Long-term Results of Subtotal vs Total Parathyroidectomy Without Autotransplantation in Kidney Transplant Recipients

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Hypothesis: Total parathyroidectomy without autotransplantation in kidney transplant recipients leads to reduced recurrence rates and similar improvement of clinical symptoms compared with subtotal parathyroidectomy.

Design: A retrospective cohort study.

Setting: University clinic.

Patients: Thirty-three patients with functioning renal grafts who underwent primary total (n=17; group 1) or subtotal (n=16; group 2) parathyroidectomy for renal hyperparathyroidism.

Main Outcome Measures: Long-term levels of intact parathyroid hormone, serum calcium, phosphate, alkaline phosphatase, creatinine, and vitamin D; bone pain; use of medication; and incidence of persistent or recurrent hyperparathyroidism.

Results: The mean length of follow-up was 31 months in group 1 and 41 months in group 2. In all patients, postoperative serum calcium and phosphate levels normalized and bone pain markedly decreased. Persistent hypocalcemia was not observed. Serum creatinine levels intermittently increased in both groups but returned to preoperative levels in most of the patients. In group 1, all patients had undetectable intact parathyroid hormone levels throughout the study period. In group 2, 2 patients had persistent and 3 patients developed recurrent hyperparathyroidism (31%) that required therapy with cinacalcet hydrochloride in 3 cases. In 4 of these 5 patients, intact parathyroid hormone levels were greater than 54 ng/L directly after operation. In all, 27 of 33 patients (82%) received cholecalciferol therapy. Additional calcium supplementation was used by 12 group 1 patients (71%) and 3 group 2 patients (19%).

Conclusions: Total parathyroidectomy in kidney transplant recipients appears to be safe and protective against persistent and recurrent disease. If subtotal parathyroidectomy is performed, the remnant should be small.

Arch Surg. 2008;143(8):756-761

Surgery for renal hyperparathyroidism is indicated in 15% to 38% of patients with end-stage renal disease, depending on the duration of dialysis.1 Even after successful renal transplantation, 25% of the patients have elevated levels of intact parathyroid hormone (iPTH) after 1 year, despite functioning grafts and improved medical management,2 and about 5% require parathyroidectomy.3,4

See Invited Critique at end of article

Currently, subtotal parathyroidectomy with a cervical remnant and total parathyroidectomy with autotransplantation are the standard procedures for renal hyperparathyroidism.3 In both cases, only vague recommendations exist with regard to the size of the remnant gland, and there are no guidelines for the optimal postoperative iPTH level. Most authors advise leaving only unaltered tissue.6 In the German guidelines, a remnant of about 60 to 80 mg is recommended.7 Both of these requirements are difficult to fulfill.

Despite an initial successful operation, recurrence rates after subtotal parathyroidectomy are relatively high and increase with time.8,9 In addition, reoperations for recurrent disease are technically demanding and often wearisome.10 Therefore, some authors have performed total parathyroidectomy without autotransplantation in recent years, a procedure that was first described in 196711 and then abandoned owing to the potential complications of adynamic bone disease and hypocalcemia.12 So far, experience with this procedure is very limited and is mainly applied in patients receiving dialysis.
In an initial study with 11 patients receiving long-term dialysis, our group showed that total parathyroidectomy followed by calcium and cholecalciferol (vitamin D) therapy led to rapid and sustained improvement of bone pain and to regression of high-turnover osteopathy.13 Owing to these and other encouraging results,14 the referring nephrologists extended the indication to kidney transplant recipients.

The aims of this study were to determine the long-term results of total parathyroidectomy without autotransplantation in patients after kidney transplantation and to compare the outcomes with those of subtotal parathyroidectomy.

METHODS

SELECTION OF PATIENTS

From January 5, 1997, to May 31, 2006, 125 kidney transplant recipients underwent surgery for renal hyperparathyroidism at our center. The operation was considered mandatory by the consulting nephrologists in the case of elevated iPTH level, symptomatic hypercalcemia, progressive skeletal and articular pain, or extraskeletal ossifications. Two groups were studied. From December 1, 2000, through May 31, 2006, 17 patients underwent total parathyroidectomy without autotransplantation (group 1). A second group of 16 comparable patients who underwent subtotal parathyroidectomy with a cervical remnant within the same period served as the control group (group 2). The decision to perform subtotal or total parathyroidectomy was made by the referring nephrologists and depended on the individual course and symptoms of each patient. Indications for total parathyroidectomy were exceedingly high blood levels of calcium and iPTH despite adequate medical treatment, low patient compliance, and impaired kidney graft function. The individual surgeons had no influence on the type of procedure.

