



Treatment strategy of end stage renal disease-related hyperparathyroidism before, during, and after the era of calcimimetics [☆]



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ARTICLE INFO

Article history:

Accepted 7 April 2018

Available online 6 November 2018

ABSTRACT

Background: Since 2004, end-stage renal disease related hyperparathyroidism patients are treated mainly with cinacalcet, which ceased to be subsidized through the Australian Pharmaceutical Benefits Scheme in 2015. We aimed to investigate the impact of these changes on the treatment strategy in the Australian end-stage renal disease population.

Methods: The following groups were formed according to the date of parathyroidectomy: A, before calcimimetics; B, during the era of calcimimetics; and C, after cinacalcet removal by the Australian Pharmaceutical Benefits Scheme. The primary outcome was time from start of dialysis to parathyroidectomy. Regression analysis was used to examine trends in parathyroidectomy rates.

Results: Between 1998 and 2016, 195 parathyroidectomies were performed. Median time to referral was 69 (33–123), 67 (31–110) and 44 (23–102) months for groups A, B, and C, respectively ($P = .55$). Parathyroidectomy rates increased throughout the years (CI 0.09–1.13, $R^2 = 0.27$, $P = .02$). A trend toward a dip in parathyroidectomy rates was seen during the era of cinacalcet ($P = .08$). Median preoperative parathyroid hormone levels increased significantly (842 [418–1,553] versus 1,040 [564–1,810] versus 1,350 [1,037–1,923] pg/mL, for groups A, B, and C, respectively [$P < .01$]).

Conclusion: Parathyroidectomy rates seem to vary according to the availability of cinacalcet. This change in treatment strategy is accompanied with increased preoperative parathyroid hormone levels, reflecting delayed surgery and increased disease severity.

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Introduction

Patients with end-stage renal disease (ESRD) inevitably develop hyperparathyroidism (HPT). Because of a deregulated calcium and phosphate metabolism, the parathyroid glands are stimulated to produce excess parathyroid hormone (PTH). ESRD-related HPT is associated with mineral and bone disorders, cardiovascular complications, increased mortality, and a decreased quality of life.^{1–3} Internationally, no multidisciplinary consensus with regard

to the optimal treatment for this complex multifactorial disease has been reached. Current Kidney Disease-Improving Global Outcomes (KDIGO) guidelines recommend a step-up approach, starting with noncalcium based phosphate binders and vitamin D supplements.⁴ If HPT progresses despite initial treatment, calcimimetics (ie, cinacalcet) are recommended. Cinacalcet binds to the G-protein-coupled calcium sensing receptor (CaSR), lowering the set point of PTH, which leads to a reduced PTH excretion of the parathyroid glands.⁵ The alternative is surgical resection of the hyperfunctioning parathyroid glands, which is an effective and definitive method to normalize serum PTH, calcium and phosphate levels and thus often improving quality of life.^{3,6}

In January 2005, cinacalcet was registered in Australia by the Therapeutic Goods Administration and was placed on the Pharmaceutical Benefits Scheme (PBS) subsidized drug list in November

[☆] Presented at the 2018 Annual Meeting of the American Association of Endocrine Surgeons.

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2007.⁷ In Australia, consistent with the KDIGO guidelines, parathyroidectomy (PTx) was only recommended in patients with severe HPT who were refractory to pharmacologic therapy (2B recommendation). The Australian guidelines date from April 2006 and reflect the KDIGO recommendations, stating that PTx should only be considered for patients in whom a therapeutic trial of cinacalcet did not effectively lower PTH levels.⁸

The introduction of cinacalcet contributed anecdotally to a dramatic change in the strategy with treating renal physicians often prescribing cinacalcet and avoiding PTx as long as possible. However, in August 2015, the calcimimetic agent was removed from the Australian PBS listing after reassessment of its cost-effectiveness by the Pharmaceutical Benefits Advisory Committee.⁹ This decision was mainly based on results of the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) trial, a randomized controlled trial comparing cinacalcet with a placebo.¹⁰ The EVOLVE investigators concluded that cinacalcet did not significantly reduce the risk of cardiovascular and all-cause mortality. Surprisingly, the Australian guidelines and recommendations have not been updated since 2006 in regard to the potential management change of ESRD-related HPT. However, as a consequence of the removal of cinacalcet from the reimbursed drug list, treatment options for ESRD-related HPT in Australia are limited to vitamin D supplements, phosphate binders, or PTx.

