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Endocrine

Parathyroidectomy for patients with secondary hyperparathyroidism in a changing landscape for the management of end-stage renal disease

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ABSTRACT

Background: The landscape of patients with end-stage renal disease is changing with the increasing availability of kidney transplantation. In the near future, a less aggressive approach to treat secondary hyperparathyroidism might be beneficial. We report outcomes of parathyroidectomy for end-stage renal disease-related hyperparathyroidism comparing the outcomes of limited, subtotal, and total parathyroidectomy.

Methods: We performed a retrospective analysis of prospectively collected data. Patients were divided into 3 parathyroidectomy subgroups: limited (<3 glands removed), subtotal (3–3.5 glands), and total (4 glands) parathyroidectomy. Primary outcome was serum levels of parathyroid hormone. Secondary endpoints were serum levels of calcium, phosphate, and alkaline phosphatase, postoperative complications, and persistent or recurrent disease rates.

Results: In total, 195 patients were included for analysis of whom 13.8% underwent limited parathyroidectomy, 46.7% subtotal parathyroidectomy, and 39.5% total parathyroidectomy. Preoperative parathyroid hormone levels (pg/mL) were 471 (210–868), 1,087 (627–1,795), and 1,070 (475–1,632) for the limited, subtotal, and total parathyroidectomy groups, respectively ($P < .001$). A decrease in serum parathyroid hormone was seen in all groups; however, postoperative levels remained greater in the limited parathyroidectomy group compared to the subtotal and total parathyroidectomy groups ($P < .001$). Serum calcium, phosphate, and alkaline phosphatase levels decreased in all groups to within the reference range. In the limited parathyroidectomy group, persistent disease and recurrence occurred more frequently ($P = .02$ and $P = .07$, respectively).

Conclusion: Subtotal parathyroidectomy is the optimal strategy in an era with an increasing availability of kidney transplantation and improved regimens of dialysis. In this changing practice, the approach to parathyroid surgery, however, might shift to a less aggressive and patient-tailored approach.

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Introduction

The development of secondary hyperparathyroidism (HPT) is a common consequence in patients with end-stage renal disease (ESRD) undergoing long-term dialysis. The prevalence of patients in

Australia on renal replacement therapy was 1,026 per million people in 2018.¹ Approximately half of the patients developed serum parathyroid hormone (PTH) levels >300 pg/mL requiring treatment.^{2–4} By treating its underlying cause, kidney transplantation (KTx) would be the optimal strategy to correct ESRD-related HPT. Indeed, HPT is cured in 57% of the patients receiving a renal transplant.⁵ In patients with HPT, vitamin D analogs, phosphate binders, and a calcimimetic agent are administered commonly to decrease serum PTH levels.⁴ According to current

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guidelines, parathyroidectomy (PTx) is only advised in case of insufficient response to pharmacologic therapy or calcimimetic intolerance.⁴ Commonly, subtotal PTx or total PTx with or without autotransplantation of a single gland are advocated to treat secondary HPT. Previous studies have reported significant improvement of HPT-related symptoms postoperatively.^{6,7} Recently, Chen et al conducted a meta-analysis showing that total PTx + autotransplantation and subtotal PTx have similar outcomes with respect to effect on serum PTH levels and recurrence and persistent rates of HPT.⁸ The majority of these included studies dated from before the year 2000, and the 2 most recent included studies were retrospective analyses with only a small number of patients in at least 1 of the study arms.^{9,10} However, between 2000 and 2017, the number of kidney transplantations almost doubled in Australia.¹¹ Therefore, in patients eligible for KTx, HPT secondary to ESRD becomes more and more a temporary problem, and the strategies for HPT treatment should focus on bridging time until KTx. To maintain the patient in optimal condition for KTx, it is important to decrease the number of complications and to avoid (persistent) hypocalcaemia and the risk of recurrent HPT. Transient hypocalcaemia occurs frequently after both subtotal and total PTx (15%–30%), whereas permanent hypocalcaemia is less commonly seen (0–7%) after subtotal PTx.^{12–15} Hypocalcaemia is potentially unbeneficial for the kidney graft.

