

Effect of Incomplete Parathyroidectomy Preserving Entire Parathyroid Glands on Renal Graft Function

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Hypothesis: Parathyroidectomy (PT) corrects tertiary hyperparathyroidism in patients who have received renal grafts but can result in deterioration of renal function.

Objective: To compare different surgical procedures for their effect on renal function and efficacy to cure tertiary hyperparathyroidism.

Design: A retrospective cohort study.

Setting: University clinic.

Patients: Eighty-three patients with functioning renal grafts receiving PT for the first time.

Interventions: Group 1 received an incomplete PT, with at least 1 entire parathyroid gland (PG) remaining in situ (n=12). Group 2 received an incomplete PT, with the most morphologically conserved PG partially resected (n=22). Group 3 received a complete PT, with autotransplantation of PG tissue (n=49).

Main Outcomes Measures: The primary end point was the postoperative change in glomerular filtration rate.

Secondary end points were rates of redialysis, hypercalcemia, and hyperparathyroidism within 5 years.

Results: A decrease in glomerular filtration rate occurred postoperatively in 75 patients (90%) and correlated significantly with the extent of PG resection. Recovery of renal function at month 6 was observed in group 1, but not in groups 2 and 3 ($P < .001$). Seven patients (8%) needed permanent dialysis (1 in group 2 and 6 in group 3). Hypercalcemia was abrogated in 78 patients (94%), without significant differences among the groups. Assessment of parathyroid hormone levels in accordance with target ranges from the Kidney Disease Outcomes Quality Initiative guidelines did not reveal significant differences in the rates of recurrent hyperparathyroidism.

Conclusion: Incomplete PT preserving at least 1 entire PG does not cause deterioration of renal graft function and provides long-term correction of hypercalcemia and tertiary hyperparathyroidism.

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TERTIARY HYPERPARATHYROIDISM (tHPT) is present in up to 17% of renal transplant recipients.¹ Most clinicians consider tHPT with hypercalcemia to be the main indication for parathyroidectomy (PT) after renal transplant.² The prevalence of posttransplant PT reported recently³⁻⁸ ranges from 0.9% to 5.6%. The success of the surgical

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procedure is determined by permanent absence of hypercalcemia and HPT after the intervention. To achieve this goal, reported^{5,6,9-11} strategies range from complete PT without autotransplantation of parathyroid tissue to incomplete PT with preservation of 3 normal-sized parathy-

roid glands (PGs). In most of these studies, it was assumed that an amount of parathyroid tissue equivalent to approximately 2 normal-sized PGs should be retained in patients who have undergone renal transplant.^{2,11}

Recently published analyses¹²⁻¹⁵ pointed out that extensive PT could be associated with deterioration in renal graft function. Because renal function is correlated with quality of life and the prevention of vascular diseases in renal transplant recipients, iatrogenic deterioration of renal graft function should be avoided.

To address the recent awareness of possible harmful effects associated with PT after renal transplant, we evaluated whether the surgical method to leave PG tissue in situ would influence renal graft function. We were able to analyze the medical records of 83 patients who underwent PT for

the first time and were monitored for at least 5 years. With these data, we could compare 3 surgical procedures: incomplete PT, preserving at least 1 entire PG in situ; incomplete PT, partially resecting the most morphologically conserved PG; and complete PT, with autotransplantation of PG tissue. The goal in all these procedures was to leave an amount of parathyroid tissue equivalent to approximately 2 normal-sized PGs in situ.

The study assessed postoperative changes in renal function for the different surgical procedures. In addition, the long-term cure rates for hypercalcemia and HPT were analyzed to reflect the established outcomes in PT after renal transplant.

METHODS

PATIENTS AND INDICATIONS

Between September 9, 1997, and December 6, 2004, 83 patients with functioning renal grafts underwent initial PT at Medizinische Hochschule Hannover, Hannover, Germany. Sixty-one patients experienced permanent hypercalcemia. Twenty-two patients had a borderline increase of calcium levels but severely increased parathyroid hormone (PTH) levels in combination with renal osteopathy (n=20), severe nephrocalcinosis within the renal graft (n=1), or pruritus and a few bluish skin lesions as mild symptoms of calciphylaxis (n=1). None of the patients underwent PT within 6 months after renal transplant.

