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Impact of parathyroidectomy on allograft outcomes in kidney transplantation

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Summary

We performed retrospective, multi-center study of the impacts of parathyroidectomy (PTX) after or before kidney transplantation on allograft outcomes. A total of 63 patients who underwent PTX after kidney transplantation were identified. Deterioration in eGFR by more than 25% at 1 month after PTX occurred in 20% of the patients. The baseline eGFR was significantly lower in impairment group than nonimpairment group [adjusted odds ratio (OR) 0.87, 95% confidence interval (CI) 0.77–0.99, $P = 0.033$]. Low iPTH concentration after PTX was also a significant risk factor for the renal impairment (OR 0.96, CI 0.94–0.99, $P = 0.009$). A total of 37 patients who underwent PTX before transplantation were identified. Thirty-six percent of the patients had persistent hyperparathyroidism by 1 year after transplantation. A high iPTH level before PTX was a significant risk factor for persistent post-transplant hyperparathyroidism (adjusted OR 1.002, CI 1.000–1.005, $P = 0.039$). Finally, eGFR values during the first 5 years after transplantation were significantly lower in the patients who underwent PTX at less than 1 year after transplantation, than the pretransplant PTX patients ($P = 0.032$). As PTX after kidney transplantation has a risk of deterioration of allograft function, pretransplant PTX should be considered for patients with severe hyperparathyroidism, who could undergo post-transplant PTX.

Introduction

Secondary hyperparathyroidism is defined as the overproduction of parathyroid hormone (PTH) secondary to constant stimuli. The overproduction of PTH can be seen frequently in chronic kidney disease (CKD), and develops in response to hyperphosphatemia, 1,25-dihydroxyvitamin D deficiency, and hypocalcemia [1]. Hyperparathyroidism improves gradually within 1 year after kidney transplantation, because the hormonal and metabolic stimuli disappear after renal function recovers [2–4]. However, even after successful kidney transplantation, 10–50% of kidney transplant recipients have persistent hyperparathyroidism by the acquired autonomy of parathyroid glands, and when it occurs it is called tertiary hyperparathyroidism [5,6]. The reduction of the 1,25-dihydroxyvitamin D3 receptor in parathyroid glands in CKD leads to the parathyroid hyperplasia. The acquired autonomy and oversecretion of PTH might be demonstrated by failure of normalization of the hypertrophied parathyroid glands despite normal or slightly elevated level of serum calcium (Ca) concentration even after kidney transplantation [7]. Besides, the decreased Ca sensing receptor in the parathyroid glands has been suggested to be another mechanism

of less effective control of PTH secretion [8]. Tertiary hyperparathyroidism might lead to loss of bone mass [9] or nephrocalcinosis, and has been related to reduced kidney function in a protocol biopsy study [10]. Surgical resection has been recommended for tertiary hyperparathyroidism, because nodular hyperplasia in parathyroid glands represents monoclonality and aggressive proliferation refractory to medical treatment [11].

The indications for parathyroidectomy (PTX) include treatment-resistant hypercalcemia and hypophosphatemia, both accompanied by the presence of markedly elevated PTH level, with or without related complications, such as nephrolithiasis, renal function deterioration, pathologic fracture, pancreatitis, calciphylaxis, or severe vascular calcification. In the case of tertiary hyperparathyroidism, PTX is generally performed when sustained hypercalcemia does not respond to medical treatment for more than a year after kidney transplantation [12–14].

Interestingly, renal function deterioration has been reported in kidney transplant patients who underwent PTX [15–17]. However, most of the previous studies have been small-scaled, single center-based studies [15–17]. Moreover, there has been no study that compared the impact of post-transplant PTX with that of pretransplant PTX. The aim of this multi-center study was to analyze the impacts of PTX on renal allograft outcomes and metabolic abnormalities, and the risk factors that influence renal functional deterioration. Furthermore, we compared the impact of PTX on allograft function between pretransplant PTX patients and post-transplant PTX patients.