The aim of this study was to investigate the impact of calcimimetic availability on the treatment strategy for patients with ESRD-related HPT.

Methods

Patient selection

Data for a consecutive series of ESRD patients undergoing PTx within the University of Sydney Endocrine Surgical Unit (Australia) were prospectively collected. Information gathered included patient demographics; preoperative, intraoperative, and postoperative variables; histopathology results surgical outcomes; and complication rates. This study was approved by the Northern Sydney Local Health District Human Research Ethics Committees (HREC). Informed consent was obtained from every patient to record these data.

For this study, all patients who underwent parathyroid surgery for the indication ESRD-related HPT between January 1998 and December 2016 were included. Patients who were on dialysis or who had already received a kidney transplantation were included. Additional data were extracted from electronic patient record systems, including body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, medical history, use of calcimimetics before or at time of parathyroid surgery, type and duration of dialysis, and relevant laboratory investigations.

Study design

Patients were separated into three groups according to the date of their parathyroid surgery: group A, having undergone PTx before the introduction of calcimimetics; group B, undergoing PTx during the era of calcimimetics; and group C, having undergone PTx after calcimimetics were removed from the PBS medicine listing. Cut-off dates were November 2007 and August 2015, between groups A and B, and B and C, respectively. Data were retrospectively analyzed.

Primary and secondary end points

The primary outcome measure was time from start of dialysis until PTx. Levin et al.¹¹ showed that more than 85% of patients

with glomerular filtration rates < 20 ml/minute presented with PTH levels above the upper limit of normal. Therefore, the moment a patient commences with renal replacement therapy was chosen as a surrogate date of the beginning of HPT development. For patients who were not receiving dialysis and did not have a kidney transplantation in their medical history at time of PTx, date of HPT onset was retrieved from medical records.

Secondary end points were surgery rates, baseline patient characteristics, use of calcimimetics, serum PTH, calcium, phosphate, alkaline phosphatase (ALP) and creatinine levels, reoperation rate, and PTx-related morbidity (including hypocalcaemia, temporary or permanent palsy of the recurrent laryngeal nerve [RLN], hemorrhage, wound infection, and keloid formation), and mortality rates. Cause for reoperation was either persistent disease or recurrent hyperparathyroidism. Persistent disease was defined as persistent serum PTH levels above the upper limit of normal in the first 6 months after the operation. Recurrent disease was defined as serum PTH levels above the upper limit of the assay ≥ 6 months after initial surgery. Serum calcium values were corrected for albumin, using the following equation: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + (0.025 × (40 – [albumin (g/L)])). The following reference ranges were applied: PTH, 10–55 pg/mL; corrected calcium, 2.2–2.6 mmol/L; phosphate, 0.8–1.5 mmol/L; ALP, 50–100 U/L; creatinine, 80–130 μ mol/L.

Statistical analyses

For statistical analysis, SPSS Statistics v 24.0 (IBM Corporation, Armonk, NY, USA.) was used. Categorical variables are described as count (*n*) and percentage (%). Distribution of continuous variables was investigated using Shapiro-Wilk normality test. Normally distributed variables are expressed as mean \pm standard deviation (SD), skewed distributed data as median (interquartile range [IQR]). Results were compared among the three groups, using the χ^2 test, ANOVA, and Kruskal-Wallis test. Regression analysis was used to examine trends in the number of performed PTxs, shown as 95% confidence interval (CI) with R^2 - and *P* value.