SURGICAL PROCEDURE

Each PT was the first surgical intervention at the neck. In general, at least 1 PG per quadrant (≥ 4 PGs overall) was explored before the decision on the appropriate surgical procedure was made. Cervical thymectomy was performed if 4 PGs could not be detected. Twelve patients underwent incomplete PT, with 3 or fewer PGs resected, leaving at least 1 entire PG in situ (group 1). The volume of the remaining PG tissue was estimated as equivalent to 2 normal-sized PGs. The estimation was performed by endocrine surgeons who were trained to use the aliquot method to estimate volumes of PG tissue. Twenty-two patients underwent incomplete PT, with the most morphologically conserved PG partially resected (group 2). The resulting PG remnant was approximately the size of 2 normal PGs. Complete PT with autotransplantation was performed in 49 patients (group 3). An autograft was obtained from the smallest and most morphologically conserved PG, consisting of 30 pieces ranging from 1 to 2 mm³. The PG tissue was implanted into the sternocleidomastoid muscle, which has been the preferred technique in our clinic for 20 years without adverse effects. All specimens were microscopically examined to confirm the diagnosis.

DATA ACQUISITION

Diagnostic assessment included repeated measurements of serum creatinine, PTH, and total calcium. Glomerular filtration rate (GFR) values were calculated using the Cockcroft-Gault formula.¹⁶ Mean values were calculated. Preoperative values for calcium and GFR were calculated from all values determined 3 months before PT. The preoperative value for PTH was calculated from all values obtained 12 months before PT but at least 6 months after renal transplant. Preoperative GFR values were calculated according to established intervals: -6 months (8-4 months before PT) and -12 months (15-9 months before PT). Values for follow-up time points were calculated as well:

2 months (1-3 months), 6 months (4-8 months), 12 months (9-15 months), 36 months (30-42 months), and 60 months (54-66 months).

Information on medications, treatments, and trough concentrations of calcineurin inhibitors was taken from the database of our renal transplant outpatient clinic and from reports of treating nephrologists. Adjustments of calcium and PTH levels were based on the administration of calcium, cholecalciferol, or calcimimetics.

Institutional review board approval was obtained for this investigation.

ASSAYS

Intact PTH was measured with 2 different second-generation assay commercial kits based on the immunochemiluminometric method. One was used from 1997 until January 2006 (Allegro-intact PTH; Nichols Institute, San Clemente, California; reference range 10-65 pg/mL [to convert PTH levels to picomoles per liter, multiply by 1.1053]), and use of the second was instituted in January 2006 (LIAISON N-tact PTH; DiaSorin, Stillwater, Minnesota; reference range 10-65 pg/mL). Standard automated techniques were used to measure calcium and creatinine in serum.

DATA ASSESSMENT

Changes in GFR were assessed by using the preoperative value from the interval 3 months before PT as the baseline. Percentage changes of GFR were calculated for the 12 months before PT (-6 and -12 months) as well as up to 60 months after PT (2, 6, 12, 36, and 60 months).

Levels of calcium were categorized as above, within, or below the reference range (8.60-10.4 mg/dL). (To convert calcium levels to millimoles per liter, multiply by 0.25.) The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation¹⁷ defines PTH target ranges for different stages of chronic kidney disease (CKD). These target ranges are 10 to 65 pg/mL for CKD stages 1 and 2 (GFR >60 mL/min), 35 to 70 pg/mL for CKD stage 3 (GFR 30-59 mL/min), 70 to 110 pg/mL for CKD stage 4 (GFR 15-29 mL/min), and 150 to 300 pg/mL for CKD stage 5 (GFR <15 mL/min). Levels of PTH at month 60 after PT were categorized as above, within, or below these target ranges.

