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ORIGINAL ARTICLE

Outcomes of parathyroidectomy versus calcimimetics for secondary hyperparathyroidism and kidney transplantation: a propensity-matched analysis

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Abstract

Purpose Calcimimetics are currently indicated for severe secondary hyperparathyroidism (SHPT). However, the role of parathyroidectomy (PTX) for these patients is still under debate, and its impact on subsequent kidney transplantation (KTX) is unclear. In this study, we compare the outcomes of kidney transplantation after PTX or medical treatment.

Methods Patients who underwent KTX and had SHPT were analyzed retrospectively. Two groups were selected (patients who had either PTX or calcimimetics prior to KTX) using a propensity score for sex, age, donor type, and parathyroid hormone levels (PTH) during dialysis. The primary outcome was graft failure, and secondary outcomes were surgical KTX complications, survival, serum PTH, serum calcium, and serum phosphate levels post-KTX.

Results Matching succeeded for 92 patients. After PTX, PTH was significantly lower on the day of KTX as well as at 1 and 3 years post-KTX (14.00 pmol/L (3.80–34.00) vs. 71.30 pmol/L (30.70–108.30), $p < 0.01$, 10.10 pmol/L (2.00–21.00) vs. 32.35 pmol/L (21.58–51.76), $p < 0.01$ and 13.00 pmol/L (6.00–16.60) vs. 19.25 pmol/L (13.03–31.88), $p = 0.027$, respectively). No significant differences in post-KTX calcium and phosphate levels were noted between groups. Severe KTX complications were more common in the calcimimetics group (56.5% vs. 30.4%, $p = 0.047$). There were no differences in 10-year graft failure and overall survival.

Conclusion PTX resulted in lower PTH after KTX in comparison to patients who received calcimimetics. Severe complications were more common after calcimimetics, but graft failure and overall survival were similar.

Keywords Secondary hyperparathyroidism · Parathyroidectomy · Calcimimetics · Kidney transplantation

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Introduction

Secondary hyperparathyroidism (SHPT) is common in patients with end-stage renal disease (ESRD). SHPT increases the risk of complications such as renal osteodystrophy and vascular calcification in these patients and also decreases quality of life [1, 2]. In addition, SHPT increases the risk of graft failure in patients who undergo kidney transplantation (KTX) [3]. Treatment of SHPT by means of correcting PTH and calcium metabolism may improve outcomes of KTX.

The initial treatment of this disorder consists of dietary phosphate restriction, calcium supplements, vitamin D analogs, and phosphate binders. For patients with SHPT who fail to respond to first-line agents, current guidelines recommend initiation of calcimimetic therapy and only advise PTX when all medical treatment options are exhausted [4]. However, calcimimetics have not shown any benefits in terms of cardiovascular morbidity or overall survival [5]. In addition, up to 40% of patients have to significantly lower their dose of calcimimetics and up to 18% of patients discontinue therapy due to adverse effects [6]. Certain cases also remain in which SHPT is refractory to medical management [6, 7].

While parathyroidectomy (PTX) is currently only indicated in patients who fail to respond to medical or pharmacological therapy, studies have demonstrated that PTX is superior to calcimimetics for patients with severe SHPT in terms of PTH levels and resolution of symptoms [8]. PTX is also more cost effective after a period of 7 months or more on dialysis, which is significant considering that the median time to first KTX in the USA is 3.6 years [9, 10]. Furthermore, studies suggest that PTX prior to KTX decreases the risk of graft failure (odds ratio 0.55) in comparison to treatment with medical management [11]. Other studies have shown an increased risk of graft failure if PTx is performed during KTx instead of prior to KTx [12, 13]. Due to the lack of head-to-head comparisons of PTX versus calcimimetics for the treatment of SHPT prior to KTX, the aim of this study is to compare the effects of PTX and calcimimetics on graft survival and overall survival after KTX in patients with ESRD-related SHPT.