Patients and methods

Study population

We identified the patients who underwent PTX among kidney transplantation patients in four university-affiliated, teaching hospitals in Korea (Seoul National University Hospital, Severance Hospital, Asan Medical Center, and Samsung Medical Center) from 1992 to 2011. The patients were divided into two groups: one group underwent PTX after kidney transplantation, and the other group underwent PTX before kidney transplantation. To evaluate the effects of PTX on renal allograft function, we excluded nine patients who lost their allograft function before PTX among the post-transplant PTX group. In addition, when we analyzed the risk factors for persistent hyperparathyroidism or renal impairment, a total of 14 patients who had PTX together with thyroidectomy as a result of thyroid cancer were excluded from analysis because they did not have hyperparathyroidism or hypercalcemia before surgery. The study protocols were approved by the Institutional Review Boards of the four participating hospitals (IRB number: H 1104 098 359).

Collection of clinical data

The demographic and laboratory findings were retrospectively obtained from the patients' medical records. We checked the serum levels of creatinine concentration, immunoreactive PTH (iPTH), Ca, phosphate (P), alkaline phosphatase, and hemoglobin before PTX and at postoperative 1 day, 2 days, 7 days, 1 month, 3 months, and then every 3 months up to 12 months after PTX. The same values before transplantation, and those at 7 days, 1 month, and 3, 6, 9, and 12 months after transplantation were also obtained. The iPTH levels were measured using immunoradiometric assay test, and serum levels of creatinine were determined with kinetic alkaline picrate (Jaffe) reaction. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [18], and the serum total Ca level was adjusted by serum albumin concentration.

Data analysis and statistical methods

First, impact of the post-transplant PTX on renal allograft function and metabolic parameters were investigated. The paired *t*-test was used to assess the impact of PTX on renal function at several points in time. Next, we classified patients into the impairment group or nonimpairment group according to the changes in their renal function. The impairment group was defined as patients whose eGFR decreased from the baseline value by more than 25% at 1 month after PTX, based on risk category of the RIFLE (Risk-Injury-Failure-Loss-End-stage renal disease) classification [19]. Risk factors for impairment of renal function after PTX were analyzed using backward stepwise, multivariate logistic regression analysis. Age, gender, variables with *P*-values less than 0.2 in the univariate analysis, and clinically plausible variables that have been suggested by previous studies (i.e., type of PTX, biopsy-proven acute rejection episode, BK nephropathy, acute tubulointerstitial nephropathy, and infection events), were included in the initial step of multivariate analysis.

Second, the impact of pretransplant PTX on post-transplant outcomes and metabolic parameters were also investigated. Persistent post-transplant hyperparathyroidism was defined as iPTH levels more than 65 pg/ml for 1 year after kidney transplantation. The risk factors for the persistent post-transplant hyperparathyroidism were analyzed using backward stepwise, multivariate logistic regression analysis. Age, gender, variables with *P*-values less than 0.2 in the univariate analysis, and clinically plausible variables that have been suggested by previous studies (i.e., type of PTX, Ca & vitamin D supplementation), were included in the initial step of multivariate analysis.

Finally, renal allograft function for the first 5 years after transplantation was compared between the pretransplant PTX group and the post-transplant PTX group to assess the overall impact of PTX on graft functions. Next, we divided the post-transplant PTX group into two groups: one group underwent PTX at less than 1 year after transplantation (the early post-transplant PTX group), and the other group underwent PTX 1–5 years after transplantation (the late post-transplant PTX group). The renal function in the pretransplant PTX group was compared with that in the early post-transplant PTX group or in the late post-transplant PTX group. We excluded the patients that underwent PTX at more than 5 years after kidney transplantation ($n = 8$), when comparing the two groups' eGFRs during the first 5 years after transplantation. Cases of death with a functional graft were also excluded from the analysis, and the GFR values were regarded as 10 ml/min when graft failure occurred in live patients. The generalized estimating equation was used for this analysis by adjusting covariates. The SPSS statistical package (Version 18.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and a *P*-value of <0.05 was considered significant.

Results

Baseline characteristics of patients

Between 1992 and 2010, a total of 100 kidney transplant patients that underwent PTX were identified. Among them, 63 patients underwent PTX after kidney transplantation (post-transplant PTX group), and 37 patients underwent PTX before kidney transplantation (pretransplant PTX group). Their clinical characteristics were summarized in Table 1. The mean time between transplantation and PTX was 31.2 ± 40.7 months in the post-transplant PTX group, whereas it was 26.2 ± 23.9 months in the pretransplant PTX group. The median follow-up duration was 67.17 months in the post-transplant PTX group, and 63.97 months in the pretransplant PTX group.

