Cholecalciferol in haemodialysis patients: a randomized, double-blind, proof-of-concept and safety study

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ABSTRACT

Background. The role of cholecalciferol supplementation in end-stage renal disease (ESRD) patients has been questioned. The objective of this randomized double-blinded study is to assess whether cholecalciferol therapy can increase serum 25-hydroxyvitamin D [25(OH)D] levels in haemodialysed patients and the safety implications of this therapy on certain biological parameters and vascular calcifications score.

Methods. Forty-three haemodialysis patients were randomized to receive placebo or cholecalciferol (25 000 IU) therapy every 2 weeks. The biological parameters, serum calcium, phosphorus, 25(OH)D and parathormone (PTH) levels, were monitored monthly for 12 consecutive months. Vascular calcifications were assessed by lateral X-ray radiography.

Results. At baseline, the mean serum 25(OH)D levels were low and similar in both groups. Thirty patients (16 treated and 14 placebo) completed the study: 11 patients died (5 placebo and 6 treated), 1 patient dropped out and 1 patient was transplanted (both from the placebo group). After 1 year, the percentage of 25(OH)D deficient patients was significantly lower in the treated group. None of the patients developed hypercalcaemia. The PTH levels tended to increase over the study period under placebo and to decrease in the cholecalciferol group. The median changes in PTH levels from baseline to 1 year were statistically different between the two groups [+80
However, all these studies were observational. \[\text{INTRODUCTION}\]

In the general population, prescription of nutritional (or native) vitamin D like ergocalciferol or cholecalciferol is recommended not only because of its beneficial effect on bone health but also its relevant pleiotropic effects \[1, 2\]. Since the kidney plays a central role in vitamin D activation with 1-α hydroxylation, the role of cholecalciferol or ergocalciferol versus active vitamin D supplementation has been questioned for a long time in chronic kidney disease (CKD) patients, and even more in end-stage renal disease (ESRD) patients \[2–7\]. In recent years, there has been increasing evidence indicating that cholecalciferol supplementation may be effective in treating ESRD patients. Indeed, 1-α-hydroxylase also exists in many extra-renal tissues and 1,25-dihydroxyvitamin D may then act as a paracrine hormone, at least if the substrate, 25-hydroxyvitamin D \[ 25(\text{OH})\text{D} \], is sufficiently available \[2, 8–11\]. All vitamin D components act via the vitamin D receptor (VDR) which is present in every cell type and explains the pleiotropic effect of vitamin D therapy; 25(OH)D may also directly activate the VDR. Since 25(OH)D has an ∼2400-fold lower affinity for the VDR than the active form of vitamin D, the 25(OH)D plasma concentration must reach much higher levels to adequately stimulate the VDR \[6, 11–13\].

The prevalence of vitamin D deficiency, defined as serum 25(OH)D levels <12 ng/mL, and insufficiency, defined as serum 25(OH)D levels <30 ng/mL, is impressive in CKD and ESRD patients \[6, 14–22\]. Studies on ESRD patients have recently underlined a possible link between serum 25(OH)D levels and global mortality rates \[17, 23–28\]. The most interesting study published by Wolf et al. described a higher risk of mortality associated with low serum 25(OH)D levels in their prospective cohort of 825 incident haemodialysis patients \[17\]. However, all these studies were observational \[2, 11\]. Nevertheless, the Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) guidelines suggest to measure serum 25(OH)D levels and to correct deficiency and insufficiency in CKD patients (as well as in the general population), including in dialysis patients. However, the level of evidence for such a recommendation remains low \[29\]. There are two goals of this randomized-double-blinded study: (i) to test the ability of cholecalciferol therapy to increase the serum 25(OH)D levels in haemodialysed patients, and (ii) to test the safety of this therapy for any adverse effects on the biological CKD–MBD parameters and progression of vascular calcifications.