STATISTICAL ANALYSIS

Statistical analysis was performed (Statistics 17.0; SPSS Inc, Chicago, Illinois). Data are presented as mean (SE) values. The Wilcoxon matched-pairs test was used for paired variables. The Mann-Whitney test and Kruskal-Wallis test were used for independent variables of 2 and more than 2 groups, respectively. Correlations were calculated by the Spearman rank correlation coefficients. Linear regression analysis was used to identify predictors for GFR changes. *P* values $<.05$ were considered statistically significant.

RESULTS

COHORT AND DROP-OUTS

Eighty-three renal transplant recipients underwent PT for the first time. Demographic and baseline data of each group are shown in the **Table**. Five patients (6%) died during the follow-up period of 60 months; all were members of group 3. Reasons for death were lung failure in 2

Table. Groups Defined by Extent of PG Resection, Demographic, and Laboratory Values Before PT

	PT Group ^a		
	1 (n=12)	2 (n=22)	3 (n=49)
	Incomplete PT, PG Preserved	Incomplete PT, PG Partially Resected	Complete PT + AT
PGs resected, No.	≤3	≈3 ½	≥4
Age, y	47 (12)	48 (14)	48 (10)
Period of dialysis, y	5.9 (1.8)	7.7 (3.3)	6.2 (3.5)
Period after renal transplant, y	2.2 (2.1)	3.2 (3.5)	2.7 (3.7)
GFR level, ^b mL/min	48 (17)	62 (28)	60 (22)
Calcium level, mg/dL	10.56 (0.72)	10.96 (0.56)	10.6 (0.72)
iPTH level, pg/mL	456 (240)	474 (264)	638 (408)

Abbreviations: AT, autotransplantation; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; PG, parathyroid gland; PT, parathyroidectomy.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; iPTH to picomoles per liter, multiply by 0.1053.

^aValues reported as mean (SD), unless otherwise indicated. Significance between groups was tested by the Mann-Whitney test.

^bSignificance existed only between groups 1 and 3; $P=.04$.

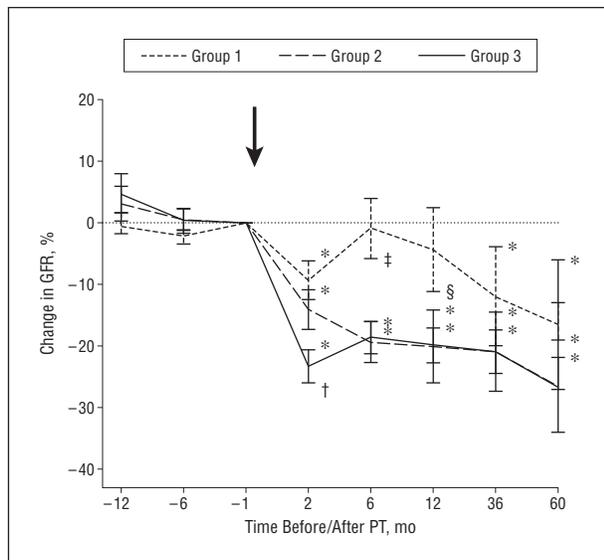


Figure 1. Change in glomerular filtration rate (GFR) before and after different types of parathyroidectomy (PT). All percentage changes were calculated with reference to baseline (-1). Values are given as mean with SE. The arrow marks the point in time of PT. * $P<.05$ between baseline, preoperative (-12 or -6 months), and postoperative (2, 6, 12, 36, or 60 months) values within a single group (Wilcoxon matched pairs test). Unpaired variables between 2 groups were analyzed with the Mann-Whitney test. † $P<.05$ between group 3 and groups 1 and 2 at month 2. ‡ $P<.05$ between group 1 and groups 2 and 3 at month 6. § $P<.05$ between groups 1 and 3 at month 12.

patients at months 31 and 32, heart failure in 1 patient at month 52, and unknown in 2 patients, who died 41 and 48 months after PT.

