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Parathyroidectomy versus Cinacalcet in the Management of Tertiary Hyperparathyroidism: Surgery Improves Renal Transplant Allograft Survival ☆

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ABSTRACT

Background: Renal transplant allograft function in patients with tertiary hyperparathyroidism who are treated with cinacalcet versus parathyroidectomy remains unclear.

Methods: This is a retrospective, single-center review of patients with tertiary hyperparathyroidism between 2000 and 2017. We compared clinical parameters and outcomes, including renal allograft failure in patients who had undergone parathyroidectomy versus treatment with cinacalcet therapy.

Results: A total of 133 patients were included (33 who received parathyroidectomy and 100 who received cinacalcet); median renal allograft survival was 5.9 years (interquartile range 4.0–9.0). There were no differences in age, sex, body mass index, comorbidities, duration of pretransplant dialysis, cadaveric donor utilization, or rates of delayed allograft function between cohorts. In the parathyroidectomy cohort, normalization of parathyroid hormone occurred more frequently (67% vs 15%, $P < .001$) and renal allograft failure rates were less (9% vs 33%, $P = .007$), with similar median posttransplant follow-up (7.0 years [interquartile range 4.5–10.0]). On multivariable analysis, parathyroidectomy was inversely associated with allograft failure (odds ratio 0.20, 95%-confidence interval 0.06–0.71, $P = .013$); there were no other associated factors. A greater median parathyroid hormone (pg/mL) 1 year posttransplant (348 [interquartile range 204–493] vs 195 [interquartile range 147–297], $P = .025$) was associated with allograft failure in the cinacalcet cohort.

Conclusion: Parathyroidectomy for tertiary hyperparathyroidism is associated with lesser rates of renal allograft failure compared with cinacalcet management. Patients with inadequate parathyroid hormone control on cinacalcet at 1 year posttransplant should be considered for parathyroidectomy to prevent potential allograft failure.

Introduction

Tertiary hyperparathyroidism (hPTH) occurs in patients with end-stage renal disease (ESRD) who have developed secondary hPTH and undergo successful renal transplantation. Up to 25% of patients with secondary hPTH will have persistent parathyroid disease—tertiary hPTH—1 year after transplantation in the form of diffuse and nodular hyperplasia.[1–3] Risk factors include prolonged pretransplant dialysis, markedly increased pretransplant parathyroid hormone (PTH), enlarged parathyroid glands detected pretransplant, and immediate posttransplant hypercalcemia.[4] In addition to mineral imbalances, such as hypercalcemia and hypophosphatemia, prolonged increases in PTH can increase the risk for long-term bone loss and decrease allograft and patient survival rates after renal transplant.[5,6]

Options for therapy include medical management with cinacalcet or operative management with subtotal parathyroidectomy (PTX). Cinacalcet is a calcimimetic that allosterically activates the calcium-sensing receptor on human tissue; this ultimately decreases PTH secretion and thus minimizes PTH-mediated calcium release from bones and renal phosphate wasting. It appears to be a safe and effective short-term therapy for decreasing calcium and PTH levels posttransplant; however, long-term data are lacking.[7] PTX has been associated with high biochemical cure rates in

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several retrospective cohorts.[8,9] In fact, PTX has been shown prospectively to be superior to cinacalcet in normalizing calcium and PTH levels in tertiary hPTH at 1-year posttreatment.[10] This finding has also been observed in primary hPTH as well.[11] Nonetheless, cinacalcet remains a mainstay therapy for tertiary disease despite only being approved by the US Food and Drug Administration for secondary hPTH and hypercalcemia of malignancy. Accordingly, only 7% of tertiary hPTH patients end up undergoing PTX.[12] Moreover, no consensus guidelines for PTX versus cinacalcet therapy exist, but several authors suggest the following indications for PTX: persistent hypercalcemia or hypercalciuria, renal phosphorous wasting, low bone mineral density, nephrocalcinosis, symptomatic disease, and enlarged (>500mg) parathyroids on imaging.[13]

With regard to renal function, prolonged hPTH has been associated with decreased renal allograft survival.[6,14] Although PTX has been associated with improved clinical outcomes in tertiary hPTH, such as bone density,[8,10] it is unclear whether the long-term effects of normalized PTH after PTX improve renal transplant function. Because PTX appears to control PTH and calcium levels better than cinacalcet, we hypothesized that PTX would be associated with improved renal allograft function in patients with stable renal function after transplantation.

