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Very High-dose Cholecalciferol and Arteriovenous Fistula Maturation in ESRD: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Purpose—While vitamin D is critical for optimal skeletal health, it also appears to play a significant role in vascular homeostasis. This pilot study compared arteriovenous access outcomes following cholecalciferol supplementation compared to placebo in end-stage renal disease patients preparing to undergo AV access creation.

Methods—52 adult hemodialysis patients preparing for AVF creation were randomized to receive peri-operative high dose cholecalciferol vs. placebo in this double-blind, randomized placebo-controlled pilot study. The primary outcome was mean response to high-dose oral cholecalciferol vs. placebo, and secondary outcome arteriovenous access maturation at 6 months. Logistic regression was used to assess the association between AV access maturation and baseline, post-treatment and overall change in vitamin D concentration.

Results—45% of cholecalciferol-treated and 54% of placebo-treated patients were successfully using their AVF or AVG at 6 months ($p=0.8$). Baseline serum concentrations of 25(OH)D and 1,25(OH)₂D did not differ between those who experienced AVF or AVG maturation and those who did not ($p=0.22$ and $p=0.59$, respectively). Similarly, there was no relationship between AVF or AVG maturation and post-treatment serum 25(OH)D and 1,25(OH)₂D concentration ($p=0.24$ and 0.51 , respectively).

Conclusions—Peri-operative high dose vitamin D₃ therapy does correct 25(OH)D level but does not appear to have an association with AV access maturation rates. Future research may

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include extended pre-operative vitamin D₃ therapy in a larger population or in certain sub-populations at high risk for AVF failure.

Keywords

AVF; Dialysis access; ESRD; Vitamin D

Introduction

Vitamin D is an essential nutrient that is often deficient in end-stage renal disease (ESRD) patients, primarily due to insufficient sunlight exposure, low dietary intake and loss of renal function. As a result, 78%-91% of ESRD patients are vitamin D deficient or insufficient at the time of dialysis initiation.^{1,2}

While vitamin D is critical to maintaining calcium and phosphorus homeostasis for optimal skeletal health, it also appears to play a significant role in vascular homeostasis. Circulating vitamin D [(25(OH)D] is converted to 1,25(OH)₂D in local tissues by the enzyme 1-alpha-hydroxylase. This further up-regulates the vitamin D receptor found in many tissues, including vascular smooth muscle cells (VSMC), and further increases the expression of 1-alpha-hydroxylase resulting in locally produced 1,25(OH)₂D, which is believed to have many important immunomodulatory effects.³⁻¹¹ The importance of local vitamin D production is supported by the observation that 25(OH)D deficiency is associated with many forms of vascular disease and endothelial dysfunction.¹²⁻¹⁶ Among its many actions, vitamin D suppresses extracellular matrix remodeling factors, which play a key role in VSMC migration and development of vascular neointimal hyperplasia, modulates VSMC growth in vitro, and retards VSMC proliferation.^{5,10,17-20} Furthermore, vitamin D has anti-oxidant and anti-inflammatory properties.²¹⁻²⁴

Given vitamin D's ability to suppress factors known to promote development of progressive venous neointimal hyperplasia and to affect expression of oxidative and inflammatory markers detected within failing AV access²⁵⁻²⁷, we hypothesized that nutritional vitamin D supplementation (25(OH)D) may improve arteriovenous fistula (AVF) outcomes by providing adequate substrate to enable local, active vitamin D production within the vasculature.

We therefore conducted a double-blind randomized controlled pilot study to provide critical estimates to determine the distribution of vitamin D levels in our ESRD patient cohort in those who receive high-dose oral vitamin D₃ (cholecalciferol) compared to placebo for the planning of subsequent, larger studies examining the effect of vitamin D on AVF maturation and to show feasibility for patient recruitment in the proposed time frame.

Materials and Methods

Subjects and Protocol

The protocol for this double-blind, randomized, placebo-controlled pilot study has been previously described.²⁸ Briefly, we enrolled 52 adults with end-stage renal disease (ESRD)

receiving in-center outpatient hemodialysis who were preparing to receive an AVF creation within 4 weeks. Suitability of a patient for AVF creation was based