Materials and methods

Patient selection

We performed a retrospective propensity-matched analysis of PTX versus calcimimetic therapy on outcomes of KTX. All patients who underwent their first kidney transplantation at 4 different academic centers in the Netherlands between 1995 and 2015 were included in a multicenter database. These centers included the University Medical Center Groningen, Leiden University Medical Center, Erasmus Medical Center Rotterdam, and Academic Medical Center Amsterdam. From this multicenter database, all patients with a history of calcimimetic use or parathyroidectomy prior to KTX were identified. Two groups were selected: the first consisted of patients who were treated with calcimimetics to control HPT prior to KTX whereas the second group consisted of patients who required PTX to control HPT prior to KTX. This study was approved by the institutional review boards of all participating centers, and informed consent was not required due to the retrospective nature of this study.

Data collection

Medical records were reviewed for patient data. Patient demographics were age, sex, diabetes mellitus, cardiovascular disease (coronary artery or peripheral arterial disease), cause of ESRD (hypertension, diabetes mellitus, unknown or "other," including glomerulonephropathies, postrenal obstructive disease, recurrent pyelonephritis, Alport syndrome, and polycystic kidney disease), dialysis vintage, dialysis types (including hemodialysis or peritoneal dialysis), baseline serum calcium, phosphate, PTH, and bone mineral density(s). PTH values were in pmol/L with a reference range of 2.00–7.00 pmol/L. Calcium and phosphate were both in mmol/L with reference ranges of 2.20–2.55 mmol/L and 0.90–1.50 mmol/L, respectively. Kidney transplant data included donor type, cold ischemia time, delayed graft function (requiring dialysis within first week after transplantation), graft survival, and overall survival. In addition, serum PTH, calcium, and phosphate levels 1-, 3-, and 5-year post-transplantation were collected.

The primary outcome is graft failure, which is defined as permanent dialysis requirement or transplant removal > 1 week after primary transplantation. The secondary outcomes are KTX complications (according to the Clavien-Dindo scale, a 5-point scale of complications based on severity (Table 1) [14]), overall survival, serum PTH, serum calcium, and serum phosphate levels after kidney transplantation. Persistent hypoparathyroidism is defined as PTH < 2.00 pmol/L 1 year after KTX. Persistent hyperparathyroidism is defined as PTH > 9× upper normalized limit 1 year after KTX. Persistent hypocalcemia is defined as calcium below the lower boundary of the normal range (i.e., < 2.15 mmol/L for LUMC and < 2.20 mmol/L for other centers) and persistent hyperphosphatemia as serum phosphate > 1.50 mmol/L 1 year after KTX. Technical appendix, statistical code, and dataset have been made available at https://doi.org/10.5061/dryad.kd1gq6f.

Patient and public involvement

Patients were not involved in the development of this study.

Table 1 Baseline characteristics of the study population and differences between the calcimimetic and parathyroidectomy group

Variable	Calcimimetics $n = 46$	PTX $n = 46$	p value
Male	27 (48.2%)	29 (51.8%)	0.831[a]
Age (years)	53 (45–60)	54 (41–61)	0.297[b]
DM	11 (23.9%)	4 (8.7%)	0.029[a]
CVD	8 (17.4%)	8 (17.4%)	1.000[a]
Dialysis vintage (months)	56 (27–77)	69 (37–87)	0.046[b]
Type of dialysis			
Hemodialysis	32 (69.6%)	26 (56.5%)	0.234[a]
Peritoneal dialysis	13 (28.3%)	18 (39.1%)	
ESRD cause			
Hypertension	18 (39.1%)	13 (28.3%)	0.340[a]
DM	5 (10.9%)	1 (2.2%)	
Unknown	7 (15.2%)	8 (17.4%)	
Other	17 (36.9%)	23 (50.0%)	
Mineral metabolism pre-treatment			
Serum calcium (mmol/L)	2.38 (2.27–2.52)	2.59 (2.39–2.72)	0.002[b]
Serum phosphate (mmol/L)	1.67 (1.32–2.12)	1.89 (1.67–2.21)	0.382[b]
Serum PTH (pmol/L)	97.65 (50.09–154.05)	124 (74.98–169.18)	0.144[b]
Donor characteristics			
DCD	19 (41.3%)	23 (50.0%)	0.734[a]
DBD	19 (41.3%)	16 (34.8%)	
Living related	3 (6.5%)	4 (8.7%)	
Living unrelated	5 (10.9%)	3 (6.5%)	
Cold ischemia time (hours)	17 (13.50–21)	18.22 (13.40–23.50)	0.821[b]