Methods

Study design

A retrospective review was performed on 133 consecutive patients diagnosed with tertiary hPTH after renal transplantation at New York Presbyterian Hospital–Weill Cornell Medicine (New York, NY) with follow-up between 2000 and 2017. Patients with tertiary hPTH were defined as those diagnosed with secondary hPTH, having received a successful renal transplant, and having continued to have persistent hPTH posttransplant (PTH >88 pg/mL). This definition includes all patients who have autonomous disease in the setting of a functioning renal allograft. Two treatment cohorts were analyzed: those who underwent PTX versus those managed medically with cinacalcet alone. Exclusion criteria included PTX before renal transplant, failed renal transplant, and insufficient data. Weill Cornell Medicine Institutional Review Board approved this study.

Clinical variables

Clinical variables for analysis included age, sex, body mass index (BMI), race, etiology of ESRD, duration of pretransplant dialysis, cinacalcet usage and duration (pretransplant and posttransplant), American Society of Anesthesiologists (ASA) classification, cadaveric donor utilization, and rates of delayed allograft function. Biochemical markers, including PTH, calcium, and estimated glomerular filtration rate (eGFR) were analyzed at multiple posttransplant time points; normal values for PTH and calcium were defined as <88 pg/mL and <10.3 mg/dL, respectively. The eGFR was reported in mL/min/1.73m^2, using the Modification of Diet in Renal Disease equation; transplant allograft failure was defined as eGFR <30 as agreed upon between transplant surgery and nephrology. Indications for PTH and postoperative complications were analyzed. Operative treatment for patients with tertiary hPTH at our institution is 3.5-gland PTX and bilateral thymectomy; a 4-gland excision with parathyroid autoimplantation is performed only if the remnant gland appears unviable at the conclusion of the case. Posttransplantation outcomes for the PTX and cinacalcet-alone cohorts included PTH levels, calcium levels, and transplant allograft function. Persistent hPTH was defined as increased PTH levels within 6 months post-PTX. Postoperative hypoparathyroidism was defined as calcium and PTH less than the normal range in the immediate postoperative period. Follow-up was maintained by endocrine surgery, transplant surgery, and transplant nephrology.

Statistical analysis

Statistical analyses were performed using STATA v 13.1 (StataCorp, College Station, TX). For comparison of categorical variables, the Fisher exact and χ^2 tests were used for ≤5 and >5 observations, respectively. The Student t test or Mann-Whitney U test were used to analyze continuous parametric and nonparametric variables, respectively. Means with standard deviation (SD) and medians with interquartile ranges (IQRs) are reported accordingly. Independent predictors with P value of < .1 on univariable analysis were included in multivariable analysis. Multivariable logistic regression was performed to evaluate association of clinical variables with transplant allograft failure; odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported, as appropriate. Finally, Cox regression analysis was performed to compare renal transplant allograft survival between the PTX and cinacalcet-alone cohorts.

