Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: effects on mineral metabolism and bone markers

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Abstract

Background. Vitamin D deficiency is frequently observed in end-stage renal disease (ESRD) patients; however, the effects of vitamin D supplementation have rarely been reported. We aimed to assess the effects of daily 25(OH)D3 supplementation on mineral metabolism, bone markers and Kidney Disease Outcomes Quality Initiative (KDOQI) targets in haemodialysis (HD) patients for a period of 6 months.

Methods. HD patients were included in this study if their serum 25(OH)D level was < 75 mmol/L. Oral 25(OH)D3 was administered daily at 10–30 µg/day based on the severity of the deficiency. Characteristics of the patients were compared from the baseline to 6 months on the basis of their response to 25(OH)D3 administration and the patients were divided into three groups. Patients who showed partial response [serum 25(OH)D < 75 nmol/L] were placed in group 1, those who showed normal response [serum 25(OH)D ranging from 75 to 150 nmol/L] were placed in group 2 and those who showed excessive response [serum 25(OH)D > 150 nmol/L] were placed in group 3.

Results. Of the 253 HD patients, 225 (89%) showed vitamin D insufficiency or deficiency, 172 were included in the study and 149 patients completed the study. After 6 months of treatment [mean daily 25(OH)D3: 1.6 ± 5 µg/day], the serum 25(OH)D level increased (30 ± 19 to 126 ± 46 nmol/L, P < 0.001), with 13% of patients in group 1, 57% in group 2 and 30% in group 3. The serum intact parathyroid hormone (iPTH) level decreased (235 ± 186 to 189 ± 137 pg/mL, P = 0.05), except in group 1. Bone alkaline phosphatase (BALP) showed a tendency to normalize (23 ± 16 to 18.3 ± 11 µg/L, P < 0.05), leading to a decrease in alfacalcidol administration from 66% to 43% (P < 0.05), except in group 1. The KDOQI targets achieved increased significantly for serum calcium (76% to 85%) and phosphate levels (66% to 77%) in all patients. The serum albumin level increased in all groups (34.6 ± 4 to 36.8 ± 4 g/L, P < 0.05), without any significant improvement in normalized protein catabolic rate (nPCR) or C-reactive proteins (CRP).

Conclusion. With a daily dose ranging from 10 to 30 µg, daily oral 25(OH)D3 supplementation corrects most vitamin D deficiencies or insufficiencies in HD patients, without any evident toxicity. The main effects observed included correction of excessive bone turnover, despite less alfacalcidol administration, increase in serum albumin level and increase in the percentage of patients with serum calcium and phosphorus levels within the recommendation of the KDOQI guidelines.

Keywords: bone markers; haemodialysis; 25-hydroxyvitamin D; mineral metabolism; vitamin D deficiency

Introduction

Vitamin D deficiency is a worldwide epidemic that affects both the elderly and children, particularly white women and African American individuals [1]. Recently, this deficiency has been reported to be associated with an increased risk of cancer, cardiovascular and autoimmune diseases, diabetes mellitus and tuberculosis [2,3], and in the elderly, with low mood and cognitive impairment [4], musculoskeletal pain [5] and mortality [6]. However, vitamin D deficiency is most commonly known to be involved in bone changes associated with hyperparathyroidism, osteoporosis, ostearthrosis and risk for fractures [7–9].

Vitamin D deficiency has been reported to be highly prevalent in chronic kidney disease (CKD) patients [10,11]. This deficiency correlates with hyperparathyroidism, low calcium and calcitriol serum levels, female gender, obesity and insufficient sunlight exposure. In CKD stage 3, vitamin D supplementation can be a valuable treatment for preventing secondary hyperparathyroidism (SHPT) [12]; however, it appears to be less useful in CKD stage 4,
proceed probably due to insufficient renal 1-α-hydroxylation [13]. Therefore, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines do not recommend any native vitamin D supplementation in CKD stage 5, in contrast to its recommendation in CKD stages 3 and 4 [14], although the deficiency has been found to be highly prevalent in dialysis patients [15–18]. Recently, data obtained from a US prospective cohort study have revealed that vitamin D-deficient dialysis patients have a higher mortality rate [18]. It is hypothesized that vitamin D deficiency may be an underestimated risk factor for cardiovascular diseases in CKD patients [19].