Therefore, it can be argued that in carefully selected patients with moderately increased PTH levels who are likely to receive a KTx in the near future a less aggressive operative approach is sufficient or even beneficial. This study describes operative and biochemical outcomes of PTx for ESRD-related HPT, comparing the 3 operative procedures: limited PTx, subtotal PTx, and total PTx.

Methods

Patient population

The Endocrine Surgery Unit of the University of Sydney collected surgical data prospectively of all patients undergoing PTx from 1967 onward, including patient demographics, history of KTx before PTx, histopathology results, outcomes, and complication rates. Informed consent was retrieved from every patient to record these data.

For this analysis, all patients who underwent parathyroid operations for ESRD-related HPT between January 1998 and December 2016 were included. The following data were extracted from electronic patient record systems: patient characteristics such as body mass index, American Society of Anesthesiologists physical status classification, medical history, and relevant laboratory results. These data were analyzed retrospectively. This study was approved by the Northern Sydney Local Health District Human Research Ethics Committee.

Study design

Primary and secondary endpoints

Three groups of patients were identified according to the number of parathyroid glands removed during the operation: 4 glands removed (total PTx); 3–3.5 glands removed (subtotal PTx); and <3 glands removed (limited PTx). The primary outcome measure was serum PTH levels during follow-up, measured at discharge, 3 months, 6 months, and 1 year post PTx. Secondary endpoints were baseline characteristics, pre and postoperative laboratory values including serum levels of calcium, phosphate, albumin, and alkaline phosphatase, and rates of postoperative complications and persistent or recurrent disease. Persistent disease was defined as a postoperative decrease in serum PTH of less

than 70% compared to preoperative PTH levels. Recurrent hyperparathyroidism was defined as patients with an initial decrease in PTH of $\geq 70\%$ and an increase of PTH of ≥ 5 times the postoperative value at 1 year postoperatively. Calcium levels were adjusted for albumin using the following equation: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + $(0.025 \times (40 - [\text{albumin (g/L)}]))$. The following reference ranges were applied: PTH, 10–55 pg/mL; corrected calcium, 2.15–2.55 mmol/L; phosphate, 0.75–1.50 mmol/L; alkaline phosphatase, 30–110 U/L.

Statistical analyses

Categorical variables are described as count (*n*) and percentage (%). The Shapiro-Wilk normality test was used to determine distribution of continuous variables. Normally distributed variables are expressed as mean $\pm$ standard deviation (SD), skewed distributed data as median (interquartile range). Results were compared among the 3 groups using the χ^2 test, analysis of variance, and Kruskal-Wallis test. Statistics were performed using SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY). *P* values equal or less than .05 were considered statistically significant. A power analysis was performed, and a study population of at least 63 patients was required to detect a 20% relative difference in the primary outcome variable of serum PTH level between groups, with a power of 80% and an alpha of 0.05.

Results

Baseline characteristics

In total, 195 patients underwent PTx to treat ESRD-related HPT between 1998 and 2016. Baseline characteristics are provided in Table 1. Mean age of all patients was 56 ± 15 years and did not differ among the 3 groups. Furthermore, there was no difference in sex, body mass index, American Society of Anesthesiologists classification, type of renal replacement therapy, and duration of dialysis between the groups. Thymectomy was performed more frequently in patients who underwent subtotal and total PTx compared to patients with <3 glands removed (limited PTx group: 58%, subtotal PTx: 91%, total PTx 90%; $P < .001$). Of the 77 patients who underwent total PTx, 8 (10%) underwent autotransplantation of parathyroid tissue in the sternocleidomastoid muscle, compared with 0% in both the limited PTx and subtotal PTx groups ($P = .002$). The majority of all patients did not receive a KTx at all (80%). In the limited PTx group, 4% of the patients underwent KTx before PTx, whereas 22% and 9% of the patients received a KTx in the subtotal and total PTx groups, respectively ($P = .05$).

