Cholecalciferol therapy; is it the gold standard for vitamin D deficiency and mineral disorders in hemodialysis?

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Abstract

Introduction: Vitamin D deficiency is frequently observed among dialysis patients. Previous studies suggested that 50 to 90% of end-stage renal disease patients are deficient in vitamin D. In Tunisia, studies regarding hypovitaminosis D in patients on dialysis are not numerous. Actually, many data support the use of native vitamin D in hemodialysis (HD) patients. In Tunisia, using native vitamin D is not part of therapeutic habits of all dialysis centers.

Objectives: The aim of this study was to determine the prevalence of vitamin D deficiency in patients with chronic kidney disease stage 5 undergoing HD and to evaluate the effect of oral cholecalciferol supplementation, in intact parathormone (iPTH), serum calcium and serum phosphorus.

Patients and Methods: We conducted a pre-experimental study among HD patients. Monthly oral supplementation with Cholecalciferol, was instituted for six months.

Results: Forty-three participants were included. The mean 25-hydroxy vitamin D concentration was 17.89 ng/mL. Vitamin D deficiency was observed in 83.7% of our patients. We observed a significant increase in 25-hydroxy vitamin D and calcium levels and a significant decline in iPTH levels. No evidence of toxicity, nor severe hypercalcemia or hyperphosphatemia was noted.

Conclusion: The supplementation with cholecalciferol seems reasonable and well tolerated in HD patients if reasonable doses are used with regular monitoring.

Keywords: Vitamin D, Hemodialysis, Chronic kidney disease, Hemodialysis, Parathormone, End-stage renal disease

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Introduction

Vitamin D deficiency is frequently observed among hemodialysis (HD) patients. Previous studies suggest that 50% to 90% of end-stage renal disease (ESRD) patients are deficient in vitamin D (1). Significant evidence has been accumulated these recent years supporting the benefit of using vitamin D in HD patients. In fact, vitamin D deficiency has been associated with secondary hyperparathyroidism (SHPT) (2), since serum 25-hydroxyvitamin D (25(OH)D) levels should be maintained above 30 ng/mL in order to prevent parathyroid hormone (PTH) from increasing (3).

Its correction is relatively easy and well detected in a subject with normal renal function. Unfortunately in patients with chronic kidney disease (CKD), especially HD patients, the correction is not yet well codified due to the lack of prospective studies.

To be active, vitamin D must benefit from a double hydroxylation; the first hydroxylation, is carried out by the liver and the second is carried out under the action of 1-alpha-hydroxylase, mainly at the level of the proximal convoluted tubule to form calcitriol (4).

CKD is associated with loss of renal 1 α hydroxylase activity. Classically, nephrologists use active vitamin D to compensate this deficit. Both the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) experts recommend checking and supplementing low serum 25(OH)D levels in CKD and HD patients (5,6) why active vitamin D is usually administered.

Over the last fifteen years, many scientific advances have profoundly changed the understanding of the vitamin D physiology, the co-expression of vitamin D receptors with 1-α-hydroxylase, in many peripheral tissues, has come to light a new concept, while the active form of vitamin D, the 1.25 (OH) D3, can be synthesized in extrarenal sites and

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■ **Implication for health policy/practice/research/ medical education**

In a pre-experimental study on HD patients, we found vitamin D supplementation using cholecalciferol (800 000 UI during 6 months) was associated with significant increase in serum 25OH vitamin D and calcium and a significant decline in intact parathormone (iPTH) serum levels. No evident toxicity, nor severe hypercalcemia or increase in phosphorus level was noted.

generate local autocrine effects (7,8). Actually many data support the use of native vitamin D in HD patients (9). There has been renewed interest in studying the effects of supplementation with native vitamin D (cholecalciferol) in CKD patients with low 25(OH) D levels (10,11). Likewise, this interest has been shown by the studies that have demonstrated several potential non-skeletal benefits of vitamin D. These benefits include effect of vitamin D on immune system, cardiovascular disease, diabetes, and some cancers (12,13).

In Tunisia, studies regarding hypovitaminosis D in patients with CKD stage 5 on dialysis are not numerous and using native vitamin D is not part of therapeutic habits of all dialysis centers.

Objectives

In the present study, we examined the prevalence of vitamin D deficiency in patients with CKD stage 5 undergoing HD and evaluated the effect of oral cholecalciferol supplementation, in intact parathyroid hormone (iPTH), serum calcium (Ca) and serum phosphorus in this population.