The most common indication of PTX was persistently severe hypercalcemia and hyperparathyroidism, followed by bone pain, thyroid cancer, and nephrocalcinosis. A subtotal PTX was performed in 71.4% in the post-transplant PTX group, and 62.2% in the pretransplant PTX group. In contrast, total PTX with or without autotransplantation into the forearm was done in 12.7% in the post-transplant PTX group, and 29.7% in the pretransplant PTX group. Routine preoperative examinations including neck ultrasonography or scintigraphy with 99-mTc MIBI were conducted. Suspicious parathyroid adenoma was the most common finding of preoperative examinations, but the final pathology revealed that parathyroid hyperplasia was the most common finding in both groups. There was one patient with parathyroid adenocarcinoma, and the patient was excluded in the analysis because he lost his allograft function before PTX.

Outcome of the patients that underwent PTX after kidney transplantation

Table 2 showed the outcomes during the first year after PTX in patients that underwent PTX after kidney transplantation. After a significant decline in immunoreactive parathyroid hormone (iPTH) levels immediately after PTX, the iPTH levels began to rise after post-PTX 1 week. Renal function showed acute deterioration, which improved and was stabilized 1 week after PTX. However, neither mean serum creatinine nor eGFR levels returned to baseline values by 1 year after PTX (Fig. 1a). Serum Ca levels decreased, and were maintained at normal value after PTX by administration of Ca and active vitamin D supplementation.

The deterioration in eGFR by more than 25% at 1 month after PTX occurred in 11 (20%) patients (impairment group), whereas 44 (80%) patients exhibited no such decrease in eGFR (nonimpairment group). The age at PTX, gender, duration of dialysis before transplantation, interval between transplantation and PTX, Ca levels, donor type, immunosuppressant agents (cyclosporine versus tacrolimus), body mass index (BMI), diabetes mellitus (DM), type of PTX, final pathologic finding of parathyroid gland, acute rejection episodes, Ca & vitamin D supplementation, BK nephropathy, acute tubulointerstitial nephropathy, and infection events did not differ between the impairment and the nonimpairment groups (Table 3). However, the baseline eGFR was significantly lower in the impairment group than the nonimpairment group (58.69 ± 15.64 vs. 71.30 ± 15.72 ml/min, respectively, $P = 0.036$, *t*-test). Although iPTH levels before PTX were not significantly different between the two groups ($P = 0.686$, *t*-test), the impairment group had a lower iPTH concentrations after PTX, than the nonimpairment group (34.1 ± 36.7 vs. 113.0 ± 78.2 pg/ml, respectively, $P = 0.005$, *t*-test). In multivariate logistic regression analysis, low baseline eGFR (OR = 0.87, 95% confidence interval [0.77–0.99], $P = 0.033$) and low iPTH concentration after PTX (OR = 0.96, 95% confidence interval [0.94–0.99], $P = 0.009$) were statistically significant risk factors for renal impairment after PTX (Table 3).

Outcome of the patients that underwent PTX before kidney transplantation

Table 4 showed the outcomes from PTX to the first year after kidney transplantation in the pretransplant PTX group. Post-PTX outcomes were estimated at 1 month

Table 1. Clinical characteristics of the study population.

