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Efficacy of weekly administration of cholecalciferol on parathyroid hormone in stable kidney-transplanted patients with CKD stage 1–3

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Abstract

Objectives: Kidney transplant (KTx) recipients frequently have deficient or insufficient levels of serum vitamin D. Few studies have investigated the effect of cholecalciferol in these patients. We evaluated the efficacy of weekly cholecalciferol administration on parathyroid hormone (PTH) levels in stable KTx patients with chronic kidney disease stage 1–3.

Methods: In this retrospective cohort study, 48 stable KTx recipients (37 males, 11 females, aged 52±11 years and 26 months post-transplantation) were treated weekly with oral cholecalciferol (7500–8750 IU) for 12 months and compared to 44 untreated age- and gender-matched recipients. Changes in levels of PTH, 25(OH) vitamin D (25[OH] D), serum calcium, phosphate, creatinine and estimated glomerular filtration rate (eGFR) were measured at baseline, 6 and 12 months.

Results: At baseline, clinical characteristics were similar between treated and untreated patients. Considering the entire cohort, 87 (94.6%) were deficient in vitamin D and 64 (69.6%) had PTH ≥130 pg/mL. Serum calcium, phosphate, creatinine and eGFR did not differ between groups over the follow-up period. However, 25(OH)D levels were significantly higher at both 6 (63.5 vs. 30.3 nmol/L, $p < 0.001$) and 12 months (69.4 vs. 30 nmol/L, $p < 0.001$) in treated vs. untreated patients, corresponding with a significant reduction in PTH at both 6 (112 vs. 161 pg/mL) and 12 months (109 vs. 154 pg/mL) in treated vs. untreated patients, respectively ($p < 0.001$ for both).

Conclusions: Weekly administration of cholecalciferol can significantly and stably reduce PTH levels, without any adverse effects on serum calcium and renal function.

Keywords: cholecalciferol; chronic kidney disease; kidney transplant; parathyroid hormone; secondary hyperparathyroidism.

Introduction

Alterations in bone and mineral metabolism are frequently observed in patients with kidney failure and often persist after successful kidney transplant (KTx) [1]. Post-transplantation bone disease is influenced by multiple factors, of which the negative effect of immunosuppressive therapy on bone is still considered one of the major causes [2, 3]. However, another important risk factor for bone morbidity seems to be represented by secondary hyperparathyroidism (SHPT), which is present in up to 50% of patients, even after successful transplantation [4–9]. Regardless of whether optimal parathyroid hormone (PTH) levels in KTx patients remain a black box [10], values ≥130 pg/mL have repeatedly been shown to be associated with bone loss and fragility fractures [5, 11, 12]. This condition is mainly related to the long-term persistence of parathyroid gland enlargement, the

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lengthy time required for the involution of parathyroid gland hyperplasia and an alteration in calcium set-point. Studies examining the role of genetic factors may help in our understanding of SHPT and vitamin D metabolism; however, current evidence is weak and much still remains to be elucidated [13]. Actually, the vitamin D receptor polymorphism has been linked to a higher incidence of sporadic primary hyperparathyroidism and SHPT in patients with chronic renal insufficiency [8, 14]. Furthermore, this polymorphism can also predict higher PTH levels in KTx patients [6, 8], while calcium-sensing receptor polymorphisms do not affect PTH levels after KTx [5].

Interestingly, low or very low serum levels of 25(OH) vitamin D (25[OH]D) have repeatedly been reported in KTx patients [5, 15–18]. Indeed, KTx subjects may be more susceptible to reduced levels of 25(OH)D, because of decreased sun exposure, following recommendations specifically aimed to prevent skin cancer [19–21] and because of increased 25(OH)D catabolism, possibly induced by immunosuppressive drugs and FGF-23 [22]. It is worth noting that similar to the general population, low 25(OH) D levels are also implicated with an increase in PTH in KTx patients [5, 18, 23, 24].

