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Original Article

Parathyroidectomy for Tertiary Hyperparathyroidism: A Single-Center Experience

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ABSTRACT

Introduction: Tertiary hyperparathyroidism (THPT) refers to the development of hypercalcemia and hyperparathyroidism following a prolonged period of secondary hyperparathyroidism. THPT is most commonly observed in patients after successful kidney transplantation (KTx). The treatment guidelines for post-KTx THPT are still unclear; thus, this study aimed to examine patients who underwent parathyroidectomy (PTx) for THPT and to assess the effects of PTx on long-term graft function.

Methods: We performed a retrospective study of patients who underwent PTx for THPT between 2009 and 2017 at our institution. Levels of serum calcium (Ca) and intact-parathyroid hormone (i-PTH) were measured before and after PTx (one day, one month, three months, six months, one year, and three years) to evaluate the effects of PTx. Estimated glomerular filtration rate (eGFR) was measured to investigate the effect on graft function after PTx.

Results: Seven males and six females were included in this study. The post-PTx levels of serum Ca and i-PTH significantly decreased at one day compared with the pre-PTx levels ($p < .001$). The mean eGFR level decreased at three and six months after PTx. However, at one year post-PTx, the eGFR level had improved to the pre-PTx level. There was no recurrence or loss of graft function during a 58-month follow-up period.

Conclusions: After PTx, the levels of serum Ca and i-PTH significantly improved. The level of eGFR tended to decrease within the first year. We recommend that clinicians follow-up closely with PTx patients during the first year post-PTx due to unstable renal function.

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KEYWORDS: tertiary hyperparathyroidism, parathyroidectomy

Introduction

Tertiary hyperparathyroidism (THPT) is described as persistent hyperparathyroidism, from chronic renal failure, with hypercalcemia. The condition has been reported to occur within the first year in up to 50% of patients who undergo kidney transplantation (KTx), and within four years in about 17% of these patients.[1, 2] The occurrence of THPT is thought to be related to the severity of pretransplant hyperparathyroidism[3] and the duration of dialysis prior to transplantation.[1, 4, 5]

The symptoms and signs of THPT (i) may be similar to

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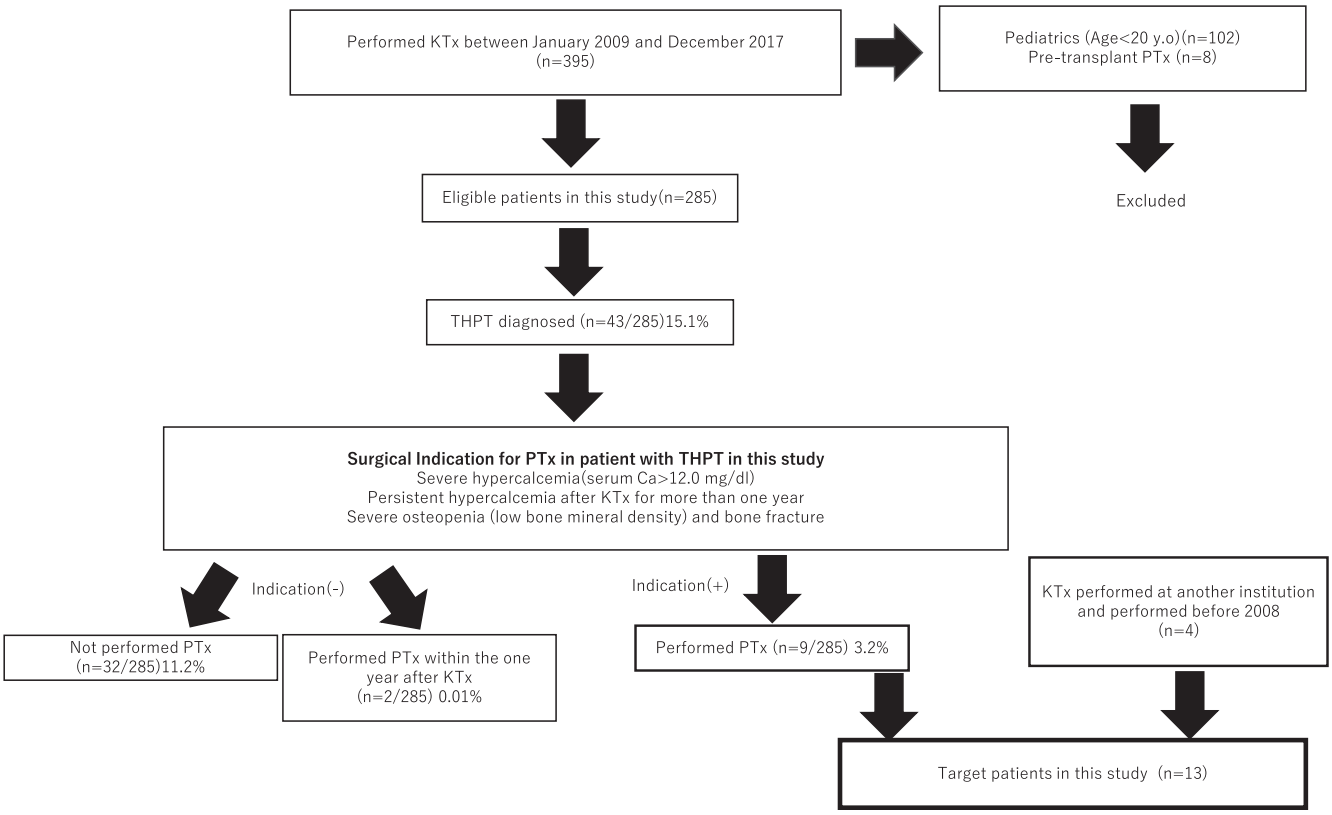

