Article

Ergocalciferol Supplementation in Children with CKD Delays the Onset of Secondary Hyperparathyroidism: A Randomized Trial

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Summary

Background and objectives Vitamin D deficiency is an important contributor to the development of hyperparathyroidism and is independently associated with cardiovascular and bone disease. The hypothesis was that nutritional vitamin D (ergocalciferol) supplementation in children with CKD stages 2–4 delays the onset of secondary hyperparathyroidism.

Design, setting, participants, & measurements A randomized, double-blinded, placebo-controlled study in children with CKD2–4 who had 25-hydroxyvitamin D [25(OH)D] deficiency was conducted. Ergocalciferol (or a matched placebo) was given daily as per Kidney Disease Outcomes Quality Initiative guidelines. The primary endpoint was the time to development of hyperparathyroidism.

Results Seventy-two children were screened. Forty-seven children were 25(OH)D-deficient and randomly assigned to receive ergocalciferol or placebo. Twenty children in each arm completed the study; median follow-up was 12 months. Groups were well matched for age, race, estimated GFR, and season when recruited. Nine of 20 children on placebo and 3 of 20 children on ergocalciferol developed hyperparathyroidism (odds ratio, 4.64; 95% confidence interval, 1.02–21.00). The time to development of hyperparathyroidism was significantly longer with ergocalciferol treatment compared with placebo (hazard ratio, 0.30; 95% confidence interval, 0.09–0.93, P=0.05). With ergocalciferol treatment, normal 25(OH)D levels were achieved in all 8 children with CKD2, 8 of 11 children with CKD3, but not in the single patient with CKD4. There were no ergocalciferol-related adverse events. 25(OH)D levels >100 nmol/L were required to achieve normal levels of 1,25-dihydroxyvitamin D.

Conclusions Ergocalciferol is an effective treatment that delays the development of secondary hyperparathyroidism in children with CKD2–3.

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Introduction

Secondary hyperparathyroidism is common in adults and children with CKD, and it begins early in the course of renal decline (1,2). Emerging data suggests that elevated parathyroid hormone (PTH) levels are a significant and independent risk factor for the development of bone disease (3,4), vascular calcification (5,6), and all-cause and cardiovascular mortality (7,8) even in subjects without CKD (9). A growing body of evidence now stresses the importance of keeping PTH levels within the normal range in all predialysis patients (3,10) to promote optimal bone turnover without causing ectopic calcification. A key factor that leads to elevated PTH is vitamin D deficiency (11), involving both nutritional 25-hydroxyvitamin D [25(OH)D] and the activated form (1,25-dihydroxy vitamin D [1,25(OH)$_2$D]). When significant depletion of 25(OH)D occurs, PTH levels rise even with a GFR as high as 70 ml/min per 1.73 m^2 and can worsen despite stable renal function (2,12).

Vitamin D deficiency is widespread in both the general population (13) and CKD patients, with prevalence rates of 60–80% even in predialysis CKD children (12,14–18). Importantly, increasing evidence from clinical, epidemiologic, and animal studies suggest that vitamin D is not simply a calcemic hormone but plays an important role in cardiovascular and bone health, immune responses, autoimmune conditions, renoprotection, glycemic control, and prevention of some common cancers (11,12,19). Observational studies suggest that vitamin D supplementation may confer a significant survival advantage on dialysis patients (20–22). Moreover, it has been shown that the vitamin D receptor as well as the 1-α hydroxylase enzyme system is distributed in most tissues, suggesting that 25(OH)D can act in an autocrine/paracrine manner on virtually all tissues (19). The parathyroid cells also express 1-α hydroxylase and can produce their own active 1,25(OH)$_2$D in an autocrine fashion to regulate PTH production (23). It is, therefore,

important to ensure that 25(OH)D levels are adequate, especially as the use of activated vitamin D analogs has been associated with increased cardiovascular risk with escape from normal negative feedback control through the 24-hydroxylase enzyme (11,12).

In the absence of robust evidence, opinion-based guidelines from the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) recommend that, if PTH levels are elevated and serum 25(OH)D levels low, ergo or cholecalciferol supplements should be prescribed (24,25). Observational studies have shown that ergocalciferol provides adequate substrate for the synthesis of 25(OH)D and can reduce PTH levels without any risk of hypercalcemia in CKD stages 2–3 but not in advanced CKD (15,16,26–32). However, no studies to date have used ergocalciferol supplementation in the early stages of CKD for the prevention of secondary hyperparathyroidism. We hypothesized that ergocalciferol (vitamin D_2) supplementation to achieve normal 25(OH)D levels in children with CKD2–3 would delay the onset of secondary hyperparathyroidism and tested this hypothesis through a randomized, double-blinded, placebo-controlled trial. We also assessed whether the KDOQI recommendations for ergocalciferol supplementation can achieve and maintain adequate 25(OH)D levels in children with CKD stages 2–4.