Results

Patient demographics and clinical variables are summarized in Table 1. A total of 133 patients were included in the analysis (33 received PTX and 100 received cinacalcet alone), with a median transplant allograft survival of 5.9 years (IQR 4.0–9.0). The mean age of the entire cohort at the time of transplantation was 59 ± 13 years. In the cohort, 46 percent of patients were female and median BMI was 26.1 [IQR 22.7-31.2]. Race distribution was 41% white, 30% black, 17% Hispanic, 11% Asian, and 1.5% other. Etiology of ESRD was most commonly hypertension (45%); diabetes mellitus (10%); systemic lupus erythematosus (6%); and, more rarely, polycystic kidney disease, Alport syndrome, IgA nephropathy, and lithium toxicity, among others. Patients spent a median of 6 years (IQR 2–9) on dialysis before renal transplantation. The type of kidney used during transplantation was 70% cadaveric (N = 93) and 30% living (N = 40) donors. Delayed allograft function occurred in 14% of patients (N = 19) postoperatively. Comparing patients who underwent PTX versus cinacalcet-alone management, there were no differences in age, sex, BMI, comorbidities, duration of pretransplant dialysis, cadaveric donor utilization, or rates of delayed allograft function between cohorts.

Cinacalcet was used in 125 patients (100 received cinacalcet alone, 25 received PTX), with a median duration of therapy of 51 months (IQR 26–81). Patients in the cinacalcet-alone cohort were more likely to have been initiated on the medication pretransplant (42% vs 12%, P = .001) and had a greater overall duration of therapy (58 months [IQR 32–84] vs 21 months [IQR 8–55], P < .001). Patients treated with cinacalcet alone, who were started on cinacalcet posttransplant, began therapy much later (48 months vs 0.4 months, P < .001) and had a greater median posttransplant duration of treatment (48 vs 19 months, P < .001) compared with PTX patients treated with cinacalcet posttransplant. Of note, patients who did not start cinacalcet until 48 months after renal transplant still had increased levels of PTH at 1 year posttransplant (median 288, IQR 155–479). Finally, 46% of the cinacalcet-alone cohort was maintained on therapy for more than 5 years compared with only 15% of the PTX cohort (P = .002).

Table 2 summarizes the details of the PTX cohort. PTX was performed at a median of 21 months (IQR 9–45) posttransplantation. Hypercalcemia was the most common indication for PTX, followed by failure of medical management, osteoporosis, and bone pain. There was a significant postoperative decrease in median PTH (417 pg/mL vs 62 pg/mL, P < .001) and calcium (10.3 mg/dL vs 9.6 mg/dL, P < .001) after PTX at the most recent follow-up. Cinacalcet was used in 76% of patients pre-PTX for a median of

Table 1
Patient demographics and clinical characteristics.

	Parathyroidectomy (N = 33)	Cinacalcet alone (N = 100)	*P* value
Age at transplant, mean ± SD	59 ± 13	60 ± 13	.795
Sex (female)	14 (42%)	47 (47%)	.647
Race			
White	13 (39%)	42 (42%)	
Black	9 (27%)	31 (31%)	.750
Asian	3 (9%)	11 (11%)	
Hispanic	7 (21%)	15 (15%)	
Other	1 (3%)	1 (1%)	
BMI (kg/m^2), median [IQR]	25 [23–28]	27 [23–32]	.189
Etiology of ESRD			
HTN	18 (54%)	42 (42%)	
DM	3 (9%)	11 (11%)	.918
SLE	2 (6%)	6 (6%)	
Time on dialysis pretransplant (y), median [IQR]	6 [1–8]	6 [3–9]	.480
Cadaveric donor kidney transplant	19 (58%)	74 (74%)	.074
Posttransplant delayed allograft function	5 (15%)	1 (14%)	.870
Cinacalcet initiation			
Pretransplant	4 (12%)	42 (42%)	.001
Posttransplant	21 (64%)	58 (58%)	.568
Cinacalcet start date (months), median [IQR]			
Pretransplant	24 [5–64]	22 [8–36]	.815
Posttransplant	0.4 [0–1.3]	48 [2.2–74]	<.001
Duration of cinacalcet therapy (months), median [IQR]			
Initiated pretransplant	69 [41–96]	68 [48–91]	.921
Initiated posttransplant	19 [4–36]	48 [26–81]	<.001

HTN, hypertension; *DM*, diabetes mellitus; *SLE*, systemic lupus erythematosus.

