cyclophosphamide, which is known to suppress Tregs, and that the secondary increase could represent Treg repopulation.[S32] Analysis at further time points would reveal additional information.

This, to our knowledge, is the first study to comprehensively analyze Bregs and Tregs in patients with new-onset LN and to systematically follow them after treatment. We recognize that our study has certain limitations, including the small sample size and the lack of functional studies of different subsets of B and T cells. Thus, further validation of these findings in a larger population is warranted.

In conclusion, we found that Bregs were deficient in new-onset LN patients and increased in responders with immunosuppression. The findings from this study provide new insights into the mechanisms underlying the pathogenesis of LN and the mechanism by which IS therapy achieves immunological remission. A better understanding of these processes can aid in the design of new immunotherapies for the intervention of LN.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Individual clinical characteristics of subjects.

Table S2. List of antibodies used.

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Clinical and Healthcare Utilization Outcomes of Parathyroidectomy in CKD and Dialysis Patients

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Secondary hyperparathyroidism is common among patients with CKD and those with end-stage kidney disease (ESKD) receiving dialytic renal replacement therapy.[1,2] Cohort studies have suggested an association between elevated parathyroid hormone levels and adverse patient outcomes.[2–4] Current guidelines suggest that patients with CKD stages 3–5D with severe hyperparathyroidism who fail to respond to medical therapy should consider surgical parathyroidectomy.[4]

Ishani *et al.*[2] report 2% mortality among 4435 patients within 30 days following parathyroidectomy. Within 30 days of discharge, 23.8% of patients were rehospitalized. Similar 30-day mortality was shown by Kestenbaum *et al.*[5] with 30-day postoperative mortality of 3.1% in a cohort of 4558 patients. Ishani *et al.*[2] found a 1-year mortality of 9.8%. Further, 7571 hospitalizations (excluding those for outpatient renal replacement therapy) occurred among 2832 unique individuals in the year after parathyroidectomy, and an average of 2.7 hospitalizations per person among those hospitalized. All-cause hospitalizations were 39% higher, and admissions for hypocalcemia were 17-fold higher.

In Australia, these data need to be considered in the context of the Pharmaceutical Benefits Scheme changes that were made subsequent to the EVOLVE clinical trial, including removal of cinacalcet from the Pharmaceutical Benefits Scheme listing in August 2016.[6–8] Accordingly, we undertook a single-center pilot study to review the practice and outcomes of parathyroidectomy in CKD/ESKD patients in our center (HREC/17/QRBW/231). We analyzed health service utilization and the comparative costs of length of hospital stay post-parathyroidectomy.

A total of 34 parathyroidectomies were performed for CKD/ESKD patients between January 2011 and June 2017. A total of 24 parathyroidectomies were performed in the 67 months before cinacalcet was delisted (0.35/month), and 10 parathyroidectomies were performed in the 11 months after cinacalcet was delisted (0.91/month; $P < 0.05$). The median age of patients undergoing parathyroidectomy was 51.5 years (range, 24–70 years). The causes of CKD, CKD stage, dialysis vintage, and perioperative comorbidities are listed in Table 1.

Perioperative medical therapy for hyperparathyroidism included 9, 18, 10, 16, and 31 patients treated preoperatively with cinacalcet, calcium carbonate, cholecalciferol, calcitriol, and one or more phosphate binders, respectively. Six patients were on all 4 medications preoperatively. Of those on cinacalcet preoperatively, 8 of 9 patients underwent surgery before August 2016. A total of 3 of 34 patients were not on any phosphate binders pre-parathyroidectomy, and there was no clinical documentation detailing reasons for this.

The perioperative protocol for parathyroidectomies in our center specified that 0.25 micrograms calcitriol, 10 tablets taken orally daily, for 4 days prior to surgery, was to be commenced. Five of 34 patients were adherent to the perioperative protocol. The majority of preoperative reviews did not reference the hospital parathyroidectomy protocol.

Postoperative parathyroidectomy protocol compliance was observed in 18 of 34 (52%) patients. A total of 28 of 34 (82%) patients were reviewed by the renal registrar immediately postoperatively, but overall protocol compliance was not impacted. A formal copy of the protocol was found in 13 of 34 (38%) patient charts, suggesting that in the event of a change in patient status, the institutional protocol could not easily be referred to at the bedside.

