Pharmacokinetic Comparison of Vitamins D_2 and D_3 in Stage 5 Chronic Kidney Disease Patients on Chronic Hemodialysis

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Abstract

Background and Objectives: Recent understanding of extrarenal production of calcitriol has lead to the exploration of calciferol treatment in dialysis patients. This paper reports the pharmacokinetics of 25-hydroxyvitamin D (25(OH)D) response to a single, 50,000 IU dose of cholecalciferol, ergocalciferol, or placebo in subjects on chronic hemodialysis.

Design, setting, participants, & measurements: This randomized, single blind, placebo controlled trial of calciferol in subjects with stage 5 chronic kidney disease requiring hemodialysis was conducted from November 2012 to March of 2013. The results for 26 subjects were analyzed and the time course of serum 25(OH)D was measured at days 0, 2,4,7,21, and 28 for intervention groups and days 0 and 28 for placebo. Additionally, blood was drawn at each time point calcium, phosphorus, and albumin.

Results: The median baseline 25(OH)D level was 18.3 ng/ ml in the Vitamin D_2 group and 15.9 ng/ ml in the D_3 group, a nonsignificant difference. There was a significant increase in 25(OH)D levels in both the Vitamin D_2 and D_3 groups and a statistically significant decline in the 25(OH)D levels in the placebo controlled group. The mean C_{max} rise from baseline (mean ±standard deviation) was 7 ± 2.04 ng/ml in the D_2 group and 8.66± 2.96 ng/ml in the D_3 group. The peak occurred at (median T_{max}) day 7 for D_2 and day 14 for D_3, and the serum concentration maintained thereafter. In our study, the median Area Under the Curve (AUC) for day 28 for vitamin D_2 was 183.025 ng·d/ml, whereas the median AUC_{28} for vitamin was 163.3 ng·d/ml. There was no significance difference between the AUC_{28} for the two groups (p=.368) at the 28 day data analysis. There was a statistically significant decline in calcium levels for the Vitamin

D_2 group but no other statistically significant changes in levels of albumin, phosphorus, or calcium in any other group.

Conclusions: To our knowledge, this is the first study quantifying the 25(OH)D dose response and pharmacokinetics of oral cholecalciferol and ergocalciferol in subjects on chronic hemodialysis. Supplementation with calciferol to increase levels of 25(OH)D appears to be an important therapeutic management technique for patients in stage 5 Chronic Kidney Disease. In the 28 days that participants were studied, there were significant increases in 25(OH)D levels for both intervention groups. There appears to be no significant difference in the rise between the vitamin D_2 and vitamin D_3 groups, implying that either form of vitamin D can be used in this population. Our study highlighted that repletion of 25(OH)D levels with the use calciferol is a safe, efficient, and cost effective strategy to increase concentrations in hemodialysis patients.

Introduction

The role of Vitamin D in human physiology is one that gained attention in the early 20th century through recognition that deficient levels caused a childhood skeletal condition known today as “rickets.” Through the fortification of foods and dietary supplementation, this childhood disease became a condition of the past. Many health care providers presumed the prevalence and implications of vitamin D deficiency disappeared along with it. Researchers now know that although this disease sparked initial interest in vitamin D, it was just the beginning of present day clinical research. Investigations regarding the role of vitamin D progressed, and the implications of calcium and vitamin D in osteoporosis, osteomalacia, osteopenia, and muscle weakness were recognized. While Vitamin D deficiency’s effect on bone health has been widely accepted, it is only in the past ten years that we have recognized the potential implications of this vitamin in other disease states independent of its effect on calcium (Lappe, 2011). There is an evolving link and inverse relationship between vitamin D deficiency and nonskeletal conditions. This includes the potential prevention of conditions such as cancer of epithelial cell origin, immunodeficiency, autoimmune diseases, cardiovascular disease, schizophrenia, and depression (Holick, 2007).