To date, no randomized controlled trials have been carried out to specifically assess the possible benefits of native vitamin D treatment in this setting, even though some studies are currently ongoing [25, 26]. Few studies have evaluated the effects of increasing 25(OH)D levels on serum PTH in KTx patients. Available data support the view that cholecalciferol supplementation may also improve SHPT in this setting [27–30]. However, current evidence is derived from studies that although differ in terms of doses employed and administration schedules, share in common the inclusion of newly renal transplanted patients [27–29]. In these subjects, a trend toward a decrease in PTH levels is expected, due to improvement in renal function, as well as in calcium and phosphate metabolism that is somehow independent of 25(OH) D status [8, 9, 31]. In contrast, studies designed to assess the effects of cholecalciferol treatment on SHPT in stable KTx (i.e. patients with relatively long time since transplant) are completely lacking. For this reason, it remains unknown if cholecalciferol may induce an improvement in SHPT, even in subjects in which this condition is also determined by several other factors that are no longer modifiable.

The aim of this study was to evaluate, in the framework of a retrospective cohort study, the efficacy of weekly cholecalciferol administration on PTH in stable kidney-transplanted patients with chronic kidney disease (CKD) stage 1–3.

Materials and methods

Study population

Patients who had undergone renal transplantation at our University Hospital were retrospectively selected patients who had 25(OH)D serum levels lower than 75 nmol/L (see following text) following a laboratory measurement undertaken no more than 4 months previously. These patients were started on treatment with cholecalciferol. Other inclusion criteria were (1) age ≥18 years, (2) ≥1 month since transplant, (3) estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, (4) a weekly administration schedule of oral cholecalciferol (in drops) at a dose ranging from 7500 IU to 8750 IU (corresponding to 30–35 drops per week, DiBase, Abiogen Pharma, Pisa, Italy). In contrast, patients were excluded if they had (1) eGFR <30 mL/min/1.73 m^2, (2) age <18 years, (3) serum calcium ≥2.7 mmol/L, (4) history of diabetes mellitus before and after transplantation, (5) treatment with estrogens or anti-resorptive drugs after the graft, (6) calcium and/or vitamin D treatment (including active vitamin D or vitamin D analogs) in the last 3 months before starting cholecalciferol treatment. The final study population comprised 48 adult Caucasian subjects (37 males and 11 females, aged 52 ± 11 years), transplanted a median time of 26 (interquartile range [IQR] 7.43) months before. The causes of end-stage renal failure were as follows: hypertensive nephropathy (n = 10), chronic glomerulonephritis (n = 8), Berger's disease (n = 4), polycystic kidney disease (n = 3), nephrolithiasis (n = 1), membranous glomerulonephritis (n = 2), focal segmental glomerulosclerosis (n = 2), lupus nephritis (n = 1), Alport syndrome (n = 1) and unknown (n = 16). Prior to undergoing kidney transplantation, 25 (52.1%) patients had undergone hemodialysis, 20 (41.7%) were on peritoneal dialysis and three (6.3%) had not undergone dialysis. Patients were receiving treatment with different combinations of oral immunosuppressive therapies (cyclosporine A, prednisone, mycophenolate mofetil, tacrolimus, rapamycin, belatacept).

Cholecalciferol-treated patients were compared with 44 age- and sex-matched subjects not on cholecalciferol treatment in spite of the presence of low vitamin D serum levels. Based on clinical records review, the reason for not starting cholecalciferol treatment in these patients was only due to the personal choice of the referring physician. The remaining inclusion and exclusion criteria were identical to those of the treatment group.

At our Unit, serum levels of 25(OH)D are usually checked every 6 months after renal transplantation. Because of this, we decided to search for clinical and laboratory information on clinical records at baseline and then after approximately 6 and 12 months, in order to collect data based on two follow-up visits.

This study was approved by our Institutional Ethical Committee and complies with the ethical standards laid down by the 1964 Declaration of Helsinki. Given the retrospective nature of the study, the informed consent by patients was not required.

