



Article scientifique

Article

2009

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Secondary hyperparathyroidism after kidney transplantation: a cross-sectional study

Marcén, R; Ponte, Belen; Rodríguez-Mendiola, N; Fernández Rodríguez, A; Galeano, C; Villafruela, J J; Teruel, J L; Burgos, F J; Ortuño, J

How to cite

MARCÉN, R et al. Secondary hyperparathyroidism after kidney transplantation: a cross-sectional study. In: Transplantation proceedings, 2009, vol. 41, n° 6, p. 2391–2393. doi: 10.1016/j.transproceed.2009.06.047

This publication URL: <https://archive-ouverte.unige.ch/unige:90695>

Publication DOI: [10.1016/j.transproceed.2009.06.047](https://doi.org/10.1016/j.transproceed.2009.06.047)



Secondary Hyperparathyroidism After Kidney Transplantation: A Cross-Sectional Study

R. Marcén, B. Ponte, N. Rodríguez-Mendiola, A. Fernández Rodríguez, C. Galeano, J.J. Villafruela, J.L. Teruel, F.J. Burgos, and J. Ortuño

ABSTRACT

Introduction. The purpose of the present study was to investigate the prevalence of hyperparathyroidism among a population of kidney graft recipients.

Patients and Methods. We investigated biochemical bone parameters of 509 renal transplant recipients with a mean follow-up of 113 ± 76 months. Among these patients, 257 patients were treated with either vitamin D or calcium supplements or both.

Results. The mean estimated glomerular filtration rate (eGFR) was 47.2 ± 18.4 mL/min/1.73 m² and the mean intact parathyroid hormone (iPTH) level was 144 ± 149 pg/mL. A total of 70 patients (13.7%) had hypercalcemia defined by a corrected serum calcium >10.2 mg/dL. When the patients were classified according to iPTH concentrations following the Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines: 22.4% had iPTH <70 pg/mL; 30.8% between 70 and 110 pg/mL; 16.5% between 110 and 150 pg/mL; 24.3% between 150 and 300 pg/mL; and 6.9% >300 pg/mL. There were no differences in biochemical bone parameters between those that were or were not on calcium and vitamin D supplements, but there was a higher percentage of patients with normal iPTH among the treated group (28.0% vs 16.7%; $P = 0.003$). In patients not receiving calcium and/or vitamin D supplements, multiple linear regression demonstrated that only time on dialysis, eGFR, and serum 25-hydroxyvitamin D (25OHD) levels were significantly predictive of iPTH concentrations ($R^2 = 0.21$; $P = .000$).

Conclusions. About 80% of patients displayed high iPTH concentrations. The persistence of hyperparathyroidism was associated with graft dysfunction, longer time on dialysis, and low concentrations of 25OHD. Treatment with vitamin D produced a slight improvement in the prevalence of hyperparathyroidism.

ALTHOUGH a successful renal transplantation corrects some metabolic mineral disorders, spontaneous resolution of secondary hyperparathyroidism is uncommon. The mechanisms involved in its persistence are not completely established. Among the possible causes of permanent hyperparathyroidism are the severity of pretransplantation hyperparathyroidism, the duration of dialysis, and the incomplete normalization of renal function.¹⁻³ Therefore, some authors have observed a relationship between 25-hydroxyvitamin D (25OHD) deficiency or insufficiency and high intact parathyroid hormone (iPTH) concentrations.^{4,5} However, despite the importance of hyperparathyroidism as a source of morbidity, systematic iPTH determinations have received little attention in the care of renal transplant recipients and the percentage of patients with iPTH mea-

surements is low.^{6,7} The aim of the present study was to document the prevalence of hyperparathyroidism among a nonselected cohort of renal transplant recipients, seeking to examine the factors related to serum parathyroid hormone concentrations as well as the effects of calcium and vitamin D supplements.

From the Departments of Nephrology (R.M., B.P., N.R.-M., A.F.R., C.G., J.J.V., J.L.T., J.O.) and Urology (F.J.B.), Hospital Ramón y Cajal, Madrid, Spain.