	PTX after transplantation (n = 63)	PTX before transplantation (n = 37)	P-value†
Gender (male:female)	30:33 (47.6:52.4%)	12:25 (32.4:67.6%)	0.156
Age at transplantation	40.1 ± 10.7	39.8 ± 12.0	0.396
Age at PTX	42.6 ± 9.5	37.1 ± 11.4	0.011
ESRD cause			
DM	2 (3.2%)	0 (0%)	0.253
Glomerulonephritis	20 (31.7%)	17 (45.9%)	
Hypertension	15 (23.8%)	5 (13.5%)	
Cystic disease	2 (3.2%)	0 (0%)	
Unknown	24 (38.0%)	15 (40.5%)	
Dialysis type			
Pre-emptive	1 (1.6%)	0 (0%)	0.203
Hemodialysis	39 (61.9%)	16 (43.2%)	
Peritoneal dialysis	16 (25.4%)	15 (40.5%)	
Both	6 (9.5%)	6 (16.2%)	
Time on dialysis			
Before transplantation (month)	95.3 ± 47.5	135.9 ± 54.8	<0.001
Donor type (living donor)	31 (49.2%)	18 (48.6%)	0.636
Cyclosporin:Tacrolimus	25:37 (39.7:58.7%)	13:24 (35.1:64.9%)	0.716
Mycophenolate mofetil derivatives*	43 (68.3%)	27 (73.0%)	0.247
DM (including PTDM)	13 (20.6%)	4 (10.8%)	0.293
BMI (kg/m^2)	21.3 ± 3.8	20.4 ± 3.0	0.159
Year of PTX	1992–2010	1995–2009	
Before 2005	21 (33.3%)	19 (51.4%)	0.112
After 2005	42 (66.7%)	18 (48.6%)	
F/U duration (median, range, month)	67.17 (10.1–245.4)	63.97 (16.6–185.3)	0.804
Acute rejection	11 (17.4%)	8 (21.6%)	0.609
Calcium supplementation	33 (57.9%)	18 (51.4%)	0.545
Vitamin D supplementation	34 (59.6%)	20 (57.1%)	0.813

PTX, parathyroidectomy; DM. diabetes mellitus; PTDM, post-transplantation diabetes mellitus; BMI, body mass index; F/U, follow-up.
Most numerical values are expressed as mean ± standard deviation.
*Mycophenolate mofetile derivatives included mycophenolate mofetil and myfortic acid.
†The Chi-squared test or Fisher's exact test was used for categorical data, as appropriate, and numerical data was compared using t-test or ANOVA test, as appropriate.

Table 2. Outcome of the patients that underwent parathyroidectomy after kidney transplantation.

	Post-PTX time								
	Pre-PTX	POD1	POD2	7 days	1 month	3 months	6 months	9 months	12 months
SCr (mg/dl)	1.15 ± 0.30	1.44 ± 0.42	1.48 ± 0.49	1.32 ± 0.46	1.34 ± 0.50	1.31 ± 0.53	1.34 ± 0.53	1.36 ± 0.57	1.40 ± 0.62
eGFR (ml/min)	68.0 ± 17.4	54.3 ± 16.6	53.7 ± 19.9	60.5 ± 20.5	60.6 ± 19.7	62.2 ± 19.8	61.4 ± 20.6	59.9 ± 18.3	59.7 ± 20.3
iPTH (pg/ml)	327.3	28.5	44.2	75.9	81.9	80.4	78.3	88.0	58.3
Ca (mg/dl)	11.2 ± 1.0	9.5 ± 1.1	9.0 ± 1.2	9.3 ± 1.4	9.4 ± 1.1	9.4 ± 1.1	9.5 ± 0.8	9.4 ± 1.0	9.4 ± 1.0
P (mg/dl)	2.6 ± 0.6			3.3 ± 0.8	3.3 ± 0.8	3.3 ± 0.7	3.5 ± 0.6	3.2 ± 0.6	3.3 ± 0.7
ALP (IU/l)	221.8			340.3	256.3	120.8	114.8	99.8	94.4
Hb (g/dl)	12.6 ± 2.3			11.7 ± 2.2	12.3 ± 1.9	12.8 ± 1.9	12.8 ± 1.7	12.6 ± 1.8	12.7 ± 1.8

PTX, parathyroidectomy; POD, postoperative day; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; iPTH, immunoreactive parathyroid hormone; Ca, calcium; P, phosphate; ALP, alkaline phosphatase; Hb, hemoglobin.
Most values are expressed as mean ± standard deviation.

