeks

Parameters	*N*	Mean	SD	*T* value	*P* value
Δ25(OH)D (6-0): Intervention group	25	9.99	6.83	2.64	0.0082*
Δ25(OH)D (6-0): Control group	7	2.51	5.73		

Δ 25(OH)D (6-0) = Change in serum levels of 25(OH)D from baseline to 6 weeks. 25(OH)D: 25-hydroxy vitamin D

Indian studies in non-CKD population report vitamin D deficiency in 70%-91.2%,[18-21] while in CKD patients between 77% and 88%,[14-16] both being similar.

Studies of cholecalciferol supplementation in CKD patients are heterogenous with regards to their baseline 25(OH)D (from <7 to 20 ng/mL), cholecalciferol doses used (from 4000 to 50,000 units daily), duration of study (from 1 month to 1 year), and response to supplementation.[4]

In this study, 25(OH)D levels rose form 9.59 to 19.51 ng/mL in 6 weeks with 60,000 units cholecalciferol weekly. In an apparently normal north Indian population, Malhotra *et al.*,[22] had observed rise in 25(OH)D from a mean of 4.8-31.6 ng/mL with much less cholecalciferol doses, that is, 60,000 units monthly for 3 months. In another study,[23] 60,000 units cholecalciferol weekly raised the mean 25(OH) levels from 5.4 to 33 ng/mL. This implies that CKD patients on MHD show less response to cholecalciferol supplementation than healthy individuals. This is despite most of them also being on active vitamin D supplements or calcium supplements. One of the explanations could be stimulation of 24-hydroxylase by elevated FGF23 in CKD, thus increasing metabolism of 25(OH)D.[24,25]

In this study, there was neither correlation of baseline PTH with 25(OH)D, nor did PTH levels change significantly with supplementation. In a recent meta-analysis, there was a significant decrease in PTH levels with vitamin D supplementation and the benefit was higher in dialysis patients compared with the nondialysis-dependent CKD and transplant recipients.[4] This study was not sufficiently powered to test the effect of cholecalciferol supplementation on PTH.

Although calcium levels increased significantly at 6 weeks in intervention group, no patient developed hypercalcemia despite being on active vitamin D analogues as well. In the same meta-analysis, calcium levels were similar before and after cholecalciferol supplementation, although 2% subjects developed mild hypercalcemia.[4]

Change in serum levels of 25(OH)D from baseline to 6 weeks in the intervention group was 9.99 ± 6.83 ng/mL, suggesting that there is high individual variability in response to cholecalciferol supplementation. In this study, the change in serum levels of 25(OH)D from baseline to 6 weeks was found to be inversely correlated to baseline serum 25(OH)D level and weight. In a study in non-CKD population, baseline 25(OH)D, baseline calcium, body mass index, and baseline season were significantly affecting rise in 25(OH)D levels.[26] This correlation with baseline 25(OH)D was, however, not seen in studies done in CKD population.[27]

Conclusion

This study showed that cholecalciferol doses in 60,000 units weekly for 6 weeks were inadequate to raise 25(OH)D levels optimally, in Indian CKD patients on MHD. The response of serum 25(OH)D level to cholecalciferol supplementation was inversely related to baseline 25(OH)D level and weight. Serum calcium levels did not rise significantly in the intervention group, and no patient developed hypercalcemia despite patients being on both inactive and active vitamin D.

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