Data collection and biochemical assays

Serum and 24-h urinary parameters were evaluated in all subjects at baseline (t_0), and after 182.9 ± 15.3 (t_1) and 363.1 ± 33.2 (t_2) days. The last serum calcium, phosphate and PTH values available before transplantation (3.4 ± 4.1 months prior to surgery) were obtained

by consulting existing clinical records of patients. Serum and urine calcium, serum phosphate and creatinine were analyzed using an automatic analyzer (Technicon Instruments Corp., Tarrytown, NY, USA). PTH levels were measured using a direct, two-site, sandwich-type chemiluminescent immunoassay (N-tactTM PTH DiaSorin S.p.A. Saluggia, Vercelli, Italy). The normal reference range for this method in patients with normal renal function is 10–65 pg/mL. Quantification of 25(OH)D was performed by a direct competitive chemiluminescence immunoassay (Liason 25 OH Vitamin D total Assay, DiaSorin S.p.A., Saluggia, Vercelli, Italy). According to the Endocrine Society position [32], patients with 25(OH)D serum levels of <50 nmol/L were defined as vitamin D-deficient and those with 25(OH)D serum levels between 50 and 75 nmol/L were defined as vitamin D-insufficient. eGFR was calculated using the Modification of Diet in Renal Disease formula [33].

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation, whereas non-parametric data were expressed as medians and IQRs. Categorical data were expressed as absolute frequencies and rates. Student's t-test and the Mann-Whitney test were used to compare differences among variables between independent groups for normal and non-parametric data, respectively. The chi-squared (χ^2) test was used to analyze binary data. A p-value of 0.05 was considered statistically significant. During the follow-up period, the ANOVA and Friedman test were used for intra-group comparisons for normal and non-parametric laboratory variables, respectively. For the same variables and at the same time-points, linear mixed models (LMMs) were used for intergroup comparisons. The independent correlates of baseline values of PTH levels, were identified by univariate and multiple linear regression analyses. Tested covariates included all variables listed in Table 1. Among these, those having a relationship with baseline PTH with $p < 0.10$ at univariate analysis (i.e. phosphate before KTx, baseline phosphate, baseline 25(OH)D, baseline diuresis, baseline weight, baseline eGFR and months since KTx) were simultaneously included into the same multiple linear regression model. In such model, data are expressed as standardized regression coefficients (beta) and p-value. The effect of treatment with cholecalciferol on repeated measurements of PTH over time was investigated by multiple LMMs adjusting for weight, baseline phosphate, baseline PTH and follow-up time. To comply with the normality assumption underlying LMMs, repeated measurements of PTH (the dependent variable) were introduced into the model as natural logarithm. In LMMs, data were expressed as unstandardized regression coefficients (b), 95% CI and p-values. Data were analyzed using SPSS 23.0 statistical software (Chicago, IL, USA).

Results

Patient clinical characteristics

Baseline (t_0) and pre-transplant demographic, clinical and biochemical variables for treated and untreated patients are summarized in Table 1. The majority of patients were male (72/92; 78.3%) with a mean age of 52.5 ± 11 years and median time since transplant of 25 (IQR 7–43) months. No differences were observed among a range of demographic and clinical characteristics between groups, with the exception of 24-h urine calcium, which was slightly higher in treated patients (3.4 ± 0.9 vs. 3.3 ± 0.7, p = 0.015). PTH values were substantially elevated before transplantation and decreased after surgery in both groups. However, at baseline, no patients

Table 1: Main demographic, clinical and laboratory characteristics of the study cohort.

