AJKD

Original Investigation

Biochemical Parameters After Cholecalciferol Repletion in Hemodialysis: Results From the VitaDial Randomized Trial

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Background: The 2009 KDIGO (Kidney Disease: Improving Global Outcomes) chronic kidney disease–mineral and bone disorder clinical practice guideline suggests correcting 25-hydroxyvitamin D_3 (25[OH]D) levels < 30 ng/mL in patients treated with maintenance hemodialysis, but does not provide a specific treatment protocol.

Study Design: 2-center, double-blind, randomized, 13-week, controlled trial followed by a 26-week open-label study.

Setting & Participants: 55 adult maintenance hemodialysis patients with 25(OH)D levels < 30 ng/mL were recruited from June 2008 through October 2009.

Intervention: Cholecalciferol, 25,000 IU, per week orally versus placebo for 13 weeks, then 26 weeks of individualized cholecalciferol prescription based on NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines.

Outcomes: Primary end point was the percentage of patients with 25(OH)D levels ≥ 30 ng/mL at 13 weeks. Secondary outcomes included the percentage of patients with normal calcium, phosphorus, and intact parathyroid hormone (iPTH) blood levels. Safety measures included incidence of hypercalcemia and hypervitaminosis D.

Measurements: Blood calcium and phosphate were measured weekly; iPTH, 25(OH)D, 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D$), and bone turnover markers, trimonthly; fetuin A and fibroblast growth factor 23 (FGF-23) serum levels and aortic calcification scores were determined at weeks 0 and 39.

Results: The primary end point significantly increased in the treatment group compared with the placebo group (61.5% vs 7.4%; $P < 0.001$), as well as $1,25(OH)_2D$ levels (22.5 [IQR, 15-26] vs 11 [IQR, 10-15] pg/mL; $P < 0.001$) and the proportion of patients achieving the target calcium level (76.9% vs 48.2%; $P = 0.03$). Incidence of hypercalcemia and phosphate and iPTH levels were similar between groups. The second 26-week study phase did not significantly modify the prevalence of 25(OH)D level ≥ 30 ng/mL in patients issued from the placebo group.

Limitations: Small size of the study population.

Conclusions: Oral weekly administration of 25,000 IU of cholecalciferol for 13 weeks is an effective, safe, inexpensive, and manageable way to increase 25(OH)D and $1,25(OH)_2D$ levels in hemodialysis patients. Further evaluation of clinical end points is suggested.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Cholecalciferol; vitamin D; calcium; parathyroid hormone (PTH); hemodialysis; clinical practice guidelines; calcitriol; vascular calcification; aortic calcification score; fetuin A; fibroblast growth factor 23 (FGF-23); 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; nutritional vitamin D; vitamin D deficiency; vitamin D repletion; bone fracture; falls.

Levels of calcidiol (25-hydroxyvitamin D_3 (25[OH]D) < 30 ng/mL are observed frequently in patients treated with maintenance hemodialysis (HD) in Northern latitudes.[1-4] As with the general population, this is associated with poor outcomes in chronic kidney disease (CKD; for review, see Nigwekar et al[5]), including stage 5.[4,6-9]

To date, a limited number of randomized controlled trials designed to study the effect of nutritional vitamin D (either cholecalciferol or ergocalciferol) have been conducted in HD patients.[3,10-13] This lack of interest probably is multifactorial. As kidney function declines, production of calcitriol (1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$]) decreases in

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Received July 9, 2013. Accepted in revised form April 14, 2014.

