Long-Term Cholecalciferol Administration in Hemodialysis Patients: A Single-Center Randomized Pilot Study

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Statistical Analysis C
Data Interpretation D
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Background: Data on the potent pleiotropic extraskeletal effects of vitamin D have renewed interest in its use in selected populations, including patients with chronic kidney disease, but the available data are still insufficient to make recommendations. This study assessed the long-term effect of small cholecalciferol doses on serum vitamin D, parathormone (PTH), and bone mineral density (BMD) in hemodialysis patients.

Material/Methods: Nineteen patients with serum 25(OH)D <20 ng/mL were randomized into cholecalciferol (2000 IU 3×/week) and no-treatment groups, then observed for 1 year. Patients with hypercalcemia, hyperphosphatemia, and receiving vitamin D/calcimimetics were excluded. Serum 25(OH)D, $1,25(OH)_2D$, PTH, and alkaline phosphatase activity were examined every 2 months and BMD was measured before and after the study.

Results: We observed normalization of serum 25(OH)D with an increase in medians from 11.3 to 44.9 ng/mL (P=0.02) in the cholecalciferol group and no change in the controls (P<0.001). Simultaneously, median serum $1,25(OH)_2D$ increased from 18.2 to 43.1 pmol/L (P=0.02) in the cholecalciferol group and from 10.6 to 21.2 pmol/L (P=0.02) in controls (P=0.013). The treatment was associated with a small increase in serum calcium, but serum phosphate, PTH, alkaline phosphatase, and BMD remained unchanged in both groups.

Conclusions: Oral cholecalciferol at a dose of 2000 IU/3×/week is an effective and safe way to treat vitamin D deficiency in hemodialysis patients, leading to a significant increase in serum $1,25(OH)_2D$. However, it was insufficient to suppress the activity of parathyroid glands or to significantly change BMD.

MeSH Keywords: Calcitriol • Cholecalciferol • Dialysis • Renal Insufficiency, Chronic • Vitamin D Deficiency

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Background

Vitamin D insufficiency or deficiency is very common in patients with chronic kidney disease (CKD) [1–3]. In a recent Polish cross-sectional study, serum 25(OH)D concentrations of <30 ng/mL were observed in 78% and 96% of the population of dialyzed patients in the summer and winter, respectively [4]. A common belief held at the end of the 1980s was that 1α-hydroxylation of 25(OH)D occurs only within kidneys, and therefore administration of vitamin D supplements at stage 5 CKD was considered useless. However, in the next decades it was found that due to widespread distribution of 1α-hydroxylase (CYP27B1) and vitamin D receptor (VDR), the process occurs in most tissues and cells, and the locally produced active hormone $1,25(OH)_2D$ (calcitriol) exerts a number of biological effects in a para- or autocrine manner [5–8]. These pleiotropic effects of calcitriol may explain the described relationship between vitamin D deficiency and mortality rates [9,10]. In this situation, particularly in light of the cardioprotective properties of calcitriol, supplementation of vitamin D deficiency in advanced CKD patients becomes particularly important. However, despite numerous publications on the metabolism of vitamin D, available data are still insufficient to permit formulation of clear guidelines for the monitoring of vitamin D supply and supplementing its deficits in patients undergoing hemodialysis due to end-stage renal disease [11]. Until recently, the reports on vitamin D supplementation in this patient population were limited to single-armed, unblinded, uncontrolled, or historical-control studies [12–21]; the results of the first randomized studies became available only in the last 2 years [22–25]. The studies demonstrated the efficacy of cholecalciferol supplementation; however, 3 of these studies had relatively short observation periods of 6 to 15 weeks; moreover, some of the study patients in all studies were concurrently treated with medications affecting vitamin D metabolism.

This small, randomized pilot study aimed to assess the long-term impact of small doses of cholecalciferol given 3 times weekly on serum 25(OH)D and $1,25(OH)_2D$ concentrations in patients with vitamin D deficiency undergoing chronic hemodialysis. The secondary endpoints consisted of changes in serum parathormone (PTH), calcium, and phosphate serum concentrations during the therapy and the effect of treatment on bone mineral density (BMD).

