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HYPERPARATHYROIDISM IN KIDNEY TRANSPLANT CANDIDATES AND POSTOPERATIVE PARATHYROID GLAND FUNCTION IN RECIPIENTS

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Objective: to evaluate the effects of secondary hyperparathyroidism (HPT) in kidney transplantation (KT) candidates on recipients' parathyroid gland function in the first postoperative year. **Materials and methods.** The retrospective cohort study included 210 patients (103 women, 107 men, age 45 ± 9 years) with stage 5 chronic kidney disease (stage 5 CKD, including dialysis-dependent patients), who had undergone cadaveric KT. Biochemical screening before kidney transplantation and in the postoperative period at 3 and 12 months determined serum levels of parathyroid hormone (PTH), calcium, phosphorus, alkaline phosphatase activity, albumin and creatinine using standard methods. PTH levels of 130–595 pg/mL and ≤130 pg/mL were taken as the target level in the pre- and post-transplant periods, respectively. **Results.** Fifty-six KT candidates (group 1) had HPT and 154 (group 2) had the target PTH levels. PTH level was 897 (722; 1136) and 301 (229; 411) pg/mL, respectively, $p < 0.001$. PTH decreased in all recipients at 3 months after KT: by 595 (420; 812) in group 1 and 148 (77; 230) pg/mL in group 2, $p < 0.001$, to 254 (180; 455) and 150 (118; 212) pg/mL, respectively, $p < 0.001$; the target level was detected in 10.7% and 42.2% of recipients, respectively, $p < 0.001$. At 12 months, blood PTH was 171 (94; 239) pg/mL in group 1 and 112 (90; 135) pg/mL in group 2, $p = 0.004$; target level was found in 48.2% and 73.4% of recipients, respectively, $p < 0.001$. Kidney graft function was identical in both recipient groups: acute tubular necrosis in 41.1% and 54.5%; at 3 months, median glomerular filtration rates (GFR) of 60 and 65 mL/min (n.d.); at 12 months, 56 and 54 mL/min (n.d.). Post-transplant PTH levels correlated directly with preoperative levels in both groups and inversely with renal graft function in group 2 recipients. **Conclusion.** HPT in kidney transplant candidates is a major, graft function-independent predictor of excess PTH secretion in recipients, increasing the risk of persistent HPT 1.9-fold, one year after KT.

Keywords: kidney transplantation, parathyroid glands, secondary hyperparathyroidism, chronic kidney disease.

INTRODUCTION

Secondary hyperparathyroidism (HPT) is a common complication associated with CKD. HPT develops following a decline in renal function, which triggers a cascade of physiological and pathophysiological processes leading to excessive PTH release by parathyroid glands (PTG). HPT in CKD patients is a common condition, especially at the dialysis therapy stage. The disease is accompanied by damage to many organs and systems, it significantly worsens patient quality of life and increases mortality. Despite personalized approach and emergence of new medications, there are still challenges in treating secondary HPT [1–5].

Kidney transplantation (KT) is the treatment of choice for stage 5 CKD, and the number of such operations is increasing annually [6]. Patients with varying degrees of severity of secondary HPT among KT candidates have unavoidably resulted from the recent growth in the number of CKD patients, including the dialysis population with a high prevalence of secondary HPT, and the growing number of kidney transplants. A successful KT modifies HPT's trajectory, leading to either complete regression or persistence. The latter adversely affects clinical outcomes in kidney transplant recipients. Recent reports discuss various aspects of posttransplant HPT: risk factors, impact on renal graft function, quality of life and survival of patients [7–11].

The aim of this study was to evaluate the effects of secondary HPT in candidates awaiting KT on recipients' PTG function in the first postoperative year.

MATERIALS AND METHODS

The retrospective cohort single-center study included 210 patients with stage 5 CKD (including dialysis-dependent patients) who underwent cadaveric KT. Patient inclusion criteria: 1. presence of stage 5 CKD (including dialysis-dependent patients); 2. pre-KT PTH level ≥130 pg/mL; 3. successful primary KT not earlier than 12 months ago; 4. functioning kidney graft in the first postoperative year. Non-inclusion/exclusion criteria: 1. history of KT; 2. removal of kidney graft in the first

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postoperative year; 3. parathyroidectomy prior to KT or in the first postoperative year.