A total of 23 of 34 (67%) patients experienced postoperative complications, with 13 of 23 (50%) patients experiencing ≥2 complications (Table 2). There was one patient death due to a thromboembolic stroke while on dialysis, 2 days postoperatively, which was considered an unexpected cardiovascular complication.

The average initial postoperative ionized calcium level was 1.16 mmol/l (range, 0.93–1.53 mmol/l). Average ionized calcium levels upon hospital discharge were 1.23 mmol/l (range, 0.97–1.46 mmol/l). Our postoperative protocol recommended continuation and titration of oral calcitriol and calcium supplementation, with additional titration of intravenous calcium infusion in response to serum ionized calcium levels until stable. There was a median of 5 (range, 0–37) postoperative outpatient visits required before patients

Table 1. Causes of CKD, CKD stage, dialysis vintage, and perioperative comorbidities in 34 parathyroidectomy patients

Causes of CKD	No. of patients	CKD stage	No. of patients
Diabetic nephropathy	6	Stage 5	2
Hypertension	6	ESRD on dialysis	30
Glomerulonephritis including IgA nephropathy	6		
ADPKD	4	**Dialysis vintage**	
Drug-induced including AIN	2	0–3 yr	12
Structural or functional	4	3–5 yr	9
Metabolic	1	5–8 yr	4
Multifactorial or cause unclear	4	8–11 yr	4
Vasculitis	1	11–14 yr	1
Perioperative comorbidities			
Hypertension	30	Hyperlipidemia	19
Ischemic heart disease	7	Diabetes mellitus	10
Congestive cardiac failure	3		

ADPKD, autosomal dominant polycystic kidney disease; AIN, acute interstitial nephritis; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table 2. Postoperative complications experienced by 23 patients

Complication	No. of patients (%)
Hungry bones syndrome	13 (56)
Infection	6 (26)
Bleeding requiring transfusion	3 (13)
Cardiovascular events	5 (21)
Calcium infusion injury	4 (17)
Other complications[a]	15 (65)
Postoperative cardiovascular events (N = 5 patients)	
NSTEMI	1
Arteriovenous fistula thrombosis	1
Thromboembolic stroke	1
Jugular venous thrombosis	1
Atrial fibrillation/atrial flutter	2
Complications requiring readmission within 28 d (N = 10 patients)	
Hypercalcemia with acute kidney injury	1
Arrhythmia with electrolyte disturbance and gastroenteritis	1
Surgery for calcium infusion injury	2
Pneumonia	1
Symptomatic hypocalcemia	1
Severe hypertension	1
Diarrhea	1
Necrotic toes with sepsis	1
Arteriovenous fistula thrombosis and surgical repair	1

[a]Included PD peritonitis (1), unwitnessed fall (1), hyperkalemia (3), hypertensive urgency (2), symptomatic hypocalcemia (1), AKI with hypercalcemia (1), clinically significant diarrhea (3), inadequate oral intake (1) requiring nasogastric tube (1), and additional central venous line (1).

achieved stable ionized calcium levels on oral therapy. The median follow-up period for patients post-parathyroidectomy was 25.5 months.

The median length of stay (LOS) for the 34 patients was 8.5 days (range, 2–36 days). A total of 29% were readmitted to the hospital within 28 days post-parathyroidectomy for a variety of reasons and complications (Table 2). A total of 14% received a renal transplant within 2 years. All-cause mortality was 14% at 12 months postoperatively. By comparison, the expected 1-year mortality for patients commencing renal replacement therapy in Australia and New Zealand during the 2008–2017 time period was 2%–27% across all age groups.[9] Specifically, this was 7% for those aged 45–64 years,[9] with this age group spanning the median study cohort age and the majority of included cases.

The average cost of hospitalization in this parathyroidectomy cohort was $25,146 per patient. The average cost of cinacalcet at a dose of 60 mg daily over 3.5 years was $16,776 per patient. The 60-mg dosage of cinacalcet chosen represented the mean dose for our patient cohort, with a range from 30 mg to 120 mg. A 3.5-year time period was chosen, as this was the approximate average waiting time for transplantation in Queensland in 2017. All post-parathyroidectomy inpatient complications were included in this cost analysis. The total cost of surgery reported is only for the initial hospital admission and does not include associated readmissions (29%), additional pathology, calcium treatment, or medical/nursing monitoring required after discharge.