on vein diameter >2.5 mm, and inflow artery diameter of > 2 mm.²⁹ Enrolled subjects were randomized to 200,000 IU oral vitamin D₃ (cholecalciferol) or matching placebo (Bio-Tech Pharmacal Inc, Fayetteville, AR) weekly for 3 weeks. In a recent publication, we reported that our dosing regimen of high-dose cholecalciferol versus placebo is safe and effectively increases circulating serum 25(OH)D concentrations to the normal range of > 30 ng/mL, lowers serum parathyroid hormone (PTH) concentration, and does not cause hypercalcemia.²⁸ The study coordinator directly observed all patients taking their assigned medication, and there was 100% overall medication compliance. A blood sample was collected at study enrollment and again three weeks following study drug completion for measurement of serum 25(OH)D and 1,25(OH)₂D. Monthly dialysis unit laboratory test results collected 4 weeks prior to study enrollment date and 4 weeks after study completion were abstracted to include in the analysis. The Emory University Institutional Review Board approved the study protocol, and all participants provided informed consent prior to study enrollment. The study was registered at clinicaltrials.gov (NCT00912782).

Outcome Definition

The primary study outcome was mean response to high-dose oral vitamin D₃ (cholecalciferol) vs. placebo. The secondary study outcome was AVF maturation, defined as the ability to cannulate the AVF with two large bore needles at 6 consecutive dialysis sessions, and achievement of an AVF blood flow >300 ml/min, assessed at six months following AVF creation.

Analytic Methods

Serum 25(OH)D was assayed by using a chemiluminescence immunoassay (Diasorin Inc: CV over multiple runs: 6.3-12.9%) and 1,25 (OH)₂D was assayed by using solid-phase extraction and radioimmunoassay by ARUP laboratories. All samples were batched and analyzed with known standards to ensure test quality. Vitamin D deficiency was defined as < 20 ng/mL, and insufficiency was defined as 20 to 30 ng/mL. Levels to define vitamin D status were derived from The Endocrine Society clinical practice guidelines for vitamin D³⁰ because the Institute of Medicine guidelines are intended for a normal healthy population, not those with chronic disease.

Statistical Analysis

Baseline characteristics and post-treatment blood chemistry measures including serum 25(OH)D concentration were compared between the placebo group and the cholecalciferol group using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables. Wilcoxon signed rank tests were used to test whether changes of blood chemistry measures from baseline to post-treatment were different from 0. AVF or AVG maturation status, was compared between the two study groups using Fisher exact tests. Logistic regression analysis was performed to test the association between AVF/AVG maturation status and baseline and post-treatment vitamin D concentration and between

AVF/AVG maturation status and changes in vitamin D concentration from baseline to post-treatment, first unadjusted and then adjusted for age, diabetes, and race. The analyses were performed on an intention-to-treat basis using the free programming language and software environment for statistical computing, R. A p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 52 subjects were enrolled: 25 were randomly assigned to the cholecalciferol treatment group, and 27 to receive placebo, as previously reported.²⁸ During follow-up, one subject was lost to follow-up, 3 died, and 4 never received a permanent vascular access. Of these 8 subjects, 5 were in the vitamin D group and 3 were in the placebo group. Characteristics of these 8 patients were similar to the remaining patient cohort, except for female gender ($p=0.04$). Overall, 44 subjects (24 in placebo group; 20 in cholecalciferol group) remained for analysis (Figure 1).

Clinical and laboratory characteristics

Clinical and laboratory characteristics were similar in the groups at baseline (Table 1), with the exception of baseline serum 25 (OH) D and 1,25 (OH)₂ D concentrations, which were greater among the placebo group ($P=0.04$ and $P=0.02$, respectively). At baseline, 95.5% of subjects were vitamin D insufficient (serum 25(OH) D < 30 ng/mL); mean serum 25(OH)D was 16.8 ± 6.5 ng/mL, and mean serum 1,25(OH)₂D was 17.4 ± 8.9 pg/mL. Following treatment, vitamin D sufficiency (25(OH)D ≥ 30 ng/mL) was achieved in 90% of cholecalciferol-treated patients (mean serum 25(OH)D = 53.4 ± 17.7 ng/mL) and only 13.6% in the placebo-treated patients (mean serum 25(OH)D = 18.4 ± 7.4 ng/mL) ($p<0.001$), while serum 1,25(OH)₂D significantly increased in cholecalciferol-treated patients ($p<0.001$). There was no significant change in serum calcium, phosphorus or intact PTH.

AV access outcome

Overall, 15 radial-cephalic, 13 brachial-cephalic, 7 brachial-basilic AVFs were created and 9 AVGs surgically placed. At follow-up, 45% of cholecalciferol-treated and 54% of placebo-treated patients were successfully using their AVF or AVG at 6 months ($p= 0.8$). Excluding AVG patients, 41% of cholecalciferol-treated and 50% of placebo-treated patients achieved AVF maturation ($p=0.7$). Baseline concentrations of serum 25(OH)D and 1,25(OH)₂D were similar between patients who experienced AVF or AVG maturation and those who did not ($p=0.22$ and $p=0.59$, respectively). Similarly, there was no relationship between AVF or AVG maturation and post-treatment serum 25(OH)D and 1,25(OH)₂D concentration ($p=0.24$ and 0.51 , respectively).

