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Monitoring 25-OH and 1,25-OH vitamin D levels in hemodialysis patients after starting therapy: Does it make sense?

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ABSTRACT

Background and aims: In hemodialysis patients, monitoring 25-hydroxyvitamin D (25(OH)D) levels is recommended. It is however unclear if monitoring 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels is interesting.
Materials and methods: We repeatedly measured $1,25(OH)_2D$ (DiaSorin Liaison analyser) and 25(OH)D (LCMS/MS) concentrations in patients newly treated by active or native vitamin D to study the impact of such treatments on serum concentrations.
Results: Ten patients were included in the native and 12 in the active vitamin D group. In the native group, a significant increase was observed between the baseline and the last 25(OH)D concentrations available (21.65 [17.39;25.26] *versus* 33.49[28.60;40.30] ng/mL, p = 0.0059). The baseline and last available $1,25(OH)_2D$ concentrations were not different (12.15[4.25;15.40] *versus* 11.35[9.72;21.85] pg/mL, p = 0.5566). In the active group, no difference was observed between the baseline and the last 25(OH)D concentrations (51.70 [42.97;63.95] *versus* 50.89[42.02;64.49] ng/mL, p = 0.5186). The same observation was made for 1,25 $(OH)_2D$ concentrations (25.65[17.05;41.85] *versus* 28.70[23.36;43.73] pg/mL, p = 0.6221). Using a linear mixed model, a significant change over time was only observed in 25(OH)D serum levels for patients treated by with native vitamin D.
Conclusion: Measuring 1,25(OH)2D levels in patients newly treated by active vitamin D does not seem useful in monitoring active vitamin D therapy.

1. Introduction

Both native (nutritional) and active vitamin D therapies are largely prescribed in hemodialysis patients to improve bone health and/or to prevent or treat hyperparathyroidism [1–4]. In hemodialysis patients, the international KDIGO (for "Kidney Disease Improving Global Outcomes") guidelines recommend to monitor 25-hydroxyvitamin D (25(OH)D) levels, even if the level of evidence is not high: "In patients with chronic kidney disease, we suggest that 25(OH)D levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C)."[1]. Active vitamin D therapy should be prescribed to control hyperparathyroidism in hemodialysis patients [1,3]. However, there are no recommendations about the interest of monitoring 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels in this context. Even if $1,25(OH)_2D$ concentrations are frequently measured in studies in hemodialysis [5,6], it is still unknown if such a measurement makes sense to guide therapy with active vitamin D, especially with calcitriol or alphacalcidol. In the current analysis, we repeatedly

Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; KDIGO, Kidney Disease Improving Global Outcomes.

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Table 1
Clinical, biological and dialysis-related characteristics of the population.