Materials and Methods

We conducted a prospective, randomized, double-blinded, placebo-controlled study to test our hypothesis that ergocalciferol supplementation prescribed according to KDOQI guidelines will achieve normal 25(OH)D levels [>75 nmol/L (>30 ng/ml)] in children with mild to moderate CKD and will delay the onset of secondary hyperparathyroidism. Children were recruited from nephrology clinics at Great Ormond Street Hospital. The inclusion criteria were age <18 years, estimated GFR (eGFR) between 15 and 70 ml/min per 1.73 m^2, and normal intact PTH levels (normal range in our laboratory was 0.7–5.6 pmol/L) but low 25(OH)D levels (<75 nmol/L). The eGFR was determined by the Schwartz formula using a locally determined k value of 0.33 (33). In this study, hyperparathyroidism was defined as an intact PTH level above normal on two consecutive occasions 3 months apart, despite correction of hyperphosphatemia. Exclusion criteria were preexisting hyperparathyroidism, comorbid conditions that may interfere with the absorption or metabolism of ergocalciferol such as malabsorption syndromes or liver cell dysfunction, and use of glucocorticoids or anticonvulsant therapy. Informed written consent was obtained from all caregivers, and assent from children was obtained when appropriate. The study was approved by the national research ethics committee.

As per European guidelines on prevention and treatment of renal osteodystrophy (10), we aim to keep PTH levels within the normal range in children with predialysis CKD stages 2–4 using an activated vitamin D analog 1-α-hydroxycholecalciferol (α-calcidol). Children on α-calcidol had their medication stopped, and if their PTH level remained normal after a 4-week washout period, they were recruited into the study. Patients with high PTH and high phosphate (P) levels had hyperphosphatemia treated with

dietary restriction and/or phosphate binders. Children with 25(OH)D levels >75 nmol/L were seen every 3 months for two subsequent visits; if their 25(OH)D levels fell to <75 nmol/L, they were entered into the study with randomization to ergocalciferol or placebo treatment. No children were taking proprietary vitamin-containing preparations or feeds fortified with vitamin D or were prescribed nutritional forms of vitamin D; 13 children (7 children in the ergocalciferol arm) were on phosphate binders (calcium carbonate or calcium acetate).

The primary endpoint was the time to development of secondary hyperparathyroidism as defined above. The secondary endpoints were to determine if the KDOQI recommended dosage of ergocalciferol could achieve and maintain adequate 25(OH)D levels in children with CKD 2–4 and assess adverse effects.

Children were randomized in a 1:1 ratio using a block size of 10 to ensure equal recruitment to the two groups during the various seasons (Figure 1). Ergocalciferol (2000 IU/ml in sunflower oil) and a placebo (sunflower oil only) matched for color, odor, and taste in identical bottles were prepared by prior arrangement by Specials Laboratory. Randomization was carried out by the trial pharmacist using a random number generator. The clinicians and participants were blinded to the treatment code until all data were collected and evaluated and the *a priori* hypotheses was reviewed.

Ergocalciferol was prescribed as per the KDOQI clinical practice guidelines for nutrition in CKD (25), with an intensive replacement phase [depending on baseline 25(OH)D levels] for 3 months followed by a maintenance phase thereafter (Figure 1). Children were seen every 3 months in the clinic and had routine investigations [serum albumin, creatinine, calcium (Ca), P, alkaline phosphatase, and PTH] as well as 25(OH)D and 1,25(OH)$_2$D levels were measured. All patients were followed up for a minimum of 6 months, unless they reached the study endpoint earlier. If the albumin-adjusted serum Ca level was above the upper limit for age, it was determined that the child would be withdrawn from the study, the randomization code was broken, and the case reported to the Data Monitoring Committee. If 25(OH)D levels were above normal (>250 nmol/L) but without hypercalcemia, the trial medication was stopped, and every 3 months clinic visits and monitoring continued with no additional ergocalciferol treatment.

