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ORIGINAL RESEARCH

Management of pre-renal transplant secondary hyperparathyroidism: parathyroidectomy *versus* cinacalcet

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Abstract

Background: Secondary hyperparathyroidism is a common consequence of end-stage renal disease. Despite the efficacy of kidney transplantation in treating renal failure, many transplant recipients still suffer from persistent or tertiary hyperparathyroidism. Furthermore, the impact of secondary hyperparathyroidism therapy choices on other renal transplant outcomes is poorly understood.

Methods: We retrieved the clinical data of 334 patients who received a kidney allograft between January 2007 and December 2014 at the Sheffield Teaching Hospitals, NHS Foundation Trust, United Kingdom. We identified three groups: parathyroidectomy group (34 patients), including patients who had parathyroidectomy before transplantation; cinacalcet group (31 patients), including patients who received cinacalcet before transplantation; and control group (269 patients), including patients who receive a transplant in the same period but did not have any evidence of hyperparathyroidism. We reviewed the demographic data, biochemical parameters and graft survival of all groups.

Results: Patients who underwent parathyroidectomy before transplantation had significantly better post-transplant calcium and parathyroid hormone levels than patients in the cinacalcet group (p=0.003). In addition, a significantly lower number of patients had tertiary hyperparathyroidism in the parathyroidectomy group than in the cinacalcet group at 1 year of follow-up (p=0.001). However, short-term and long-term graft survival was comparable in all groups.

Conclusions: Renal allograft survival was comparable in all groups. However, tertiary hyperparathyroidism was less likely to occur in patients who underwent parathyroidectomy than in those who were administered cinacalcet.

Keywords: cinacalcet, graft survival, kidney transplantation, parathyroidectomy, secondary hyperparathyroidism.

Citation

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Introduction

One of the main current challenges in nephrology is secondary hyperparathyroidism (SHPT), a major complication in end-stage renal disease (ESRD). SHPT is a severe health problem, leading to bone fractures and increased vascular calcification. Additionally, high concentrations of parathyroid hormone (PTH), calcium, phosphorus, fibroblast growth factor 23 (FGF23), and alkaline phosphatase have been linked to an increased risk of cardiovascular events and mortality.[1,2]

The ideal PTH target for patients with advanced chronic kidney disease (CKD) has been the subject of considerable debate for many years. Guidelines differ greatly in what they suggest for target ranges.[3] The Japanese Society for Dialysis Therapy, for instance, suggests aiming for a PTH level anywhere from 60 to 240 ng/mL, or roughly 1–4 times the upper limit of normal,[4] which is much lower than recommended by KDIGO guidelines (2–9 times the upper limit of normal).[5]

The initial treatment for SHPT involves calcium supplementation, phosphate binders, dietary phosphate restriction

and vitamin D analogues. Patients who do not respond to first-line medication should be switched to calcimimetic therapy. According to the current guidelines, parathyroidectomy (PTX) should be recommended after all other pharmacological options have been exhausted.[2]

Although cinacalcet administration leads to a 40% decrease in mean PTH levels, only 43% of patients achieve acceptable levels (600 pg/ml) as suggested by KDIGO.[6,7] As an added downside, adverse effects of cinacalcet can lead to a lack of adherence to the treatment regimen, reducing efficiency and utility.[8] Therefore, debate exists over whether or not calcimimetics should be used initially. PTX is an excellent long-term management strategy because it reduces PTH levels below the standard laboratory reference range in the majority of patients.[9,10]

SHPT can be alleviated to some degree by kidney transplantation, but only if the graft is functioning properly.[11] Unfortunately, despite improvements in kidney function, hyperparathyroidism frequently persists with detrimental clinical outcomes.[12] In addition, many reports have indicated that the severity of pre-transplant SHPT can lead to post-transplant hyperparathyroidism – also called tertiary hyperparathyroidism (THPT) – and an increased risk of graft loss.[13,14] Therefore, several nephrologists stress the importance of treating SHPT before kidney transplantation to reduce the incidence and prevent complications of THPT in transplant recipients.[15] Nevertheless, available evidence poorly supports the ideal treatment strategy for SHPT before transplantation. Further, it is unclear how different SHPT treatments affect post-transplant outcomes like mortality and graft function. Therefore, this research compares the effectiveness of PTX *versus* cinacalcet for the treatment of SHPT, assessing the short-term and long-term impact on renal allograft survival and the CKD and mineral bone disorder (MBD) profile following transplantation.

