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# Timing of parathyroidectomy in kidney transplant candidates with secondary hyperparathryroidism: effect of pretransplant versus early or late post-transplant parathyroidectomy

Simon A. Littbarski [a], Alexander Kaltenborn [a], Jill Gwiasda [a], Jan Beneke [a], Viktor Arelin [a,b], Ysabell Schwager [a], Julia V. Stupak [a], Indra L. Marcheel [a], Nikos Emmanouilidis [c], Mark D. Jäger [d], Georg Friedrich Wilhelm Scheumann [c], Jürgen Klempnauer [c], and Harald Schrem [a,c,*]

[a] *Core Facility Quality Management and Health Technology Assessment in Transplantation, Integrated Research and Treatment Facility Transplantation (IFB-Tx), Hannover Medical School, Hannover, Germany*
[b] *Department of Nephrology, Hannover Medical School, Hannover, Germany*
[c] *General, Visceral and Transplant Surgery, Hannover Medical School, Hannover, Germany*
[d] *General, Visceral and Minimally Invasive Surgery, Municipal Hospital Wolfenbüttel, Hannover, Germany*

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ABSTRACT

**Background.** The timing of parathyroidectomy in kidney transplant candidates suffering from secondary hyperparathyroidism before versus early or late after transplantation remains controversial.
**Methods.** The short-term follow-up cohort comprised 66 patients with 1-year post-transplant follow-up, while the long-term follow-up cohort contained 123 patients. Risk-adjusted identification of independent risk factors for compromised renal graft function (KDIGO stage ≥ IV) was performed using multivariable regression analysis adjusted for propensity score logits for parathyroidectomy before versus after renal transplantation. Intra-individual matched-pairs analyses were used to identify significant effects of post-transplant parathyroidectomy on graft function as assessed by estimated glomerular filtration rate (eGFR) and paired *t* tests.
**Results.** Donor kidney function KDIGO stage III ($P = .030$; OR = 5.191, 95% CI: 1.100–24.508), donor blood group 0 ($P = .005$; OR = 0.176, 95% CI: 0.048–0.642), and post-transplant parathyroidectomy ($P = .032$; OR = 17.849, 95% CI: 1.086–293.268) were revealed as independent significant risk factors for compromised renal graft function in the short-term follow-up cohort using propensity score risk adjustment while post-transplant parathyroidectomy had no independent influence in the long-term follow-up cohort ($P = .651$). Parathyroidectomy after renal transplantation compromised graft function early after parathyroidectomy and at last follow-up in all post-transplant parathyroidectomy cases ($P \leq .004$). Parathyroidectomy within the first post-transplant year was associated with compromised renal graft function until last follow-up ($P = .004$), while parathyroidectomy late post-transplant was not.
**Conclusion.** Parathyroidectomy should be conducted before transplantation or, if this is not possible, preferably after the first post-transplant year.



## Introduction

Secondary hyperparathyroidism (sHPT) is a frequent morbidity in patients with end-stage renal disease. It has potentially devastating consequences, including high mortality and morbidity because of accompanied coronary artery disease and renal osteodystrophy.[1] Successful kidney transplantation (KTx) does not, unfortunately, guarantee reversal of sHPT. Despite adequate renal graft function 1 year after KTx, increased serum levels of intact parathyroid hormone

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* Corresponding author. General, Visceral and Transplantation Surgery, Hannover Medical School, Carl-Neuberg-Str. 1, 30625, Hannover, Germany.
*E-mail address:* schrem.harald@mh-hannover.de (H. Schrem).

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(iPTH) can be found in up to 25% of kidney transplant recipients.[2] Especially women receiving KTx with high serum levels of iPTH, calcium, phosphate, and alkaline phosphatase at the time of transplantation are at risk for persisting sHPT (sometimes also labelled as *tertiary hyperparathyroidism*) after renal transplantation, particularly when graft function is suboptimal. Persisting sHPT often requires parathyroidectomy (PTX) because of limited spontaneous improvement of parathyroid function after KTx.[3,4] After effective PTX, serum levels of calcium and iPTH decrease; whereas levels of serum phosphate increase.[4] Conservative treatment with cinacalcet is an alternative to PTX, which has been reported to be very effective in controlling hypercalcemia and hypophosphatemia[5]; however, cinacalcet treatment after KTx is still a matter of controversy and classified as off-label use because it lacks FDA-approval for this indication.[6,7] Furthermore, recent studies question the effectiveness of cinacalcet with regard to its impact on cardiovascular and overall mortality, its effect on quality of life, as well as its ability to decrease serum PTH levels.[8,9]

Low-baseline estimated glomerular filtration rate (eGFR) and low iPTH levels after post-transplant PTX for persisting sHPT were shown to be significant risk factors for renal graft function impairment.[10] High levels of serum iPTH before post-transplant PTX seem to be associated with a more substantial decrease in graft function.[11] Only 1 other study has been published so far contrasting the impact of pre- versus post-transplant PTX directly.[10]

Evidence guiding the clinically relevant decision of the timing of PTX in regard to KTx is scarce. Furthermore, the impact of early versus late PTX after renal transplantation on graft function is also a matter of controversy.[10,12] Therefore, the current study aims to address these issues in a propensity score– (PS–) adjusted analysis.