RENAL GRAFT FUNCTION

Changes in GFR are given as percentages from corresponding baseline values. No significant changes in GFR were observed in any group during the 12-month preoperative period. The postoperative GFR increased in only 8 patients (10%), all of whom received incomplete PT. Four of these patients (33%) were members of group 1 and another 4 patients (18%) were members of group 2. A postoperative decrease of GFR occurred in 75 patients (90%).

Overall, the GFR at month 2 was significantly decreased in all groups ($P<.05$; **Figure 1**). Because of the decline in renal function after PT, biopsies of renal grafts were performed in 19 patients during the interval of 3 months after PT (1 patient in group 1, 4 in group 2, and 14 in group 3). Examination of 14 biopsy specimens did not reveal a cause for an acute decrease in graft function. An infection was diagnosed on the basis of findings from 2 biopsies (1 patient in group 2 and the other in group 3), and changes suggesting acute rejection were found in 3 biopsy specimens of patients from group 3. All 5 patients received appropriate treatment for infection or rejection, but renal graft function did not recover. Trough concentrations of cyclosporine before PT did not differ significantly from those at month 2 after PT in any group (group 1, 142 [54] vs 130 [31] ng/mL; group 2, 169 [80] vs 154 [75] ng/mL; and group 3, 142 [31] vs 134 [37] ng/mL). (To convert cyclosporine to nanomoles per liter, multiply by 0.832.) Also, trough concentrations of tacrolimus and daily dosages of prednisolone before PT did not differ significantly from corresponding values at month 2 after PT in any group.

The level of GFR decrease at months 2, 6, and 12 was correlated with the extent of PG resection ($r=0.51$, $r=0.37$, and $r=0.41$, respectively). Linear regression analysis was performed to examine predictors for GFR changes and included the extent of PG resection, GFR, calcium levels, and PTH levels before PT. The analysis indicated that only extensive PG resection was associated with the decrease in GFR at month 2 ($P=.002$). Renal graft function recovered after incomplete PT only with preservation of at least 1 PG (group 1). In contrast, renal graft function remained significantly decreased in groups 2 and 3 ($P<.001$). Seven patients (8%) lost renal graft function during the follow-up of 60 months: 1 patient in group 2 and 6 patients in group 3. Renal graft biopsies were performed in 6 of these patients. Acute or chronic rejection was the reason for graft loss in 1 patient at month 12 and another at month 16 after PT. Recurrent kidney disease was identified in 3 patients at months 7, 18, and 45 after PT. In 1 patient, graft function was lost at month 6 after PT; no specific reason was identified.

