ORIGINAL RESEARCH

Vitamin D Deficiency and Associated Factors in Hemodialysis Patients

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Background: Vitamin D deficiency is prevalent in the general elderly population, and is related to an increased risk of osteoporosis, fractures, and cardiovascular calcification. Only limited data and no guidelines are available on vitamin D deficiency in hemodialysis patients.

Objective: We aimed to assess the frequency of, and factors associated with, 25(OH) vitamin D deficiency in hemodialysis patients in a French dialysis center.

Design: In March 2006, we studied all prevalent hemodialysis patients who had not received native vitamin D supplements in the recent past. According to the Kidney Disease Outcomes and Quality Initiative guidelines, patients were assigned to the following 3 groups: group 1, with a sufficient vitamin D serum level (>75 nmol/L); group 2, with an insufficient level (25 to 75 nmol/L); and group 3, with severe deficiency (<25 nmol/L). Patients' characteristics and biochemical findings were compared between patients of groups 1 and 3.

Results: Of 253 patients, 11% patients were in group 1; 47% were in group 2; and 42% were in group 3. The proportions of female and diabetes patients were 42% and 34%, respectively. The mean (± SD) age of all patients was 66.7 ± 14 years, and the mean duration of dialysis was 62 ± 74 months, with a mean schedule of 3 × 6.5 hours and administration of a 1.5 mmol/L calcium dialysate. Concomitant treatment included alfacalcidol (66% of patients) and sevelamer (34% of patients) as a standard phosphate binder. Group 3 patients had a lower dialysis vintage (53 ± 66 vs. 73 ± 85 months, $P < .05$), a higher number of diabetes patients (45% vs. 21%, $P < .05$), a higher number of female patients (53% vs. 28%, $P < .05$), and a higher level of intact parathyroid hormone (260 ± 227 vs. 213 ± 153 pg/mL, $P < .05$) than group 1 patients. No relationship was found between vitamin D storage levels and bone markers, serum calcium, phosphorus, albumin, body mass index, normalized protein catabolic rate, radiologic vascular calcification score, and hip bone mineral density. In multivariate logistic regression analyses, no factors were significantly associated with vitamin D deficiency.

Conclusions: Calcidiol deficiency was highly prevalent in a French dialysis population. The associated factors mainly included female sex, diabetes, shorter dialysis duration, and higher intact parathyroid hormone level. Although there are no guidelines for the therapy of patients with chronic kidney disease at stage 5, the usefulness of vitamin D supplementation may be assessed by considering its potential direct action, the need for providing fuel for renal and extrarenal calcitriol production in particular, and the numerous potential favorable effects on health.

VITAMIN D DEFICIENCY remains highly prevalent in the general population, and particularly in elderly and medical inpatients.[1] This deficiency may be of nutritional origin; however, insufficient exposure to sunlight is certainly a major cause of the deficiency. In addition, black race,[2] obesity,[3] and a vegetarian diet may aggravate this deficiency.[4] Vitamin D deficiency was reported to be associated with cardiovascular calcification,[5] low mood and cognitive performance,[6] decreased muscle strength and mass,[7] osteoporosis, osteomalacia,[8] low bone mineral density (BMD) and fractures,[9] and according to a recent study, mortality.[10] In nondialyzed patients with chronic kidney disease (CKD), vitamin D deficiency is highly prevalent, and is associated with hyperparathyroidism.[11,12] The serum level of 25(OH) vitamin D (calcidiol) reflects the vitamin D storage level in the body.

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In the kidney, calcidiol is 1α-hydoxylated and transformed to calcitriol, but it is thought to have a direct effect on the nuclear vitamin D receptor.[13] A healthy serum level of vitamin D in the general population ranges from 75 to 125 nmol/L.[14] Limited data on vitamin D status were reported in hemodialysis patients, particularly in European countries. The aim of the present study was to assess vitamin D deficiency in hemodialysis patients free from supplementation, and to point out the associated risk factors of deficiency.

Methods

We investigated all prevalent hemodialysis (HD) patients at our center in March 2006. We verified that patients had not received native vitamin D supplementation for at least 6 months. The serum levels of 25(OH) vitamin D2 and D3 were measured using chemiluminescence (Liaison, DiaSorin, Inc., Stillwater, MN). Patients were assigned to the following 3 groups according to their vitamin D serum level and Kidney Disease Outcomes and Quality Initiative (KDOQI) guidelines: group 1, with sufficient vitamin D concentration (>75 nmol/L); group 2, with insufficient vitamin D storage (25 to 75 nmol/L); and group 3, with severe deficiency (<25 nmol/L). We simultaneously measured the following parameters in midweek blood samples: serum calcium (corrected for albumin), phosphorus, intact parathyroid hormone (iPTH) (Roche Elecsys Immunoenzymatic, Basel, Switzerland), beta-cross laps (Roche Elecsys, Basel, Switzerland), bone alkaline phosphatase (chemiluminescence), and calcitriol 1,25(OH) (normal range, 45 to 150 pmol/L, radioimmunoassay). We applied a radiologic semiquantitative (0 to 6) score of vascular calcification by using x-rays, in accordance with London et al.,[15] and recorded the hip T-score of BMD. The characteristics of the 3 groups were compared using the Wilcoxon rank test for continuous data, and Fisher's exact test for comparison of proportions. Logistic regression analysis was used to determine the factors associated independently with vitamin D deficiency (group 3). Data are reported as mean ± SD. $P < .05$ was considered statistically significant. Statistical analyses were performed using MedCalc software (Shoonjans, Marakerke, Belgium).