Fig. 1 Study flow diagram.

those of primary hyperparathyroidism, (ii) are attributed to the level of parathyroid hormone (PTH) or the level of hypercalcemia, and (iii) can include bone pain, decreased bone mineral density, fractures, pruritus, nephrolithiasis, peptic ulcer disease, pancreatitis, soft tissue or vascular calcifications, muscle weakness, mental status change, and impaired graft function.[6)]

There are neither evidence-based guidelines for the treatment of THPT nor large trials comparing interventions. The main indication for treatment is persistent hypercalcemia and/or an increased PTH level, and the primary treatment modality is parathyroidectomy (PTx). Another potential treatment option for hyperparathyroidism is medical treatment with calcimimetics such as cinacalcet. However, calcimimetics have not been approved for treating THPT in Japan.

Most previous studies have evaluated graft function after PTx within the first year. Few studies have evaluated long-term graft function after PTx. Therefore, the aims of this study were to examine patients who underwent PTx for THPT after KTx and to assess the effects of PTx on long-term graft function.

Patients and Methods

We conducted a retrospective study of patients who underwent KTx at our institution from January 2009 to December 2017. At our institution, 395 patients underwent KTx during the past nine years. Patients who underwent pretransplant PTx (n = 8) and pediatric patients (age < 20 years, n = 102) were excluded from the study. Of a total of 285 eligible patients, 43 patients (15.1%) were diagnosed with THPT after KTx. PTx along with this study criterion was performed in nine patients (3.2%) and was not performed in 32 patients (11.2%). Two patients underwent PTx after KTx within the first year; these patients were excluded from this study. Four patients with KTx at another institution and with KTx before 2008 were added to the target patients. Fig. 1 shows the study flow diagram.

Most cases of hypercalcemia with THPT improved within the first year after KTx. Park et al. recommended that PTx should be considered one year after KTx.[7)] Therefore, the target patients in this study were patients with severe hypercalcemia (serum Ca > 12.0 mg/dL), persistent hypercalcemia after KTx for more than one year, and severe osteopenia (low bone mineral density) and bone

Table 1 Patients' characteristics

Gender	Male	7
	Female	6
Cause of renal failure	Primary glomerulonephritis	6
	Congenital disease	2
	Unknown	5
Type of dialysis	Hemodialysis	11
	Peritoneal dialysis	2
Duration of dialysis (y)	Median	18
	Range	10-35
Type of renal graft origin	Living donor	9
	Deceased donor	4
Number of times the patients underwent KTx	First	10
	Second	3
Treatment medical history	Cinacalcet use	8
	PEIT/PMIT performed	9

KTx: kidney transplantation
PEIT: percutaneous ethanol injection therapy
PMIT: percutaneous maxacalcitol injection therapy

fracture.

