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Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation

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Abstract
Background. There is growing evidence of the usefulness of vitamin D supplementation in dialysis patients who are most often vitamin D deficient. Due to the long half-life of vitamin D, there is much interest in administering it intermittently for long-term adherence. However, there are no data to indicate which dosage would be most efficient.

Objective. The aim was to assess the long-term efficiency and safety of a monthly oral dose of cholecalciferol (100 000 IU) in vitamin D-deficient haemodialysis (HD) patients.

Methods. HD patients with a serum 25-hydroxyvitamin D (25(OH)D) level <75 nmol/L were enrolled in a 15-month prospective study. The exclusion criteria were as follows: use of any vitamin D derivatives, prescription of cinacalcet and bisphosphonates, uncontrolled hypercalcemia (>2.55 mmol/L), hyperphosphataemia (>2 mmol/L) and severe secondary hyperparathyroidism (SHPT; serum

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Results. Of the 250 patients screened, 161 were enrolled, and the results from 107 were recorded at the end of the study. Of these 107 patients, 56% were male, and the average age of the patient group was 66.4 ± 15 years. Diabetes accounted for 36% of the total patients. The dialysis schedule ranged from 3 × 5 to 3 × 8 h, with a mean dialysate calcium concentration of 1.48 ± 0.6 mmol/L. After 15 months, the mean serum 25(OH)D level increased from 32 ± 13 to 105.8 ± 27 nmol/L (P < 0.001) and plateaued after M3. Of the patients, 91% had a level higher than the target level (>75 nmol/L), while none had levels >200 nmol/L. The serum calcitriol (1,25(OH)₂D) level increased from 13.7 ± 14 to 45 ± 13 pmol/L (P < 0.001) and plateaued after M9. The levels of serum PTH (median 295–190 pg/mL, P < 0.001), bone alkaline phosphatase (20.5 ± 9–17.1 ± 7 µg/L, P < 0.05) and β-cross-laps (2.5 ± 1–2.07 ± 0.8 µg/L, P < 0.05) decreased significantly. No significant changes were observed in the values of the following: caemia, phosphataemia, blood pressure, serum albumin, haemoglobin and C-reactive protein.

Conclusions. Long-term monthly administration of oral cholecalciferol (100 000 IU) was a safe, effective, inexpensive and simple method for correcting vitamin D deficiency in almost 90% of the HD patients in this study and led to optimal compliance. The most evident consequences were a slight decrease in the levels of PTH and bone markers and an increase in the level of serum 1,25(OH)₂D.

Keywords: cholecalciferol; haemodialysis; mineral metabolism; vitamin D

Methods

Between January and September 2007, all patients in the centre were informed about the study; after obtaining their consent, they were enrolled in it. The exclusion criteria were as follows: a serum 25(OH)D level >75 nmol/L, actual or recent treatment with vitamin D derivatives (<3 months), treatment with active 1α-hydroxylated vitamin D derivatives, cinacalcet and bisphosphonates treatment, hypercalcaemia (total serum calcium ≥2.55 mmol/L), severe hyperphosphataemia (serum phosphate ≥2 mmol/L) and severe hyperparathyroidism (serum PTH >600 pg/mL). It was hypothesized that mild hyperparathyroidism (PTH 300–600 pg/mL) could be treated by cholecalciferol supplementation and calcium intake (oral and dialysate calcium). We wanted to assess the biological effects of cholecalciferol treatment on patients in whom PTH was <150 pg/mL. We aimed for a stable dialysis regimen and maintenance of the levels of calcium and phosphate binders during the follow-up.

The serum levels of 25(OH)D and D₂ were measured by a chemiluminescence assay (LIAISON; DiaSorin Inc., Stillwater, MN, USA). The detection limit was 10 nmol/L, and the laboratory interassay CV was 11%. A serum 25(OH)D level <75 nmol/L was regarded to be indicative of 25(OH)D insufficiency, based on the KDOQI guidelines [9]. The target serum 25(OH)D level was 75–250 nmol/L since hypervitaminosis has been defined as a serum 25(OH)D level >250 nmol/L [17]. Calcitriol (1,25(OH)₂D) was measured after extraction by using a radioimmunoassay (LIAISON; DiaSorin Inc., Stillwater, MN, USA); the detection limit was <4.8 pmol/L, laboratory interassay CV was 6% and the reference values were in the range 60–158 pmol/L. Intact PTH was measured using a second-generation assay (ElecsysG; Roche Diagnostics, Meylan, France), and the reference values were 14–72 pg/mL. Specific bone alkaline phosphatase (BALP; chemiluminescence, reference values 3.7–20 µg/L) and β-cross-laps (CTX; Elecsys, Roche Diagnostics, Meylan, France) were used as bone markers.