Materials and Methods

This was a pre-experimental study conducted in HD department of Charles Nicolle hospital during six months. All measurements were carried out at the biochemistry laboratory of the hospital.

We included patients of CKD stage 5 who were on maintenance HD for more than one year. They were adults (age >18 years). Patients were not included if they had a history of active vitamin D or calcimimetic treatment in the last year, parathyroidectomy, iPTH <300 pg/mL, hepatic failure or digestive malabsorption. Those with serum calcium greater than 2.55 mmol/L or serum phosphorus greater than 2 mmol/L were not included. The calcium concentration during HD sessions was set at 1.5 mmol for all patients. Informed consent was required for all patients.

25(OH) vitamin D serum levels, intact PTH (iPTH), as well as serum calcium and phosphorus were analyzed in fasting samples before and 15 days after the end of treatment. Blood samples for 25(OH) vitamin D levels were obtained before dialysis. Serum 25(OH) vitamin D levels were measured using a commercially available

radioimmunoassay. Intact PTH was determined by an automated chemiluminescence immunoassay. Serum calcium and phosphorus were measured by standard laboratory methods.

In this study, we considered adequate vitamin D levels those above 30 ng/mL (US National Kidney Foundation DOQI guidelines), vitamin D insufficiency when levels were between 20 and 30 ng/mL, vitamin D moderate deficiency when levels were between 10 and 20 ng/mL and severe deficiency when levels were below 10 ng/mL.

Monthly oral supplementation with cholecalciferol (200 000 UI), was then instituted for six months (M1, M2, M4 and M6) totaling 800 000 UI. For better compliance cholecalciferol was given in the morning on empty the day of non-HD.

The response to treatment was evaluated as follows;
- Partial response if 25 (OH) vitamin D level is <30 ng/mL at M6.
- Adequate response if 25 (OH) vitamin D level is between 30 ng/mL and 60 ng/mL at M6.
- Excessive response if 25 (OH) vitamin D level is > 60 ng/mL at M6.

For all statistical analyses, *P* value ≤0.05 was considered to be significant. All statistical analyses were performed with Statistica software. We used a paired sample *t* test to compare means of quantitative variables before and after supplementation.

Results

Forty-three Caucasian participants were included in the study. Mean age was 51.3 years. Of these, 18 were females and 25 were males. Median duration of dialysis was 6.5 years (range 1–19 years). Six (13.9%) patients had diabetic nephropathy.

We found that 83.7% of our patients had vitamin D insufficiency or deficiency (a serum 25-OH vitamin D level below 30 ng/mL) (n = 36). Before treatment, the mean 25 (OH)D was 17.89 ng/mL [6-57.3 ng/mL] (Table 1).

Changes in vitamin D, calcium, phosphorus and iPTH, after cholecalciferol supplementation

The cholecalciferol supplementation allowed a significant increase of 25 (OH) vitamin D levels (from 17.89 ng/mL to 51.8 ng/mL). The average plasma concentration of calcium has significantly increased between M0 and M6, 2.05 (M0) versus 2.15 mmol/L (M6). No episode of hypercalcemia was noted.

Basal iPTH concentration observed before vitamin D

Table 1. Biomedical characteristics before treatment

Vitamin D (ng/mL)	17.89 (6-57.3)
PTH (pg/mL)	956 ± 413.24
Phosphorus (mmol/L)	1.56 ± 0.27
Calcium (mmol/L)	2.05 ± 0.24

supplementation was 956 pg/mL. After treatment, the mean concentration decreased significantly. Overall, iPTH concentration decreased from 956 pg/mL to 699 pg/mL between M0 and M6.

The average serum phosphorus level progress was not significant: 1.56 mmol/L at M0, to 1.49 mmol/L at M6. These values remain lower than the upper limit (1.78 mmol/L) according to the K/DOQI recommendations (Table 2).

The increase of serum 25 (OH) vitamin D level was conditioned by initial concentrations of 25 (OH) vitamin D (Table 3).

Discussion

Our study confirms the high prevalence of the 25 (OH) vitamin D deficiency in HD patients, with a mean 25 (OH) vitamin D concentration of 17.89 ng/mL. Vitamin D deficiency was observed in 83.7% of our patients.

