Influence of Pre-renal Transplant Secondary Hyperparathyroidism on Later Evolution After Transplantation

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ABSTRACT

Persistence of secondary hyperparathyroidism (SHPT) is common after renal transplantation. Good diagnosis and treatment are important to avoid complications. The objective of our work was to perform a retrospective analysis of the evolution of SHPT after renal transplantation.

We selected patients who had received a kidney transplant at our hospital between 2000 and 2014. The biochemical variables of chronic kidney disease–metabolic bone disorders (CKD-MBD) were collected at pretransplantation and at 3, 6, 12, and 24 months post-transplantation. Treatments related to SHPT were also analyzed.

Five hundred forty-three renal transplants were included. The average preoperative parathyroid hormone (PTH) was 241.14 pg/mL, 115.7 pg/mL at 3 months, and at 12 and 24 months postoperatively, PTH levels stabilized to 112 pg/mL. Treatment related to SHPT was present in 27.3% of patients during the preoperative period, 40.4% at 3 months postoperatively, 24.2% at 12 months postoperatively, and 23.2% at 24 months postoperatively. There was a significant association between requiring some type of treatment preoperatively and the rest of the postoperative periods ($P < .005$).

The sample was later divided into 3 groups based on preoperative PTH (1: <150 pg/mL, n = 223 [41.1%]; 2: 150–300 pg/mL, n = 173 [31.9%]; 3: >300 pg/mL, n = 147 [27.1%]) and their evolutions were compared. Higher levels of postoperative PTH in group pre-PTH 3 were observed. Group 3 also presented with greater need for treatment in the postoperative periods, with significant association ($P < .05$). A regression analysis was performed and found that postoperative PTH were dependent on preoperative PTH adjusted by glomerular filtration.

In conclusion, parameters related to CKD-MBD (mainly PTH) after kidney transplant, dependent on preoperative levels and glomerular filtration. Patients with a greater grade of SHPT presented with higher levels of postoperative PTH despite receiving more intensive treatment.

ABNORMALITIES in serum calcium, phosphate, and parathyroid hormone plasmatic levels are common in patients with chronic kidney disease (CKD) [1] and might persist in up to 25% of patients after kidney transplantation. Post-transplantation hyperparathyroidism (HPT) contributes to worsen bone and cardiovascular outcomes [2,3].

Successful kidney transplantation is expected to correct the endocrine and metabolic imbalances associated with CKD in the first months [4]. After renal transplantation, there is a gradual decrease in HPT levels in the first year, although not in all patients [5,6]. Persistent HPS post-transplantation is common and its treatment is not always clear. Regarding long-term natural history of HPT

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after renal transplantation, there is little data available in the literature.

The aim of the present study was to evaluate the natural history of HPT after renal transplantation. We performed a retrospective descriptive analysis in a renal transplant population of our center using the data available in our database. The results of this study could help us to find the best management of these patients in order to minimize any detrimental effect of persistent HPT on bone and cardiovascular systems.

MATERIAL AND METHODS

We performed a retrospective descriptive analysis in a renal transplant population of our center using the data available in our database. We collected all the parameters related to chronic kidney disease–metabolic bone disorders (CKD-MBD) (before and at 3, 6, 12 and 24 months after transplantation). The variables included were plasmatic levels of calcium, phosphate, parathyroid hormone (PTH), magnesium, and the glomerular filtration rate estimated using the Modification of Diet in Renal Disease Study equation. They also included the different types of treatments related to secondary hyperparathyroidism (SHPT): cinacalcet, paricalcitol, and vitamin D or analogues thereof.

Descriptive analyses of the variables in each period was done (average and standard deviation of plasmatic levels and percentages of treatments), and the Student *t*-test was used to compare the average and χ^2 for analyses of the relationship between categorical variables. The 3 groups of PTH pretransplantation were studied using an analysis of variance test. The statistical software SPSS version 15 (IBM, Armonk, NY, United States) was used.