Methods

Patient population

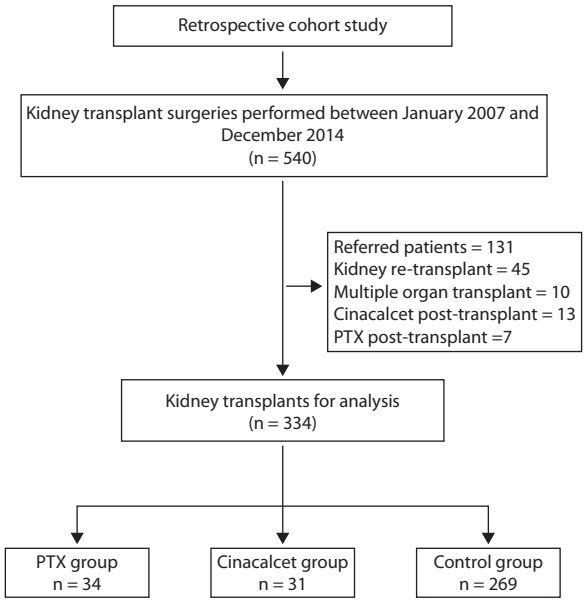
This research retrieved information from the clinical data registry at the Sheffield Teaching Hospitals, NHS Foundation Trust, United Kingdom, for 540 kidney transplant recipients. Inclusion criteria for patient selection were patients who underwent kidney transplantation between January 2007 and December 2014 and had at least 24 months of follow-up. Exclusion criteria were recipients who had their follow-up at another hospital (n=131), kidney re-transplant recipients (n=45), patients with multi-organ transplants (n=10), and patients who underwent PTX (n=7) or were administered cinacalcet (n=13) post-transplantation. Patients were assigned into three groups: PTX group, including patients who had undergone PTX before transplantation; cinacalcet group, including patients who received cinacalcet before transplantation; and control group, including patients who received a transplant in the same period but did not have any evidence of hyperparathyroidism (Figure 1). Our centre protocol for the diagnosis and management of SHPT defined it as the presence of high levels of PTH three to nine times the standard upper limit in patients undergoing dialysis. All patients who underwent PTX had a subtotal PTX, with a remnant the size of a normal gland (approximately 6 mm in the craniocaudal dimension and 3–4 mm in the transverse dimension).

We compared the three groups regarding demographic data, including age, sex, donor source, duration of dialysis, original kidney disease, comorbidities before transplantation, number of HLA mismatches, immunosuppressive regimen, vitamin D levels within 1 month before transplantation, post-transplant malignancy, and duration of post-transplantation follow-up. Of note, follow-up occurred at different times for each patient, depending on the time of transplantation. No patient received evolutionary drugs – related to SHPT – over the follow-up duration. Groups were also compared regarding short-term and long-term graft survival. Furthermore, a two-group analysis (PTX *versus* cinacalcet) was performed for estimated glomerular filtration rate (eGFR) and CKD-MBD profile (serum calcium, serum phosphorus and PTH) at different post-transplantation times. Finally, PTX *versus* cinacalcet groups were compared regarding the incidence of THPT. Because there is no universally accepted definition of THPT and no precise cut-off date for a diagnosis, we defined THPT as PTH >1.5 times the upper limit of the assay at 6 months or 1 year post-transplantation.

The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Calcium levels were adjusted for albumin using the following equation: corrected calcium (mmol/L) = measured calcium (mmol/L) + (0.025 × (40 - albumin (g/L)). The reference values for corrected calcium, phosphorus and PTH are 2.2–2.6 mmol/L, 0.8–1.5 mmol/L and 1.6–6.9 pmol/L, respectively.

The study involved no prospectively collected data; therefore, there was no access to patients or opportunity to seek informed consent. Nevertheless, this study poses no greater than minimal risk and will have no direct impact on patient rights, welfare or clinical care. However, prior IRB approval was obtained from Sheffield Teaching Hospitals, NHS Foundation Trust, United Kingdom, under code number: MD/17.08.109. All procedures performed in the study were conducted following the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

Figure 1. Flowchart of patient selection.