The number of men and women included in the study was almost equal. The age of patients ranged from 19 to 70 years. Most patients suffered from various variants of non-diabetic kidney disease (91%). The predominant dialysis modality was hemodialysis. Duration of dialysis therapy ranged from 1 to 158 months; some patients were not placed on dialysis. All patients underwent cadaveric KT. Almost half of the patients had delayed renal graft function that required continuation of dialysis therapy (acute hemodialysis in 4 patients with pre-dialysis CKD). Duration of acute tubular necrosis ranged from 2 to 30 days (Table 1).

Biochemical examination was performed before KT and at 3 and 12 months postoperatively. Standard techniques were used to determine the serum levels of PTH, calcium, phosphorus, total alkaline phosphatase (ALP), albumin and creatinine. PTH levels of 130–585 pg/mL and ≤130 pg/mL were taken as the target level in the pre- and post-transplant period [12–15]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; CKD stages were stratified by eGFR level [16].

Table 1

Clinical characteristics of patients included in the study

Parameter	All patients (n = 210)
Men/women (n (%))	103/107 (49/51)
Age (years, M ± m)	45 ± 9
Body mass index	24.5 ± 3.5
Kidney disease	
Chronic glomerulonephritis (n (%))	94 (44.8)
Congenital nephrotic syndrome (n (%))	46 (21.9)
Chronic tubulointerstitial nephritis (n (%))	24 (11.4)
Diabetic kidney disease (n (%))	19 (9.0)
Kidney disease in systemic diseases (n (%))	10 (4.8)
Other (hypertensive nephrosclerosis, typical/atypical hemolytic uremic syndrome, kidney cancer, nephrolithiasis) (n (%))	17 (8.1)
Dialysis modality	
Hemodialysis (n (%))	145 (69.0)
Peritoneal dialysis (n (%))	34 (16.2)
Hemodialysis + peritoneal dialysis (n (%))	22 (10.5)
No dialysis (n (%))	9 (4.3)
Duration of dialysis therapy (months, [Me (Q1–Q3)])	19 (9; 35)
Kidney graft function	
Immediate (n (%))	107 (51.0)
Delayed (n (%))	103 (49.0)
Duration of acute tubular necrosis (day, [Me (Q1–Q3)]).	6 (3; 12)
Day of minimal blood creatinine recording after KT (day, [Me (Q1–Q3)])	7 (4; 13)

Statistical analysis of the material was performed using the GraphPad v.8.0.1 program. The form of distribution of characteristics was evaluated by the Kolmogorov–Smirnov test. Description of quantitative characteristics was presented in the form of arithmetic mean and standard deviation (M ± SD) in normal distribution, and in the form of median, 25% and 75% quartiles [Me (Q25–Q75)] in asymmetric distribution. Qualitative features were presented as absolute numbers (n) and proportions (%). The Mann–Whitney U test and Student t-test were used to compare quantitative data, while the chi-squared test was used for qualitative features. The strength of association between quantitative characteristics was assessed using Spearman's rank correlation coefficient. Relative risk (RR) with calculation of 95% confidence interval (95% CI) was used as a quantitative measure of effect when comparing relative indicators. The critical level of significance for testing statistical hypotheses in this study was taken to be 0.05.

RESULTS

Characteristics of traditional biochemical markers of secondary HPT in patients with stage 5 CKD (including dialysis-dependent patients) in the preoperative period is presented in Table 2.

PTH levels fluctuated widely (110–2500 pg/mL), and were outside the upper limit of the target interval in almost one third of patients. Serum phosphorus levels in most patients exceeded the reference values, while serum calcium levels were within target levels. Some patients had elevated blood alkaline phosphatase enzyme activity