**CONCLUSIONS.** Cholecalciferol is effective and safe, and does not negatively affect calcium, phosphorus, PTH levels and vascular calcifications. Additional studies are needed to compare the impacts of nutritional and active vitamin D agents on vascular calcification and mortality.

**MATERIALS AND METHODS**

This study included haemodialysis patients from three independent centres in Liège, Belgium and its surrounding areas (Centre Hospitalier Universitaire du Sart Tilman, Centre Hospitalier Regional de La Citadelle, Centre Hospitalier Bois de l’Abbaye de Seraing).

The inclusion criteria were 18 years of age or older, dialysis vintage of at least 12 months, serum 25(OH)D levels <30 ng/mL, phosphorus levels <65 mg/L and serum calcium <2.57 mmol/L at 5 weeks prior to randomization. Subjects with hepatic failure, sarcoidosis, digestive malabsorption or hypercalcaemia, undergoing cinacalcet or cholecalciferol (or ergocalciferol) therapy in the last year, were excluded. Patients with intact parathormone (PTH) levels >800 pg/mL or PTH >400 pg/mL with a duplicate value over the last 3 months were also excluded \[1\]. Figure 1 shows the flow diagram of the study, from eligibility assessment to final analysis.

Patients were randomized to receive placebo or cholecalciferol (25 000 IU) therapy every 2 weeks (block randomization process with stratification on the centre, the 25(OH)D level and calcification score index). Pharmaceutical presentation of the placebo and vitamin D were identical (oily solutions), and phials were provided by the pharmacy of the Liège University Hospital. Both the placebo and cholecalciferol phials were administrated per os under direct supervision of the dialysis nurses in each centre. The treatment arm was not revealed to patients until study completion.

We underline the fact that all subjects were randomized at the same time (in April 2009) and were then perfectly synchronized in their follow-up scheme, notably to avoid seasonal variation. The biological parameters were measured before randomization, monthly during, and at 12 months after randomization. Serum calcium and phosphorus were measured on the Modular (Roche, Mannheim, Germany). Because albumin-corrected calcium has not shown any superiority over non-corrected total calcium, we only used the last form \[30\]. PTH was measured with a second generation assay (DiaSorin, Liaison, Stillwater, MN). We used the DiaSorin Liaison 25(OH)D TOTAL assay (DiaSorin, Liaison, Stillwater, MN) to measure 25(OH)D. All measurements were performed at the Laboratory of Clinical Chemistry of the University Hospital of Liège (EC). The tests are accredited against the ISO 15189 and the laboratory participates in the DEQAS and RPCAQ proficiency testings.

Therapies influencing the calcium and phosphorus metabolism (especially treatment with sevelamer or a calcium-based chelator) were closely monitored during the study.

Vascular calcifications were assessed by lateral X-ray radiography (the ‘Kauppila’ method) at random time points and 12 months later \[29, 31\]. All radiographs were initially masked and subsequently analysed by a single investigator (LM).

The main outcome criterion was the variation of serum 25(OH)D levels over 12 months. Vitamin D insufficiency and deficiency were defined as 25(OH)D levels <30 and 12 ng/mL, respectively \[32\]. The safety of cholecalciferol therapy was assessed by following the changes in calcium, phosphorus,
and PTH serum concentration levels, and vascular calcification score at 12 months in comparison to the placebo therapy.

Human subjects’ procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975.

Our study received approval from the Ethics Committee of Liège University Hospital and it is registered with a Belgian clinical trial number (B70720084117). All patients provided written informed consent before entering the study.

**FIGURE 1:** Flow chart of the study.
Statistical analysis

Data were expressed as mean ± standard deviation (SD) for normal value distribution and as median and interquartile range (IQR) for abnormal distribution. As appropriate, the baseline characteristics were analysed using Student’s t-test, Mann–Whitney U-test or \( \chi^2 \) test.