Statistical analysis

The Shapiro–Wilk test was used to define the distribution's normality of continuous variables. The median and interquartile range were adopted for continuous variables and percentages (%) for categorical variables. The three groups were compared using the one-way ANOVA test for continuous variables and the Pearson χ^2 or Fisher's exact test for categorical variables. PTX group data were compared against that of the cinacalcet group using the Student *t*-test and Mann–Whitney *U*-test for normally and non-normally distributed data. A Cox regression hazard model was used to determine the risk factors associated with graft failure. Finally, Kaplan-Meier curve was used to show the renal allograft survival of all groups, and a log-rank test was used to calculate the difference. A *p* value of less than 0.05 was considered statistically significant. The statistical analysis was performed using SPSS software (version 25).

Results

Baseline characteristics

Table 1 reveals the demographic data of our patients. The median age of all patients did not differ between the three groups. Furthermore, there was no difference in sex, body mass index, original kidney disease, immunosuppressive regimen (including corticosteroids) or the number of HLA mismatches. In addition, vitamin D levels prior to transplantation were below the average level. However, no significant difference was observed between groups. Additionally, the median post-transplantation follow-up duration was comparable (nearly 7 years in all groups).

Interestingly, the control group had fewer deceased donors (62.5%) compared with the PTX group (91.2%) and the cinacalcet group (90.3%; $p<0.001$), indicating that the control group had a higher number of living donors and hence a shorter time on the transplant waiting list. Furthermore, this also explains why the control group had a shorter dialysis duration (median = 2.8 years) than other groups (median = 5 and 5.4 years for PTX and cinacalcet groups, respectively). Moreover, 94.1% of patients in the PTX group had dialysis pre-transplantation *versus* 93.5% in the cinacalcet group and only 67.7% in the control group. These results explain why patients in the control group did not need to undergo PTX or receive cinacalcet, whilst vitamin D analogues probably controlled their hyperparathyroidism state.

Laboratory data at post-transplantation

Table 2 presents data for the two groups (PTX *versus* cinacalcet) at post-transplantation. The PTX group had a lower eGFR than the cinacalcet group at 1 year post-transplantation and the last follow-up date. However, no statistical difference between the two groups was evident. There was a significant difference between the two groups regarding serum calcium and PTH (at 1-year and last follow-up date) favouring the PTX group. Further analysis showed that serum phosphorus was lower in the PTX group at the short-term follow-up ($p=0.003$). However, no significant differences were found at the long-term follow-up.

Interestingly, the PTX group had a lower percentage of THPT at post-transplantation. At 6 months post-transplantation, 76.5% of patients in the PTX group had THPT *versus* 93.5% in the cinacalcet group ($p=0.05$). Moreover, at 1-year post-transplantation, 67.6% of patients in the PTX group had THPT *versus* 100% in the cinacalcet group, with a significant difference ($p=0.001$).

Cardiovascular system complications at post-transplantation

Table 3 compares both groups (PTX *versus* cinacalcet) regarding post-transplantation cardiovascular complications. Despite some cardiac complications in the study period in all groups, no significant differences were observed.

Short-term and long-term renal allograft survival

Figures 2 and 3 show the short-term and long-term renal allograft survival of patients in the three groups. Although

Table 1. Baseline characteristics.

	PTX	Cinacalcet	Control	*p* value
Number of patients	34	31	269	
Age (years)	56.5 (43.7–65)	52 (44–58)	50 (40–61)	0.3
Sex (male)	70.6%	54.8%	64.7%	0.4
BMI (kg/m^2)	25.6 (23.2–30.9)	27 (22.9–30.6)	26.4 (22.9–30.5)	0.8
Donor source (deceased)	91.2%	90.3%	62.5%	<0.001[a]
Type of RRT				
Dialysis	94.1%	93.5%	67.7%	<0.001[a]
Pre-emptive	5.9%	6.5%	32.3%	
Dialysis duration before transplantation (years)	5 (4.1–7.3)	5.4 (3.1–7.7)	2.8 (1.1–4.4)	<0.001[a]
Original kidney disease				
Diabetic nephropathy	5.9%	16.1%	13.4%	0.1
Glomerulonephritis	38.2%	22.6%	31.2%	
Hypertensive nephropathy	8.8%	16.1%	3.7%	
Polycystic kidney disease	14.7%	16.1%	18.6%	
Others	32.4%	29.1%	33.1%	
DM before transplantation	14.7%	22.6%	20.8%	0.6
HLA mismatch				
0 mismatch	15.6%	6.5%	15.1%	0.5
1 mismatch	3.1%	6.5%	5.8%	
2 mismatch	21.9%	29%	20.2%	
3 mismatch	37.5%	38.7%	27.5%	
4 mismatch	18.8%	16.1%	17.1%	
5 mismatch	3.1%	0%	9.7%	
6 mismatch	0%	3.2%	4.7%	
Induction immunosuppression				
Basiliximab	88.2%	96.8%	91.4%	0.2
Campath	5.9%	3.2%	7.4%	
ATG	2.9%	0%	1.2%	
Rituximab	2.9%	0%	0%	
Baseline vitamin D[b]	37.5 (28.3–62.1)	36 (29.3–48.2)	44.7 (30–63)	0.3
Corticosteroids	76.5%	83.9%	88.1%	0.1
Acute rejection episodes	17.6%	6.5%	11.9%	0.4
Post-TX malignancy	8.8%	9.7%	14.5%	0.6
Follow-up period after transplantation (years)	7.2 (5–8.9)	7.7 (5.7–9.8)	7.8 (5.9–10.1)	0.1