Trial registration: www.clinicaltrialsregister.eu; study number: EUDRACT (European Union Drug Regulating Authorities Clinical Trials) 2008-002387-33.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2014.04.020

parallel.[14,15] Since the 1980s, 1α-hydroxylated forms of vitamin D (also called active vitamin D) became widely used in HD patients and low-priced nutritional forms of vitamin D were neglected.[5] The existence of extrarenal 1α-hydroxylases was suggested by the observation that anephric individuals were able to produce $1,25(OH)_2D$ in response to supraphysiologic nutritional vitamin D challenge.[16,17] However, these findings did not modify prescription habits. Further experimental studies demonstrated that extrarenal 1α-hydroxylases were present in a wide range of tissues acting locally in paracrine or autocrine circuits.[18] That led to the understanding of the pleiotropic properties of 25(OH)D[19-21] and revived interest in this molecule.[22-24] In addition, it was noted that 25(OH)D has an excellent safety profile.[16,22,25] For these reasons and despite the absence of any controlled trial or large prospective study, in 2009, KDIGO (Kidney Disease: Improving Global Outcomes) recommended restoration of 25(OH)D levels > 30 ng/mL in patients treated with maintenance HD.[26] However, targeted protocols are still lacking. The high cost of the 25(OH)D assay further complicates drug prescription and the setup of larger clinical trials.[22]

The present study, combining a 13-week randomized trial of oral cholecalciferol repletion versus placebo with an open-label study of customized cholecalciferol prescription derived from the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines[27] for 26 additional weeks aimed to provide valuable information about vitamin D repletion strategies and their possible impact on mineral and bone markers.

METHODS

Definitions

In this study, we defined levels of 25(OH)D ranging from 20 to <30 ng/mL as "insufficient" and levels < 20 ng/mL as "deficient."[5]

Study Design

Overview

This was an investigator-driven, prospective, multicenter, partly randomized, controlled trial (VitaDial) performed in 2 Belgian nephrology centers (Epicura [in Baudour] and Erasme university hospitals [in Brussels]). It was approved by the institutional review board at each site. This 39-week trial was divided into 2 periods as follows: a randomized period (13 weeks) during which enrolled patients were randomly assigned to receive either cholecalciferol or a placebo, and an open-label period (26 weeks) during which all patients, regardless of initial allocation, received a cholecalciferol dose adjusted to their most recent 25(OH)D assessment (at weeks 13 and 26; Fig 1). This design allowed investigators to collect data for a new cholecalciferol repletion protocol using substantial doses under safe conditions (first period limited to 13 weeks) and, in a second phase, gather data reflecting the use of NKF-KDOQI guidelines, usually prescribed for 6 months (second period of 26 weeks). Finally, by combining both periods, we investigated the biochemical outcomes of cholecalciferol repletion over a total period of 39 weeks. Another interest of the present design was to offer cholecalciferol access to all

2003 KDOQI GUIDELINES
Ergocalciferol administration in patients with CKD Stages 3 and 4
(to be revised after 6 months)

Serum 25(OH)D (ng/mL)	Ergocalciferol dose
< 5 ng/mL	50,000 IU/wk x 12 wks, then monthly
5 - 15 ng/mL	50,000 IU/wk x 4 wks, then 50,000 IU/mo
16 - 30 ng/mL	50,000 IU/mo
> 30 ng/mL	Vitamin-D-containing multi- vitamin preparation

VITADIAL STUDY
Cholecalciferol administration in patients with CKD Stage 5

PHASE I
RANDOMIZATION
(13 wks)

Serum 25(OH)D (ng/mL)	Cholecalciferol dose
< 30 ng/mL	25,000 IU/wk orally X 13 wks VS (1:1) Placebo

PHASE II
OPEN-PHASE
(26 wks with dose adjustment at midpoint)

Serum 25(OH)D (ng/mL)	Cholecalciferol dose
< 6 ng/mL	50,000 IU/wk x 13 wks
6 - 15 ng/mL	50,000 IU/wk x 4 wks, then 50,000 IU/mo x 2 mo
16 - 30 ng/mL	50,000 IU/mo x 3 mo
30 - 60 ng/mL	25,000 IU/mo x 3 mo
> 60 ng/mL	None

Figure 1. Diagram compares cholecalciferol prescription during both phases of the study to the reference 2003 NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines. Abbreviations: 25(OH)D, 25-hydroxyvitamin D_3; CKD, chronic kidney disease.