Repeated-measures analysis of variance was used to determine time-dependent variations in serum 25(OH)D levels, the primary outcome and to compare those variations between treatment groups. The same strategy was applied to the secondary outcomes that were measured monthly during the study, except for PTH because its distribution was not normal. For variables that were only determined at baseline and at 1 year, variations over the study period were analysed by paired Student’s t-test within each treatment group. Finally, we calculated the difference between 1 year and baseline values for the variables of interest (e.g. \( \Delta \)PTH) and compared the treatment effect with either a Student’s t-test or a Mann–Whitney U-test for normally or not-normally distributed variables, respectively. All statistical tests were performed with Statview version 5 software for Windows, SAS Inc.

RESULTS

Forty-three Caucasian patients were included in this study. The subjects were well matched according to age, dialysis vintage, serum calcium, phosphorus and PTH levels and calcification scores. The two groups were well balanced in terms of treatment with chelators and active vitamin D. The weekly dose of active vitamin D was low in both groups. As expected, the mean serum 25(OH)D levels were very low, but not significantly different between the placebo group and the treated group (12 ± 5 and 11 ± 5 ng/mL, respectively). All patients could be considered as vitamin D insufficient; 52% and 48% of the patients could be considered as deficient in the placebo and treated groups, respectively. During the 12 months follow-up, 11 patients died (5 placebo and 6 vitamin D treated, respectively). From the placebo group, one dropped out and one was transplanted. The causes of death were cardiovascular events in five, infectious diseases in three and other causes in the remaining three patients. The high-mortality rate observed in this study is probably related to the high mean age and dialysis vintage of the included population. Thirty subjects completed the study protocol at 12 months (16 in the treated and 14 in the placebo group) and their baseline characteristics are summarized in Table 1. All results reported hereafter pertain to the 30 patients who completed the study.

Proof-of-concept study

The effect of cholecalciferol on serum 25(OH)D levels is shown in Figure 2. Usual seasonal variations were found in the placebo group. In the treated group (25 000 IU, every 2 weeks), the serum 25(OH)D concentration levels increased rapidly. After 3 months, the mean serum 25(OH)D levels were >30 ng/mL and no patients remained vitamin D deficient.

Table 1. Clinical and biological characteristics of patients that have completed the study. Data are expressed as mean ± SD if the distribution is normal and median (IQR) if not specified

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 14</th>
<th>Cholecalciferol n = 16</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73 ± 12</td>
<td>75 ± 9</td>
<td>0.50*</td>
</tr>
<tr>
<td>Sex ratio (% female)</td>
<td>36</td>
<td>25</td>
<td>0.52</td>
</tr>
<tr>
<td>Dialysis vintage (month)</td>
<td>56 ± 39</td>
<td>44 ± 46</td>
<td>0.47*</td>
</tr>
<tr>
<td>( K/V )</td>
<td>1.36 ± 0.17</td>
<td>1.37 ± 0.17</td>
<td>0.87*</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.16 ± 0.15</td>
<td>2.18 ± 0.12</td>
<td>0.75*</td>
</tr>
<tr>
<td>Phosphorus (mg/L)</td>
<td>45 ± 11</td>
<td>46 ± 13</td>
<td>0.79*</td>
</tr>
<tr>
<td>Parathormone (pg/mL)</td>
<td>Median (IQR)</td>
<td>240 [195–410]</td>
<td>312 [206–447]</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D(ng/mL)</td>
<td>12 ± 6</td>
<td>12 ± 5</td>
<td>0.90*</td>
</tr>
<tr>
<td>Use of phosphate binder (all) (%)</td>
<td>58</td>
<td>38</td>
<td>0.28</td>
</tr>
<tr>
<td>Use of phosphate binder (calcium-based) (%)</td>
<td>43</td>
<td>32</td>
<td>0.51</td>
</tr>
<tr>
<td>Use of phosphate binder (sevelamer) (%)</td>
<td>36</td>
<td>50</td>
<td>0.43</td>
</tr>
<tr>
<td>Use of calcitriol analogue (%)</td>
<td>57</td>
<td>31</td>
<td>0.15</td>
</tr>
<tr>
<td>Caltril analogue doses (µg/week)</td>
<td>0.88 ± 1.05</td>
<td>0.59 ± 1.04</td>
<td>0.5*</td>
</tr>
<tr>
<td>Abdominal calcification score</td>
<td>8 ± 8</td>
<td>8 ± 5</td>
<td>0.52*</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients randomized in the study who completed the study. These values were compared between placebo and vitamin D-treated patients with Student’s t-test (*), Mann–Whitney U-test (**) or \( \chi^2 \) test. Values are expressed as mean ± SD, if not specified.
although 56% were deficient at initial visit. After 12 months, four patients (25%) were still in the 25(OH)D insufficiency status. In the placebo group, 50% of the patients were vitamin deficient at the initial visit. At the final visit, 100% and 29% of the patients were insufficient or deficient, respectively. After 12 months of treatment, the percentage of deficient patients in the treatment group was significantly lower in comparison to the placebo group (25% versus 100%, respectively, \( P < 0.0001 \)).

