# Persistent disorders of mineral metabolism after one year of kidney transplantation

## Alterações do metabolismo mineral e ósseo após um ano de transplante renal

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## Abstract

**Introduction:** The persistence of mineral metabolism disorders after renal transplant (RT) appears to possess a negative impact over graft and patient's survival. **Objectives:** To evaluate the parameters of mineral metabolism and the persistence of hyperparathyroidism (HPT) in transplanted patients for a 12-month period after the procedure. **Methods:** Retrospective analysis of 41 transplants (18 women- 44%, mean age of 39 ± 15 years) performed in a University Hospital, evaluating changes of calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) and the prevalence of persistent HPT. The patients were divided into two groups accordingly to PTH levels prior to Tx: Group 1 with PTH ≤ 300 pg/mL (n = 21) and Group 2 with PTH > 300 pg/mL (n = 20). The persistency of HPT after transplant was defined as PTH ≥ 100 pg/mL. The evolution of biochemical parameters and the persistency of HPT were analyzed in each group after 1 year of transplant. **Results:** After a one-year of follow up, 5% of the patients presented hypophosphatemia ($p$ < 2.7 mg/dL), 24% hypercalcemia (Ca > 10.2 mg/dL) and 48% persistency of HPT (PTH ≥ 100 pg/mL). There was a positive correlation between the PTH pre and post Tx (r = 0.42/$p$ = 0.006) and a negative correlation between PTH and Ca pre-Tx (r = -0.45/$p$ = 0.002). However, there was no significant difference among groups 1 and 2 regarding PTH levels pre and post Tx. **Conclusion:** The findings in this article suggest that mineral metabolism alterations and the persistency of HPT may occur after one year of renal Tx, mainly in patients which present high PTH levels prior toTx.

**Keywords:** hypercalcemia; hyperparathyroidism; hypophosphatemia; kidney transplantation.

## Resumo

**Introdução:** A persistência de distúrbios do metabolismo mineral ósseo após o transplante renal (Tx) parece possuir um impacto negativo sobre a sobrevida do enxerto e do paciente. **Objetivos:** avaliar os parâmetros do metabolismo mineral e a persistência de hiperparatiroidismo (pHPT) 12 meses após o Tx. **Métodos:** Análise retrospectiva de 41 transplantes (18 mulheres- 44%, idade de 39 ± 15 anos) realizados em um Hospital Universitário, avaliando cálcio (Ca), fósforo (P), hormônio da paratireóide (PTH) e a prevalência de pHPT. Pacientes foram divididos em dois grupos de acordo com os níveis de PTH pré Tx: Grupo 1: PTH ≤ 300 pg/ml (n = 21) e Grupo 2: PTH > 300 pg/ml (n = 20). pHPT foi definida como PTH ≥ 100pg/mL após o Tx. A evolução dos parâmetros bioquímicos e a pHPT foram analisadas após 1 ano de Tx. **Resultados:** após um ano, 5% dos pacientes apresentaram hipofosfatemia ($p$ < 2,7mg/dL), 24% hipercalcemia (Ca > 10,2 mg/dL) e 48% persistência de HPT (PTH ≥ 100 pg/mL). Houve correlação positiva entre PTH pré e pós Tx (r = 0,42/$p$ = 0,006) e correlação negativa entre PTH e Ca pré-Tx (r = -0,45/$p$ = 0,002). Entretanto, não houve diferença significativa entre os grupos 1 e 2 em relação aos níveis de PTH pré e pós-Tx. **Conclusão:** Os resultados sugerem que alterações do metabolismo mineral e a pHPT podem ocorrer após um ano do Tx, principalmente em pacientes com níveis elevados de PTH pré-Tx.

**Palavras-chave:** hipercalcemia; hiperparatireoidismo; hipofosfatemia; transplante de rim.

## Introduction

The history of renal transplantation (RTx) in Brazil is characterized by a successful track record. In the last decade, the number of kidney transplantation procedures grew by 40%. Brazil ranks second in absolute number of transplant procedures in the world, with 5,433 procedures carried out in 2013.[1]

Therapeutic advances, and the introduction of new immunosuppressants in particular, have significantly increased patient and graft survival and improved the quality-of-life of transplant patients. According to the Brazilian Transplant Registry (RBT), the four-year survival of patients and grafts is greater than 90% for living donor and approximately 80% for deceased donor procedures.[1] Despite the promising outlook, new challenges have emerged with late RTx complications such as chronic kidney disease-mineral and bone disorder (CKD-MBD).[2,3]