Etiology of Deficiency

Patients with stage 5 Chronic Kidney Disease (CKD) undergoing hemodialysis are at an unusually high risk for developing vitamin D deficiency. According to Jones (2010), vitamin D deficiency affects between 80-100% of renal dialysis patients across the nation. The causative agents are likely multifactorial, and are not necessarily unique to the dialysis population, including poor nutrition and decreased UV-B exposure (attributed to time spent indoors,

sunscreen use, and residence in the Northern hemisphere). It is also important to recognize that increased skin pigmentation can reduce cutaneous vitamin D_3 production as much as 99.9% (Holick, 2006a). A factor that is unique to patients on chronic hemodialysis include elevations in uremic toxin levels, which affects the 25-hydroxylation of vitamin D_3 to 25(OH)D in the liver (Jones, 2010).

Physiology

Vitamin D is a fat soluble vitamin which functions via numerous endocrine and autocrine pathways to carry out essential biological functions. Vitamin D is formed in the dermis through Ultraviolet B rays which formulate previtamin D_3 from the precursor, 7-dehydrocholesterol. This is then converted to native vitamin D_3 by the warmth of the skin (Armas, 2009). There are also two forms used in supplements: ergocalciferol, or Vitamin D_2, which is the plant form made from irradiated yeast; and Vitamin D_3, or cholecalciferol which is formed from irradiating 7-dehydrocholesterol derived from lanolin.

Vitamin D_3 is the more commonly prescribed form of vitamin D because of the greater efficacy in raising 25(OH)D levels, which is the best indicator of vitamin D status. In healthy individuals, vitamin D_3 has been reported to be two to nine times more effective than vitamin D_2 (Armas, Hollis, & Heaney, 2004). A study examining the efficacy of a single 50,000 IU dose of vitamin D_2 versus vitamin D_3 demonstrated a much more rapid decline of 25(OH)D levels in the vitamin D_2 group than in the vitamin D_3 group after 3 days, demonstrating the lower potency of vitamin D_2 (Armas et al., 2004). The rise at day 1 was virtually identical for both calciferols, indicating equivalent absorption and 25-hydroxylation (Armas et al., 2004). The mean concentration in D_2 treated subjects fell quickly and was near baseline at day 14, whereas the D_3

treated group demonstrated a rise through day 14 and by day 28 remained at a higher level than the peak value for the D_2 treated group (Armas et al., 2004).

Once absorbed, cholecalciferol is carried by vitamin D-binding-proteins to the liver where it is metabolized by 25-hydroxylase to produce 25(OH)D (calcidiol) (Lappe, 2011). In the extensively established role of the endocrine pathway, 25(OH)D is converted in the renal system to its most potent and active metabolite $1,25(OH)_2D$ (1,25 dihydroxyvitamin d or Calcitriol) by parathyroid stimulated 25(OH)D renal 1- α -hydroxylases (Armas et al., 2004).

There are two areas of low 25(OH)D productivity in patients with chronic kidney disease. These individuals have low 25(OH)D levels, because of ill health, poor diet, avoidance of dairy foods that are fortified with D, which is the substrate of calcitriol (Mathias et al., 2010). This is coupled with the loss of renal 1- α -hydroxylase activity and causes a progressive calcitriol deficiency (Mathias et al., 2010). The endocrine pathway uses circulating serum calcitrol as a regulator mineral, enabling both skeletal homeostasis and gastrointestinal reuptake of calcium via the intestinal mucosa (Lappe, 2011). Current therapy addresses replacement of calcitriol with supplementation with calcitriol or its analogues but these do not effect 25(OH)D levels. Deficient levels prevents peripheral cells of 25(OH)D use for conversion to calcitriol for their own internal use.

When examining the role of 25(OH)D in the autocrine pathways, conversion to calcitriol occurs in various immune, breast, prostate, lung, and colon epithelial cell types by means of 25(OH)D 1- α -hydroxylases (Lappe, 2011). These peripheral or extra-renal 1 α -hydroxylases remain intact despite the loss of kidney α -hydroxylases in renal failure (Mathias et al., 2010). The conversion to calcitriol in peripheral cells promotes the role of vitamin D beyond that of

mineral metabolism, including nonskeletal functions (Lappe, 2011), but require sufficient levels of 25(OH)D to adequately function in these microenvironments.