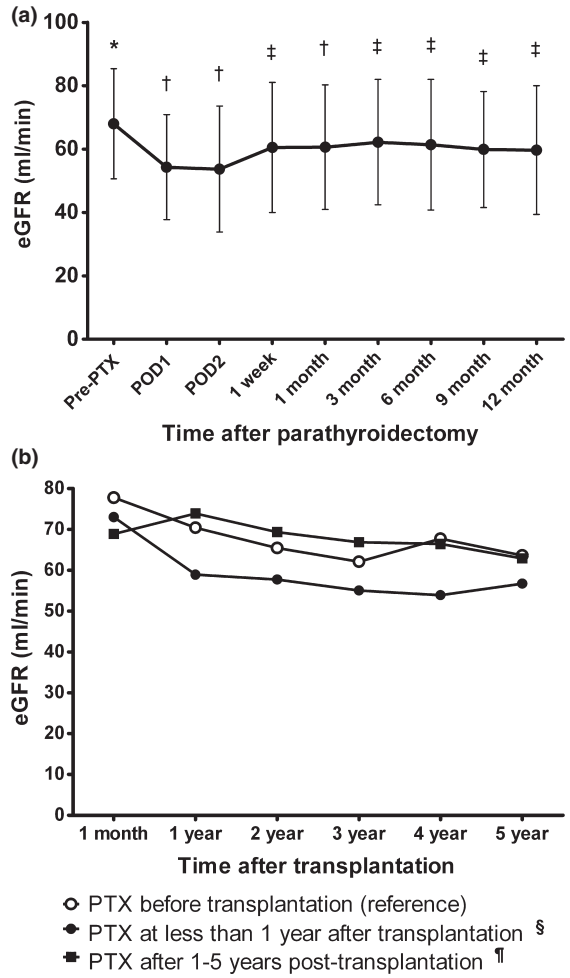

Figure 1 Impacts of parathyroidectomy on renal allograft function in kidney transplantation. (a) Impact of post-transplant PTX on renal allograft function. PTX after kidney transplantation significantly decreased renal allograft function immediately after surgery, and the renal deterioration persisted up to 1 year after PTX. The eGFR values at the multiple time-points were compared with the baseline eGFR value (mean ± standard deviation), and *P*-values were calculated by paired *t*-test (*reference, †$P < 0.001$, ‡$P < 0.01$). (b) Overall comparison of renal allograft functions between patients who underwent PTX before kidney transplantation and patients who underwent PTX after kidney transplantation. When eGFR values from baseline (1 month after transplantation) to 5 years after transplantation were compared, renal function in the group of PTX at less than 1 year after transplantation was significantly lower than that in the group of PTX before transplantation (§$P = 0.032$, the generalized estimation equations adjusted by age, gender, donor type, type of PTX, calcineurin inhibitors, acute rejection episode, calcium & vitamin D supplementation, BK viral nephropathy, acute tubulointerstitial nephropathy, and infection events). However, there was no significant difference in renal function between patients who underwent PTX 1–5 years after transplantation and those who underwent PTX before transplantation (¶$P = 0.351$, the generalized estimation equations adjusted by the covariates). eGFR, estimated glomerular filtration rate; iPTH, immunoreactive parathyroid hormone; PTX, parathyroidectomy.

after PTX. The renal function had been stable after kidney transplantation. After iPTH levels decreased significantly by PTX, they increased gradually until kidney transplantation. Although iPTH levels decreased after kidney transplantation, they did not fall to the normal range. Serum Ca levels decreased after PTX and were relatively stable after transplantation.

Next, we analyzed the risk factors for persistent post-transplant hyperparathyroidism in the pretransplant PTX group. Twelve (36%) patients had persistent hyperparathyroidism by 1 year after transplantation. The time on dialysis, and iPTH levels before and after PTX showed a trend of higher risk for persistent hyperparathyroidism after kidney transplantation in univariate analysis ($P = 0.110$, 0.090, 0.112, respectively), whereas serum Ca, and P concentrations before and after transplantation, and type of PTX were not significant risk factors (Table S1). In multivariate analysis, high iPTH level before PTX was the significant risk factor for persistent post-transplant hyperparathyroidism (adjusted OR = 1.002, 95% confidence interval [1.000–1.005], $P = 0.039$) (Table S1).

Comparison between PTX after and before kidney transplantation

Finally, we compared the impact of PTX on renal function between the pretransplant PTX group and the post-transplant PTX group. There was no significant difference in eGFR values from 1 month to 5 years after transplantation between the two groups ($P = 0.712$, by generalized estimating equations adjusted with age, gender, donor type, type of PTX, calcineurin inhibitor, acute rejection episodes, Ca & vitamin D supplementation, BK viral nephropathy, acute tubulointerstitial nephropathy, and infection events).