Table 2

Traditional biochemical markers of HPT before kidney transplantation

Blood parameter	All patients (n = 210)
PTH (pg/mL [Me (Q1–Q3)])	400 (261; 620)
PTH 130–585 pg/mL (n (%))	154 (73.3)
PTH >585 pg/mL (n (%))	56 (26.7)
Phosphorus (mmol/L [Me (Q1–Q3)])	1.74 (1.44; 2.04)
Target level 0.87–1.49 mmol/L (n (%))	70 (33.3)
Hyperphosphatemia (>1.49 mmol/L (n (%)))	140 (66.7)
Hypophosphatemia (<0.87 mmol/L (n (%)))	0
Calcium (mmol/L, [Me (Q1–Q3)])	2.2 (2.3; 2.4)
Target level (2.1–2.6 mmol/L (n (%)))	193 (91.9)
Hypercalcemia (>2.6 mmol/L (n (%)))	9 (4.3)
Hypocalcemia (<2.1 mmol/L (n (%)))	8 (3.8)
Elevated blood AP levels (n (%))	19 (9.0)

Note. PTH, parathyroid hormone; AP, alkaline phosphatase.

(from one and a half to five times the upper limit of the reference interval).

Kidney transplant candidates were split into two groups based on their serum PTH levels. Group 1 included 56 patients with secondary HPT, and group 2 included 154 patients with target PTH levels. The clinical and laboratory characteristics of patient groups in the pre-transplant period are presented in Table 3. Group 1 patients received dialysis therapy for nearly 1.5 times as long. When analyzing routine biochemical markers of secondary HPT, these patients were found to be significantly more likely to have hyperphosphatemia, hypercalcemia and increased serum activity of alkaline phosphatase enzymes.

Three months after KT, PTH levels fell in all patients, fluctuating in the 80–1977 pg/mL range in group 1, and 10–535 pg/mL range in group 2 (Table 4, Fig. 1). The proportion of patients who achieved a PTH ≤130 pg/mL in group 1 was four times lower than in group 2, 10.7% and 42.2%, respectively. Pronounced changes were found in serum phosphorus, which reached normal or even low values in all recipients. The groups did not differ in absolute serum phosphorus levels, but patients with hypophosphatemia were slightly more frequent in group 1. Serum calcium levels remained stable; the incidence of hypercalcemia predominated in group 1 patients. The proportion of patients with increased ALP activity decreased 4-fold in group 1 and 3-fold in group 2; there was no intergroup difference in this parameter.

In the next 9 months, PTH levels further decreased from several to 670 pg/mL in 49 group 1 patients and from few to 221 pg/mL in 96 group 2 patients; the median was 81 (30; 145) and 25 (0; 61), respectively, $p < 0.001$; the remaining patients (7 in group 1 and 58 in group 2) had either an increase or no dynamics. All group 1 patients and 151 patients from group 2 generally showed decreased PTH levels of varying severity during the first postoperative year. This decrease was most pronounced in group 1 patients. At year 1 after the operation, the percentage of patients with the target PTH level was 1.5 times less than in group 2. The probability of normalization of PTG function in the first postoperative year was found to be significantly lower in renal transplant candidates with HPT compared with patients with the target range of pre-transplant serum PTH (Table 5).