This retrospective review and pilot study of parathyroidectomy outcomes in a single Australian tertiary center highlight a number of important points. First, the number of parathyroidectomies across Australian tertiary centers are likely to have risen as a result of the Pharmaceutical Benefits Scheme delisting of cinacalcet. Although a significant driver of the delisting of cinacalcet was the EVOLE trial,[8] our findings suggest that further consideration of therapeutic utility could be considered, pending replication of our findings. Patients in our center were generally older, with high body mass index and multiple cardiovascular risk factors, which all dispose patients to higher perioperative and anaesthetic risk. The relatively long LOS coupled with the 29% readmission rate further increases the likelihood of patients developing complications attributable to surgery. Although cinacalcet may not have altered cardiovascular end points for many patients, it may have led to patients at higher operative risk forgoing surgery to avoid potential complications. Examination of the cost of parathyroidectomy in this cohort, and comparison to the cost of cinacalcet, suggests that parathyroidectomy may not require fewer resources overall. This analysis becomes more complex when considering that the patient-related costs included only those related to the primary parathyroidectomy admission and not those related to follow-up visits, additional medications, or postdischarge readmission.

In the context of the EVOLVE trial,[8] it is worth noting that of 1983 and 1948 participants randomized to placebo and cinacalcet, respectively, those in the cinacalcet group who discontinued their involvement in the study accounted for only 15.8% of the 66.7% in total who did so due to adverse drug reactions. Among the placebo group, only 11.8% of the total 70.5% who discontinued did so due to adverse drug reactions. These percentages suggest that the magnitude of effect of cinacalcet adverse drug reactions may not be a significant factor and would be further addressed by examining larger patient numbers. Those not tolerating cinacalcet owing to adverse drug reactions may tolerate newer calcimimetic agents currently under investigation.

Second, our analysis highlights the importance of appropriate patient selection and clear and focused approaches to both perioperative and postoperative management of CKD/ESKD patients undergoing parathyroidectomy. Low overall perioperative compliance with the institutional pre-parathyroidectomy protocol requires review. A multidisciplinary approach to perioperative review may alleviate inadequate perioperative

compliance and lead to optimized outcomes. The low postoperative compliance rate of 52%, despite a majority of patient having prompt and appropriate renal registrar review, suggests inadequate broader recognition of potential complications and negative consequences. This inadequacy is highlighted by the low levels of documentation of hospital protocol adherence and policy (38%), which are freely available in the hospital intranet and protocol database. The high postoperative complication rate (67%), which is predominantly made up of patients experiencing hungry bones syndrome (56%) or hungry bones syndrome with a second associated complication (50%), could in some part be rectified through improved perioperative and postoperative protocol compliance and optimized patient selection. Improved compliance might reduce LOS and the number of postoperative visits required to achieve stable serum calcium status, leading to improved outcomes, fewer patient complications, and reduced healthcare utilization costs.

Our study is limited by the retrospective nature of data collection, the small patient numbers,and the single-center nature of this study. These limitations could be alleviated with prospective and larger patient numbers across multiple sites. Further, our study observation period is relatively short (maximum 2 years postoperatively), and longer-term observational studies are required to better appreciate longitudinal survival and clinical outcomes.

Our review showed results similar to those of Ishani *et al.*,[2] demonstrating concerning rates of postoperative mortality, high rates of possibly avoidable complications, long LOS, and increased burden on emergency department and outpatient clinics. These findings need to be locally considered and addressed within a quality-improvement framework. To date, this process has included review and reimplementation of our institutional CKD/ESKD patient parathyroidectomy protocol and clinical pathway, the outcomes of which will be audited in coming years.

The risk of parathyroidectomy in CKD and ESKD patients in terms of LOS and complications may be related to optimization of perioperative management and compliance with relevant clinical protocols. Consideration should be given to making this risk assessment part of local practice when individualizing clinical management, as well as in broader clinical quality assurance efforts. At a national level, replication of our observations would be required as part of reconsidering the availability and utilization of all medical and surgical therapies for secondary hyperparathyroidism among CKD and ESKD patients in Australia.

DISCLOSURE

AM is an investigator in an investigator-initiated university-sponsored clinical study undertaking Fabry Disease screening among those with kidney disease (aCQuiRE Study; HREC/17/QRBW/91), which has received competitive research grant funding from Sanofi-Genzyme. AM is a local site investigator for an industry-sponsored clinical trial in autosomal dominant polycystic kidney disease (NCT03523728). All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

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