Table 2
Characteristics of patients undergoing PTX.

	PTX (N = 33)
ASA classification, median [range]	3 [2–4]
Time from transplant to PTX (months), median [IQR]	21 [9–45]
Pre-PTX cinacalcet	25 (76%)
Duration of preparathyroidectomy cinacalcet (months), median [IQR]	21 [8–55] (N = 25)
Parathyroidectomy Indications for PTX	
Hypercalcemia	14 (42%)
Failure of medical management	12 (36%)
Osteoporosis	4 (12%)
Bone pain	3 (9%)
PTH 6–12 months posttransplant (pg/mL), median [IQR]	417 [210–802]
PTH 1-year post-PTX (pg/mL), median [IQR]	64 [43–156]
Calcium 6–12 months posttransplant (mg/dL), median	10.3 [9.6–11.2]
Calcium 1-year post-PTX (mg/dL), median [IQR]	9.5 [9.1–9.9]
Normalized PTH	9.4 [8.8–9.6]*
Persistent hyperparathyroidism	9.6 [9.3–10.0]*
Complications of PTX	
Hematoma	0
Hypoparathyroidism	
Temporary	7 (21%)
Permanent	0
Recurrent laryngeal nerve palsy	
Temporary	1 (3%)
Permanent	0
Persistent hPTH	11 (33%)
Reoperation	1
Cardiovascular morbidity	0
30-day mortality	0

* $P = .235$

21 months. There were no differences in posttransplant (within 12 months) median PTH (552 pg/mL [IQR 301–1007] vs 285 pg/mL [IQR 148–541], $P = .133$) or calcium (10.2 mg/dL [IQR 9.6–11.1] vs 10.7 mg/dL [IQR 10.1–11.6], $P = .156$) comparing patients treated with and without cinacalcet before PTX, respectively. Persistent hPTH occurred in 33% of PTX patients, with a median postoperative PTH of 128 pg/mL (IQR 108–156) in these patients, but normal calcium levels (median 9.6 [IQR 9.3–10.0]). One patient underwent reoperative exploration; that patient's PTH is now normalized 47 months post-index PTX. Most patients were ASA classification 3, and there was no cardiovascular morbidity or mortality within 30 days. Complications occurred in 8 patients, yielding an overall complication rate of 24%, all of which were temporary. Finally, patients undergoing PTX did not have a decrease in median eGFR within 1-year postoperative (61 preoperative [IQR 48–83] vs 63 postoperative [IQR 49–77], $P = .918$), or at the most recent follow-up (60 preoperative [IQR 49–75] vs 67 postoperative [IQR 47–84], $P = .761$) when allograft failure patients were excluded.

Posttransplantation and hPTH outcomes are compared between the PTX and cinacalcet-alone cohorts in Table 3. Within 1 year of renal transplantation, patients in the PTX cohort had a greater median PTH compared with the cinacalcet-alone cohort (417 pg/mL

Table 3
Posttransplantation and hPTH treatment outcomes.

	Parathyroidectomy (N = 33)	Cinacalcet alone (N = 100)	*P* value
Posttransplant PTH at 6–12 months (pg/mL), median [IQR]	417 [210–802]	246 [164–366]	.002
Posttransplant calcium at 6–12 months (mg/dL), median [IQR]	10.3 [9.6–11.2]	10.1 [9.6–10.7]	.153
Posttransplant eGFR at 6–12 months, median [IQR]	59 [49–75]	55 [47–72]	.570
Posttreatment normalized PTH	22 (67%)	15 (15%)	<.001
Most-recent PTH (pg/mL), median [IQR]	62 [48–113]	151 [109–261]	<.001
Posttreatment normalized calcium	3 (97%)	69 (69%)	.001
Most-recent calcium (mg/dL), median [IQR]	9.6 [9.2–9.8]	9.9 [9.5–10.5]	<.001
Allograft failure (eGFR < 30)	3 (9%)	33 (33%)	.007
Posttransplant follow-up (y), median [IQR]	7.0 [4.2-9.3]	7.0 [5.0-10.2]	.719