Biochemical Assays

PTH levels were measured by the Immulite 2500 Intact PTH assay (Siemens Healthcare Diagnostics, Frimley, Surrey, United Kingdom). 25(OH)D was analyzed by isotope dilution liquid chromatography–tandem mass spectrometry (34) by a single technician in the Pathology Department at Northwick Park Hospital. The 25(OH)D level was the sum of 25(OH)D$_2$ and 25(OH)D$_3$. Serum 1,25(OH)$_2$D was measured by enzyme immunoassay (ImmunoDiagnostic Systems, Boldon, Tyne & Wear) at baseline, month 3, and the end of study visit by a single technician at Great Ormond Street Hospital. The interassay coefficients of variation for 25(OH)D and 1,25(OH)$_2$D were 2.7% and 4.2%, respectively.

Nutritional Ca and vitamin D intake were analyzed from a 3-day diet diary that was completed by the child or parents between months 3 and 6 of the study. The diet
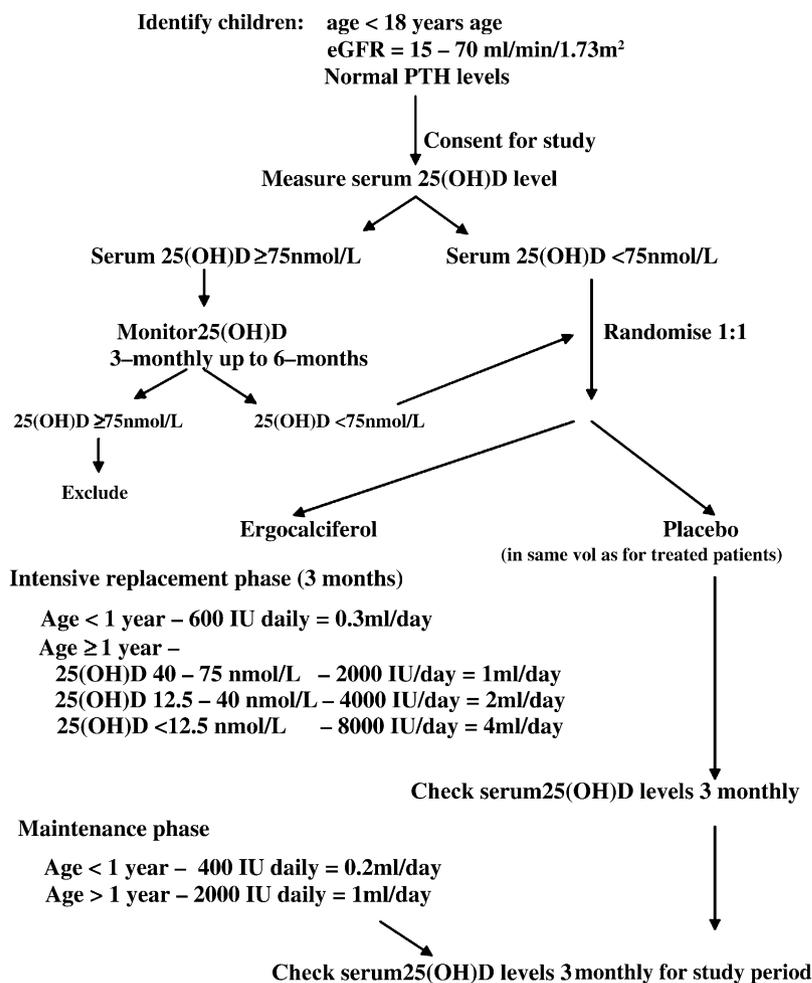
Figure 1. | **Flow diagram showing protocol for recruitment, randomization, and treatment schedule.**

diaries were analyzed using the CompEat Nutrition System and Electronic Diet Manager by a single dietician who was blinded to the child's treatment.

Statistical Analyses

The primary objective was to determine the efficacy of ergocalciferol versus a placebo in preventing the development of secondary hyperparathyroidism in children with CKD2–4. In the absence of published randomized trials, the initial sample size was based on experience from our own clinical setting and the published reports on hyperparathyroidism in CKD patients (3,17,25). We estimated that, for children with eGFR between 15 and 70 ml/min/1.73 m², the relative risk of developing hyperparathyroidism is 50% (between 20% and 65%) per year. Observational studies in adult CKD2–4 patients with established secondary hyperparathyroidism have shown that ergo or cholecalciferol reduces PTH levels to the KDOQI-defined normal range in 20–40% of patients (26,28,30,32), but the treatment regimen used and results were highly variable. We estimated that, to detect a 30% reduction in the relative risk of developing secondary hyperparathyroidism and 80% power, 50 children per group would be needed. The study was designed to run over 2 years, including a minimum follow-up of 6 months.

