

# High doses of cholecalciferol alleviate the progression of hyperparathyroidism in patients with CKD Stages 3–4: results of a 12-week double-blind, randomized, controlled study

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## ABSTRACT

**Background.** Calcidiol insufficiency may accelerate the development of secondary hyperparathyroidism (SHPT). We tested the effect of a substantial increase in calcidiol on mineral metabolism in patients with chronic kidney disease (CKD).

**Methods.** Ninety-five patients with CKD Stages 3–4, parathyroid hormone (PTH) above 6.8 pmol/L and calcidiol below 75 nmol/L were randomized to receive either cholecalciferol 8000 IU/day or placebo for 12 weeks. The primary endpoint was difference in the mean change in iPTH after 12 weeks. The proportion of participants having a 30% reduction in PTH and the effect on hand grip strength, fatigue and different biochemical variables were also investigated.

**Results.** Baseline calcidiol was  $57.5 \pm 22$  and  $56.8 \pm 22$  nmol/L in the cholecalciferol and placebo groups, respectively. The corresponding concentrations of PTH were  $10.9 \pm 5$  and  $13.1 \pm 9$  pmol/L. Calcidiol increased to  $162 \pm 49$  nmol/L in patients receiving cholecalciferol, and PTH levels remained constant at  $10.5 \pm 5$  pmol/L. In the placebo group, calcidiol remained stable and PTH increased to  $15.2 \pm 11$  pmol/L. The mean change in PTH differed significantly between the two groups ( $P < 0.01$ ). The proportion of subjects reaching a 30% decrease in PTH did not differ. No effect on grip strength, fatigue, phosphate or fibroblast growth factor 23 was observed. Cholecalciferol treatment resulted in stable calcium concentrations and a substantial increase in calcitriol.

**Conclusion.** Treatment with high daily doses of cholecalciferol in patients with CKD Stages 3–4 halts the progression of SHPT and does not cause hypercalcaemia or other side effects.

**Keywords:** cholecalciferol, chronic renal failure, FGF23, secondary hyperparathyroidism, vitamin D

## INTRODUCTION

A plasma concentration of calcidiol [25-hydroxy vitamin D (25(OH)D)] below 75 nmol/L is associated with an increase in parathyroid hormone (PTH) in healthy subjects [1–3]. Chronic kidney disease (CKD) patients are prone to develop 25(OH)D deficiency and clinical guidelines recommend replenishment with nutritional vitamin D, as ergo- or cholecalciferol, to attain a 25(OH)D plasma concentration above 75 nmol/L [4, 5]. Furthermore, low 25(OH)D levels have been suggested to be associated with impaired muscle and bone function [2, 6]. As various tissues express the ability to internalize, metabolize and elicit responses to vitamin D, it has been hypothesized that 25(OH)D may have multiple beneficial pleiotropic effects apart from being a substrate for the formation of calcitriol {1,25(dihydroxy) vitamin D [1,25(OH)<sub>2</sub> vitamin D]} [6, 7].

The primary aim of this study was to determine if treatment with high-dose cholecalciferol (8000 IU/day as oral drops) for 12 weeks in CKD Stages 3–4 patients with secondary hyperparathyroidism (SHPT) resulted in differences in change in PTH levels as compared with placebo. Secondary outcomes were differences in mean change in PTH after 6 weeks and evaluation of fatigue, hand grip strength and different biochemical variables.

## MATERIALS AND METHODS

### Subjects

Consecutive patients from three outpatient renal clinics in Sweden (Uppsala, Malmö and Gothenburg) with CKD Stages 3 and 4, PTH above 6.8 pmol/L, and 25(OH)D below 75 nmol/L were invited to participate in the study. All subjects had to be 18–85 years of age, have an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease formula between 15 and 59 mL/min/1.73 m<sup>2</sup> and sign informed consent. Exclusion criteria were presumed need for renal replacement therapy within 6 months, ionized calcium above 1.30 mmol/L, ongoing acute or chronic systemic inflammatory disease, pregnancy, renal transplant, known disease with significant effect on mineral metabolism such as granulomatous diseases, malabsorption, primary hyperparathyroidism or active malignancy. Ongoing treatment with paricalcitol, calcimimetics or a daily intake of pharmaceutical ergo- or cholecalciferol in a dose above 400 IU were exclusions, whereas a stable low per oral dose of 1-alfacalcidol was accepted if the dose remained unchanged during the study.