Table 3

Clinical and laboratory characteristics of patient groups

Parameter	Patients		p
	Group 1 (n = 56)	Group 2 (n = 154)	
Men/women (n (%))	32/24 (57.1/42.9)	71/83 (46.1/53.9)	NS
Age (years (M ± m))	44 ± 10	45 ± 9	NS
Body mass index (kg^2/cm (M ± m))	24.6 ± 4.1	25.7 ± 4.7	NS
Chronic glomerulonephritis (n (%))	18 (32.1)	75 (48.7)	NS
Congenital nephrotic syndrome (n (%))	13 (23.2)	33 (21.4)	NS
Chronic tubulointerstitial nephritis (n (%))	8 (14.3)	16 (10.4)	NS
Diabetic kidney disease (n (%))	4 (7.1)	15 (9.7)	NS
Kidney disease in systemic diseases (n (%))	3 (5.4)	8 (5.2)	NS
Other (hypertensive nephrosclerosis, typical/atypical hemolytic uremic syndrome, kidney cancer, nephrolithiasis) (n (%))	10 (17.9)	7 (4.6)	0.004
Hemodialysis (n (%))	45 (80.4)	100 (64.9)	0.049
Peritoneal dialysis (n (%))	5 (8.9)	29 (18.8)	NS
Hemodialysis + peritoneal dialysis (n (%))	4 (7.1)	18 (11.7)	NS
No dialysis (n (%))	2 (3.6)	7 (4.6)	NS
Duration of dialysis therapy (months, [Me (Q1–Q3)])	26 (12; 44)	16 (8; 34)	0.009
Blood PTH, pg/mL [Me (Q1–Q3)]	897 (722; 1136)	301 (229; 411)	<0.001
Blood phosphorus, mmol/L [Me (Q1–Q3)]	1.92 (1.62; 2.31)	1.72 (1.42; 1.97)	<0.001
Target level (0.87–1.49 mmol/L) (n (%))	6 (10.7)	65 (42.2)	<0.001
Hyperphosphatemia (>1.49 mmol/L) (n (%))	50 (89.3)	89 (57.8)	<0.001
Hypophosphatemia (<0.87 mmol/L) (n (%))	0	0	NS
Calcium (total) blood, mmol/L [Me (Q1–Q3)]	2.3 (2.2; 2.5)	2.3 (2.2; 2.4)	NS
Target level (2.1–2.6 mmol/L) (n (%))	46 (82.1)	147 (95.5)	0.004
Hypercalcemia (>2.6 mmol/L) (n (%))	6 (10.8)	3 (1.9)	0.017
Hypocalcemia (<2.1 mmol/L) (n (%))	4 (7.1)	4 (2.6)	NS
Elevated blood AP levels (n (%))	12 (21.4)	7 (4.5)	<0.001

Note. PTH, parathyroid hormone; AP, alkaline phosphatase; p, statistical significance of differences between groups 1 and 2 parameters; NS, not significant.

Changes in serum phosphorus and calcium levels were minimal. Serum phosphorus in the majority of patients was within the reference range, a few patients in group 2 had hyperphosphatemia, while hypophosphatemia prevailed in group 1 patients. Serum calcium remained relatively stable throughout the entire follow-up

Table 4

Traditional biochemical markers of HPT in patients before KT, 3 and 12 months after KT

	Group 1 (n = 56)			Group 2 (n = 154)			p_1	p_2
	Pre-KT	3 months after KT	12 months after KT	Pre-KT	3 months after KT	12 months after KT		
Blood PTH, pg/mL [Me (Q1–Q3)]	897 (722; 1036)	254 (180; 455)*	171 (94; 239)** #	301 (229; 411)	150 (118; 212)*	112 (90; 135)** #	<0.001	0.004
ΔPTH (pg/mL)	0	595 (420; 812)	853 (705; 1178)	0	148 (77; 230)	196 (117; 340)	<0.001	0.001
Blood PTH ≤130 pg/mL (n (%))	0	6 (10.7)*	27 (48.2)**	0	65 (42.2)*	113 (73.4)** #	<0.001	<0.001
Blood phosphorus, mmol/L [Me (Q1–Q3)]	1.92 (1.62; 2.31)	0.97 (0.78; 1.21)*	0.94 (0.79; 1.05)#	1.72 (1.42; 1.97)	1.04 (0.91; 1.21)*	1.09 (0.99; 1.35)	NS	0.002
Hyperphosphatemia (>1.49 mmol/L) (n (%))	50 (89.3)	0*	0#	89 (57.8)	0*	6 (3.9)#	NS	NS
Hypophosphatemia (<0.87 mmol/L) (n (%))	0	18 (32.1)*	20 (35.7)#	0	29 (18.8)*	22 (14.3)#	0.051	0.001
Calcium (total) blood, mmol/L [Me (Q1–Q3)]	2.3 (2.2; 2.5)	2.5 (2.3; 2.6)	2.5 (2.4; 2.7)	2.3 (2.2; 2.4)	2.4 (2.3; 2.5)	2.4 (2.3; 2.5)	NS	NS
Hypercalcemia (>2.6 mmol/L) (n (%))	6 (10.8)	8 (12.7)	11 (19.6)	3 (1.9)	1 (0.7)	2 (1.3)	<0.001	<0.001
Hypocalcemia (<2.1 mmol/l) (n (%))	4 (7.1)	0	0	4 (2.6)	0	0	NS	NS
Elevated blood AP levels (n (%))	12 (21.4)	3 (4.8)*	5 (8.9)	7 (4.5)	2 (1.4)	1 (0.6)	NS	0.007

Note. PTH, parathyroid hormone; KT, kidney transplantation; ALP, alkaline phosphatase; *, differences are statistically significant between parameters before and 3 months after KT; **, differences statistically significant between parameters 3 and 12 months after KT; #, differences are statistically significant between parameters before and 12 months after KT; p_1, statistical significance of differences between groups 3 months after KT; p_2, statistical significance of differences between groups 12 months after KT; NS, not significant.