Next, the renal function in the pretransplant PTX group was compared with that in the early post-transplant PTX group or in the late post-transplant PTX group. There was no difference in baseline eGFR at 1 month after kidney transplantation among the three groups [77.76 ± 41.44 ml/min (the pretransplant PTX group, reference) vs. 73.02 ± 25.26 ml/min (the early post-transplant PTX group, $P = 0.623$) vs. 68.88 ± 21.66 ml/min (the late post-transplant PTX group, $P = 0.320$)]. There was also no significant difference in baseline characteristics or proportions of the total PTX (16.7% vs. 6.7%, $P = 0.390$) between the early post-transplant PTX group and the late post-transplant PTX group. The acute rejection rates during the first 5 years (20.0% vs. 15.8%, $P = 0.667$) or during the first year (16.0% vs. 10.5%, $P = 0.526$) were not significantly different between the two post-transplant PTX groups.

When eGFR values during the first 5 years after transplantation were compared, renal function in the early

Table 3. Risk factors for impairment in renal function after post-transplant parathyroidectomy.

	With impairment (n = 11)	Without impairment (n = 44)	Univariate analysis* *P*-value	Multivariate analysis† Odds ratio	95% CI	*P*-value
Age at PTX (years)	39.6 ± 11.8	43.8 ± 9.2	0.240	–	–	–
Gender (% male)	33.3	55.3	0.245	–	–	–
Time on dialysis (months)	81.8 ± 23.5	102.9 ± 48.3	0.212	–	–	–
Time from kidney TPL to PTX (months)	11.2 ± 5.8	25.2 ± 26.7	0.102	–	–	–
Baseline eGFR (ml/min)	58.69 ± 15.64	71.30 ± 15.72	0.048	0.873	0.770–0.989	0.033
iPTH before PTX (pg/ml)	322.5 ± 186.4	286.5 ± 247.2	0.680	–	–	–
iPTH after PTX (pg/ml)	34.1 ± 36.7	113.0 ± 78.2	0.012	0.965	0.939–0.991	0.009
Ca before PTX (mg/dl)	11.39 ± 0.82	11.52 ± 0.79	0.675	–	–	–
Ca at 1 month after PTX	9.18 ± 1.56	9.48 ± 1.02	0.507	–	–	–
Donor type (living %)	33.3	42.1	0.631	–	–	–
CNI (Cyclosporin %)	22.2	31.6	0.583	–	–	–
BMI (kg/m^2)	22.49 ± 5.40	21.32 ± 3.83	0.444	–	–	–
DM (%)	11.1	26.3	0.544	–	–	–
Type of PTX (total %)	22.2	8.1	0.241	107.93	1.004–11 601	0.050
Pathology (adenoma %)	44.4	23.7	0.734	–	–	–
Acute rejection episodes (%)	33.3	10.5	0.101	–	–	–
Ca & vitamin D supplementation (%)	77.8	58.3	0.292	–	–	–
BK nephropathy (%)	11.1	5.3	0.528	–	–	–
Acute tubulointerstitial nephropathy (%)	11.1	10.5	0.959	–	–	–
Infection events (%)	22.2	18.4	0.795	–	–	–

CI, confidence interval; eGFR, estimated glomerular filtration rate; TPL, transplantation; PTX, parathyroidectomy; iPTH, immunoreactive parathyroid hormone; Ca, calcium; CNI, calcineurin inhibitor; BMI, body mass index; DM, diabetes mellitus.
Renal function impairment was defined as eGFR decrease by more than 25% from the baseline value at 1 month after PTX. Most values were expressed as mean ± standard deviation.
*Univariate logistic regression analysis was used.
†Multivariate logistic regression analysis with a backward stepwise method was used. Age, gender, time from TPL to PTX, baseline eGFR, iPTH after PTX, type of PTX, acute rejection episode, Ca and vitamin D supplementation, BK nephropathy, acute tubulointerstitial nephropathy, and infection events were included in the initial step of multivariate analysis. Variables in the final model were displayed.

Table 4. Outcome of the patients that underwent parathyroidectomy before kidney transplantation.