The patient’s data, including the serum levels of 1,25(OH)₂D, 25(OH)D, PTH, BALP, CTX, total calcium and phosphate were collected at baseline (M0) and 3 months before baseline to obtain a stable value (M-3) and then after 1 month (M1), 3 months (M3), 9 months (M9) and 15 months (M15) immediately prior to cholecalciferol administration. Standard parameters, including the values of the blood pressure (mean of the predialysis values of the month), normalized protein catabolic rate (nPCR), Kt/V sp (Daugirdas-2), erythropoietin-stimulating agents (ESA,
Results

Of the 250 HD patients present in the clinic at the time of the study, 89 were excluded since they did not have vitamin D insufficiency (n = 8). Other patients excluded were those undergoing treatment with calcifediol (n = 7), alfacalcidol (n = 42), cinacalcet (n = 15) and bisphosphonates (n = 5). Some patients were also excluded for biological reasons such as the occurrence of hypercalcaemia (n = 2), hyperphosphataemia (n = 4) and severe secondary hyperparathyroidism (SHPT) (n = 6). Of the 161 patients enrolled in the study, 33 died, 14 received a functional kidney transplant and 7 changed their dialysis centre during the study period.

Data from 107 patients were recorded for analysis. The average age of the patient group was 66.4 ± 15 years and 56% were males. All patients had been on dialysis for 65 ± 74 months, and 36% of the total were diabetics. The dialysis treatment consisted of a mean 3 × 6 h (3 × 5 to 3 × 8 h) schedule in which polysulphone low- and high-flux membranes (FX 8, 10 and FX 80, 100; Helixone, Fresenius S.E., Bad-Homburg, Germany) were used. The mean dialysate calcium concentration was 1.48 ± 0.16 mmol/L, which provided a mean of 2.3 ± 0.6 single pool Kt/V. The associated baseline treatments are shown in Table 1 and were maintained at stable levels during the study. The blood pressure, Kt/Vsp, nPCR, serum albumin level and CRP level remained stable between M0 and M15 (Table 1). In comparison to M0, at M15, a dialysate with a calcium concentration of 1.25 mmol/L tended to be prescribed more frequently than one with a concentration of 1.75 mmol/L.

Oral cholecalciferol treatment was always clinically well tolerated. The changes in the serum 25(OH)D levels are shown in Figure 1. A significant increase was observed from M0 to M1 and M1 to M3, with a plateau around a mean value of 100 nmol/L after M3. After 15 months of treatment, 91% of the HD patients had a serum 25(OH)D level higher than the target level (75 nmol/L). The changes in the vitamin D and mineral metabolism levels are reported in Table 2. No patient had a serum 25(OH)D level >250 nmol/L, which was the upper limit of our desired range. Only 10 patients did not achieve the recommended target level after administration of this cholecalciferol dosage. Of these, four were obese (BMI > 35 kg/m²), three had chronic liver disease, two had chronic pancreatic disease and one had undergone intestinal bypass. The serum 1,25(OH)2D levels progressively increased and plateaued around 45 pmol/L after M9 (Figure 2). The serum PTH levels significantly decreased after M1, from a median value of 295–249 pg/mL, and tended to stabilize thereafter around 45 pmol/L. In comparison to M0, at M15, there were more patients with a serum PTH level <150 pg/mL (25% versus 7.5%, P = 0.001) and fewer patients with a serum PTH level >300 pg/mL (25% versus 56%, P < 0.001). The calcium and phosphate levels did not change significantly. No episode of hypercalcaemia or hyperphosphataemia occurred. The bone ALP level decreased slightly from 20.5 ±
Table 2. Changes in vitamin D and mineral metabolism parameters