Skeletal implications of vitamin D deficiency in CKD

One of the most prominent roles of vitamin D in patients with CKD is the absorption of calcium and phosphorous. Without sufficient levels, only 10-15% of calcium and 60% of phosphorous is absorbed (Holick, 2006a). According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines from the National Kidney Foundation (NKF), 25(OH)D levels should be maintained at 30 ng/ml or higher (NKF, 2003) to adequately absorb calcium. Deficient calcium absorption stimulates the release of the parathyroid hormone, causing secondary hyperparathyroidism (SHPT). SHPT is a complication that progresses as the glomerular filtration rate decreases, and stimulates the formation of mature osteoclasts. Osteoclasts dissolve the bone matrix, directly increasing serum calcium levels but results in osteopenia and osteoporosis. Prolonged elevation of parathyroid hormone levels causes declines in bone density and renal osteodystrophy, which is a term that has been used to describe the skeletal abnormalities that develop as a result of CKD (Moe, 2006).

Treatment of SHPT in patients with chronic renal failure includes the use of active vitamin D therapies decrease parathyroid levels and prevent skeletal complications (National Kidney Foundation, 2003). Active vitamin D therapies include calcitriol and paricalcitriol, both of which inhibit PTH secretion and are approved for use in patients with stages 3-5 CKD (NKF, 2003). A major problem that is associated with activated vitamin D/calcitriol therapy is an elevated level of calcium and phosphorus which can lead to extra skeletal calcifications (Gesek & Desmond, 2008).

Treatment with these activated forms of calcitriol does not address 25(OH)D levels. Matthias et al. (2010) administered cholecalciferol to hemodialysis patients, significantly increasing their 25(OH)D from 22.3 ± 12 ng/ml to 42.0 ± 12.1(P=<0.001). Administration of cholecalciferol also significantly decreased calcium and phosphorus to ranges considered within normal levels and significantly decreased the weekly dosage of paricalcitol needed.

Nonskeletal Implications of Vitamin D in patients with CKD

The generalized knowledge of Vitamin D's role in human health has rapidly advanced with a new focus aimed at preventing disease and optimizing current health status. In the past, $1,25(OH)_2D$ was thought act exclusively in calcium homeostasis. Simply replacing it with calcitriol was sufficient in CKD patients who had deficient $1,25(OH)_2D$ levels. An understanding the ability of 25(OH)D to be activated by many other extrarenal cells is necessary. In addition, knowledge of its role in conditions including hypertension and cardiovascular disease, upregulation of adaptive immunity, and treatment of acute infections (Lappe, 2011) This knowledge has led to recommendations that native vitamin D supplementation should be addressed in patients with CKD (Armas et al., 2012). Of particular importance for individuals with CKD are the implications of vitamin D in cardiovascular disease, as this is responsible for much of the morbidity and mortality in this population.

Cardiovascular Disease

Cardiovascular disease accounts for at least half of the deaths among dialysis patients and emerging data indicates that vitamin D therapy may prolong survival in patients with CKD (Andress, 2006). It has been recognized that the incidence of cardiovascular disease is higher in Northern latitudes and studies indicate that increasing 25(OH)D levels to proficient levels has a positive impact on cardiovascular disease (Wang et al., 2010). Low levels of 25(OH)D have been

associated with low levels of calcitriol in patients with CKD (Andress, 2006), and analysis of retrospective studies indicate decreased mortality in CKD patients when treated with active forms of vitamin D (Kovedsy et al., 2008). Decreased levels of calcitriol have been linked with arterial calcification in cardiovascular disease (Andress, 2006). A correlation between low levels of calcitriol and elevated serum renin, which is associated with hypertension was demonstrated in a clinical study (Resnick, Muller, & Laragh, 1986).