Data are presented as % or median (25th to 75th percentile).
[a]Statistically significant.
[b]Normal range: Vitamin D (>50 nmol/L).
ATG, antithymocyte globulin; BMI, body mass index; DM, diabetes mellitus; HLA, human leucocytic antigen; PTX, parathyroidectomy; RRT, renal replacement therapy; TX, transplant.

Table 2. Laboratory data post-transplantation.

	PTX	Cinacalcet	*p* value
eGFR after 1 year (mL/min/1.73m^2)	43 (31–58)	55 (37–69)	0.1
eGFR at last follow-up (mL/min/1.73m^2)	34.5 (17.5–50)	47 (22–68)	0.1
Serum corrected calcium after 1 year (mmol/L)	2.3 (2.2–2.5)	2.5 (2.3–2.6)	0.001[a]
Serum corrected calcium at last follow-up (mmol/L)	2.3 (2.1–2.4)	2.4 (2.3–2.5)	0.01[a]
Serum phosphorus after 1 year (mmol/L)	1 (0.7–1.2)	0.8 (0.7–0.9)	0.003[a]
Serum phosphorus at last follow-up (mmol/L)	1 (0.9–1.2)	0.9 (0.7–1.3)	0.2
Serum PTH after 1 year (pmol/L)	5.8 (2.9–9.6)	21.9 (13.2–29.2)	0.01[a]
Serum PTH at last follow-up (pmol/L)	7.2 (4.7–16.4)	15.2 (11.1–24)	0.002[a]
THPT at 6 months	76.5%	93.5%	0.05
THPT at 1 year	67.6%	100%	0.001[a]

Data are presented as % or median (25th to 75th percentile).
Normal range: calcium (2.2–2.6 mmol/L), phosphorus (0.8–1.5 mmol/L), PTH (1.6–6.9 pmol/L).
[a]Statistically significant.
eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; THPT, tertiary hyperparathyroidism.

the PTX group had a relatively lower survival, no significant difference was observed (p=0.05 and p=0.1 for short-term and long-term survival, respectively).

Cox proportional hazard regression for the factors associated with the time to graft failure showed that age, donor source, dialysis duration before transplantation, and 5-year PTH were significantly associated with graft failure (Table 4). The association between graft failure and other factors was further studied using a multiple Cox proportional hazard regression, which showed that age and 5-year PTH are significantly associated with graft failure. Age showed a statistically significant association with graft failure. For each unit increase in age, the hazard ratio of graft failure increased by 1.081-fold (95% CI 1.037–1.127). In addition, for each unit increase in 5-year PTH, the hazard ratio of graft failure increased by 1.027-fold (95% CI 1.013–1.042).

Discussion

Previous studies have found that 25% of kidney transplant recipients may still have SHPT despite improvements in their renal function.[16] This research describes a group of SHPT patients treated with either PTX or cinacalcet and shows the impact of each medication on post-transplantation graft survival and the CKD-MBD profile.

Patients who were administered cinacalcet before transplantation had worse calcium homeostasis, as demonstrated by the higher PTH and calcium levels in the cinacalcet group. Despite the statistically significant difference in serum calcium between the two groups, no clinical significance was found since the median calcium level of both groups was within the accepted range. This paradoxical result can be attributed to the small sample size of our study. Short-term and long-term graft survival was comparable in all groups, with a trend of lower graft survival in the PTX group, albeit without statistical significance.