Material and Methods

The study was carried out as an interventional, prospective, randomized open-label trial. Nineteen patients, including 10 females and 9 males, out of the total number of 78 patients undergoing hemodialysis at the Department of Nephrology, Dialysis and Internal Diseases of the Medical University of Warsaw were enrolled into the study. The inclusion criteria were: serum 25(OH)D concentration of <20 ng/mL, hemodialysis treatment duration of at least 3 months, age of >18 years, and written consent to participate in the study. The exclusion criteria were: total serum calcium concentrations of >2.55 mmol/L, serum phosphate of >2.08 mmol/L, administration of any vitamin D supplements, calcitriol, its analogs, or calcimimetics within last 6 months, and serious overall condition or cachexia. The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw.

Patients were randomized into 2 groups: Group A – patients receiving cholecalciferol and group B – the control group, which did not received vitamin D. Block randomization was performed using sealed envelopes. All patients entered the 1-year observation period at the same time. Cholecalciferol (Vigantoletten 1000; Merck), was administered at doses of 2000 IU p.o., 3 times a week, during the hemodialysis, under the supervision of medical staff. The dosage remained unchanged throughout the study. At the same time, previous treatment was continued in all patients. Hemodialyses were performed using single-use polysulphonate or polyamide dialyzers and bicarbonate-based dialysis fluid. The duration of the procedures ranged from 3.5 to 5.5 h., with dialysis dosage being modified monthly so that Kt/V for urea was ≥1.2.

Vitamin D deficiency was defined according to recent Endocrine Society Clinical Practice Guidelines as serum 25(OH)D concentration of <20 ng/mL, and vitamin D insufficiency as a serum 25(OH)D concentration of 21–29 ng/mL [26]. Besides routine monthly investigations, serum levels of intact PTH (iPTH), 25(OH)D and $1,25(OH)_2D$ were determined every 2 months. Blood for the analyses was collected from fasting patients before the dialysis; after centrifugation of samples, serum was immediately frozen at ca. -70°C until used for determinations. In addition, bone density scans were performed before and after the 12-month observation period.

Serum concentrations of iPTH and 25(OH)D were measured using highly sensitive electrochemiluminescence immunoassays on an Elecsys 2010 automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The reference manufacturer's data were 15–65 pg/mL for iPTH and 11.1–42.9 ng/mL (27.7–107 nmol/L) for 25(OH)D. Serum $1,25(OH)_2D$ was measured with the use of complete, manual assay system cat. no. AC-62F1 (Immunodiagnostic Systems, Frankfurt, Germany) according to the manufacturer's protocol. The system utilizes immuno-extraction of $1,25(OH)_2D$ from serum followed by enzyme immunoassay and is more specific towards $1,25(OH)_2D_3$ (100%) than towards $1,25(OH)_2D_2$ (39%). The reference manufacturer's data were 39–193 pmol/L (n=120) for healthy adults and <6–22 pmol/L (n=24) for end-stage renal disease patients. Fluoroscan Ascent FL microplate fluorometer and luminometer (Labsystems,

Table 1. Characteristics of study patients: median (range).

Parameter	Group A		Group B		P
Gender (F/M)	5/3		4/7		
Age (years)	63	(52–79)	46	(29–79)	NS
Duration of dialysis treatment (months)	53	(3–131)	50	(16–265)	NS
BMI (kg/m^2)	22	(18–29)	23	(18–36)	NS
25(OH)D (ng/mL)	11	(6.6–19)	15	(7.9–18)	NS
1,25(OH)$_2$D (pg/mL)	18	(6.2–48)	11	(7.4–24)	NS
iPTH (pg/mL)	308	(129–693)	321	(128–1443)	NS
Calcium (mmol/L)	2.2	(1.9–2.4)	2.1	(1.5–2.3)	NS
Phosphate (mmol/L)	1.7	(1.0–1.9)	1.3	(0.99–1.9)	NS
Calcium-phosphate product (mmol^2/L^2)	3.5	(2.2–4.4)	2.8	(2.0–3.9)	NS
CRP (mg/L)	6.6	(0.80–49)	5.2	(2.1–48)	NS
Albumin (g/dL)	4.1	(3.7–4.3)	4.1	(3.3–4.6)	NS

Helsinki, Finland) was used to measure the intensity of emitted light and Ascent Software v. 2.6 (Labsystems, Helsinki, Finland) was used for the development of standard curves, curve-fitting, and concentration calculations. Serum concentrations of total calcium, phosphates, albumins, bicarbonate, high-sensitive C-reactive protein (hcCRP), and alkaline phosphatase activity were measured using a COBAS INTEGRA automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Bone mineral density (BMD) within posteroanterior lumbar spine level L_1–L_4, proximal femur and distal forearm were assessed by dual-energy X-ray absorptiometry (DEXA) with the use of a Discovery Densitometer (Hologic, Waltham, USA), using the manufacturer's recommended standard procedures. The same investigator performed all measurements.