Results

All 253 HD patients at the center were studied. None of the patients were excluded. The

Table 1. Comparison of Data for the Three Groups

	Sufficient (Group 1) (n = 25)	Insufficient (Group 2) (n = 122)	Deficient (Group 3) (n = 106)	Total (n = 253)
Age (y)	67 ± 15	65.3 ± 15	68.2 ± 13	66.7 ± 14
Female (%)	28	40	53*	42
Vintage (mo)	73.8 ± 85	67.1 ± 77	53.5 ± 66*	62 ± 74
Session time (min)	401 ± 110	395 ± 90	376 ± 60	388 ± 87
Diabetes (%)	21	28	45*	34
Body mass index (kg/m^2)	25.1 ± 5	25.8 ± 7	24 ± 6	25.3 ± 6
Body weight (kg)	76 ± 19	70.4 ± 22	65 ± 20*	70 ± 20
Bone mineral density T-score, hip	2.8 ± 0.6	2.9 ± 0.7	3.1 ± 0.7	2.9 ± 0.7
Calcification score	2.6 ± 1.7	2.4 ± 1.3	2.8 ± 1.4	2.6 ±1.6
Normalized protein catabolic rate (g/kg/day)	1.18 ± 0.3	1.27 ± 0.2	1.19 ± 0.3	1.23 ± 0.2
Sevelamer % (tablets/day)	36 (5.1 ± 6)	34 (5 ± 7)	25 (4 ± 4)	34 (5 ± 7)
Phosphorus (mmol/L)	1.5 ± 0.5	1.38 ± 0.6	1.33 ± 0.4	1.38 ± 0.4
Albumin-corrected calcium (mmol/L)	2.2 ± 0.1	2.23 ± 0.1	2.21 ± 0.1	2.22 ± 0.1
Intact parathyroid hormone (pg/mL)	213 ± 153	269 ± 291	260 ± 227*	259 ± 253
Bone alkaline phosphatase (μg/L)	24 ± 17	22 ± 18	22 ± 15	22.2 ± 16
β-CrossLaps (μg/L)	2.2 ± 1.4	2.2 ± 1.3	1.97 ± 1	2.1 ± 1.2
Albumin (g/L)	35.2 ± 5	34.6 ± 5	33.9 ± 4	34.3 ± 5
C-reactive protein (mg/L)	15.2 ± 20	17 ± 27	18.5 ± 30	17.5 ± 28
25(OH) (nmol/L)	97 ± 19	43 ± 12	16 ± 7†	37 ± 26
1,25(OH) (pmol/L)	16.1 ± 14	15.3 ± 15	14.5 ± 12	15.2 ± 14
Alfacalcidol % (μg/week)	65 (2.45 ± 4)	66 (2.8 ± 4)	66 (2.4 ± 4)	66 (2.5 ± 4)

Values are given as mean ± SD or as percentages.
*$P < .05$ between groups 1 and 3.
†$P < .005$ between groups 1 and 3.

characteristics of patient are provided in Table 1. Of all patients, 42% were female, and 34% had diabetes. The mean age of all patients was 66.7 ± 14 years. The mean duration of hemodialysis treatment was 62 ± 74 months, with a mean schedule of 3 × 6.5 hours, and the administration of a 1.5 mmol/L calcium dialysate. Initial nephropathies were undetermined in 17% of cases, diabetes in 28% of cases, nephrosclerosis in 16% of cases, glomerular in 20% of cases, interstitial in 9% of cases, polycystic kidney disease in 6%, and miscellaneous in 4% of cases. Concomitant treatments included oral alfacalcidol (66% patients) administered after each dialysis session for secondary hyperparathyroidism, and sevelamer as a standard phosphate binder (in 34% of patients). No oral calcium was prescribed.