### Protocol

This was a 12-week double-blind, randomized, placebo-controlled clinical trial (EudraCT 2011-002586-38). Eligible subjects were randomly assigned to receive 8000 IU cholecalciferol (12 drops daily Vitamin D3 Forte Renapharma 20 000 IU/mL), or matching placebo provided by Merck KGaA. The dose was selected to be close to 50 000 IU/week, which was used in a study where 25(OH) D sufficiency was reached, however, without significant effect on PTH. We aimed for a substantial increase in 25(OH) D, well above 75 nmol/L in all treated subjects, to fully examine the effects on mineral metabolism and also possible pleiotropic effects on fatigue and muscle function.

Cholecalciferol and placebo were manufactured in identical vials by the manufacturer. Each vial had a batch number and each subject an identification number based on site and order of inclusion in the study. A statistician employed by the sponsor performed block randomization, which was blinded to all in the staff performing the study. A study nurse provided each participant with the numbered vials allocated to them on the first visit after inclusion in the study.

Participants were seen as outpatients at respective clinics at baseline, after 6 weeks and after 12 weeks. Physical examination, medical history and concomitant medication were registered at baseline, and any changes in medication or adverse events (AEs) were registered at each visit. After an overnight fast, blood was drawn and centrifuged and serum was stored in –70°C for future biochemical analyses. Urine, second morning void, was collected for analysis of phosphate, creatinine and albumin. Hand grip strength was assessed in a standardized manner using a hand dynamometer (model SH-5001, Medema, Saehen). Fatigue was assessed by a validated questionnaire consisting of an 11-item fatigue scale and a visual analogue scale (0–100 mm) [8].

Compliance with the study medication was assessed by documenting all the vials given to the subjects at visits 1 and 2.

At visits 2 and 3, the patients were asked whether they had taken the prescribed dose of the study drugs. All the vials were returned to the clinic by the patients at visits 2 and/or 3. In case any vial still contained study medication, the amount was measured and the volume documented in the case report form. In the cholecalciferol group, 42 subjects of 47 (90%) had been compliant at week 12 and in the placebo group 47 of 48 (98%). Non-compliant subjects included those who ended their participation for some reason or were informed to temporarily suspend their treatment while resolving an AE.

The study protocol was approved by the Regional Ethical Review Board in Uppsala (Ref 2011/313) and by the Swedish Medical Products Agency, and the study was conducted in accordance with the Declaration of Helsinki. An independent data monitoring safety committee (Prof. Håkan Melhus, Uppsala University Hospital; and statistician Johan Bring, Statisticon, Uppsala) was used during the study, a precondition laid down by the Medical Products Agency for approval of the study.

### Biochemical analyses

Biochemical analysis for the screening procedure was done at each hospital. iPTH was analysed with standardized automated immunoassay (Cobas E, Roche). The 25(OH)D was analysed with a chemiluminescent method (Diasorin) in Uppsala, while high-performance liquid chromatography mass spectrometry (HPLC-MS) was used in Malmö and Gothenburg for screening. In the study, the HPLC-MS was used for all further analysis of 25(OH)D. The 1,25(OH)D was analysed using an immunological method (IDS-iSYS 1,25vitD<sup>xp</sup>, Boldon), and intact fibroblast growth factor 23 (FGF23) with an enzyme-linked immunosorbent assay (Kainos, Japan). Ionized calcium, calcium, phosphate, creatinine in serum and urinary phosphate, creatinine and albumin were analysed using standardized clinical laboratory methods. Fractional excretion (FE) of phosphate was calculated  $\{[\text{urine phosphate (mmol/L)} \times \text{serum creatinine (mmol/L)}] / [\text{urine creatinine (mmol/L)} \times \text{serum phosphate (mmol/L)}]\}$ .

### Statistical analyses

Values are given as means  $\pm$  standard deviation (SD), median, range and interquartile range or proportions.