Address reprint requests to Roberto Marcén, Servicio de Nefrología, Hospital Ramón y Cajal, Avenida de Colmenar Viejo km 9.1, 28034 Madrid, Spain. E-mail: rmarcen.hrc@salud.madrid.org

PATIENTS AND METHODS

The 509 of 522 renal transplant recipients followed by our department who had serum levels of iPTH, as well as vitamin D metabolites of 25OHD and 1.25-dihydroxyvitamin D (1.25OHD), within 6 months of the last follow-up, were included in the study. The mean age of the patients was 45.4 ± 14.5 years (range, 18–74 years), including 295 males and 214 females. The follow-up after transplantation was at least 12 months (mean, 113 ± 76 months; range, 12–324 months). At the time of the study 245 patients were on a tacrolimus-based immunosuppressive regimen; 205 were on a cyclosporine-based regimen; and 469 were on steroids. In addition, 222 patients were on treatment with mycophenolate mofetil associated either with tacrolimus or with cyclosporine. Patients receiving any vitamin D supplement were not excluded from the present analysis.

After an overnight fast, plasma concentrations of creatinine, total calcium, phosphate, and alkaline phosphatase activity were measured using an autoanalyzer. Serum calcium was adjusted according to the following formula: adjusted Ca (mg/dL) = total calcium (mg/dL) + $0.0176 \times (34 - \text{serum albumin [g/L]})$. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated form of the Modification of Diet in Renal Disease (MDRD) equation. Fasting iPTH, 25OHD, and 1.25OHD were measured at the same time. Serum iPTH levels were determined using an immunochromatographic assay (Elecsys, Roche Diagnostic GmbH, Mannheim, Germany). The 25OHD levels were measured using enzyme-linked immunosorbent assay (ELISA; IDS Systems, Bolton, United Kingdom) and 1.25OHD levels were determined using radioimmunoassay (RIA; Biosource Europe, Nivelles, Belgium). In analyzing serum iPTH, the results were stratified as follows: <70 pg/mL, 70–110 pg/mL, 110–150 pg/mL, 150–300 pg/mL, and >300 pg/mL, according to the Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease. The results were expressed as mean values \pm SD. Phosphate, eGFR, iPTH, 25OHD, 1.25OHD, and duration of transplant required natural logarithmic transformation because they were not normally distributed. Differences between the 2 groups were assessed using Student *t* test and the Mann-Whitney test for parametric and nonparametric continuous data, respectively. When assessing differences between more than 2 groups, analysis of variance (ANOVA) and

Kruskal-Wallis test were performed for parametric and nonparametric continuous data. Simple regression analysis was performed with the logarithm of iPTH as the dependent variable. Multiple linear regression analysis with backward selection included the variables with *P* values of <.1; *P* < .05 was considered significant.

RESULTS

The mean eGFR was 47.2 ± 18.4 mL/min/1.73 m². The mean iPTH was 144 ± 149 pg/mL (range, 36–1853 pg/mL) and the mean corrected calcium was 9.6 ± 0.6 mg/dL. There were 257 patients on treatment with either vitamin D or calcium supplements or both: 171 patients received calcitriol (0.25 or 0.5 μ g/d \times 3 d/wk); 18 patients received cholecalciferol (400 IU/d) and calcium supplements; and 68 patients received calcium supplements alone. According to the iPTH concentrations, patients were distributed as follows: 22.4% with iPTH <70 pg/mL; 30.8% between 70 and 110; 16.5% between 110 and 150; 24.3% between 150 and 300; and 6.9% >300 pg/mL. The characteristics of patients according to iPTH levels are shown in Table 1. The levels of iPTH increased as graft function deteriorated. There was no trend toward a progressive increase in corrected calcium and serum phosphate as iPTH levels increased. Serum levels of 25OHD decreased as iPTH increased. Treatment with vitamin D supplements was more common among the graft recipients with the highest or the lowest iPTH levels. Patients on treatment with vitamin D supplements were older at the time of transplantation (47.0 ± 13.9 vs 43.8 ± 15.1 years; *P* = .012) and had been followed for a shorter period of time (95.4 ± 69.1 vs 131.7 ± 77.8 months; *P* = .000). There were no differences among mean iPTH concentrations between treated versus untreated patients (147 ± 175 vs 142 ± 117 pg/mL; *P* = .727), but the percentage of patients with normal iPTH concentrations was greater in the treated group (28.0% vs 16.7%; *P* = .003). Corrected calcium was 9.7 ± 0.6 and 9.5 ± 0.6 mg/dL in the treated and untreated patients, respectively (*P* = .016). Hypercalcemia defined as corrected calcium >10.2 mg/dL was