Results

Patient characteristics

In total, 206 PTxs were performed in the setting of ESRD during the period 1998–2016. Data were incomplete for 11 cases, thus providing 195 patients with sufficient data available for further analysis. Group A, patients who underwent PTx before the introduction of cinacalcet, consisted of 98 patients, group B consisted of 68 patients, and group C consisted of 29 patients. The median age of all patients was 57 (44–68) years, and 64% of the patients were female. Baseline characteristics, including BMI, diabetes mellitus, ASA classification, and type of renal replacement therapy, did not significantly differ among the 3 groups. Patient demographics are summarized in [Table 1](#).

Although not yet listed on the PBS, cinacalcet had been prescribed for 2 patients (2.1%) in group A.

Change in management

In all patients, the median time from onset of ESRD-related HPT to PTx was 62 (31–109) months. Median referral did not differ between group A and group B (69 [33–123] months versus 67 [31–110] months, respectively). Although not statistically significant, the median referral time tended to be decreased in group C to 44 (24–102) months.

As presented in [Fig 1](#), the number of PTxs per year increased in the period from 1998 to 2007. Linear regression during 1998

Table 1
Patient characteristics

	Total N = 195	Group A N = 98	Group B N = 68	Group C N = 29	P Value
Age, years	57 (44–68)	53 (42–66)	48 (45–68)	63 (51–70)	.12
Sex, female	124 (63.6)	68 (69.4)	36 (52.9)	20 (69.0)	.08
BMI, kg/m ²	26.4 (22.8–31.9)	24.1 (22.9–28.0)	26.6 (22.3–32.5)	27.9 (23.0–36.7)	.14
History of DM, n (%)					.12
Type 1	10 (6.9)	4 (7.4)	4 (6.6)	2 (7.1)	
Type 2	28 (18.4)	5 (9.1)	14 (23.0)	9 (32.1)	
ASA classification, n (%)					.10
II	4 (2.8)	2 (3.4)	0 (0.0)	2 (7.1)	
III	110 (75.9)	110 (81.0)	47 (79.7)	16 (57.1)	
IV	30 (20.7)	9 (15.5)	11 (18.6)	10 (35.7)	
Type of renal replacement therapy					.24
None	11 (7.5)	2 (3.3)	6 (10.2)	3 (10.7)	
Hemodialysis	82 (55.8)	40 (66.7)	28 (47.5)	14 (50)	
Peritoneal dialysis	24 (16.3)	7 (11.7)	10 (6.9)	7 (25)	
History of KTx, n (%)	30 (20.4)	11 (18.3)	15 (25.4)	4 (14.3)	
Use of calcimimetics					
Use of calcimimetics in history	43 (26.7)	2 (2.1)	25 (62.5)	16 (66.7)	< .001
Use of calcimimetics at time of PTx	31 (17.1)	2 (2.1)	20 (33.9)	9 (32.1)	< .001
Time from start dialysis to PTx	62 (31–109)	69 (33–123)	67 (31–110)	44 (23–102)	.55

DM, diabetes mellitus; KTx, kidney transplantation.