The primary statistical hypothesis to be tested was a difference in mean change in PTH after 12 weeks between groups. This was tested using analysis of covariance (ANCOVA), with baseline PTH as covariate in the model and treatment as a fixed factor. Analysis was done on the full analysis set (FAS) population. The mean change in the secondary endpoint continuous variables was evaluated using the same approach. Categorical variables were evaluated using the chi-square test. Predefined subgroup analyses of participants with CKD Stage 3 or 4 were done. Moreover, subgroups of high or low baseline 25(OH)D levels were analysed where the border was data driven and defined as above or below 57 nmol/L. All statistical analyses were performed using SAS (version 9.3), and all tests were two-sided using the significance level of  $P < 0.05$ .

Sample size calculation for the primary endpoint was based on our own observational data [9] and a published pilot study

[10]. These data were used to calculate a hypothetical mean and SD of PTH. The PTH values were logarithmically transformed due to skewed distribution. To detect a 30% difference between groups after 12 weeks with a statistical power of 80% and  $P < 0.05$ , 45 patients were estimated to be required per treatment group. With an expected withdrawal rate of 10%, a total sample size of 100 patients was targeted.

## RESULTS

### Enrolment

The inclusion and randomization took place between 12 March 2012 and 14 March 2014. Following screening a total of 99 patients signed informed consent for participation in the trial. A total of 97 patients (48 in the cholecalciferol and 49 in the placebo group) continued the study after randomization. The FAS population was the primary analysis population and was defined for all patients who took at least one dose of the study drug and had at least one baseline and one post-baseline measure of the primary efficacy variable. The FAS population consisted of 95 subjects, 47 in the cholecalciferol group and 48 in the placebo. During the study, five subjects were withdrawn: two in the cholecalciferol group and three in the placebo group (Figure 1).

### Characteristics

Baseline serum concentrations of 25(OH)D, PTH and renal diagnoses are presented in Table 1. The proportion of males was higher in the placebo group: 80% as compared with 56% in the cholecalciferol group ( $P = 0.013$ ). Otherwise the groups were comparable, with a baseline 25(OH)D of  $57.5 \pm 22$  and  $56.8 \pm 22$  nmol/L and a PTH on  $10.9 \pm 5$  and  $13.1 \pm 9$  pmol/L in the cholecalciferol and placebo groups, respectively.

### Primary endpoint

The results at baseline and after 12 weeks are presented in Table 2. In the cholecalciferol-treated group, the mean change of PTH was  $-0.7 \pm 3$  pmol/L, whereas in the placebo group the

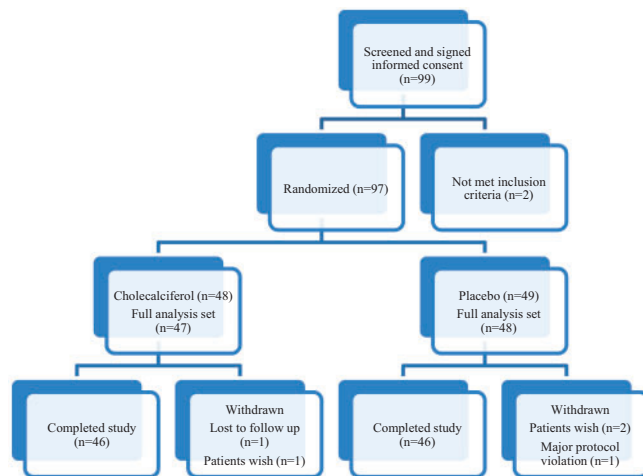


FIGURE 1: Patient disposition.

mean change in PTH was  $1.6 \pm 5$  pmol/L. The difference in mean change between groups was significant when analysed by ANCOVA ( $P = 0.0048$ ).

### Secondary and other endpoints

After 6 weeks there was a difference in mean change in PTH between groups ( $P = 0.036$ ). There was no significant difference in the proportion of subjects reaching a 30% decrease in PTH at 6 weeks (14.9 versus 6.3%,  $P = 0.32$ ) or 12 weeks (10.6 versus 4.2%,  $P = 0.27$ ). Eight patients in the treatment group experienced an iPTH level  $< 6.8$  pmol/L. Seven of these patients were in CKD Stage 3.