A subtotal parathyroidectomy was performed in the remaining 92 patients who were not part of the study population. Of these patients, 4 (4%) have had persistent hyperparathyroidism and 19 (21%) developed recurrent hyperparathyroidism by the last follow-up examination, but long-term data are still missing.

DEFINITION OF TOTAL AND SUBTOTAL PARATHYROIDECTOMY

In all patients, 4 parathyroid glands were identified. In cases of subtotal parathyroidectomy, a small cervical remnant of the least altered gland was left in situ. Cervical thymectomy was not routinely performed. All removed glands were divided for histological examination and cryopreservation. In some of the patients, iPTH levels were measured intraoperatively by means of an immunological rapid assay as previously described.15 The operation was defined as total parathyroidectomy if the iPTH level was higher than 1 ng/mL directly after operation. In case of an iPTH level of more than 1 ng/mL, the operation was defined as subtotal parathyroidectomy. The definition was based on the postoperative result only and not on the intended type of operation to make postoperative results comparable. Subsequent operations were excluded from the analysis.

FOLLOW-UP

Before and after surgery and in the long term, the following laboratory values were measured at regular intervals in the outpatient clinic: iPTH level with a commercially available antibody assay (reference range, 12-72 pg/mL), serum calcium level (reference range, 8.6-10.6 mg/dL), serum phosphate level (reference range, 0.8-1.5 mmol/L), alkaline phosphatase level (reference range, 60-180 U/L), creatinine level (reference cutoff value, \( \leq 1.3 \) mg/dL), glomerular filtration rate (reference range, 80-140 mL/min), 1,25 dihydroxyvitamin D level (reference range, 28.8-67.3 pg/mL), and 25-hydroxyvitamin D level (reference range, 14.0-60.1 ng/mL). In addition, the course of bone pain, use of calcium supplements and cholecalciferol, and kidney graft function were regularly recorded.

MANAGEMENT ALGORITHM POSTOPERATIVELY

All patients received oral calcium gluconate (2.3 g/d) directly after operation. Serum calcium levels were monitored at least twice daily and in cases of hypocalcemic symptoms. The target serum level was 7.6 to 8.0 mg/dL. In case of lower serum calcium levels despite oral therapy, intravenous calcium gluconate, 10%, was given continuously (4-12 g/d). In addition, patients routinely received oral cholecalciferol (1.25 dihydroxyvitamin D, 2-3 µg/d). Patients were discharged from the hospital as soon as serum calcium levels stabilized with oral calcium and cholecalciferol therapy. In the long term, calcium and cholecalciferol dosages were adjusted according to serum calcium levels.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS statistical software (version 10.0; SPSS Inc, Chicago, Illinois). Variables with gaussian distribution are expressed as mean (SD). To compare discrete variables, we performed the \( \chi^2 \) test. Statistical significance was considered with \( P < .05 \), with a power of 80%.

SI CONVERSION FACTORS

To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, by 88.4; iPTH to nanograms per liter, by 2.496; phosphate, alkaline phosphatase, and creatinine and the glomerular filtration rate (Table 1 and Table 2). Intraoperative measurement of iPTH levels was available in 12 of 17 total and 6 of 16 subtotal parathyroidectomies. Mean intraoperative iPTH levels were monitored in 12 of 17 total and 6 of 16 subtotal parathyroidectomies. Intraoperative measurement of iPTH levels was available in 12 of 17 total and 6 of 16 subtotal parathyroidectomies. Mean intraoperative iPTH levels were compared in group 1 and group 2 (Table 1 and Table 2). Intraoperative measurement of iPTH levels was compared in group 1 and group 2 (Table 1 and Table 2). Intraoperative measurement of iPTH levels was compared in group 1 and group 2 (Table 1 and Table 2).