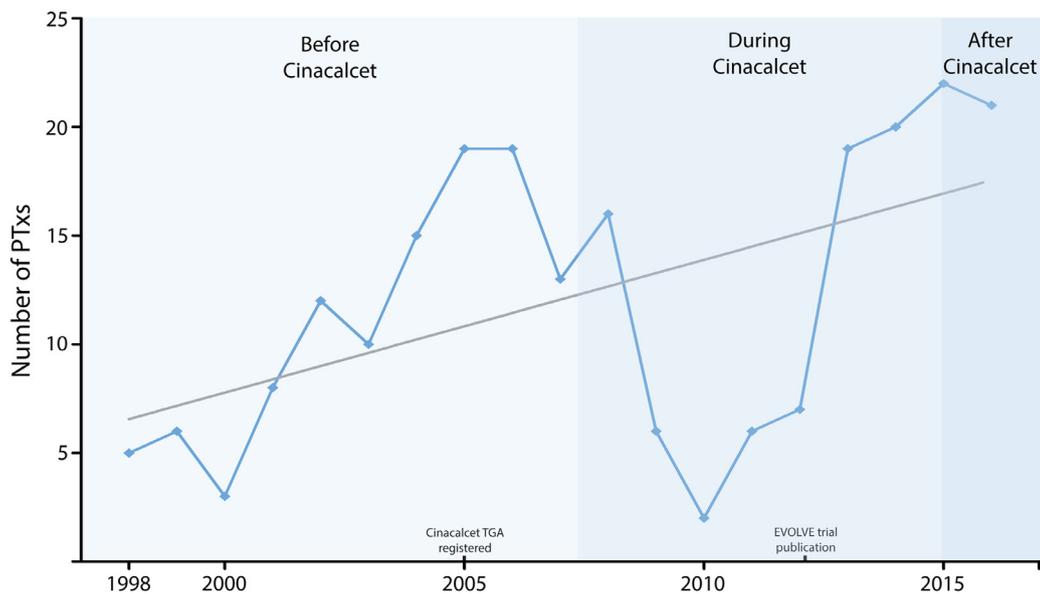


Fig 1. Number of parathyroidectomies (PTxs) over time.

to 2006 indicated a positive trend line (CI 1.33–2.71, $R^2=0.87$, $P < .001$). During the periods 2007 to 2014 and 2015 to 2016, no trends in number of PTxs could be calculated. A linear trend line of the total period is presented in Fig 1 (CI 0.09–1.13, $R^2=0.27$; $P=.02$). Median number of PTxs per year were 11 (6–9), 7 (6–19), and 21.5 (21–22) for groups A, B, and C respectively ($P=.08$).

Type of PTx

In all patients, 77 patients (39.5%) underwent total PTx and 91 (46.7%) a subtotal PTx. In 27 patients (13.7%), fewer than 3 parathyroid glands were removed. In group A, the majority of patients underwent a total PTx (62.2%), versus 16.2% in group B, and 17.2% in group C ($P < .001$). Subtotal PTx was performed in 23.5% of the patients in group A, 67.6% of group B, and 75.9% of group C ($P < .001$). Of the 77 patients who underwent total PTx, 8 (10.4%) received autotransplantation of parathyroid tissue.

Biochemical outcomes

Preoperative PTH levels were significantly higher in group B compared with group A. Group C had significantly higher levels of PTH compared with groups A and B (Table 2). Postoperative PTH levels were also significantly higher in patients of group C compared with groups A and B ($P < .001$). Patients within group B who were using cinacalct at time of PTx had significantly higher preoperative levels of PTH compared with those who were not using cinacalct in group B (1,504 [933–2,066] pg/mL versus 824 [414–1,479] pg/mL, $P=.01$).

Serum calcium corrected for albumin, phosphate, and ALP did not differ significantly among the three groups at any moment of measurement during follow-up. Median corrected calcium levels decreased significantly from the preoperative to postoperative periods ($P < .001$). After 1 year of follow-up, serum-corrected calcium levels were still significantly improved compared with preoperative levels ($P < .001$). Furthermore, phosphate levels improved significantly after PTx from a median of 1.66 (1.20–2.05) mmol/L to 1.26

