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ORIGINAL ARTICLE

Outcome of Cholecalciferol Supplementation on Bone Mineral metabolism in End Stage Renal Disease Patients in Comparison with Placebo-Randomized Control Trial

HAROON AYUB[1], KOMAL NASEEM[2], FAISAL AMIN BAIG[3], AFRAZ AHMED[4], SUMIT ACHARYA[5], WAQAR AHMED[6]
[1]*Assistant Professor, Department of Nephrology, University College of Medicine & Dentistry, The University of Lahore*
[2] *Postgraduate Resident, Postgraduate Medical Institute/Ameer-ud-Din Medical College, Lahore General Hospital, Lahore*
[3]*Professor, Department of Medicine, University College of Medicine & Dentistry, The University of Lahore*
[4]*Medical Officer, Evercare Hospital, Lahore.*
[5]*Consultant Nephrologist, Norvic International Hospital, Shahid Dharma Bhakta National Transplant Center, Nepal*
[6]*Professor, Department of Nephrology, Shaikh Zayed Postgraduate Medical Institute, Lahore.*
Correspondence to: Haroon Ayub, Email: haroonayub177@gmail.com, Cell: 0344-4442844

ABSTRACT

Objectives: This study was conducted to evaluate the impact of oral cholecalciferol intake on Bone Mineral Metabolism [i.e. levels of 25-hydroxyvitamin-D, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), calcium (Ca), phosphorus (P), calcium-phosphorus product (CaxP)] and to ascertain its effects on markers of inflammation [i.e. C-reactive protein (CRP), white blood cell count (WBC)] and chronic musculoskeletal symptoms (musculoskeletal pain or fatigue)

Study Design: Double blind randomized controlled trial.

Place and Duration of Study: Shaikh Zayed Hospital, Lahore, over a period of 2 months from November 2015 to Jan 2016.

Methods: 70 patients on maintenance hemodialysis in Shaikh Zayed Hospital Lahore, fulfilling inclusion criteria received weekly doses of cholecalciferol or placebo according to 25-hydroxyvitamin-D levels. All patients were evaluated at 0 month and 2 months after supplementation. Level of 25-hydroxyvitamin-D, hemoglobin, white blood cell count, intact PTH, alkaline phosphatase, calcium, phosphorus, calcium phosphorus product, C reactive protein, albumin and scale of chronic pain/fatigue with visual analog scale was compared at day 0 and after 2 months of treatment.

Results: There was substantial increment in 25 OH vitamin D levels after cholecalciferol intake whereas there was reduction in vitamin D levels in patients receiving placebo. In the cholcalciferol group only 14% achieved therapeutic levels of >30 pg/dl while 60% had levels >25 pg/dl. There was minor change in iPTH, calcium, phosphorus, calcium phosphorus product and alkaline phosphate levels in cholcalciferol group as compared to placebo (p value = 0.484, 0.067, 0.359, 0.061, 0.12 respectively). There was significant improvement of chronic musculoskeletal pain (p value=0.00) and CRP (p value=0.005) with cholecalciferol supplementation compared to placebo. Hemoglobin, white blood cell count, albumin level had no significant difference in both the groups.

Conclusion: Cholecalciferol supplementation was effective in reduction of chronic musculoskeletal symptoms and marker of inflammation like CRP but does not show difference in term of iPTH, calcium, phosphorus calcium phosphorus product, alkaline phosphate, hemoglobin, albumin level and WBC count.

Keywords: ESRD, Vitamin D3, 25 hydoxyvitamin D, Metabolic Bone disease

INTRODUCTION

It has been shown that nearly 50%–100% of patients on hemodialysis have nadir vitamin-D status[1,2]. There is rising keenness in vitamin-D supplementation owing to the recent evidence of extra renal formation of calcitriol by cells of almost all of systems of the body. It is also postulated that vitamin D binding receptors exist in various tissues along with 1-α hydroxylase activity outside the kidney[3,4].