Data collected and evaluated for this study included patient demographics; cause of renal failure; type and duration of dialysis; type of renal graft origin; number of times the patient underwent KTx; medical treatment history for hyperparathyroidism before PTx; duration from KTx to PTx; pre-PTx levels of serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), and intact PTH (i-PTH); indication for PTx; symptoms; type of operation; postoperative complications; pathological findings; and outcomes. The accuracy of the data was verified by reviewing selected medical records of all the patients.

To assess the effects of PTx, the serum Ca and i-PTH levels were observed before PTx, and at one day, one month, three months, six months, one year, and three years after PTx. To assess graft function, the estimated glomerular filtration rate (eGFR) was observed before PTx, and at one month, three months, six months, one year, and three years after PTx. To the extent possible, we collected data regarding serum Ca, P, and i-PTH levels before KTx to assess the severity of pretransplant hyperparathyroidism.

Technetium-99 m sestamibi scintigraphy, computed tomography, and ultrasound examination were performed for all patients routinely before PTx. The surgical treatment for THPT involved either total parathyroidectomy with autograft (total PTx with AG) or subtotal PTx. All PTx surgeries were performed via cervical incision. For autograft, a pocket was made in the brachioradialis muscle of the forearm without an A-V shunt, and a piece of parathyroid tissue was placed in the pocket. Approximately 90-100 mg of parathyroid tissue was autografted. All surgeries were performed by the four surgeons at our institution.

All statistical analyses were performed using JMP version 11 (SAS Institute, Inc., Cary, NC, USA). The Student's *t*-test was used to analyze continuous parametric data, and the Wilcoxon signed rank test was used for nonparametric data. A p-value of less than. 05 was considered statistically significant.

The study protocol was approved by the Ethical Committee of our university with number 26-256 and was conducted in accordance with the tenets of the Declaration of Helsinki (1975) and its later amendment (1983); each patient provided informed consent.

Results

A total of seven males and six females were included in this study. The characteristics of all 13 patients are summarized in Table 1. The causes of renal failure were primary glomerulonephritis (n = 6), congenital disease (n = 2), and unknown (n = 5). Eleven patients received hemodialysis, and two patients received chronic ambulatory peritoneal dialysis. The median duration of dialysis was 18 (range: 10-35) years. Four patients received allografts from deceased donors, and nine patients from living donors. Three patients underwent a second KTx because they experienced loss of graft function after the first KTx. Eight patients received cinacalcet as medical treatment before

Table 2 Result of parathyroidectomy

Age at PTx	Median (range)	46 (37-67) y
Duration from KTx to PTx	Median (range)	63 (12-267) months
Serum Ca	Median (range)	10.7 (10.0-12.2) mg/dL
Serum P	Median (range)	2.3 (1.5-2.7) mg/dL
Serum ALP	Median (range)	303 (162-701) U/L
Intact PTH	Median (range)	245 (129-1240) pg/dL
Symptoms	Soft tissue calcification	3
	Decrease of bone density	2
	Arthralgia	1
	Asymptoms	6
Reason for PTx	Severe or persistent hypercalcemia	13
	Bone and joint pain	1
	Bone fracture	1
Maintenance Immunosuppression	Steroids	13
	Everolimus	2
	Cyclosporin A	3
	Tacrolimus	8
	Imuran	1
	Mycophenolate mofetil	8
Type of operation	Total PTx with autograft	11
	Subtotal PTx	2
Length of operation	Median	173 min
	Range	146-262 min
Bleeding during PTx	Median	34 mL
	Range	8-199 mL
Postoperative complications	Bleeding after PTx	0
	Permanent recurrent nerve palsy	0
	Need for vitamin D replacement by mouth	11
Pathological findings	Diffuse hyperplasia	13

PTx: parathyroidectomy
KTx: kidney transplantation
ALP: alkaline phosphatase
PTH: parathyroid hormone

PTx. Nine patients received percutaneous ethanol injection therapy and/or percutaneous maxacalcitol injection therapy prior to PTx.