The serum concentration of 25(OH)D increased from  $57.5 \pm 22$  to  $161.6 \pm 49$  nmol/L after 12 weeks in the treatment group but remained unchanged in the placebo group. All subjects in the treatment arm were 25(OH)D sufficient ( $> 75$  nmol/L) after 12 weeks (Figure 2).

The 1,25(OH)D increased from  $64.5 \pm 43$  to  $101.5 \pm 54$  pmol/L in the cholecalciferol group.

The calcium concentration remained constant on 2.2 mmol/L in the cholecalciferol group, but decreased from  $2.3 \pm 0.12$  to  $2.2 \pm 0.13$  mmol/L in the placebo group. The difference in mean change was significant ( $P < 0.01$ ).

There were no differences in mean change between the groups in FGF23 or FE of phosphate.

Additionally, there were no differences at 12 weeks between groups in fatigue scores: for physical fatigue score ( $P = 0.11$ ), for mental fatigue score ( $P = 0.25$ ), and for the visual analogue scale ( $P = 0.96$ ) or hand grip strength ( $P = 0.98$ ).

### Subgroup analysis

A subgroup analysis was performed to investigate the effect of CKD stage on outcome. In the CKD Stage 3 subgroup, PTH did not change in either treatment group. In the cholecalciferol group, it was  $8.6 \pm 2.0$  pmol/L at baseline and  $9.1 \pm 3.9$  pmol/L after 12 weeks. The corresponding values in the placebo group were  $8.8 \pm 3.0$  at baseline and  $8.7 \pm 3.3$  after 12 weeks. There were no differences in mean change between groups ( $P = 0.95$ ). In CKD Stage 4, the mean PTH changed from  $12.5 \pm 6.6$  to  $11.5 \pm 5.8$  pmol/L in the treatment group, and from  $16.4 \pm 11.0$  to  $19.1 \pm 12.4$  pmol/L in the placebo group. The mean (confidence interval) difference in change between groups was  $-3.8$  ( $-6.5; -1.1$ ) ( $P = 0.006$ ).

Of the subjects, 50% had baseline 25(OH)D  $< 57$  nmol/L. They had a significant difference in mean change in PTH between treatment groups  $-3.15$  ( $-6.0; -0.3$ ) ( $P = 0.03$ ), whereas in the subgroup with 25(OH)D  $> 57$  nmol/L it was  $-1.5$  ( $-3.2; 0.2$ ) ( $P = 0.09$ ).

When further analysed, we found a correlation between 25(OH)D level and iPTH in the treatment group, indicating that even when vitamin D is sufficient it is possible to suppress iPTH with native vitamin D. The linear correlation line could be expressed as  $[iPTH \text{ (pmol/L)}] = 17.05 - 0.0407 \times [25(OH)D \text{ (nmol/L)}]$ , theoretically implicating that a mean iPTH of 12 pmol/L corresponds to 25(OH)D of 120 nmol/L and a 'normal' level  $< 6.9$  pmol/L correlates with 25(OH)D of  $\sim 250$  nmol/L.

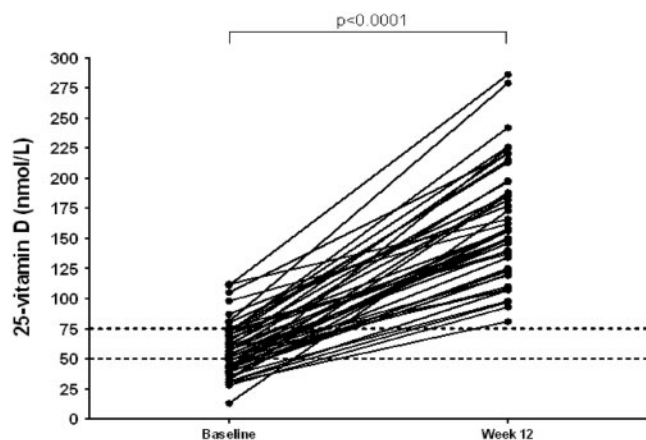
**Table 1. Characteristics of patients randomly selected to cholecalciferol or placebo treatment**