Following adjustment for age, diabetes and race, there was no association between AVF maturation and baseline, post-treatment or change in serum 25(OH)D concentrations ($p=0.97$, 0.54 , 0.56 , respectively), or serum 1,25(OH)₂D concentrations ($p=0.51$, 0.61 , 0.43 , respectively). These findings were similar when including AVG's in the analysis.

Discussion

We found that peri-operative correction of 25(OH)D insufficiency and deficiency was achieved with high-dose cholecalciferol, but did not appear to have an association with AV access maturation among ESRD patients who received an AVF or AVG, although serum 25(OH)D concentrations normalized in 90% of cholecalciferol-treated subjects.

While no previous study has examined serum 25(OH)D concentration as a predictor of AV access maturation, previous work supports a role for vitamin D in the regulation of vascular smooth muscle cell proliferation. Vitamin D receptors (VDR) are present in numerous tissues, including the endothelium and vascular smooth muscle cells, which also express 1-alpha-hydroxylase, the enzyme that converts 25(OH)D to 1,25(OH)₂D.^{11,31}

Animal experiments suggest that vitamin D concentrations are associated with intimal proliferation, and that vitamin D inhibits VSMC proliferation.^{4,32} Gupta et al recently demonstrated that serum 25(OH)D concentration may affect the extent of resultant neointimal thickening in an atherosclerotic swine model following arterial injury.³² Six-months following balloon angioplasty to the coronary arteries, the percent area of arterial neointimal hyperplasia was significantly greater ($P < 0.05$) among the group of animals fed a vitamin D-deficient high cholesterol diet ($72.5 \pm 4.5\%$) compared with those fed a vitamin D-sufficient high cholesterol diet ($54.9 \pm 3.7\%$). Proliferating cell nuclear antigen (PCNA), a marker of smooth muscle cell proliferation, was more abundant in cells within the balloon-injured arteries of vitamin-D deficient animals compared with vitamin-D sufficient animals, suggesting that vitamin D has an antiproliferative effect. Moreover, Gupta et al found that VDR expression was significantly downregulated and that TNF-alpha expression was increased in proliferating VSMC's within neointimal lesions following vessel injury. They also showed that VDR expression in cultured VSMC's increased with calcitriol stimulation, yet significantly decreased with TNF-alpha treatment, suggesting that the presence of inflammation following vessel injury may downregulate VSMC VDR and contribute to VSMC proliferation and restenosis.

In the mouse aortic allograft, a model of immune mediated vascular intimal hyperplasia, VDR expression is present in aortic cells.⁴ Adorini et al reported that mice receiving aortic allografts that were treated with vitamin D3 analogue supplementation had significantly less intimal cell proliferation within allogeneic aortic segments 60 days after transplant, compared with vehicle mice.

While these findings suggest the potential benefit of vitamin D on the attenuation of VSMC proliferation and neointimal hyperplasia following injury from percutaneous angioplasty, they may be relevant to CKD and ESRD patients undergoing AV access creation. First, our group and others^{33,34} have shown that venous intimal hyperplasia pre-exists in late-stage non-dialysis CKD patients, a population with a high prevalence of vitamin D insufficiency and deficiency³⁵. While pre-existing intimal hyperplasia has not been linked to AV access failure, it remains unclear whether these lesions progress following AV access creation. Second, it is estimated that approximately 30% of patients with newly created AVF undergo AVF PTA to promote maturation³⁶, or develop stenosis in vessel segments typically

manipulated during surgical AVF creation.³⁷ Therefore, a cost-effective intervention that could potentially reduce the magnitude of subsequent AVF restenosis may have significant impact.