	Native vitamin D	Active vitamin D	P values	All
	n = 10	n = 12		
Clinical parameters				
Age (years)	74.5 [65;82]	69.5 [52;75.5]	NS	71.5 [60.0;79.0]
Sex Ratio (% female)	30 %	30 %	NS	30 %
Ethnicity n (% of non-White)	0 (0)	2 (17)	NS	2 (9)
Dry weight (kg)	79 [64;87] N = 9	70 [60;76]	NS	71 [63;83] N = 21
Main diagnosis n (%)				
Glomerulonephritis	1 (10)	2 (17)	NS	
Diabetes and/or Hypertension	8 (80)	2 (17)	0.0039	3 (14)
Polycystic disease	1 (10)	2 (17)	NS	10 (45)
Other	0 (0)	6 (50)	0.0104	3 (14) 6 (27)
Cardiovascular profile n (%)				
Diabetes	4 (40)	1 (8)	NS	5 (23)
Hypertension	9 (90)	9 (75)	NS	18 (82)
Tabagism	3 (30)	2 (17)	NS	5 (23)
Dyslipemia	5 (50)	7 (58)	NS	12 (55)
History of vascular disease	6 (60)	6 (50)	NS	12 (55)
Biological parameters				
Baseline 25-hydroxyvitamin D (ng/mL)	16.77 [10.38;23.57]	51.70 [43.45;63.13]	p = 0.0004	40.38 [18.57;55.10]
Baseline 1,25-dihydroxyvitamin D (pg/mL)	12.15 [4.25;15.40]	25.65 [17.05;41.85]	p = 0.0034	17.05 [12.50;27.10]
Baseline parathormone (pg/mL) Median [P25-P75]	235 [214–334] (n = 9)	327 [240–425]	NS	313 [214;408]
Baseline hemoglobin (g/L)	10.9 [10.6;11.4]	11.3 [10.6;11.5]	NS	11.0 [10.6;11.4]
Baseline calcium (mmol/L)	2.09 [2.00;2.19]	2.12 [1.98;2.28]	NS	2.11 [1.99;2.25]
Baseline phosphate (mmol/L)	1.55 [1.22;1.93]	1.78 [1.05;1.37]	NS	1.55 [1.22;1.93]
Baseline albumin (g/L)	38 [32;39]	40 [38;42]	NS	39 [36;41]
Therapeutic parameters (before inclusion)				
Treatment with calcium-based chelators (%)	6 (60)	9 (75)	NS	15 (68)
Treatment with non-calcium-based chelators (%)	2 (20)	7 (58)	NS	9 (41)
Treatment by cinacalcet (%)	1 (10)	1 (8.3)	NS	2 (9)
Treatment by active vitamin D n (%)	0	0	NS	0 (0)
Treatment by native vitamin D n (%)	0	11 (92)	<0.0001	11 (50)
Dialysis parameters				
Dialysate Calcium 1.25 or 1.5	2 vs 8	10 vs 2	0.0039	12 vs 10
High Flux or low flux membrane	9 vs 1	9 vs 3	NS	18 vs 4
Catheter or fistula	4 vs 6	8 vs 4	NS	12 vs 10
Hemodialysis or hemodiafiltration	9 vs 1	9 vs 3	NS	18 vs 4
Dialysis vintage (months)	9 [1;26]	26 [12;51]	NS	19 [7;46]
Dialysis time per week (minutes)	240 [210;240]	240 [240;240]	NS	240 [229;240]

measured both $1,25(OH)_2D$ and 25(OH)D concentrations in patients newly treated by calcitriol or cholecalciferol to study the impact of such treatments on $1,25(OH)_2D$ and 25(OH)D concentrations. If the impact of native vitamin D on 25(OH)D concentrations is well illustrated in the literature, our main goal was to study the impact of active vitamin D on $1,25(OH)_2D$.

2. Material and methods

2.1. Patients

From two different hemodialysis centers (Centre Hospitalier Universitaire du Sart Tilman, Centre Hospitalier Regional de La Citadelle, Liège, Belgium), we included adult patients newly treated by cholecalciferol or calcitriol (or alphacalcidol). The indication and the choice of therapy were not the goal of the current study. Indication of starting therapy, initial drug dosage and potential adaptations were left to the discretion of the usual practitioners. Patients were excluded if they had the following characteristics: dialysis vintage less than one month, mean phosphate levels (i.e. mean of the last three results) > 2.1 mmol/L, mean calcium levels (i.e. mean of the last three results) > 2.57 mmol/L, lack of adherence, absence of contraception by women of childbearing age, pregnancy, hepatic failure, sarcoidosis, active tuberculosis disease and bowel inflammatory disease.

Calcitriol (or alphacalcidol) is mainly prescribed in patients with hyperparathyroidism or severe hypocalcemia, and most of them were thus already treated with native vitamin D. Vitamin D analogs are not available in Belgium. At the opposite, prescription of native vitamin D was dependent on 25(OH)D concentrations, and thus no patient newly treated by native vitamin D was already treated by active vitamin D.

The goal of our study was to test the impact of cholecalciferol or calcitriol treatments on serum $1,25(OH)_2D$ and 25(OH)D concentrations. Both $1,25(OH)_2D$ and 25(OH)D levels were measured at each dialysis session (thrice a week) in the first four weeks of treatment, then once a week (the first dialysis session of the week) from week 5 to week 16, then once every 4 weeks (from week 16 to week 28). Each patient should thus theoretically have $1,25(OH)_2D$ and 25(OH)D levels measured 28 times over a 28-week period. A first measurement (baseline) was obtained before starting the treatment with vitamin D.