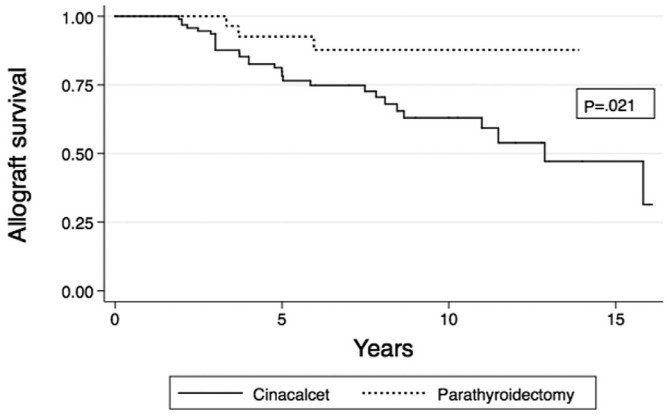

Fig. 1. Renal transplant allograft survival analysis. Parathyroidectomy is associated with improved renal transplant survival compared with cinacalcet-alone therapy on Cox regression analysis.

vs 246 pg/mL, $P = .002$), but similar median calcium (10.3 vs 10.1, $P = .153$) and eGFR (59 vs 55, $P = .570$) levels, respectively. More patients undergoing PTX experienced normalization of PTH (67% vs 15%, $P < .001$) and calcium (97% vs 69%, $P < .001$) compared with cinacalcet-alone therapy. As such, the PTX cohort had lesser posttreatment median PTH (62 pg/mL vs 151 pg/mL, $P < .001$) and calcium levels (9.6 vs 9.9, $P < .001$).

With regard to renal function, overall rates of transplant allograft failure were less in the PTX cohort (9% vs 33%, $P = .007$), with no difference in years of posttransplant follow-up (7.0 [IQR 4.2–9.3] vs 7.0 [IQR 5.0–1 .2], $P = .719$). The overall biopsy-confirmed rejection rate was 20% (7% acute, 13% chronic) in the entire cohort. When rejection-associated allograft failures were excluded, the failure rates remained less in the PTX cohort (6% vs 29%, $P = .008$). On multivariable logistic regression, PTX was inversely associated with renal allograft failure (OR 0.20, 95%-CI 0.06–0.71, $P = .013$). On univariable analysis, there were no other associated factors including age; sex; BMI; etiology of ESRD; duration of pretransplant dialysis; cadaveric donor utilization; rates of delayed allograft function; pretransplant cinacalcet usage; or PTH, calcium, and eGFR values within 12 months posttransplant. On Cox regression analysis, renal transplant allograft survival was improved ($P = .021$) in the PTX cohort (Fig. 1). Notably, patients in the cinacalcet-alone cohort who suffered eventual allograft failure had a greater median PTH (pg/mL) at 1 year posttransplant (348 [IQR 204–493] vs 195 [IQR 147–297], $P = .025$).

Discussion

Tertiary hPTH affects up to 25% of renal transplant patients, and persistent exposure to increased levels of PTH after renal transplantation can lead to poor outcomes, such as deteriorating bone mineral density, renal transplant allograft failure, and mortality.[1,2,5,6] Cinacalcet remains a widely utilized treatment option for tertiary hPTH, based on short-term studies demonstrating improvement in biochemical profiles; however, long-term data are lacking, particularly regarding renal allograft function.[7] PTX appears to reliably normalize PTH and calcium levels,[8,9] and in a prospective randomized study it was shown to have superior biochemical normalization and be more cost-effective than prolonged cinacalcet usage.[10] However no long-term data comparing renal allograft function between these two treatments are available to guide the management of tertiary hPTH. Our data suggest that PTX for the treatment of tertiary hPTH is associated with improved renal allograft function compared with cinacalcet-alone therapy. We also observed that renal allograft failure in patients who are maintained on cinacalcet-alone therapy is associated with greater increases in PTH levels at 1-year posttransplant.