The results of PTx are shown in Table 2. Patients were followed up for a median of 58 (range: 22-107) months after PTx. The median age at PTx was 46 (range: 37-67) years. The median duration from KTx to PTx was 63 (range: 12-267) months. All patients had persistent hypercalcemia for more than one year after KTx; of these, seven patients (54%) had symptomatic THPT while six patients (46%) were asymptomatic. Three patients developed calcification of soft tissue. Two patients experienced a decrease in bone mineral density, and two patients reported arthralgia. All patients underwent PTx due to severe or persistent hypercalcemia after KTx; in addition, one patient underwent PTx due to bone fracture while another underwent PTx due to bone and joint pain. Immunosuppression and steroids were utilized and were continuously used among all patients within the perioperative period.

Eleven patients underwent total PTx with AG, while two patients underwent subtotal PTx. The median operating time was 173 (range: 146-262) min, and the median amount of blood loss during surgery was 34 (range: 8-199) mL. There were no postoperative deaths, morbidity of bleeding after the operation, or permanent recurrent nerve palsy. However, at the last follow-up, 11 patients required oral vitamin D (VitD) replacement, and two patients were eucalcemic without VitD replacement after PTx. According to microscopic examination, all patients had diffuse hyperplastic glands. The preoperative and postoperative data are shown in Fig. 2.

In patients who underwent PTx, the median±standard

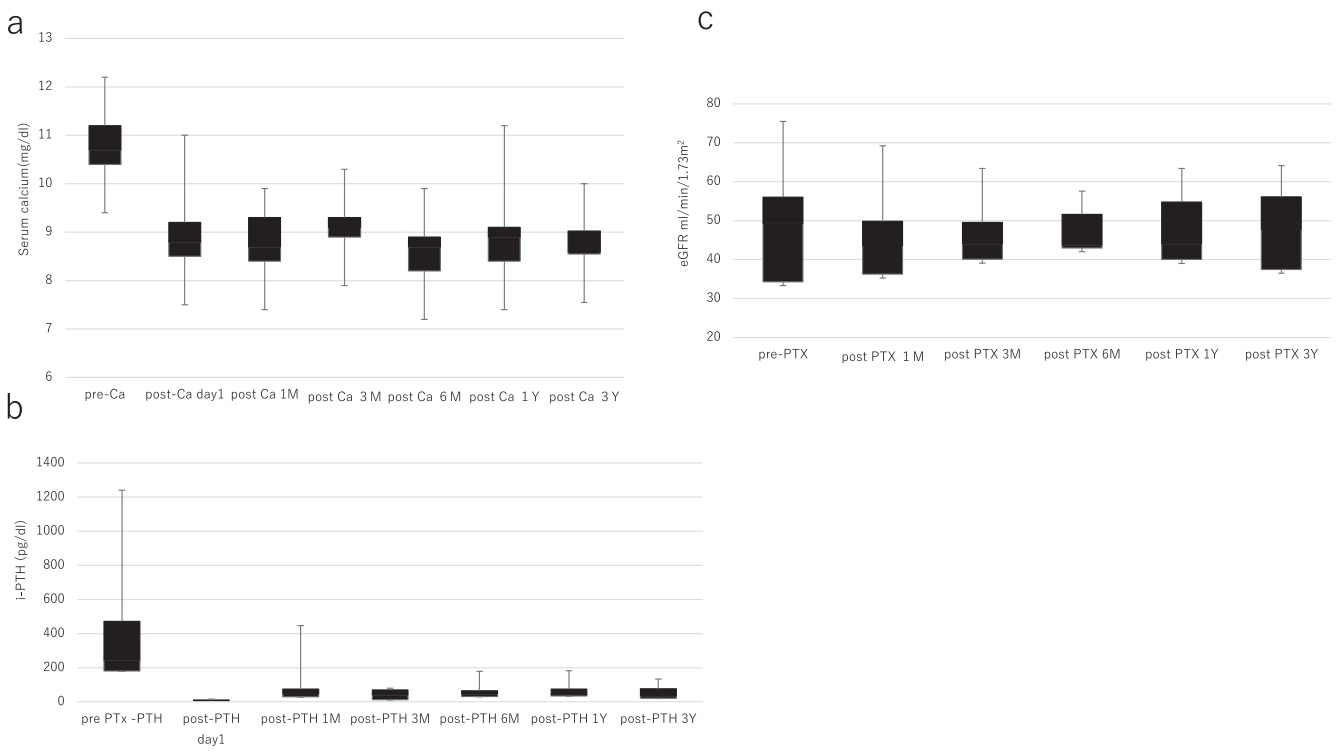

Fig. 2 Median ± standard error of (a) serum calcium, (b) intact PTH, and (c) eGFR.

