Behavior of Bone Mineral Metabolism in Renal Posttransplantation Patients with Severe Hyperparathyroidism

Paola Karina Garcia-Padilla*, Jossie Esteban Quijano, Karen Navarro, and Camilo Gonzalez Gonzalez

Department of Internal Medicine, Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogota, Colombia

ABSTRACT

Background. Secondary hyperparathyroidism usually improves after renal transplantation. When it becomes persistent, it is associated with deleterious effects on the graft, bone demineralization, fractures, calcifications, and cardiovascular events. In this study we describe the development of cases of severe hyperparathyroidism occurring after renal transplantation.

Objective. To describe the behavior of the indicators of bone mineral metabolism in the renal transplantation patient with severe secondary hyperparathyroidism before transplantation, treated with or without parathyroidectomy.

Methods. This is a case series study conducted between 2004 and 2017 on renal transplantation patients presenting with PTH > 800 pg/mL or who required pretransplantation parathyroidectomy.

Results. We found 36 patients with severe hyperparathyroidism, corresponding to 10.8% of transplantation recipients, with an average age of 54.5 years (±12.35). The median follow-up after transplantation was 128 months (16-159). Fourteen patients underwent parathyroidectomy before transplantation, with a median intact parathyroid hormone at the time of transplantation of 56 (3-382) pg/mL, with more episodes of hypocalcaemia and oral calcium requirement. The other patients were transplanted with a median intact parathyroid hormone of 1010 (range, 802-1919) pg/mL, reaching a median intact parathyroid hormone of 98.8 (43.8-203) at 3 years of follow-up. Only 2 patients underwent parathyroidectomy for tertiary hyperparathyroidism.

Conclusions. Renal transplantation improves secondary hyperparathyroidism. Sixty-eight percent of patients presented PTH of less than 130 pg/mL after renal transplantation. Only 2 patients underwent posttransplantation parathyroidectomy.

BONE mineral metabolism disorders are common in chronic kidney disease, and their prevalence increases as renal function decreases [1]. According to Colombian statistics, in 2017 the prevalence of stage 5 chronic kidney disease was 759 per million population, with an increase of 3.4% over the previous year [2].

Secondary hyperparathyroidism is an adaptive response that develops as renal function declines owing to impaired phosphorus excretion, secondary hypocalcaemia, and decreased vitamin D synthesis [1]. With regard to treatment, diet changes, use of vitamin D analogues, phosphorus chelants, and calcimimetics have been described [3]. Parathyroidectomy is reserved for patients unresponsive to medical therapy, defined as parathyroid hormone levels from 2 to 9 times the upper limit of normal or the presence of complications such as calciphylaxis, as proposed by the KDIGO guidelines [4,5].

Although hyperparathyroidism improves in the majority of patients after renal transplantation [6], in some cases elevated PTH persists, with a deleterious effect on renal graft

*Address correspondence to Paola Karina Garcia Padilla, Carrera 7 No 40-62 Piso 6, 110111, Hospital Universitario San Ignacio, Bogotá, Colombia. Tel: (+57-1) 5946176. E-mail: pkgarcia@husi.org.co

230 Park Avenue, New York, NY 10169

0041-1345/20
https://doi.org/10.1016/j.transproceed.2020.01.055

function owing to tubulointerstitial calcifications and renal vasoconstriction [7]. At the systemic level, hyperparathyroidism manifests itself with bone mineral density loss, fractures, ectopic calcifications, and cardiovascular events [8]. Among the alterations most frequently associated with cardiovascular morbidity and mortality are hyperphosphatemia and increase in fibroblast growth factor 23 level. The latter favors an antagonistic effect on PTH levels. Elevated levels of fibroblast growth factor 23 are associated with alterations at the cardiovascular level, such as systemic hypertension, left ventricular hypertrophy, and hypertrophic heart disease. These act as predictors of renal graft failure [9]. PTH levels decrease significantly during the first year of renal transplantation [6]. Giovale describes a 50% decrease in PTH within the first 6 months of transplantation. Persistent elevations are associated with greater bone mass loss and hypercalcemia [10] and may be secondary to nodular hyperplasia with limited reversibility potential, favoring a state of autonomous glandular function. Elevated pretransplantation levels of PTH have been associated with renal graft failure [11]. Callender et al showed that parathyroidectomy before transplantation is associated with lower renal graft failure rates [12].