Types of PTxs over time

Of the 195 patients who underwent a PTx, 13.8% underwent a <3 gland removal, 46.7% a subtotal PTx, and 39.5% a total PTx. Over the past 2 decades, the percentage of total PTxs decreased ($R^2 = 0.18$; $P = .07$), whereas the rate of subtotal PTxs increased ($R^2 = 0.53$; $P < .001$). The percentages of patients who underwent a <3 gland removal remained stable over the years ($R^2 = 0.04$; $P = .42$).

Parathyroid hormone levels

Pre and postoperative PTH levels are shown in Fig 1. Preoperative PTH levels differed between the 3 groups ($P < .001$). There was no difference between preoperative PTH levels comparing only the subtotal with the total PTx group (1,087 [627–1,795] pg/mL vs 1,070 [475–1,632] pg/mL; $P = .67$). Postoperatively, PTH levels decreased in all 3 groups with a median reduction of 98% (93–99)

Table I
Baseline characteristics

	Total (n = 195)	<3 glands (n = 27)	3–3.5 glands (n = 91)	4 glands (n = 77)	P value
Age, y	56 ± 15	57 ± 16	54 ± 15	57 ± 15	.53
Sex, female (%)	124 (63.6)	17 (63)	58 (64)	49 (64)	1.0
BMI, kg/m ²	26.4 (22.8–31.9)	28.4 (24.0–33.7)	25.5 (22.2–31.7)	26.5 (23.0–31.9)	.72
ASA classification					.78
II	4 (2.8)	0 (0.0)	3 (3.8)	1 (2.0)	
III	110 (75.9)	123 (81.3)	56 (70.9)	41 (82.0)	
IV	30 (20.7)	3 (18.7)	19 (24.1)	8 (16.0)	
Type of RRT (%)					.11
None	8 (5.4)	3 (18)	4 (5)	1 (2)	
Hemodialysis	85 (57)	8 (47)	44 (55.)	33 (64)	
Peritoneal dialysis	24 (16.1)	2 (12)	11 (14)	11 (21)	
Kidney transplantation	32 (21.5)	4 (24)	21 (26)	7 (14)	
Duration of dialysis, mon	62 (31–109)	41 (9–178)	71 (33–111)	51 (31–83)	.37
Thymectomy, n (%)	166 (86.0)	11 (58)	83 (91)	68 (90)	.0001
Autotransplantation, n (%)	8 (4.1)	0	0	8 (10.4)	.002

ASA, American Society of Anesthesiologists; BMI, body mass index; RRT, renal replacement therapy.

($P < .001$ for all groups). At discharge, 3, 6, and 12 months postoperatively, PTH levels were greater in the limited PTx group compared with the other 2 groups ($P = .002$). Postoperative PTH levels of the subtotal PTx group remained greater at 1-year follow-up compared to the total PTx group (67 [12–210] pg/mL vs 4 [4–31] pg/mL, respectively; $P < .001$).

Calcium, phosphate, and alkaline phosphatase

Pre and postoperative corrected serum calcium levels are shown in Table II and Fig 2 and did not differ between the 3 groups. Three months after PTx, serum corrected calcium was ameliorated in all 3 groups ($P = .012$, $P < .001$, and $P < .001$ for the limited PTx, subtotal PTx, and the total PTx groups, respectively). After 1 year of follow-up, serum corrected calcium levels were still improved compared to preoperatively in the subtotal PTx group and the total PTx group (both $P < .001$); in contrast, the levels in the limited PTx comparing preoperative and 1-year corrected calcium measurements were not different ($P = .46$). In the subtotal PTx and total PTx groups, serum phosphate levels decreased after PTx ($P < .001$). There was no difference in the limited PTx group during follow-up with respect to serum phosphate levels.