Characteristics	Cholecalciferol (n = 47)	Placebo (n = 48)	P
Age (years) (mean ± SD)	62.6 ± 15	64.0 ± 14	0.62
Males, n (%)	26 (56)	38 (80)	$\chi^2$
Females, n (%)	21 (44)	10 (20)	0.013
Weight (kg)	83.5 ± 18	91.1 ± 22	0.06
Body mass index (kg/m <sup>2</sup> )	28.4 ± 5	29.3 ± 6	0.41
eGFR (mL/min/1.73 m <sup>2</sup> )	32.0 ± 13	29.5 ± 13	0.29
CKD Stage 3	28 (60)	21 (43)	$\chi^2$
CKD Stage 4	19 (40)	27 (57)	0.09
25(OH)D (nmol/L)	57.5 ± 22	56.8 ± 22	0.94
Intact PTH (pmol/L)	10.9 ± 5	13.1 ± 9	0.09
Renal diagnosis, n (%)			$\chi^2$
Diabetes	16 (34)	15 (31)	0.41
Glomerulonephritis	10 (21)	9 (19)	
Renovascular disease	14 (30)	13 (27)	
Polycystic kidney disease	3 (6)	8 (17)	
Other	4 (9)	3 (6)	

**Table 2. Means ± SD for different variables before and after 12 weeks on treatment with cholecalciferol or placebo**

	Cholecalciferol		Placebo		P
	Baseline	Week 12	Baseline	Week 12	
25(OH)D (nmol/L)	57.5 ± 22	161.6 ± 49	56.8 ± 22	61.5 ± 24	<0.001
iPTH (pmol/L)	10.9 ± 5	10.5 ± 5	13.1 ± 9	15.2 ± 11	0.0048
Calcium (mmol/L)	2.24 ± 0.14	2.23 ± 0.13	2.27 ± 0.12	2.22 ± 0.13	<0.001
Phosphate (mmol/L)	1.2 ± 0.28	1.3 ± 0.28	1.2 ± 0.27	1.2 ± 0.29	0.22
1,25(OH)D (pmol/L)	64 ± 43	102 ± 54	64 ± 40	64 ± 37	<0.001
FGF23 (pg/mL)	132 ± 115	160 ± 131	138 ± 87	162 ± 132	0.76
Urinary phosphate (mmol/L)	14.7 ± 9.6	15.8 ± 9.3	16.3 ± 7.8	16.6 ± 8.5	0.48
Hand grip strength (kg)	26.5 ± 11	27.7 ± 12	33.2 ± 13	33.6 ± 12	0.98
Fatigue score, total	14.7 ± 5	12.3 ± 5	13.7 ± 4	13.8 ± 5	0.10
Physical	9.6 ± 4	8 ± 4	9 ± 3	9.1 ± 4	0.11
Mental	5 ± 2	4.2 ± 2	4.7 ± 2	4.6 ± 2	0.25
VAS (mm)	42.6 ± 26	36.0 ± 23	38.8 ± 25	34.5 ± 24	0.96

Data are presented as mean ± SD. P denotes difference in mean change between groups based on ANCOVA with baseline value as covariate. VAS, visual analogue scale.

**FIGURE 2: Individual observations of 25(OH)D before and after 12 weeks on cholecalciferol treatment.**

### Safety

No deaths were recorded during the course of the trial. In total, 56 AEs were registered during the study, most of which

were reported as mild and due to infections or musculoskeletal complaints. None was judged to be related to the study medication. No event of hypercalcaemia defined as ionized calcium above 1.35 mmol/L was recorded. There were no differences in mean change in eGFR between groups. eGFR estimated from cystatin C decreased  $0.6 \pm 5$  mL/min/1.73 m<sup>2</sup> in the cholecalciferol group and  $1.0 \pm 5$  mL/min/1.73 m<sup>2</sup> in the placebo group (P = 0.086).