<table>
<thead>
<tr>
<th>Months</th>
<th>M-3</th>
<th>M0</th>
<th>M1</th>
<th>M3</th>
<th>M9</th>
<th>M15</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (nmol/L) (range)</td>
<td>31 ± 11 (3–55)</td>
<td>32 ± 13 (7–70)</td>
<td>68.3 ± 19 (30–130)</td>
<td>97.7 ± 28 (45–198)</td>
<td>105.7 ± 28 (49–190)</td>
<td>105.8 ± 27 (52–192)</td>
</tr>
<tr>
<td>% 25(OH)D &gt; 75 nmol/L</td>
<td>0</td>
<td>0</td>
<td>46</td>
<td>82</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>1,25(OH)2D (pmol/L) (range)</td>
<td>14 ± 14 (4–56)</td>
<td>13 ± 14 (4–55)</td>
<td>23.8 ± 14 (4–70)</td>
<td>30.7 ± 14 (4–82)</td>
<td>49.2 ± 17 (13–88)</td>
<td>45</td>
</tr>
<tr>
<td>PTH (pg/mL) (median, inter-quartile range)</td>
<td>294 (180–435)</td>
<td>295 (190–450)</td>
<td>249 (158–378)</td>
<td>220 (113–300)</td>
<td>220 (145–280)</td>
<td>220 (110–273)</td>
</tr>
<tr>
<td>BALP (µg/L) (range)</td>
<td>21 ± 10 (6–45)</td>
<td>20.5 ± 9 (7–41)</td>
<td>18.7 ± 9 (6–37)</td>
<td>17 ± 6 (8–35)</td>
<td>17 ± 6 (8–35)</td>
<td>17.1 ± 7 (6–35)</td>
</tr>
<tr>
<td>β-cross-laps (µg/L) (range)</td>
<td>2.5 ± 1 (0.8–6)</td>
<td>2.5 ± 1 (0.9–5)</td>
<td>2.27 ± 1 (0.6–5)</td>
<td>2.1 ± 1 (0.6–4.8)</td>
<td>2.07 ± 0.8 (0.7–4.2)</td>
<td>2.05 ± 0.8 (0.5–4.1)</td>
</tr>
<tr>
<td>Calcaemia (mmol/L) (range)</td>
<td>2.27 ± 0.14 (1.9–2.53)</td>
<td>2.24 ± 0.12 (2.1–2.31)</td>
<td>2.28 ± 0.1 (2.1–2.53)</td>
<td>2.28 ± 0.1 (2.1–2.53)</td>
<td>2.25 ± 0.1 (2.1–2.53)</td>
<td>2.25 ± 0.1 (2.1–2.53)</td>
</tr>
<tr>
<td>Phosphataemia (mmol/L) (range)</td>
<td>1.34 ± 0.3 (0.8–2.2)</td>
<td>1.32 ± 0.3 (0.8–2.2)</td>
<td>1.36 ± 0.3 (0.8–2.2)</td>
<td>1.36 ± 0.3 (0.8–2.2)</td>
<td>1.36 ± 0.3 (0.8–2.2)</td>
<td>1.36 ± 0.3 (0.8–2.2)</td>
</tr>
</tbody>
</table>

**P < 0.05, ***P < 0.001 with the previous value.

9 to 16.5 ± 6 µg/L after M3 and remained stable thereafter. In comparison to M0, at M15, the number of patients with a serum BALP level < 10 µg/L (9% versus 7.5%) was not higher, suggesting that the risk for low-turnover bone disease had not increased. Fewer patients had a serum BALP level ≥30 µg/L (9% versus 21%, P = 0.02), suggesting that the treatment had a favourable effect on high-turnover bone disease. The same was true for the β-cross-laps, with a slight decrease from 2.5 ± 1 at baseline to 2.1 ± 1 µg/L after M3.

Discussion

In the present study, administration of a monthly cholecalciferol dose of 100 000 IU during a 15-month period appeared to be a simple, inexpensive and efficient strategy to correct vitamin D insufficiency in ∼90% of the HD patients and did not result in any evident mineral metabolism toxicity. The most significant consequences were a decrease in the levels of PTH and bone markers and an increase in the serum 1,25(OH)2D level.

Vitamin D deficiency (i.e. a low serum 25(OH)D level) is a very common problem in patients undergoing dialysis [6,19]. Low sun exposure and insufficient dietary intake contribute to vitamin D deficiency. In the absence of vitamin D supplementation, ∼95% of the HD patients in our centre had an insufficient serum 25(OH)D level. This has, however, been ignored in ESRD patients because 1,25(OH)2D was thought to be the only active vitamin D compound. It was considered that treatment with 1α-hydroxylated vitamin D could sufficiently compensate for the low serum calcitriol level in ESRD patients due to renal mass decrease, FGF-23 increase [20], phosphate retention [21] and a high serum level of PTH fragments [22]. However, many published reports indicate that in the general population, 25(OH)D deficiency is a risk factor for SHPT and osteoporosis [23], high incidence of cancer, muscle weakness, infections [24] and impaired immunity [25]. London et al. reported an association between vitamin D deficiency and arterial calcification and pulse wave velocity in ESRD patients [26]. Incident dialysis patients with 25(OH)D deficiency displayed a higher mortality rate [11].
Apart from its well-known effect on mineral metabolism, vitamin D regulates gene expression in numerous cells through local 1,25(OH)\(_2\)D production and serves as an important cell-differentiating factor and antiproliferative agent in an autocrine or paracrine manner [27] and also perhaps in an endocrine manner [12]. This local production of 1,25(OH)\(_2\)D depends on the presence of an adequate level of the circulating substrate 25(OH)D [28], and by itself, it could justify systematic vitamin D supplementation in HD-deficient patients even if renal 1α-hydroxylation is impaired. Furthermore, a direct effect of 25(OH)D on the parathyroid glands has been demonstrated in a bovine model [29]. The widespread local production of 1,25(OH)\(_2\)D in cells and the possible direct action of 25(OH)D strongly support the idea of providing adequate 25(OH)D supplementation even in ESRD patients. Hence, although the KDOQI guidelines do not recommend the determination and correction of vitamin D deficiency in ESRD patients [9], the new insights on vitamin D provided by this study should help in formulating a new treatment strategy.