Recruitment was slower than anticipated, because the proportion of children with normal PTH but low 25(OH)D levels was lower than expected.

Results are presented as mean ± SD or median and range, depending on the distribution, for continuous variables and frequency for categorical variables. The primary outcome, time to development of secondary hyperparathyroidism, was assessed by Kaplan–Meier survival analysis. Differences of absolute laboratory results between treatment groups at baseline were compared by two-sample t test or Chi-squared tests for continuous and categorical variables, respectively. The changes from baseline to end of study were tested using paired t tests. The treatment effect difference was studied using the repeated measurement ANOVA model, with baseline and end of study measurements as response variables and treatment, visit, and their interaction as covariates. To evaluate the treatment effect differences between CKD stages, we used two-way ANOVA models, with percentage of change of PTH and 25(OH)D as response variables and treatment, CKD stage, and their interaction as the factors. All P values are described as two tailed, and $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL).

Results

Seventy-two children were screened for eligibility between February of 2009 and March of 2010. Forty-seven children were enrolled into the study and randomized to ergocalciferol or placebo treatment (Figure 2). Twenty-five patients were excluded. Of these patients, 22 (30% of the study cohort) patients had 25(OH)D levels > 75nmol/L, 2 patients withdrew consent, and 1 patient was on vitamin D-supplemented feeds (Figure 2). Four patients in the ergocalciferol arm and three patients in the placebo arm were excluded from the analysis before any trial medication was started (Figure 2): one patient in each group withdrew consent, two children randomized to receive ergocalciferol and one child randomized to placebo treatment refused to take any medication from the outset, one child (ergocalciferol arm) was started on proprietary vitamin D supplements, and one child (placebo arm) was lost to follow-up. All children who took even one dose of the trial medication were entered into the analysis, and data are presented as an intention to treat exposed analysis. Baseline demographic, clinical, and biochemical characteristics are shown in Table 1.

The baseline 25(OH)D showed an inverse correlation with CKD stage ($P=0.034$, $r=-0.22$), and PTH ($P=0.04$, $r=0.13$) showed a direct correlation. There was no correlation between CKD stage and baseline albumin-adjusted Ca or P levels. The 25 children excluded after screening were comparable in age, race, and underlying renal diagnoses but had higher eGFR (54.6 ± 12.1 ml/min per 1.73 m^2) and higher 25(OH)D levels (114.3 ± 29.3 nmol/L) compared with patients who were randomized. There was no difference in their anthropometric measures or dietary intake of calcium or vitamin D. They were followed up for 6 months, and all maintained normal PTH levels.

Hyperparathyroidism developed in 9 of 20 children on placebo and 3 of 20 children on ergocalciferol treatment (odds ratio=4.64, 95% confidence interval=1.02–21.00). Children receiving ergocalciferol had a significantly longer time to development of secondary hyperparathyroidism

(hazard ratio=0.30, 95% confidence interval=0.09–0.93, $P=0.05$) compared with those children on placebo (Figure 3). There was no significant change in PTH levels between baseline and final follow-up in the ergocalciferol group (median=-8.0%, range=$+74$ to -88%, $P=0.30$), but a significant rise in PTH was noted in the placebo-treated arm (median=$+22.4$%, range=$+267$ to -13%, $P=0.046$).

In the ergocalciferol-treated children, there was an expected rise in 25(OH)D level between baseline and 3 months of intensive replacement treatment (median of 56 versus 96.5 nmol/L, $P<0.0001$), but no change in 25(OH)D between the 3-month and final study visit (median of 96.5 versus 83 nmol/L, $P=0.15$) (Figure 4A). Sixteen of 20 (80%) children achieved 25(OH)D levels in the normal range after intensive replacement treatment (month 3), whereas only 12 of 20 (60%) children continued to have normal 25(OH)D levels after maintenance treatment (final study visit, $P=0.06$). However, when stratified for CKD stage, it became clear that it was more difficult to achieve and maintain normal 25(OH)D levels in CKD stages 3–4 compared with stage 2 (Figure 4B). All eight children in CKD stage 2 achieved normal 25(OH)D levels after intensive replacement, and seven of eight (88%) children were able to maintain normal 25(OH)D levels; however, 8 of 11 (72%) children in CKD stage 3 achieved normal levels with the intensive replacement therapy, and only 5 of 11 children (45%) were able to maintain normal levels. The child in CKD stage 4 had 25(OH)D deficiency despite ergocalciferol treatment; he did not have proteinuria or any problems associated with vitamin D absorption or metabolism to explain the poor response to treatment. None of the patients developed vitamin D toxicity.

