Published in final edited form as:

Am J Med Sci. 2010 May ; 339(5): 420–424. doi:10.1097/MAJ.0b013e3181d8b6ff.

Exploring the Effect of Parathyroidectomy for Tertiary Hyperparathyroidism After Kidney Transplantation

Emad Kandil, MD, Sandy Florman, MD, Haythem Alabbas, MD, Obai Abdullah, MD, Jennifer McGee, MD, Salem Noureldine, MD, Douglas Slakey, MD, and Rubin Zhang, MD, FASN

From the Departments of Surgery (EK, SF, HA, OA, JM, SN, DS, RZ) and Medicine (RZ), Tulane University School of Medicine, New Orleans, Louisiana.

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

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 D₃ 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 auto-transplantation. 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 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, hypertension, and hypercalciuria.¹⁰ In particular, hypercalciuria not only causes renal tubular injury but also increases the risk of kidney stone, which is particularly deleterious in a kidney graft.¹⁰ PTX is a reliable and preferred treatment in patients with persistent hypercalcemia after kidney transplant because it can cure symptoms and disease processes specifically associated with tHPT.¹¹

PTX is reportedly performed in 0.6% to 5.6% of patients after kidney transplant.^{8,12,13} The mechanism of refractory PTH hypersecretion after renal transplantation is due, in part, to a high parathyroid cell mass, leading to an inappropriately high basal PTH secretion (diffuse parathyroid hyperplasia); it may also result from parathyroid adenomas (nodular hyperplasia).¹⁴ The risk for developing post-transplant tHPT increases with the duration of dialysis¹⁵ and severity of pretransplant HPT.¹⁶ Schwarz et al⁵ studied 76 patients (of 2192 kidney recipients) who underwent PTX for persisting tHPT. Patients who experienced deteriorating renal function had higher PTH concentrations before undergoing PTX compared with patients with a stable renal function. Schmid et al⁶ studied 37 patients who underwent PTX after renal transplantation, 13 of the 37 patients experienced rejection and became dialysis dependent, and 7 of the 37 patients died after an average of 43.1 months after PTX. However, 6 of the 7 patients who died had a functional renal graft at the time of death. Lee et al⁷ also described a negative effect of subtotal PTX on graft function in 22 patients after kidney transplantation. They reported a worsening of graft function after PTX. Consequently, graft survival was significantly decreased by 60% in 6 years. Another 2 retrospective studies^{17,18} also noted that patients had acute deterioration of renal function until the third month post-PTX. However, none of these studies offered a good explanation.

Persistent hypercalcemia can impair the GFR as a result of vasoconstriction, acute tubular necrosis, and nephrocalcinosis. Therefore, when hypercalcemia is corrected, graft function should improve. The renal function deterioration in the early postoperative period may be related to the hemodynamic effects of PTH. Indeed, PTH has vasodilatory effects on preglomerular vessels at the same time as efferent arterioles are constricted, presumably secondary to rennin release.¹⁹ When glomerular hyperfiltration is reversed by PTX, GFR may deteriorate acutely. In the long term, however, these hemodynamic corrections should decrease hyperfiltration injury and attenuate the progression of renal failure.²⁰

The decision to recommend parathyroid surgery after kidney transplantation is usually a difficult one. Evidence-based guidelines are currently lacking. In our study, persistent HPT

with hypercalcemia represents the main indication for PTX after kidney transplant. Whether PTX affects renal graft function or survival remains a controversial issue. The lack of unequivocal indications for PTX, as well as registration bias, case-mix, and differences in duration of follow-up represent plausible explanations of the previous reports. This study examines the long-term effect of PTX on renal graft function and survival. Our data indicate that renal transplant patients who require PTX for persistent tHPT may have a worse renal function GFR at 3 years. However, their 3-year graft survival was not statistically different from those that did not undergo PTX. Similar to the previous reports, our study is also limited by its retrospective nature, and possible alpha error cannot be ruled out because of the relatively small sample size.