The major form of circulating vitamin D is 25-hydroxycholecalciferol [25(OH)D], and its serum level reflects the status of the vitamin D storage. A serum 25(OH)D level >75 nmol/L is recommended for the general population [20] and also for CKD stage 3 and 4 patients [14]. A few studies have defined the optimal dose and duration of vitamin D supplementation for 25(OH)D-deficient haemodialysis (HD) patients and have determined the safety and benefits of the supplementation. In the present study, we aimed to assess the effects of daily 25(OH)D supplementation on mineral metabolism, bone markers and KDOQI targets in HD patients.

Subjects and methods

In March 2006, the HD patients at our centre were included in the present study if their serum 25(OH)D level was <75 nmol/L and they had not received any native vitamin D supplementation for the past 6 months or more. The serum levels of 25(OH)D$_2$ and 25(OH)D$_3$ were measured by a chemiluminescence assay (LIAISON®, DiaSorin Inc., Stillwater, MN, USA) in the second and third week of March and September 2006. Patients who had uncontrolled hyperphosphataemia (>2 mmol/L), hypercalcaemia (>2.55 mmol/L), who were undergoing cinacalcet treatment or had undergone parathyroidectomy were excluded from the study. Oral 25(OH)D$_3$ (Calcifediol, Dedrogyl®) was prescribed at a daily dose of 10 µg when serum 25(OH)D was between 50 and 75 nmol/L, 10–20 µg/day when it was between 25 and 50 nmol/L and 20–30 µg/day when it was <25 nmol/L. The serum 25(OH)D target level was 75–150 nmol/L. The patients were divided into three groups based on their response to the 25(OH)D$_3$ treatment. Patients who showed partial response [serum 25(OH)D $<$ 75 nmol/L] were placed in group 1, those who showed normal response [serum 25(OH)D ranging from 75 to 150 nmol/L] in group 2 and those who showed excessive response [serum 25(OH)D > 150 nmol/L] in group 3.

Hypervitaminosis D has been defined as a serum 25(OH)D level >250 nmol/L [20]. Sevelamer was used as the standard phosphate binder and was prescribed based on the serum phosphate level in order to attain the KDOQI targets. Oral calcium was not administered as a phosphate binder but was administered between meals only in the case of hypocalcaemia (serum calcium <2.1 mmol/L). The standard dialysate calcium concentration was 1.5 mmol/L, and it was not changed during the study period. Alfacalcidol dose was adjusted to maintain the Ca $\times$ P product and intact parathyroid hormone (iPTH; Roche Elecsys) levels within the KDOQI targets. Additionally, from our experience, we adjusted the alfacalcidol dose on the basis of the serum levels of bone markers: bone alkaline phosphatase (BALP; chemiluminescence) with a 10–20 µg/L serum target level and β-CrossLaps (CTX, chemiluminescence) with a 1.3–2.6 µg/L serum target level (Jean G et al., Rio 2007, World Congress of Nephrology). Intravenous phosphate was administered during the dialysis session when the predialysis serum phosphate level was <$0.5 mmol/L. We recorded midweek values for serum calcium (corrected for albumin), phosphorus, albumin (by nephelometry) and the percentage of biological KDOQI targets achieved.

Statistical analysis

The serum biochemical data and KDOQI targets were compared at baseline (T-0) and after 6 months (T-6) of therapy by using the paired Wilcoxon rank test for continuous data and Fisher’s exact test for proportion comparison. The data for each group were compared using analysis of variance (ANOVA). The data are expressed as mean ± SD. A P-value <0.05 was considered to be statistically significant. Statistical analyses were performed using MedCalc® software, Mariakerke, Belgium.

