Exploring the Effect of Parathyroidectomy for Tertiary Hyperparathyroidism After Kidney Transplantation

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Abstract: Tertiary hyperparathyroidism (tHPT) usually regresses after renal transplantation. Persistent tHPT after successful renal transplantation may require parathyroidectomy (PTX). PTX has been reported to be associated with deterioration of renal function and graft survival. We retrospectively analyzed 794 kidney transplants performed at our center with at least 3 years of follow-up to examine the effect of PTX on the renal function and graft survival. Forty-nine of the 794 renal transplant recipients were diagnosed with hyperparathyroidism (HPT) before transplant. Nineteen of 49 patients had persistent tHPT and underwent PTX after kidney transplants. Patients with HPT and non-HPT had similar 3-year graft survival (88% versus 84%, $P = 0.51$). PTX was associated with a decreased glomerular filtration rate at 3 years (44.7 ± 20.0 versus 57.7 ± 23.7 mL/min, $P = 0.04$); however, there was no statistical difference in the 3-year graft survival (71% versus 88%, $P = 0.06$). PTX in renal transplant recipients seems to be a safe and effective therapy for persistent tHPT. PTX may be associated with worsening glomerular filtration rate, but it may not be associated with significantly decreased long-term graft survival.

Key Indexing Terms: Hyperparathyroidism; Parathyroidectomy; Kidney transplant; Graft function; Graft survival. **[Am J Med Sci 2010; 339(5):420–424.]**

Nowadays, the term tertiary hyperparathyroidism (tHPT) is used almost exclusively in the context of persistent hyperparathyroidism (HPT) after successful renal transplantation. Development of tHPT is multifactorial, although phosphate retention and loss of renal 1-hydroxylase activity with low 1,25-$(OH)_2$ vitamin D_3 level are the principal factors.[1]

For hyperparathyroidism in patients with end-stage renal disease, the currently accepted practice for management is initially medical therapy with parathyroidectomy (PTX) reserved for refractory disease.[2] The incidence of tHPT is reported in up to 50% of patients who undergo kidney transplantation,[3] and its occurrence is thought to be related to the duration of dialysis before transplantation.[3,4] Although tHPT has been recognized for a long time, the management of the disease is still controversial. Currently, guidelines for referral of these patients for surgery do not exist. Hypercalcemia usually gradually resolves within the first year after successful kidney transplantation.[4] Therefore, patients with persistent hypercalcemia should be considered for PTX, which includes subtotal or total PTX with autotransplantation. Indications for surgical intervention include persistent hypercalcemia, symptomatic tHPT, or deterioration of kidney function associated with tHPT.[4] Although it was previously reported that patients with functioning kidney grafts had unaffected renal function after PTX, there are recent reports that PTX might seriously endanger the long-term graft survival.[5–7]

The purpose of this study was to examine our 10-year experience with patients with end-stage renal disease who underwent PTX for tHPT after renal transplantation and to assess the effects of PTX on long-term renal function and graft survival.

METHODS

This is a retrospective analysis of kidney transplants performed between January 1996 and August 2005 at the Tulane University Medical Center with at least 3 years of follow-up. Various demographic, clinical, and biochemical data were collected. Information on graft status and/or death was obtained from (or verified with) the United Network for Organ Sharing and National Death Index, respectively. Patients were excluded from analyses if data on the details of surgical intervention, reliable intact parathyroid hormone (iPTH) levels, and loss of follow-up were missing. There

TABLE 1. Demographic characteristics of study population

Variables	Overall (N = 794)	Hyperparathyroidism Present (N = 49)	Hyperparathyroidism Absent (N = 745)	*P*
Recipient				
Mean age (SD), yr	42 (17)	41 (19)	42 (17)	0.68
Male, %	58	57	58	0.86
African American, %	53	55	52	0.71
BMI, kg/m^2				
Mean (SD)	26.7 (7.3)	25.1 (6.9)	26.8 (7.3)	0.13
Obese (BMI ≥30), %	26	18	26	0.19
Current smoker, %	18	28	17	0.08
Medical history				
Hypertension, %	86	82	86	0.38
Diabetes, %	25	23	26	0.63
Parathyroidectomy before Tx, n (%)	19 (3.45)	3 (9.38)	16 (3.08)	0.11
Donor				
Mean age (SD), yr	34 (16)	35 (17)	34 (16)	0.56
Male, %	52	53	52	0.84
African American, %	23	26	23	0.63
Living donor, %	29	20	30	0.15

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TABLE 2. Clinical parameter of study population before kidney transplant