RESULTS

It was included a total of 543 renal transplantation with more than 12 months of follow-up. The median time of renal replacement therapy was 17 months (minimum 1 month, maximum 313 months). The mean of renal graft survival was 93.3 months.

Means (mean ± SD) of PTH serum levels at different moments were as follows: 241.14 ± 213.81 pg/mL at pretransplantation, 115.7 ± 105.8pg/mL 3 months post-transplantation, 127.9 ± 135.2 ng/mL 6 months post-transplantation, 112 ± 115.6 pg/mL 12 months post-transplantion, and 112 ± 114.5 pg/mL 24 months post-transplantation.

Regarding the parameters related to CKD-MBD (calcium, phosphorous, and magnesium), we obtained the following results (mean ± SD). At pretransplantation, serum calcium was 9.3 ± 0.8 mg/dL, serum phosphorous was 4.9 ± 1.3 mg/dL, and serum magnesium was 2.5 ± 0.45 mg/dl. At 3 months post-transplantation, serum calcium was 10.1 ± 0.7 mg/dL, serum phosphorous was 3.1 ± 0.7 mg/dL, and serum magnesium was 1.8 ± 0.3 mg/dL. At 6 months post-transplantation, serum calcium was 10.05 ± 0.7 mg/dL, serum phosphorous was 3.4 ± 0.8 mg/dL, and serum magnesium was 1.8 ± 0.3 mg/dL. At 12 months post-transplantation, serum calcium was 10 ± 0.7 mg/dL, serum phosphorous was 3.3 ± 0.8 mg/dL, and serum magnesium was 1.8 ± 0.3 mg/dL. Finally, at 24 months post-transplantation: serum calcium 9.9 ± 0.6 mg/dL, serum phosphorous was 3.4 ± 0.8 mg/dL, and serum magnesium was 1.8 ± 0.3 mg/dL (Table 1).

Regarding treatment related to CKD-MBD in our sample population, at pretransplantation 27.3% received drug therapy (6.3% received paricalcitol, 9% received cinacalcet, and 15.7% received vitamin D or an analogue thereof). At 3 months post-transplantation, 40.4% were receiving treatment (35.3% received vitamin D or analogues, 6.3% received cinacalcet). At 6 months post-transplantation, 23.5% were receiving treatment (19% received vitamin D or analogues, 0.3% received paricalcitol, and 5.1% received cinacalcet). At 12 months post-transplantation, 24.2% were receiving treatment (17.9% received vitamin D or analogues, 0.5% received paricalcitol, and 7.1% received cinacalcet). Finally, at 24 months post-transplantation, 23.2% were receiving treatment (15.8% received vitamin D or analogues, 0.9% received paricalcitol, and 8.2% received cinacalcet). The χ^2 test demonstrated a statistically significant relationship between treatment related to SHPT at pretransplant and treatment during the rest of periods ($P < .05$); our results were similar when we considered cinacalcet specifically ($P < .05$) (Table 1).

Later, we divided our cohort according to pretransplantation PTH levels. We obtained three groups: group 1 had a PTH level <150 pg/mL, n = 223; group 2, 150–300 pg/mL, n = 173; and group 3, >300, n = 147. Mean of levels of PTH, calcium, and phosphorous were compared between groups and between the different periods of study using an analysis of variance test. PTH levels at 3, 6, 12, and 24 months post-transplantation were different for each group of PTH pretransplantation ($P < .01$). At 3 months post-transplantation, differences between the 3 groups were present (group 1: 67.5 pg/mL; group 2: 107.4 pg/mL; group 3: 197.2 pg/mL). At 6, 12, and 24 months post-transplantation, there were only differences between group 3 compared to groups 1 and 2 (at 6 months, group 1: 57.7 pg/mL, group 2: 118.2 pg/mL vs group 3:197.3 pg/mL; at 12 months, group 1: 76.3 pg/mL, group 2: 100.35 pg/mL vs group 3: 174.9 pg/mL; at 24 months, group 1: 82.2 pg/mL, group 2: 110.7 pg/mL vs group 3: 153.3 pg/mL). There were no differences with regard to PTH levels at post-transplantation intervals from 6 months between group of PTH pretransplantation 1 and 2 (PTH < 300 pg/mL) (Fig 1A). With regard to calcium levels, there was a greater difference in group 3 (>300 pg/mL), with higher levels of serum calcium post-transplantation in groups 1 and 2 (levels of 10.5, 10.3, 10.1 mg/dL in group 3 at 3, 6, and 12 months post-transplantation, respectively; Fig 1B). Differences in serum phosphorous levels varied greatly in the different periods of study, but lower levels after renal transplant were observed in the patients in group 3 (higher PTH levels pretransplantation) (Fig 1C).