Referring to the concentrations recommended by the American Nephrology Society, only 16.3% of our patients reach desirable concentrations of 25 (OH) vitamin D >30 ng/mL (3).

At the dialysis stage, the deficit in vitamin D affects 53.5 to 89 % of HD (1). In Asian countries, studies have shown a high prevalence of vitamin D deficiency. The study of Hashemipour et al reported that 81.3% subjects had a decline in vitamin D reserves with a prevalence of vitamin D deficiency between 30% and 93% (14). Recently, a French team reported vitamin D insufficiency with serum 25(OH) vitamin D level <30 ng/mL in 72% of their HD patients (15). In Africa, data on dialysis are not numerous. In Nigeria, a study reports a deficit in *1,25(OH)2*D in 83.3% of patients (16). In Tunisia, a cumulative prevalence of vitamin D deficiency of 47.6% was reported in healthy population (17). In a study conducted in southern Tunisia involving 63 dialysis patients (HD, peritoneal dialysis), the average level of 25(OH) vitamin D was 10.5±9.13 ng/mL.

Serum 25OH vitamin D level <15 ng/mL was shown in 41.3% of patients and between 15 and 30 ng/mL in 50.8% of patients (18).

Vitamin D is a hormonal system involved in the regulation of hundreds of genes and metabolisms by the local or endocrine production of 1,25-OH 2 vitamin D with a primary effect on cellular differentiation and proliferation (19). Vitamin D deficiency has been associated with the risk of cancer (20) diabetes (13), autoimmune and cardiovascular diseases, osteoporosis, musculoskeletal function impairment, and neuropsychiatric disorders (12). Therefore, it has an important role in the prevention of diabetes, different types of cancer, autoimmune diseases, and in the defense against tuberculosis (21).

In the general population, the optimal serum 25(OH) vitamin D level is not known, but it is thought to be above 30 ng/mL (22).

This deficiency is due to a restrictive diet in vitamin D, as well as low exposure to sunlight, which leads to a decrease in the cutaneous synthesis of vitamin D. In our study, all female population was veiled women with a low-sunlight exposure. In addition, chronic HD patients have decreased photoproduction of cholecalciferol, despite a normal epidermal content of the substrate, 7-dehydrocholesterol (23). A study suggests a decrease in hepatic 25-hydroxylase activity related to uremia too (24).

Vitamin D deficiency among dialysis patients has become an increasingly important problem for nephrologists in the last 10 years. In fact, end-stage renal disease is associated with a decrease in vitamin D activity by mechanism including the increase of plasma phosphate concentration, secretion of fibroblast growth factor-23 and decrease in 1 alpha hydroxylase activity. Currently is well established that a patient has to be substituted when 25OH vitamin D level is less than 30 ng/mL. The goals of vitamin D treatment in case of ESRD are to substitute the deficiency and to prevent or treat hyperparathyroidism. Lowering excessive serum PTH levels have many beneficial effects by increasing myocardial contractility, decreasing myocardial fibrosis and vascular calcification, increasing immune function, insulin sensitivity, and erythropoiesis. But the beneficial effects of vitamin D may also involve a direct action on hypertension, cardiac hypertrophy, tumorigenesis, immunologic function, atherosclerosis, and thrombosis (25). With the Kidney Disease: Improving Global Outcomes 2016 recommendation being recently released, it is hypothesized that nephrologists will

Table 2. Changes in vitamin D, calcium, phosphorus and PTH, after cholecalciferol supplementation

	Pre-supplementation	Post-supplementation	*P* value
Vitamin D (ng/mL)	17.89	51.8	<0.001
Ca (mmol/L)	2.05	2.15	0.014
Phosphorus (mmol/L)	1.56	1.49	0.78
PTH (pg/mL)	956	699	<0.001

Table 3. Changes in the 25(OH) D after cholecalciferol treatment according to the baseline vitamin D level

Baseline vitamin D level (ng/mL)	Partial response (Vit D <30 ng/mL)	Adequate response (Vit D between 30 and 60 ng/mL)	Excessive response (Vit D >60 ng/mL)
<10	54.5%	45.5%	0%
10-20	46.2%	46.2%	7.6%
20-30	0%	62.5%	37.5%

implement a strategy for 25(OH) vitamin D deficiency checking and supplementation more systematically (5).

However, the more appropriate vitamin D compounds for HD patients remain an unavoidable subject. The controversy about active vitamin D and native vitamin D heats up.