Human subjects' procedures were in accordance with the ethical

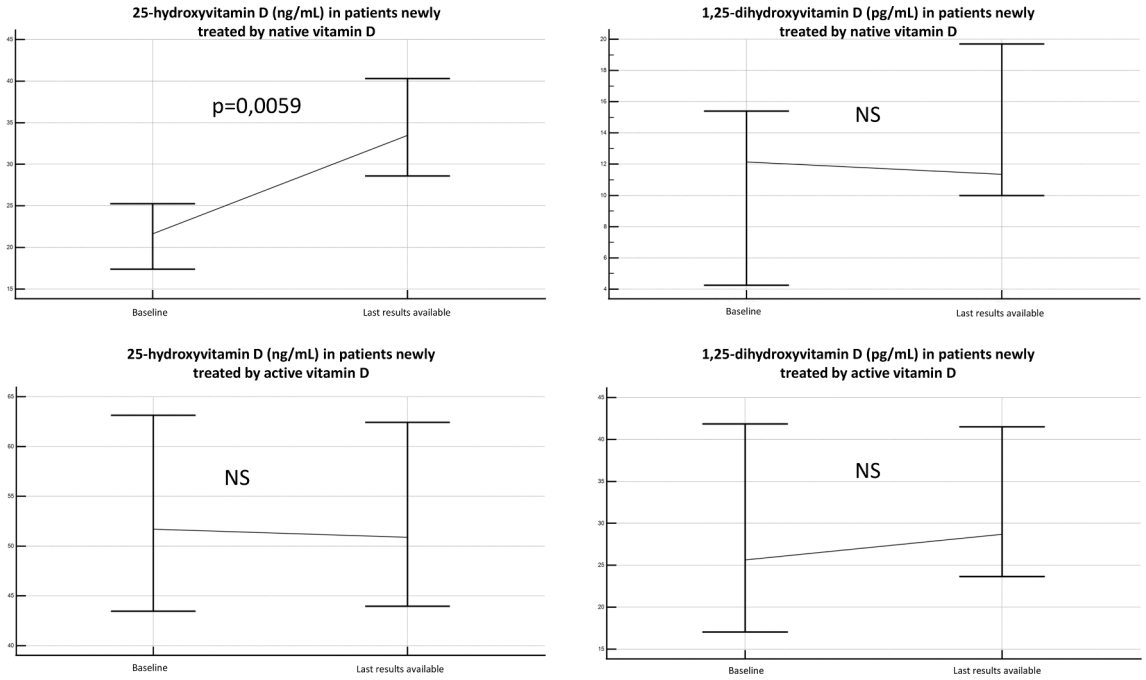

Fig. 1. Comparison of 25-hydroxyvitamin D (left) and 1,25-dihydroxyvitamin D (right) concentrations between baseline values and last results available in patients newly treated by native (upper) and active vitamin D (lower).

standards of the Helsinki Declaration of 1975. Our study has been approved by the Ethic Committee of Liège University Hospital and it is registered with a Belgian clinical trial number (B707201317596). All patients provided written informed consent before entering the study.

2.2. Analytical methods

Routine chemistry analytes (calcium, phosphate, albumin, prealbumin and bicarbonates) as well as haemoglobin were measured locally, but with the same analytical methods. Parathormone, 1,25 $(OH)_2D$ and 25(OH)D measurements were all centralized in the Clinical Chemistry Department of CHU Sart Tilman, accredited against the ISO 15189. Samples were stored at −80 °C until determination by batches. Third generation (1–84) parathormone and 1,25$(OH)_2D$ [7] were measured on the DiaSorin Liaison analyser, with coefficients of variation (CV) < 8 %. 25(OH)D was determined with a validated LCMS/MS [8]. The method presented a CV < 5 %.

2.3. Statistical methods

Most data were not normally distributed (Shapiro-Wilk test) and variables were thus expressed as median with interquartile range [IQR]. A Mann-Whitney test was used for comparison of variables between groups. First, we simply compared, in the two groups, the baseline 1,25 $(OH)_2D$ and 25(OH)D concentrations with the last concentrations available with a Wilcoxon test. Then, to account for the intra-individual correlation of longitudinal data, linear mixed models were fitted to assess the changes of 25(OH)D and 1,25$(OH)_2D$ over time, with time defined as fixed variable and individuals as random effect. Missing data were imputed using linear interpolation. Statistical analyses were performed with R 4.2.0 (R foundation for statistical analysis, Vienna, Austria).