Wolf et al. (2007) noted the incidence of cardiovascular related mortality was 7.6/100 persons in the calcitriol analogue group as compared to 14.6/100 in the untreated group. Mathias et al. (2010) noted a significant decrease in plasma brain naturetic peptide (BNP) levels (P= 0.008) and a significant decrease in Left Ventricular Mass Index (P=0.01), a marker synthesized in response to ventricular stretch and cardiomyocyte overload, and a significant decrease in left ventricular mass index in response to Vitamin D_3 treatment.

Vitamin D Repletion in Chronic Kidney Disease

Recent guidelines have recommended vitamin D supplementation recommendations for the healthy U.S. population and for patients with specific diseases such as CKD (KDIGO, 2009). The National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines (2003) recommend native vitamin D supplementation with Vitamin D_2 in stage 3 and 4 CKD and a calcitriol analogue in patients with stage 5 requiring dialysis. Vitamin D_2 has been routinley used in dialysis patients as it has historically been considered safer. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2009) incorporated vitamin D's extraskeletal effects into its recommendations, suggesting that 25(OH)D levels be measured in patients with CKD 3-5 and if deficient, treatment strategies that are used in the general population be implemented. Both guidelines include treatment with native vitamin D_2 or D_3, but

there is no consensus in recommendations because there have been no studies directly comparing 25(OH)D or 1,25$(OH)_2$D dose responses between D_2 and D_3 in hemodialysis patients. Thus, the purpose of this study was to compare the pharmacokinetic profiles of 25(OH)D response to a single oral dose of vitamin D_2 or vitamin D_3 in a group of Stage 5-CKD subjects requiring chronic hemodialysis. Our hypothesis was that the 25(OH)D dose response will be greater in those subjects receiving vitamin D_3 than in those subjects receiving Vitamin D_2.

Design & Randomization

This was a randomized, single blind placebo controlled study. This trial was registered on clinicaltrials.gov in August 2012 (NCT01675557). Subjects were randomly assigned using block randomization to receive a single dose of: 1) placebo (control group); or 2) one tablet labeled to contain 50,000 IU (1.25 mg) ergocalciferol (the vitamin D_2 group); or 3) 4 tablets labeled to contain 50,000 IU (1.25 mg) cholecalciferol (the vitamin D_3 group).

Subjects

Thirty subjects (21 male and 9 female) from two hemodialysis centers in Omaha, Nebraska (latitude 41.2˚). The study was approved by the Creighton University(do we need to de-identify?) Institutional Review Board and all subjects provided signed written consent. The subjects were included if they were ages 20-65 years of age, had a Body Mass Index (BMI) of 18-32, and required chronic (>3 months) hemodialysis at the Dialysis Clinics Incorporated dialysis sites in Omaha NE. The reasons for hemodialysis in these participants included diabetic nephropathy, hypertensive kidney disease, glomerulonephritis, and other types of kidney disease.Subjects were required to habitually consume less than 16 oz of milk per day and get less than 10 hours of sun exposure per week. They were excluded if they had been diagnosed with granulomatous conditions, cirrhotic liver disease, or had taken anticonvulsants, barbiturates,

steroids in any form, or any investigational drugs within 4 weeks of the study onset. Individuals with pregnancy or planned pregnancy, hypercalcemia (>10.2 mg/dl) previously recorded, chronic GI disease which would interfere with absorption, any allergy to vitamin D, or prolonged vitamin D intake >1,000 IU daily were also excluded. Patients were also excluded if they were judged unlikely to complete the study. Peritoneal dialysis patients were excluded. Thirty patients were consented, and four were excluded from final data analysis due to consumption of anticonvulsants or steroids. Subjects continued to take their calcitriol analogue and phosphorus binder as prescribed by their nephrologist, which was documented and remained constant throughout study.

Intervention

Enrollment began in August of 2012 and data was collected through January 2013. The cholecalciferol was an over-the-counter product (oil based capsule preparation – commercially available as Maximum D_3®, cholecalciferol 10,000 IU, 0.25 mg, BTR Group, Inc. Pittsfield, IL). Four capsules of cholecalciferol were analyzed independently by Heartland Assays, Inc. and found to contain 10,935 + SD 360 IU per capsule. Four capsules were used for the D_3 group intervention with a total measured dose (43,730 IU) which was used for all calculations. The vitamin D_2 was obtained from Creighton University pharmacy and was also analyzed by Heartland Assays, Inc (Ames, IA) Protocol and contained 47, 095 IU ± per pill.