Variable	Cases (n = 48)[a]	Controls (n = 44)[b]	p-Value
Age, years	52 ± 11	53 ± 11	0.94
Male gender, n (%)	37 (77.1)	35 (79.5)	0.77
Weight, kg	67.9 ± 10.0	68.5 ± 9.0	0.37
Duration of PD before RTx, months	23.9 ± 12.9	23.2 ± 12.4	0.91
Duration of HD before RTx, months	26.0 (16, 42.5)	31.0 (18, 46)	0.70
Months since RTx	26.0 (7, 43)	25.0 (6.2, 43)	0.94
Serum calcium before RTx, mmol/L	2.34 ± 0.16	2.33 ± 0.16	0.45
Serum phosphate before RTx, mmol/L	1.69 ± 0.48	1.65 ± 0.42	0.55
PTH before RTx, pg/mL	213 (144, 388)	219 (141, 399)	0.93
Serum creatinine at baseline, mg/dL	1.33 ± 0.4	1.35 ± 0.37	0.91
eGFR at baseline, mL/min	50.5 (43.5, 72)	48.0 (42.2, 69.0)	0.73
Serum calcium at baseline, mmol/L	2.4 ± 0.11	2.41 ± 0.11	0.66
Serum phosphate at baseline, mmol/L	1 (0.91, 1.11)	0.99 (0.88, 1.1)	0.66
PTH at baseline, pg/mL	147 (114, 204)	160 (123, 213)	0.54
25(OH)D at baseline, nmol/L	31.6 ± 12.1	30.7 ± 11.8	0.73
Urine calcium at baseline, mg/24 h	3.4 ± 0.9	3.3 ± 0.7	0.015

Data are presented as mean ± SD, number (%) or median and interquartile range. Comparisons are between case and control groups. [a]Cases, treated patients, [b]Controls, untreated patients. eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; PTH, parathyroid hormone; RTx, renal transplant.

had PTH values ≤65 pg/mL, while 64 out of 92 subjects (69.6%) had values ≥130 pg/mL. Four patients (4.34%) were hypercalcemic (serum calcium >2.62 mmol/L), three in the treated and one in the control group, with a mean serum calcium of 2.66 ± 0.26 mmol/L. Fourteen subjects (15.2%) were hypophosphatemic (serum phosphate levels <0.80 mmol/L), seven in the treated and seven in the control group, with a mean value of 0.58 ± 0.18 mmol/L. Mean serum 25(OH)D levels ranged from 13 to 63 nmol/L. Thus, none of the patients were vitamin D-sufficient. Only five subjects (5.4%) were in the range of insufficiency, while 87 (94.6%) were vitamin D-deficient.

In a multivariate linear regression analysis model, only serum 25(OH)D (β-coefficient = −0.34, $p < 0.001$), serum phosphate (β coefficient = −0.27, $p = 0.003$) and eGFR (β-coefficient = −0.30, $p = 0.003$) levels emerged as significant correlates of baseline log-transformed PTH in the whole group of renal transplanted patients ($R^2 = 0.39$, $p < 0.005$).

Effect of cholecalciferol on calcium and phosphate and renal function

Changes in laboratory parameters for treated and untreated patients for the whole observation period are shown in Table 2. The number of days of observation at t_1 did not differ between treated (183.2 ± 14.5) and untreated patients (183.1 ± 16.4). This was also observed at the t_2 time point (363.3 ± 32.9 vs. 362.8 ± 34.0).

Serum and urine calcium, serum phosphate, creatinine and eGFR did not differ between groups at t_1 and t_2 time points. However, serum calcium was observed to increase slightly in treated patients ($p = 0.001$), although none of the subjects achieved values exceeding 2.7 mmol/L (Table 2). At the end of the study, four patients remained hypercalcemic (serum calcium >2.62 mmol/L), two in the treated and two in the untreated group of subjects, respectively. Serum phosphate increased slightly over the follow-up period in the control group ($p = 0.001$) with no difference between groups. In both groups, there was little change in serum creatinine and eGFR, without differences between groups (Table 2).

Effect of cholecalciferol on 25(OH)D

Serum 25(OH)D levels were unchanged in untreated patients, while there was a significant increase in treated patients over the follow-up period (Table 2). In particular, at t_1, 16.7% of treated patients remained vitamin D-deficient,

Table 2: Biochemical parameters during follow-up of the study (t_0, t_1, t_2) in treated (cases) and untreated (controls) patients.