3. Results

Ten hemodialysis patients were included in the native vitamin D arm and 12 in the active vitamin D arm. Patients characteristics (clinical, biological and dialysis parameters) are described in Table 1. In each group, there was 30 % of women and median age was similar. Most characteristics were not different between the two groups, keeping in mind that the measurement of the *intraindividual* variation of 1,25 $(OH)_2D$ and 25(OH)D concentrations associated with newly prescribed vitamin D therapies was the goal of the study.

As expected by protocol (11 patients in the active group were already treated by native vitamin D at inclusion), the median 25(OH)D concentration at baseline was significantly higher in the group newly treated by active vitamin D compared to patients newly treated by native vitamin D. In the group previously treated by native vitamin D, the median 1,25$(OH)_2D$ concentration at baseline was also significantly higher (Table 1).

During the follow-up, there were 25 (8.1 %) lacking values for 1,25 $(OH)_2D$ concentration and 25 (8.1 %) values for 25(OH)D in the active vitamin D arm. In this group, one patient died after week 20. In the native vitamin D arm, there were 28 (9.1 %) lacking values for 1,25 $(OH)_2D$ concentration and 28 (9.1 %) values for 25(OH)D. In this group, two patients deceased at week 5 and 13.

Among patients newly treated by native vitamin D, seven were treated by cholecalciferol 25,000 U once a week and three by 25,000 U once every-two weeks (mean weekly dose of 12,250 U). This dosage remained constant during the follow-up. Among patients treated by active vitamin D, five patients were treated by calcitriol 0.5 μg thrice a week (taken at the end of the dialysis session), one patient got calcitriol 0.25 μg thrice a week, two patients got calcitriol 0.25 μg once a day, two patients got alphacalcidol 0.25 μg once a day, and two patients received alphacalcidol 1 μg thrice a week (after dialysis session) (mean weekly dose of 1.58 μg). Among these patients, one subject stopped his treatment at week 24, and two got a larger dose (doubled) at week 11 and 16. The treatment dosage was not modified in all other subjects.

In the group of patients newly treated by native vitamin D, a significant increase was observed between the baseline 25(OH)D concentration and the last 25(OH)D concentration available in each patient (21.65 [17.39;25.26] *versus* 33.49 [28.60;40.30] ng/mL, p = 0.0059). In the same group, the median baseline 1,25$(OH)_2D$ concentration and the median last 1,25$(OH)_2D$ concentration available were not different (12.15 [4.25;15.40] *versus* 11.35 [9.72;21.85] pg/mL, p = 0.5566). In the group of patients newly treated by active vitamin D, no difference

Table 2
Slopes over time in the different linear mixed models.

Treatment	Variable	Slope over time (Change per day)	p-value
Active	25(OH) vitamin D	$-1.3.10^{-3}$ ng/ml per day	0.97
Active	$1,25(OH)_2$ vitamin D	0.02 pg/ml per day	0.27
Native	25(OH) vitamin D	0.06 ng/ml per day	0.003*
Native	$1,25(OH)_2$ vitamin D	$5.1.10^{-5}$ pg/ml per day	0.99

was observed between the baseline 25(OH)D concentration and the last 25(OH)D concentration available in each patient (51.70 [42.97;63.95] *versus* 50.89 [42.02;64.49] ng/mL, p = 0.5186). In the same group, the median baseline 1,25 $(OH)_2$D concentration and the median last 1,25 $(OH)_2$D concentration available were not different (25.65 [17.05;41.85] *versus* 28.70 [23.36;43.73] pg/mL, p = 0.6221). These results are shown in Fig. 1.

Then, we assessed the changes of 25(OH)D and $1,25(OH)_2$D using a linear mixed model. In patients treated with active vitamin D, neither the serum levels of 25(OH)D nor $1,25(OH)_2$D were significantly changing over the time (p 0.97 and 0.27 respectively). In patients treated with native vitamin D, there was no significant change over time in the $1,25(OH)_2$D serum level (p = 0.99), in contrast, 25(OH)D serum level significantly increased over time, with a slope of 0.06 ng/ml per day (p = 0.003) (Table 2). Graphically, we noticed on the scatter plot two distinct periods in the evolution of serum levels of 25(OH)D over time (Fig. 2). The optimal cut-off was got after 30 days, with a slope of 0.22 ng/ml per day (p = 0.001) in the first 30 days of treatment with native vitamin D, and no further significant change after the 30th day of treatment (slope 0.01, p = 0.185) (Fig. 3).