At baseline, prior to starting a hemodialysis session, venous blood was drawn for calcium, albumin, and 25(OH)D. After the baseline blood was obtained, the subjects were observed while they took the assigned dose, ensuring 100% compliance. For the two groups receiving a vitamin D supplement, serum samples were obtained at days 0, 2, 4, 7, 14, 21, and 28 for 25(OH)D. The control group had serum samples obtained at days 0 and 28 so as to quantify any seasonal

changes in 25(OH)D. Height was measured at baseline. At each visit the subject's dry weight was measured and recorded.

Analytical Methods

Serum 25(OH)D was measured by the DiaSorin Liaison method (DiaSorin, Inc., Stillwater, MN) in the Creighton Osteoporosis Research Center laboratory. Serum calcium and albumin was measured by Beckman Coulter DXC600i in the medical laboratory of Creighton University. Serum calcium and phosphorus were measured by Roche Cobas Integra autoanalyzer (F Hoffmann-La Roche Ltd, Basel, Switzerland) in the medical laboratory of Creighton University. The amount and duration of skin sun exposure was assessed using the method described by Barger-Lux (Barger Lux & Heaney, 2002). Phos

Statistical Analyses

Descriptive statistics were generated using the statistics package PASW Statistics 21.0 (SPSS Inc., Chicago, IL) and Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA). The 25(OH)D signal produced by the vitamin D dose was analyzed as the increment in total 25(OH)D concentration above baseline. Area under the serum curves (AUC) of 25(OH)D increments at 28 days was calculated by the trapezoidal method individually for each subject. AUC was calculated using pharmacokinetic models (Microsoft Excel, 2007) fitted to the mean 25(OH)D values at each time point. Mean values for and AUC_{28} for the two calciferols were compared by Mann Whitney U measurements.

Results

Data from 26 subjects was analyzed. Ten subjects were randomized to the cholecalciferol group, eight to the ergocalciferol group, and eight subjects were randomized to the placebo group. Their ages ranged from 27 to 64 years. Races reported were African American (14; 54%),

Caucasian (12; 46%), and American Indian (1; <0.1%). Table 1 provides subjects' demographics. There were no significant differences between the groups in age, height, weight, body mass index, years on dialysis, diabetes occurrence, or vitamin D analog use. The primary focus of this pharmacokinetic study was to analyze the rise in 25(OH)D in hemodialysis patients.

Baseline 25(OH)D

Participants in this study demonstrated low vitamin D status. The median (interquartile range) of 25(OH)D in the D_2 group at baseline was 18.0 ng/ml (16.5-36.2 ng/ml), 15.9 ng/ml (8.33-27.6 ng/ml) for the D_3 group, and 14.5 ng/ml (13.9-29.2 ng/ml) in the placebo group. The 25(OH)D levels were not significantly different between groups.

25(OH)D Results

Serum 25(OH)D levels were measured at baseline and days 2, 4, 7, 14, 21, and 28. Baseline values for all three groups were low and the rise at day two for the two treatment groups were very similar.

At 28 days 25(OH)D levels rose to (median (interquartile range)) 28.2 (23.8–40.6) ng/ml in the D_2 group, 24.7 (16.5–34.2) ng/ml in the D3 group, and there was a drop in the placebo group to 12.96 (10.85-28.3) ng/ml. The increase in 25(OH)D levels in the D_2 and D_3 groups was statistically significant (P values of 0.018 and 0.011 respectively). There was a statistically significant decline in the placebo group's 25(OH)D levels (P=0.028). The mean rise in maximum concentration from baseline (mean ±standard deviation) was 7 ± 2.04 ng/ml in the D_2 group and 8.66± 2.96in the D_3 group. The peak occurred at (median T_{max})day seven for D_2 and day 14 for D_3, and the serum concentration maintained thereafter. . The median AUC28 for vitamin D2 was 183.025 ng·dl/ml, and the median AUC28 for vitamin D3was 163.3 ng·dl/ml. There was no significant difference between the AUC for the two groups (p=.368) (See figure 1).