According to a study in hemodialysis population, 1, 25-dihydroxvitamin-D3 levels increased after addition of nutritional vitamin-D, proposing that there is enough extra renal activity of 1-α hydroxylase to alter serum levels even in ESRD[5]. Dusso et al. had similar findings, confirming the extra-renal formation of calcitriol in macrophages of uremic patients[6]. Other sites of the body where 1-α-hydroxylase is expressed are parathyroid gland, pancreas, adrenal medulla, skin, nodes and cerebellum, prostate, breast, colon, and macrophages[7]. Therefore, autocrine genesis of 1,25-dihydroxyvitamin-D3 may be pertinent for many biologic activities in these sites. The levels of these substances may be even more relevant when the production is reduced in the renal tissues[8].

This study was conducted to ascertain the influence of oral cholecalciferol supplementation on Bone Mineral Metabolism (i.e levels of 25-hydroxyvitamin-D, alkaline phosphatase, intact parathyroid hormone, calcium, phosphorus, calcium-phosphorus product) and to determine the effects of its use on marker of inflammation (i.e. C-reactive protein, white blood cell count, S. albumin) and chronic musculoskeletal symptoms (musculoskeletal pain or fatigue). This study may be helpful regarding therapeutic benefits of oral vitamin-D intake in ESRD Pakistani population where the frequency of hypovitaminosis D is even very high in healthy population. Furthermore correction of vitamin D deficiency has not been studied greatly in maintenance hemodialysis population.

MATERIAL AND METHODS

The study was carried out after taking ethical approval from Institutional Review Board (IRB) of the institute. Patients undergoing maintenance hemodialysis thrice per week for more than 1 year at our institute were included in the study. These included patients from both genders, age more than 18 years and with corrected serum calcium <10.2 mg/dl and serum phosphorus <6mg/dl. Patients were recruited after written informed consent. Patients presenting with active bleeding (melena, hematemesis, hematochezia); taking nutritional vitamin D3 and D2 (ergo cholecalciferol) in preceding 3 months; using cinacalcet and intravenous iron along with blood transfusion 1 month prior to enrollment; having malignancy, tubercular infection, sarcoidosis, pregnancy and whose calcitriol, alfacalcidol, phosphate binder or erythropoietin dosage adjustment was made 1 month prior to enrollment were precluded from the study. Measurement of serum 25-hydroxyvitamin D3 levels was carried out in all patients.

Randomization was done in 25 hydoxyvitamin D deficiency patients by lottery method by hemodialysis staff making 35 patients in each group. All the patients were asked for chronic pain (musculoskeletal pain or fatigue) evaluated by visual analog scale for pain. Intact parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, albumin, calcium, phosphorus and C - reactive protein (CRP) were then measured.

Oral cholecalciferol was given in patients with 25 hydoxyvitamin D deficiency depending upon 25-hydroxyvitamin D3 serum levels. Patients with 25-hydroxyvitamin D levels <15 ng/ml were given 50,000 IU cholecalciferol once a week, whereas10,000

IU once a week was prescribed if the levels were between 16 and 30 ng/ml.1 Similar placebo was given to patients according to serum 25-hydroxyvitamin D levels . Cholecalciferol capsule or placebo was given supervised orally once a week with meals during their hemodialysis treatment. Levels of 25-hydroxyvitamin D3 level, iPTH, alkaline phosphatase, Ca, P, albumin, complete blood count, and CRP were repeated after two months of supplementation. All patients were under treatment with same dose of active vitamin D, erythropoietin, oral iron tablets, phosphate binders and antihypertensive medications. Type of dialyzer, dialysis dose and calcium content of dialysate was similar for all the patients throughout the study. A sample size of 35 was calculated by using 95% confidence level, 90% power of the test with the anticipated iPTH level at baseline and 2 month 295± 90 and 249± 80 respectively9. Categorical variables (like gender, presence/absence of diabetes, presence/absence of Hepatitis C) were analyzed with chi square test. Quantitative variables (age, duration of dialysis, 25-hydroxyvitamin D3 level, Complete blood count, Albumin, iPTH, alkaline phosphatase, Calcium, Phosphorus, calcium phosphorus product, CRP level and musculoskeletal chronic pain by visual analog scale) were analyzed with paired t test. Independent t test was utilized to compare means and normal distribution variables. Wilcoxon Signed-Rank Test or Mann – Whitney test was applied when distribution was not normal. SPSS version 18 was used for statistical analysis with a p value is <0.05 as significant.