Variables	Mean (SD)	Hyperparathyroidism		*P*
		Present	Absent	
PTH (pg/mL)	369 (385)	1084 (396)	244 (205)	<0.01
Calcium (mg/dL)	9.35 (1.1)	10.75 (1.6)	9.26 (0.98)	<0.01
Alkaline phosphatase (U/L)	139 (116)	142 (123)	138 (116)	0.82
Serum creatinine (mg/dL)	9.36 (3.7)	9.68 (3.7)	9.33 (3.7)	0.54
Peak PRA (%)	16.35 (29.6)	23.47 (35.4)	15.89 (29.1)	0.37
Cold ischemia time (hr)	8.64 (10.6)	10.29 (12.4)	8.53 (10.5)	0.33

were a total of 749 subjects included in this study. All patients had iPTH levels measured during their pretransplant workup in our hospital, and iPTH was measured by electrochemiluminescence immunoassay. The normal values for iPTH were 8 to 74 pg/mL. Pretransplant HPT was diagnosed based on history of HPT, which was further verified by increased iPTH levels in our hospital. Tertiary HPT was diagnosed by persistent hypercalcemia (>10 mg/dL) with increased iPTH after successful kidney transplant.

Pre- and postoperative laboratory results were compared between kidney transplant recipients with or without PTX and persistent HPT. Clinical outcome included 3-year renal function and graft survival. Renal function was assessed by estimated glomerular filtration rate (GFR) using the modification of diet in renal disease equation. Graft failure was excluded from renal function calculation. Death with a functioning graft was excluded from graft survival estimate (death censored). All statistical analyses were performed using SAS 9.1.3 (Cary, NC), and P values <0.05 were considered statistically significant. χ^2 test was used for count data and t test for continuous measures. Product-limit estimates of survival curves were generated by Kaplan-Meier method, and the survival difference was analyzed by log-rank test. A P value <0.05 was considered statistically significant.

All patients received standard triple immunosuppression of steroids, a calcineurin inhibitor, and mycophenolic acid. Recipients who had a previous transplant, 6 antigen mismatches, and/or a panel reactive antibody >20% were categorized as high risk and were given induction therapy with the IL-2 receptor antagonist basiliximab. Patients received standard antifungal, antibacterial, and cytomegalovirus prophylaxis per protocol.

RESULTS

Among the 794 renal transplant recipients, patients with and without HPT had similar age, sex, race, body mass index medical history, and donor factors (Table 1). Forty-nine patients were diagnosed with HPT before their kidney transplantation and exhibited significantly increased preoperative iPTH level (1084 ± 396 pg/mL versus 244 ± 205 pg/mL, $P < 0.01$) and serum calcium (10.75 ± 1.63 versus 9.26 ± 0.98 mg/dL, $P < 0.01$) compared with other patients (Table 2). Nineteen patients developed tHPT after successful kidney transplants and eventually underwent PTX (Table 3). The decision for PTX was made by our transplant nephrologists who followed up these patients closely at transplant clinic. Compared with the pretransplant iPTH levels, the iPTH levels of 11 of the 19 patients did not decrease significantly, whereas other 8 patients had a reduction in their iPTH levels. PTX was usually performed after 1 year of transplant (median, 13.8 months; range, 8.2–17 months). Patients with preoperative PTH had similar 3-year GFR (Figure 1) and renal graft survival (88% versus 84%, $P = 0.51$) as the other patients without HPT. For patients with tHPT, PTX was associated with a worse GFR at 3 years (44.7 ± 20.0 versus 57.7 ± 23.7 mL/min, $P = 0.04$; Table 4 and Figure 2). However, it was not associated with a significant decrease in 3-year graft survival (71% versus 88%, $P = 0.06$; Table 5 and Figure 3). We also had several cases of clinically treated bone fracture in this study population. Further analysis did not detect any significant association with HPT or PTX (data not shown).

DISCUSSION

tHPT is usually defined as persistent hypercalcemia with increased iPTH level after successful renal transplantation and is reportedly observed with an incidence of 30% to 50%.[8,9] However, in most patients, the hypercalcemia resolves in a few months with or without medical treatment. Only a small percentage of patients require surgical intervention.[9] In a recent study including >1200 renal transplant recipients, hypercalcemic episodes were observed in 30% and 12% of the patients during the first and fifth year after transplantation, respectively.[9] Persistent tHPT may cause serious problems such as soft tissue calcification, myopathy,

TABLE 3. Prevalence of graft loss among overall patients and by tertiary hyperparathyroidism status

Variables	Overall (N = 794)	Hyperparathyroidism		*P*	Parathyroidectomy		*P*
		Present (N = 49)	Absent (N = 745)		Yes (N = 19)	No (N = 532)	
Graft loss							
N	123	6	117	N/A	5	65	N/A
Prevalence, %	15.5	12.2	15.7	0.50	26.3	12.2	0.10