In our results, we found no differences in glomerular filtration rates at 3, 6, 12, and 24 months between the post-transplantation and PTH pretransplantation groups.

Table 1. Differences of Variables at the Different Periods of Study

	Pretransplant	3 Months Post-transplant	6 Months Post-transplant	12 Months Post-transplant	24 Months Post-transplant
PTH (pg/mL)	241.1*,† ± 213.8	115.7 ± 105.8	84.6*,‡ (4–902)	80.9 (4–1036)	79 (4–1014)
Calcium (mg/dL)	9.3*,† ± 0.8	10.1*,§ ± 0.7	10.05 ± 0.7	10.03 ± 0.7	9.9 ± 0.6
Phosphorous (mg/dL)	4.9*,† ± 1.3	3.1*,§ ± 0.7	3.4 ± 0.7	3.35 ± 0.8	3.4 ± 0.8
GF–MDRD (mL/min)	6.7*,† ± 4.2	51.7*,§ ± 18.4	53.6 ± 20.2	54.05 ± 19.4	52.8 ± 21.3
Treatment SHPT: Paricalcitol (%)	6.3	0	0.3	0.5	0.9
Treatment SHPT: Cinacalcet (%)	9*,†	6.3	5.1	7.1	8.2
Treatment SHPT: vitamin D analogues (%)	15.7*,†	35.3*,§	19	17.9	15.8
Treatment SHPT (%)	27.3*,†	40.4*,‖	23.5*,‡,¶	24.2*,**	23.2

Abbreviations: GF–MDRD, glomerular filtration measured by MDRD equation; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.
*$P < .05$.
†Pre vs others.
‡6 mo vs 12 mo.
§3 mo vs 6 mo.
‖3 mo vs others.
¶6 mo vs 24 mo.
**12 mo vs 24 mo.

The relationship between groups regarding PTH at pretransplantation and the treatment requirements at post-transplantation was analyzed using χ^2. A higher number of patients in group 3 received cinacalcet at 3, 6, 12 and 24 months post-transplantation (52.9%, 50%, 50%, and 47.7%, respectively). If we consider all the different types of treatment on the whole, only significant association at 24 months post-transplantation was observed in the PTH pre-transplantation group.

Finally, a regression analysis was performed; PTH levels at each post-transplantation follow-up were dependent on PTH pretransplantation levels and glomerular filtration of the renal graft at the moment of measurement.

DISCUSSION

Abnormalities in serum calcium, phosphate, and PTH levels are common in patients with chronic kidney disease (CKD) [1]. After renal transplantation, there is a gradual decrease in HPT levels in the first year, but not in all patients [5,6]. There was little data available in the literature about the long-term natural history of HPT after renal transplantation. In our study we described what happened during the first 2 years after transplantation with regard to serum levels of PTH, calcium, and phosphate. We found that PTH levels decreased progressively until 12 months after transplantation and the calcium levels increased progressively until 6 months after transplantation. After that, both parameters remained stable until the end of follow-ups (24 months after transplantation). However, phosphate levels showed a different pattern. During the first 3 months, phosphate levels decreased, but after 3 and 6 months they increased again and remained stable until the end of follow-ups. These parameters therefore remained similar after 12 months after transplantation (PTH and phosphate levels lower and calcium level higher than pretransplantation).