Importantly, our two cohorts were similar in demographics and peri-operative transplant characteristics, with the exception that cinacalcet-alone patients were more likely to have cinacalcet started pre-transplant and had longer durations of post-transplant cinacalcet therapy. The differences in cinacalcet management in our cohort are reflective of the wide variability in treatment of tertiary hPTH. Nonetheless, our data are congruent with treatment patterns reported in the literature, where tertiary hPTH patients are typically managed with long-term cinacalcet therapy, and only 7% of patients are being referred for PTX.[12] Whether duration of cinacalcet therapy before PTX has any effect on long-term outcomes remains unclear, and our cohort was underpowered to detect any differences. Nevertheless, failure of medical management and hypercalcemia were the most common indications for PTX in our study, as evidenced by increased median pre-PTX calcium (10.3 mg/dL) and PTH (417 pg/mL) levels. It was a well-tolerated procedure, with acceptable rates of temporary hypoparathyroidism (21%) and temporary recurrent laryngeal nerve palsy (3%). There were no severe, postoperative morbidities, and only one patient (3%) had recurrent hPTH requiring re-exploration. As observed in earlier studies,[10] PTX in our cohort had more durable, long-term normalization of PTH and calcium compared with cinacalcet-alone therapy. Of note, PTX normalized PTH in more patients (67% vs 15%, $P < .001$) despite having a greater median posttransplant PTH compared with the cinacalcet-alone cohort (417 pg/mL vs 246 pg/mL, $P = .002$). This further supports PTX as a more effective treatment for tertiary hPTH; whereas cinacalcet-alone therapy still exposes patients to a greater median PTH posttherapy (151 pg/mL vs 62 pg/mL, $P < .001$).

The etiology of improved renal allograft function in patients undergoing PTX in our cohort remains to be fully elucidated. Although there are conflicting reports on associations between hypercalcemia and renal transplant allograft failure, there does appear to be a role regarding renal calcium deposition and overt nephrocalcinosis. Several studies have associated increased calcium oxalate levels and nephrocalcinosis with poor allograft function. Pinheiro et al[15] demonstrated significantly worse 12-year allograft

survival in patients with calcium oxalate deposits in kidney biopsies compared with those without deposits (50% versus 74%, respectively). Bagnasco et al[16] correlated increased calcium oxalate deposition on biopsy with tubule-interstitial scarring and worse renal function compared with a control group without calcium deposition. In addition, Schwarz et al[17] found nephrocalcinosis as a predictor for chronic allograft nephropathy on multivariable analysis. Moreover, increased pretransplant PTH levels are associated with allograft failure.[18] Perhaps our finding of improved allograft survival after PTX is secondary to improved PTH and calcium control, thus leading to lower risk of nephrocalcinosis.

Despite these studies, recent data suggest that PTX in tertiary hPTH patients may transiently decrease eGFR postoperatively, but without compromise of long-term allograft survival.[19–21] Evenepoel et al[21] reported a significant increase in mean creatinine from 1.76 to 1.91 mg/dL within 1 month of PTX; however, renal function stabilized thereafter, and no difference in long-term allograft survival was detected when compared with a medically managed cohort. Tseng et al[19] showed a transient decrease in mean eGFR from 74 to 68 mL/min/1.73m^2 1 year after PTX, but noted recovery to pre-PTX baseline by 2 years. Notably, these studies did observe an improvement in cardiovascular hemodynamics—specifically, PTX was associated with an improvement in systolic blood pressure and pulse pressure.[19,20] Although our study did not address hemodynamic changes between cohorts, we did not observe a decline in median eGFR after PTX within 1 year postoperative (61 preoperative vs 63 postoperative, $P = .918$), or at the most recent follow-up (60 preoperative vs 66 postoperative, $P = .761$), when allograft failure patients were excluded.