Statistical analysis

The acquired data were collected in Microsoft Excel 2010 spreadsheets. The data were subjected to statistical analysis using SAS 9.2 software. Due to the limited study population the second-stage comparisons between groups A and B were conducted using non-parametric Mann-Whitney's U test and Friedman's ANOVA test. Statistical significance level was set at $P<0.05$ for all analyses performed as a part of the study. Post hoc power analyses were carried out for explained parameters 25(OH)D and 1,25(OH)$_2$D in groups A and B with assumed $\alpha=0.05$, means in groups equal 43.5 and 19.3 for 25(OH)D and 41.6 and 25 for 1,25(OH)$_2$D, and groups sizes 7 and 8, respectively. Results are: for the first variable 25(OH)D=100%, for the second variable 1,25(OH)$_2$D=93%.

Results

There were no significant differences between study groups in terms of basic clinical and biochemical data (Table 1), and bone density data. Changes in the serum levels of both vitamin D metabolites over the 1-year follow-up period are shown in Table 2 and Figure 1. In group A, a significant increase in 25(OH)D levels was observed as early as after 2 months, with maximum values (a 4-fold increase in the median) being reached after 4 months and maintained at similar level through the end of the follow-up period. Normalization of 25(OH)D levels was observed after 1 year of treatment in all patients in this group. In group B, a moderate increase in 25(OH)D levels was observed within the first months (a maximum increase from 14.9 to 24.5 ng/mL, $P=0.017$, after 4 months); however, the levels later dropped to values similar to the baseline. Significant differences between groups were maintained throughout the study.

The baseline serum 1,25(OH)$_2$D concentrations in group A were higher than in group B (median of 18.5 *vs.* 10.6 pmol/L); however, the difference was not statistically significant. After cholecalciferol administration a significant, gradual increase in 1,25(OH)$_2$D was observed from 18.5 at baseline to 43.1 pmol/L at the end of the study ($P=0.02$). After 1 year, a normalization of serum 1,25(OH)$_2$D was observed in 9 study subjects. In group B, a significant increase in 1,25(OH)$_2$D concentrations was also observed ($P=0.02$); however, it was significantly smaller and the differences between both groups were statistically significant at all time points except month 6.

Table 2. Changes in serum 25(OH)D and 1,25(OH)$_2$D levels over the follow-up period in the study groups: median (range).

Months of treatment	25(OH)D (ng/mL)						1,25(OH)$_2$D (pmol/L)					
	Group A		Group B		P		Group A		Group B		P	
Before*	11.3	(6.63–19.3)	14.9	(7.91–17.8)	NS		18.2	(6.23–47.6)	10.6	(7.40–23.7)	NS	
2	37.5	(30.5–42.7)	20.8	(7.18–35.4)	0.005		35.4	(27.4–87.2)	25.1	(16.7–41.4)	0.028	
4	48.0	(30.2–64.9)	24.5	(10.5–48.8)	0.007		38.5	(25.0–58.7)	21.1	(14.8–55.5)	0.018	
6	44.4	(32.5–65.2)	20.4	(7.00–36.2)	0.002		39.0	(19.1–48.8)	20.5	(17.0–46.7)	0.064	
8	43.5	(31.3–62.1)	16.3	(8.35–27.2)	0.002		41.5	(33.2–43.4)	24.2	(20.1–48.1)	0.030	
10	43.7	(29.7–56.2)	18.3	(8.72–26.6)	0.001		44.8	(29.4–52.4)	21.9	(17.7–49.3)	0.013	
12	44.9	(31.0–59.0)	18.0	(7.23–26.4)	0.001		43.1	(36.8–54.6)	21.2	(16.4–51.9)	0.013	