Serum alkaline phosphatase levels early postoperatively did not improve; however, they were significantly ameliorated at 3 months after PTx ($P < .001$) in all groups. Also, at 1-year follow-up, the levels were still within the reference range and decreased compared to preoperative measurements ($P = .028$, $P < .001$, and $P < .001$ for the limited PTx, subtotal PTx, and total PTx group, respectively).

Parathyroid weight

Of all patients, the median weight of resected parathyroid glands was 1,643 (interquartile range, 812–3,105) milligrams. Median weight differed among the 3 groups; 658 (257–2,000) vs 1,667 (812–3,027) vs 2,000 (1,120–3,501) for the limited PTx, subtotal PTx, and total PTx group, respectively ($P = .002$).

Persistence, recurrence, and complication rates

Persistent disease was seen in 7 (3.6%) of the patients overall. The prevalence of persistent disease was greater in the limited PTx group (11%) compared to the subtotal and total PTx group ($P = .02$).

After 1 year of follow-up, 15 patients (7.7%) had recurrent disease. Recurrence developed more frequently in patients who underwent a <3 gland removal compared to the subtotal and total PTx

groups (15% vs 10% vs. 23%, respectively; $P = .07$). Postoperative complications are listed in Table III. There was no difference in complication rates between the 3 groups ($P = .48$).

Discussion

In a changing era with an increasing rate of KTx, the treatment strategy of HPT related to ESRD might have to shift toward a less aggressive approach in a carefully selected group of patients, ensuring adequate parathyroid function before and after KTx. This study is the first to report a limited PTx as a new operative strategy in the treatment of patients with ESRD-related HPT. We aimed to describe recent operative outcomes in a dedicated endocrine surgery unit and to compare the biochemical and operative outcome of limited PTx, subtotal PTx, and total PTx.

Although subtotal PTx and total PTx are considered standard of care both globally as within our endocrine surgery department, <3 parathyroid glands were resected during PTx in a considerable number of our patients (14%). Potential indications to deviate from standard practice include relatively low PTH levels but calcimimetic intolerance, a planned living-donor KTx in the near future, or the identification of normal appearing parathyroid glands intraoperatively. Finally, in some patients no more than 3 parathyroid glands could be found during exploration.

The efficacy of PTx has been shown in many previous studies.^{9,16} Studies comparing different operative approaches in patients with ESRD-related HPT date from before the year 2000 or have a small number of patients in at least 1 of the study arms.⁸ Moreover, studies investigating the outcome of a <3 gland removal in the ESRD population are scarce. Subtotal PTx (3–3.5-gland removal) seems equally effective in decreasing serum levels of PTH, calcium, and phosphate compared to total PTx (4-gland removal), and a median decrease in PTH levels after PTx of 98% was observed, which is consistent with previous comparative studies.^{8,9}

Postoperative PTH levels were greater in patients who underwent a limited PTx or subtotal PTx compared to patients who underwent total PTx, but we found a statistically significant decrease in PTH levels and normalization of serum calcium, phosphate, and alkaline levels in all groups. In the ESRD population, a delicate equilibrium of mineral and bone disorder markers is required. The Kidney Disease Improving Global Outcomes chronic kidney disease-mineral and bone disorder recommends maintaining PTH levels in stage 5 patients with chronic kidney disease in the range of 2 to 9 times the upper limit of normal to prevent hypocalcemia.⁴ It could be argued that this target range should be applied for postPTx PTH values as

Fig. 1. PTH preoperative, at discharge, 3 months, 6 months, and 12 months after PTx.

well, especially because hungry bone syndrome is a common complication after PTx in the ESRD population, often leading to prolonged calcium supplementation.¹⁶ Because both the relationship between serum calcium concentration and PTH levels with the risk of all-cause mortality are J- or U-shaped, it is of utmost importance for these already fragile patients to aim for optimal mineral and bone status after PTx.^{17,18} Total PTx led to postoperative PTH levels less than the reference range, which might be too low for this patient population, and total PTx without autotransplantation might no longer be appropriate given these results.