Patients are expected to show normal serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) levels one year after successful transplantation. However, many individuals have persistent mineral metabolism disorders caused by a complex interposition of factors such as poor graft function, preexisting bone disease, and use of immunosuppressants - specifically glucocorticoids - with toxic effects on bone tissue.[4-7]

Some patients develop hypercalcemia secondary to hypophosphatemia, persistent hyperparathyroidism (HPT), and use of steroids.[8,9] Hypophosphatemia occurs in 90% of the patients as a result of the phosphaturic action of FGF23 and PTH.[8,10] Secondary hyperparathyroidism (SHPT) affects approximately 45% of the patients on dialysis and may persist in 25%-50% of them, even when the graft functions adequately.[11] Serum PTH levels drop rapidly immediately after RTx, decrease more slowly between three to six months after the procedure, and stabilize one year from transplantation.[12]

The main predictors of persistent HPT are the time with chronic kidney disease (CKD), elevated serum PTH prior to transplantation, parathyroid glands with probable nodular hyperplasia and incomplete recovery of renal function.[13,14] Despite the several studies assessing persistent HPT, there is still no consensus on the ideal post-transplant serum PTH levels.[15,16] Two papers stand out from studies published in Brazil on CKD-MBD, in which bone biopsies were carried out six and twelve months after transplantation.[7,17]

This study aimed to assess the changes in mineral metabolism markers and the prevalence of persistent HPT in a population of renal transplantation patients seen 12 months after the procedure.

## Method

This retrospective study was performed at the Evangélico University Hospital in Curitiba, Brazil. Three hundred and twenty-two patients underwent renal transplantation from April of 2005 to September of 2011. Forty-one were enrolled in the study, based on the following criteria: subjects had to be aged 18 years or older; have a glomerular filtration rate ≥ 30 ml/min (using the MDRD method); have complete clinical and biochemistry workup records at the time and one year after transplantation. The charts of the other patients were incomplete and they were excluded from the study.

Changes in mineral metabolism parameters were assessed based on serum Ca, P, and PTH levels before and 12 months after transplantation. In order to assess the impact of SHPT prior to transplantation on mineral metabolism parameters and persistence of HPT, the patients were divided into two groups according to the KDOQI[18] guidelines: Group I: PTH ≤ 300 pg/mL (n = 21); and Group II: PTH > 300 pg/mL (n = 20).

The patients were diagnosed with hypophosphatemia when $p$ < 2.7 mg/dL; with hypercalcemia when Ca > 10.2 mg/dL; and persistent HPT when PTH ≥ 100 pg/ml in association or not with hypercalcemia.[16] Other variables apparently associated with persistent HPT, such as age, gender, and time on dialysis, were also analyzed.

### Statistical analysis

The distribution of the data was analyzed for normality. When in a normal distribution, the data belonging to each of the groups were analyzed using Student's *t*-test with the Welch correction when needed. Otherwise, the data sets were compared using the Mann-Whitney U test. Association analysis was carried out with Fisher's exact test. The correlations between the variables were assessed with Pearson's correlation coefficient (when in a normal distribution) or Spearman's rank correlation coefficient (when not in a normal distribution). The results were expressed

in the form of mean values ± standard deviations or medians (minimum; maximum); *p*-values < 0.05 were deemed statistically significant. Statistical analysis was carried out with the aid of software program *GraphPad Prism* version 4.

## Results

Eighteen (44%) of the 41 patients enrolled in the study were females; the mean age of the study group was 39 ± 15 years. Most patients (90%) were on hemodialysis and 10% on peritoneal dialysis; they had been on dialysis for a mean of 33 ± 31 months. The etiology of CKD was as follows: 20 patients (49%) had chronic glomerulonephritis; 10 (25%) had hypertensive nephropathy; and 11 (26%) had CKD for other causes.

The patients were on different immunosuppression schemes: 66% were prescribed prednisone, mycophenolate mofetil (MMF), mycophenolate sodium (MMS), and tacrolimus; 30% were on a regimen with prednisone, MMF/MMS, and cyclosporine; 2% on prednisone, rapamycin, and cyclosporine; and 2% on prednisone, rapamycin, and tacrolimus.

### Biochemistry tests performed before and after transplantation

The patients included in the study had significant reductions on their serum P, PTH, and creatinine levels and significant increases in their GFR and serum Ca levels (Table 1).