* Concentrations determined 2 months before the start of the treatment.
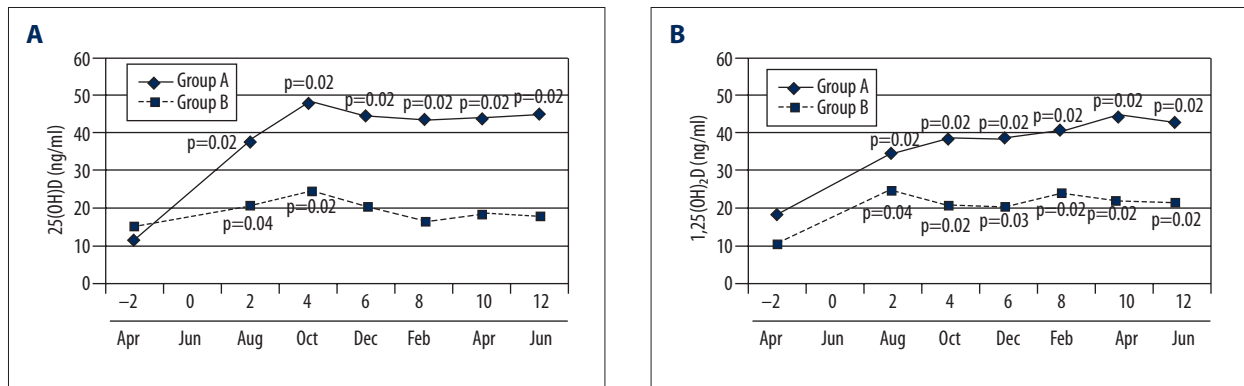

Figure 1. Changes in the medians of serum 25(OH)D (**A**) and 1,25(OH)$_2$D (**B**) concentrations over the follow-up period in both study groups. *P* – level of significance compared to the baseline examination.
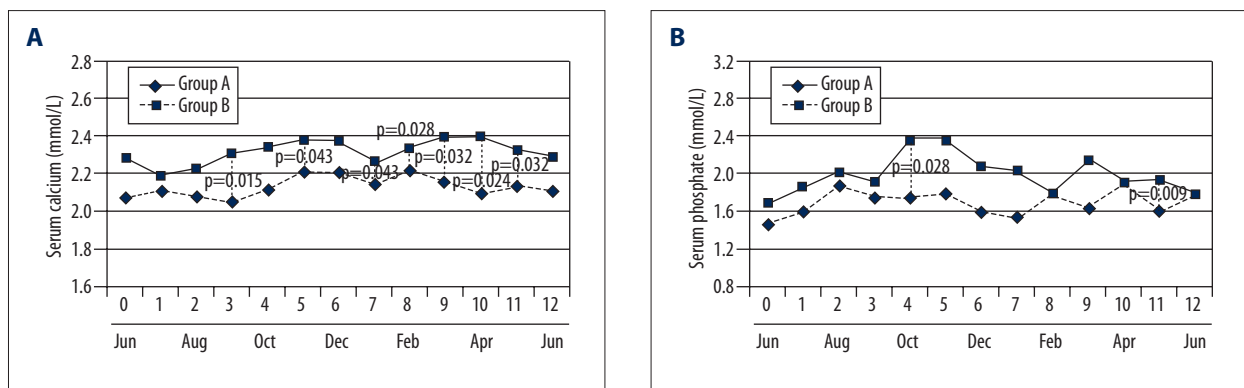

Figure 2. Changes in the medians of serum total calcium (**A**) and phosphate (**B**) concentrations over the follow-up period in both study groups. *P* – level of significance for the comparison between the groups.

No significant changes were observed in serum iPTH concentrations or alkaline phosphatase activity, but a slight increase in iPTH concentration medians was observed in both groups. Pre-treatment serum total calcium and phosphate concentrations (Figure 2) were slightly higher in group A (NS). The

differences were maintained throughout the study, periodically reaching the statistical significance level. During the observation period, the highest recorded serum calcium concentrations were 2.66 mmol/L in group A and 2.44 mmol/L in group B. Occasional episodes of slight increases of serum calcium to
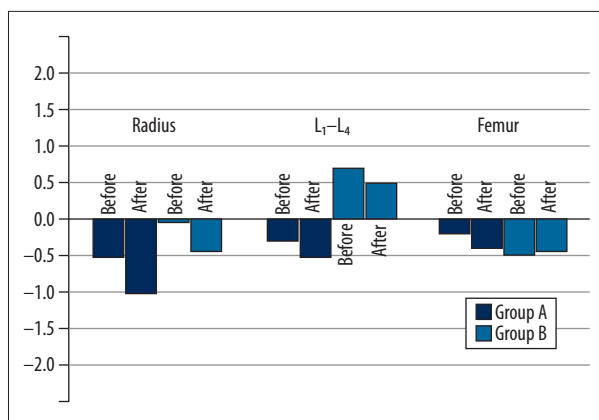
Figure 3. Z-score medians in 3 study areas: distal radius, L_1–L_4 and proximal femur on both study groups, before and after treatment.

the level between 2.51 and 2.66 mmol were observed in 3 patients receiving cholecalciferol; however, these increases were transient and did not require vitamin D dose adjustments.