Patients in the PTX group had lower eGFR than those in the cinacalcet group at short-term follow-up, albeit without statistical significance. Similarly, graft survival was reduced in the PTX group at both short-term and long-term follow-up. Again, however, the differences were non-significant. On the other hand, the cinacalcet group had a better – yet non-significant – graft survival, likely due to the lower incidence of acute rejection episodes in the cinacalcet group (6.5%) compared with the PTX (17.6%) and control (11.9%) groups.

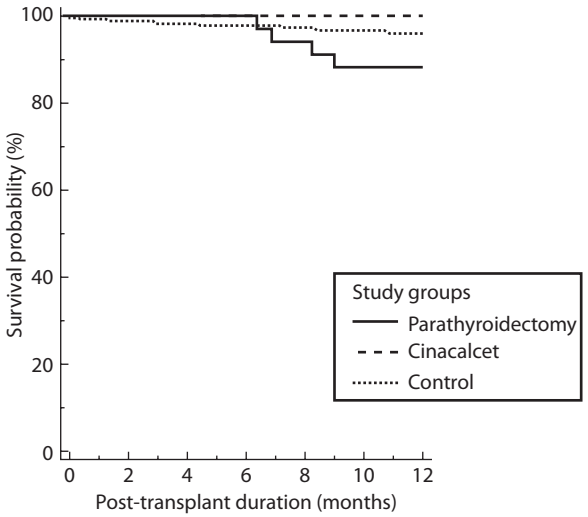
Like our study, Mathur et al. discovered no correlation between SHPT treatment and graft failure following transplantation.[17] Nonetheless, Callender et al. showed that PTX given before kidney transplantation increased

Table 3. Cardiac complications post-transplant.

	PTX	Cinacalcet	*p* value
Pulmonary embolism	2.9%	3.2%	1
Myocardial infarction	2.9%	0%	
Heart failure	2.9%	6.5%	
Atrial fibrillation	2.9%	3.2%	
Angina	11.8%	9.7%	
Peripheral vascular disease	5.9%	3.2%	
No complications	70.6%	74.2%	

Data are presented as %.

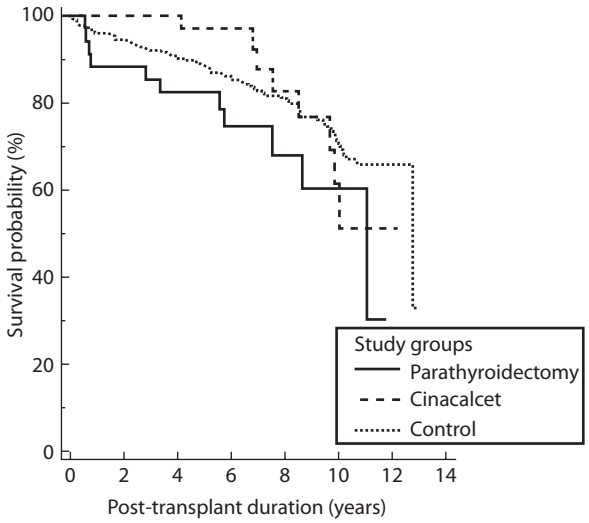
Figure 2. Short-term graft survival.



graft survival.[18] In addition, other studies reported that pre-transplant PTX improves graft survival more than post-transplant PTX.[19,20] However, these studies did not compare PTX *versus* cinacalcet, likely explaining differences with our results.

Serum PTH was higher in the cinacalcet group than in the PTX group at both short-term (21.9 *versus* 5.8 pmol/L) and long-term follow-up (15.2 *versus* 7.2 pmol/L), with a statistically significant difference (p=0.01 and p=0.002, respectively). In addition, THPT was significantly higher in the cinacalcet group at 1-year post-transplantation. Similarly, previous reports have shown that cinacalcet administered pre-transplantation is related to elevated

Figure 3. Long-term graft survival.



calcium and PTH levels that could persist up to 4 years post-transplantation.[21–23]

No difference in serum phosphorus was found in the long-term follow-up. However, a statistically – though not clinically – significant difference was observed at 1 year post-transplantation. Again, this could be linked to the small sample size of our study. Compared to patients with CKD with a comparable lowered eGFR, serum phosphate levels in kidney transplant recipients were ~0.5 mg/dL lower.[24]

Upon renal function decline, circulating levels of phosphorus, PTH and FGF23 increase. Therefore, patients undergoing transplantation often present with abnormally elevated levels of PTH and FGF23. Even when renal function is restored throughout the post-transplant recovery period, PTH and FGF23 levels may remain increased for several months.[25] Both high PTH and FGF23 levels have been linked to post-transplantation hypophosphataemia in up to 10% of paediatric patients.[26] The significantly higher intact PTH in the cinacalcet group can explain this, contributing to post-transplantation hypophosphatemia. Therefore, it has been assumed that SHPT with persistently elevated levels of PTH can lead to post-transplantation hypophosphataemia.[27] One of the limitations of our study is that we did not assess FGF23 levels, which may provide additional insight on our results.