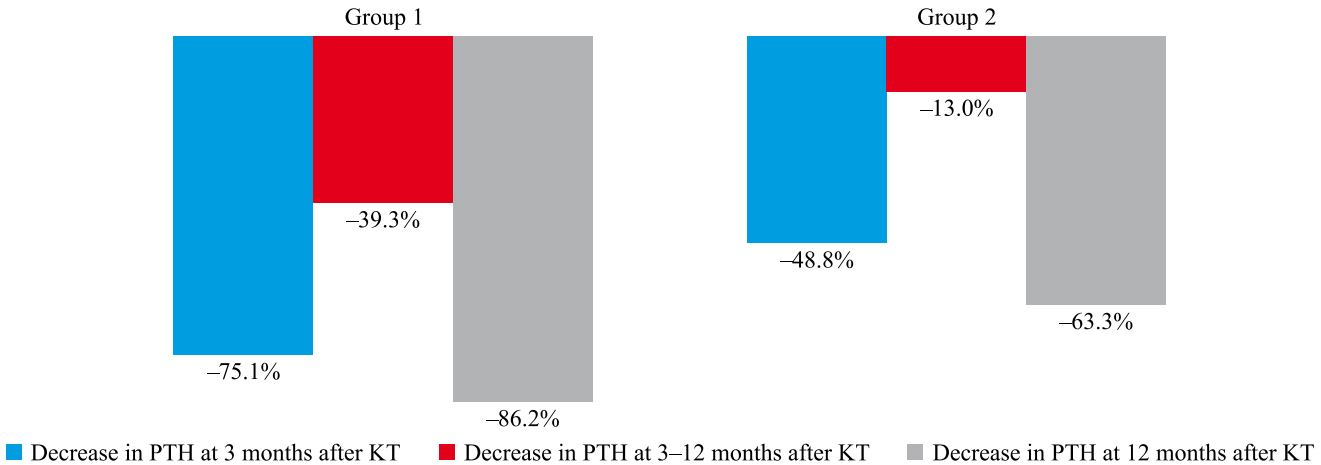

Fig. 1. Level of decrease in blood PTH levels in kidney transplant recipients during the first postoperative year. Differences between groups are statistically significant for each time interval; KT, kidney transplantation

time; hypercalcemia, as in the early postoperative period, was found more often in group 1 patients. Patients with increased ALP activity became more frequent in group 1.

When analyzing initial kidney graft function, differences between the groups was on duration of acute tubular necrosis only, which was longer in group 1 patients. The two remaining parameters – onset of kidney function and the day minimum serum creatinine level was detected – were identical. There were no differences in serum creatinine levels and eGFR between the groups at 3 or 12 months (Table 6). There were no intra- and intergroup differences in patient distribution by CKD stage (Fig. 2).

Table 7 presents data from correlation analysis for post-transplant PTH levels at 3 and 12 months.

In group 1 patients, postoperative PTH levels had a moderately close direct association with preoperative PTH levels and there was no such relationship with kid-

Table 5

Effect of HPT in KT candidates on normalization of parathyroid gland function in the first year after surgery

Factor	Normal thyroid function in the HPT group (n = 56)	Normal thyroid function in the no HPT group (n = 154)	Relative risk [95% CI]	p
At 3 months post KT	6 (10.7%)	65 (42.2%)	0.254 [0.116; 0.522]	<0.0001
At 1 year post KT	27 (48.2%)	113 (73.4%)	0.657 [0.480; 0.851]	0.0009