Successful kidney transplantation corrects abnormal mineral metabolism, but persistent HPT is still observed in up to 25% of patients 1 year after transplantation despite renal function improvement [7]. Persistent hyperparathyroidism after renal transplantation (tertiary HPT, or THPT), continues to be an ongoing problem [8]. However, risk factors and appropriate operative procedures for THPT are poorly understood. In previous studies, long dialysis duration, large maximum parathyroid gland size before renal transplant, high PTH pretransplantation, high calcium post-transplantation, and high alkaline phosphatase post-transplantation were identified as risk factors for THPT [9]. In our study we analyzed whether the PTH values pretransplantation could have any influence on THPT. The study population was divided into 3 groups based on pre-transplantation PTH values; we found that the patients in group 3 (PTH levels >300) had higher PTH values and calcium plasmatic levels despite more of them being treated with cinacalcet throughout the study period (follow-ups at 3, 6, 12 and 24 months after transplantation). Our data confirmed that the importance of controlling post-transplantation CKD-MBD starts in the predialysis period and continues through the dialysis period [10]. When such patients receive a kidney graft, the recovery of renal function and the correction of metabolic and endocrine disturbances generally induced a slow regression of polyclonal parathyroid hyperplasia. This did not happen with tumoral growth, where the response of parathyroid secretion and proliferation to physiologic regulatory mechanisms was reduced or stopped [11]. High-risk patients should be evaluated for parathyroid enlargement and parathyroidectomy must be considered before kidney transplantation [12]. Spontaneous resolution of THPT after transplantation is uncommon, despite lengthy follow-up and satisfactory graft function [13].

In fact, current guidelines recommend parathyroidectomy if serum PTH is persistently elevated 1 year after kidney transplant, because persistent HPT has recently been associated with poor graft outcomes. The persistence of mineral metabolism disorders after renal transplant appears to have a