Table 2
Laboratory values

	Total	Group A N=98	Group B N=68	Group C N=29	P value
PTH, pg/mL					
Preoperatively	1073 (507–1606)	842 (418–1553)	1040 (564–1810)	1350 (1037–1923)	.009
At discharge	17 (4–59)	7 (4–19)	29 (10–62)	37 (10–133)	.000
3 mo postop	21.4 (4–139)	4 (4–21)	70 (9–180)	44 (9–220)	.000
6 mo postop	18 (4–156)	4 (4–17)	82 (13–204)	59 (12–291)	.000
1 y postop	31 (4–137)	4 (4–32)	77 (26–196)	62 (13–297)	.000
Corrected calcium, mmol/L					
Preoperatively	2.54 (2.33–2.71)	2.56 (2.34–2.73)	2.58 (2.29–2.72)	2.50 (2.35–2.61)	.67
At discharge	2.33 (2.18–2.48)	2.27 (2.21–2.46)	2.36 (2.21–2.51)	2.39 (2.25–2.52)	.06
3 mo postop	2.27 (2.10–2.41)	2.21 (2.04–2.40)	2.27 (2.12–2.42)	2.27 (2.13–2.48)	.39
6 mo postop	2.28 (2.09–2.45)	2.26 (2.08–2.46)	2.29 (2.11–2.40)	2.39 (2.15–2.65)	.23
1 y postop	2.31 (2.20–2.43)	2.26 (2.14–2.36)	2.34 (2.19–2.46)	2.24 (2.23–2.63)	.10
Phosphate, mmol/L					
Preoperatively	1.66 (1.20–2.05)	1.49 (1.17–1.92)	1.66 (1.08–2.11)	1.78 (1.39–2.07)	.23
At discharge	1.26 (0.96–1.60)	1.24 (1.00–1.60)	1.34 (0.97–1.82)	1.19 (0.85–1.42)	.11
3 mo postop	1.28 (1.01–1.80)	1.29 (0.98–1.75)	1.44 (1.05–1.86)	1.27 (0.92–1.81)	.81
6 mo postop	1.50 (1.10–1.91)	1.54 (1.12–1.84)	1.36 (0.98–2.10)	1.51–1.35–2.16)	.57
1 y postop	1.47 (1.12–1.87)	1.49 (1.18–1.86)	1.38 (1.02–1.69)	1.67 (1.06–2.32)	.36
ALP, U/L					
Preoperatively	140 (91–196)	156 (106–208)	133 (84–186)	153 (94–185)	.41
At discharge	127 (81–252)	141 (80–294)	115 (79–154)	175 (90–314)	.18
3 mo postop	91 (60–127)	93 (60–126)	85 (59–130)	97 (63–151)	.66
6 mo postop	72 (56–96)	76 (55–96)	72 (58–105)	66 (55–89)	.59
1 y postop	73 (55–96)	71 (55–98)	74 (51–95)	72 (45–89)	.54

Reference ranges: PTH, 10–55 pg/mL; corrected calcium, 2.2–2.6 mmol/L; phosphate, 0.8–1.5 mmol/L; ALP, 50–100 U/L; creatinine, 80–130 μ mol/L.

Table 3
PTx-related complications

	Total	Group A	Group B	Group C
Temporary hypocalcaemia	18 (9.8)	11 (12.1)	4 (6.3)	3 (10.3)
Permanent hypoparathyroidism	1 (0.5)	1 (1.1)	0 (0.0)	0 (0.0)
Temporary RLN paralysis	3 (1.6)	2 (2.2)	1 (1.6)	0 (0.0)
Hematoma	2 (1.1)	1 (1.1)	0 (0.0)	1 (3.4)
Reoperation for hemorrhage	4 (2.2)	3 (3.3)	0 (0.0)	1 (3.4)
Keloid formation	1 (0.5)	1 (1.1)	0 (0.0)	0 (0.0)

Number of complications showed as n (%).

(0.96–2.48) mmol/L ($P < .001$). Phosphate levels increased slightly during follow-up; however the levels stayed within the reference range ($P < .001$) and significantly ameliorated compared with preoperative values ($P < .001$).

Preoperative ALP levels were above the reference range (140 [91–196]). At discharge, ALP levels were not significantly different from before PTx ($P = .46$). However, after 3 months, ALP levels were significantly lower ($P < .001$). After 1-year follow-up, ALP levels were still within the reference range and significantly lower than preoperatively ($P < .001$).

Parathyroid weight

Median cumulative weight of the parathyroid glands was 1,498 (751–3,005), 1,900 (812–3,501), and 1,637 (873–4,269) milligrams for groups A, B, and C, respectively. There was no significant difference in total weight of the resected parathyroid glands between the 3 groups ($P = .70$).