Other Laboratory Results

Table 2 demonstrates baseline levels and change for calcium, albumin, phosphorus, and 25(OH)D. There was a significant decrease in the overall average calcium levels seen in the Vitamin D_2 group. There were no significant changes in levels of albumin, or phosphorus, in either the treatment or placebo group (table 2).

Discussion/ Implications on Practice

Pharmacokinetic studies of vitamin D are important clinically to determine the best repletion regimen in patients on hemodialysis. To our knowledge, this is the first study quantifying the 25(OH)D dose response of a single oral cholecalciferol or ergocalciferol dose in subjects on chronic hemodialysis. The vitamin D_2 group had a (non significant) 2.4 ng/dl higher baseline 25(OH)D concentration as compared to the vitamin D_3 dose group. In this study, a single dose of vitamin D_2 or vitamin D_3 raised 25(OH)D levels to a range considered near proficient at the time of maximum concentration (median absolute 25(OH)D from D_3 at C_{max} was 25.1 ng/ml, D_2 was 28.4). This study demonstrated that there were no significant differences between the rises of 25(OH)D levels when comparing vitamin D_2 to vitamin D_3 at the 28 day data analysis point. Since this is the first study analyzing the rise in 25(OH)D levels in hemodialysis patients, there are no other directly comparative studies.

The best measurement of total exposure of participants to the administered Vitamin D is demonstrated by the AUC of the serum concentration against time (Armas et al., 2004). Armas et al. (2004) compared the rise in 25(OH)D levels in the healthy population after a single dosing of 50,000 IU vitamin D_2 or vitamin D_3. In this study, the AUC at 28 days was 60.2 ± 23.4 ng·d/ml for vitamin D_2 and 204.7 ± 32.4 ng·d/ml for vitamin D_3. In the present study, the median AUC_{28} for vitamin D_2 was 183.025 ng·dl/ml, and the median AUC_{28} for vitamin $D_3$was 163.3 ng·dl/ml.

There was no significant difference between the AUC for the two groups (p=.368). At the end of the 28 days there was no significant drop in 25(OH)D levels in either group. It would be desirable to have longer term dosing data with a greater number of participants to analyze the dosing curve, since this would provide a greater contribution to actual recommendations regarding prescribing practices.

Summary

Because of our gains in knowledge regarding the extrarenal activation of 25(OH)D to the active state of 1,25(OH)2D recommendations can be made regarding native vitamin D supplementation. This study highlighted that repletion of 25(OH)D levels with the use calciferol is an efficient and cost effective strategy to increase concentrations in hemodialysis patients. Historically, calcitriol was thought to be exclusively acting in calcium homeostasis and simply replacing it with a calcitriol analogue was thought to be sufficient in CKD patients (Armas et al, 2012). In our study, the median AUC_{28} for vitamin D_2 was 183.025 ng·d/ml, and the median AUC_{28} for vitamin $D_3$was 163.3 ng·d/ml, showing much better response to D_2 in the dialysis patients compared to healthy people. There was no significant differences between AUC for the two groups (p=.368). At the end of the 28 days there was no significant drop in 25(OH)D levels in either group. Based on the significant rise demonstrated in 25(OH)D levels after the consumption of either calciferol in hemodialysis participants in this study, one can conclude that that either form can be used to raise 25(OH)D levels. Potentially, raising 25D levels in CKD patients would have beneficial effects on other outcomes such as heart disease and infection. While longer investigations with other outcome measures are required to confirm or reject this finding, this study is important to assessing the best clinical treatment regimen in raising 25(OH)D levels in hemodialysis patients.

Limitations/ Recommendations for Future Research

This study was limited by the use of only one dose of vitamin D_2 or D_3. It was also limited by a small sample size and short time span. Additional studies with a larger sample size and of longer duration would be required to confirm or reject study findings. Increased frequency of dosing would be necessary to establish accurate prescribing practices.