In the ergocalciferol arm, there was no difference in the achieved 25(OH)D level in those children who did and did not show an increase in PTH (88.3 ± 3.7 versus 91 ± 39 nmol/L; $P=0.86$). All three children who developed hyperparathyroidism in the ergocalciferol-treated group were in CKD stage 3 (median eGFR=46 ml/min per 1.73 m^2). Among the three children who were previously on
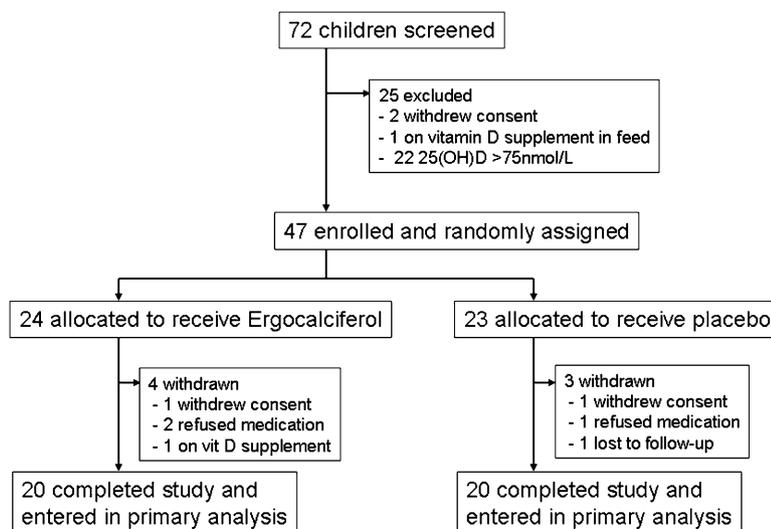

Figure 2. | **Trial profile.**

Table 1.   Baseline subject characteristics by treatment groups

Patient Characteristics	Ergocalciferol (n=24)	Placebo (n=23)	P
Age (years)	10.6 ± 2.5	7.9 ± 4.8	0.06
Sex (♂)	15 (63%)	16 (69%)	0.80
Race (Caucasian/Asian/Afro-Caribbean)	18/4/2	16/2/5	0.74
Estimated GFR (ml/min per 1.73 m^2)	47 ± 8.1	48 ± 9.2	0.68
CKD stages 2/3/4	10/13/1	8/13/2	0.73
Underlying diagnoses			
congenital abnormalities of the kidney and urinary tract	21 (88%)	19 (83%)	
renal venous thrombosis	1	0	
reduced renal mass after surgery for malignancy	2	2	
Beckwith Wiedermann Synd	0	1	
sepsis with multiorgan failure	0	1	
Season of recruitment			
winter/spring	13 (54%)	14 (61%)	0.32
summer/autumn	11 (46%)	9 (39%)	0.32
Mean systolic BP SDS	0.5 ± 0.2	0.2 ±0.2	0.84
Dietary intake			
calcium [mg; median (range)]	808 (400–1463)	920 (724–2021)	0.22
vitamin D (μg)	1.05 ± 0.2	0.9 ± 0.5	0.08
Ca intake from P binders			
n	7	6	0.82
elemental Ca intake (mg/d)	80 ± 18.6	102 ± 22.3	0.68
Serum biochemistry at study recruitment			
albumin-adjusted calcium (mmol/L)	2.37 ± 0.2	2.37 ± 0.4	0.92
phosphate (mmol/L)	1.5 ± 0.3	1.4 ± 0.4	0.71
PTH (pmol/L)	4.7 ± 2.4	4.6 ± 2.1	0.91
25(OH)D (nmol/L)	50.1 ± 19.5	52.1 ± 17.3	0.69
Urine dipstick for protein			
negative	14	16	0.82
trace	8	4	0.82
1+	2	3	0.82

All data are expressed as mean ± SD unless stated otherwise.