Past studies have recommended the use of native vitamin D in HD patients. As knowledge improves, this use then fell somewhat into disuse; especially for the benefit of active vitamin D. Actually, native vitamin D has regained an important place in our arsenal therapy. In a descriptive study conducted in 2011 in the Sahel of Tunisia involving 50 HD patients belonging to the same center, 38% of them were treated by active vitamin D versus 50% using native vitamin D (26).

In our study, vitamin D supplementation using cholecalciferol (800 000 UI during 6 months) was associated with significant increase in serum 25(OH) vitamin D and calcium and a significant decline in iPTH serum levels. No evident toxicity, nor severe hypercalcemia or increase in phosphorus level was noted.

Several studies have assessed the effect of native vitamin D on mineral parameters in HD patients. We will compare our results to the studies that used cholecalciferol in HD patients. We have deliberately omitted studies that have used other native vitamin D.

Indeed, several scientific data suggest that these forms do not have the same bioavailability (23).

A significant improvement in 25 OH vitamin D level after cholecalciferol supplementations was reported by all previous studies. Jean et al observed a significant improvement of 25 (OH) vitamin D levels (from 13±5 ng/mL to 42 ±11 ng/mL) in one cohort of 107 HD patients after 15 months of monthly doses of cholecalciferol. Serum PTH levels also decreased significantly (median 295-190 pg/mL, $P < 0.001$). No significant changes were observed in the values of serum calcium and phosphate (15). Matias et al reported (11), a significant increase in 25OH vitamin D levels (from 22 ± 12 ng/mL to 42 ± 12 ng/mL) in one study of 158 HD patients receiving cholecalciferol treatment. Conversely, serum calcium, phosphorus, and iPTH were decreased (11). In 2013, Delanay et al (29) reported a decrease of PTH levels from 312 to 175 pg/mL after cholecalciferol treatment for one year but it was a small patient number. In 2018, Tunisian authors compared the effect of cholecalciferol versus ergocalciferol on mineral discords in HD patients and reported a significant increase of vitamin D levels and a significant decrease of PTH levels with cholecalciferol. We specify that these patients have already received ergocalciferol for three months before cholecalciferol which could represent a bias of the study (30).

However, many studies reported that cholecalciferol treatment had an effect on only 25(OH) vitamin D levels and did not change either calcium, phosphorus or iPTH values (31-36).

The question that arises now is why there is disparity from results especially regarding changes in iPTH levels after cholecalciferol treatment?

This disparity can be explained by several reasons. First, in some previous studies reporting the effect of cholecalciferol supplementation, patients receiving therapy influencing calcium metabolism were not excluded. Some authors included patients having parathyroidectomy. Thus the effect of 25(OH) vitamin D on parathyroid is less than expected. Secondly, this disparity can be explained by the variability of bioavailable 25(OH) vitamin D level between the Tunisian population and others. Bioavailable vitamin D is the free portion of 25(OH) vitamin D not bound to vitamin D binding protein (DBP). This is the only active fraction responsible for the biological effects of 25(OH) vitamin D (Table 4).

Prior studies demonstrated that bioavailable vitamin D but not 25(OH)D and 1,25(OH) vitamin D is significantly associated with iPTH and calcium level (37-39). The free 25(OH) vitamin D is influenced by vitamin D binding protein concentration and affinity and it varies in different clinical conditions. It may be affected by genetic, gender, hormones, ethnic and racial factors (33-39).

To assess the effect of cholecalciferol on PTH level; we noticed that previous studies included patients from different races. Our results suggest that Tunisian people may have lower DBP level and thus higher vitamin D bioavailability and greater PTH suppressing. This finding must be confirmed by genetic studies. It should be noted that the essential role of the kidney in producing the active form of vitamin D (1,25-hydroxy-vitamin D3 (1,25 (OH) D3) is an ancient concept. Dusso et al (39) confirmed that 1alpha hydroxylase secretion is stimulated by 25 (OH) vitamin D deficiency and can be produced by extra-renal sites. Additionally, 25(OH)vitamin D can be independent of calcitriol generation.

Indeed, many studies demonstrated that in vitro 25(OH) vitamin D can directly activate vitamin D receptor.

