



ORIGINAL ARTICLE

Kinetics of serum 25-hydroxyvitamin D in haemodialysis patients treated with monthly oral cholecalciferol

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Abstract

Background: We previously reported that oral cholecalciferol (CCF) (100 000 IU) taken monthly by haemodialysis patients is effective in accomplishing serum 25-hydroxyvitamin D (25-D) levels >75 nmol/L in >80% of cases. We aimed to study the weekly kinetics of serum 25-D in HD patients receiving oral CCF during the first 6 months of HD.

Methods: All new HD patients at our dialysis centre during the autumn months of 2011–2014 were offered entry into the study if their baseline serum 25-D level was <75 nmol/L. Oral CCF (100 000 IU) was administered monthly during an HD session. The kinetic study included weekly serum sampling for 16 weeks, and every other week thereafter. Biological and treatment data were compared between baseline and 6 months after starting HD and CCF. Patients who required calcimimetics, calcitriol and analogues were excluded from the study.

Results: The data from 21 patients were available for analysis. These patients had a mean age of 72.2 ± 12 years, 33% were women, 28.5% had diabetes, and 33% had a central venous catheter. Serum 25-D levels increased from 26.8 ± 13 nmol/L at baseline to 102.3 ± 24 nmol/L after 6 months ($P < 0.001$). Serum calcium and albumin levels both increased during the study period. Serum phosphate level did not change significantly, and serum parathyroid hormone (PTH) level decreased. Serum 25-D level reached a plateau after 11 weeks of oral CCF. Two patients (9.5%) with low baseline 25-D values, had a stable 25-D level <75 nmol/L after 6 months. No peak effect was observed 48 h after the first dose of CCF.

Conclusion: The oral administration of 100 000 IU CCF once a month maintains a normal serum level in 90% of HD patients. Serum 25-D level reaches a plateau level after 12 weeks of therapy.

Key words: 25-hydroxyvitamin D, calcium, haemodialysis, serum kinetics, vitamin D

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Introduction

Vitamin D deficiency or insufficiency is present in >80% of dialysis patients [1–3]. In one French haemodialysis (HD) cohort, and one cohort from the USA, vitamin D deficiency was associated with poor outcomes mostly in patients not receiving calcitriol or analogues [4, 5]. Some observational studies have reported that vitamin D supplementation restores serum levels of both 25-hydroxyvitamin D (25-D) and 1,25-dihydroxyvitamin D (1,25-D) to normal levels. These authors also observed lower parathyroid hormone (PTH) levels, fewer side effects and a reduction of cost as compared with calcitriol or analogues or calcimimetics [6].

In 2009, the *Kidney Disease Improving Global Outcomes* group recommended vitamin D supplementation in HD patients with insufficient serum 25-D levels [7]. The optimal regimen for vitamin D supplementation in HD patients is not known. In 2003, the *Kidney Disease Outcomes Quality Improvement (KDOQI)* group recommended the use of oral ergocalciferol 50 000 IU weekly or monthly depending on the baseline levels of 25-D. They suggested measuring serum 25-D levels after 6 months of vitamin D supplementation [8]. In some studies employing this strategy, both ergocalciferol and cholecalciferol (CCF) failed to restore serum 25-D level to the recommended level in a majority of studied patients [9, 10]. We previously reported that oral monthly CCF 100 000 IU in HD patients results in serum 25-D level >75 nmol/L in >80% of patients after 3 months of therapy [11]. The weekly kinetic of serum 25-D in HD patients receiving monthly CCF is not known. The aim of this study was to determine the weekly kinetics of serum 25-D in new HD patients treated with monthly oral CCF and the optimal time for 25-D sampling to measure success with this therapy.

Methods

From January 2011 to January 2014, during the autumn months, all incident patients starting chronic HD therapy at our centre were offered entry into the study if their baseline serum 25-D was <75 nmol/L. Patients treated with calcitriol or analogues, calcimimetics or bisphosphonate, those with hypercalcaemia (total serum calcium ≥ 2.55 mmol/L), severe hyperphosphataemia (serum phosphate ≥ 2 mmol/L), or severe hyperparathyroidism (serum PTH ≥ 600 pg/mL), and those with history of parathyroidectomy (PTX) were excluded from the study. The study protocol was conducted according to national standards of human experimentation and the principles of the Declaration of Helsinki. Individual informed consent was obtained.