The treatment had no significant effect on the bone density parameters. Both the absolute BMD values and the Z-scores (Figure 3) and T-scores were similar before and after the follow-up period in spinal segment L_1–L_4 as well as within the proximal femur, and similar decreases in the respective values were observed at distal forearm.

Discussion

Auto- and paracrine pleiotropic effects of calcitriol and the substrate dependence of its tissue production provide a significant basis for supplementation and maintenance of normal 25(OH)D levels in patients undergoing hemodialysis due to CKD. In clinical practice, this problem has been exceptionally neglected. Due to the lack of sufficient evidence, the group of experts developing the KDIGO 2009 guidelines provided no precise rules for vitamin D supplementation, suggesting only that recommendations valid for the general population should be followed [11]. As a result, deficiency of 25(OH)D is maintained in most patients undergoing dialysis treatment, usually unrecognized. The clinical aftermath of this deficiency may be significant, particularly in patients who cannot, for a variety of reasons, receive active vitamin D metabolites.

The results of our pilot study, as well as the results of other recently published randomized studies suggest the efficacy of cholecalciferol in supplementation of 25(OH)D deficiency [22–25]. However, only 1 of them, conducted by Delanaye et al., had a longer follow-up similar to our observation period [25]. In their study, 25 000 IU of cholecalciferol was given every 2 weeks to 16 patients with baseline serum 25(OH)D

concentrations of <30 ng/mL, which after 12 months increased to a normal range in 75% of subjects. Due to the incomplete efficacy of supplementation, the authors concluded that additional studies using a doubled dosage are recommended. However, as shown by our study, even a 4 times smaller dose of as little as 6000 IU/week may prove efficacious when administered in a more physiological fashion. In the group receiving cholecalciferol, normalization of serum 25(OH)D levels was observed in 100% of subjects, with a significant, 4-fold increase in the medians and means of these concentrations achieved after 2 months of treatment and maintained at a constant level throughout the whole year. Similar to the study by Delanaye et al., serum 25(OH)D concentrations in the control group increased after commencing the treatment in summer months to reach the maximum in September and then gradually returned to baseline over the remaining months of the observation.

When analyzing all 25(OH)D measurements, a note should be made of the distribution of maximum values, observed in both groups after 4 months of study in September, after the summer season (medians of 44.0 and 24.5 ng/mL, respectively). The lowest values were observed in March (43.5 and 16.3 ng/mL, respectively). This was in line with the assessment of the seasonality of 25(OH)D concentration changes as determined by Drechsler for our climate zone [9]. Despite the seasonal oscillations of the serum 25(OH)D concentrations, in the cholecalciferol group the mean values were maintained at a significant, approximately doubled level (when comparing to the controls) throughout the study. Similar results were presented recently by Descombes et al. in their observational study [27]. The authors administered the same dose of cholecalciferol (2000 IU post hemodialysis) for the first month, then the dose was subsequently adapted every 2 months to achieve 25(OH)D levels within the target range of 30 to 60 ng/mL. At the same baseline serum 25(OH)D concentrations and a mean weekly dosage of cholecalciferol 6000±4000 IU (albeit oscillating within the range of 0 to 12 000 IU), they observed similar mean concentrations of 25(OH)D throughout the treatment. However, in contrast to our study, 14% of subjects had vitamin D insufficiency after 12 months of its supplementation [27]. Therefore, it is difficult, at least for the time being, to consider the dose-response approach proposed by the authors to be justified, especially since the incidence of the episodes of hypercalcemia in the reported study was similar to that observed in our study material.