Recently, calcimimetics have been proposed to offer an alternative option to surgery.^{21,22} Serra et al²² examined the effect of cinacalcet on 11 renal transplant recipients. They concluded that this treatment was effective in normalizing serum calcium in renal transplant patients, and the effect was sustained over 10 weeks and renal graft function remained stable. However, patients with persistent tHPT would need long-term daily treatment. Many patients with severe disease may fail to achieve adequate control and/or eventually need surgical intervention. Future studies are needed to prospectively compare medical treatment of tHPT with calcimimetics to parathyroid surgery in this subset of high-risk patients.

CONCLUSION

Patients with a pretransplant tHPT have similar renal graft survival to other patients without this disease. Persistent hyperparathyroidism after successful renal transplantation can be corrected with PTX. PTX was not associated with significantly worse long-term graft survival. Our findings support PTX as a safe and effective therapy for patients with persistent tHPT after kidney transplantation.

Acknowledgments

We thank Tareq Islam for the statistical analysis.

REFERENCES

1. Brown AJ, Slatopolsky E. Drug insight: vitamin D analogs in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. *Nat Clin Pract Endocrinol Metab* 2007;3:134–144. [PubMed: 17237840]
2. de Francisco AL. Secondary hyperparathyroidism: review of the disease and its treatment. *Clin Ther* 2004;26:1976–1993. [PubMed: 15823762]
3. Apaydin S, Sariyar M, Ereğ E, et al. Hypercalcemia and hyperparathyroidism after renal transplantation. *Nephron* 1999;81:364–365. [PubMed: 10050101]
4. D'Alessandro AM, Melzer JS, Pirsch JD, et al. Tertiary hyperparathyroidism after renal transplantation: operative indications. *Surgery* 1989;106:1049–1055. discussion 1055–6. [PubMed: 2588112]
5. Schwarz A, Rustien G, Merkel S, et al. Decreased renal transplant function after parathyroidectomy. *Nephrol Dial Transplant* 2007;22:584–591. [PubMed: 17035377]
6. Schmid T, Müller P, Spelsberg F. Parathyroidectomy after renal transplantation: a retrospective analysis of long-term outcome. *Nephrol Dial Transplant* 1997;12:2393–2396. [PubMed: 9394329]
7. Lee PP, Schiffmann L, Offermann G, et al. Effects of parathyroidectomy on renal allograft survival. *Kidney Blood Press Res* 2004;27:191–196. [PubMed: 15256817]
8. Kerby JD, Rue LW, Blair H, et al. Operative treatment of tertiary hyperparathyroidism: a single-center experience. *Ann Surg* 1998;227:878–886. [PubMed: 9637551]
9. 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* 2004;19:1281–1287. [PubMed: 14993493]