4. Discussion

Hemodialysis patients are prone to 25(OH)D and $1,25(OH)_2$D deficiencies, which themselves will enhance the development of secondary hyperparathyroidism. Such deficiency is also associated with a higher risk of mortality [3–5,9,10]. In hemodialysis patients, KDIGO guidelines suggest that 25(OH)D levels might be measured, and repeated testing determined by baseline values and therapeutic interventions but there is no recommendation for measurement of $1,25(OH)_2$D [1]. In the current analysis with repeated measurements, we confirmed that a treatment with native vitamin D will, as expected, lead to a significant increase in 25(OH)D levels [2,10,11]. With a very close monitoring (measurement at every dialysis session), we can show that 25(OH) levels rise after the first month of therapy to reach a plateau thereafter, at least when cholecalciferol was given at 25,000 once a week or every-two weeks. Our methodology did not allow us to know if this drug dosage was sufficient in every patient to reach the target level and/or to control hyperparathyroidism. Interestingly, we did not confirm data from other authors who suggested that native vitamin D treatment in hemodialysis patients was associated with a significant increase in $1,25(OH)_2$D serum level [4,10,12–15]. On the other hand, even if our sample is too low to draw conclusions, the baseline $1,25(OH)_2$D concentrations in patients

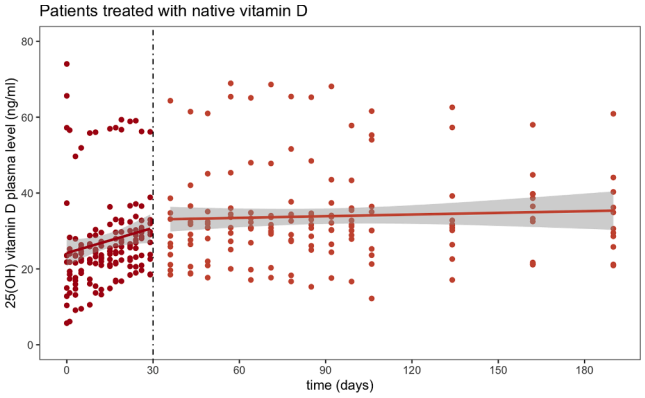

Fig. 3. Evolution of serum levels of 25(OH) vitamin D in the group of patients treated with native vitamin, and linear regression modeling prior to 30 days of treatment and after 30 days of treatment.