deviation (SD) values of serum Ca decreased rapidly and significantly from 10.7±0.7 mg/dL before PTx to 8.8 ± 0.90 mg/dL at one day ($p < .001$), 8.7 ± 0.97 mg/dL at one month ($p < .001$), 9.1 ± 0.69 mg/dL at three months ($p < .001$), 8.7 ± 0.96 mg/dL at six months ($p < .001$), 8.9 ± 0.98 mg/dL at one year ($p < .001$), and 8.8 ± 0.91 mg/dL at three years ($p < .001$). The level of i-PTH decreased similarly, from 245 ± 373 pg/dL before PTx to 6.0 ± 4.5 pg/dL at one day ($p = .008$), 50 ± 114.6 pg/dL at one month ($p = .008$), 41 ± 27.9 pg/dL at three months ($p = .004$), 46 ± 46.2 pg/dL at six months ($p = .004$), 41 ± 56.6 pg/dL at one year ($p = .004$), and 36 ± 43.9 mg/dL at three years ($p = .004$). The level of eGFR did not change significantly within the first one month, from 49.3 ± 15.9 mL/min/1.73 m^2 before PTx to 43.7 ± 15.2 mL/min/1.73 m^2 at one month ($p = .21$). However, at three and six months, the levels of eGFR decreased significantly, from 44.1 ± 15.0 mL/min/1.73 m^2 at three months ($p = .02$) to 43.8 ± 13.0 mL/min/1.73 m^2 at six months ($p = .05$). At one year and three years after PTx, there were no significant changes in eGFR from before PTx, with 44.1 ± 14.6 mL/min/1.73 m^2 at one year ($p = .1$) and 47.8 ± 17.7 mg/dL at three years ($p = .4$).

During the median follow-up period of 58 (range: 22-107) months, there was no recurrence of THPT or PTx-related deterioration of graft function, and death.The data for pre-KTx levels of serum Ca and P were confirmed for 11 of 13 patients, and the levels of i-PTH were confirmed for eight patients (Table 3). The median ± SD values of serum Ca and P before KTx were 9.6 ± 0.64 and 5.54 ± 1.09 mg/dL, respectively. The median ± SD value of i-PTH levels before KTx was 598.5 ± 358 pg/dL.

Discussion

THPT is a complication that can occur among patients undergoing KTx, and it may increase the risk of graft loss and mortality. In this study, the levels of serum Ca and i-PTH significantly improved after PTx. The levels of eGFR decreased within the first year. However, one year after PTx, the levels of eGFR had improved to the same level as before PTx. There were no recurrences of THPT or loss of transplant kidney.

For inclusion in this study and an indication of PTx, patients were required to have persistent hypercalcemia for at least one year after KTx. In a literature review by Tang et al.,[8] which summarized 13 reports, all studies required persistent hypercalcemia as an indication of PTx, whether symptomatic or asymptomatic. On the other hand, a few studies required an elevated serum PTH in addition to hypercalcemia. Although an elevation of i-PTH was defined in our study as not an indication of PTx, all the included

Table 3 Data before KTx

Case	Age/ gender	Duration of HD (Y)	Serum Ca before KTx (mg/dL)	Serum P before KTx (mg/dL)	Intact PTH before KTx (pg/dL)
1	52/M	18	9.7	6	224
2	42/M	12	8.7	4.3	277
3	49/F	10	9	7.4	522
4	46/M	18	9.2	5.2	675
5	64/M	18	9.6	4.1	837
6	63/F	10	8.3	6.8	988
7	37/M	16	9.6	5.4	1180
8	44/M	20	10.2	4.9	NA
9	59/F	31	10.1	5.6	NA
10	43/F	14	9.9	7	NA
11	67/M	25	NA	NA	NA
12	45/F	35	NA	NA	NA
13	42/F	19	10.3	4.8	276
Average			9.51	5.13	622
Range			8.7-10.3	4.1-7.4	224-1180

KTx: kidney transplantation
HD: hemodialysis
NA: not available

patients did have highly elevated levels of i-PTH.