Table 6

Kidney graft function in the first year after surgery

Parameter	Patients		p_2
	Group 1 (n = 56)	Group 2 (n = 154)	
Initial kidney graft function Immediate (n (%)) Delayed (n (%))	 23 (41.1) 33 (58.9)	 84 (54.5) 70 (45.5)	 NS NS
Duration of acute tubular necrosis (days, [Me (Q1–Q3)])	7 (4; 15)	6 (3; 9)	0.034
Day of minimal blood creatinine recording after KT (day, [Me (Q1–Q3)])	7 (4; 18)	7 (4; 13)	NS
Blood creatinine at 3 months (μmol/L [Me (Q1–Q3)]) Blood creatinine after 12 months (μmol/L [Me (Q1–Q3)])	117 (88; 146) 123 (110; 146) $p_1 = 0.311$	110 (78; 124) 120 (96; 140) $p_2 = 0.019$	NS NS
eGFR at 3 months (mL/min) eGFR at 12 months (mL/min)	60 (46; 77) 56 (47; 63) $p_1 = 0.228$	65 (51; 88) 54 (46;70) $p_1 = 0.02$	NS NS
eGFR <60 mL/min at 3 months (n (%)) eGFR <60 mL/min at 12 months (n (%))	27 (48.2) 36 (64.3) $p_1 = 0.128$	74 (48.1) 94 (61.0%) $p_1 = 0.03$	NS NS

Note. eGFR, estimated glomerular filtration rate; p_1, statistical significance of differences between parameters at 3 and 12 months; p_2, statistical significance of differences between group 1 and 2 parameters; NS, not significant.

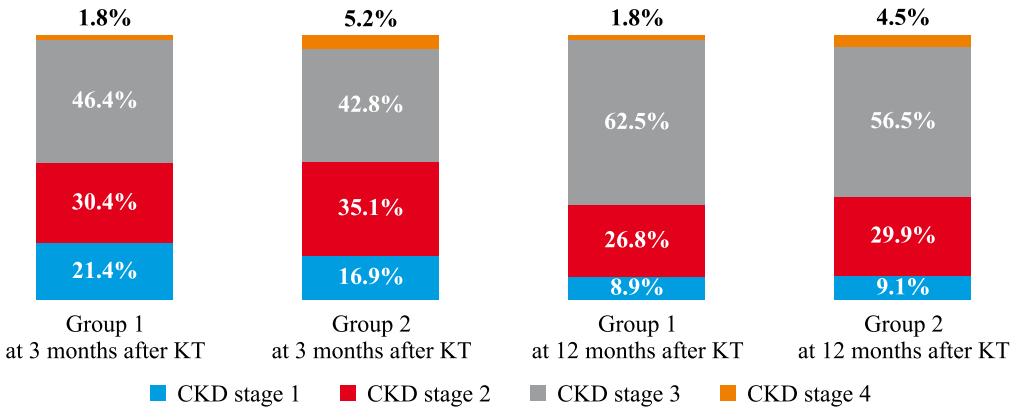

Fig. 2. Distribution of kidney transplant recipients by CKD severity. Differences between groups are not statistically significant for each time interval; KT, kidney transplantation

ney graft function at 3 months and by the end of the first postoperative year. In group 2 patients, there was also a direct correlation between post- and pre-transplant PTH levels, which was closer at 3 months following surgery. Unlike group 1 patients, this patient cohort showed a greater correlation between post-transplant PTH levels and renal graft function at 12 months of operation. In both groups, there was no association between post-transplant PTH levels and length of dialysis sessions.

DISCUSSION

Excessive synthesis and release of PTH is a natural reaction of PTG to various metabolic changes that develop in CKD patients – hypocalcemia, hyperphosphatemia, vitamin D deficiency, accumulation of fibroblast growth factor-23 in the blood, and others. Persistent excessive release of PTH with the formation of PTG hyperplasia leads to secondary HPT. Due to its prevalence, severe HPT often occurs in patients undergoing KT. In our study, 26.7% of such patients had pre-transplant PTH levels that persistently remained above 600 pg/mL.

Successful KT levels out the pathophysiological processes that lead to secondary HPT. It spontaneously normalizes PTG function within six months to a year, sometimes longer. However, this process does not occur in all patients; it may be absent in some patients due to formed structural changes in PTG [9, 17]. In general, among all the patients we observed, the incidence of post-transplant HPT at three months after surgery was 66.2% (89.3% in patients with previous HPT and 57.8% in patients without HPT); by the end of the first year, it decreased twofold, 33.3% (51.8% in patients with previous HPT and 26.6% in patients without HPT).