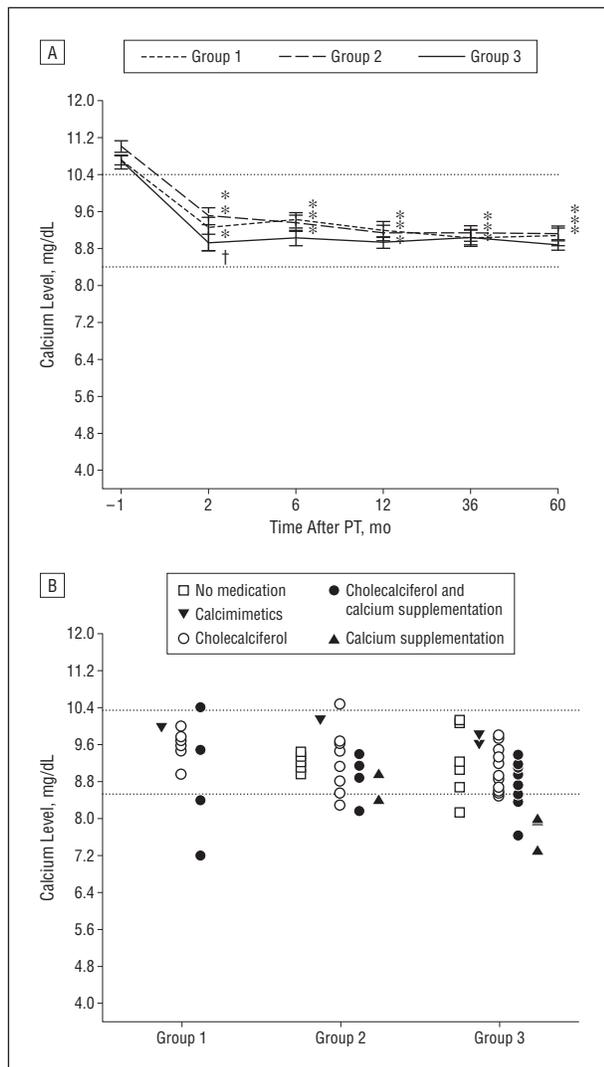


Figure 2. Calcium levels in serum after different types of parathyroidectomy (PT). Dotted lines indicate the reference range (8.6-10.4 mg/dL). (To convert calcium to millimoles per liter, multiply by 0.25.) A, Courses of calcium levels per group. Values are given as mean with SE. * $P < .01$ between preoperative (-1 month) and postoperative values within a single group (Wilcoxon matched pairs test). Unpaired variables between 2 groups were analyzed with the Mann-Whitney test. † $P < .01$ between groups 3 and 2. B, Individual calcium levels at month 60, including medication with influence on calcium levels.

CORRECTION OF HYPERCALCEMIA

Serum calcium levels were significantly lower during the postoperative period than before PT in all groups (**Figure 2A**). The only significant difference between the groups was observed at month 2, when group 3 showed a lower calcium level than group 2 ($P < .01$). Figure 2B depicts calcium levels in each patient in correspondence to the use of medications with influence on calcium homeostasis at month 60 after PT. Five patients (6%) developed hypercalcemia within the follow-up period. Four of those patients were treated with calcimimetics: 1 patient from group 1 because of persistent hypercalcemia, and 1 patient from group 2 and 2 patients from group 3 because of recurrent hypercalcemia at months 37, 41, and 57 after PT. One patient from group

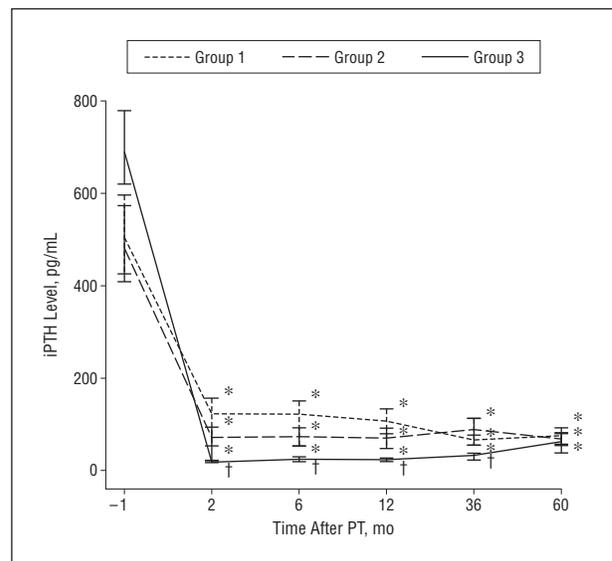


Figure 3. Levels of intact parathyroid hormone (iPTH) in serum after different types of parathyroidectomy (PT). Values are given as mean with SE. (To convert iPTH levels to picomoles per liter, multiply by 0.1053.) * $P < .005$ between preoperative (-1 month) and postoperative values (Wilcoxon matched pairs test). Unpaired variables between 2 groups were analyzed with the Mann-Whitney test. † $P < .05$ between group 3 and groups 1 and 2.

2 developed mild hypercalcemia and was treated with cholecalciferol. In summary, rates of hypercalcemia were 8% (1 of 12 patients) in group 1, 9% (2 of 22) in group 2, and 4% (2 of 49) in group 3. Only 1 patient had to undergo reoperation as the result of recurrence of calciophylaxis at month 55, although levels of calcium and PTH were consistently within target ranges. Overall, hypocalcemia was found in 19 of 83 patients (23%), with similar frequencies in the groups (25% [3 of 12 patients] in group 1, 23% [5 of 22] in group 2, and 23% [11 of 49] in group 3).