Variable	t_0	t_1	t_2	p-Value within groups[a]	p-Value between groups[b]
Serum calcium, mmol/L					
Cases	2.40 ± 0.11	2.39 ± 0.13	2.45 ± 0.09	0.001	0.209
Controls	2.41 ± 0.11	2.4 ± 0.10	2.41 ± 0.1	0.177	
Serum phosphate, mmol/L					
Cases	1.00 (0.91, 1.11)	0.98 (0.79, 1.16)	1.06 (0.90, 1.18)	0.740	0.798
Controls	0.99 (0.88, 1.1)	1 (0.94, 1.16)	1.03 (0.99, 1.2)	0.001	
Serum creatinine, mg/dL					
Cases	1.33 ± 0.4	1.47 ± 0.45	1.45 ± 0.42	0.001	0.778
Controls	1.35 ± 0.37	1.47 ± 0.44	1.45 ± 0.41	0.005	
eGFR, mL/min					
Cases	50.5 (43.5, 72)	48.4 (39.2, 64.7)	47 (39.2, 67.7)	0.002	0.957
Controls	48.0 (42.2, 69)	50.5 (38.5, 67)	46 (39.2, 67)	0.014	
PTH, pg/mL					
Cases	147 (114, 204)	112 (86, 146)	109 (82, 142)	<0.001	<0.001
Controls	160 (123, 213)	161 (127, 207)	154 (121, 204)	0.478	
25(OH)D, nmol/L					
Cases	31.6 ± 12.1	63.5 ± 14	69.4 ± 15.7	<0.001	<0.001
Controls	30.7 ± 11.8	30.3 ± 12	30 ± 11.8	0.499	
Urine calcium, mmol/24 h					
Cases	3.4 ± 0.9	3.4 ± 0.8	3.4 ± 0.8	0.388	0.331
Controls	3.3 ± 0.7	3.3 ± 0.7	3.3 ± 0.7	0.548	

Data are presented as mean ± SD or median and interquartile range. [a]ANOVA or Friedman test, when appropriate. [b]Derived by linear mixed model analysis. eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone. t_0, t_1 and t_2 refer to baseline, 6- and 12-month time points, respectively.

while this proportion was 95.5% in those untreated ($p < 0.001$) (Figure 1). At the end of the study period, only 8.3% of treated subjects were still vitamin D-deficient, compared to 97.7% of patients not administered cholecalciferol. The percentage of treated patients achieving vitamin D sufficiency at t_1 and t_2 time points was 27% and 33.3%, respectively, without any change in this proportion in untreated patients.

Effect of cholecalciferol on PTH

Serum PTH levels were significantly reduced in cholecalciferol-treated patients (Table 2), while remaining stable in untreated subjects. This reduction in PTH in cholecalciferol-treated patients was observed at both t_1 and t_2 time points (Table 2). Changes in PTH levels in treated patients corresponded to a concomitant increase in 25(OH)D, while both of these parameters remained virtually unchanged in untreated patients (Table 2).

The effect of cholecalciferol treatment on PTH levels over time was confirmed in a multiple LMM analysis. As shown in Table 3, treatment with cholecalciferol significantly reduced serum PTH over time ($b = -0.328$, $p < 0.001$) independently of baseline PTH and other potential confounders. Of note, time acted neither as a confounder ($p = 0.109$) nor as an effect modifier ($p = 0.49$).