Figure 1. Area Under the Curve for 28 days

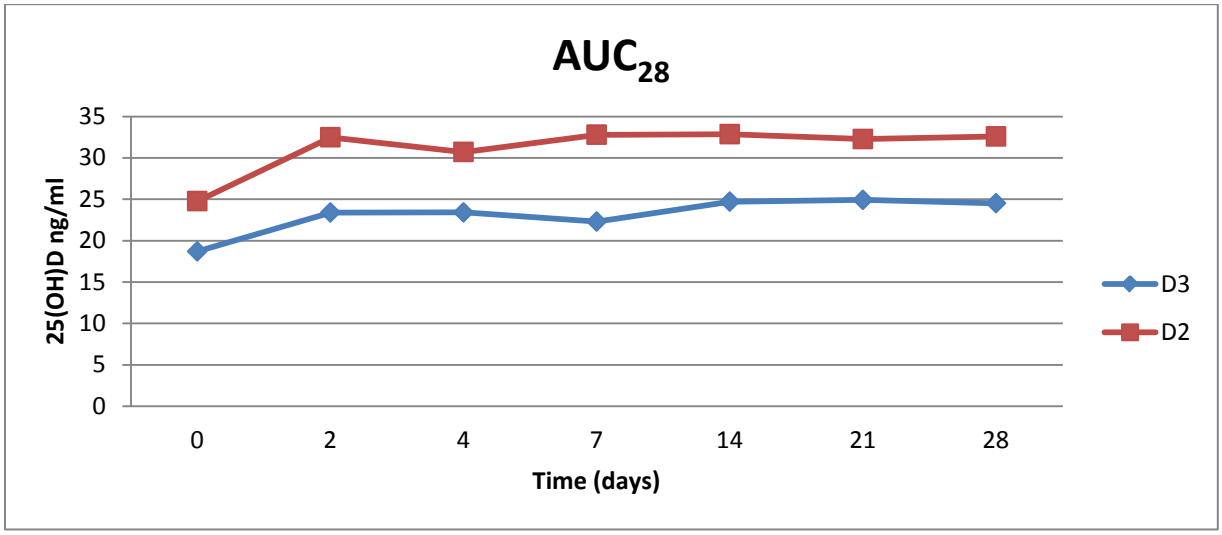

Table 1. Subject demographics			
Group	Vitamin D_2	Vitamin D_3	Placebo
N	8	10	8
Sex (Male/Female)	7/1	6/4	5/3
Race (AA/C/Ot)	3/5/0	6/4/0	2/5/1
Age (years)	60.8 (58.0-63.7)	56.1(47.9-58.7)	48.2 (47.5-51.9)
Height (M)	1.81 (1.8-1.89)	1.7 (1.57-1.76)	1.72 (1.64-1.82)

Dry Weight (Kg)	74 (66-82)	74 (66-83)	74.3 (65-83)
Body mass index	22 (20-26)	25 (23-30)	25 (21-28)
Years on dialysis	4.4(2.7- 6)	2.8 (1 -1)	5 (3-9)
On cacitriol analog (Y/N)	7/1	9/1	8/0
Diabetic (Y/N)	4/4	7/3	6/2
Values are given as median (interquartile range). None of the variables were significantly different between the groups (P=) AA, African American; C, Caucasian; Ot, other.			

Table 2. Subjects laboratory Results (Median)

	Vitamin D_2			Vitamin D_3			Placebo		
N	Baseline	Day 28	*P* value	Baseline	Day 28	*P* Value	Baseline	Day 28	*P* value
25(OH)D (ng/ml)	18.3	26.35	0.018	15.9	24.7	0.011	14.5	13.25	0.028
Calcium (mg/dl)	9.1	9.1	0.027	9.25	9.0	0.182	9.3	9.7	0.399
Albumin (g/dl)	3.5	3.55	0.590	3.75	3.6	0.500	3.7	3.65	0.527
Phosphorus (mg/dl)	5.75	5.2	0.917	5.75	5.6	0.292	6.9	5.85	0.833

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