PTX parathyroidectomy, *DM* diabetes mellitus, *CVD* cardiovascular disease, *ESRD* end-stage renal disease, *DCD* donation after cardiac death, *DBD* donation after brain death

[a] Chi-square test

[b] Non-parametric *t* test

Statistical analysis

Patients were matched using a propensity score based on the covariates sex, age, highest PTH prior to KTX (pre-PTX for those in the PTX group), and donor type. All matched pairs were included for further analysis. Continuous data are presented as mean ± standard deviation or median (interquartile range), according to distribution. Categorical data are presented as *n* and percentage. Baseline characteristics were compared between groups using the Student *t* test or non-parametric tests for continuous variables (according to distribution) and the chi-square test for categorical variables. Additionally, to identify independent risk factors for early death and severe complications, a univariable and multivariable analysis was performed. Only variables with a p value < 0.2 were considered for multivariable analysis. A p value < 0.05 was considered significant. SPSS 21.0 (IBM Corp., Chicago, IL, USA) software was used for the statistical analyses.

Results

Patients and matching

After initial screening, 354 ESRD patients with SHPT were identified who underwent KTX. Of these patients, a total of 187 received either PTX or calcimimetics. Fifty-four patients had missing data for one of the covariates for matching and were therefore excluded. In total, 133 patients were included for matching. Matching based on propensity score succeeded for 46 patients per group, which resulted in comparable groups in terms of sex, age, and pre-treatment serum PTH levels and kidney donor type (Table 2). The calcimimetics group had significantly more patients with diabetes, whereas the baseline serum calcium value was higher in the PTX group. In the PTX group, 30% of patients had prior calcimimetic therapy. Additionally, duration of dialysis prior to KTX was longer in the PTX group.

Table 2 Outcomes and complications after kidney transplantation

Variable	Calcimimetics *n* = 46	PTX *n* = 46	*p* value
Overall mortality	7 (17%)	12 (26.1%)	0.201[a]
Cardiovascular events	6 (13.0%)	12 (26.1%)	0.160[a]
Complications after KTX (Clavien-Dindo)			
Grade I	0 (0%)	5 (10.9%)	0.047[a]
Grade II	7 (15.2%)	10 (21.7%)	
Grade III	4 (8.7%)	3 (6.5%)	
Grade IV	22 (47.8%)	11 (23.9%)	
Persistent hypoparathyroidism	0 (0%)	3 (6.5%)	0.151[a]
Persistent hyperparathyroidism	3 (6.5%)	1 (2.2%)	0.411[a]
Persistent hypophosphatemia	22 (47.8%)	16 (34.8%)	0.199[a]
Persistent hyperphosphatemia	1 (2.2%)	2 (4.4%)	0.689[a]
Persistent hypocalcemia	1 (2.2%)	5 (10.9%)	0.273[a]
Persistent hypercalcemia	23 (50.0%)	10 (21.7%)	0.006[a]

KTX kidney transplantation

[a] Chi-square test

Parathyroidectomy

Of the 46 patients in the PTX group, 24 patients (54%) underwent total parathyroidectomy, 10 patients (22%) underwent subtotal parathyroidectomy, and in 12 patients (24%), the type of parathyroidectomy was unable to be determined. Postoperative hypocalcemia was observed in 24 patients (52%). There were no cases of recurrent laryngeal nerve palsies or surgical site infections. However, 5 patients (11%) required re-exploration for persistent hypercalcemia. Overall, PTH decreased by 98%, from 124.00 (74.98–169.18) preoperatively to 4.00 (0.90–12.68) postoperatively (non-parametric test, $p < 0.01$).

PTH and electrolytes

PTH was significantly lower in the PTX group on the day of KTX as well as at 1 and 3 years post-KTX (Fig. 1a). Mean serum calcium and phosphate levels were similar over both groups during follow-up (Fig. 1b and c). There were no differences in incidence of persistent hypoparathyroidism, hypocalcemia, and hyperphosphatemia between groups. The incidence of persistent hypercalcemia was significantly higher in the group of patients who were treated with calcimimetics (Table 2). Calcimimetics were used more frequently at 3 and 6 months, as well as 1 year post-KTX in patients with PTX (34% vs 3%, $p < 0.01$; 27% vs 3%, $p < 0.01$; 33% vs 9%, $p = 0.01$). At 3 and 5 years post-KTX, there was no significant difference in calcimimetic use between both groups (22% vs 4%, $p = 0.06$; 24% vs 7%, $p = 0.14$).