Results

Of the 253 HD patients, 225 (89%) had vitamin D deficiency or insufficiency. Of the 225 patients, 172 were included in the study and 149 completed the study and were retained for analysis. Of these 149 patients, 65% had deficiency with their serum 25(OH)D level <25 nmol/L, 25% had vitamin D insufficiency with their serum 25(OH)D level ranging from 25 to 50 nmol/L and 20% had vitamin D insufficiency with their serum 25(OH)D level ranging from 50 to 75 nmol/L. Compared with patients who had sufficient vitamin D stores, patients with initial deficiency of vitamin D had a greater incidence of diabetes (45% initial deficiency versus 28% sufficient vitamin D stores, P < 0.05) and showed a higher PTH serum level (260 ± 227 pg/mL initial deficiency versus 213 ± 153 pg/mL sufficient vitamin D stores, P < 0.05).

Initial nephropathies were undetermined in 17% of the patients, diabetes in 28%, nephrosclerosis in 16%, glomerular nephritis in 20%, interstitial nephritis in 9%, polycystic kidney disease in 6% and miscellaneous causes in 4%. The dialysis schedule was 5–8 h three times weekly, which provided a high dialysis dose of 2.35 ± 0.6 Kt/V.

The patients received oral 25(OH)D$_3$ daily at a mean dose of 16 ± 5 µg (640 ± 200 U) for 6 months. The distribution of serum 25(OH)D levels at baseline and after 6 months are shown in Figure 1. After 6 months of 25(OH)D supplementation, the mean serum 25(OH)D level increased from 30 ± 19 nmol/L to 126 ± 48 nmol/L (P < 0.001). Only 13% of the patients showed low 25(OH)D serum levels (<75 nmol/L) at T-6, and most of these patients admitted a poor compliance. Besides, in group 1 patients, the
25(OH)D$_3$ dose was higher based on the lower initial serum 25(OH)D levels. None of the patients achieved a toxic level [25(OH)D $>250$ nmol/L]. Serum biochemical data, treatment evolution and comparison within the three groups at T-0 and T-6 are shown in Table 1. The serum BALP level decreased significantly and showed a tendency to normalize with not very high or low serum values. Serum iPTH level also decreased significantly, except in group 1. The percentage of KDOQI targets for iPTH achieved remained stable, except in group 2, where it increased significantly. The serum CTX level did not show a significant change and frequently remained within the desirable target range. No change was noted in the mean serum calcium level. However, after 6 months of treatment, a larger number of patients had their mean serum calcium level within the range recommended by the KDOQI guidelines. Patients in group 1 were less frequently hypocalcaemic after 25(OH)D$_3$ administration (8% at T-0 versus 11.5% at T-6) even if not statistically significant. Hypercalcaemia ($>2.55$ mmol/L) was observed in rare cases during the study phase (3%); however, the calcium levels rapidly normalized after alfacalcidol discontinuation. The initial daily administration dose of 25(OH)D ranged from 10 to 30 µg; however, it was decreased to a range of 5–25 µg after the study phase and was adjusted based on the 25(OH)D serum level in the sixth month.

Most patients had their serum phosphate level within the KDOQI target range after 6 months; however, some patients, particularly in group 1, were less frequently hypophosphataemic (22% at T-0 with serum phosphate $<1.1$ mmol/L versus 13% at T-6, $P = 0.05$). Sevelamer use and dosage (4.2 tab/day) remained stable and did not differ between the three groups. Intravenous phosphate was administered in 7% of the patients at baseline as compared to 4% of the patients after 6 months. Severe hyperphosphataemia was observed in rare cases, and the phosphate binder dose level remained stable, indicating that 25(OH)D$_3$ did not have a hyperphosphataemic effect. The Ca $\times$ P product remained stable and did not differ between the three groups (ranging from 2.9 to 3.1 mmol$^2$/L$^2$).