Twelve months after transplantation, two patients (5%) were hypophosphatemic, 10 (24%) had hypercalcemia, and 20 (48%) had persistent HPT.

Variables age, gender, baseline disease, time on dialysis, and immunosuppressant therapy were not associated with HPT. Conversely, a positive significant correlation was found between PTH levels before and after transplantation (r = 0.42/*p* = 0.006); a negative significant correlation was found between pre-transplantation PTH levels and pre-transplantation calcium levels (r = 0.45/*p* = 0.002).

### Comparisons between patients in groups I and II

#### *Group I: PTH ≤ 300 pg/mL*

Serum Ca and PTH levels were mildly increased; a significant drop was observed in serum P levels; and the GFR was increased, as seen in Table 2. One patient had hypophosphatemia, seven were diagnosed with hypercalcemia, and six with persistent HPT.

#### *Group II: PTH > 300 pg/mL*

Serum Ca levels and renal function were significantly increased, while serum P and PTH levels dropped significantly, as shown in Table 3. Two patients had hypophosphatemia, three were diagnosed with hypercalcemia, and nine had persistent HPT.

### *Comparison of persistent HPT in groups I and II*

A non-significant greater incidence of patients with PTH ≥ 100 pg/mL was seen in Group II (Table 4).

## Discussion

This study looked into the changes in mineral metabolism parameters of RTx patients 12 months after the procedure and the incidence of persistent HPT and its predisposing factors. The main findings point out to a trend toward persistent HPT after RTx, mainly in the population with elevated serum PTH levels before transplantation.

Brazil ranks high in number of kidney transplants performed. Therefore, persistent HPT is a relevant issue, given that it introduces negative impacts on graft function and patient clinical progression.

Most metabolic alterations are expected to normalize 12 months after RTx. The behavior of calcium, phosphorus, and PTH levels observed in our study seem to be in agreement with the literature.[12,13,19] Serum P levels were assumed to have dropped immediately after RTx; P levels were measured only a year after transplantation, and almost all patients had normal serum phosphorus levels then. Hypophosphatemia can be explained by the predominance of phosphaturic action by FGF23 occurring within the first months after RTx, and later by the phosphaturic action of PTH when serum FGF23 and calcitriol levels have decreased.[10]

Serum Ca levels increased slightly after RTx. Approximately a quarter of the patients still had hypercalcemia, probably due to some of the factors discussed above (hypophosphatemia, persistent HPT, and steroid therapy). Other authors[8,20] have described incidences of hypercalcemia ranging between 5% and 50%.[8] One of the most deleterious consequences of persistent HPT, hypercalcemia may lead to late graft loss by nephrocalcinosis and adversely affect the hematopoietic, gastrointestinal, and cardiovascular systems, thus increasing patient mortality.[20] In the present study, hypercalcemia not

**Table 1** Study population clinical and workup findings

| | | Total (n = 41) | *p* |
|---|---|---|---|
| Age (years) | | 39 ± 15 | -- |
| Gender (female) | | 18 (44%) | -- |
| Time on dialysis (months) | | 33 ± 31 | -- |
| Creatinine (mg/dL) | Before RTx | 9.9 ± 2.9 | < 0.0001 |
| | After RTx | 1.4 ± 0.3 | |
| Calcium (mg/dL) | Before RTx | 9.5 (6.1 ; 11.5) | 0.02 |
| | After RTx | 9.8 (8.8 ; 11.0) | |
| Phosphorus (mg/dL) | Before RTx | 5.7 ± 1.3 | < 0.0001 |
| | After RTx | 3.6 ± 0.9 | |
| PTH (pg/mL) | Before RTx | 300 (16 ; 2172) | 0.0009 |
| | After RTx | 85 (38 ; 530) | |
| GFR (mL/min.1.73m$^2$) | Before RTx | 6.4 ± 2.8 | 0.0001 |
| | After RTx | 58.1 ± 18.7 | |

Variables expressed as mean values ± standard deviation or median values (minimum; maximum).

**Table 2** Group I (PTH ≤ 300 pg/mL) clinical and workup findings

| | | Total (n = 21) | *p* |
|---|---|---|---|
| Age (years) | | 33 ± 11 | -- |
| Gender (female) | | 9 (42%) | -- |
| Time on dialysis (months) | | 30 ± 31 | -- |
| Calcium (mg/dL) | Before RTx | 9.7 ± 0.8 | 0.24 |
| | After RTx | 9.9 ± 0.6 | |
| Phosphorus (mg/dL) | Before RTx | 5.5 ± 1.4 | < 0.0001 |
| | After RTx | 3.6 ± 0.8 | |
| PTH (pg/ml) | Before RTx | 76 (16; 300) | 0.40 |
| | After RTx | 78 (38; 238) | |
| RFG (mL/min.1,73 m$^2$) | Before RTx | 5.4 ± 1.6 | < 0.0001 |
| | After RTx | 57.9 ± 14.8 | |

Variables expressed as mean values ± standard deviation or median values (minimum; maximum).