RESULTS

Out of 100 patients screened 96% have Vitamin D deficiency. Of these 70 patients were randomized. Mean age of patients was 49 ±10.11 years in cholecalciferol group and 46 ±14 years in placebo group. 54.2 % were males and 45.8 % were females in cholecalciferol group where as 65.7 % were males and 34.3 % were females in placebo group. Mean duration of hemodialysis was 58.7 ±35 months in cholecalciferol group and 63 ±56.26 months in placebo group. 48.5% were diabetic in both the groups and 48.5% had chronic hepatitis C infection in placebo group whereas 51.4% have chronic hepatitis C infection in cholecalciferol group. Mean BMI was 23.89 ±4.49 in placebo group and 23.60 ±4.20 in cholecalciferol group. Mean 25 hydooxyvitamin D level was 15.13 ±5.34 ng/ml in cholecalciferol group and 17.03 ±5.6 ng/ml in placebo group. Mean calcium level was 8.45±0.9 mg/dl in cholecalciferol group and 8.11 ±1 placebo group whereas mean phosphorus was 4.6 ±0.87 mg/dl in cholecalciferol group and 4.5 ±0.93 mg/dl in placebo group. Mean iPTH level was 442 ±277 pg/ml in cholecalciferol group and 358 ±269 pg/ml in placebo group. Mean alkaline phosphate level was 235 ±122 mg/dl in cholecalciferol group and 287.65 ±169 mg/dl placebo group. Mean leucocyte count was 7.44 ±2.37 x103 cell/mm3 in cholecalciferol group and 7.46 ±1.8 x103 cells/mm3 in placebo group. Mean hemoglobin level was 10.14 ±1.4 g/l in cholecalciferol group and 10.2 ±1.58 g/l in placebo group. Mean CRP level was 6.8 ±4.18 mg/dl in cholecalciferol group and 7.9 ±4.46 mg/dl in placebo group. Mean VAS of musculoskeletal pain or fatigue was 7.09 ±1.42 in cholecalciferol group and 6.37 ±1.68 in placebo group.

There was significant decrement in vitamin D levels (p value 0.01) and significant increment in levels of phosphorus (p value 0.001), calcium phosphorus product (p value 0.005) and iPTH (p value 0.000) after placebo supplementation. There was no significant difference in level of calcium (p value 0.312), alkaline phosphate (p value 0.064), albumin (p value 0.528), WBC count (p valuen0.544) after supplement in placebo group however there was also significant improvement VAS of chronic musculoskeletal pain (p value 0.003). There was significant increase in levels of vitamin D (p value <0.001), calcium (p value 0.002), phosphorus (p value <0.001), CaxP product (p value <0.001) after cholecalciferol supplementation. There was no significant difference in levels of iPTH (p value 0.164), alkaline phosphate (p value 0.418), hemoglobin (p value 0.317), albumin (p value 0.555) and WBC count (p value 0.302) after cholecalciferol supplementation. There was significant improvement in VAS chronic pain (p valve <0.001) and CRP level (p value 0.011) in cholecalciferol group. There was no significant difference in level of calcium (p value 0.067), phosphorus (p value 0.359), alkaline phosphate (p value 0.120), CaxP product (p value 0.061), WBC count (p value 0.098), hemoglobin (0.503), albumin (p value 0.818), iPTH (0.484) after supplementation with cholecalciferol in comparison to placebo group. Vitamin D levels were significantly higher (p value <0.001) with significant improvement in chronic musculoskeletal pain VAS (p value <0.001) and CRP levels (p value 0.005) in patients with cholecalciferol supplementation as compared to placebo.