By eliminating its underlying cause, KTx is theoretically the optimal treatment for ESRD-related HPT. The transplanted kidney is again able to maintain adequate concentrations of serum calcium and phosphate, thus the parathyroid glands are no longer stimulated to synthesize and release PTH excessively. Indeed, in 57% of the cases, serum PTH levels resolve spontaneously within 2 years after KTx.⁵ Because the rates of both deceased donor and living donor KTx is increasing and waiting time for KTx is expected to decrease, a less aggressive operative approach to parathyroid operations for HPT in this population might be needed. Especially if the patient will receive a kidney transplant in the near future,

Table II
Laboratory values

	Total	<3 glands	3–3.5 glands	4 glands	P value
PTH, pg/mL					
Preoperatively	1,037 (507–1,606)	471 (210–868)	1,087 (627–1,795)	1,070 (475–1,632)	< .0001
At discharge	17 (17–59)	35 (11–61)	23 (9–76)	7 (4–22)	< .0001
3 mo postop	21 (4–139)	25 (13–282)	37 (7–173)	4 (4–26)	.001
6 mo postop	18 (4–156)	19 (4–226)	32 (6–188)	4 (4–19)	< .0001
1 y postop	31 (4–138)	119 (18–265)	63 (10–164)	4 (4–32)	< .0001
Corrected calcium, mmol/L					
Preoperatively	2.54 (2.33–2.71)	2.53 (2.18–2.70)	2.56 (2.45–2.72)	2.54 (2.33–2.71)	.73
At discharge	2.33 (2.18–2.48)	2.29 (2.20–2.50)	2.37 (2.18–2.47)	2.28 (2.13–2.49)	.56
3 mo postop	2.27 (2.10–2.41)	2.21 (2.11–2.37)	2.27 (2.11–2.45)	2.28 (2.06–2.43)	.75
6 mo postop	2.28 (2.09–2.45)	2.28 (2.13–2.38)	2.33 (2.09–2.44)	2.26 (2.06–2.48)	.78
1 y postop	2.31 (2.20–2.43)	2.17 (2.06–2.43)	2.36 (2.20–2.46)	2.30 (2.20–2.35)	2.35
Phosphate, mmol/L					
Preoperatively	1.66 (1.21–2.05)	1.31 (1.01–1.61)	1.66 (1.14–2.06)	1.77 (1.31–2.19)	.55
At discharge	1.25 (0.96–1.60)	1.21 (0.97–1.69)	1.30 (0.94–1.60)	1.22 (0.98–1.58)	.82
3 mo postop	1.28 (1.05–1.74)	1.25 (1.07–1.90)	1.45 (1.06–1.74)	1.26 (0.96–1.67)	.74
6 mo postop	1.51 (1.09–1.92)	1.17 (0.90–2.11)	1.49 (1.08–2.00)	1.55 (1.18–1.90)	.80
1 y postop	1.49 (1.15–1.88)	1.43 (1.17–2.14)	1.48 (1.02–2.12)	1.53 (1.23–1.82)	.87
Alkaline phosphatase					
Preoperatively	140 (91–196)	108 (80–159)	150 (90–196)	138 (99–209)	.25
At discharge	109 (64–222)	125 (86–253)	146 (80–294)	127 (81–252)	.76
3 mo postop	91 (60–127)	107 (57–145)	93 (61–136)	79 (58–113)	.66
6 mo postop	72 (56–96)	96 (54–100)	72 (62–97)	65 (52–89)	.21
1 y postop	73 (55–96)	94 (68–113)	72 (53–95)	70 (54–94)	.35

postop, postoperatively.

Fig. 2. Pre- and postoperative laboratory values.

limited PTx might be the optimal strategy for patients intolerant to calcimimetics and in kidney transplant recipients with moderately increased PTH levels. By averting the need for a 4-gland exploration, the risk of recurrent laryngeal nerve damage and vocal cord palsy will decrease substantially as do the postoperative risks during reoperation for persistent or recurrent disease. In our cohort, although not statistically significant, recurrence seemed to occur more frequently in patients undergoing a limited PTx compared with patients who underwent conventional subtotal or

total PTx. It should be noted that this study was not designed to assess the difference in recurrence rates between the different operation types, so the study might be underpowered to find a statistically significant difference.