Survival and complications

Overall rates of complications and mortality were comparable between the two groups. However, there were significantly more severe (Clavien-Dindo ≥ 3) complications after kidney transplantation in the group treated with calcimimetics (Table 2). This difference was due to a higher rate of grade 4 complications in the calcimimetics group (49% vs. 25%, $p = 0.02$). All of these cases were due to delayed graft function requiring hemodialysis. The mean time to graft failure was 96 months for the calcimimetic group and 91 months for the PTX group. The graft failure rate was similar during 10-year follow-up ($p = 0.333$, Fig. 2a). The mean overall survival was 95 months for calcimimetic and PTX groups. The overall survival rate did not differ significantly between groups during the 10-year follow-up ($p = 0.759$, Fig. 2b). PTX-related complications occurred in 39% of patients, but only 3% had severe complications (Clavien-Dindo ≥ 3), and the mortality rate was 0%. Univariable and multivariable analyses showed that age was the only independent predictor for early death and that cerebrovascular accident and serum calcium level were negatively associated with severe complications (Tables 3 and 4). Additionally, PTX performed turned out to be independently associated with lower change of severe complications (Table 4).

Discussion

In this study, we compared KTX outcomes of patients with SHPT who were treated with calcimimetics or PTX prior to their first transplantation. Our results show that PTH levels were significantly lower up to 3 years following KTX in