This study aims to describe the behavior of bone mineral metabolism indicators after renal transplantation in patients with severe secondary hyperparathyroidism and its complications in a transplantation center.

METHODS

This is a case series study conducted between 2004 and 2017 on renal transplantation patients presenting with PTH > 800 pg/mL or who required pretransplantation parathyroidectomy. The study included patients with an age older than 18 years who had been diagnosed with severe secondary hyperparathyroidism (PTH > 800 pg/mL). In order to be included, patients had to be receiving medical management or have a past medical history remarkable for parathyroidectomy before transplantation and to have been followed for at least 1 year. Patients with parathyroidectomy owing to other indications were excluded.

RESULTS

We found 36 patients with severe hyperparathyroidism within the cohort of 332 patients who had undergone renal transplantation, a number that corresponds to 10.8%. The average age was 54.5 years (range, 20-79), 52.8% were men, and all patients were Hispanic. Regarding causes of chronic kidney disease, most were unknown, followed by diabetic kidney disease and systemic hypertension.

Most (94.5%) of the patients received a deceased donor transplantation. The median follow-up period after transplantation at the time of analysis was 128 months (range, 16-159). Three patients (8.33%) had been recipients for renal transplantation at least once before. Four patients in the cohort (11%) had to return to dialysis during the follow-up period.

In 94.4% of the patients, the immunosuppression regimen included an anticalcineurinic agent, mainly tacrolimus and an antimetabolite (mycophenolate), and all but 1 patient received prednisolone. Two patients received an MTOR inhibitor (mammalian target of rapamycin).

Regarding dialysis modality, 77.8% received hemodialysis, 16.7% peritoneal dialysis, and the rest used both therapies before renal transplantation. As a management strategy for severe hyperparathyroidism, 16 patients (41%) required parathyroidectomy, 14 of them before renal transplantation and 2 after renal transplantation. The average time on dialysis was longer in patients undergoing parathyroidectomy before transplantation (125 [6-216] vs 43 [2-273] months, $P < .009$). Table 1 displays demographic and clinical characteristics according to a past medical history of parathyroidectomy or medical treatment before transplantation.

Fourteen patients underwent parathyroidectomy before renal transplantation and did so with a median of 1.6 years before transplantation (2 months to 3.1 years). In this group, 3 patients presented 7 events of severe posttransplantation hypocalcemia and characteristically required a high dose of oral calcium supplement, 5040 mg (1680-13440 mg).

Two patients required parathyroidectomy owing to persistent hyperparathyroidism despite transplantation. The procedure was performed at 55 and 59 months posttransplantation owing to high PTH values and persistent hypercalcemia > 11 mg/dL. PTH, calcium, and phosphorus values normalized after surgery. In Table 2 we describe the variables according to the history of pre- or posttransplantation parathyroidectomy and those with medical treatment.

The 22 patients with secondary hyperparathyroidism on medical therapy showed improvement in PTH levels after renal transplantation; 15 of them achieved levels below 130 pg/mL at 12 and 36 months of follow-up. At 12 months after transplantation, 9 patients had corrected calcium levels greater than 10.2 mg/dL and 7 patients had phosphorus levels greater than 4.5 mg/dL. Regarding the 12-month therapeutic regimen, 2 patients needed elemental calcium with an average weekly dose of 3360 mg (range, 1680-5040), 11 required vitamin D analogues, and 1 received calcimimetic drugs for persistently elevated PTH levels at 12 months after transplantation (742 pg/mL), achieving normalization and lowering to 21 pg/mL, so parathyroidectomy was not considered.