All the four mineral metabolism KDOQI targets (corrected calcium, Ca $\times$ P, phosphate and PTH levels) were achieved more frequently after 6 months (22% at T-0 versus 34% at T-6, $P < 0.05$), and an improvement in achieving calcium and phosphate targets was largely responsible for this. The serum albumin level increased significantly, without any significant improvement in the normalized protein catabolic rate (nPCR) or the C-reactive protein (CRP) serum level.

The patients in group 3 had their alfacalcidol dose more frequently decreased as compared to those in the other groups; however, this difference was not statistically significant. In group 1, after 25(OH)D$_3$ supplementation, the achievement of the KDOQI targets for calcium and phosphate appeared to have improved in most cases in contrast to the target achievement for PTH.

**Discussion**

Our study confirmed the high incidence of vitamin D deficiency or insufficiency in end-stage renal disease (ESRD) patients, which has been reported previously [15–17], and the safety and efficiency of daily oral supplementation of 25(OH)D$_3$. Like the treatment guidelines available for CKD stages 3 and 4, no guidelines, particularly KDOQI [14] and
Effects on mineral metabolism and bone markers

<table>
<thead>
<tr>
<th>25(OH)D after 6 months</th>
<th>Time</th>
<th>All patients</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tr>
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<td>Vintage (months)</td>
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<td>Male gender (%)</td>
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<tr>
<td>Diabetes (%)</td>
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<td>25(OH)D3 (µg/day)</td>
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<tr>
<td>25(OH)D (nmol/L)</td>
<td>T-0</td>
<td>30 ± 19</td>
<td>10 ± 14</td>
<td>20 ± 14</td>
<td>30 ± 20</td>
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<td></td>
<td>T-6</td>
<td>126 ± 4 ± 8**</td>
<td>50 ± 25**</td>
<td>114 ± 50**</td>
<td>36 ± 20*</td>
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<td>Calcemia (mmol/L)</td>
<td>T-0</td>
<td>2.2 ± 0.1</td>
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<td>2.2 ± 0.1</td>
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<td></td>
<td>T-6</td>
<td>2.2 ± 0.1</td>
<td>2.19 ± 0.1</td>
<td>2.22 ± 0.1</td>
<td>2.22 ± 0.1</td>
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<td>Calcium KDOQI (%)</td>
<td>T-0</td>
<td>76 ± 35</td>
<td>73 ± 35</td>
<td>73 ± 35</td>
<td>83 ± 35</td>
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<td></td>
<td>T-6</td>
<td>86* ± 92</td>
<td>84 ± 92</td>
<td>84 ± 92</td>
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<tr>
<td>Phosphataemia (mmol/L)</td>
<td>T-0</td>
<td>1.3 ± 0.3</td>
<td>1.37 ± 0.3</td>
<td>1.28 ± 0.3</td>
<td>1.23 ± 0.3</td>
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<td></td>
<td>T-6</td>
<td>1.3 ± 0.3</td>
<td>1.32 ± 0.3</td>
<td>1.35 ± 0.3</td>
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<td>Phosphate KDOQI (%)</td>
<td>T-0</td>
<td>66 ± 35</td>
<td>68 ± 35</td>
<td>75* ± 35</td>
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<td>T-6</td>
<td>77* ± 71</td>
<td>75 ± 71</td>
<td>75 ± 71</td>
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<tr>
<td>PTH (pg/mL)</td>
<td>T-0</td>
<td>235 ± 186</td>
<td>173 ± 150</td>
<td>245 ± 170</td>
<td>240 ± 170</td>
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<td></td>
<td>T-6</td>
<td>189 ± 136*</td>
<td>190 ± 150</td>
<td>193 ± 130*</td>
<td>175 ± 120*</td>
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<tr>
<td>PTH KDOQI (%)</td>
<td>T-0</td>
<td>43 ± 50</td>
<td>47 ± 50</td>
<td>47 ± 50</td>
<td>37 ± 46</td>
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<tr>
<td></td>
<td>T-6</td>
<td>46 ± 30</td>
<td>51* ± 30</td>
<td>51* ± 30</td>
<td>46 ± 30</td>
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<tr>
<td>BALP (µg/L)</td>
<td>T-0</td>
<td>23 ± 16</td>
<td>25 ± 17</td>
<td>22 ± 15</td>
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<tr>
<td></td>
<td>T-6</td>
<td>18.3 ± 15*</td>
<td>19 ± 12*</td>
<td>17 ± 11*</td>
<td>19 ± 12*</td>
</tr>
<tr>
<td>CTX (µg/L)</td>
<td>T-0</td>
<td>1.96 ± 1</td>
<td>1.6 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
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<tr>
<td></td>
<td>T-6</td>
<td>2.2 ± 1.1</td>
<td>2.1 ± 1</td>
<td>2.2 ± 1</td>
<td>2.3 ± 1</td>
</tr>
<tr>
<td>Sevelamer (%)</td>
<td>T-0</td>
<td>34 ± 40</td>
<td>32 ± 40</td>
<td>32 ± 40</td>
<td>32 ± 40</td>
</tr>
<tr>
<td></td>
<td>T-6</td>
<td>36 ± 40</td>
<td>35 ± 40</td>
<td>35 ± 40</td>
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<tr>
<td>Alfacalcidol (%)</td>
<td>T-0</td>
<td>66 ± 50</td>
<td>65 ± 50</td>
<td>65 ± 50</td>
<td>70 ± 50</td>
</tr>
<tr>
<td></td>
<td>T-6</td>
<td>43* ± 55</td>
<td>45* ± 55</td>
<td>45* ± 55</td>
<td>30** ± 55</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>T-0</td>
<td>34.6 ± 4</td>
<td>32 ± 4</td>
<td>35 ± 4</td>
<td>35 ± 4</td>
</tr>
<tr>
<td></td>
<td>T-6</td>
<td>36.8 ± 4**</td>
<td>34 ± 4*</td>
<td>37.5 ± 4*</td>
<td>36.5 ± 4*</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>T-0</td>
<td>15.6 ± 27</td>
<td>19 ± 30</td>
<td>10 ± 22</td>
<td>25 ± 35</td>
</tr>
<tr>
<td></td>
<td>T-6</td>
<td>14 ± 25</td>
<td>27 ± 37</td>
<td>12 ± 20</td>
<td>13 ± 25</td>
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<tr>
<td>nPCR (g/kg/day)</td>
<td>T-0</td>
<td>1.22 ± 0.3</td>
<td>1.20 ± 0.3</td>
<td>1.22 ± 0.3</td>
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<tr>
<td></td>
<td>T-6</td>
<td>1.26 ± 0.3</td>
<td>1.22 ± 0.3</td>
<td>1.27 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. 25(OH)D, 25-hydroxycholecalciferol; KDOQI, Kidney Disease Outcomes Quality Initiative; PTH: parathyroid hormone; BALP, bone alkaline phosphatase; CRP, C-reactive proteins; nPCR, normalized protein catabolic rate.