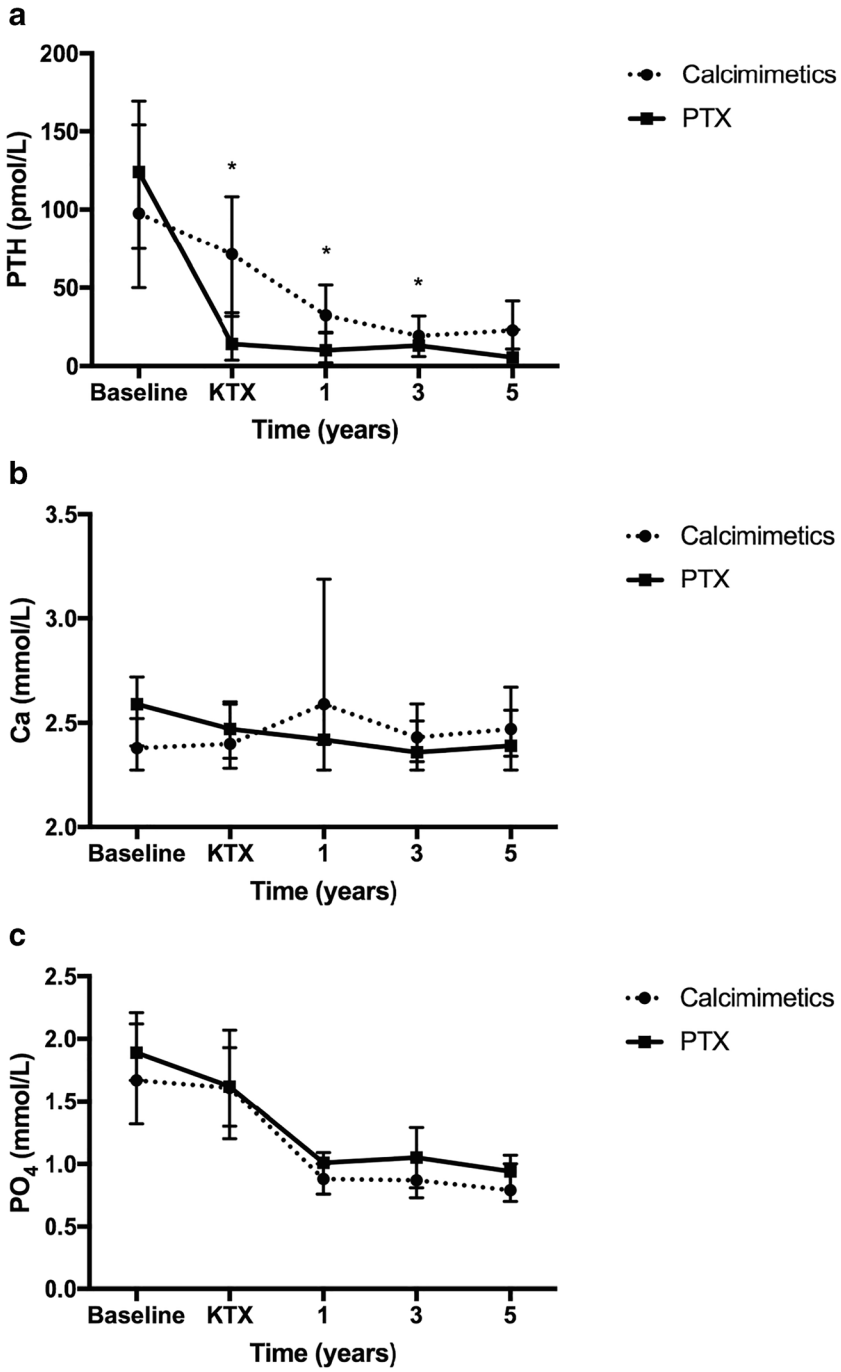

Fig. 1 Trends for PTH (**a**), calcium (**b**), and phosphate (**c**) levels during 5-year follow-up. KTX day of kidney transplantation. *Statistical significance

patients with PTX prior to KTX compared with patients who were treated with calcimimetics. Post-KTX calcium and phosphate levels were similar between groups. The rate of severe KTX-related complications (Clavien-Dindo ≥ 3) was significantly lower in the group of patients who were managed with PTX for SHPT.

Since the introduction of calcimimetics, the management of SHPT has changed and caused a debate regarding the role of parathyroid surgery in ESRD patients. While medical management has always been the primary approach, the emergence of calcimimetics has resulted in decreased utilization of PTX as well as a 2-year delay in referral for surgery [14]. While calcimimetics improve serum calcium, phosphate, and PTH levels, studies have not demonstrated any benefit in cardiovascular morbidity or mortality [5]. Therefore, the use of calcimimetics in SHPT remains controversial, and one can argue that therapeutic therapies such as PTX should be implemented more liberally.

PTX has been shown to be effective in improving PTH levels in patients with SHPT [15, 16]. Studies comparing