RESULTS

GENERAL DATA AND PERIOPERATIVE iPTH LEVELS

The mean follow-up was 41 (range, 15-78) months in group 1 and 31 (range, 10-97) months in group 2. Patients were comparable regarding age, sex, and levels of preoperative iPTH, vitamin D, serum calcium, phosphate, alkaline phosphatase, and creatinine and the glomerular filtration rate (Table 1 and Table 2). Intraoperative measurement of iPTH levels was available in 12 of 17 total and 6 of 16 subtotal parathyroidectomies. Mean intraoperative iPTH levels were lower in group 1 than in group 2 (45 [33] vs 654 [721] pg/mL, compared with preoperative levels of 724 [779] pg/mL in group 1 and 654 [721] pg/mL in group 2). In 1 patient of group 2, the criterion of successful surgery, an iPTH level of less than 150 pg/mL, was not achieved according to serum calcium levels.

On the second day after parathyroidectomy, all patients were comparable regarding age, sex, and levels of preoperative iPTH, vitamin D, serum calcium, phosphate, alkaline phosphatase, and creatinine and the glomerular filtration rate (Table 1 and Table 2). Intraoperative measurement of iPTH levels was available in 12 of 17 total and 6 of 16 subtotal parathyroidectomies. Mean intraoperative iPTH levels were lower in group 1 than in group 2 (45 [33] vs 654 [721] pg/mL, compared with preoperative levels of 724 [779] pg/mL in group 1 and 654 [721] pg/mL in group 2). In 1 patient of group 2, the criterion of successful surgery, an iPTH level of less than 150 pg/mL, was not achieved according to serum calcium levels.

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### Table 1. Patient Demographics and Laboratory Values Before and After Surgery and Treatment After Total Parathyroidectomy

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Time, mo</th>
<th>Ca</th>
<th>P</th>
<th>iPTH</th>
<th>1VD</th>
<th>1,25 VD</th>
<th>Cr</th>
<th>GFR</th>
<th>AP</th>
<th>Low Ca Levels&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Long-term Levels</th>
<th>Calcium Gluconate, g/d</th>
<th>Cholecalciferol, µg/d</th>
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<td>79</td>
</tr>
</tbody>
</table>

Abbreviations: AP, alkaline phosphatase; Ca, calcium; Cr, creatinine; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; NA, not available; P, phosphate; 1VD, 25-hydroxyvitamin D; 1,25 VD, 1,25 dihydroxyvitamin D.

SI conversion factors: To convert Ca to millimoles per liter, multiply by 0.25; Cr to micromoles per liter, multiply by 88.4; iPTH to nanograms per liter, multiply by 1; 1VD to nanomoles per liter, multiply by 2.496; and 1,25 VD to picomoles per liter, multiply by 2.6.

<sup>a</sup>Alkaline phosphatase is reported in units per liter; Ca and Cr, milligrams per deciliter; GFR, milliliters per minute; iPTH, picograms per liter; P, millimoles per liter; 1VD, nanograms per liter; and 1,25 VD, picograms per liter.

<sup>b</sup>Indicates time from kidney transplantation and parathyroidectomy.

<sup>c</sup>Indicates lowest serum Ca level.

<sup>d</sup>The postoperative and long-term levels of iPTH were zero for all patients.
iPTH levels of more than 2000 pg/mL. The individual courses of iPTH levels after subtotal parathyroidectomy are depicted in the Figure. After total parathyroidectomy, iPTH levels were undetectable in all patients and remained unchanged throughout the study period.

Two patients who originally intended to have a total parathyroidectomy had detectable iPTH levels (71 and 6 pg/mL) postoperatively, despite removal of 4 parathyroid glands. Therefore, the operations were classified as subtotal parathyroidectomies and the patients were distributed to group 2 (patients 1 and 2). Long-term iPTH levels remained stable in both of these patients. Likewise, 2 other patients who were scheduled for subtotal parathyroidectomy had undetectable iPTH levels after the operation and during long-term follow-up, probably because of an insufficient blood supply to the cervical remnant. Both of these patients were classified as group 1 (patients 3 and 11).

CLINICAL COURSE AND SERUM CALCIUM, PHOSPHATE, ALKALINE PHOSPHATASE, AND VITAMIN D LEVELS

The courses of serum calcium levels (preoperative, lowest postoperative, and long-term) in both groups are shown in Tables 1 and 2. As expected, postoperative calcium levels were lower in group 1, but in the long term, they increased to values within the reference range. None of the patients experienced short- or long-term severe hypocalcemia or hypocalcemic symptoms. The length of the hospital stay was comparable in both groups.