When operating less aggressively, we question whether the assistance of surgical adjuncts, such as frozen section and intraoperative PTH measurement, might become more important in these procedures. Quick intraoperative PTH measurements between resections of the separate gland might guide the surgeon in

Table III
Postoperative complications

	Total	<3 glands	3–3.5 glands	4 glands	P value
Temporary hypocalcaemia	21 (10.8)	2 (7)	10 (11)	9 (12)	.82
Permanent hypoparathyroidism	0	0	0	0	1.0
Temporary RLN paralysis	3 (1.6)	2 (7.4)	0	1 (1.3)	.02
Hemorrhage requiring reoperation	4 (2.1)	0	2 (2.2)	2 (2.6)	.71

Number of complications shown as n (%).

RLN, recurrent laryngeal nerve.

deciding whether to continue to resect yet another gland or to terminate the procedure.

There are a few limitations that should be addressed. The retrospective nature of this study may have led to various biases. For example, the exact reason for the resection of <3 parathyroid glands or the absence of thymectomy could not be ascertained in retrospect, which could have led to selection bias because preoperative PTH levels were different among the 3 groups. Because preoperative PTH levels were significantly less in the limited PTx group, it is likely that the surgeon took these measurements into account when deciding on the operative strategy to prevent hypocalcemia. The majority of total PTxs were performed before the introduction of calcimimetics and in an era with a lower prospect on KTx compared to the last decade. The aim of decreasing PTH levels and decreasing the risk of persistent or recurrent disease changed over time toward a less aggressive strategy with the availability of cinacalcet and KTx. Also, because of the single-center set-up of this study, our results may not be generalizable to low-volume medical centers.

Although significantly decreased in 94% of patients, PTH levels remained greater in the limited PTx group compared to postoperative PTH measurements in the other groups, up to 2 times the upper limit of normal after 12 months of follow-up. These results along with previous studies could imply that a <3 gland removal is not an adequate procedure in patients with HPT caused by ESRD.² Therefore, subtotal PTx might be the optimal approach in the current era. The expectancy of KTx should be taken into account because postoperative serum PTH levels were less in patients who underwent total PTx compared to patients in the subtotal PTx group. Because PTH levels often further decrease after KTx, subtotal PTx might be the best approach in patients who are likely to receive KTx.³

In Australia, the calcimimetic agent, cinacalcet, is no longer listed on the Pharmaceutical Benefits Scheme since 2015, mainly owing to the results of the EVOLVE trial, concluding that cinacalcet does not decrease the risk of all-cause and cardiovascular mortality.^{19,20} In the rest of the world, cinacalcet still has a prominent position in the treatment algorithm of ESRD-related HPT as stated in the Kidney Disease Improving Global Outcomes guidelines.⁴ Since its introduction in 2004, it seems that clinicians are reluctant to refer their patients for PTx and administer cinacalcet, despite the high prevalence of side effects and questionable impact on PTH of cinacalcet.^{20,21} Potentially, a less aggressive operative approach is a more optimal alternative to cinacalcet in a selected group of patients.

In conclusion, patients who underwent a limited PTx had greater postoperative PTH levels, and persistent disease was more prevalent compared to patients who underwent a subtotal or total PTx. This study takes the first step to explore the possibility of a less aggressive approach in a changing practice. A patient-tailored strategy of the operative treatment of ESRD-related HPT based on the severity of the disease, both biochemical and clinical, expected

KTx in the near future, patient's quality of life, and patient's preference may become more important in the near future. Further research is required to confirm the potentially beneficial effect of a limited PTx for patients with ESRD-related HPT on biochemical values and quality of life in a randomized controlled setting.

Conflict of interest/Disclosure

All authors declare no conflicts of interest.

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