Of the available data from randomized studies, the cholecalciferol dose most similar to that used in our study was used by Armas et al. (11 333 IU/week), who achieved a significant increase in the median 25(OH)D concentration (by 23.6 ng/mL) over 15 weeks in 20 patients with no changes in the placebo group [22]. However, the authors did not mention whether the

treatment was efficient in all patients; in addition, only 79% of subjects had serum 25(OH)D concentrations of <20 ng/mL, and normal levels were observed in 7% of subjects. Another important fact to be kept in mind when interpreting that study is that only 31% of the studied patients were Caucasians. Marckmann et al., using significantly higher doses of cholecalciferol (40 000 IU/week) achieved control of vitamin D deficiency within 8 weeks in all 13 hemodialyzed patients, with a 6-fold increase in 25(OH)D concentration compared to the placebo group [23]. This, however, was a very short observation period; in addition, the effects of a treatment given prior to the study cannot be excluded since it included patients on a supplementary intake of a total of <10 000 IU of ergocalciferol or cholecalciferol within the last 3 months. The highest doses of cholecalciferol were used by Wasse et al. [24] who administered 200 000 IU (*vs.* placebo) once a week for 3 weeks, followed by 3 weeks of observation. However, despite such giant doses, control of the 25(OH)D levels could not be achieved in 10% of subjects, and the mean increase in 25(OH)D levels was comparable to that obtained in our study material in study month 4. Again, the limitation of this study is that some of the subjects received cholecalciferol (up to 2000 IU per day) before the observation period.

Reports published to date with regard to the impact of cholecalciferol supplementation on the serum $1,25(OH)_2D$ concentration are inconsistent. In some studies, both observational [17,18,20] and randomized [22,24], a significant increase of its values was reported, while according to other authors the values remained essentially unchanged [23,27], even despite high doses being used [23]. However, in the study by Armas et al. [22], despite a significant increase in serum $1,25(OH)_2D$ concentrations, compared to that observed in our patients, they remained below the normal reference range in all but 1 subject. The fact that one-half of our cholecalciferol-treated group achieved normalization of serum calcitriol levels might be due to the longer study period because as we observed, the process is slower than that of the increase of serum 25(OH)D. The highest increase in mean serum calcitriol concentration was observed by Wasse et al. (from 29.3 to 69.8 pmol/l), probably as the result of the megadoses of cholecalciferol used in their study [24]. Unfortunately, the authors did not report on the number of patients who achieved the normalization of serum $1,25(OH)_2D$ levels. However, even

such increase as that achieved by Wasse et al. does not afford the most desirable effect – the reduction in PTH levels. The lack of effect of 25(OH)D supplementation on PTH concentration in hemodialyzed patients was also observed by other authors [15,16,21–23,25,27]; no such effect was achieved in our study. Suppression of parathyroid activity due to vitamin D supplementation has been reported to date only in observational studies [17–19]. The treatment has no significant effect on the bone density parameters, but it was a pilot study with a small sample size and relatively short follow-up interval.

In contrast to serum 25(OH)D, no seasonal variability in $1,25(OH)_2D$ concentrations were observed in either study group. Thus, on the one hand, vitamin D supplementation causes a significant increase in serum calcitriol levels, while on the other hand, serum 25(OH)D seasonal variations (related to UV exposure) have no effect of this type. Most probably these variations are either too small or vitamin D administered orally has different activity or biological availability than the endogenous form produced in the skin.

The drug was well tolerated, with no other adverse effects being observed. Occasional episodes of slight hypercalcemia were noted in 3 patients receiving cholecalciferol; however, these increases were transient and did not require vitamin D dose adjustments.

Conclusions

The results of our study demonstrate that administration of oral cholecalciferol 3 times a week in the total dose of 6000 IU/week is a safe and fully efficient method to supplement 25(OH)D deficiencies. A significant increase in serum concentrations of the active form of vitamin D highlights the role of extrarenal 1α-hydroxylation processes. However, despite the last effect, no suppression of parathyroid activity could be achieved, and no effect in BMD was observed.

Conflict of interest

None declared.

References:

1. Porter A, Gilmartin C, Srisakul U et al: Prevalence of 25-OH vitamin D deficiency in a population of hemodialysis patients and efficacy of an oral ergocalciferol supplementation regimen. Am J Nephrol, 2013; 37: 568–74

2. Bhan I, Burnett-Bowie SA, Ye J et al: Clinical measures identify vitamin D deficiency in dialysis. Clin J Am Soc Nephrol, 2010; 5: 460–67

3. Anand S, Kaysen GA, Chertow GM et al: Vitamin D deficiency, self-reported physical activity and health-related quality of life: the Comprehensive Dialysis Study. Nephrol Dial Transplant, 2011; 26: 3683–88