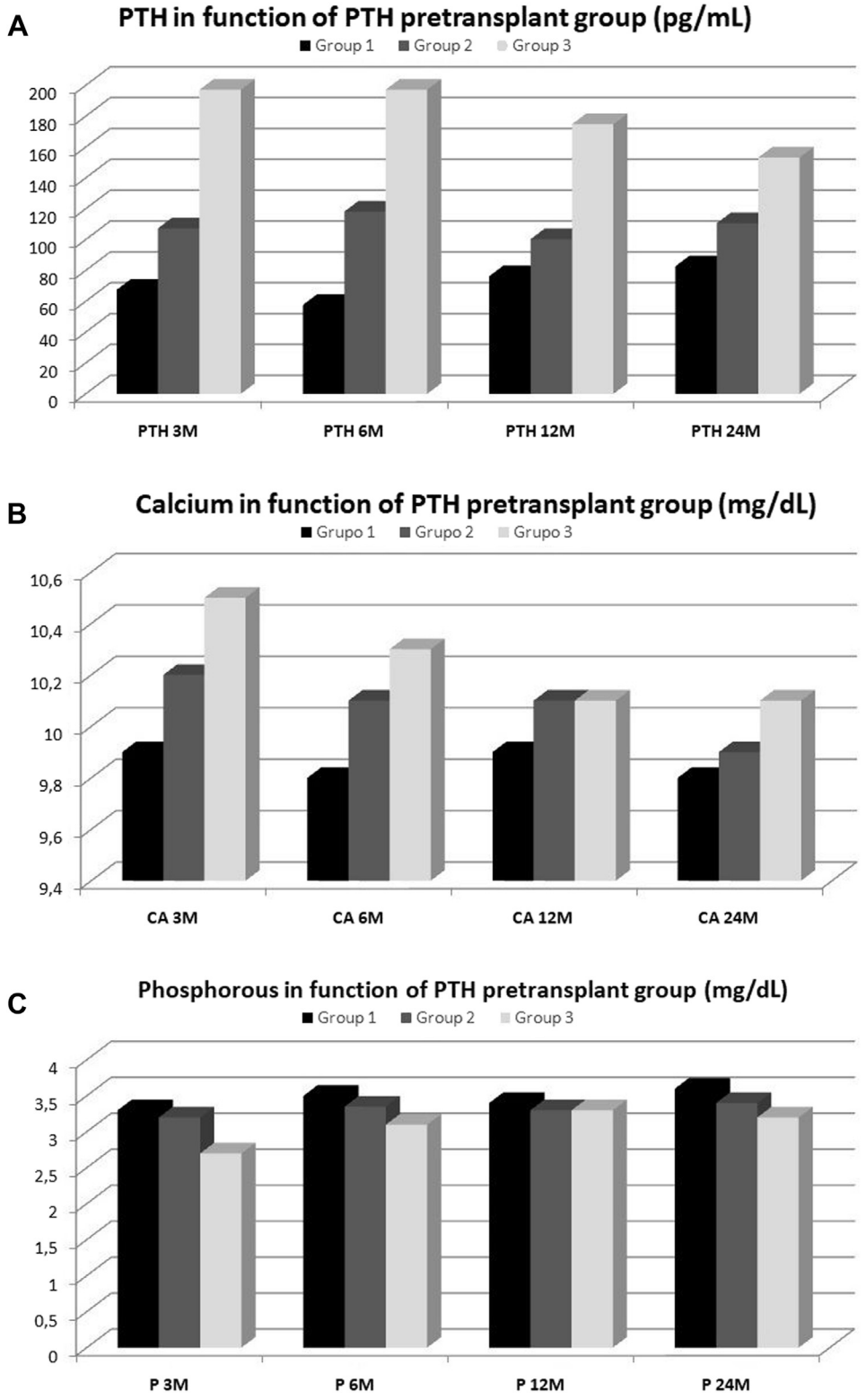

Fig 1. Differences of variables for PTH pretransplantation group. Measurements at post-transplantation periods. **(A)** PTH levels. **(B)** Calcium levels. **(C)** Phosphorous. PTH, parathyroid hormone.

negative impact on graft and patient survival [14] and the influence of persistent HPT in patients with adequate renal function could have any influence in long-term graft failure [15]. However, in our study, we found no differences in glomerular filtration rates at 3, 6, 12, or 24 months post-transplantation depending on the PTH pretransplantation group, so we concluded that the pretransplantation PTH levels did not influence renal graft survival. Nevertheless, post-transplantation PTH levels were related to glomerular filtration at every follow-up. Further studies should determine if persistent hyperparathyroidism or its treatment influences long-term post-transplantation clinical outcomes [16].

On the other hand, a standard treatment for HPT post-transplantation is not yet established. Vitamin D or analogues are used if possible and/or cinacalcet if the patient's calcium rises too much. Cinacalcet is a promising therapy widely used in dialysis patients with hyperparathyroidism resistant to conventional therapy. However, reports regarding the influence of cinacalcet cessation after long-term use on kidney transplantation patients are few. Serum levels of calcium, alkaline phosphatase, and PTH after kidney transplantation were higher in patients treated with cinacalcet than in those treated without. However, serum phosphate levels in the cinacalcet group were slightly higher at the time of kidney transplantation and significantly lower 3 months later. The effects of treating HPT with cinacalcet before transplantation on post-transplantation PTH and calcium levels have not yet been conclusively determined [17]. In fact, there are studies that affirm that serum levels of calcium, alkaline phosphatase, and PTH after kidney transplantation were higher in patients treated with cinacalcet than in those without this drug [18]. Transplant recipients discontinuing cinacalcet had higher post-transplantation PTH and calcium levels, although the clinical significance of this is unclear. No difference was seen in renal function, graft loss, post-transplantation parathyroidectomy rate, or mortality [19]. We did not analyze separately the patients treated with cinacalcet before transplantation (9% of the study population) because this was not the aim of our study, but we repeated the analysis of the influence of PTH pretransplantation divided into groups and confirmed our previous results.