Safety study

None of the patients in the treated group developed supraphysiological levels of 25(OH)D, as the highest observed level was 50 ng/mL throughout the study. Figure 3 illustrated the therapy effect on calcium and phosphorus levels. There was no significant difference between the two groups. None of the patients developed hypercalcaemia and the chelator therapies were not modified during the study period. Regarding the PTH results, we did not observe any significant difference between the two groups at basal and 1-year levels. However, in the treated group, the median PTH levels tended to decrease [from 312 (206–447) pg/mL to 175 (95–337) pg/mL], whereas an opposite trend was observed in the placebo groups [from 240 (195–410) pg/mL to 337 (203–557) pg/mL]. In other words, if we consider the \( \Delta \)PTH levels, we found a statistically significant difference between the treated and placebo groups \( \Delta \)PTH of \(-115\) pg/mL and \(+80\) pg/mL, respectively, \( P = 0.02 \) for the Mann–Whitney \( U \)-test).

Calcification scores were assessed at initial and final visits for 13 and 11 patients in the treated and placebo groups, respectively. The mean calcification score significantly increased (\( P < 0.0001 \)) within 12 months in both the groups (placebo: from 8 ± 8 to 10 ± 7; treated: from 8 ± 5 to 10 ± 6) and the increase was similar in both groups (+2.3/year). All these results are summarized in Table 2.

DISCUSSION

The recent KDIGO guidelines recommend providing cholecalciferol or ergocalciferol therapy to dialysis patients; however, the level of evidence for such a recommendation is very low [29]. In this proof-of-concept study, we demonstrate and confirm that such a therapy is effective and safe, without producing negative effects on both calcium and phosphorus levels, but also on PTH levels and vascular calcifications.