Several studies have reported that the long-term duration of dialysis is a risk factor of PTx for THPT. Nakamura et al. reported that the mean duration of dialysis for patients awaiting KTx from a living donor was three years.[9] In our study, the median duration of dialysis before PTx was 18.9 years. From this result, it was supported that the long-term duration of dialysis was one of the risk factors for PTx in THPT patients.

Previous studies have also reported that the occurrence of THPT was related to the severity of pretransplant hyperparathyroidism.[1, 4, 5] In our study, the pre-KTx levels of serum Ca and P were calculated in 11 patients, and the pre-KTx level of i-PTH was calculated in eight patients. In spite of very high pre-KTx levels of i-PTH and serum P, the levels of serum Ca were nearly within the normal range. Furthermore, many of the patients were prescribed cinacalcet before PTx. We concluded that most of the patients who underwent PTx for THPT were in severe pretransplant hyperparathyroidism, although they were using cinacalcet.

The recommended extent of resection (total or subtotal PTx) is still controversial. From a review of 13 studies, Tang et al. summarized that there were no differences in the recurrence rates between patients who underwent total or subtotal PTx.[8] Yamamoto et al. recommended total PTx with AG rather than subtotal PTx, because THPT might recur after PTx.[10] In this study, there were no recurrences of THPT or loss of transplanted kidney in patients with total PTx with AG or with subtotal PTx. However, more cases are needed to evaluate the difference between total PTx with AG and subtotal PTx.

In our study, there was no significant change in the eGFR within the first one month after PTx. However, the decrease in the levels of eGFR at three and six months after PTx was statistically significant. In one year after PTx, the levels of eGFR had improved to the same level as before PTx. Furthermore, there was no PTx-related deterioration of kidney graft function in this study. Although some studies have reported a slight decrease in kidney function,[7, 10–12] most studies have reported the improvement of kidney graft function within the first year after PTx, similar to our results. The underlying mechanism of temporal deterioration of kidney function has been unclear. However, we considered that general anesthesia and operative invasion may be connected lately with it. It has also been hypothesized that transient hypoparathyroidism may be a possible explanation for the impairment of kidney graft function; PTH has vasodilatory effects on preglomerular vessels, whereas efferent arterioles undergo vasoconstriction, perhaps due to renin release.[13]

Six patients underwent follow-up until five years after

PTx, which was longer than that reported in many previous studies. In these six patients, there was no significant change in the eGFR from one year to five years after PTx. However, our study had few cases. Therefore, our findings suggest that kidney graft function after PTx should be observed closely within the first year after PTx, although deterioration of kidney function was temporary in our study.

There is a slight limitation to this study. We did not compare the kidney graft function of patients with PTx and without PTx for THPT. Most patients in our study required VitD replacement by mouth and continued to need it at the last follow-up. This suggested that the autograft parathyroid tissue volume was small. There is a need to review the dose of autograft parathyroid tissue. Goodman et al. reported that VitD reduces the secretion of creatinine from renal tubes and thus influences the level of serum creatine.[14] Therefore, administration of VitD may induce the deterioration of kidney graft function. However, although most patients in this study required oral VitD replacement after PTx, there was no loss of renal graft.

Regarding the definition of success after PTx for THPT, Lou et al. suggested that normal serum Ca and normal PTH at six months after PTx could be considered a success.[15] However, there is no clear definition in this regard. Most reports have evaluated serum Ca and i-PTH at six months after PTx. In our study, the serum Ca and PTH levels were normal at six months. This could be considered a success of PTx for THPT.

Conclusion

We analyzed the outcome of PTx in 13 THPT patients. The levels of serum Ca and i-PTH significantly improved the day after PTx. Within the first year, the levels of eGFR tended to decrease. However, after one year, the levels of eGFR recovered to the same levels as before PTx. Thus, we suggested that clinicians follow-up closely with PTx patients during the first year after PTx.

Most patients required oral VitD replacement, and thus the dose of implanted parathyroid tissue should be the subject of future study. However, our findings showed no decay of the transplanted kidney or recurrence of THPT.

Conflicts of interest: None declared.

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