Recent data suggest the benefits of PTX as definitive treatment for tertiary hPTH. It has been associated with improved bone mineral density at 12 months postoperatively,[10] and in our study, was associated with improved renal allograft function as compared with cinacalcet. Considering that the introduction of cinacalcet therapy has been associated with a significant 2-year delay of PTX with continuously increased preoperative PTH levels,[22] perhaps more multidisciplinary collaborations among transplant surgeons, endocrine surgeons, endocrinologists, and transplant nephrologists should occur to investigate the best treatment algorithm for patients with tertiary hPTH. We observed in the cinacalcet-alone cohort that renal allograft failure was associated with increased PTH within 12 months posttransplant compared with patients with a functioning allograft (348 pg/mL vs 195 pg/mL, $P = .025$). This may imply that PTX may be indicated when PTH remains persistently increased at >200 pg/mL. Furthermore, until cinacalcet is proven to have long-term benefit-managing tertiary hPTH, it may be best reserved for patients who are not surgical candidates.

This study has several limitations. First, it is a retrospective review of a heterogeneous cohort. Referral to an endocrine surgeon was left at the discretion of the transplant nephrologist and not necessarily on any defined guidelines regarding symptoms, absolute PTH or calcium levels, or timing posttransplant. In addition, a consistent panel, including a comprehensive metabolic profile and PTH levels, were not obtained at routine intervals. Such data would be very useful to define the specific time course and trend of deteriorating renal transplant allograft function, along with a correlation to PTH values. Furthermore, because of the size limitation of the cohort, we were unable to evaluate whether the utilization and duration of cinacalcet before PTX had a negative effect on allograft function. Similarly, the PTX cohort was too small to perform a subgroup analysis evaluating differences in long-term allograft function, comparing early versus late PTX. Finally, to broadly include all patients who have autonomous hPTH after undergoing successful renal allograft transplantation, our definition for tertiary disease includes both hypercalcemic and eucalcemic patients with an increased PTH. The limitation of this definition is that there is a "gray area," where not every patient posttransplant has a robust GFR, and thus, there can be overlap between secondary and tertiary disease, particularly in those who have a functioning renal allograft but GFR < 50. These patients do present for PTX and thus we decided to include them in our cohort. Overall, our data with these limitations provide good reason to study this outcome in a prospective, randomized controlled study, particularly to explore the etiology of the protective effects of PTX in tertiary hPTH patients.

In conclusion, we have found that patients with tertiary hPTH who undergo PTX have improved renal transplant allograft function compared with those who are treated with prolonged cinacalcet-alone therapy. Allograft failure in patients who are maintained on cinacalcet therapy is associated with greater increases in PTH at 1 year posttransplant. Early referral to an endocrine surgeon for these patients should be sought, particularly in those with symptomatic disease, osteoporosis, or inadequate control of PTH and calcium metabolism.

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Discussion

Dr Herb Chen (Birmingham, AL): Great talk about important data to share with our nephrology colleagues.

Your study occurred over a 15-year period. So, with 33 patients, only 2 patients on average per year were referred to surgery.

Was there any variability over time? For instance, did those surgical referrals happen more recently than back in the past? Can you shed some light on that?

Dr Brendan M. Finnerty: The surgical referrals were distributed more in the earlier period of the study. With the introduction of cinacalcet, the trend of surgical referrals did decrease as time went on. But as you suggested, about two to three cases per year is probably on average what we are seeing currently. We have reached out to our transplant nephrologists to show them these data and to look at this prospectively, so we hope that will change.

Dr Scott Grant (New York, NY): I enjoyed your study. I think your conclusions mirror things we have seen before in the literature, showing that parathyroidectomy improves transplant allograft survival.