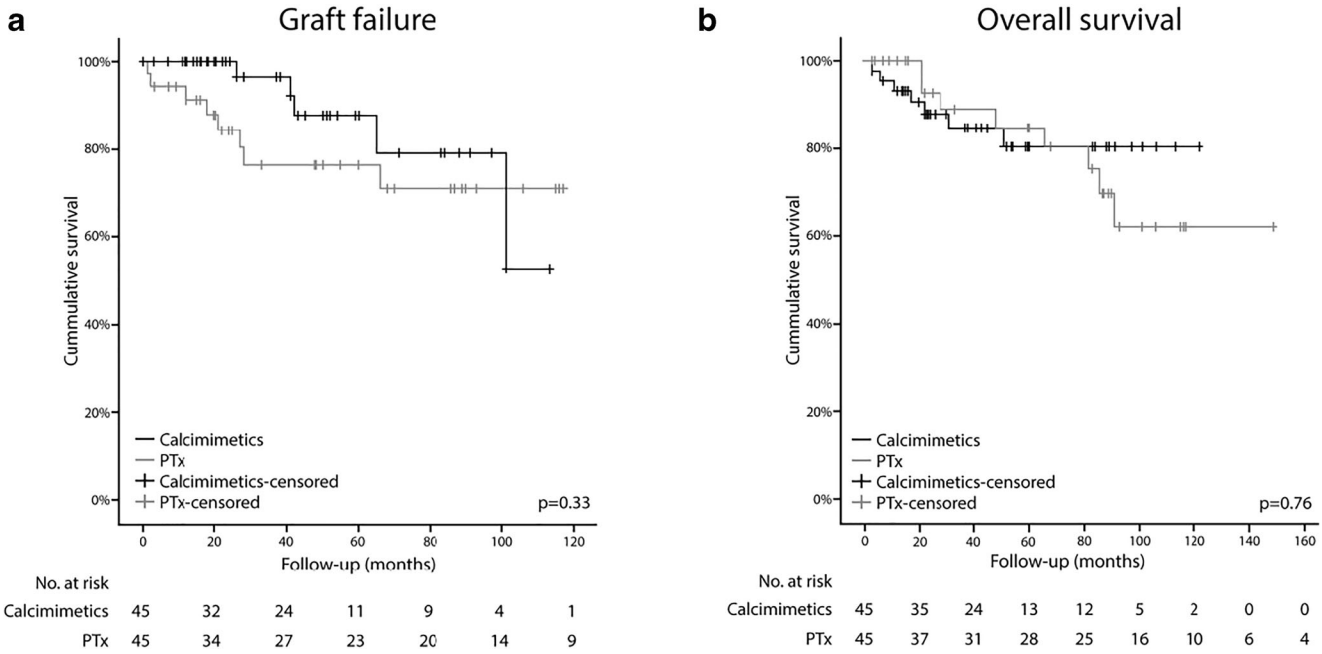

Fig. 2 Ten-year survival analysis for graft failure (**a**) and overall mortality (**b**). PTX parathyroidectomy

outcomes between calcimimetics and surgical management of SHPT have demonstrated similar survival and superior cost effectiveness in the PTX group after 7 months as well as higher graft survival after KTX [9, 11]. However, despite this encouraging data, there still appears to be reluctance towards performing PTX for SHPT. Although these patients are generally at a high operative risk, the peri-operative risks of mortality and complications for PTX in the dialysis population are minimal [17]. Moreover, as shown in a recent systematic review, several studies show improvement in quality of life after PTX, which is not seen with calcimimetics [18]. In addition, a recent randomized controlled trial showed superiority of PTX in comparison to calcimimetics for persistent hyperparathyroidism after kidney transplantation, which suggests that these effects could also be seen in SHPT [19].

Elevated PTH levels have previously been associated with mortality in patients with SHPT [3, 20]. However, there was no difference in patient survival between both groups in our study, despite a significant difference in PTH levels during the early post-KTX stage. In our study, the average PTH was above the reference range in both groups, which may suggest that the degree of elevation does not have an effect on overall survival. Interestingly, despite the difference in PTH levels, there were no differences in calcium or phosphate levels between both groups. Both the peak in serum calcium 1 year post-KTX and the slow return to normal for serum PTH after

Table 3 Univariable and multivariable analyses for risk factors for early death

	Univariable analysis			Multivariable analysis		
Variable	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Male sex	1.052	− 0.997 to 1.099	0.925			
Age	1.068	0.009 to 0.1222	0.022	1.069	0.011–0.122	0.019
DM	0.476	− 1.854 to 0.369	0.191	0.465	− 1.903 to 0.371	0.187
MI	0.996	− 0.039 to 0.030	0.800			
CVA	0.996	− 0.037 to 0.029	0.796			
Creatinine	1.000	− 0.001 to 0.002	0.637			
Ca	1.000	− 0.001 to 0.002	0.616			
PO4	1.000	− 0.001 to 0.002	0.781			
PTH	0.999	− 0.007 to 0.005	0.793			
Dialysis type	0.994	− 0.065 to 0.054	0.855			
PTX	2.089	− 0.306 to 1.780	0.166			

Table 4 Univariable and multivariable analyses for risk factors for severe complications

	Univariable analysis			Multivariable analysis		
Variable	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Male sex	0.716	− 1.220 to 0.553	0.461			
Age	1.018	− 0.020 to 0.056	0.362			
DM	1.201	− 0.424 to 0.789	0.555			
MI	0.258	− 2.930 to 0.221	0.092	0.110	− 4.524 to − 0.102	0.061
CVA	4.732	− 0.148 to 3.257	0.074	13.433	0.117–5.079	0.040
Creatinine	0.999	− 0.002 to 0.001	0.213			
Ca	1.001	− 0.000 to 0.003	0.074	1.002	0.000–0.004	0.026
PO4	1.001	− 0.000 to 0.003	0.141			
PTH	1.001	− 0.004 to 0.007	0.569			
Dialysis type	0.993	− 0.092 to 0.078	0.870			
PTX	0.359	− 1.924 to − 0.123	0.026	0.284	− 2.311 to − 0.208	0.019

KTX in the group whose SHPT was managed with calcimimetics only may suggest that PTX results in a better stabilization of this metabolic disorder after KTX.