COURSES OF PTH LEVELS

Significant decreases in intact PTH levels occurred in all groups (**Figure 3**). Complete PT with PG autotransplantation caused significantly lower PTH values compared with both types of incomplete PT between months 2 and 36 (all $P < .05$). The PTH levels at month 60 were correlated with those at month 2 after PT ($r = 0.62$), indicating stable levels postoperatively. None of the following variables correlated with the PTH level at month 60: extent of PG resection, period of dialysis before PT, stage of CKD at month 60 or the necessity to reinstitute dialysis, GFR at month 60, and GFR, calcium, and PTH levels before PT.

Because the stage of CKD determines the target range for PTH levels according to the Kidney Disease Outcomes Quality Initiative guidelines,¹⁷ we categorized PTH levels at month 60 as to whether their value was above, within, or below the corresponding target range. **Figure 4** depicts individual PTH levels at month 60 in correspondence to target ranges for each stage of CKD and any medication with influence on PTH secretion. Patients with values above the upper limit of the target ranges were observed in all groups: 2 of 12 patients (17%) in group

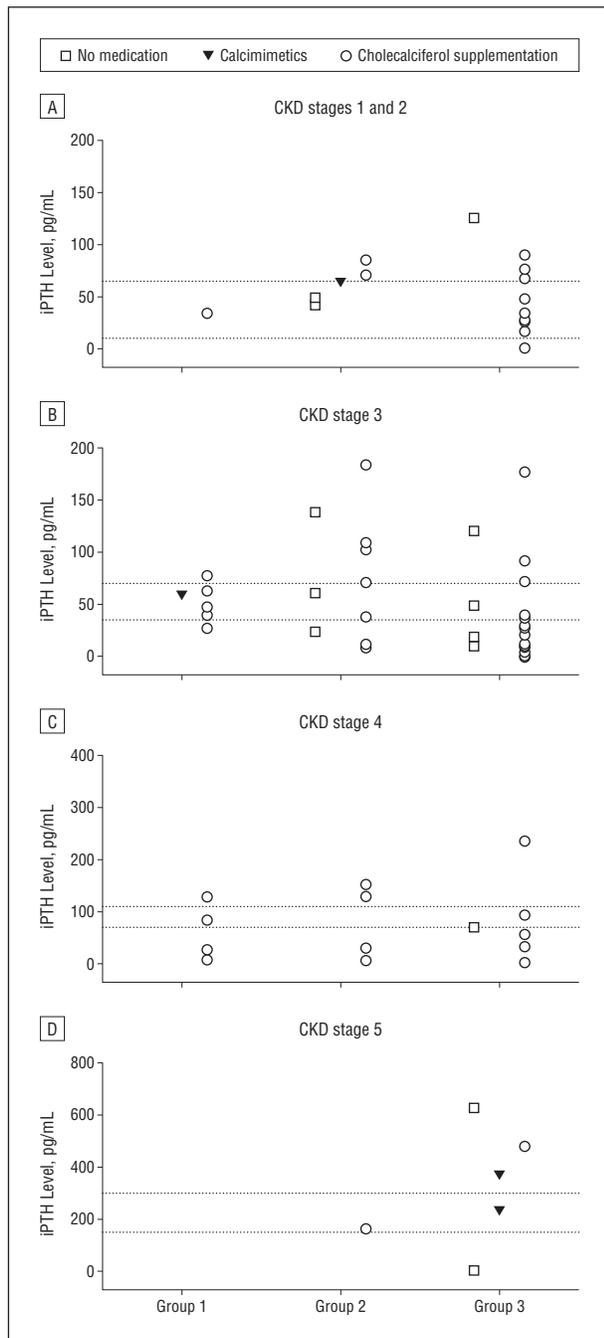


Figure 4. Individual levels of intact parathyroid hormone (iPTH) in serum at month 60 after parathyroidectomy. Target ranges of iPTH are given between dotted lines and depend on the stage of chronic kidney disease (CKD) according to Kidney Disease Outcomes Quality Initiative guidelines.¹⁷ Shown are iPTH levels at month 60 for CKD stages 1 and 2 (A), 3 (B), 4 (C), and 5 (D). Each patient is represented by a symbol at the position of individual iPTH value. Symbols indicate the administered medication with influence on PTH secretion. (To convert iPTH levels to picomoles per liter, multiply by 0.1053.)