Discussion

Findings from the present retrospective study confirmed that SHPT persistence is very common after renal transplantation and that 25(OH)D serum levels are low in this setting and may contribute to the high PTH values [6, 8]. In addition, our results also confirm that cholecalciferol treatment is effective in reducing PTH levels in KTx patients [5, 18, 23, 24]. However, to the best of our knowledge, this is the first study in which this effect has been specifically demonstrated in stable KTx patients, i.e. with a median duration of the transplant of 26 months and not in recently transplanted ones. Indeed, all evidence currently available examining the role of cholecalciferol in lowering PTH levels come exclusively from studies carried out on newly renal transplanted patients [27–29], in which some degrees of spontaneous reductions in serum PTH are commonly seen [34]. In the study by Wissing et al. [28] conducted on KTx patients immediately after surgery and then followed for a year, serum PTH levels decreased in the same proportion in patients treated with oral calcium only or with a combination of oral calcium and cholecalciferol, 25,000 IU/monthly. Consequently, it is difficult to attribute changes in serum PTH to only cholecalciferol administration. Starting from the second day since surgery, Sahin et al. [29] treated KTx subjects with 400 IU daily of oral cholecalciferol and oral calcium, 600 mg daily. They observed a significant decrease in PTH levels after 1 year adopting this regimen. However, an untreated control group was not available. Again, a clear-cut relationship between cholecalciferol supplementation and PTH decrease is questionable in this study as well. More convincing data have been provided by Courbebaisse et al. [27], who followed a group of KTx recipients for a year, in which cholecalciferol treatment was initiated 3 months after surgery, then compared to a historical control group of untreated age- and sex-matched renal transplanted patients. In that study, serum 25(OH)D was found to be increased in treated patients and a significant decrease in serum PTH was also observed. In the control group, neither vitamin D nor PTH varied significantly over the 1-year period of observation, even if the latter showed a slight decrease. However, the relationship between the improvement in vitamin D status and the reduction in PTH was not specifically investigated. In our stable KTx patients, with a median transplant duration of more than 2 years, we found that low serum vitamin D was the most important predictor of PTH values at baseline, even after adjusting for a number of potential contributors to the persistence of SHPT. More importantly, we also showed that cholecalciferol treatment was the most relevant factor contributing to the substantial decrease in PTH over the study period, without any influence of time of follow-up. These findings support the view that, even if SHPT persistence in long-term KTx subjects is also conditioned

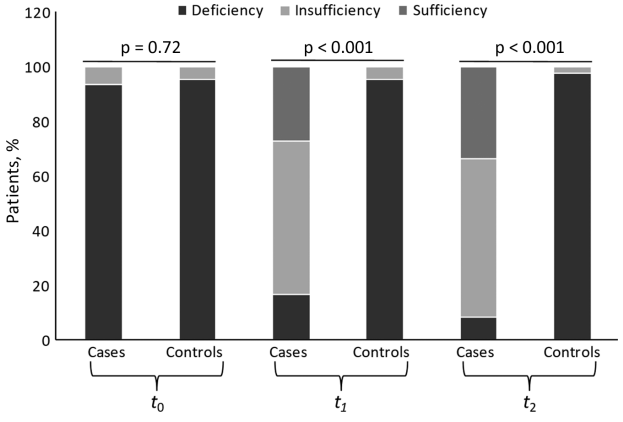

Figure 1: Proportion of patients showing deficient, insufficient and sufficient levels of 25(OH)D in treated (cases) compared to untreated (controls) patients over the study period (t_0, t_1 and t_2).

Table 3: Linear mixed model with log-transformed PTH as the dependent variable.

Variables	Coefficient (b)	p-Value
Treatment with cholecalciferol (0 = untreated; 1 = treated)	−0.328	<0.001
PTH at t_0, pg/mL	0.004	<0.001
Baseline body weight, kg	0.002	0.414
Baseline serum phosphate, mmol/L	−0.009	0.911
Follow-time, months	−0.005	0.109

Data are regression coefficients and p values. Each coefficient represents the estimated change in log serum PTH across time associated with 1 unit increase in each independent variable. PTH, parathyroid hormone.

by several other no longer modifiable factors [35, 36], cholecalciferol administration may improve PTH serum values in this setting as well.