	Time after kidney transplantation								
	Pre-PTX	Post-PTX*	Pretransplant	7 days	1 month	3 months	6 months	9 months	12 months
SCr (mg/dl)	10.38 ± 3.77	10.14 ± 4.20	10.27 ± 3.69	1.54 ± 1.08	1.16 ± 0.48	1.15 ± 0.34	1.25 ± 0.49	1.29 ± 0.59	1.38 ± 0.92
eGFR (ml/min)	5.78 ± 2.49	6.17 ± 2.61	6.9 ± 6.8	67.9 ± 43.9	77.0 ± 42.3	71.8 ± 37.5	68.3 ± 31.2	67.2 ± 30.6	68.1 ± 32.0
iPTH (pg/ml)	1676.5	273.8	437.2	115.3	118.2	198.4	105.0	82.0	109.3
Ca (mg/dl)	10.67 ± 1.22	9.03 ± 1.67	9.4 ± 1.2	8.7 ± 1.5	9.0 ± 1.5	9.1 ± 1.7	9.6 ± 1.4	9.4 ± 1.0	9.3 ± 1.2
P (mg/dl)	6.2 ± 1.7	2.82 ± 1.31	4.9 ± 1.4	2.4 ± 0.8	2.6 ± 1.1	3.4 ± 1.2	3.5 ± 0.9	3.8 ± 0.9	3.7 ± 0.8
ALP (IU/l)	596.8	882.3	190.7	146.9	186.0	166.6	195.6	166.4	139.1
Hb (g/dl)	10.1 ± 1.3	10.1 ± 2.1	10.7 ± 1.6	10.3 ± 1.7	11.1 ± 1.5	11.6 ± 1.7	12.4 ± 2.0	12.5 ± 2.2	12.4 ± 2.5

PTX, parathyroidectomy; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; iPTH, immunoreactive parathyroid hormone; Ca, calcium; P, phosphate; ALP, alkaline phosphatase; Hb, hemoglobin.
*Post-PTX outcomes were estimated at 1 month after PTX. Most values were expressed as mean ± standard deviation.

post-transplant PTX group was significantly lower than those in the pretransplant PTX group (P = 0.032, by generalized estimating equations adjusted by covariates, Fig. 1b). However, there was no difference in the eGFRs during the first 5 years after transplantation between the late post-transplant PTX group and the pretransplant PTX group (P = 0.351, by generalized estimating equations adjusted by covariates, Fig. 1b).

Discussion

In tertiary hyperparathyroidism, successful PTX can not only prevent various complication of prolonged hypercalcemia but also improve symptoms of established complications through relief of musculoskeletal pain, limb salvage in calciphylaxis, and improvement in bone density [20,21]. As persistent hypercalcemia can lead to

nephrolithiasis and subsequently graft dysfunction, PTX has comprehensive benefits in terms of graft protection [22]. However, previous studies have reported that PTX itself could deteriorate renal allograft function, and result in long-term allograft dysfunction [16,17]. The causes of impaired renal allograft function after PTX remain unclear; however, rapid decline of serum iPTH after PTX can lead to decreased renal perfusion, subsequently causing renal function impairment, because iPTH has a positive hemodynamic effect on renal blood flow and the glomerular filtration rate in both animal models and human data [23,24]. In parallel, we observed a significant decline in both iPTH and eGFR immediately after PTX among the post-transplant PTX patients. Acute deterioration of renal function improved and stabilized after 1 week post-PTX in most patients; however, 11 patients (20%) had persistent renal function impairment. Our findings that both baseline eGFR and iPTH levels after PTX were the significant risk factors for renal function impairment were consistent with the results from previous studies [17,25]. Schwarz *et al.* reported that a higher PTH concentration before PTX, a lower PTH concentration after PTX, a higher delta iPTH decline (%), lower serum Ca levels after PTX, and total PTX with autotransplantation were the significant predictors for renal allograft deterioration among 76 transplant patients [17]. Schlosser *et al.* also showed that poor kidney function at the time of PTX and total PTX compared with subtotal PTX had a risk of impairing allograft function [25]. However, the type of PTX was not statistically significant risk factor in our study, although the impairment group had a trend toward undergoing total PTX more than the nonimpairment group (22.2% vs. 8.1%, respectively, $P = 0.050$).