1, 9 of 22 (41%) in group 2, and 12 of 49 (24%) in group 3. There were few occurrences of PTH levels exceeding twice the upper limit of the target ranges: once in group 2 (5%) and 3 times in group 3 (6%). Extensive hypoparathyroidism with PTH levels less than 10 pg/mL were observed in 8 patients (10%) overall: once in group 1 (8%); this patient had to undergo reoperation because of recurrence of calciphylaxis), twice in group 2 (9%), and 5

times in group 3 (10%). No correlation was found between the categorization of PTH values at month 60 and the extent of the PG resection ($r=0.14$).

COMMENT

Our retrospective analysis of PT after renal transplant supports that incomplete PT preserving at least 1 entire PG is less likely to cause deterioration of renal graft function than incomplete PT partially resecting the most morphologically conserved PG and complete PT with autotransplantation of PG tissue.

As reported in other retrospective studies,^{8,13,14,18-20} all 3 analyzed groups sustained, perioperatively, a significant decrease in renal graft function. Nineteen of 77 patients who developed a sudden decrease in renal function underwent renal graft biopsy within 3 months after PT. Only 5 biopsy specimens showed signs of infection or rejection episodes, but none of the grafts recovered despite appropriate treatment. This fact supports the hypothesis that the removal of PGs in itself affects renal function. Our results showed that the level of decrease in renal function correlates with the extent of PG resection. Thus, all patients who underwent complete PT with PG autotransplantation experienced deterioration of renal function. This observation is in accordance with previous retrospective analyses,^{14,20} which showed that complete PT with autotransplantation endangers renal function, particularly of compromised grafts.

No decrease in renal graft function was observed in only 8 patients. All of these patients received an incomplete PT and had significantly higher PTH levels at month 2 than did the corresponding 26 patients, who received incomplete PT and developed a decrease in renal function (intact PTH levels, 104 [39] pg/mL vs 74 [15] pg/mL; $P=.047$). Thus, the postoperative level of PTH could be crucial for preservation of renal function. The preservation of at least 1 entire PG (group 1) resulted in higher PTH levels up to 1 year after PT and was associated with recovery of renal graft function within the same period.

The level of PTH should be associated primarily with the amount of viable PG tissue. In our study, the amount of the remaining PG tissue was classified by experienced endocrine surgeons in correspondence to the size of normal PGs. In groups 1 and 2, the amount of parathyroid tissue that remained in situ was estimated as being equivalent to 2 normal-sized PGs. Since the PG remnants were not measured intraoperatively, the differences in PTH levels could result from differences in absolute amounts of retained PG tissue. Otherwise, partial resection of the PG could negatively influence the function of the retained tissue, eg, by a deficit in blood supply or inflammatory responses. So far, our retrospective analysis shows the benefit for renal graft function when PG tissue can be retained, without manipulation; however, we cannot clarify the mechanism.

To assess the adjustment of calcium and PTH levels, we used a homogenous follow-up interval of 60 months, which was based on the mean follow-up intervals of retrospective studies^{5,6,10,11,21} analyzing PT after renal transplant. This approach is different compared with that of

the other studies,^{5,6,10,11,21} which usually presented post-operative values after varying intervals, ranging from 1 to 17 years after PT. The homogeneity of follow-up intervals in our study should allow appropriate interpretation of treatment success achieved by the analyzed surgical procedures.