Five serious AEs, which required hospitalization for at least 1 day, occurred. In the treatment arm there were 34 AEs, of which three were serious. An 81-year-old male was diagnosed with a 3-mm calculus causing moderate hydronephrosis and temporary worsening of renal function. On re-examination of a computer tomography scan from 4 years earlier, the calculus was seen and the event was classified as unrelated to the study drug. The two other serious AEs in the treatment arm were a pulmonary embolism and one respiratory tract infection. In the placebo arm there were 22 AEs, of which two were serious: one case of haematochezia (due to colonic polyp) and one iron deficiency anaemia of unknown cause.

## DISCUSSION

In this double-blind, randomized, placebo-controlled clinical study in CKD Stages 3 and 4 patients with SHPT, we showed that a daily high dose of oral cholecalciferol alleviates a further increase in PTH. We also demonstrate that all cholecalciferol-treated subjects become 25(OH)D sufficient after 3 months. Despite a substantial increase in 25(OH)D and 1,25(OH)D there were no cases of hypercalcaemia in the treatment group. Furthermore, no differences in changes in FGF23 or urinary phosphate excretion between the groups were observed. On the other hand, we saw no effect on the patient-pertinent symptoms fatigue or hand grip strength.

At least to our knowledge, this is the first sufficiently powered study of high-dose cholecalciferol in CKD to show an effect on SHPT. Earlier smaller studies have consistently demonstrated a dose-related increase in 25(OH)D and a trend to lower PTH.

Chandra *et al.* [10] performed a randomized study of 50 000 IU cholecalciferol weekly ( $n = 10$ ) versus placebo ( $n = 10$ ) in CKD Stages 3 and 4 subjects and reached 25(OH)D sufficiency: median (range) 124 (85–180) nmol/L, while median PTH decreased from 30 to 21 pmol/L, but there were no differences in PTH change compared with the placebo group ( $P = 0.14$ ).

Rucker *et al.* [11] treated 128 CKD Stages 3–5 patients, not on dialysis, with 1000 IU cholecalciferol daily or placebo for 12 weeks, and found that 25(OH)D increased significantly. Though >50% of treated subjects reached a 25(OH)D exceeding 75 nmol/L after 12 weeks, there were no differences in PTH between groups.

Moe *et al.* [12] compared cholecalciferol 4000 IU daily for 1 month followed by 2000 IU daily for 2 months ( $n = 22$ ) with doxercalciferol ( $n = 25$ ) in a randomized controlled trial for 12 weeks in CKD Stages 3 and 4. The mean 25(OH)D increased from  $35 \pm 15$  to  $92.5 \pm 25$  nmol/L ( $P < 0.001$ ) in the cholecalciferol group, and mean PTH decreased with 10% from  $11.5 \pm 4.6$  to  $10.3 \pm 5.2$  pmol/L ( $P = 0.15$ ). The PTH decreased by 30% in the doxercalciferol group but there was no significant difference in mean change between groups ( $P = 0.19$ ). There was no increase in serum calcium or urinary calcium/creatinine in the cholecalciferol group. In contrast to our results, where we observed a significant change in PTH levels in CKD Stage 4 patients and no difference in CKD Stage 3, their subgroup analysis showed that the PTH reduction was in CKD Stage 3, whereas there were no effects in CKD Stage 4.

Zisman *et al.* [13] performed an open non-randomized study on 52 CKD Stages 3 and 4 patients with ergocalciferol according to K/DOQI guidelines recommendations. The effect on 25(OH)D was similar in CKD Stages 3 and 4 subjects, reaching mean levels of  $78.8 \pm 5.5$  and  $88.4 \pm 4.2$  nmol/L, respectively. They observed a median decrease in PTH of 13% ( $P = 0.04$ ) in CKD Stage 3 but no effect in CKD Stage 4.

In our study, we used a higher cholecalciferol dose and aimed for higher 25(OH)D concentrations. The PTH reduction in the treatment arm was 6.4% and the increase in the placebo arm was 12.2%. In contrast to earlier studies, the effect was non-

significant in the CKD Stage 3 subgroup, whereas it was significant only in CKD Stage 4 due to the larger increase in PTH in placebo-treated patients.