Surgical outcomes

Ten patients (5.1%) required a reoperation for persistent (3%) or recurrent (2.1%) HPT. Postoperative complications are presented in Table 3. There was no significant difference in complication rates among the 3 groups ($P = .75$). There were no deaths within 30 days of the operation.

Discussion

The past 2 decades have demonstrated changes in the treatment strategy for ESRD-related HPT within our surgical catchment of Northern Sydney, Australia. This retrospective descriptive study demonstrates the change of treatment approach to patients with ESRD-related HPT. We compared referral behavior; the number of performed PTxs; laboratory values; and surgical outcomes among patients who underwent PTx before, during, and after the era of calcimimetics. The time from HPT onset to PTx did not differ significantly among the three groups. However, we observed a decline in the number of patients referred for PTx after cinacalcet was approved by the Therapeutic Goods Administration, and PTx rate further declined after cinacalcet was approved by the Pharmaceutical Benefits Advisory Committee in 2007, despite the growing incidence of ESRD patients.¹² Since 2012, the year in which the EVOLVE trial results were published, and 2015 (removal of cinacalcet from PBS listing) the absolute number of PTxs performed per year increased again.

In an earlier study, a single-center retrospective analysis in The Netherlands, we showed that the introduction of cinacalcet led to a 22-month referral delay for surgical consultation.¹³ Australia is, to our knowledge, the only nation in which calcimimetics were first reimbursed, but subsequently removed from the reimbursed drug list because of novel insights on its cost effectiveness. Therefore, this is the first study describing the impact of the longitudinal, consecutive changes on the treatment strategy of ESRD-related HPT. In this study cohort, we did not see a significant referral change over time. Various earlier studies have indeed concluded that the introduction of cinacalcet and the KDIGO guidelines have had an impact on PTx rates.^{4,14}

This study has a few limitations we should address. First, although patients were prospectively collected, we performed a retrospective analysis. Therefore, possible biases, such as information and misclassification bias, could not be avoided. Next, only patients who underwent PTx were included. Patients who were treated pharmacologically or who were not eligible for PTx were not included in this cohort, causing a potential selection bias. Three highly specialized surgeons dedicated to endocrine surgery performed all PTxs included in this study, therefore, the outcomes

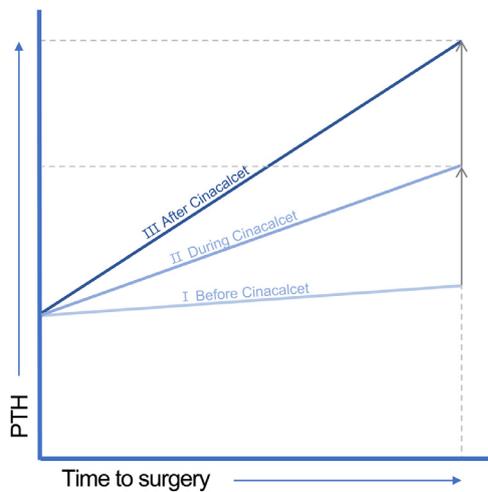


Fig 2. Schematic presentation of the change in management. *Line I* represents patients before the era of cinacalcet. *Line II* presents patients during the era of cinacalcet. *Line III* depicts the situation after the banning of cinacalcet. Time until surgery remains unchanged; whereas parathyroid hormone levels have increased over time, suggesting that only patients with more severe disease are referred for surgery.

of parathyroid surgery might not be generalizable to less experienced or low-volume medical centers.