Hypoparathyroidism was more common after PTX; however, this did not reach statistical significance. A recent meta-analysis showed that this can occur in up to 27% of patients [21]. It is important to consider the surgical management, as well as continued medical management of these patients, in order to minimize the risk of this complication. In terms of surgical technique, total parathyroidectomy with autotransplantation has been associated with lower rates of postoperative hypoparathyroidism than total parathyroidectomy alone [22, 23]. Additionally, it is important to monitor postoperative calcium levels and treat with calcium and vitamin D supplements if indicated.

Our results showed similar graft survival between both groups. This is in contrast to the results reported by Callender et al., which demonstrated improved graft survival in patients with PTX prior to KTX [11]. However, in their study, 43% of patients who were managed medically were not treated with calcimimetics, which could suggest a selection bias to patients with milder SHPT. Nonetheless, these results were somewhat in line with our results based on a propensity score–matched analysis, showing that the rate of severe KTX-related complications (Clavien-Dindo ≥ 3) was significantly lower in patients who were treated with PTX prior to KTX. However, it is important to consider that grade 4 complications, specifically dialysis requirement related to delayed graft failure, are a more frequent complication in KTX compared to other procedures. To clarify the impact of PTX on overall mortality and graft survival by reducing selection bias, a prospective randomized trial with head-to-head comparison of both PTX and calcimimetics in the treatment of SHPT is needed.

There are several limitations to our study. First of all, despite correcting for possible confounders with propensity matching, the retrospective nature of our study makes it susceptible to bias. It is plausible that patients were referred for PTX only after calcimimetics failed to control SHPT and that, consequently, the PTX group represents patients with more severe hyperparathyroidism and/or a portion of patients with tertiary hyperparathyroidism. We have tried to correct for this bias as much as possible by including pre-KTX PTH as a covariate in the propensity score analysis. Additionally, throughout the manuscript, persistent hyperparathyroidism was uniformly defined as PTH > 9 times the upper limit of normal, which may have attributed to an underestimation of hyperparathyroidism in both groups. The heterogeneity of the ESRD population is reflected in our study in the differences in baseline characteristics between both groups. However, due to the lack of prospective data, propensity matching provides the best alternative to improve the validity of retrospective data. The stringent rules for matching resulted in relatively small numbers per group, which reduced the power of our study for graft survival analysis. However, consequently, the similarity of baseline characteristics allowed a well-balanced comparison of both treatment arms. Our retrospective study design also resulted in missing data, including data on vitamin D levels, bone mineral density, type of transplant rejection, immunosuppressive therapy, and HLA mismatch, as follow-up was not uniform and split between different medical centers.

Conclusion

In conclusion, PTX prior to KTX resulted in significantly fewer severe KTX-related complications compared with patients treated with calcimimetics while graft survival and overall survival were similar. Randomized studies are needed in order to compare the outcomes of these two treatment modalities accurately without selection bias.

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Authors' contributions Ezra Y. Koh MD—data collection, statistical analyses, manuscript preparation; Philip von Forstner BS—data collection, manuscript review; Willemijn Y. van der Plas BS—data collection, manuscript review; Roderick R. Dulfer MD—data collection, manuscript review; Robert A. Pol MD PhD—study design, manuscript review; Schelto Kruijff MD PhD—study design, manuscript review; Joris I. Rotmans MD PhD—study design, manuscript review; Martin H. de Borst MD PhD—study design, manuscript review; Ewout J. Hoorn MD PhD—study design, manuscript review; Tessa M. van Ginhoven PhD—study design, manuscript review; Liffert Vogt MD PhD—study design, manuscript review; Els J.M. Nieveen van Dijkum MD PhD—study design, manuscript review; Anton F. Engelsman—study design, statistical analyses, manuscript review; Carlijn Gispen MD—study design, manuscript review, Abbey Schepers MD PhD—study design, manuscript review; Natasha Appelman-Dijkstra MD PhD—study design, manuscript review.

Data availability https://doi.org/10.5061/dryad.kd1gq6f

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Obtained from Amsterdam UMC ethics board.

Consent to participate N/A

Consent for publication N/A

Code availability N/A

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