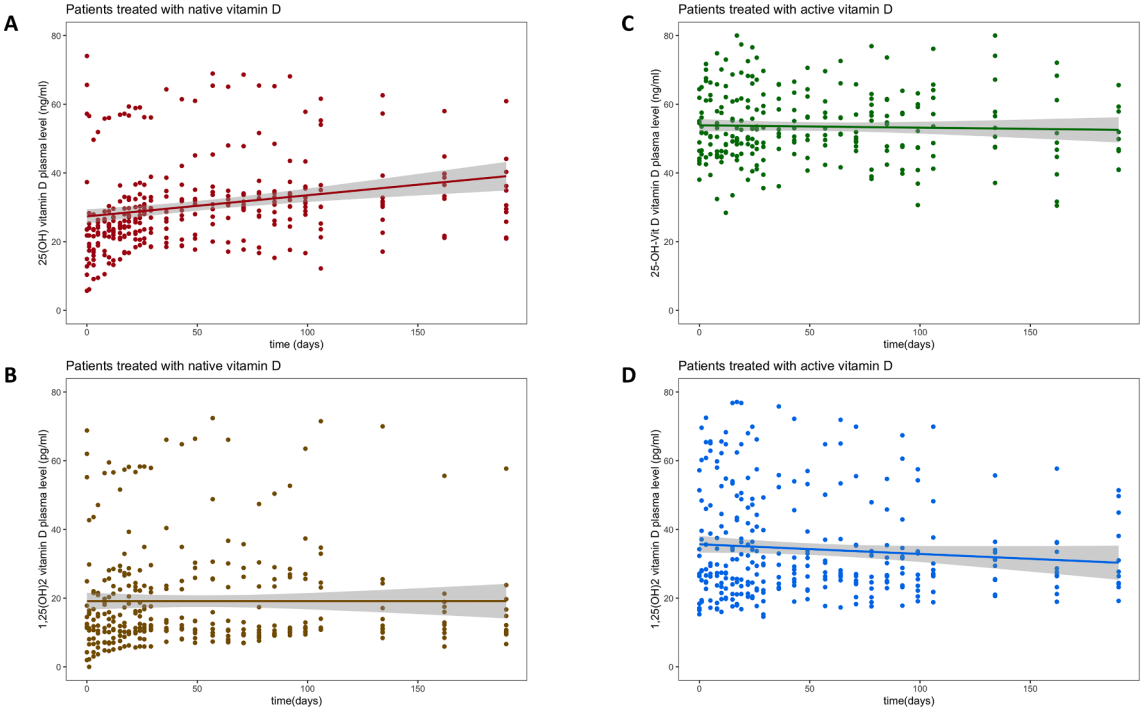

Fig. 2. Scatter plot and linear regression modeling the evolution of serum levels of: A. 25(OH) vitamin D in the group of patients treated with native vitamin D. B. $1,25(OH)_2$ vitamin D in the group of patients treated with native vitamin D. C. 25(OH) vitamin D in the group of patients treated with active vitamin D. D. $1,25(OH)_2$ vitamin D in the group of patients treated with active vitamin D.

already treated by native vitamin D were higher than in patients non-treated by this therapy. In our study, it might be hypothesized that the dosage and/or duration of native vitamin D treatment was not high enough to induce a significant increase in $1,25(OH)_2D$ concentrations after native vitamin D therapy.

As confirmed by our results, we did not expect an effect of calcitriol or alfacalcidol on the 25(OH)D levels. More interestingly, we have also shown that treatment with such therapies was not accompanied with significant increases in $1,25(OH)_2D$ serum level. So, monitoring $1,25(OH)_2D$ serum level in hemodialysis patients treated by active vitamin D is useless. The main explanation is probably the very short half-time of these drugs. Some authors have also argued that $1,25(OH)_2D$ was acting by an autocrine or paracrine mode with a possible local action, not well reflected by blood concentrations [10]. Regarding this absence of effect, we must emphasize that the methods used in this study to measure 25(OH)D and, and still more, $1,25(OH)_2D$ present a high sensitivity and should thus be able to quantify a significant increase in the concentration of both metabolites.

Our study must be analyzed in the light of its limitations. First, the sample size in each treatment arm was limited. Yet, we must emphasize that we focused on intra-individual variations in each arm. The differences in clinical characteristics between the two arms are however small, and more importantly not relevant regarding the goal of our research. Moreover, even if the number of patients was limited, samples and measurements were closely repeated, meaning that 25(OH)D and 1,25(OH)2D levels were determined 28 times each in every patient with a low rate of missing values. Second, the follow-up was relatively short (28 weeks). As already evoked, it is possible that some effects of treatment could impact 25(OH)D or 1,25(OH)2D levels after a longer period. In the same view, we were not able to study the potential effect of seasonal variations of 25(OH)D. Third, the absence of any effect of calcitriol or alfacalcidol on 1,25(OH)2D levels we observed could be different with larger, longer, and/or more frequent dosage.

5. Conclusions

We confirmed that monitoring 25(OH)D is a good practice in hemodialysis patients newly treated by native vitamin D. At the opposite, measuring 1,25(OH)2D levels in patients newly treated by active vitamin D does not seem useful in monitoring active vitamin D therapy, at least during the first 28 weeks of treatment. These results should be confirmed in a larger population.