The frequency distribution of 25(OH) vitamin D is shown in Figure 1. Of all patients, 11% were in group 1, 47% were in group 2, and 42% were in group 3. Group 3 patients had a lower dialysis vintage (53 ± 66 vs. 73 ± 85 months, $P < .05$), a higher number of diabetes patients (45% vs. 21%, $P < .05$), a higher number of females (53% vs. 28%, $P < .05$), a higher iPTH level (260 ± 227 vs. 213 ± 153 pg/mL, $P < .05$), and lower body weight (65 ± 20 vs. 76 ± 19 kg, $P < .05$) (Table 1) than group 1 patients. The 3 patients of black race exhibited vitamin D deficiency. The calcitriol serum level was always less than 20 pmol/L in patients not receiving alfacalcidol, and 20 to 85 pmol/L in patients treated with alfacalcidol. No relationship was found between vitamin D storage level and the serum level of bone markers, vascular calcification score, and BMD. Multiple logistic regression analyses, including age, sex, dialysis vintage, diabetes, and body weight, revealed no independent, significant risk factor for vitamin D deficiency.

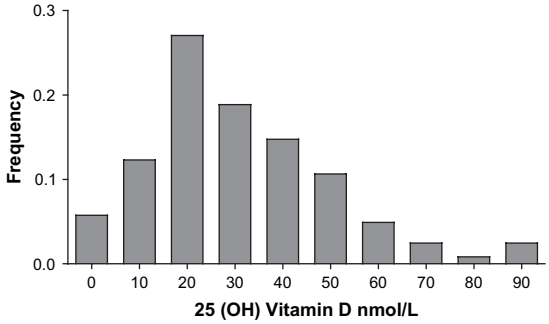

Figure 1. Frequency distribution of 25(OH) vitamin D serum level.

Discussion

Vitamin D is a hormone complex that regulates the expression of more than 60 genes. It is known to have numerous favorable effects on health, apart from those on bone and mineral metabolism. These favorable effects relate to diabetes, cardiovascular disease, cancer, autoimmunity, renal disease, and response to infection.[16]

Our study confirms that vitamin D deficiency is highly prevalent in end-stage renal disease (ESRD) patients: vitamin D sufficiency, insufficiency, and severe deficiency were observed in 11%, 47%, and 42%, respectively. The vitamin D insufficiency rate of 89% in our study is close to that reported in Europe (92% in Greece and Turkey in peritoneal dialysis[17]) and the United States (92%).[18] In Argentina, despite higher ultraviolet B exposure, vitamin D deficiency was reported to be 76.1%.[19] The KDOQI[20] and Kidney Disease Improving Global Outcomes[21] recommend the diagnosis and treatment of vitamin D deficiency in CKD stage 3 and 4, but not in stage 5. This is mainly attributable to the assumed lack of 1α-hydroxylation in the kidney. However, the extrarenal production of calcitriol is well-known in ESRD patients.[22]

The healthy calcidiol level recommended for the general population and for CKD patients was confirmed in hemodialysis patients. One histomorphometric study reported that a serum level of 50 to 90 nmol/L was associated with optimal bone turnover.[23] Recently, calcidiol-deficient incident hemodialysis patients were shown to have a higher mortality rate in the United States.[24]

Our results, particularly those of multiple logistic regression analyses, demonstrate that vitamin D deficiency cannot be predicted by any characteristics, and that all patients should be diagnosed to assess this deficiency. However, similar to the observation made in our study, type 2 diabetes patients were found to have vitamin D deficiency independent of body mass index,[25] and these patients may represent a priority for intervention studies. The lower vintage of deficient patients may be related to the higher prevalence of diabetes in incident patients. In agreement with other studies, we confirmed that women have a higher risk of vitamin D deficiency.[2,11,19] The lower body weight of deficient patients is certainly related to

female sex. In contrast with the results of London et al.,[26] in our study, the vascular calcification score was not associated with vitamin D deficiency. Furthermore, even though Mucsi et al.[27] reported a positive correlation between vitamin D deficiency and BMD, no such relationship was found in our study. Nevertheless, in our study, most hemodialysis patients were treated with alfacalcidol. Moreover, patients in all 3 groups received the same amount of treatment, which may have altered some of the results. As previously described, no relationship was observed between vitamin D deficiency and serum calcium or phosphorus level,[19] in contrast with the recent results of Wolf et al.[24] The longer dialysis sessions at our center may also have influenced our results. In contrast with the findings reported in other studies on prevalent HD and peritoneal dialysis patients,[23,28] the higher iPTH level of deficient patients in our study appears to be logical, and was also reported in predialysis studies[12] and incident dialysis patients.[24]

Conclusions

Calcidiol insufficiency was highly prevalent in a French hemodialysis population. Although there are no guidelines for vitamin D storage assessment and for deficiency treatment, we consider that after the identification of calcidiol-deficient patients, the usefulness and safety of vitamin D supplementation in ESRD patients must be assessed. Justifications for vitamin D supplementation include the expected direct effect of calcidiol on targets cells, and the provision of a stable supply of calcidiol to enable sufficient storage for calcitriol formation in kidneys and, most importantly, in other tissues.

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