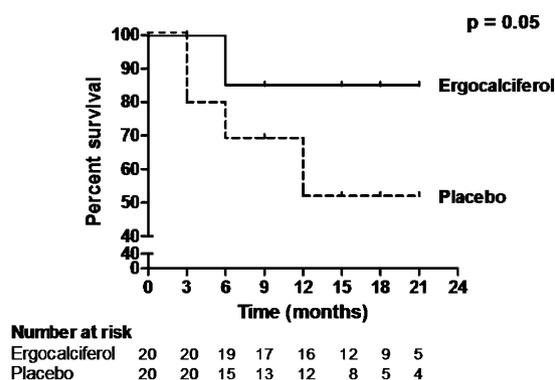**Figure 3. | Time to development of secondary hyperparathyroidism in ergocalciferol and placebo-treated patients.**

α-calcidol and underwent a washout phase, both children in the ergocalciferol arm developed hyperparathyroidism; their eGFRs were 22 and 43 ml/min per 1.73 m^2. 25(OH)D$_2$ levels were raised only in those children on ergocalciferol (baseline=59±31.9 nmol/L and study end=69±33 nmol/L), whereas 25(OH)D$_2$ was undetectable in children on placebo. Three children in the ergocalciferol arm and five children in the placebo arm went on foreign travel to warm countries during the study period; there was no difference in their 25(OH)D$_3$ levels compared with the rest of their group. There was no racial or seasonal variation in 25(OH)D levels or PTH control.

The mean 1,25(OH)$_2$D levels at baseline in the ergocalciferol- and placebo-treated arms were 38±11.4 versus 40±13.3 pmol/L (P=0.37). After 3 and 6 months of ergocalciferol therapy, 1,25(OH)$_2$D levels increased to 73±13.3 and 66±16.9 pmol/L, respectively (P=0.01) but remained unchanged in the placebo arm (43±9.7 and 39±14.1 pmol/L at 3 and 6 months, respectively (P=0.08). 25(OH)D levels >100 nmol/L were required to achieve normal levels of 1,25(OH)$_2$D above 40 pmol/L (35).

Overall, ergocalciferol was safe and well tolerated by the children. There were 48 episodes of common childhood illnesses, including upper respiratory tract infections and acute diarrheal or vomiting illnesses, two minor injuries, and one trauma-related fracture; these episodes were comparable between the two groups, and none were thought to be related to ergocalciferol. There were no hypercalcemic episodes, and all had normal P levels. Serum albumin-adjusted Ca and P levels between treated and untreated patients were comparable (Ca=2.45±0.04 versus 2.42±0.01 mmol/L, P=0.70 and serum P=1.5±0.3 versus 1.5±0.7 mmol/L, P=0.44, respectively). The mean annualized change in eGFR was −2.1±1.1 versus 1.6±0.9 ml/min per 1.73 m^2 in
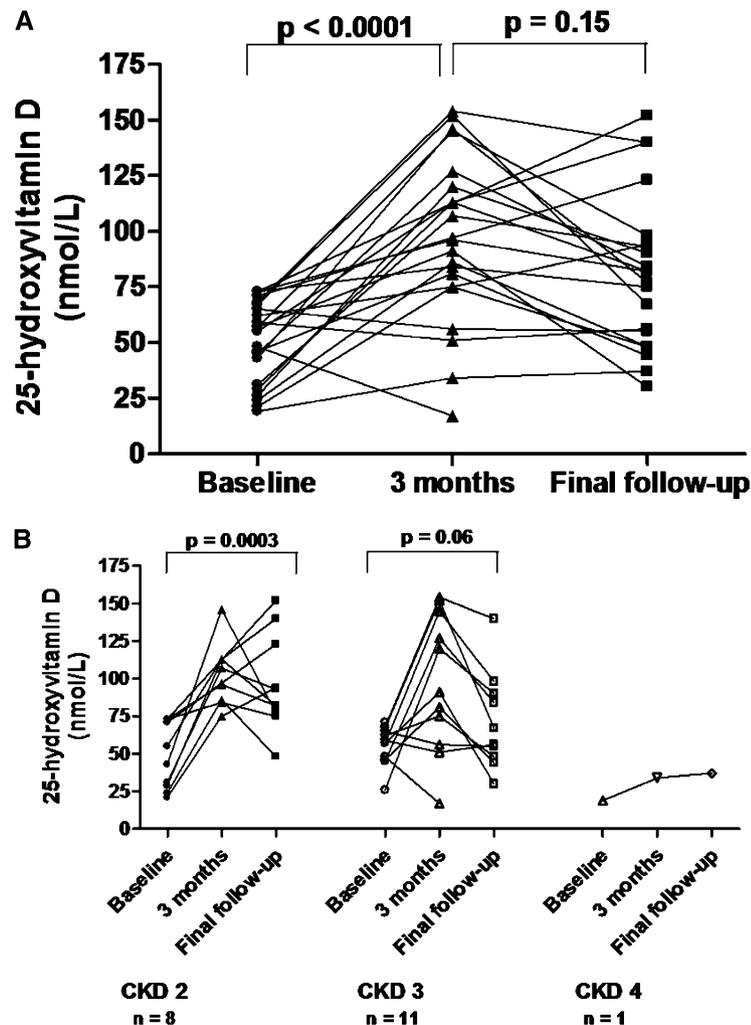
Figure 4. | 25-Hydroxyvitamin D levels in ergocalciferol-treated patients during the study period. (A) 25-Hydroxyvitamin D levels at baseline, after 3 months (after intensive replacement phase), and at final follow-up (after maintenance phase) in ergocalciferol-treated patients. (B) 25-Hydroxyvitamin D levels at baseline, after 3 months (after intensive replacement phase), and at final follow-up (after maintenance phase) in ergocalciferol-treated patients stratified for CKD stage.