Flowchart

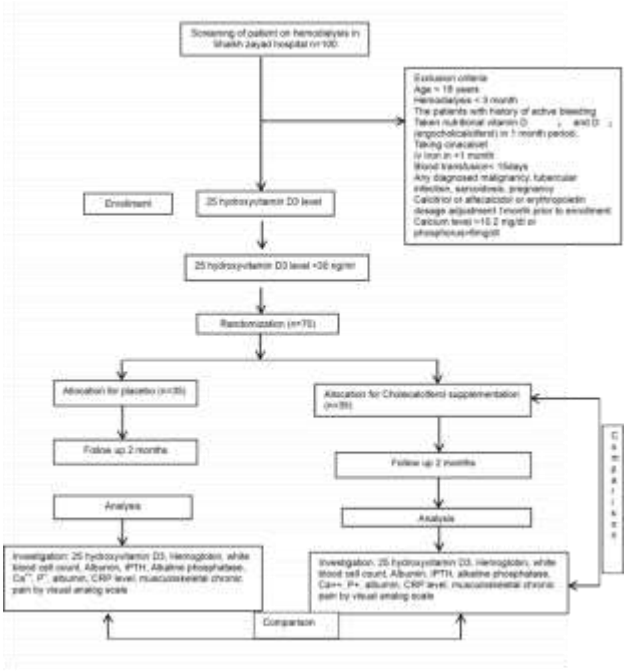

Table 1: Baseline character of patients

	Placebo group mean±SD/median(range)	Cholecalciferol group mean±SD/median(range)	P value
Age	46.94±14	49.51±10.11	0.382
Gender Male Female	 23(65.7%) 12(34.3%)	 19(54.3%) 16(45.7%)	0.329
Duration of dialysis(months) Median	63±56.26 48(12-252)	58.7±35 60(12-144)	0.583*
Weight (kg)	65.37±13.58	63.08±12.5	0.467
Height (cm)	165.17±7.56	163.2±7.97	0.299
BMI Median	23.89 ±4.49 23.42(16.8-38.54)	23.60 ±4.20 23.66(17.11-36.10)	0.916*
Diabetes	17(48.6%)	17(48.6%)	1

No diabetes	18(51.4%)	18(51.4%)	
Hepatitis c Hepatitis C negative	17(48.6%) 18(51.4%)	18(51.4%) 17(48.6%)	0.811
Vitamin D level Median	17.03±5.6 16.81(8.24-28.91)	15.13±5.34 13(8.61-26.35)	0.114*
Calcium	8.11±1	8.45±0.9	0.140
Phosphorus	4.5±0.93 4.6(2.3-5.9)	4.6±0.87 4.9(1.7-5.9)	0.434*
CaxP product	36.88±10.28 37.8(16.33-59)	39.53±8.9 40(16.15-54)	0.253
iPTH	358.6±269 234(32-993)	442±277 375(46-972)	0.157*
Alkaline phosphatase	287.65 ±169 204(107-648)	235±122 218(78-570)	0.324*
Hemoglobin	10.2±1.58	10.14±1.4	0.874
Albumin	3.57±0.44 3.6(2-4.4)	3.65±0.38 3.7(2.6-4.7)	0.412*
CRP	7.9±4.46	6.8±4.187	0.317
WBC count(mean)	7.46±1.8 7.4(3.92-11.77)	7.44±2.37 6.9(4.8-13.3)	0.643*
Chronic pain (VAS)	6.37±1.68 7(2-10)	7.09±1.42 7(5-10)	0.077*