Four patients displayed graft failure in the study, 3 of them from the medical therapy group and 1 from the posttransplantation parathyroidectomy group. Three patients were deceased at the time of follow-up, 1 from the medical management treatment group and 2 from the pretransplantation parathyroidectomy group.

DISCUSSION

Secondary hypoparathyroidism occurs frequently in patients living with chronic kidney disease and has been reported in up to a third of transplantation patients [13]. PTH values above 9 times the upper limit of normal are associated with complications such as graft failure and infection [12].

Table 1. Demographic and Clinical Data in Renal Pretransplantation

	Pretransplant parathyroidectomy group (n = 14)	No parathyroidectomy group (n = 22)
Age, median (range) - yr	51.7 [35-66]	56.3 [20-79]
Male sex, n (%)	5 (35.7%)	14 (63.6%)
Dialysis duration median (range) - months	129.2 [6-216]	69.9 [2-233]
Diabetes mellitus, n (%)	2 (14.2%)	4 (18.1%)
Calcemia (mg/dL) median (range)	8.9 [6-12]	9.7 [8.2-11.2]
Calcemia $\geq$ 10.2 mg/dL, n (%)	3 (21.4%)	7 (31.8%)
Phosphatemia (mg/dL) median (range)	5.4 [3.8-9.4]	5.9 [3.2-8.9]
Phosphatemia $\geq$ 6 mg/dL, n (%)	4 (28.5%)	11 (50%)
iPTH (pg/mL) median (range)	95.1 [3-482]	1119.1 [802-1919]
Users of calcium supplementation, n (%)	10 (83%)	4 (17%)
Users of vitamin D analogues, n (%)	5 (41%)	9 (39%)
Users of calcimimetics, n (%)	1 (0.08%)	1 (4%)

Abbreviation: iPTH, intact parathyroid hormone.

In the cohort of studied patients, the prevalence of severe hyperparathyroidism at the time of renal transplantation was 10.8%; 38% of these patients (n = 14) underwent pretransplantation parathyroidectomy, having a longer mean time on dialysis (130 months), PTH at the time of transplantation (median 98.8 pg/mL), severe hypocalcemia, and requirement of higher doses of elemental calcium.

In the group composed of patients with secondary hyperparathyroidism on medical therapy, the average PTH value at the time of transplantation was 1119.1 pg/mL. One year after transplantation, they displayed significant decreases in PTH levels, a finding consistent with previous literature [14]. The requirement of elemental calcium in this group was much lower and there were no cases of severe hypocalcemia.

Soliman et al found that the decrease in PTH was similar for both groups of patients, with a higher frequency of hypocalcaemia, and thus a greater requirement for supplemental calcium in the group undergoing parathyroidectomy [15].

Up to a third of transplanted patients may present with persistent hyperparathyroidism, which is associated with complications such as decreased bone mineral density, myopathies, and graft calcification [16]. In our study we observed that 32% of the transplantation patients presented tertiary hyperparathyroidism.

Some studies have specified periods of 12 months for posttransplantation PTH recovery [17,18]. Perrin [19] found that PTH values above 2 times the upper limit of normal (130 pg/mL) were suggestive of persistent hyperparathyroidism and were associated with an increased risk of fractures. Perrin's study describes hypercalcemia as the most frequent indication of posttransplantation parathyroidectomy [20]. In our study, 15 of the 22 patients who did not undergo pretransplantation parathyroidectomy presented PTH levels below 130 pg/mL at 3 years after transplantation.

According to previous literature, living donor transplantation patients have a greater probability of improvement of hyperparathyroidism after transplantation [17]. In our study, 1 of them required pretransplantation parathyroidectomy with a high requirement for posttransplantation calcium. The other patient achieved PTH levels below 130 pg/mL at 12 months, with no requirement for posttransplantation calcium supplements.