Post-transplantation cardiac complications between both groups similar (Table 3). Previous studies have found that PTX improves cardiovascular outcomes in patients undergoing dialysis who suffer from severe SHPT.[28,29] However, others stated that PTX offered no significant protection against cardiac complications in patients undergoing dialysis.[30,31] On the other hand, the

Table 4. Univariable and multivariable analysis for risk factors of graft failure.

	Univariate				Multivariate			
	Crude HR	***p* value**	**95% CI for HR**		**Adjusted HR**	***p* value**	**95% CI for HR**	
Control group	Reference				Reference			
Parathyroidectomy group	1.887	0.054	0.990	3.594	3.000	0.057	0.967	9.308
Cinacalcet group	1.065	0.867	0.510	2.221	2.176	0.166	0.725	6.531
Age	1.062	<0.001[a]	1.042	1.081	1.081	<0.001[a]	1.037	1.127
Donor source (deceased)	4.464	<0.001[a]	2.302	8.659	1.655	0.436	0.465	5.890
Dialysis duration before transplant	1.189	<0.001[a]	1.107	1.278	1.065	0.414	0.915	1.239
5-year calcium	0.635	0.667	0.080	5.047	0.036	0.023	0.002	0.635
5-year PTH	1.033	<0.001[a]	1.022	1.044	1.027	<0.001[a]	1.013	1.042

[a]Statistically significant.
HR, hazard ratio; PTH, parathyroid hormone.

EVOLVE trial found that cinacalcet decreased the frequency of cardiovascular complications in older patients with SHPT undergoing dialysis. Yet, this effect was not evident in younger patients.[32] The above studies evaluated PTX alone or cinacalcet alone in the dialysis population. A study comparing pre-transplantation PTX with cinacalcet discovered that PTX was associated with considerably decreased cardiovascular events.[17] Thus, the comparable results between the two groups herein could be attributed to the small sample size.

Graft failure is strongly associated with recipient age and serum PTH. Therefore, the higher the PTH post-transplantation – with subsequent THPT – the higher risk for graft loss. This result agrees with a report where the authors concluded that high PTH levels were associated with an 85% increased risk of graft loss compared to normal values.[33] A previous study including 405 patients investigated the link between early THPT and long-term allograft status and showed that THPT persistent for more than 3 months post-transplantation is a poor prognostic factor for renal allograft survival.[34] However, this was not shown in our study due to the relatively small sample size.

The main strengths of our study are the long duration of post-transplantation follow-up of our patients (median follow-up was 7.2, 7.7 and 7.8 years for the PTX, cinacalcet and control groups, respectively). Furthermore, our study included patient-specific data from the medical records of the Sheffield Teaching Hospitals, United Kingdom, and compares two treatment options for SHPT (PTX and cinacalcet), revealing their impact on post-transplantation outcomes. Nevertheless, our study is limited by being a single-centre study, having a small sample size, missing data regarding PTH levels immediately after PTX, and inherent drawback of retrospective studies such as selection bias.

Conclusion

Patients who underwent PTX and those administered cinacalcet have comparable renal graft survival. In addition, patients who underwent PTX have a lower risk of THPT than those administered cinacalcet. Therefore, we recommend further prospective studies are performed to achieve more conclusive results on the critical management of SHPT in patients with CKD preparing for kidney transplantation.

Contributions: All authors contributed equally to the preparation of this review. The authors confirm their contribution to the paper as follows: Muhammed Elhadedy, Hussein Sheashaa, and Ahmed Halawa carried out the study conception and design. Second, Muhammed Elhadedy collected the data. Third, Muhammed Elhadedy performed the analysis and interpreted the results. Muhammed Elhadedy and Ahmed Halawa drafted the manuscript. Finally, Ghada El-Kannishy, Ayman F. Refaie, and Ahmed Halawa reviewed the results and the discussion. All authors approved the final version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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