**Table 3** Group II (PTH > 300 pg/mL) clinical and workup findings

| | | Total (n = 20) | *p* |
|---|---|---|---|
| Age (years) | | 45 ± 15 | -- |
| Gender (female) | | 11 (55%) | -- |
| Time on dialysis (months) | | 35 ± 32 | -- |
| Ionized calcium (mg/dL) | Before RTx* | 8.9 ± 1.2 | 0.008 |
| | After RTx* | 9.7 ± 0.6 | |
| Phosphorus (mg/dL) | Before RT* | 5.9 ± 1.2 | < 0.0001 |
| | After RTx* | 3.6 ± 0.9 | |
| PTH (pg/ml) | Before RTx* | 745 (360; 2172) | < 0.0001 |
| | After RTx* | 96 (40; 530) | |
| GFR (mL/min.1,73m$^2$) | Before RTx* | 7.4 ± 3.4 | < 0.0001 |
| | After RTx* | 58.2 ± 22.4 | |

Variables expressed as mean values ± standard deviation or median values (minimum; maximum).

**Table 4** Changes in PTH serum levels before and after RTx

| | | After RTx | |
|---|---|---|---|
| | | PTH < 100 pg/mL | PTH ≥ 100 pg/mL |
| Before RTx | PTH ≤ 300 pg/mL | 15 (71%) | 6 (29%)* |
| | PTH > 300 pg/mL | 11 (55%) | 9 (45%)* |

* $p = 0.275$

accompanied by increased PTH levels might indicate persistent SHPT.

The concept of persistent or tertiary HPT,[21] in which there is a persistent elevation in serum PTH levels accompanied or not by hypercalcemia, has been well established. PTH hypersecretion appears to be caused by monoclonal hyperplasia of the parathyroid glands presenting loss of vitamin D receptors, Ca receptors and altered calcium set point.[19] Authors

differ on appropriate serum PTH levels after RTx. Some diagnose patients with persistent HPT when serum PTH levels are above 2.5 times the upper limit set for normal reference values (PTH > 130-150 pg/mL).[19] In this study, the normal PTH range was set at 70-100 pg/mL,[16] based on patient renal function and CKD stage (KDOQI).

The PTH levels of the study population decreased gradually after RTx, and at the end of the first year 48% of the patients had persistent HPT. Other authors reported incidences of patients with elevated serum PTH levels ranging from 17% to 28% within an equivalent period of time.[12]

The factors related to persistent PTH were not associated with the etiology of renal disease or immunosuppression therapy. Steroids are known for significantly interfering with mineral metabolism and, in this study, drug dosages and time of treatment were similar along the various immunosuppression regimens prescribed. Time on dialysis is an important determining factor for persistent HPT, as it favors the development of severe SHPT unresponsive to medical treatment. However, there was no observable impact of this parameter on persistent HPT in this study.

The retrospective nature of this study limited the number of enrolled patients to 41 individuals, given the large number of patient charts excluded for not meeting the inclusion criteria defined it. Nonetheless, the sample appears to be a good representation of the transplant population of the State of Paraná, Brazil. Another limitation is the absence of data on bone biopsies, parathyroid imaging examination, alkaline phosphatase and vitamin D levels, all of which relevant for the interpretation of the analyzed biochemistry and clinical parameters.

## Conclusion

Until recently, bone disease was an unappreciated complication after RTx, despite the impact it has on patient and graft survival. Persistent HPT is a major concern for nephrologists as it is a condition that needs to be managed before transplantation. Cases of severe post-transplantation hypercalcemia, which are often referred to parathyroidectomy, can be thus avoided. Such procedure might lead to altered graft function, even if temporarily, and expose patients to the risk of surgery, none of which is desired for patients recently submitted to renal transplantation.[22]

Our findings suggest that changes in mineral metabolism and HPT might persist after renal transplantation, even when the procedure has been successful, in patients with elevated PTH levels before RTx in particular.

Further studies are required to add to the knowledge and management of bone diseases after renal transplantation.

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