The 25-D level analyses were performed using Architect auto-mat 25-D assays (Abbott® Laboratories, Abbott Park, IL, USA). This is a chemiluminescent microparticle immunoassay with coefficients of variation <6% (13.6 ng/mL) and 2.2% (78.1 ng/mL). The functional sensitivity of the assay is 12.5 nmol/L. The accuracy profile of the assay demonstrated that the method is valid for serum levels of 25-D between 34 and 195.2 nmol/L. The 25-D assays were performed by NOVESCIA® Medical Laboratory of Grand Vallon, Lyon, France.

Those patients found to be vitamin D insufficient or deficient (<75 nmol/L), received one oral dose of CCF 100 000 IU (UVE-DOSE®, Crinex®, France) each month during a midweek dialysis session. The nursing team ensured that the CCF dose was properly taken directly through the vial. Kinetic study requires weekly serum samples for 16 weeks followed by serum samples every other week for another 8 weeks. Sampling was performed prior to the mid-week dialysis session. One serum 25-D sample from each patient was obtained 48 h after the first dose of CCF.

Patients were dialysed thrice weekly for 4 h using conventional HD dialysis. The standard dialysate calcium concentration was 1.5 mmol/L. In those patients with low PTH level (<100 pg/mL), the dialysate calcium concentration was adjusted to 1.25 mmol/L. If the serum PTH was high (>500 pg/mL), the dialysate calcium was adjusted to 1.75 mmol/L. No changes were made in the phosphate binder therapy during the study.

Statistical analysis

The paired Wilcoxon signed-rank test was used to compare the values at baseline with those following 6 months of treatment with CCF. Repeated measures analysis of variance (ANOVA) was utilized to identify a plateau level. Data are reported as the mean \pm standard deviation. A P-value <0.05 was considered to be statistically significant. Statistical analyses were performed using the MedCalc® software (V.9.3.1.0., F. Ostend, Belgium).

Results

Twenty-five patients were initially enrolled in the study. Three patients died during the study period and one patient moved to another dialysis centre. Twenty-one patients completed the study. The mean age was 72.2 ± 12 years, 33% were of female gender, 28.5% had diabetes, and 33% had a central venous catheter. The data from baseline and after 6 months of treatment are displayed in Table 1. Fifteen of 21 (71.4%) patients were treated with CCF in the 6 months period prior to the study with a mean monthly dose of 35 000 IU. Calcimimetics and active vitamin D, have not been initiated during the entire observation period.

Mean serum calcium and albumin levels increased during the study period, whereas serum phosphate level was unchanged and serum PTH level decreased. Mean baseline serum 25-D values increased from 26.8 ± 13 nmol/L at baseline to 102.3 ± 24 nmol/L after 6 months of CCF treatment (+350%, Figure 1, $P < 0.001$). Two of 21 (9.5%) patients had serum 25-D <75 nmol/L despite CCT treatment; their baseline 25-D level was <20 nmol/L, they had diabetes and they were clinically and biologically malnourished and were dialysed using a central venous catheter. A serum 25-D level >180 nmol/L was not noted in any patient. Oral CCF treatment was well tolerated by the patients. The kinetics of serum 25-D are demonstrated in Figure 2 (serum 25-D evolution) and in Figure 3 (expressed as percentage of baseline). Serum 25-D level reached a plateau after 11 weeks (+280% above baseline) with no subsequent significant change thereafter (ANOVA). No peak effect was observed

Table 1. Biological and treatment data at baseline and after 6 months of CCF treatment

	Baseline	6 months
25-D, nmol/L	26.8 \pm 13	102.3 \pm 24**
25-D <75 nmol/L, n	21/21	2/21**
Calcaemia, mmol/L	2.15 \pm 0.2	2.22 \pm 0.15*
Phosphataemia, mmol/L	1.6 \pm 0.4	1.5 \pm 0.4
PTH, pg/mL	261 \pm 200	212 \pm 170*
Albumin, g/L	32.5 \pm 5	39 \pm 5*
Dialysate calcium, mmol/L	1.51 \pm 0.3	1.53 \pm 0.3
Oral calcium % (g/day)	47 (1.2 \pm 1.6)	52 (1.3 \pm 1.5)
Sevelamer % (g/day)	34 (2.5 \pm 3)	34 (2.5 \pm 3)
nPCR, g/kg/day	1 \pm 0.1	1.1 \pm 0.1
Kt/V Daugirdas 2	1.55 \pm 0.3	1.62 \pm 0.3

* $P < 0.05$; ** $P < 0.001$.