The optimal dose and administration schedule of cholecalciferol treatment in KTx patients are still poorly defined. Consequently, studies carried out on native vitamin D treatment in KTx subjects [27–29], including the present one, have been conceived on a very different basis. In the study by Wissing et al. [28], kidney transplanted patients with a slight vitamin D insufficiency (61.25 ± 32 nmol/L) were treated with 25,000 IU on a monthly basis. In contrast, Sahin et al. [29] treated vitamin D-deficient KTx patients (baseline median vitamin D serum levels of 30.5 nmol/L) by using 400 IU daily of oral cholecalciferol. Courbebaisse et al. [27] also selected vitamin D-deficient patients (baseline median vitamin D serum levels of 35 mmol/L), then treated with 100,000 IU of cholecalciferol every 2 weeks in the first 2 months, followed by the same dose every 2 months. None of the patients included in our study was vitamin D-sufficient and 94.6% of them were vitamin D-deficient. KDIGO guidelines suggest that vitamin D deficiency and insufficiency should be corrected in KTx using treatment strategies recommended for the general population [37]. Accordingly, we administered 7500–8750 IU of cholecalciferol weekly (about 1100–1250 IU daily), based on the evidence that this dose is usually effective in inducing vitamin D repletion in the general population [38]. From our results, it is clear that this dose is suboptimal, considering that only one third of treated patients achieved vitamin D sufficiency. However, our choice was also determined by safety reasons, having also included patients with serum calcium levels at the upper normal limit or even higher than normal. Because no new or worsening cases of hypercalcemia were detected, we can affirm that this dose is sufficient to lower PTH levels without generating safety concerns. The administration schedule we adopted was also based on some considerations. High intermittent doses of native vitamin D have been associated with poor outcomes in terms of bone remodeling and health [39]. In addition, in the study by Courbebaisse et al. [27], the use of 200,000 IU of cholecalciferol monthly for 2 months, followed by a dose tapered to 100,000 IU every 2 months for 6 months, was associated with a rapid but not sustained increase in vitamin D levels over the course of the study. In contrast, we found that the weekly administration schedule is convenient in rising and then maintaining stable both vitamin D and PTH serum levels up to 12 months follow-up. There are some additional limitations to consider when administering vitamin D as large bolus doses every 2–3 months. These doses are not only inadequate in maintaining stable normal serum 25(OH)D levels due to impaired conversion, but also because of the induction of catabolism by excessive administration [40, 41]. More importantly, large bolus dosage could transiently stimulate elevations in serum calcium and phosphate shortly upon administration, which will unlikely be detected after 2 months. Ideally, daily or weekly doses will better ensure appropriate conversion and maintenance of serum levels, with less risk of hypercalcemia. Accordingly, the monthly dose of 25,000 IU used in one of the reported trials could help maintain serum 25(OH)D levels for a short period of time [28].

Limitations

This study has several limitations. First of all, this was a retrospective study and not a randomized, placebo-controlled trial. However, patients and controls were well-matched and comparable in terms of demographic, clinical and laboratory parameters as well as the duration of follow-up. Secondly, we did not evaluate any parameters of bone remodeling, therefore precluding the possibility to demonstrate the possible benefits of a PTH-level lowering strategy. However, several observations seem to support the view that a reduction in PTH levels may be associated with better bone health. Indeed, bone fragility is a common finding in renal transplanted

patients, with fracture rates being in the order of 5%–44% [42], and SHPT is considered one of the most important risk factors for this condition [5–7, 10–12, 43]. In addition, even if optimal PTH level in KTx patients remains a black box [10], values ≥130 pg/mL have been repeatedly shown to be associated with bone loss and fragility fractures [5, 11, 12]. In spite of these observations, no robust cohort studies designed to evaluate the effects of PTH-lowering strategies on bone status as a primary end-point in KTx patients are currently available. However, it has been reported that a decrease in markers of bone remodeling, bone loss and fragility fractures can be observed by treatment options aimed to reduce PTH levels [12, 44–46]. Finally, a randomized, double-blind, placebo-controlled study by Yadav et al. [47], in which cholecalciferol was given to patients with CKD stages 3–4 before transplantation, demonstrated a fall in PTH levels similar to that observed in our study. The authors also showed a substantial decrease in bone alkaline phosphatase and C-terminal cross-linked collagen type I telopeptide, strongly suggesting that the cholecalciferol-induced decrease in PTH may exert a protective effect on bone in these patients.

Conclusions

In conclusion, SHPT is common even in stable KTx patients, with low vitamin D levels playing a very important causative role. Cholecalciferol administration given as a weekly administration schedule is able to induce a significant decrease in PTH values, whose levels then remain stable over time, without any negative effect on serum calcium and renal function. Studies aimed to identify the optimal dose of cholecalciferol to achieve vitamin D sufficiency and clearly evaluate the effects on bone of the secondary reduction in PTH are warranted.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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