the ergocalciferol- and placebo-treated patients, respectively (*P*=0.82).

Discussion

This randomized, double-blinded, placebo-controlled study suggests that ergocalciferol is safe and effective in delaying the onset of secondary hyperparathyroidism in 25(OH)D-deficient children with CKD stages 2–3. By following the KDOQI guidelines for ergocalciferol supplementation (25), normal levels of 25(OH)D were achieved in CKD2 but not CKD3 or -4 patients. Moreover, normal 1,25(OH)$_2$D levels could only be reached when 25(OH)D levels were >100 nmol/L.

In our study, 65% of children in CKD2–4 with PTH levels in the KDOQI-defined normal range for CKD stage had 25(OH)D deficiency. The prevalence of 25(OH)D deficiency in adults with CKD2–4 has been reported at 71–82% and is closely related to CKD stage (13). There are little data in children, but a prevalence of 39–83% has been reported in

children with CKD, although stratification with CKD stage is not described (14–18). Most authorities consider 25(OH)D levels >75 nmol/L (11,36,37) as adequate, but the 25(OH)D level required for its noncalcemic effects or levels required for autocrine/paracrine effects are unknown. Similarly, it is not known what levels of 25(OH)D are required to achieve adequate 1,25(OH)$_2$D levels. In this study, we have defined normal 25(OH)D as >75 nmol/L but found that 25(OH)D levels above 100 nmol/L are required to achieve normal 1,25(OH)$_2$D levels.

In the absence of randomized controlled trials, the doses of ergocalciferol or cholecalciferol required to correct and maintain adequate 25(OH)D levels in adults or children with CKD is not known. An opinion-based guideline from KDOQI suggests that serum 25(OH)D levels should be measured one time per year in children with CKD stages 3–5 and children on dialysis, and ergocalciferol or cholecalciferol should be provided if levels are <75 nmol/L (24,25). The Kidney Disease Improving Global Outcomes guidelines, which are more rigorously evidence-based

guidelines, have only suggested the use of vitamin D analogs for the treatment of secondary hyperparathyroidism in predialysis CKD stages 3–5, but the level of evidence for this suggestion is very weak; therefore, no clear recommendations are given (1).

D_2 and D_3 supplements are recommended interchangeably in most treatment regimens, and KDOQI and Kidney Disease Improving Global Outcomes make no distinction between the biopotencies of D_2 and D_3 (1,24,25). There is some suggestion that cholecalciferol has a higher bioavailability than ergocalciferol (38), but a recent randomized trial in adults has shown that vitamin D_2 supplements are as effective as vitamin D_3 in maintaining 25(OH)D levels (39). In our study, ergocalciferol was preferred over cholecalciferol, because sunlight and most vitamin D-enriched foods have the vitamin D_3 form; therefore, using ergocalciferol (a D_2 derivative) allowed us to distinguish between trial medication and natural sources of vitamin D as well as confirm patient compliance. Also, cholecalciferol is not freely and consistently available in the United Kingdom.