The decline in PTx rates during the era of cinacalcet implies that those patients were treated pharmacologically. In recent years, negative results have been published about the effectiveness, costs, and side effects of a calcimimetic agent, which resulted in prolongation in the waiting time for PTx. Current KDIGO guidelines recommend to maintain PTH levels in ESRD patients within 2 to 9 times the upper limit of normal (recommendation 2C).⁴ However, in the past 20 years, preoperative PTH levels have increased from 15 to more than 25 times the upper limit of normal. Preoperative PTH levels were significantly higher in the groups during and after the era of calcimimetics compared with before the introduction of cinacalcet. This indicates that patients are referred in a later, more progressed stage of their parathyroid disease (Fig 2). The finding that cinacalcet insufficiently lowers PTH levels might also in part explain why PTH levels remained elevated despite the advent of calcimimetics.¹⁵ This study did not investigate differences among patients who were treated with cinacalcet and patients who were not. Therefore, the group of patients who underwent PTx during the cinacalcet era also comprised patients who were not using cinacalcet. In fact, within the cinacalcet-era group, patients using cinacalcet at time of PTx, presented with significantly higher PTH levels than patients who did not use cinacalcet. Therefore, the advent of cinacalcet might have led to a change in treatment approach, accepting higher levels of PTH, without scientific evidence. This could also suggest that patients with elevated PTH levels, but below the hypothetical threshold level, are no longer referred for surgery and now treated pharmacologically. Increased preoperative PTH levels throughout the past decades are in line with earlier literature.¹⁶ Being chronically exposed to extremely elevated PTH levels has multiple implications for this already fragile patient population. It is associated with renal osteodystrophy, which may result in fractures, increased risk of cardiovascular calcification, events, immune dysfunction, anemia, and death.^{16,17} Moreover, an increased risk of renal transplant failure has been reported in patients with high pretransplant PTH levels.¹⁸ Thus, patients might be less eligible for renal transplant while having elevated PTH levels. Although preoperative PTH levels were significantly different, there was no significant difference in occurrence of postoperative hypocalcaemia among the three groups. This is in concordance with previous studies showing that preoperative PTH

is not an independent risk factor for the development of postoperative hypocalcaemia or hungry bone disease postoperatively, but might also be the result of an improved postoperative calcium management during recent years.^{19,20}

Furthermore, postoperative PTH levels were significantly higher in patients who underwent PTx during and after the era of cinacalcet compared with before the era of cinacalcet. This is probably the result of the change in surgical approach over the years. In the group of patients before the introduction of cinacalcet, total PTx was the most frequently performed procedure. The percentage of performed subtotal PTx rose throughout the years, from 23.5% to 75.9% of patients operated on after the cinacalcet era compared with before the cinacalcet. Because autotransplantations in total PTx were not routinely performed, the aim of total PTx is to remove as much parathyroid tissue as possible, leaving the patient in a hypoparathyroid state. In subtotal PTx, some parathyroid tissue remains in situ, the aim being to have some ongoing PTH production in the postoperative period, thereby avoiding hypoparathyroidism. Earlier, a small retrospective study compared outcomes of patients who underwent subtotal PTx versus total PTx without autotransplantation (AT). Higher PTH levels were seen in the subtotal PTx group.²¹ Many more studies have compared outcomes between total PTx with AT with subtotal PTx. These studies showed no significant differences in postoperative PTH levels.²² Serum calcium corrected for albumin and phosphate levels improved significantly postoperatively. After a 1-year of follow-up, PTH, calcium and phosphate levels maintained within the reference range. In earlier studies, the efficacy of PTx in restoring the calcium-phosphate homeostasis is similar to our results.^{6,14} ALP levels were also higher than the upper limit of normal, suggesting an increased bone-turnover status.²³ On top of that, Regidor et al.²⁴ showed in a large cohort of hemodialysis patients that ALP levels above 120 U/L were associated with an increased risk of death and high ALP levels have also been associated with increased fracture rates.²⁵ Three months after surgery, ALP levels were significantly improved to within the reference range. However, the impact of lowering ALP levels in ESRD patients on clinical outcomes is still unclear.