10. Triponez F, Dosseh D, Hazzan M, et al. [Results of systematic subtotal parathyroidectomy with thymectomy for tertiary hyperparathyroidism after renal transplantation-70 patients]. *Ann Chir* 2006;131:203–210. [PubMed: 16434021]
11. Milas M, Weber CJ. Near-total parathyroidectomy is beneficial for patients with secondary and tertiary hyperparathyroidism. *Surgery* 2004;136:1252–1260. [PubMed: 15657584]
12. Evenepoel P, Claes K, Kuypers DR, et al. Parathyroidectomy after successful kidney transplantation: a single centre study. *Nephrol Dial Transplant* 2007;22:1730–1737. [PubMed: 17371780]
13. Drakopoulos S, Koukoulaki M, Apostolou T, et al. Total parathyroidectomy without autotransplantation in dialysis patients and renal transplant recipients, long-term follow-up evaluation. *Am J Surg* 2009;198:178–183. [PubMed: 19217601]
14. Tominaga Y, Johansson H, Takagi H. Secondary hyperparathyroidism: pathophysiology, histopathology, and medical and surgical management. *Surg Today* 1997;27:787–792. [PubMed: 9306599]
15. Kinnaert P, Nagy N, Decoster-Gervy C, et al. Persistent hyperparathyroidism requiring surgical treatment after kidney transplantation. *World J Surg* 2000;24:1391–1395. [PubMed: 11038212]
16. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. *J Am Soc Nephrol* 2002;13:551–558. [PubMed: 11805187]
17. Garcia A, Mazuecos A, Garcia T, et al. Effect of parathyroidectomy on renal graft function. *Transplant Proc* 2005;37:1459–1461. [PubMed: 15866638]
18. Evenepoel P, Claes K, Kuypers D, et al. Impact of parathyroidectomy on renal graft function, blood pressure and serum lipids in kidney transplant recipients: a single centre study. *Nephrol Dial Transplant* 2005;20:1714–1720. [PubMed: 15919696]
19. Massfelder T, Parekh N, Endlich K, et al. Effect of intrarenally infused parathyroid hormone-related protein on renal blood flow and glomerular filtration rate in the anaesthetized rat. *Br J Pharmacol* 1996;118:1995–2000. [PubMed: 8864534]
20. Ogata H, Ritz E, Odoni G, et al. Beneficial effects of calcimimetics on progression of renal failure and cardiovascular risk factors. *J Am Soc Nephrol* 2003;14:959–967. [PubMed: 12660330]
21. Gilat H, Feinmesser R, Vinkler Y, et al. Clinical and operative management of persistent hyperparathyroidism after renal transplantation: a single-center experience. *Head Neck* 2007;29:996–1001. [PubMed: 17427968]
22. Serra AL, Schwarz AA, Wick FH, et al. Successful treatment of hypercalcemia with cinacalcet in renal transplant recipients with persistent hyperparathyroidism. *Nephrol Dial Transplant* 2005;20:1315–1319. [PubMed: 15941845]

FIGURE 1.
Glomerular filtration rate (GFR) by tertiary hyperparathyroidism status.

FIGURE 2.
Glomerular filtration rate (GFR) by parathyroidectomy status.

FIGURE 3. Kaplan-Meier estimates of death-censored graft survival function by tertiary hyperparathyroidism.

TABLE 1

Demographic characteristics of study population

Variables	Hyperparathyroidism			P
	Overall (N = 794)	Present (N = 49)	Absent (N = 745)	
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

TABLE 2

Clinical parameter of study population before kidney transplant

Variables	Mean (SD)	Hyperparathyroidism		<i>P</i>
		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

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

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

TABLE 4

GFR by tertiary hyperparathyroidism and parathyroidectomy status

Variables	Mean (SD)	Tertiary hyperparathyroidism		P	Parathyroidectomy		P
		Present	Absent		Yes	No	
GFR (mL/min)							
1 month	53.6 (31.1)	58.3 (34.9)	53.3 (30.9)	0.34	57.9 (34.8)	54.5 (28.5)	0.72
6 months	59.6 (25.9)	62.4 (34.4)	59.4 (24.9)	0.59	59.1 (26.0)	59.8 (25.2)	0.91
1 yr	60.2 (25.0)	61.2 (25.1)	60.1 (25.0)	0.78	53.8 (23.3)	60.7 (24.8)	0.25
2 yr	59.0 (24.1)	65.1 (35.0)	58.5 (23.0)	0.25	48.2 (19.1)	58.6 (24.4)	0.08
3 yr	57.6 (23.8)	55.9 (28.0)	57.7 (23.5)	0.69	44.7 (20.0)	57.7 (23.7)	0.04

TABLE 5
Kaplan-Meier estimates of death-censored graft survival of renal transplant by hyperparathyroidism

	N	Percentage graft survival			Log-rank <i>P</i>
		1 yr	2 yr	3 yr	
Hyperparathyroidism					
Yes	49	90	88	88	0.51
No	745	91	86	84	
Parathyroidectomy					
Yes	19	95	83	71	0.06
No	532	93	89	88	