The current literature on ergocalciferol or cholecalciferol supplementation in adults and children (15,16,40) with predialysis CKD consists of small, mostly nonrandomized and short-term studies using (26–32) variable doses of ergocalciferol or cholecalciferol, and it is difficult to draw any clinical practice recommendations from these studies. Ergocalciferol or cholecalciferol have been used in daily (28,31), weekly (26,28,32), monthly (16,27,29,30), and even single mega dose (15,40) therapy. Although some studies did show a dose-related improvement in 25(OH)D levels, particularly in CKD3 (26), the 1,25(OH)$_2$D levels still remained below normal, and PTH levels recommended by KDOQI were only achieved in 20% of CKD3 and not at all in CKD4 or -5 patients (26–30,32). There are only three studies using ergo or cholecalciferol supplementation in children with CKD (15,16,40). Menon *et al.* (16) treated 22 children in CKD2–4 with ergocalciferol using a modified KDOQI regimen. PTH levels in their cohort improved from 122 to 80 pmol/L after 3 months but with wide variations, and the 25(OH)D and 1,25(OH)$_2$D levels achieved are not mentioned; also, there is no reference made to any CKD stage-specific responses or racial differences in outcome (16). Belostotsky *et al.* (14) found that 83% of their patients with renal disease (CKD stage not specified) had 25(OH)D levels below 30 ng/ml (75 nmol/L). Twenty children were given a single large dose (100,000 IU for children 5–10 years of age and 150,000 IU for children over 10 years) (40) of ergocalciferol. Serum 25(OH)D levels improved from a baseline of 1.5–15.8 to 7–25.6 ng/ml after 3 months. Of note, none of the patients achieved levels above 30 ng/ml (75 nmol/L), and the effect of increased 25(OH)D on PTH levels was not mentioned (40). Hari *et al.* (15) report a similarly high prevalence of 25(OH)D deficiency of 82% in Indian children with CKD stages 2–4, and treatment with cholecalciferol (600,000 IU orally over 4 days) improved 25(OH)D levels above 75 nmol/L, with a parallel improvement in PTH levels into the normal range (15). The median reduction in PTH level was 38% in CKD stage 2, 25% in CKD stage 3, and 15% in CKD stage 4 (15). There is no consensus on the choice of vitamin D preparation, its dose or frequency of treatment, or the expected benefits of treatment in pediatric or adult CKD patients.

All studies to date have shown that ergocalciferol and cholecalciferol are safe, and hypercalcemia has been reported in only one study; all cases were seen in CKD4 patients and were self-resolving (32). However, given the short follow-up in all the studies, it is not clear if pharmacologic doses of ergocalciferol used in CKD patients can either become ineffective over time or accumulate in body fat stores, producing vitamin D intoxication. In contrast, vitamin D receptor activators like α-calcidol and calcitriol have no negative feedback control, and they are more likely to cause hypercalcemia and hyperphosphatamia, have a narrow therapeutic window (35), and have links with vascular calcification in *in vitro* experiments, animal studies, and observational studies in CKD patients (4,6). Thus, slowing the time to development of hyperparathyroidism using nutritional vitamin D supplements like ergocalciferol or cholecalciferol, at least in the early stages of CKD, is to recommended.

The main limitation of our study is the small patient numbers. Our power calculations had to be based on studies using ergocalciferol or cholecalciferol in patients with established secondary hyperparathyroidism. Additionally, the proportion of eligible patients who were 25(OH)D-deficient was less than predicted, lowering our recruitment rate. We had very few patients in CKD stage 4, which was very likely a result of the strict criteria that excluded children with PTH above normal on two consecutive occasions. A large multicenter study is required to achieve the necessary sample size to adequately answer this question. We only have urine dipstick results as a qualitative measure of proteinuria but no albumin/creatinine ratios. Finally, we were only able to study the PTH-lowering effect of ergocalciferol treatment and not assess important patient-level outcomes such as cardiovascular or bone outcomes, glycemic control, effect on infection rates, immune function, or inflammatory measure. It is not known if the same 25(OH)D levels are required for its effect on different tissues, including local autocrine/paracrine production of 1,25(OH)$_2$D. There is an urgent need for a dose-finding study that takes into account both the calcemic and noncalcemic effects of vitamin D.

In conclusion, we have shown that ergocalciferol prescribed according to KDOQI recommendations delays the onset of secondary hyperparathyroidism in 25OH-deficient children with CKD2–3 but may not consistently achieve normal 25(OH)D levels in CKD3 patients. There is now an increasingly compelling body of evidence to suggest that 25(OH)D deficiency may carry its own burden of disease, and the benefits of supplementation with ergocalciferol or cholecalciferol need to be tested in large randomized, controlled studies in children looking at key patient-level outcomes including cardiovascular and bone disease.

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