In this study, we confirm that vitamin D therapy (cholecalciferol, 25 000 IU, every 2 weeks) is efficient. None of the treated patients were still vitamin D insufficient and only 25% of them were deficient at the end of the study. These results are evidently superior compared with those observed in the placebo group. From the biological point of view, cholecalciferol therapy seems to be safe, as we did not observe any hypercalcaemic episodes and the calcium and phosphorus levels remained unchanged after 1 year of therapy. This observation confirmed previously published results. In 2007, Saab et al. administered ergocalciferol 50 000 IU per month for 6 months in 119 haemodialysis patients. The authors described the therapy to be efficient [serum 25(OH)D levels increased from 17 ± 9 to 54 ± 16 ng/mL] and without any negative effects on the calcium and phosphorus serum levels [18]. In 2008, Blair et al.
prescribed ergocalciferol 50 000 IU per week to 171 haemodialysis patients with baseline serum 25(OH)D levels <40 ng/mL (18 ± 9 ng/mL). After 6 months, the average 25(OH)D concentration reached 42 ± 25 ng/mL, without any significant effect on the phosphorus and a slight decrease in the calcium serum levels [19]. In the same year, Jean et al. reported their own results. The authors gave between 10 and 30 µg of calcifediol per day to 149 dialysis patients with baseline serum 25(OH)D levels <30 ng/mL. After 6 months, the mean serum 25(OH)D levels increased from 12 ± 9 to 50 ± 19 ng/mL with a neutral effect on calcium and phosphorus levels [33]. The same authors reported similar results with a cholecalciferol dose of 100 000 IU per month for 15 months [34]. Tokmak et al. also used cholecalciferol at 20 000 IU per week for 9 months in 64 dialysis patients with serum 25(OH)D levels <30 ng/mL. The mean serum 25(OH)D levels increased from 7 ± 4 to 32 ± 11 ng/mL with a neutral effect on calcium and phosphorus levels [35]. In 2010, Matias et al. prescribed cholecalciferol, between 10 000 and 50 000 IU per week, according to the serum 25(OH)D levels to 158 patients for 1 year. The mean serum 25(OH)D levels increased from 22 ± 12 to 42 ± 12 ng/mL. After supplementation, the authors observed few but significant decreases in calcium and phosphorus levels. Of interest, the authors also observed a positive effect on C-reactive protein, brain natriuretic peptide levels and on left ventricular mass index assessed by echocardiography. Recently, in 2012, Jakopin et al. reported their investigation involving 101 haemodialysis patients with serum 25(OH)D levels < 30 ng/mL. These patients were treated with cholecalciferol 40 000 IU for 3 months. After 3 months, the monthly doses were varied according to time and serum 25(OH)D levels, for 2 years. The mean serum 25(OH)D levels increased from 12 ± 7 to 22 ± 6 ng/mL; serum calcium concentrations tended to decrease during the study period [36]. The above-listed findings from various studies were promising. However, none of these studies were randomized. Thus, the therapy effect remained questionable [2, 11]. To the best of our knowledge, only one publication (excluding publications limited to abstracts) studied the effect of cholecalciferol in haemodialysis patients in comparison to a placebo-controlled group [2]. Wasse et al. studied 27 placebo and 25 treated patients for 3 weeks. The treated group was prescribed high cholecalciferol dose (100 000 IU per week) and 94% of the treated subjects had serum 25(OH)D levels >30 ng/mL at the end of the study. Similarly, as in previous investigations, the authors did not find any adverse effects on calcium and phosphorus levels [37]. In comparison to our study, the treatment period was very short (3 weeks versus 1 year) and the prescribed cholecalciferol dose was far from physiological; the dose received in 3 weeks was equivalent to the dose we prescribed in 6 months.

The safety profile of all these studies must be emphasized as hypercalcemia and hyperphosphatemia have been reported in studies with active vitamin D (i.e. calcitriol analogues) therapy. The potential advantage of cholecalciferol over active vitamin D is most likely linked to the fact that monitoring of cholecalciferol is easier and more accurate through measuring serum 25(OH)D levels, while measuring serum 1,25(OH)2D is more cumbersome and not recommended for monitoring of an active vitamin D treatment [29]. A positive effect of cholecalciferol therapy on PTH levels could be expected, since it has been demonstrated in vitro [38]. Some authors have shown that cholecalciferol therapy decreased PTH levels in dialysis patients [2, 22, 33, 34], but this finding has not been confirmed by others [19, 35–37]. In our randomized, placebo-controlled study, this effect is not fully observed, as PTH levels did not change significantly between the two groups after 1 year. However, we found opposite trends in the two groups which translate in a significant difference when ΔPTH over 1 year are actually considered. It must also be recognized that our sample is probably too limited to assess the full effect on the PTH parameter with a high intra- and inter-individual variability [39].