Looking at data at the University of Chicago, we actually found a different outcome, and we are trying to understand some of the reasons why.

Correct me if I am wrong, but it looked like you had people who were on dialysis for 6 years, and the average PTH was in the 400s for your study. Do you happen to know what the reasons were that people were on dialysis in the first place, and what the racial makeup was of your cohort?

Dr Brendan M. Finnerty: Yes, that's correct, the median duration of pretransplant dialysis was 6 years.

The PTH of 400 was the PTH of the parathyroidectomy cohort 1 year after transplantation, so it's not the PTH during dialysis. We did not include that in this analysis. I think that's something to address going forward to make those kinds of correlations.

Dr Scott Grant (New York, NY): Did you find that you had a lack of biochemical data at various time points in the pre- and posttransplant periods? That was something that we had difficulty with in our data set.

Dr Brendan M. Finnerty: We are fortunate to be at a center that performs a large volume of kidney transplantation, and there's an organization that permeates through the tri-state area which provides dialysis, so we do have pretty consistent data. But even with that set-up, we still didn't have reliable data in terms of vitamin D levels, urinary calcium levels, phosphorus levels, other relevant biochemical markers.

Dr David Schneider (Madison, WI): Really great study. Congratulations on your work.

Many of these patients are usually on cinacalcet pretransplant. As you looked through these records, could you figure out in how many patients that represented a conscious decision? Because the cinacalcet sort of carries through after transplant sometimes. So, I'm wondering how many patients had a truly dedicated decision to treat their tertiary hyperparathyroidism with cinacalcet versus just having it carry through without anyone recognizing that surgery can help them?

Dr Brendan M. Finnerty: That's a good question, and I don't have a good answer for it. I will say that, for patients receiving cinacalcet-alone, almost 50% were managed on cinacalcet for greater than 5 years as compared with about 10% of the surgically managed cohort. So, it was at times difficult to delineate from the nephrologist's notes about why they were continuing treatment and not perhaps considering a surgical evaluation.

Dr Jacob Moalem (Rochester, NY): Thank you for your presentation. I was staggered by a 33% graft failure rate among the medically treated patients. Can you help me put that number into perspective? What is the incidence of tertiary hyperparathyroidism among patients who received kidney transplants in the first place?

Dr Brendan M. Finnerty: Because we didn't focus on secondary disease, I don't have an incidence to report to you. It does vary in the literature, ranging between 25% and 50%, but we did not calculate an incidence from our data.

Dr Jacob Moalem (Rochester, NY): I think it would be interesting to look at the number of kidney transplants that were done during that period and get a rough estimate of the actual number of patients who developed this problem. Any risk factor that leads to a one-third graft failure rate is something that needs to be very carefully scrutinized moving forward. My thinking before hearing your presentation was that tertiary hyperparathyroidism was very common in this group. Thank you.

Dr Geeta Lal (Iowa City, IA): Thank you for a very nice study.

If I understood correctly from one of your slides, 33% of patients after parathyroidectomy had persistent disease. Do you know whether those were the patients that failed medical management (ie, were on cinacalcet), and whether they came to surgery for that reason? If they are failing on cinacalcet, perhaps they are already part of a preselected group with a different type of disease that you can't really cure.

Dr Brendan M. Finnerty: That's an excellent point, but our numbers were too small. Anytime we tried to do any subgroup analysis, particularly on the surgical cohort, it was impossible because the numbers were insufficient. I will say that those patients with persistent disease had median calcium levels that were right in the normal range, so it wasn't severe persistent disease. Only one patient had to undergo a reoperation to cure their disease. But it's an excellent point and it would be good to analyze that in a larger cohort.

Dr Geeta Lal (Iowa City, IA): It's sort of along the same lines as patients with primary hyperparathyroidism after surgery who have normal calcium but persistently elevated PTH levels.

Dr Brendan M. Finnerty: Exactly. Thank you.