Table 1. Characteristics of Patients and iPTH Levels

	<70	70–110	110–150	150–300	>300	<i>P</i>
N	114	157	84	119	35	
Age (y)	42.1 ± 14.7	43.1 ± 14.4	50.8 ± 13.8	47.9 ± 14.5	45.5 ± 12.9	.000
Gender (male/female)	65/49	79/78	63/21	63/56	25/10	.002
Time on dialysis (mo)	25.1 ± 23.4	29.7 ± 28.4	29.9 ± 28.4	35.0 ± 36.1	38.5 ± 49.9	.148
Time of follow-up (mo)	116 ± 76	119 ± 76	116 ± 81	106 ± 72	102 ± 71	.578
SCr (mg/dL)	1.5 ± 0.8	1.5 ± 0.5	1.7 ± 0.5	1.8 ± 0.8	2.8 ± 1.8	.000
eGFR (mL/min/1.73 m ²)	54.2 ± 19.7	50.0 ± 16.2	46.0 ± 15.7	41.6 ± 26.5	34.3 ± 22.5	.000
Corrected calcium (mg/dL)	9.5 ± 0.4	9.6 ± 0.5	9.4 ± 0.4	9.7 ± 0.7	9.6 ± 0.9	.021
Total CO ₂ (mmol/dL)	25.7 ± 2.5	25.3 ± 2.9	25.2 ± 2.9	24.6 ± 3.0	22.7 ± 2.9	.000
Phosphate (m/dL)	3.3 ± 0.6	3.2 ± 0.5	3.1 ± 0.6	3.2 ± 0.7	3.5 ± 1.3	.070
iPTH (pg/mL)	53.1 ± 13.1	87.8 ± 11.5	128.0 ± 12.3	206.1 ± 44.6	528.0 ± 339.0	.000
25OHD (ng/mL)	21.7 ± 9.4	22.0 ± 13.0	20.8 ± 10.4	16.6 ± 7.5	14.7 ± 8.1	.000
1.25OHD (pg/mL)	39.3 ± 34.9	38.0 ± 24.2	35.4 ± 19.5	37.1 ± 20.6	34.6 ± 19.0	.967
Calcium supplements (no/yes)	63/51	108/49	52/32	84/35	21/14	.092
Vitamin D supplements (no/yes)	58/56	108/49	55/29	78/41	21/14	.040

Abbreviation: SCr, serum creatinine.

present in 13.8% of patients, without a difference between the 2 groups. Concentrations of 25OHD (20.0 ± 10.6 vs 20.1 ± 10.6 ng/mL; $P = .941$) and 1.25OHD (35.9 ± 20.6 vs 37.7 ± 20.5 pg/mL; $P = .336$) were also similar among those treated or untreated with vitamin D supplements. We investigated the variables that correlated with iPTH concentrations among patients who were not on treatment with calcium or vitamin D supplements. Upon univariate analysis iPTH levels correlated with age at transplantation (coefficient = 0.003; $P = .003$); time on dialysis (coefficient = 0.082; $P = .04$); eGFR (coefficient = -0.590 ; $P = .000$); serum albumin (coefficient = -0.124 ; $P = .009$); serum bicarbonate (coefficient = -0.017 ; $P = .001$); and 25OHD concentrations (coefficient = -1.028 ; $P = .000$). Upon multivariate analysis, only eGFR, time on dialysis, and 25OHD concentrations remained in the model ($R^2 = 0.21$; $P = .000$).