Vitamin D levels were within reference ranges in most patients of both groups, and phosphate levels were comparable (Tables 1 and 2). Levels of alkaline phosphatase decreased postoperatively in both groups (Table 2). All patients reported that bone pain was markedly relieved after the operation.

KIDNEY FUNCTION

Serum creatinine levels and glomerular filtration rates were comparable in both groups (Tables 1 and 2). In most of the patients, creatinine levels increased shortly after the operation; however, they remained stable in 2 patients of each study group. Long-term creatinine levels returned to preoperative values except in 3 group 1 patients and 2 group 2 patients. Overall, 1 patient in each group developed graft failure that was not attributable to the parathyroidectomy. In addition, 1 patient in group 1 had primary nonfunction of the graft.

LONG-TERM MEDICATION USE

At the last follow-up visit, 14 patients in group 1 (82%) and 13 patients in group 2 (81%) received cholecalciferol (dosage range, 0.25-2.0 µg/d). Twelve of 17 group 1 patients (71%) and 3 of 16 group 2 patients (19%) received additional calcium gluconate therapy (dosage range, 0.5-2.0 g/d). The difference in calcium medication use was statistically significant (P = .005). Individual dosages of calcium and cholecalciferol are shown in Tables 1 and 2.

PERSISTENT AND RECURRENT DISEASE

None of the patients in group 1 developed long-term recurrent hyperparathyroidism. In contrast, 5 of the patients in group 2 (31%) had iPTH levels above the reference range; the 2 patients with persistent hyperparathyroidism had further long-term increases in iPTH levels. Three additional patients developed true recurrences. One of the 5 patients had graft failure; however, the others had functioning grafts. In 4 of the 5 patients, iPTH levels were more than 54 pg/mL immediately after the operation. Three patients required cinacalcet hydrochloride. The course of iPTH levels in these 5 patients is shown in Table 3. The difference in rates of recurrent or persistent disease was statistically significant (P = .02).

### Table 3. Data of the 5 Patients With Persistent or Recurrent Disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>iPTH Levels, pg/mL</th>
<th>Long-term Ca Level, mg/dL</th>
<th>Medication Use</th>
<th>Graft Function</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>Long-term</td>
<td></td>
</tr>
<tr>
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<td>2000</td>
<td>123</td>
<td>240</td>
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<td>5</td>
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<td>6</td>
<td>149</td>
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</table>

Abbreviations: Ca, calcium; iPTH, intact parathyroid hormone.

SI conversion factors: To convert Ca to millimoles per liter, multiply by 0.25; iPTH to nanograms per liter, multiply by 1.
In this retrospective analysis, subtotal and total parathyroidectomy without autotransplantation led to a normalization of serum calcium and phosphate levels, a decrease of alkaline phosphatase levels, and improvement of bone pain in all patients. Severe hypocalcemia was not observed.

In group 2, 2 patients had persistent disease with increasing iPTH levels over time, and 3 patients developed recurrence in the long term. Two aspects are especially interesting in these 5 patients. First, 4 of the 5 patients had functioning renal grafts. This fact contradicts the thesis that recurrent disease needs an ongoing stimulus for parathyroid growth. Second, recurrence was seen even in patients with very low iPTH levels directly after the operation. The cutoff for the development of recurrence was 56 pg/mL. On the other hand, this means that only 1 patient with a postoperative iPTH level of less than this cutoff had recurrent disease (7.6%). Because 3 of the 5 patients required cinacalcet therapy, the hyperparathyroidism was clinically relevant. None of the patients with total parathyroidectomy had a recurrence.

From these preliminary results it seems that, even in patients with good renal function, the parathyroid remnant should be small if a subtotal parathyroidectomy is performed.