Alvarez *et al.* [14] performed a 1-year clinical trial of high-dose cholecalciferol. They included 46 CKD Stages 2 and 3 patients who were randomized to cholecalciferol 50 000 IU weekly for 12 weeks followed by 50 000 IU every other week for 40 weeks or matching placebo. The 25(OH)D sufficiency was reached and maintained in the cholecalciferol group, and there was a significant decrease in PTH after 12 weeks ( $P = 0.01$ ), whereas there were no differences between groups after 52 weeks ( $P = 0.16$ ). Like in our study, the effect of cholecalciferol on PTH was driven by participants with higher PTH and worse renal function.

Shroff *et al.* [15] showed in children with CKD that treatment with ergocalciferol can postpone the development of SHPT. Like in that study, we showed that cholecalciferol counteracts the development of SHPT in CKD. To reach an effect, especially as eGFR decreases below 30 mL/min/1.73 m<sup>2</sup> it seems necessary to use a dose that increases the 25(OH)D concentration above 75 nmol/L.

In the treatment arm there was a marked increase in 1,25(OH)D, but ionized calcium remained constant and there were no observations of hypercalcaemia. The FE-Pi is the fraction of filtered phosphate that is actually excreted in the urine. It increases as renal function declines to counteract hyperphosphataemia. Both PTH and FGF23 down-regulate the sodium-phosphate cotransporters NaPi2a and 2c in the renal tubules. PTH and FGF23 are highly and independently correlated in cross-sectional studies. Higher 1,25(OH)D is expected to increase FGF23, but we did not detect any difference in change in FGF23 between groups.

Fatigue is a common symptom in CKD, and vitamin D deficiency has been proposed as a treatable cause of fatigue in different patient groups. Using a validated questionnaire of self-estimated fatigue we could not detect any effect of high-dose cholecalciferol on fatigue in our study.

Musculoskeletal function may be impaired in situations with vitamin D deficiency. It has mostly been described as proximal muscle weakness in the elderly. However, we could not detect any effect on peripheral muscle strength measured as hand grip strength in the present study.

The dosing of cholecalciferol drops 8000 IU daily for 12 weeks seems safe and well tolerated in CKD patients with a 25(OH)D level that could be expected in most CKD patients not receiving vitamin D supplementation. There were no cases of significant hypercalcaemia, and mean difference in eGFR showed no difference between groups. The AEs were judged to be unrelated to the treatment even in the case with ureteral obstruction due to a known calculus.

The strengths of this study are that it was carefully performed as a randomized double-blind placebo-controlled clinical study with adequate power on representative CKD patients. We analysed several parameters of mineral metabolism, such as 1,25(OH)D and FGF23, which may help in mechanistically interpreting the dynamics of renal SHPT.

The limitations are that it is only a 3-month study of a disease process that develops and continues during years and

decades. The randomization led to a higher proportion of males in the placebo group. Efficacy parameters were mostly biochemical and it is unknown how they translate into a clinically significant outcome. The vast majority of subjects were Caucasian, which limits the generalizability of the findings. Analyses of urinary calcium would also have been important in assessing the mechanisms and safety of the treatment. Also, no dietary data were collected.

In conclusion, high-dose cholecalciferol (8000 IU/day) alleviates the development of SHPT in CKD as it attains complete 25(OH)D sufficiency and induces a substantial increase in 1,25(OH)D, thereby avoiding the tendency to hypocalcaemia that otherwise develops. High-dose cholecalciferol (8000 IU/day) does not cause hypercalcaemia or accelerated loss of GFR. Furthermore, high-dose cholecalciferol (8000 IU/day) does not induce an increase in phosphate or FGF23, yet, on the other hand, does not improve fatigue or hand grip strength.

Our data support the guidelines that 25(OH)D insufficiency should be addressed before calcium-based phosphate binders or active vitamin D analogues are introduced in CKD patients with SHPT. We also suggest that the 25(OH)D sufficiency should be reached early in CKD and maintained, to slow the development of SHPT.

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## CONFLICT OF INTEREST STATEMENT

This study was investigator-initiated and sponsored by Renapharma AB, Sweden, which provided the study medication and monitored the study.

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