CRediT authorship contribution statement

Pierre Delanaye: Conceptualization, Methodology, Investigation, Resources, Writing – original draft. **Antoine Lanot:** Formal analysis, Writing – review & editing, Visualization. **Antoine Bouquegneau:** Formal analysis, Writing – review & editing. **Xavier Warling:** Investigation, Resources, Writing – review & editing. **Luc Radermacher:** Investigation, Resources, Writing – review & editing. **Catherine Masset:** Investigation, Resources, Writing – review & editing. **Jean-Marie Krzesinski:** Funding acquisition, Supervision, Writing – review & editing. **Olivier Moranne:** Funding acquisition, Writing – review & editing. **Etienne Cavalier:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

[1] KDIGO, Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), Kidney. Int. Suppl. 7 (2017) (2017) 1–59.
[2] P. Delanaye, L. Weekers, X. Warling, M. Moonen, N. Smelten, L. Medart, J.-M. Krzesinski, E. Cavalier, Cholecalciferol in haemodialysis patients: a randomized, double-blind, proof-of-concept and safety study, Nephrol. Dial. Transplant. 28 (2013) 1779–1786.
[3] V. Brandenburg, M. Ketteler, Vitamin D and Secondary Hyperparathyroidism in Chronic Kidney Disease: A Critical Appraisal of the Past, Present, and the Future, Nutrients. 14 (2022) 3009.
[4] G. Jean, J.C. Souberbielle, C. Chazot, Vitamin D in chronic kidney disease and dialysis patients, Nutrients. 9 (2017) 328.
[5] M. Wolf, A. Shah, O. Gutierrez, E. Ankers, M. Monroy, H. Tamez, D. Steele, Y. Chang, C.A. Camargo, M. Tonelli, R. Thadhani, Vitamin D levels and early mortality among incident hemodialysis patients, Kidney. Int. 72 (8) (2007) 1004–1013.
[6] Sharon M Moe 1 , Glenn M Chertow 2 , Patrick S Parfrey 2 , Yumi Kubo 2 , Geoffrey A Block 2 , Ricardo Correa-Rotter 2 , Tilman B Drüeke 2 , Charles A Herzog 2 , Gerard M London 2 , Kenneth W Mahaffey 2 , David C Wheeler 2 , Maria Stolina 2 , Bastian Dehmel 2 , William G Goodman 2 , Jürgen Floege 2 , Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators*.
[7] J.C. Souberbielle, E. Cavalier, P. Delanaye, C. Massart, S. Brailly-Tabard, C. Cormier, D. Borderie, A. Benachi, P. Chanson, Serum calcitriol concentrations measured with a new direct automated assay in a large population of adult healthy subjects and in various clinical situations, Clin. Chim. Acta. 451 (2015) 149–153.
[8] E. Cavalier, P. Lukas, Y. Crine, S. Peeters, A. Carlisi, C. Le Goff, R. Gadisseur, P. Delanaye, J.-C. Souberbielle, Evaluation of automated immunoassays for 25 (OH)-vitamin D determination in different critical populations before and after standardization of the assays, Clin. Chim. Acta. 431 (2014) 60–65.
[9] E. Slatopolsky, S. Lopez-Hilker, J. Delmez, A. Dusso, A. Brown, K.J. Martin, The parathyroid-calcitriol axis in health and chronic renal failure, Kidney. Int. Suppl. 29 (1990) S41–S47.
[10] I. Capelli, G. Cianciolo, L. Gasperoni, A. Galassi, P. Ciceri, M. Cozzolino, Nutritional vitamin D in CKD: Should we measure? Should we treat? Clin. Chim. Acta. 501 (2020) 186–197.
[11] P. Kandula, M. Dobre, J.D. Schold, M.J. Schreiber Jr., R. Mehrotra, S. D. Navaneethan, Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials, Clin. J. Am. Soc. Nephrol. 6 (2011) 50–62.
[12] C. Xu, Y.C. Li, S.M. Zhao, Z.X. Li, Evaluation of responses to vitamin D3 (cholecalciferol) in patients on dialysis: a systematic review and meta-analysis, J. Invest. Med. 64 (2016) 1050–1059.
[13] A. Dusso, S. Lopez-Hilker, N. Rapp, E. Slatopolsky, Extra-renal production of calcitriol in chronic renal failure, Kidney. Int. 34 (1988) 368–375.
[14] J. Cunningham, H. Makin, How important is vitamin D deficiency in uraemia? Nephrol. Dial. Transplant. 12 (1997) 16–18.
[15] A. Massart, F.D. Debelle, J. Racape, C. Gervy, C. Husson, M. Dhaene, K.M. Wissing, J.L. Nortier, Biochemical Parameters After Cholecalciferol Repletion in Hemodialysis: Results From the VitaDial Randomized Trial, Am. J. Kidney. Dis. 64 (2014) 696–705.