Comparison with other reports is difficult for several reasons. Experience with total parathyroidectomy is still limited. From 1989 to 2006, 8 studies including 147 patients have been published. Only 4 of the 147 patients had functioning renal grafts and 2 were on the waiting list for transplants. Results of total parathyroidectomy were generally good and comparable to those of the control groups undergoing subtotal parathyroidectomy. Similar to our previous and present observations, no adynamic bone disease or symptomatic hypocalcemia occurred during cholecalciferol treatment. Astonishingly, recurrent or persistent disease after total parathyroidectomy was observed in 6 of the 8 published reports, with recurrence rates ranging from 8% to 35%. Nearly all of the patients with presumed total parathyroidectomy had measurable iPTH levels directly after the operation. Especially in patients with renal failure, it seems nearly impossible to completely eliminate parathyroid function.

In the present study, the operation was only defined as total parathyroidectomy if the postoperative iPTH level was less than 1 pg/mL. If this definition is adopted, it would be easier to compare future data.

Most of our patients had increased serum creatinine levels shortly after the operation. This phenomenon has been previously described; however, it is not fully understood. Possible explanations for the intermittent deterioration of graft function are changes in glomerular filtration rate owing to alterations in renal hemodynamics after cessation of iPTH action. Creatinine levels decreased again in the long term. No differences regarding kidney function were observed between the 2 operations.

The only advantage of subtotal parathyroidectomy was the lower number of patients who required additional long-term calcium supplements. Whether the avoidance of calcium supplementation is an advantage of this procedure remains debatable. The reasons why some of the patients did not require calcium supplements and cholecalciferol after total parathyroidectomy to maintain long-term calcium and vitamin D levels within the reference range remain unclear.

In conclusion, total parathyroidectomy is a safe procedure in patients with a functioning renal graft leading to improvement of bone pain and avoidance of persistent or recurrent disease. Nearly all patients need long-term cholecalciferol therapy and calcium supplementation. Further prospective, randomized studies are needed to confirm these preliminary results.

Accepted for Publication: March 28, 2008.
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Author Contributions: Study concept and design: Rayes, Seehofer, Schindler, Reinke, Neuhaus, and Nüssler. Acquisition of data: Rayes, Seehofer, and Schindler. Analysis and interpretation of data: Rayes, Seehofer, Schindler, Kahl, and Ulrich. Drafting of the manuscript: Rayes. Critical revision of the manuscript for important intellectual content: Seehofer, Schindler, Reinke, Kahl, Ulrich, Neuhaus, and Nüssler. Statistical analysis: Rayes and Seehofer. Administrative, technical, and material support: Rayes, Seehofer, Reinke, and Ulrich. Study supervision: Schindler, Kahl, Neuhaus, and Nüssler.

Financial Disclosure: None reported.

REFERENCES
Tertiary hyperparathyroidism (t-HPT) is a complex disorder, typically referring to approximately 5% of patients whose parathyroid secretion fails to normalize within 1 year after renal transplant. Correction of hypercalcemia is important to avoid urolithiasis, bone disease, cardiovascular disease, or impaired renal function. In particular, the osteodystrophy associated with chronic kidney disease is exacerbated by immunosuppressive agents. The standard surgical approach for t-HPT is either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. There are multiple conflicting reports as to the frequency of single- vs multiple-gland involvement and the risks or benefits of routine subtotal parathyroidectomy vs a more selective approach. Associated variables include the adequacy and completeness of the parathyroid resection, the size of the parathyroid remnant, possible implantation of cells from the cut surface of a parathyroid gland, eventual hyperfunction of supernumerary parathyroid glands, the frequency of the transplanted kidney failing, and the limited value of preoperative parathyroid localization or intraoperative parathyroid hormone monitoring.

Rayes et al offer a potential solution for total parathyroidectomy without autotransplantation. Although this option has been used in secondary HPT, its use in t-HPT is very limited. Such a defined, standard option may be appealing as it removes any question of remnant size or viability. Although postoperative medication is mandatory, transplant patients might not view this as a significant inconvenience.

Surprisingly and in contradistinction to vast experience in primary and secondary HPT, significant hypocalcemia in the early postoperative period of these patients with t-HPT was not a problem in the experience of Rayes et al. However, the lack of symptomatic postoperative hypocalcemia, in the total absence of parathyroid hormone levels, may reflect the lack of incorporation of calcium into woven, unmineralized bone (“bone hunger”). There is very realistic concern that total parathyroidectomy may predispose to adynamic bone disease.

With these questions and uncertainties, we believe that either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation must remain the surgical treatment of choice.

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Financial Disclosure: None reported.