It has been widely shown that patients who have kidney transplants, including those who do not receive dialysis therapy, have a high incidence of HPT both in

Table 7

Correlation of PTH levels in KT recipients

Parameter	Group 1 (n = 56)		Group 2 (n = 154)	
	Post-KT PTH levels (pg/mL)			
	At 3 months	At 12 months	At 3 months	At 12 months
Pre-KT PTH levels (pg/mL)	r = 0.347 p = 0.009	r = 0.379 p = 0.005	r = 0.508 p < 0.001	r = 0.216 p = 0.007
Post-KT PTH levels at 3 months (pg/mL)	–	r = 0.542 p < 0.001	–	r = 0.581 p < 0.001
ΔPTH (0–3 months) (pg/mL)	r = –0.107 p = 0.433	r = 0.206 p = 0.134	r = –0.071 p = 0.386	r = 0.003 p = 0.971
ΔPTH (0–3 months) (%)	r = –0.780 p < 0.001	r = –0.293 p = 0.031	r = –0.516 p < 0.001	r = –0.019 p = 0.815
ΔPTH (0–12 months) (pg/mL)	–	r = –0.105 p = 0.449	–	r = –0.410 p < 0.001
ΔPTH (0–12 months) (%)	–	r = –0.399 p = 0.003	–	r = –0.509 p < 0.001
ΔPTH (3–12 months) (pg/mL)	–	r = 0.189 p = 0.162	–	r = –0.324 p < 0.001
ΔPTH (3–12 months) (%)	–	r = 0.114 p = 0.402	–	r = –0.699 p < 0.001
Duration of dialysis therapy (months)	r = –0.097 p = 0.478	r = 0.219 p = 0.104	r = 0.052 p = 0.523	r = –0.083 p = 0.306
Duration of acute tubular necrosis (days)	r = 0.318 p = 0.017	r = 0.440 p < 0.001	r = 0.134 p = 0.099	r = 0.047 p = 0.583
Minimum creatinine level (day)	r = 0.210 p = 0.124	r = –0.008 p = 0.952	r = 0.251 p = 0.002	r = 0.157 p = 0.062
Creatinine level at 3 months (μmol/L)	r = 0.201 p = 0.144	r = 0.163 p = 0.24	r = 0.186 p = 0.021	r = 0.246 p = 0.002
Creatinine level at 12 months (μmol/L)	–	r = –0.044 p = 0.749	–	r = 0.474 p < 0.001
eGFR at 3 months (mL/min)	r = –0.205 p = 0.129	r = –0.139 p = 0.308	r = –0.118 p = 0.146	r = –0.172 p = 0.033
eGFR at 12 months (mL/min)	–	r = 0.036 p = 0.799	–	r = –0.292 p < 0.001

Note. PTH, parathyroid hormone; ΔPTH, magnitude of parathyroid hormone reduction; eGFR, estimated glomerular filtration rate; NS, not significant.

the early and late periods following surgery [7, 17–19]. In our study, patients with preoperative secondary HPT had higher mean PTH levels at year following KT, and the percentage of patients with the target PTH levels was lower than in patients without HPT. However, group 1 patients had a significantly higher PTH reduction than group 2 patients. A similar pattern of dependence of HPT persistence after KT on preoperative PTH levels has been established by other teams of authors [8, 18–20].

It should be noted that in our study, we used the pre-transplant range of the target serum PTH level of 130–585 pg/mL (2–9 upper limits of the reference interval) proposed by international guidelines (Kidney Disease Improving Global Outcomes, KDIGO) and the post-transplant level of less than 130 pg/mL (2 upper limits of the reference interval) previously proposed by some authors [12–15]. At the same time, some recent foreign studies have used lower serum PTH levels as a diagnostic criterion for pre- and post-transplant HPT [18, 19]. This changes the data on HPT prevalence in kidney transplant candidates and recipients and complicates the process of comparing study findings.