Successful AVF maturation is also dependent upon compensatory dilatation of the inflow artery and adequate dilation and blood flow to the outflow vein.³⁸⁻⁴⁰ Data suggests that vasoactive function is influenced by vitamin D sufficiency. Tare et al⁴¹ examined the effect of vitamin D insufficiency on endothelial and smooth muscle function in the arteries of offspring of vitamin D deficient rats. The vitamin D deficient rat offspring had only half of the endothelium-derived nitric oxide-evoked arterial dilation and virtually no endothelium-derived hyperpolarizing factor compared with control rats, reflecting a pronounced impairment in arterial relaxation. In accordance with these findings are the results showing that vitamin D therapy increases flow-mediated dilation in adult humans.⁴²

Other favorable effects of vitamin D on AVF maturation may include suppression of matrix metalloproteases (MMP) and a reduction in thrombotic factors. MMP's are linked to the development of intimal hyperplasia^{43,44} and identified in vein segments of failed AVF.⁴⁵ Greater local vitamin D activity may reduce intimal hyperplasia by lessening the effect of MMP remodeling within the vein, as treatment with vitamin D3 is shown to suppress MMP 2 and 3 in vitro, and circulating serum 25(OH)D is inversely associated with plasma MMP-9 concentration in ESRD patients.⁵⁴⁶

Reports also suggest that VDR activation has antithrombotic effects. Plasminogen activator inhibitor type 1 (PAI-1), a procoagulant, proinflammatory protein, is reduced in vitro by paricalcitol, a vitamin D analogue.^{7,8} It is also noted that VDR activation in vivo decreases platelet aggregation via regulation of anti-thrombin gene expression in the liver.⁴⁷ When evaluated in humans, vitamin D appears to play a role in coagulation. Cancer patients treated with high dose 1,25 (OH)₂D had significantly fewer venous and arterial thrombotic events than did those treated with standard dose 1,25(OH)₂D.⁴⁸

Our study has some limitations worth mentioning. Although this was a pilot study, a sample size of 50 patients (25 per group) was determined to achieve power of 0.8 when estimating that 52% of placebo-treated patients vs 88% of cholecalciferol-treated patients would experience AVF maturation. Instead, we found that 54% of placebo-treated patients vs. 45% of cholecalciferol-treated and were successfully using their AVF or AVG at 6 months. This finding suggests that any advantage that vitamin D confers is much lower than our original estimate, in which case our study was underpowered to detect it. It is possible that AV access outcome was influenced by variability in surgical technical expertise, however, we attempted to address this by limiting the vascular surgeons performing AV access procedures to two highly experienced individuals (W.M., G.S.) and there was no difference in AV access outcome. In addition, postoperative AV access cannulation and vascular access management may have varied between intervention and control subjects. We attempted to limit variation by recruiting patients from dialysis units with a uniform cannulation protocol and dialysis providers. Finally, we may have failed to see a benefit with cholecalciferol on AVF maturation because longer pre-surgical vitamin D sufficiency (> 6 months, for example) may be required.

We found that high-dose vitamin D3 therapy in patients with ESRD undergoing AVF creation successfully corrected vitamin D insufficiency and deficiency, but did not appear to improve AVF maturation rates compared to a cohort of matched controls in our pilot, double-blind randomized controlled study. Conclusive results will likely require a larger patient sample to achieve adequate effect size. Further, the role for vitamin D in AV access maturation may need to be explored in larger studies with extended pre-operative supplementation or in certain sub-populations at high risk for AVF failure.