## Patients and Methods

### *Type of study and setting*

This is a single-center retrospective analysis from a German transplant center within the Eurotransplant community based on ongoing data collection and retrospective data completion. Recipient and transplant-specific data were obtained from patient medical records, while donor data were extracted from the Eurotransplant database.

### *Ethics*

According to the Professional Code of the German Medical Association (article B.III. § 15.1), neither informed consent nor approval of Hannover Medical School's ethics committee (Germany) was needed for this retrospective study. At the time of hospital admission, patients provided informed consent that their data may be used for scientific purposes, which is the general policy of our institution. Before analysis, patient records and patient data were anonymized and deidentified.

### *Inclusion and exclusion criteria*

Included were all patients who received KTx and pre- or post-transplant PTX because of sHPT at Hannover Medical School January 1, 2000–December 31, 2012. Pediatric patients (<18 years of age at KTx) were excluded. The remaining number of patients was divided into 2 groups: A pre-KTx-PTX cohort including patients undergoing PTX before KTx; and a post-KTx-PT cohort, including patients who underwent PTX after KTx. In the post-KTx-PTX cohort, 13 patients were excluded because of graft loss before PTX within the initial post-transplant hospital stay. In addition, 2 patients underwent PTX before and after KTx; these cases were also excluded. Furthermore, we excluded 21 patients who received PTX before KTx, before they were listed on the kidney transplant waiting list, and 11 patients without follow-up data at our transplant outpatient clinic. The flow of patients through the study leading to the analyzed short-term follow-up and long-term follow-up cohorts is presented in Fig 1.

Other than patients who underwent PTX before transplantation, only patients who underwent PTX within the first year after KTx were included in the short-term follow-up cohort to investigate the influence of pretransplant versus early post-transplant PTX on graft function 1 year after transplantation: 66 patients were identified for analysis in this short-term follow-up cohort (Fig 1).

The long-term follow-up cohort consisted of 123 patients who either underwent PTX before KTx or after KTx with a median follow-up time after transplantation of 7.0 years (range: 0.1–14.4 years). Patients with PT later than 6.8 years after KTx were excluded because of the lack of meaningful follow-up data (Fig 1). A schematic presentation of both cohorts regarding the timing of PTX is presented in Fig 2.

### *Definition of variables and outcome*

Kidney graft function was staged into 5 ordinal categories of Kidney Disease Improving Global Outcomes (KDIGO), according to Stevens et al.[13] Calculation of the eGFR was applied by the 4-variable Modification of Diet in Renal Disease (MDRD) equation by Levey et al[14] [$eGFR = 30849 \times \text{standardized serum creatinine [µmol/l]}^{-1.154} \times \text{age [years]}^{-0.203} \times 0.742$ (if a woman) $\times$ 1.212 (if race is black)].

### *Study endpoints*

Primary study endpoints were compromised kidney graft function as defined by KDIGO stages ≥ 4 one year after transplantation and at last follow-up. Because not every patient visited the outpatient clinic exactly one year after transplantation, a grace period +/– 80 days after one year after transplantation was accepted to define one-year follow-up visits. The last follow-up after KTx was defined as the last noted visit at the transplant outpatient clinic and thus represented the date of last data collection.

### *Statistical methods*

The distribution of continuous variables is presented as mean and standard deviation (SD) if normally distributed or as median and range if not normally distributed, while binary variables (yes/no) are described with their frequency and percentage of occurrence.

Groups of pre-KTx versus post-KTx were compared using the Wilcoxon test for data that are not normally distributed, the Student *t* test for data that are normally distributed data, and Pearson $\chi^2$ test for data that are binary.

Risk factors for compromised renal graft function (KDIGO stage ≥ IV) were entered into multivariable logistic regression analysis after determination of their influence on primary study endpoints in univariable logistic regression analysis applying an $\alpha$ level of ≤ 0.200 and after conducting a principal component analysis to avoid multicollinearity in multivariable regression analysis.

Two PSs for post-transplant versus pretransplant PTX were calculated for the short-term and the long-term follow-up cohorts separately, using multivariable logistic regression analysis after purposeful selection of variables with *P* values < .200 in univariable logistic regression analysis to avoid over fitting. The logits of the PS models were used as risk-adjustment factors in subsequent multivariable regression modeling to identify independent significant risk factors for compromised renal graft function after KTx. PS adjustment was used to account for potential confounders for post-PTX kidney function with different distributions between post-transplant versus pretransplant PTX. The principles of this methodologic deployment of PS adjustment has been reviewed by Blackstone before.[15]

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