The cure rate in our study was 94% if hypercalcemia is interpreted as treatment failure. Overall, only 5 patients developed hypercalcemia after PT, and no statistically significant accumulation of patients with hypercalcemia was found in any group. Four patients were treated successfully with calcimimetics, and 1 patient remained mildly hypercalcemic while receiving cholecalciferol. Our rates of hypercalcemia, which were below 10% in each group, are similar to those of other studies^{6,8,9,11,22,23} that analyzed incomplete PT after detection of at least 4 PGs per patient. Rates of 33% for persistent hypercalcemia or of 73% for repeated PT were reported only when 4 PGs were not detected.^{5,10} Thus, the cure rate might depend mainly on the surgical accuracy to detect at least 4 PGs rather than the extent of PG resection, as long as the decision for resection is based on evaluation of 4 PGs.

An important tool used to define the appropriate extent of PG resection in patients with tHPT might be the intraoperative measurement of PTH (ioPTH). A recently published study²⁴ reported that ioPTH altered the management in 18 of 72 patients with tHPT (25%); of these, 15 patients received an incomplete PT, preserving 2 (n=6) or 3 (n=9) entire PGs. On the other hand, in 3 cases, a supranumerary PG could be detected because ioPTH did not show an adequate decrease despite subtotal PT. Thus, ioPTH might represent an important adjunctive tool to resect PGs to an adequate extent to avoid persistent HPT and deterioration of renal graft function.

Treating tHPT in renal transplant recipients is complex; the most important goal in treatment is preservation of renal graft function, since quality of life, as well as low risk for bone disease and vascular calcification, is determined primarily by good renal function.

Our study shows that preservation of a least 1 entire PG is less hazardous for renal graft function. We conclude that identification and evaluation of at least 4 PGs is mandatory in patients who have received renal transplants to determine the appropriate surgical procedure, with the first goal to preserve renal function and the second goal to provide long-term regulation of calcium homeostasis and PTH secretion. The experience of an endocrine surgeon to detect and assess PGs is important to reach these goals. The ioPTH could be an adjunctive tool to assess the adequate extent of PG resection. Based on our data, the preservation of at least 1 entire PG is preferred. If the most morphologically conserved PG is far larger than 2 normal-sized PGs, an incomplete PT with partial resection of the most morphologically conserved PG would be more appropriate than a complete PT with autotransplantation. The PG remnant should be handled very carefully so that no deficit in blood supply, hematoma, or severe inflammatory reaction will interfere with the function of the tissue. The PG remnant should be tagged so that it can be detected more easily if surgical intervention is required again to cure recurrent tHPT.

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INVITED CRITIQUE

Sometimes Less Is More

The most effective therapy for tertiary hyperparathyroidism (tHPT) after renal transplantation is parathyroidectomy (PT).¹ Most patients present with 4-gland hyperplasia, which is successfully treated with subtotal (3.5-gland) PT. However, a subset of patients with tHPT will have only 1 or 2 enlarged glands at the time of the operation, and the surgical management of these patients has been a topic of considerable debate. Some experienced groups advocate subtotal or total PT for all patients with tHPT; at the University of Wisconsin, we have strongly supported a practice of “limited” PT or resection of only the 1 or 2 enlarged glands in this subset of patients. Our operative strategy is based on the fact the patients who have a limited PT have an equivalent cure rate but a lower incidence of temporary and permanent hypocalcemia compared with those who undergo a more aggressive resection.^{2,3} In this article, Jäger and colleagues⁴ examined the incidence of postoperative PT renal graft deterioration in patients with tHPT. They justly emphasize that “the most important goal in treatment is preservation of renal graft function” and found that renal graft deterioration occurred with the more aggressive surgical resection of PGs. Conversely, limited or “incomplete” PT did not negatively affect renal graft function. Importantly, the cure rates following limited or aggressive resection were identical. Thus, Jäger et al provide data to support the practice of limited PT in select patients with tHPT and stress the importance of surgi-

cal experience and judgment. Sometimes, *less* surgical intervention leads to *more* benefit for the patient.

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