The effect of active vitamin D on calcification is questionable but this effect seems to be dose-dependent [11, 20, 40]. In this context, we must emphasize that the weekly dose of active vitamin D therapy was low in our patients. Regarding this potential dose effect, the monitoring of cholecalciferol therapy

### Table 2. Changes in the main safety variables over the 1-year study period

<table>
<thead>
<tr>
<th></th>
<th>Placebo (10 000 IU per week)</th>
<th>Cholecalciferol (25 000 IU, every 2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Parathormone (pg/mL) Median (IQR)</td>
<td>240 (195–410)</td>
<td>312 (206–447)</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.16 ± 0.11</td>
<td>2.18 ± 0.15</td>
</tr>
<tr>
<td>Phosphorus (mg/L)</td>
<td>45 ± 11</td>
<td>46 ± 13</td>
</tr>
<tr>
<td>Calcification score</td>
<td>8 ± 8</td>
<td>8 ± 5</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or as median (interquartile range).

*P-value for a paired t-test for within treatment groups variation over 1 year.

**P-value for the t-test or *Mann–Whitney test comparing the change from baseline to 1 year between treatment groups. Values are expressed as mean ± SD, if not specified.
by serum 25(OH)D measurement provides a significant advantage. The neutral effect of cholecalciferol on vascular calci-
cfications is reassuring. The increase in calcification score (2.3 per year) observed in our study is similar to the progression observed in the Calcification Outcome in Renal Disease (CORD) study [41]. Several different authors have described an association between increased vascular calcifications and low serum 25(OH)D levels in cross-sectional studies [11, 20, 42], but a potential protective effect of the cholecalciferol on the progression of vascular calcifications was not shown in our interventional study.

There are several limitations in our study. First, the sample size is relatively small but this work should be considered as a pilot and proof-of-concept study. This size limitation is particular relevant regarding the safety implications. Indeed, observational studies including a high number of patients might be more appropriate to detect negative side effects than ran-
domized, placebo-controlled studies including relatively few patients. Likewise, the sample is probably not sufficient to assess the stability of the calcification score. Nevertheless, the population in this study is homogenous and representative of the haemodialysis population, at least in relation to their serum 25(OH)D levels and calcification scores. The power of this study was suitable to detect the differences in serum 25 (OH)D levels. In addition, the results of this small sample must be analysed in light of the 1-year follow-up in a dialysis population with a high mortality risk and the possibility of renal transplantation. Another limitation of the sample is that only Caucasians were included; it is possible that responses to cholecalciferol might be different in other ethnicities. Second, we only included controlled patients considered as stable with respect to the phosphorus, calcium and PTH levels. Third, the lateral X-ray radiography is not the best way to assess vascular calcifications. Coronary or abdominal computed tomography scans are more precise. However, these last two methods are more costly and gives off more radiation. It must be empha-
sized that Kauppila’s method is preferred to assess vascular calcifications, as stated in the KDIGO guidelines [29, 31]. In the same vein, we have not assessed endothelial dysfunction (for example, by pulse wave velocity), which has been shown to correlate with serum 25(OH)D levels in a cross-sectional study [43]. Finally, the dose of cholecalciferol given to our patients may be considered insufficient because 25% of the treated patients were still insufficient. However, this is primar-
ily a safety study, over a long period. The dose we prescribed (25 000 IU, every 2 weeks) for 1 year may be considered as more physiological than higher doses given on a shorter period of time, such as 200 000 IU in 3 weeks. Additional studies over a longer period of time with intermediate doses of cholecalciferol (for instance, 25 000 IU per week) would cer-
tainly be of interest.

In the proof-of-concept study performed over a 1-year period, we demonstrated the effectiveness of cholecalciferol therapy in haemodialysis patients. In our limited sample, we observed no detrimental effects on several biological vari-
ables and on the progression of vascular calcifications. Additional data, from randomized controlled studies, with a larger population sample, are now needed to compare cholecalciferol therapy with placebo and active vitamin D therapies.

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script.

CONFLICT OF INTEREST STATEMENT

This study has been presented as an oral presentation at the XLVIII Congress of ERA-EDTA. Prague, 2011.

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