We want to highlight the importance of establishing an adequate treatment for CKD-MBD; we discuss the appropriate time and the type of treatment of HPT—parathyroidectomy or calcimimetics such as cinacalcet or paricalcitol. Previous studies evaluated whether subtotal parathyroidectomy is more effective than cinacalcet for controlling hypercalcemia caused by persistent hyperparathyroidism after kidney transplant. Subtotal parathyroidectomy induced a greater reduction of PTH and was associated with a significant increase in femoral neck bone mineral density; vascular calcification remained unchanged in both groups. The most frequent adverse events were digestive intolerance in the cinacalcet group and hypocalcemia in the parathyroidectomy group. Some researchers found that subtotal parathyroidectomy was superior to cinacalcet, at least with regard to short-term control of hypercalcemia in these patients with kidney transplants and persistent hyperparathyroidism [20]. The timing of parathyroidectomy in kidney transplant candidates suffering from SHPT before vs early or late after transplantation remains controversial. Parathyroidectomy within the first post-transplantation year was associated with compromised renal graft function until the last follow-up, while parathyroidectomy late post-transplantation was not. Parathyroidectomy should be conducted before transplantation, or, if this is not possible, preferably after the first post-transplantation year [21].

As limitations of our study, we highlight the retrospective characteristics of the study design and the fact that we did not collect studies parameters of bone mineral density and cardiovascular events in our patients. The post-transplantation period is associated with profound abnormalities of mineral metabolism, bone loss, and bone fragility, which confer an increased risk of fracture risk [22]. Kidney transplantation does not automatically cure renal osteodystrophy, and the development of post-transplantation bone disease with accelerated bone loss and further aggravation of fracture risk, especially during the first few years after transplantation, is common [23]. Bone and mineral disorders occur frequently in kidney transplant recipients and are associated with a high risk of fracture, morbidity, and mortality. The pathophysiology underlying bone disorders after transplantation results from a complex interplay of factors, including preexisting renal osteodystrophy and bone loss related to a variety of causes, such as immunosuppression and alterations in the parathyroid hormone-vitamin D-fibroblast growth factor 23 axis as well as changes in mineral metabolism [24].

In patients with optimal transplant function, PTH levels are associated with clinical outcomes including cardiovascular events, graft loss, and all-cause mortality [25]. SHPT and altered PTH levels are associated with vascular events in chronic kidney disease. After renal transplantation, this association is not clear. Previous studies observed the effect of PTH at the time of transplantation on risk of post-transplantation vascular events in renal transplant recipients with and without pretransplantation PTH. We concluded that low levels of parathyroid hormone before transplantation were associated with an increased risk of post-transplantation vascular events in patients both with and without pretransplantation parathyroidectomy. No conclusions can be drawn regarding the causal or direct effect of PTH on outcomes [26].

Care of kidney transplant recipients could be substantially improved, particularly with regard to CKD-MBD, when

regular check-ups for calcium-phosphate balance are implemented and proper treatment can be introduced to prevent further progression of the disease [27]. Control of CKD-MBD after kidney transplantation depends on pretransplantation levels and glomerular filtration of the renal graft. Higher pretransplantation levels of PTH are responsible for poor control of CKD-MBD after kidney transplantation.

CONCLUSION

In conclusion, parameters related to CKD-MBD (primarily PTH serum levels) after receiving a renal transplant depend on pretransplantation levels and glomerular filtration rates. Patients with a greater grade of SHPT presented higher levels of PTH at post-transplantation follow-ups, despite receiving more intensive treatment.

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