* P < 0.05, ** P < 0.01, between T-0 and T-6.

Kidney Disease: Improving Global Outcomes (KDIGO) [21] guidelines that emphasize the importance of the determination and correction of the deficiency or insufficiency, are available. The main reason for the lack of guidelines is the insufficient capacity of the kidney to promote 1-α-hydroxylation in ESRD, thereby making it impossible to produce the necessary amount of 1,25(OH)D. Recently, it has been reported that the phosphaturic bone protein fibroblast growth factor-23 (FGF-23) is elevated in CKD, and this may augment the inhibition of renal 1-α-hydroxylation of vitamin D [22]. However, the extra-renal production of 1,25(OH)2D in anephric patients has been reported [23]. This finding was confirmed by Dusso et al., who reported the extra-renal production of 1,25(OH)2D in macrophages of uraemic patients, which was proportional to 1,25(OH)2D deficiency [24]. The novel sites of 1-α-hydroxylase expression include the parathyroids, pancreas, adrenal medulla, skin, nodes and cerebellum [25]; this indicates an autocrine/paracrine function of this enzyme in the control of cell proliferation and differentiation [26]. It may be important to maintain the blood concentration of 25(OH)D > 80 nmol/L to provide fuel for the renal and extra-renal production of 1,25(OH)2D [8] and for the possible direct action of 25(OH)D on the nuclear vitamin D receptor (VDR). Recently, an in vitro study reported that 25(OH)D may directly activate VDR, independent of 1,25(OH)2D [27]. Vitamin D deficiency can occur due to inadequate sunlight exposure, poor dietary intake, inadequate absorption and proteinuria. Most people obtain >90% of their vitamin D requirement from the sunlight exposure [28], and both ageing and skin pigmentation are known to diminish the cutaneous production of cholecalciferol [29]. Our HD patients may have had an aggregation of all these risk factors; however, in contrast to the studies on the US population, only 2% of our patients showed significant skin pigmentation. Further, similar to previous studies, female gender [11] and diabetes [30] were the main risk factors for vitamin D deficiency in our HD patients.