Table 2. Data in the Renal Posttransplant

	Pretransplant parathyroidectomy group (n = 14)	No parathyroidectomy group (n = 20)	Posttransplant parathyroidectomy group (n = 2)
Dialysis duration median (range)–months	129.2 [6-216]	69.7 [2-233]	71.5 [48-95]
M6 Calcemia (mg/dL) median (range)	8.9 [7.3-11.7]	10.3 [9.3-11.5]	11.7 [11.7]
M12 Calcemia (mg/dL) median (range)	8.5 [6.8-10.4]	10.4 [9.0-13.8]	11.85 [11.8-11.9]
M6 Phosphatemia (mg/dL) median (range)	5.1 [3.4-7.1]	2.7 [1.2-3.4]	3.3 [3.3]
M12 Phosphatemia (mg/dL) median (range)	4.8 [3-6.4]	3.4 [2.3-4.3]	2.55 [2.1-3.0]
M12 iPTH (pg/mL) median (range)	31.7 [2-105]	101.4 [53-212.4]	185.5 [180-191]
M6 Users of calcium supplementation, n (%)	9 (64%)	3 (15%)	None
M6 Weekly dose of calcium supplementation (mg) median (range)	5630 [1680-13,440]	3360 [1680-5040]	None
Severe hypocalcemia, n patients: n events	3 (7)	None	None
M12 Users of calcium supplementation, n (%)	8 (57%)	2 (10%)	None
M12 Weekly dose of calcium supplementation (mg) median (range)	5915 [3360-13,440]	3360 [1680-5040]	None
M12 Users of vitamin D analogues, n (%)	6 (43%)	9 (45%)	2 (100%)
M12 Users of calcimimetics, n (%)	1 (7%)	1 (5%)	None
M6 GFR CKD-EPI (mL/min/1.73 m^2) median (range)	52.2 [10-80]	59.2 [31.9-93.2]	59.5 [57.8-61.3]
M12 GFR CKD-EPI (mL/min/1.73 m^2) median (range)	50 [9-71.5]	61.9 [32.8-93.2]	59.5 [57.8-61.3]

Abbreviations: M6, M12: Months 6, 12 post transplantation; iPTH, intact parathyroid hormone; GFR, glomerular filtration rate.

Nakai et al [21] found that the factors associated with persistent hyperparathyroidism after renal transplantation were time in dialysis greater than 6 years, calcium-phosphorus product greater than 55 mg/dL, development of nodular parathyroid hyperplasia, and treatment with cinacalcet during renal replacement therapy. The protective role of vitamin D in the development of posttransplantation hyperparathyroidism is not clear [22].

A limitation of our study is that it is a small descriptive study conducted in a single center. The sample is thus insufficient for assessing association. However, we consider our research to have an important clinical value as a starting point for cohort studies with larger populations or even clinical trials on the effectiveness of pretransplantation parathyroidectomy.

The treatment of these patients is a challenge because there are no randomized studies to guide management decisions [20]. However, in patients with persistent hyperparathyroidism, severe hypercalcemia, unexplained deterioration of renal function, and progressive bone mineral density loss, parathyroidectomy is indicated [23].

CONCLUSION

Renal transplantation improves secondary hyperparathyroidism. Sixty-eight percent of patients presented PTH levels below 130 pg/mL after renal transplantation. Only 2 patients underwent posttransplantation parathyroidectomy.

REFERENCES

[1] Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol 2011;6:913–21.

[2] Cuenta de alto costo. Situación de la enfermedad renal crónica, la hipertensión arterial y la diabetes mellitus. Cuenta alto costo. https://cuentadealtocosto.org/site/publicaciones/situacion-de-la-enfermedad-renal-cronica-la-hipertension-arterial-y-la-diabetes-mellitus-en-colombia-2017/; 2017 [accessed 18.02.20].

[3] Douthat WG, Chiurchiu CR, Massari PU. New options for the management of hyperparathyroidism after renal transplantation. World J Transpl 2012;2:41–5.