In contrast to the serum 1,25(OH)\(_2\)D level, which can be normal despite nutrient deficiency, the 25(OH)D levels are indicative of the body’s stores of vitamin D [30]. Since dietary sources account for no more than 5–10% of the daily requirement, the remainder must be obtained from the skin or by oral supplementation. No cases of vitamin D toxicity were reported for daily dosages up to 50 000 IU or for serum 25(OH)D levels <500 nmol/L [31].

Ergocalciferol (D\(_2\)) is mainly used in the United States, and cholecalciferol (D\(_3\)) is used in Europe. Ergocalciferol and cholecalciferol are considered to be equivalent for vitamin D supplementation in a daily regimen [32]; however, it has been shown that ergocalciferol derivatives are less efficient when administered in dosages that are well spaced out because these compounds have a shorter half-life than cholecalciferol [33]. Most studies reported the use of high doses to correct vitamin D deficiency, followed by a maintenance phase; a significant decrease in the serum 25(OH)D level was reported during the latter phase [15]. Chandra et al. used a weekly dose of cholecalciferol (50 000 IU) over a 12-week period in CKD stage 3–4 patients and reported an increase in the 25(OH)D level from a mean value of 42–125 nmol/L [34]. Some studies have reported data for HD patients who received monthly ergocalciferol dosages (50 000 IU) for 6 months [7] or cholecalciferol dosages with a replenishment phase (20 000 IU/week) and a maintenance phase of lower dosage (monthly 20 000 U D\(_3\)) [35]. After undergoing this treatment, only 57% of the patients achieved the target level of 75 nmol/L. Renal transplant patients who received cholecalciferol with an intensive phase of four oral (100 000 IU) doses every 2 weeks followed by a maintenance phase of 100 000 IU every 2 months exhibited a decrease in the serum 25(OH)D level during the maintenance phase, indicating that this treatment was insufficient [36]. We have previously reported the results that we obtained with daily oral 25(OH)D\(_3\) supplementation in the range of 10–30 µg/day. In this, 87% of the patients exceeded the target level after 6 months of treatment and exhibited a mean serum 25(OH)D level of 126 ± 48 nmol/L [16]. In the present study, only 10 patients (i.e. 10%) did not achieve the target serum 25(OH)D level. In each case, there was a plausible explanation for the inadequate response, such as obesity, liver disease or intestinal unpaired absorption. The relatively high doses used in the present study, equivalent to 3333 U/day, are higher than the recommended doses in the general population. However, a pharmacokinetics study in normal subjects with a mean baseline 25(OH)D level of 27 ng/mL has shown that one dose of cholecalciferol (100 000 IU) increased the 25(OH)D level to a mean 42 ng/mL after 7 days, which allowed the target level (>30 ng/mL) to be achieved in 93% of the cases. Moreover, it was reported that this initial dose had to be repeated after 2 months or less [37]. Heaney et al. reported that in a healthy population, a daily dose of 3000–5000 U is necessary to maintain the serum 25(OH)D level >80 nmol/L; this is similar to that in the vitamin D regimen followed in the present study.

Safety is a key problem when treating patients with vitamin D supplements. The 25(OH)D level of all patients in this study remained within the safe region of <250 nmol/L. The serum levels of calcium and phosphate showed no significant changes, and no hypercalcemia or hyperphosphataemia occurred. Only the levels of PTH and bone markers showed a significant decrease, but the bone ALP levels indicated that there was no adynamic bone disease and that the mild high-turnover bone disease had improved. In fact, a single dose of cholecalciferol (100 000 IU) was shown to decrease the PTH level in an elderly population [38]. Tokmak et al. used cholecalciferol (20 000 U/week) in HD patients over a period of 9 months and reported only an increase in the calcium level but no changes in the serum phosphate and PTH levels [35].