DISCUSSION

Our study showed that the majority of renal transplant recipients, independent of whether they were on treatment with calcium and/or vitamin D supplements showed iPTH concentrations above the normal range. These results agreed with those previously published. Torres et al¹ reported that only 23% of 62 patients at a mean follow-up of 69 months showed PTH concentrations in the normal range. Reinhardt et al⁴ observed persistently high PTH levels in 129 recipients followed up for 18 months. We have investigated the variables correlated with iPTH concentrations among patients who were not on treatment with calcium and/or vitamin D supplements to avoid the possible effects of this treatment. In this group of patients, we confirmed that iPTH concentrations correlated negatively with graft function^{1,2} and 25OHD concentrations,^{4,5} and positively with the length of the time on dialysis.⁴ In patients with chronic renal failure, treatment with calcitriol and other 1- α -vitamin D sterols have been shown to be efficacious, leading to control of hyperparathyroidism and to histological improvements in bone.

K/DOQI clinical guidelines recommend treatment with oral vitamin D sterol when serum levels of 25OHD are >30 ng/mL, when the levels of iPTH are above the target range for the chronic kidney disease stage, when corrected calcium is <9.5 mg/dL, and when phosphorus <4.6 mg/dL. In our study, treatment with vitamin D, mainly low doses of calcitriol, was indicated to control hyperparathyroidism and prevent post-transplantation osteopenia.⁸ The therapy showed only a slight effect to control hyperparathyroidism. The mean iPTH concentration was similar among the treated and untreated patients, but the percentage of

recipients with iPTH in the normal range was significantly higher in the treated group. Our findings agreed with those from Heaf et al,⁹ who observed that vitamin D prescription increased 25OHD and 1.25OHD serum levels without any change in the prevalence of elevated PTH. The lack of effectiveness of vitamin D treatment may be attributed to the administered doses of vitamin D. Our patients were on treatment with low doses of vitamin D to prevent the risk of adverse effects, such as hypercalcemia and renal function deterioration, as calcitriol doses <0.25 μ g/d engender a low risk of both complications. A side effect of vitamin D supplements was higher corrected calcium levels. Patients on treatment with vitamin D displayed significantly higher levels than untreated patients. However, hypercalcemia, as defined by a corrected calcium >10.2 mg/dL, was present in only 13.7% of patients, a value that was somewhat lower than the 16.7%–20.3% reported in the UK renal registry (without difference between treated and untreated patients).⁷ Treatment of secondary hyperparathyroidism after renal transplantation is far from being solved when spontaneous remission does not occur. Whether the guidelines recommended for the general population can be successfully applied to renal transplant recipients must be prospectively investigated.

REFERENCES

1. Torres A, Rodriguez AP, Concepción MT, et al: Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations. *Nephrol Dial Transplant* 13(suppl 3):94, 1998
2. Messa P, Sindici C, Cannella G, et al: Persistent hyperparathyroidism after renal transplantation. *Kidney Int* 54:1704, 1998
3. Evenepoel P, Claes K, Kuypers D, et al: Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. *Nephrol Dial Transplant* 19:1281, 2004
4. Reinhardt W, Bartelworth H, Jockenhövel F, et al: Sequential changes of biochemical bone parameters after kidney transplantation. *Nephrol Dial Transplant* 13:436, 1998
5. Boudville NC, Hodsman AB: Renal function and 25-hydroxyvitamin D concentrations predict parathyroid hormone levels in renal transplant patients. *Nephrol Dial Transplant* 21:2621, 2006
6. Karthikeyan V, Karpinski J, Nair RC, et al: The burden of chronic kidney disease in renal transplant recipients. *Am J Transplant* 4:262, 2003
7. Ansell D, Udayaraj UP, Steenkamp R, et al: Chronic renal failure in kidney transplant recipients. Do they receive optimum care?: data from the UK renal registry. *Am J Transplant* 7:1167, 2007
8. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic renal disease. *Am J Kidney Dis* 42(suppl3):S1, 2003
9. Heaf J, Tvedegaard E, Kanstrup I-L, et al: Hyperparathyroidism and long-term bone loss after renal transplantation. *Clin Transplant* 17:268, 2003