[4] Kuo LE, Wachtel H, Karakousis G, Fraker D, Kelz R. Parathyroidectomy in dialysis patients. J Surg Res 2014;190:554–8.

[5] de Francisco AL, Fresnedo GF, Rodrigo E, Piñera C, Amado JAAM. Parathyroidectomy in dialysis patients. Kidney Int 2002;61:s161–6.

[6] Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y. Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-center study. Nephrol Dial Transplant 2004;19:1281–7.

[7] Yang RL, Freeman K, Reinke CE, Fraker DL, Karakousis GC, Kelz RR, et al. Tertiary hyperparathyroidism in kidney transplant recipients. Transplant J 2012;94:70–6.

[8] Trombetti A, Stoermann C, Robert JH, Herrmann FR, Pennisi P, Martin PY, et al. Survival after parathyroidectomy in patients with end-stage renal disease and severe hyperparathyroidism. World J Surg 2007;31:1014–21.

[9] Hirukawa T, Kakuta T, Nakamura M, Fukagawa M. Mineral and bone disorders in kidney transplant recipients: reversible, irreversible, and de novo abnormalities. Clin Exp Nephrol 2015;19:543–55.

[10] Gioviale MC, Bellavia M, Damiano G, Lo Monte AI. Post-transplantation tertiary hyperparathyroidism. Ann Transplant 2012;17:111–9.

[11] Meng C, Martins P, Frazão J, Pestana M. Parathyroidectomy in persistent post-transplantation hyperparathyroidism: single-center experience. Transplant Proc 2017;49:795–8.

[12] Callender GG, Malinowski J, Javid M. Parathyroidectomy prior to kidney transplant decreases graft failure. Surgery 2014;161:44–50.

[13] Torregrosa JV, Fuster D, Duran CE, Oppenheimer F, Muxí A, Rubello D, Pons FCJ. Set point of calcium in severe secondary hyperparathyroidism is altered and does not change after successful kidney transplantation. Endocrine 2015;48:709–11.

[14] Triponez F, Clark OH, Vanrenthergem Y, Evenepoel P. Surgical treatment of persistent hyperparathyroidism after renal transplantation. Ann Surg 2008;248:18–30.

[15] Soliman AR, Maamoun HA, Soliman MA, Darwish H, Elbanna E. Cinacalcet vs parathyroidectomy in the treatment of secondary hyperparathyroidism post renal transplantation. Rom J Intern Med 2016;54:184–9.

[16] Dewberry LC, Tata S, Graves S, Weber CJ. Predictors of tertiary hyperparathyroidism: who will benefit from parathyroidectomy? Surgery 2013;156:1631–7.

[17] Lou I, Foley D, Odorico S. How well does renal transplantation cure hyperparathyroidism? Ann Surg 2015;262:653–9.

[18] Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, et al. Persistent hyperparathyroidism is a major risk factor for fractures in the 5 years after kidney transplantation. Am J Transplant 2013;13:2653–63.

[19] Perrin P, Kiener C, Javier R, Braun L, Cognard N, Gautier-Vargas G, et al. Recent changes in chronic kidney. Transplantation 2017;101:1897–905.

[20] Delos Santos R, Rossi A, Coyne D, Maw TT. Management of post-transplant hyperparathyroidism and bone disease. Drugs 2019;79:501–13.

[21] Nakai K, Fujii H, Ishimura T, Fujisawa M, Nishi S. Incidence and risk factors of persistent hyperparathyroidism after kidney transplantation. Transplant Proc 2017;49:53–6.

[22] Vangala C, Pan J, Cotton RT, Ramanathan V. Mineral and bone disorders after kidney transplantation. Front Med 2018;5:1–16.

[23] Tseng PY, Yang WC, Yang CY, Tarng DC. Long-term outcomes of parathyroidectomy in kidney transplant recipients with persistent hyperparathyroidism. Kidney Blood Press Res 2015;40:386–94.