In conclusion, in the past 20 years for patients with ESRD-associated HPT, PTx rates seem to vary according to the availability of cinacalcet. The introduction of calcimimetics temporarily decreased referral rates for surgery and subsequently resulted in higher preoperative PTH levels in patients presenting for surgical treatment. Our findings on the impact of a government decision on clinical practice are relevant for all clinicians treating HPT. Without the evidence of a randomized trial comparing cinacalcet with the former gold standard PTx, clinicians changed their practice immediately when cinacalcet was listed on the Australian PBS, and PTx was less often performed. This led to the acceptance of higher PTH levels, reflecting increased disease severity in an already fragile patient population.

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Discussion

Dr Sally E Carty (Pittsburgh, PA): Very nice study. Very well presented and very tactful. But I am going to try to draw you out. Do you think Sensipar is bad for people?

Willemijn Y van der Plas: Well, it is not necessarily bad for people, but I do have concerns about cinacalcet. It is very expensive, so it can be a huge financial burden on the patient. Also, it's associated with a lot of side effects. I think many patients have severe adverse events, such as diarrhea, vomiting, and stomach aches. Also, the evidence for cinacalcet significantly lowering PTH levels is very doubtful. There are some studies that actually suggested cinacalcet does not lower PTH levels in a real-life setting, because patients have so many side effects that they discontinued the drug. Those are my concerns.

Dr Jennifer Kuo (New York, NY): I also want to congratulate you on an excellent study.

Your study spans a very long period of time when cinacalcet was introduced and then after its popularity had fallen off. But over that period of time, we have also gained a greater understanding of parathyroidectomy and its potential benefits for this cohort of patients.

At my institution, our nephrologists have actually been much more aggressive as we consider these patients earlier for parathyroidectomy. Are you able to comment on the evolution of that process as well and potentially elaborate on the criteria that your nephrologists use to refer patients for parathyroidectomy?

Willemijn Y van der Plas: That is indeed a concern because the patients get referred to us and we don't see them initially. So, we depend on the nephrologists to say that it is time for surgery.

I guess that with an increasing number of kidney transplantations as a definitive treatment for the underlying cause of secondary hyperparathyroidism, we might pursue less aggressive surgery because patients are at risk of developing hypocalcemia, which may be bad for the kidney transplant. It is a difficult deci-

sion to make, and I think that it is important that the nephrologist actually consults the surgeon at an earlier stage of the patient's disease to discuss whether they could benefit from surgical treatment.

Dr Electron Kebebew (Stanford, CA): Excellent presentation. I have two questions for you.

You looked at time-frame analysis, and it's a single-institution study. Did you have the same group of nephrologists referring to your institution over the study?

Number two, you noted that during the latter period when Sensipar was taken off your formulary, that the average postop PTH was higher. I think you attributed it to more subtotal than total parathyroidectomies being done. I am wondering if it's because the nephrologists didn't have Sensipar to use postoperatively.

Willemijn Y van der Plas: In terms of the first question, I think that the nephrologists were mostly the same, and they are typically in close contact with the endocrine surgery group. For example, they have multidisciplinary meetings to refer patients for surgery. So, I don't think the referral time differences can be attributed merely to different nephrologists.

To your second question, it was not a nephrology decision to do a subtotal parathyroidectomy, but I think the surgeons may predict the patient may have a high risk of developing hypocalcemia. If they know that their patient might get a kidney transplantation in the near future, they may be less aggressive.

Dr Electron Kebebew (Stanford, CA): I was suggesting perhaps postoperatively the nephrologists didn't have the option of putting these patients on Sensipar.

Willemijn Y van der Plas: That could be, but I don't think that the nephrologists regularly put people on cinacalcet after they had parathyroid surgery.

Dr Schelto Kruiff (Groningen, Netherlands): Very well presented. I want to add one more thing because of the questions that



were asked earlier. In the Netherlands, we started The Dutch Hyperparathyroidism Study Group (DHSG) together with the nephrologists to make sure that we can attack this problem together. Otherwise, we will never solve the industry drive, which is behind

cinacalcet. We are not the main treating doctors of these patients, so our goal is to be involved earlier in the process with decision-making about who needs an operation and who can be treated medically.