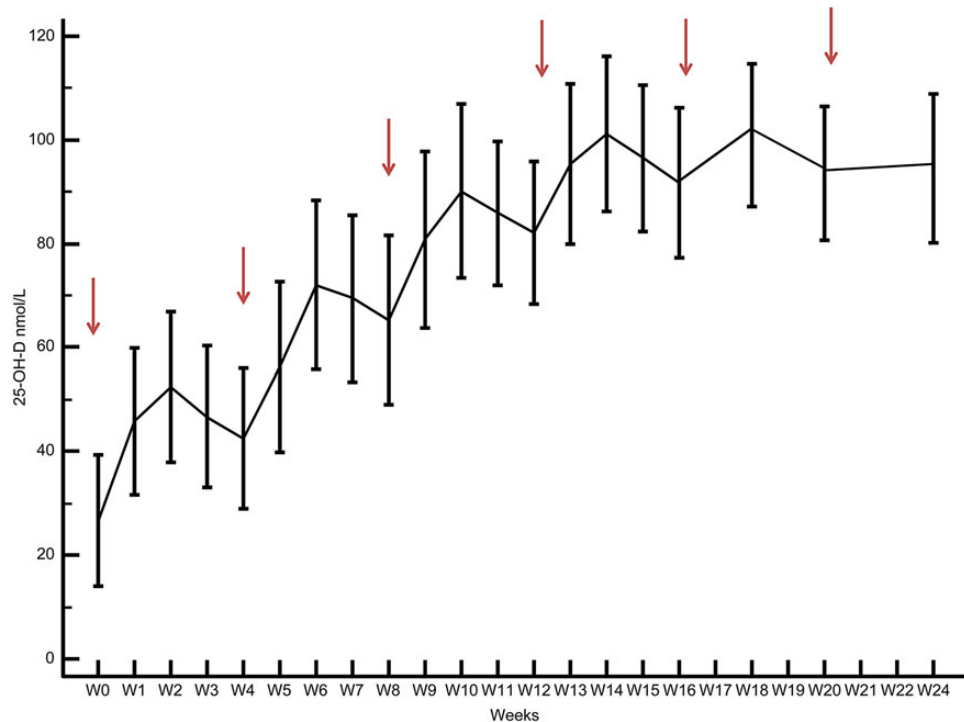


Fig. 1. Serum 25-D evolution during 6 months. Arrows represent the CCF administration.

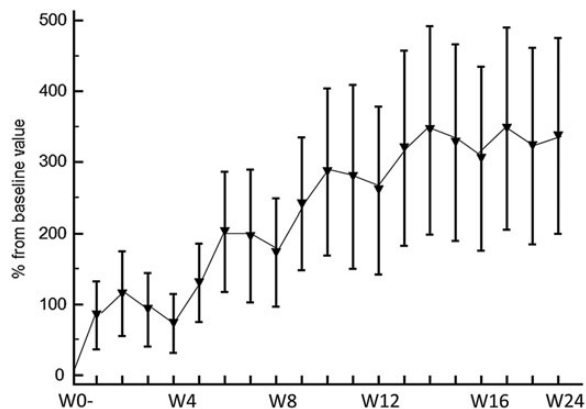


Fig. 2. Serum 25-D evolution expressed as percentage of baseline value.

48 h after receiving the first dose of CCF, with no significant difference between serum 25-D level at 48 h and those after 1 week ($+75 \pm 40\%$ versus $+84 \pm 48\%$ from baseline respectively). A peak was observed 14 days after each CCF dose ($115 \pm 62\%$ from the last pre-treatment value).

Discussion

The main results of the present study are as follow: (i) 100 000 IU of oral CCF once each month is an efficient strategy to adequately supplement 90% of 25-D deficient and insufficient HD patients; (ii) a plateau of serum 25-D level is observed after 11 weeks ($+280\%$); (iii) no peak effect is observed after 48 h; (iv) no adverse events were observed.