Otherwise, we noticed through this study that the response to cholecalciferol was better in vitamin D insufficiency group compared to vitamin D deficiency group. Therefore the more the deficit was accentuated the more difficult the correction is and we must supplement our patients earlier. In addition, 37.5% of our patients had excessive response with 25(OH) vitamin D levels >60 ng/mL but we did not notice any toxicity mainly hypercalcemia for hyperphosphatemia. In fact, supplementation with cholecalciferol seems reasonable and well tolerated in HD patients if reasonable doses are used with regular monitoring.

Conclusion

In conclusion, our study is a Tunisian study regarding the prevalence of hypovitaminosis D in patients on HD and the effects of vitamin D supplementation on the serum level of 25(OH) vitamin D, iPTH, calcium and phosphorus. In

Table 4. Literature review

Study	No. of patient	Mean Age (y)	Initial value of 25(OH) Vit D	Initial value of PTH	Treatment	Study duration	Results
Jean et al	107	66.4±15	13±5 ng/mL	295 (190-450) pg/mL	Cholecalciferol 100000 UI/month	15 months	25(OH) vit D after treatment 42±11 mg/mL Ca, phosphorus unchanged
Tokmak et al	64		7±4 ng/mL	217±217 pg/mL	Cholecalciferol 20000 UI/week	9 month	25(OH) vit D after treatment 32±11 ng/mL Ca 2.28±0.17 to 2.37±0.19 mmol/PTH
Matias et al.	158	62.8±14.8	22±12 ng/mL	233 pg/mL	Cholecalciferol 50000 UI per week if 25(OH) vit D <15 pg/mL 10000 UI per week if 25(OH) vit D between 16 and 30 pg/mL 2700 UI 3 times a week if 25(OH) vit D >30 pg/mL	1 year	25(OH) vit D after treatment 42±12 pg/mL Ca from 8.6±0.8 to 8.4±0.7 mg/dL Ph from 4.7±1.3 to 4.5±1.3 mg/dL PTH 233 to 200 pg/mL
Jakopin et al	101	63.3±13.5	12±7 ng/mL	307.3±236.9 pg/mL	Cholecalciferol 40000 UI/month for 3 months to repeat if deficit persists	2 years	25(OH) vit D after treatment 22±6 ng/mL Ca from 2.28±0.14 to 2.16±0.17 mmol/L Ph and PTH unchanged
Bucharles et al	30	59±15	18.1±6.6 ng/mL	165±80 pg/mL	Cholecalciferol 50 000 UI/week for 12 weeks 20 000 UI/week	6 months	25(OH) vit D after treatment 40±10mg/ml Ph and PTH unchanged
Our study	43	51.3	17.89 (6-57.3) ng/mL	956 ±413.24	Cholecalciferol 200 000 UI (M1-M2-M4-M6)	6 months	25(OH) vit D after treatment 51.8. PTH from 956 to 699 pg/mL Ca from 2.05 to 2.15 mmol/L

Tunisia, studies regarding hypovitaminosis D in patients with CKD stage 5 on dialysis are not numerous and we do not have protocols of supplementation with native vitamin D. In fact, most centers are used to using only active vitamin D in HD patients.

The interpretation of the results of this study is limited by the relatively low number of patients and by the absence of a control group.

With the KDIGO recommendation being recently released, it is hypothesized that Tunisian nephrologists will implement a strategy for 25(OH) vitamin D deficiency checking and supplementation by native vitamin D more systematically.

This is a Tunisian study regarding the prevalence of hypovitaminosis D in patients on HD and the effects of vitamin D supplementation on the serum level of iPTH, calcium and phosphorus. However, vitamin D deficiency appears to be widely used in Tunisian HD people and we must have a national protocol. The supplementation with cholecalciferol seems reasonable and well tolerated in HD patients if reasonable doses are used with regular monitoring to prevent the development of toxicity, mainly hypercalcemia and hyperphosphatemia.

Many unanswered questions still exist; is there long-term toxicity associated with maintaining high serum 25(OH) vitamin D levels? Which is the best frequency of vitamin D administration; monthly weekly or daily? What is the optimal serum 25(OH) vitamin D target level according to the severity of secondary hyperparathyroidism?

Other controlled studies are needed to answer these questions and must be based on hard criteria such as the risk of low bone remodeling, skeletal fractures and mortality.

Limitations of the study
The most important was the relatively small number of patients.

Authors' contribution
All authors contributed equally to the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. All patients gave written informed consent.

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