Taken together, these data emphasize the importance of early diagnosis, prevention and adequate treatment of secondary HPT in kidney transplant candidates to prevent persistent post-transplant HPT. Timely detection of secondary HPT in CKD patients on the KT waitlist is ensured by dynamic examination of PTG function and associated mineral and bone metabolism parameters, especially since there are no early clinical manifestations of the disease. International guidelines (KDIGO) recommend aggressive treatment of severe HPT before KT and, if drug therapy is ineffective, parathyroidectomy (PTx), while the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and Russian national guidelines provide no information in this regard [21–23]. Several studies have demonstrated the benefits of performing PTx in patients with CKD and severe HPT prior to kidney transplantation. For instance, in comparison to patients receiving cinacalcet, these patients have better controllability of HPT, lower risk of tertiary HPT, lower post-transplant PTH levels and the less medical care, compared with patients receiving cinacalcet [24]. On the contrary, where PTx is performed, kidney graft function has been found to worsen in the postoperative period [25, 26].

Renal graft function, another risk factor for posttransplant HPT that has been established in multiple studies, was not entirely confirmed by this observation [27, 28]. Serum creatinine levels and eGFR were identical in both groups of patients over the course of the first year following surgery. Correlation analysis in patients with HPT before KT revealed no association between post-transplant PTH levels and renal graft function in the first postoperative year, whereas patients with target blood PTH levels before surgery showed such an association. This result may be due to the short follow-up period. It is very likely that longer follow-up could reveal a correlation between posttransplant PTH levels and renal graft function in patients with preoperative HPT.

Other risk factors for postoperative HPT have been established in some cases [7, 9, 18]. In our study as well as in a study by Sutton W. et al. [18], there was no evidence of an association between posttransplant serum PTH and duration of preoperative dialysis treatment, although some authors have pointed out that such a relationship exists [8, 20].

So, preoperative secondary HPT in patients with CKD is the predominant factor in excessive PTH secretion and persistent posttransplant HPT. The impact of the latter on KT outcomes is debated. A number of studies have reported a deterioration in quality of life and increased risk of mortality in recipients with HPT.

Studies on the association between posttransplant HPT and kidney graft function are of particular importance [10, 11, 17, 29–31]. A recently published study by Molinari et al. [7] demonstrated a close association between high PTH levels in the first year after KT and long-term kidney graft loss. The exact mechanism by which PTH damages kidney grafts is not entirely understood. Experimental studies suggest that it affects renal blood flow, i.e., dilation of supply and constriction of efferent arterioles, which leads to glomerular hyperfiltration [32].

A clinical observation in patients with transplanted kidney who underwent PTx in the early postoperative period found a decrease in effective renal blood flow and GFR, reflecting a close relationship between the hemodynamic effect of PTH and renal function [33]. The longer duration of acute tubular necrosis observed in our recipients with pre-operative HPT, with the same incidence in both groups, was most likely caused by the relationship between the hemodynamic effect of PTH and renal function. Another possible mechanism of progressive graft dysfunction on the background of postoperative HPT is renal vasoconstriction, impaired urine concentration, and renal resistance to vasopressin caused by hypercalcemia; in our study, such patients were orders of magnitude more numerous among those with pre-transplant HPT [34]. In addition, high serum PTH levels are involved in renal fibrosis, vascular calcification, immunodeficiency and anemia, which may also adversely affect renal graft function [35].

In addition to worsening renal graft function, HPT in recipients is accompanied by a high risk of bone fractures and all-cause mortality [10, 13]. Obtained results on the adverse effect of persistent HPT on the posttransplant period justify the expediency of monitoring PTH levels in kidney recipients in order to develop an algorithm for the prevention and treatment of this disease.

Limitations of this study include (1) retrospective design; (2) generalization of results from a single center;

and (3) analysis of only routine markers of mineral bone disease associated with CKD.

CONCLUSION

HPT is a common complication in CKD patients, occurring in kidney transplant candidates. The disease is the main graft function-independent predictor; it prevents patients' PTG function from normalizing in the first postoperative year. Early detection, prevention, and adequate treatment of secondary HPT should be prioritized while preparing kidney transplant candidates. In the follow-up of kidney transplant recipients, monitoring PTH levels is advised to prevent and treat posttransplant HPT.

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