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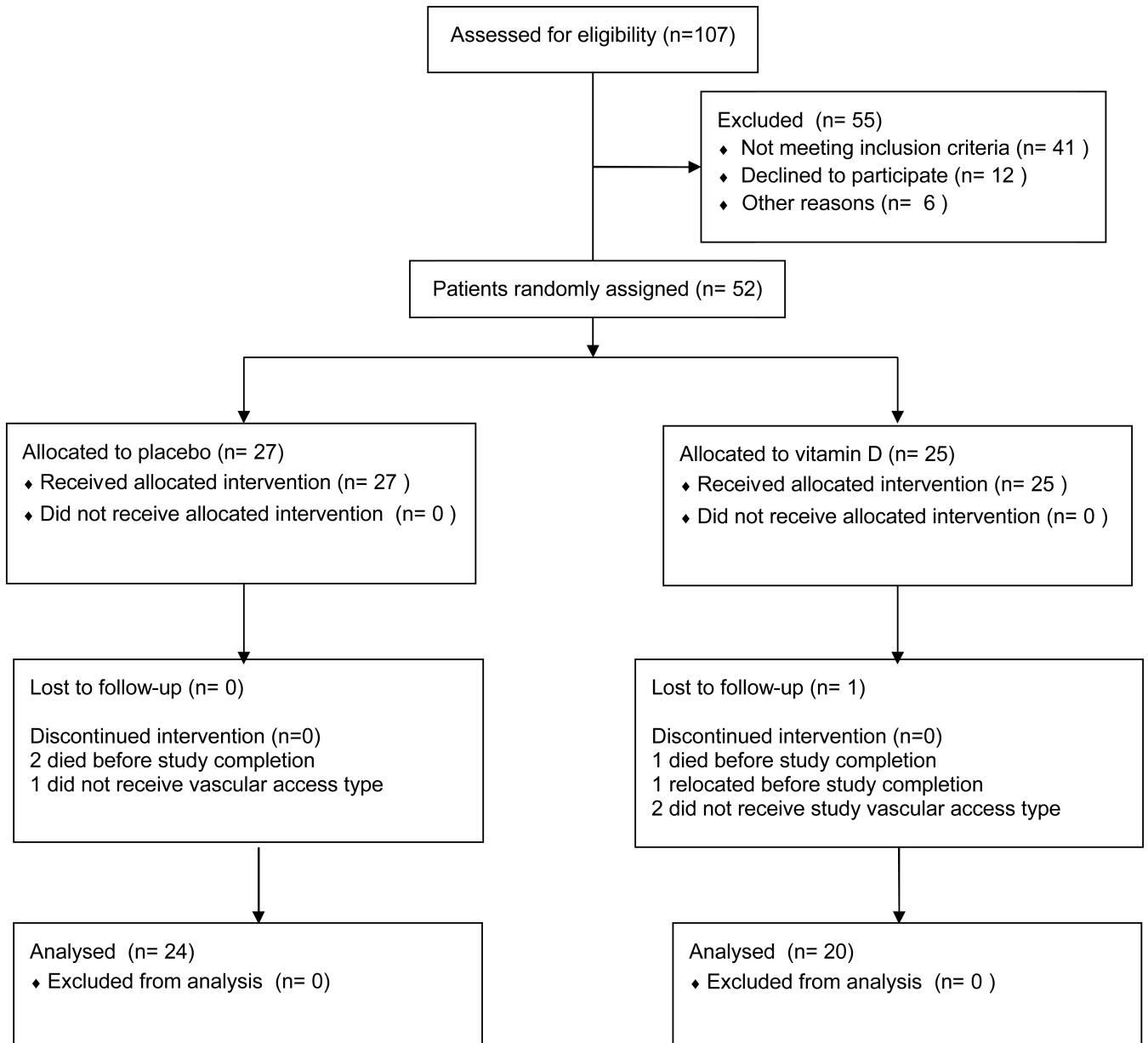


Figure 1.
Flow diagram of patient enrollment

Table 1

Baseline characteristics for subjects with observed AV maturation outcome

	All (n=44)	Placebo (n=24)	Cholecalciferol (n=20)	P value
Age (y)	51.1 ±13.2	52.1 ± 14.9	49.9 ± 10.9	0.62
Black	40 (90.9%)	21 (87.5%)	19 (95%)	0.61
Female	14 (31.8%)	9 (37.5%)	5 (25%)	0.52
Duration of Dialysis, days	636 ± 1050	924 ±1340	291 ± 301	0.20
BMI (kg/m ²)	28.2 ± 6.9	28.3 ± 7.9	28.1 ± 5.7	0.68
Clinical blood pressure (mm Hg)				
Systolic	152.7 ± 24.9	150.8 ± 23.7	155.1 ± 26.7	0.62
Diastolic	86.7 ± 17.3	85.3 ±16.9	88.3 ±18.1	0.93
Diabetes	21 (47.7%)	12 (50%)	9 (45%)	0.77
Hypertension	38 (86.4%)	21 (87.5%)	17 (85%)	1.00
HIV/AIDS	8 (18.2%)	4 (16.7%)	4 (20%)	1.00
Lactose intolerance	9 (20.5%)	3 (12.5%)	6 (30%)	0.261
Laboratory				
Intact parathyroid hormone (pg/mL)	605.3 ± 756.61	630.3 ± 944.8	575.3 ± 461.8	0.54
Ionized calcium (mg/dL)	8.9 ± 0.8	9.1 ± 0.6	8.8 ± 0.9	0.26
Phosphorus (mg/dL)	4.9 ± 1.3	4.7 ±1.2	5.0 ± 1.5	0.66
25(OH)D (ng/mL)	16.8 ± 6.5	18.6 ± 6.6	14.6 ± 5.8	0.04
1,25(OH) ₂ D (pg/mL)	17.4 ± 8.9	20.3 ± 9.9	13.9 ± 6.2	0.02
Hemoglobin (g/dL)	10.8 ± 1.7	11.2 ±1.4	10.4 ± 1.9	0.14
Current use of intravenous				
vitamin D analogs	30 (68.2%)	16 (66.7%)	14 (70%)	1.00

Results are presented as mean ± SD or n (%)