4. Matuszkiewicz-Rowińska J, Mieczkowski M, Żebrowski P et al: Vitamin D seasonal variations in dialysis patients: A prospective multicenter study. J Am Soc Nephrol, 2012; 23: 317A

5. Bendik I, Friedel A, Roos FF et al: Vitamin D: a critical and essential micronutrient for human health. Front Physiol, 2014; 5: 248–51

6. Dusso A, Brown A, Slatopolsky E: Extrarenal production of calcitriol. Semin Nephrol. 1994; 14: 144–55

7. Adams JS, Hewison M: Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Arch Biochem Biophys, 2012; 523: 95–102

8. Adams JS, Hewison M: Update in vitamin D. J Clin Endocrinol Metab, 2010; 95: 471–78

9. Drechsler C, Pilz S, Obermayer-Pietsch B et al: Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J, 2010; 31: 2253–61

10. Anand S, Chertow GM, Johansen KL et al: Vitamin D deficiency and mortality in patients receiving dialysis: the comprehensive dialysis study. J Ren Nutr, 2013; 23: 422–27

11. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Chronic Kidney Disease-Mineral and Bone Disorders. Kidney Int, 2009; 76: (Suppl.113): S1–S130

12. Bagnis C, Dutto F, Gabella P et al: Biochemical and hormonal short term effects of 25 hydroxyvitamin D3 in patients on continuous peritoneal dialysis. Ital J Min Electrol Metabol, 1998; 12: 73–76

13. Shah N, Bernardini J, Piraino B: Prevalance and correction of 25(OH) vitamin D deficiency in peritoneal dialysis patients. Perit Dial Int, 2005; 25: 362–66

14. Saab G, Young DO, Gincherman Y et al: Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. Nephron Clin Pract, 2007; 105: 132–38

15. Blair D, Byham-Gray L, Lewis E et al: Prevalence of vitamin D [25(OH)D] deficiency and effects of supplementation with ergocalciferol (vitamin D2) in stage 5 chronic kidney disease patients. J Ren Nutr, 2008; 18: 375–82

16. Tokmak F, Quack I, Schieren G et al: High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients. Nephrol Dial Transplant, 2008; 23: 4016–20

17. Jean G, Terrat JC, Vanel T et al: Evidence for persistent vitamin D 1-alpha-hydroxylation in hemodialysis patients: evolution of serum 1,25-dihydroxy-cholecalciferol after 6 month of 25-hydroxycholecalciferol treatment. Nephron Clin Pract, 2008; 110: c58–65

18. Jean G, Souberbielle JC, Chazot C: Monthly cholecalciferol administration in haemodialysis patients: A simple and efficient strategy for vitamin D supplementation. Nephrol Dial Transplant, 2009; 24: 3799–805

19. Matias PJ, Jorge C, Ferreira C et al: Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimmension parameters. Clin J Am Soc Nephrol, 2010; 5: 905–11

20. Stubbs JR, Idiculla A, Slusser J et al: Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. J Am Soc Nephrol, 2010; 21: 353–61

21. Jakopin E, Pecovnik Balon B, Ekart R, Gorenjak M: High-dose cholecalciferol supplementation for vitamin D deficiency in haemodialysis patients. J Int Med Res, 2011; 39: 1099–106

22. Armas LAG, Andukuri R, Barger-Lux J: 25-hydroxyvitamin D response to cholecalciferol supplementation in hemodialysis. Clin J Am Soc Nephrol, 2012; 7: 1428–34

23. Marckmann P, Agerskov H, Thineshkumar S et al: Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. Nephrol Dial Transplant, 2012; 27: 3523–31

24. Wasse H, Huang R, Long Q et al: Efficacy and safety of a short course of very-high-dose cholecalciferol in hemodialysis. Am J Clin Nutr, 2012; 95: 522–28

25. Delanaye P, Weekers L, Warking X et al: Cholecalciferol in haemodialysis patients: a randomized, double-blind, proof-of-concept and safety study. Nephrol Dial Transplant, 2013; 28: 1779–86

26. Holick MF, Binkley NC, Bischoff-Ferrari HA et al: Evaluation, treatment, and prevention of Vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2011; 96: 1911–30

27. Descombes E, Fellay B, Hemett OM et al: Oral postdialysis cholecalciferol supplementation in patients on maintenance hemodialysis: A dose-response approach. Int J Nephrol, 2014; 2014: 597429