Table 2: Result after supplementation

	Cholecalciferol		P value before after cholecalciferol	Placebo		P value before after placebo	P value after cholecalciferol/ placebo
In mean±SD	Before	After		Before	After		
Vitamin D level	15.13±5.34 13(8.61-26.35)	25.97±7.12 25.43(15.91-52.66)	<0.001*	17.03±5.6 16.81(8.24-28.91)	14.16±4.68 13.71(6.01-25.35)	0.000	0.000
Calcium	8.45±0.9 8.5(6.6-9.8)	8.8±0.88 9(7-10)	0.002*	8.11±1 8(6-10)	8.32±1.10 8.6(5.6-10.2)	0.215	0.067
Phosphorus	4.6±0.87 4.9(1.7-5.9)	5.7±1.77 5.3 (2-10.5)	<0.010*	4.5±0.93 4.6(2.3-5.9)	5.2±1.37 5.2(1.8-9)	0.001*	0.359
Caxp product	39.53±8.9 40(16.15-54)	50.59±16.96 48.23(19.6-102.9)	<0.001	36.88±10.28 37.8(16.33-59)	44.27±14.47 42.7(16.38-81.88)	0.005*	0.061
iPTH	442±277 375(46-972)	516±293.27 370(125-1154)	0.164*	358.6±269 234(32-993)	562±308.6 550(80-176)	0.000*	0.484
Alkaline phosphatase	235±122 218(78-570)	242±107 216(95-540)	0.408*	287.657±169 204(107-648)	319±175 273(106-698)	0.064*	0.120
Hemoglobin	10.14±1.4	10.43±1.42	0.172	10.2±1.58	10.23±1.55	0.821	0.503
Albumin	3.65±0.38 3.7(2.6-4.7)	3.66±0.42 3.6(2.7-4.6)	0.828	3.57±0.44 3.6(2-4.4)	3.59±0.44 3.7(3-4.3)	0.528*	0.818
CRP	6.8±4.187 6.2(0.3-16.4)	4.97±3.65 3.35(0.19-11.04)	0.011*	7.9±4.46 7.6(0.70-18.6)	7.54±3.8 9.37(0.52-11.97)	0.441*	0.005
WBC count	7.44±2.37 6.9(4.8-13.3)	7.04±2.37 6.7(3.38-14.84)	0.302*	7.46±1.8 7.4(3.92-11.77)	7.6±1.98 7.65(3.22-11.99)	0.419	0.098
Chronic pain (VAS)	7.09±1.42 7(5-10)	3.20±1.87 3(1-7)	<0.001*	6.37±1.6 7(2-10)	5.37±2 5(1-9)	0.004	0.000

DISCUSSION

Causes of inadequate vitamin D levels in ESRD include reduced exposure to sunlight, scanty dietary intake, poor absorption, and proteinuria [8]. According to previous studies formation of vitamin D with UV rays is significantly hampered in ESRD, indicating that dietary sources of vitamin D would be a crucial source of 25-hydroxyvitamin D3 levels in this set of patients10. Uremia also decreases the ability of the skin to activate vitamin D[11,12]. Kidney Disease: Improving Global Outcomes (KDIGO) guidance provides a non-graded suggestion to correct 25(OH)D3 deficiency as the initial step to treat secondary hyperparathyroidism (SHPT) in CKD stage III–V,[13] with no recommendations of this correction in dialysis population[14]. Levels of $25(OH)D_3$ > 30 ng/mL are regarded as adequate, levels of 21 to 29 ng/are considered as inadequate, whereas levels below 20 ng/mL are termed deficient[15]. It may be necessary to keep the blood levels of $25(OH)D_3$ >80 nmol/L(approx. 30ng/ml) for the renal and extra-renal formation of calcitriol[16]. 25 $(OH)D_3$ has a substantially longer half-life than calcitriol and the is the major form of total vitamin D store obtained from cutaneous synthesis or food[17]. In our study 96 % of patients had 25 hydroxy vitamin D deficiency; among them 21% insufficient, 75% deficient and 4% had level >30 ng/ml. Only 14.25% achieved therapeutic goal of 25 hydroxy vit D levels after supplementation, which suggest that increased dose or frequency may be needed to reach the therapeutic level. Our study also showed that levels of 25 hydroxy vit D decrease with time in placebo group, which also emphasizes the importance of maintenance doses.