A significant increase in the 1,25(OH)\(_2\)D level after vitamin D supplementation has been previously reported by our group [12] and others [39], and this effect may contribute to the decrease in the serum levels of PTH and bone markers. These results suggest that active vitamin D may not be indispensable for adequately controlling SHPT even in CKD stage 5 patients. The other key question in vitamin D treatment of CKD and ESRD patients concerns the effects of native and active vitamin D derivatives. Although 1α-hydroxylated vitamin D derivatives are effective in controlling SHPT, the risk of hypercalcemia needs to be considered [40]. HD patients treated with active vitamin D, calcidiol and mostly paricalcitol had a survival advantage in observational studies using large cohorts [41–43], and the effects appeared to be independent of mineral metabolism. In other words, if it is important to activate the VDR for health, what is the best way to activate it, and should native or active vitamin D be used?

Finally, our fixed vitamin regimen has the advantage of simplicity and low cost. The cost of 100 000 IU of cholecalciferol in France is 1.7 Euros per vial, which represents the monthly cost of the regimen proposed in this study. This is much cheaper than the costs of other active vitamin D derivatives. Recently, it was shown that less vitamin D is required in a daily regimen than in a more spaced-out regimen [44]. In our study, the monthly dose was always administered by the nurses of our unit and therefore led to a 100% adherence rate.

Our study has some limitations. We had no control group, and we excluded patients with severe SHPT and active
vitamin D and those undergoing cinacalcet treatment or suffering from uncontrolled hypercalcaemia and phosphataemia. Moreover, the dialysis strategy employed here, which consisted of a long dialysis session, may have had an impact on phosphate control and mineral metabolism.

Conclusions

The results of this study confirm that vitamin D deficiency occurs frequently in HD patients. By administering a fixed monthly dose of cholecalciferol (100 000 IU) as a vitamin D supplement, we observed a long-term stable serum 25(OH)D level within the recommended range in >90% of the vitamin D-deficient HD patients. Use of this simple and cheap regimen alongside a long HD schedule allows optimal compliance and is associated with few mineral metabolic consequences such as a slight decrease in the serum levels of PTH and bone markers without any effect on the calcium and phosphate levels. Prospective and controlled long-term studies are required to assess the therapeutic advantage of this strategy on the clinical outcomes.

Conflict of interest statement. G. Jean and C. Chazot are consultants for Fresenius Medical Care.

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G. Jean et al.
Home blood pressure monitoring in blood pressure control among haemodialysis patients: an open randomized clinical trial

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Abstract

Background. It is not known if the adjustment of antihypertensive therapy based on home blood pressure monitoring (HBPM) can improve blood pressure (BP) control among haemodialysis patients.

Methods. This is an open randomized clinical trial. Hypertensive patients on haemodialysis were randomized to have the antihypertensive therapy adjusted based on predialysis BP measurements or HBPM. Before and after 6 months of follow-up, patients were submitted to ambulatory blood pressure monitoring (ABPM) for 24 h, HBPM during 1 week and echocardiogram.

Results. A total of 34 and 31 patients completed the study in the HBPM and predialysis BP groups, respectively. At the end of study, the systolic (SBP) and diastolic (DBP) blood pressure during the interdialytic period measured by ABPM were significantly lower in the HBPM group in relation to the predialysis BP group (mean 24-h BP: 135 ± 12 mmHg/76 ± 7 mmHg versus 147 ± 15 mmHg/79 ± 8 mmHg; P < 0.05). In the HBPM analysis, the HBPM group showed a significant reduction only in SBP compared to the predialysis BP group (weekly mean: 144 ± 21 mmHg versus 154 ± 22 mmHg; P < 0.05). There were no differences between the HBPM and predialysis BP groups in relation to the left ventricular mass index at the end of the study (108 ± 35 g/m² versus 110 ± 33 g/m²; P > 0.05).

Conclusions. Decision making based on HBPM among haemodialysis patients has led to a better BP control during the interdialytic period in comparison with predialysis BP measurements. HBPM may be a useful adjuvant instrument for blood pressure control among haemodialysis patients.

Keywords: ambulatory blood pressure monitoring; haemodialysis; home blood pressure monitoring; hypertension

Introduction

The mortality rate for haemodialysis patients is 20% during the first year of treatment and 70% after 5 years [1]. Among causes of death, cardiovascular diseases are responsible for > 50% of the deaths [1,2]. The high prevalence of traditional risk factors for cardiovascular disease (hypertension, diabetes, dyslipidaemia) along with the presence of risk factors considered non-traditional (uraemia, chronic inflammatory status, oxidative stress) peculiar to this population is certainly associated with the origin of the problem [3].