The risk factors for tertiary hyperparathyroidism have been suggested to be prolonged duration of dialysis therapy and high levels of pretransplant serum Ca, alkaline phosphatase, and iPTH [26]. In parallel, the patients in this study have had a long history of dialysis before kidney transplantation (95.3 ± 47.5, and 135.9 ± 54.8 months, Table 1). The duration of dialysis before transplantation showed a trend toward an increasing risk of persistent hyperparathyroidism after transplantation in the pretransplant PTX group (150.0 ± 56.3 months, with persistent hyperparathyroidism vs. 111.2 ± 50.0 months, without persistent hyperparathyroidism, $P = 0.070$). Furthermore, iPTH concentration before PTX was the independent, significant risk factor for persistent post-transplant hyperparathyroidism in the same group of patients.

PTX at less than 1 year after transplantation had a significant negative impact on renal function during the first 5 years after transplantation compared with pretransplant PTX, whereas PTX after 1–5 years post-transplantation did not. It remains uncertain why the early post-transplant PTX was associated with the worst post-transplant renal function. Although the difference was not statistically significant, the early post-transplant PTX group showed a trend toward higher PTH both before (413.93 + 288.45 vs. 267.66 + 256.99 pg/ml, $P = 0.061$) and after PTX (74.82 + 78.13 vs. 41.12 + 51.89 pg/ml, $P = 0.083$) than the late post-transplant PTX group. These results suggest that the early post-transplant PTX had more severe hyperparathyroidism than the late post-transplant PTX group. The lower eGFRs in the early post-transplant PTX group seemed to be mainly attributed to the eGFR decrease during the first year after transplantation. The negative hemodynamic effect of PTX on renal blood flow might be more detrimental in the first year, when calcineurin inhibitor-induced renal vasoconstriction is prominent [27] and acute rejection occurs most commonly. Further studies are needed to investigate the underlying pathophysiologic mechanisms more clearly.

As decline in iPTH after PTX might lead to a decrease of renal function in an allograft, post-transplant PTX risks deterioration of allograft function, especially in patients with a decreased baseline renal function. Therefore, pretransplant PTX can be considered for the patients that had a high risk for persistent post-transplant hyperparathyroidism, and that could undergo post-transplant PTX. On the other hand, cinacalcet has been suggested as an alternative for PTX in persistent hyperparathyroidism among transplant patients. Schwarz *et al.* reported that cinacalcet had normalized Ca–Phosphorus homeostasis and decreased serum iPTH levels in hypercalcemic kidney transplant patients [28]. PTX could be delayed until 1 year after transplantation under cinacalcet, as the late post-transplant PTX did not have a negative impact on renal allograft function, and post-transplant hyperparathyroidism improves gradually within 1 year after kidney transplantation [3].

This study has several limitations. First, renal function after PTX was measured not by glomerular filtration rate (GFR) using inulin or para-amino-hippuric acid clearance, but by estimated GFR using MDRD equation. Second, we could not clarify the cause of deterioration of renal allograft function after PTX. The kidney biopsy information might be helpful for differential diagnosis for graft dysfunction after PTX. Finally, the retrospective design with the medium sample size and short-term follow-up time in this study require further large-scale, prospective studies with a longer follow-up period to confirm our findings. Despite these limitations, this study included more patients than the previous studies, which included only small numbers of patients (at most 83) [29]. Furthermore, we simultaneously analyzed the impacts of PTX both before and after kidney transplantation, and demonstrated for the first time that only early post-transplant PTX has a greater risk for post-PTX renal impairment.

In summary, early post-transplant PTX, not late post-transplant PTX, has a greater risk of deterioration of allograft function than does pretransplant PTX. Therefore, pretransplant PTX should be considered for patients with severe hyperparathyroidism, who could undergo PTX after transplantation. The prognostic factors for post-PTX renal impairment, such as the baseline renal allograft function and the type of surgery, should be considered before post-transplant PTX, and high-risk patients with a low level of iPTH after PTX should be monitored carefully.

Authorship

Each author's specific contributions to the work are indicated below. HJJ: research design, sample collection, data analysis, statistical analysis, writing of the paper. YJK, HYK, SHB, HJK, WSH, KHH, MSK, YSK, SKP: sample collection, data analysis. TYK, CA: data analysis, statistical analysis. JY: research design, sample collection, data analysis, writing of the paper.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk factors for persistent, post-transplant hyperparathyroidism in patients that underwent parathyroidectomy before kidney transplantation.

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