Lately, according to an in vitro study 25(OH) D3 may precisely activate VDR (vitamin D receptor), independent of calcitriol, contributing to the control of secondary hyperparathyroidism[10,18]. In a recent meta-analysis by Kandula and colleagues, observational studies indicate that nutritional vitamin D decreases iPTH (intact parathormone) levels in CKD (−24.24 pg/mL) as well as in ESRD (−59.49 pg/mL) patients. However, the studies were incongruous for the oral vitamin D prescription with regards to type, doses, and route of administration[19].

In our study, no significant change was observed in iPTH, calcium, and phosphorus levels after cholecalciferol supplementation as compared to placebo. Our study was unable to show the changes in the level of iPTH after cholecalciferol supplementation because the supplementation dose was not enough to increase 25 hydroxyvitamin D to >30 ng/ml and thus to

decrease iPTH level. However, inconsistent outcomes have been obtained for PTH and calcium levels with only a few randomized controlled studies describing increment of 1- 25 OH vitamin D level after cholecalciferol challenge. Out of these, none showed any significant impact on either PTH or calcium level[20]. But in our study, there was a significant increase in PTH level in the placebo group whereas these levels remained unchanged in the cholecalciferol group. It may be speculated that cholecalciferol may have played some part in hampering the increment of iPTH level in this group. In addition, cholecalciferol supplementation did not reduce iPTH levels in patients having low turnover bone disease as evidenced by iPTH levels less than <300 pg/ml at the start of the study. Thus, cholecalciferol may be a safe option in these patients as well.

Oral vitamin D (cholecalciferol, ergocalciferol, or calcifediol) is nowadays used when levels of $25(OH)D_3$ fall below 30 ng/mL in the general as well as dialysis population[14]. A few studies have defined the ideal dosage and duration of vitamin D treatment for $25(OH)D_3$ insufficient hemodialysis (HD) patients and have ascertained the safety and benefits of the supplementation[21,22]. In our study we found that supplementation with 10000 IU/week for insufficient and 50000 IU/week for deficient levels of $25(OH)D_3$ for 2 months was inadequate to increase the level to >30 pg/ml, limiting us to demonstrate additional benefit of cholecalciferol supplementation in lowering iPTH.

Levels of cathelicidin, an antimicrobial protein controlled by local vitamin D formation in macrophages, correlate with mortality risk due to infectious causes in hemodialysis patients[23]. It has been observed that vitamin D deficiency results in impaired localized innate immunity and defective antigen-specific cellular immunity[24]. In our study, CRP was significantly lower in patients with cholecalciferol supplementation which implies to anti-inflammatory properties of cholecalciferol whereas changes in other markers like WBC count, serum albumin level were not significant. In addition, Visual Analog Scale of chronic pain was significantly lower in the patients with cholecalciferol supplementation. This result may be helpful in the treatment of patients with ESRD.

Small size of study and inadequate dose of cholecalciferol in our population were the limitations of our study. High cost of 25 OH vitamin D assay and lack of resources for supplementation hinders the setup of larger clinical trials in Pakistani ESRD population. We took patients with phosphorus level< 6mg/dl and calcium level of less than 10.2 mg/dl expecting these values to rise during the course of supplementation. Strict control of serum phosphorus and calcium is necessary to prevent cardiovascular mortality.

CONCLUSION

Cholecalciferol supplementation is beneficial in reducing inflammation as demonstrated by decrease in CRP levels and in minimizing the chronic musculoskeletal symptoms. As in general population low vitamin D level is associated with poor outcome in kidney patients including CKD V.20 Cholecalciferol has some favorable effects which can be implemented in the management of ESRD patients.

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