The vitamin D endocrine system plays an essential role in calcium homeostasis and bone metabolism. Recently, it
has been revealed that vitamin D is involved in a wide range of cellular activities, including differentiation, inhibition of cell growth, immunomodulation and control of other hormonal systems [2]. The effects of 25(OH)D deficiency in HD patients are not well documented; however, a recent study has reported an increased mortality rate in vitamin D-deficient incident HD patients in the USA [18]. Some retrospective studies have reported a survival advantage of HD patients with a history of active vitamin D treatment [31–33]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort has reported no relationship between survival and vitamin D intake, mainly the active vitamin D [34]. However, only few studies had a prospective controlled design.

It has been hypothesized that 25(OH)D deficiency may lead to mineralization and bone formation defects and that the optimal 25(OH)D level is between 50 and 100 nmol/L for bone turnover in HD patients [35]. This hypothesis was clinically confirmed in an Algerian study, in which 25(OH)D deficiency was associated with hyperparathyroidism and the observation of Looser’s zone in a radiological examination [36].

We selected 25(OH)D3 for the treatment of our patients because ergocalciferol (vitamin D2) may not be correctly monitored by most of the available vitamin D assays [37]. However, the DiaSorin LIAISON assay used in our study has been reported to accurately measure both vitamin D2 and vitamin D3 [38]. A daily regimen was chosen in agreement with the choice of most patients. It should, however, be noted that due to its long half-life (15–21 days), 25(OH)D3 administration can be less frequent and a weekly dosage can be as efficient as a daily one [39]. In the vitamin D-deficient general population, a daily oral intake of 1000 IU vitamin D3 is required to sustain the serum 25(OH)D levels within the healthy range of 75–100 nmol/L [8]. In women with osteoporosis, 4000 U of 25(OH)D3 weekly (i.e. 571 U/day) was as efficient as 800 U of cholecalciferol daily, with 90% compliance at 1 year [39]. Based on this data, we administered 25(OH)D3 at a mean dose of 640 U/day in accordance with the baseline serum 25(OH)D level. This regimen was efficient in correcting 25(OH)D deficiency in most patients in cases of good compliance. However, patients with serum 25(OH)D level > 150 nmol/L after 6 months were administered lower doses of 25(OH)D3 in order to avoid toxicity. Based on our results, we feel that the initial 25(OH)D3 dose should be 10–30 µg/day for 2–3 months, and subsequently, a daily dose of 5–20 µg should be sufficient as a maintenance dose.

In patients with hypercalcaemia, hyperphosphataemia [40] and adynamic bone disease, there is a risk of deleterious mineral accumulation due to vitamin D treatment. Therefore, we chose to exclude patients who had hypercalcaemia, hyperphosphataemia, who were undergoing cinacalcet treatment or had undergone parathyroidectomy. Additionally, based on the serum levels of minerals and bone markers, we gradually terminated alfacalcidol administration to avoid toxicity. Alfacalcidol was administered because 25(OH)D3 alone may not be adequate since 1α-hydroxylation might be insufficient in CKD stage 5; thus, more active vitamin D analogues may be required occasionally to prevent and treat hyperparathyroidism [41]. With this strategy, 25(OH)D3 treatment appears to be safe, without any deleterious mineral accumulation. The effect of the schedule of long dialysis sessions provided at our centre was difficult to assess. Furthermore, in a previous study, it was found that hyperphosphataemia is less frequent and less severe since there is lesser requirement for phosphate binders using long dialysis [42].