Vitamin D deficiency is a very common problem in patients undergoing dialysis [2, 12]. Low sun exposure and insufficient

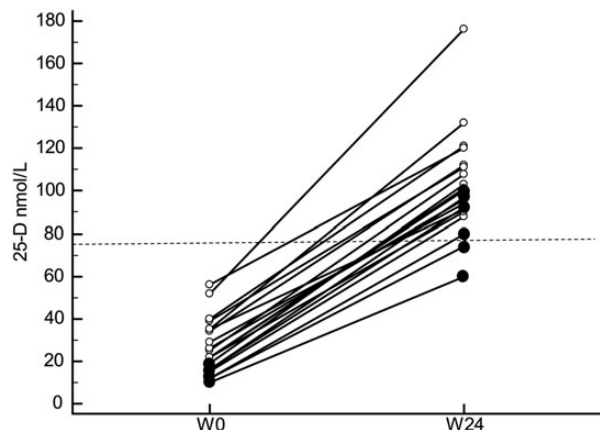


Fig. 3. Individual serum 25-D comparison between baseline and 6 months values. Open circles: patients previously treated with CCF. Black circles: patients not previously treated with CCF.

dietary intake are the main reasons. In the absence of vitamin D supplementation, $\sim 90\%$ of the HD patients at our centre had an inadequate serum 25-D level [2].

Many published reports indicate that, in the general population, 25-D deficiency is a risk factor for secondary hyperparathyroidism and osteoporosis [13], cancer, muscle weakness, infections [14], and impaired immunity [15]. In HD patients, London et al. [16] reported an association between vitamin D deficiency, arterial calcification, and pulse-wave velocity. In addition, incident [5] and prevalent [4] HD patients with 25-D deficiency displayed a higher mortality rate.

Ergocalciferol and CCF are considered to be equivalent for vitamin D supplementation in a daily regimen [17]; however, it has been shown that ergocalciferol derivatives have a shorter half-life than CCF [18]. Most studies reported the use of high doses to correct vitamin D deficiency, followed by a maintenance

phase with a significant decrease in the serum 25-D level reported during the latter phase [9]. Some studies have reported data for HD patients who received monthly ergocalciferol dosages (50 000 IU) for 6 months [19] or CCF dosages with a replenishment phase (20 000 IU/week) and a maintenance phase of lower dosage (monthly 20 000 IU D₃) [9]. After undergoing this treatment, only 57% of the patients achieved the target level of 75 nmol/L.

In the present study, only 2 of the 21 patients (i.e. 9.5%) did not achieve the target serum 25-D level. In each case, their baseline serum 25-D level was in the lower range (<20 nmol/L). This could lead to prescription of higher dosage in cases of severe 25-D deficiency.

Recently, Delanaye et al. [20] reported that CCF 25 000 IU every 2 weeks is effective and safe in HD patients as compared to placebo and reported that 75% of patients achieved a serum 25-D >75 nmol/L after 1 year.

Our kinetic study showed that the peak 25-D level was always observed after 14 days when two studies in healthy subjects reported a 25-D peak 7 days after a single dose of CCF (100 000 IU and 70 000 IU respectively) [21, 22].

Safety is important when treating patients with vitamin D supplements. The serum 25-D level of all patients in our study remained within the safe range of 75–180 nmol/L. The serum levels of calcium increased, but hypercalcaemia was not observed. In addition, phosphataemia showed no significant changes. The levels of PTH showed a significant decrease that seems related with the calcaemia evolution as a physiological response. In fact, a single dose of CCF (100 000 IU) was shown to decrease the PTH level in an elderly population without significant change in calcaemia [23]. So it is hypothesized that both the increased serum calcium and 25-D levels after 6 months of monthly CCF led to decrease the PTH level.

The main result of the present study is the stability of serum 25-D levels using monthly CCF administration. Verification that the dosage is effective can be done after 11 weeks of therapy, at any time. The lack of peak effect is also an important finding.

Due to the variability of CCF response, we suggest to measure serum 25-D at baseline in all patients and after 11 weeks of CCF treatment. Patients without baseline 25-D insufficiency should be tested at least yearly at the end of winter.

Our study has some limitations, mainly due to the small number of patients and lack of placebo group.

Conclusion

In this study of the weekly kinetics of serum 25-D in incident vitamin D-deficient HD patients receiving monthly oral CCF 100 000 IU, we observed that a plateau of 25-D values was obtained after 11 weeks (+280% from baseline value), and that 90% of patients achieved the biological target without toxicity.

Conflict of interest statement

G.J. and C.C. are consultants for Fresenius Medical Care France.

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