A higher mineral KDOQI target percentage was achieved after 6 months of 25(OH)D3 treatment because hypocalcaemia and hypophosphataemia occurred less frequently, particularly in group 1 patients who were frequently hypophosphatemic at baseline. Although the present study did not include a control group, the obtained results may indicate that 25(OH)D3 plays a role in phosphate and calcium absorption, either with a direct effect on VDR or through a local or general increase in 1,25(OH)2D production.

In a previous study on HD patients, it was found that a monthly ergocalciferol supplementation at 50 000 U was efficient and enabled in achieving a mean serum 25(OH)D level of 133 nmol/L, with no significant mineral changes [15]. Further, it was found that the serum albumin level decreased slightly during the treatment period, with no change in the administration dose of active vitamin D, and there was decreased requirement for erythropoietin (EPO); this was, however, not found in our study. Ergocalciferol D2 may have less hypercalcaemic activity than 25(OH)D3 [43,44], leading to less requirement for the gradual termination of active vitamin D administration. The favourable effect of 25(OH)D3 on the albumin level is in accordance with previous data, which demonstrates a relationship between low albumin level and vitamin D deficiency in ESRD [18,45]. Alfacalcidol has been reported to increase protein intake and serum albumin, probably by suppressing tumour necrosis factor activity [46]. Our results are in poor agreement with this previous finding since we found no improvement in nPCR and CRP levels.

Another harmful effect of vitamin D treatment is the risk for extra-skeletal calcification reported in association with active vitamin D derivates [47,48] and in CKD patients [49,50]. It is difficult to establish the direct role of vitamin D on the basis of the Ca × P product whose level increased in most cases. In addition, the vitamin D dosages reported in these studies were high, and there was an increased risk for adynamic bone disease. Cardiovascular calcification can occur due to multiple causes. Vitamin D deficiency has been associated with cardiovascular calcification, arteriosclerosis and endothelial dysfunction [53]. However, some studies have not confirmed the deleterious role of vitamin D in cardiovascular calcification [51,52]. It is thus obvious that vitamin D shows a biphasic effect on cardiovascular health, with a favourable effect in the case of low nutritional doses and deleterious effect in the case of excessive vitamin D administration achieved mainly with active derivates [54]. Thus, the ideal range for vitamin D supplementation still needs to be determined.

Our study has some important limitations. First, our study lacked a controlled design. Second, the 25(OH)D3 doses were not standardized but were based on the initial 25(OH)D serum levels. Finally, the alfacalcidol treatment was gradually terminated based on mineral metabolism and bone turnover that may have interfered with the results.
However, this study was conducted under real-life conditions and contributes to the practical knowledge about vitamin D therapy in HD patients.

Conclusion

Daily oral 25(OH)D$_3$ supplementation, ranging from 10 to 30 μg/day, corrects vitamin D deficiency without any evident toxicity. Only 13% of the treated patients remained vitamin D insufficient, in most cases due to poor compliance. The main treatment effects included correction of excessive bone turnover, increase in serum albumin level, increase in the percentage of patients with serum calcium and phosphorus levels within the recommendation of the KDOQI guidelines and decreased requirement of alfalcacidol. These effects may be related to the direct action of 25(OH)D$_3$ on target cells and/or to persistent renal or extra-renal 1-α-hydroxylation. This 25(OH)D$_3$ supplementation can serve as a simple, safe and economic treatment that may improve the outcomes. In the future, large, prospective and controlled long-term studies are required to confirm these data.

Conflict of interest statement. None declared.

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