Original Article

Surgery or no surgery: What works best for the kidneys in primary hyperparathyroidism? A study in a multi-ethnic Asian population

Yu Kwang Donovan Tay[1], Joan Khoo[2], Manju Chandran[1]

[1]Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, [2]Department of Endocrinology, Changi General Hospital, Singapore

ABSTRACT

Introduction: Whether parathyroidectomy is more beneficial to renal function when compared to medical therapy or observation in primary hyperparathyroidism (PHPT) is unclear. Neither has this premise been explored in non-Caucasian populations. The estimated glomerular filtration rate (eGFR) threshold below which parathyroid hormone (PTH) levels rise if at all in PHPT has also not been established. We determined if surgery was superior to medical therapy and observation in a multi-ethnic Asian patient population with PHPT and whether there was an eGFR threshold below which PTH levels further increased in them. **Methods:** Retrospective evaluation of patients with PHPT. **Results:** There were 68.6% Chinese, 17.4% Malays, 10.7% Indians, and 3.3% Eurasians. The median (interquartile range) follow-up was 18.0 months (4.5–46.8). At last follow-up, eGFR in the surgical (80 ± 30 ml/min) was higher than the medical (52 ± 32 ml/min) or observation groups (48 ± 33 ml/min); $P < 0.01$. This difference persisted after adjusting for age, gender, ethnicity, pre-intervention eGFR levels, nephrolithiasis, serum calcium, phosphate, urinary calcium, and duration of follow-up; $P = 0.035$. There was no definite eGFR level below which PTH values rose. **Conclusion:** Our study provides compelling evidence that in PHPT, surgery may be associated with a better renal outcome compared to medical management or observation. This has to be confirmed through prospective randomized controlled trials and the reasons for this finding have to be elucidated through functional and histological measures. The finding in our study of a lack of a specific eGFR threshold below which PTH levels further rose challenges the concept of a fixed renal threshold for secondary elevations of PTH in PHPT.

Key words: Creatinine clearance, estimated glomerular filtration rate threshold, parathyroidectomy, primary hyperparathyroidism, renal function

Introduction

Primary hyperparathyroidism (PHPT) is relatively common with an estimated prevalence of 1% in the general population[1] and an even higher prevalence in osteoporotic patients.[2] Over the last several decades, its clinical presentation in most populations has shifted from florid symptomatic disease to mostly that of an asymptomatic one.[1,3,4]

Consensus guidelines list renal impairment as a surgical indication in asymptomatic PHPT.[5,6] The most recent guidelines define the renal criteria as, reduced estimated glomerular filtration rate (eGFR) <60 ml/min, imaging evidence of renal stones/nephrocalcinosis, or marked

Corresponding Author: Dr. Manju Chandran, Department of Endocrinology, Osteoporosis and Bone Metabolism Unit, Singapore General Hospital, 20 College Road, Academia, Singapore 169856.
E-mail: manju.chandran@singhealth.com.sg

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hypercalciuria with increased stone risk on biochemical stone risk analysis.[6] However, evidence to support these recommendations is quite limited. Several studies done to date have not shown an improvement in renal function with parathyroidectomy[7-9] and the studies that have, have had very small sample sizes.[10-12] A recent study showed that patients with PHPT with concomitant renal impairment as defined by an eGFR <60 ml/min who underwent parathyroidectomy had no decline in eGFR at follow-up compared to those without renal failure (eGFR ≥60 ml/min), who had a significant decrease in eGFR at follow-up.[13] This implied that parathyroidectomy would only benefit patients with renal impairment. This study did not have any medically managed or simply observed comparison groups. A few retrospective, as well as prospective studies, have explored treatment outcomes between parathyroidectomy and simple observation for asymptomatic PHPT and a few of these have included renal function as one of the outcomes though it was not the primary outcome studied.[14-17] None of the studies have compared renal outcomes between all three current modes of treatment for PHPT, i.e., parathyroidectomy versus through medical management and simple observation. A study that did longitudinally evaluate these 3 modes of treatment in PHPT did not have renal function listed among the outcomes particularly explored.[18] All these studies have been performed exclusively on Caucasians.

Singapore has a unique ethnic mix of Chinese (74.3%), Malays (13.3%), Indians (9.1%), and others (3.3%) (year 2010 census data: http://www.singstat.gov.sg/). We thus sought to determine if different treatment modalities affect renal outcomes in our multi-ethnic non-Caucasian population of patients with PHPT.

Evidence to conclusively support the precise eGFR threshold of 60 ml/min recommended in the consensus guidelines as the level below which surgery should be performed is lacking. This threshold appears to have been chosen by extrapolating from chronic kidney disease (CKD) data where secondary elevations in parathyroid hormone (PTH) levels are noted once the eGFR decreases below 60 ml/min/1.73 m^2. However, the eGFR threshold in PHPT below which some hereto unidentified stimulus further elevates PTH levels if at all has not been established with studies published so far split equally between identifying and not identifying a threshold.[19-24] To date, only 3 published studies have shown significantly increasing levels of PTH at defined eGFR thresholds.[19-21] It has to be noted that none of these studies found the threshold of 60 ml/min identified in the consensus guidelines to be the defining cut-off point. In the first study, that was published more than 10 years ago, the investigators found higher levels of PTH in patients with a creatinine clearance below 70 ml/min.[19] However, this study could have been confounded by the lower levels of 25(OH) D_3 seen in the renally impaired group. The most recent study in which PTH levels were found to rise below a threshold of 45 ml/min[21] was conducted by the same investigators who had earlier reported secondary elevations of PTH at eGFR threshold only below 30 ml/min.[20] Significant controversy thus exists as to whether a GFR threshold for further elevations of PTH in PHPT exists at all and if it does, what that threshold is. We, therefore, also aimed to see if there was a specific eGFR threshold below which further elevations of PTH occurred in Asian patients with PHPT.

Methods

Institutional review board approval was obtained to conduct this retrospective analysis of patients with PHPT, who presented to our large public hospital. Patients with hyperparathyroidism were identified using diagnosis codes of ICD-9-CM 2520, ICD10-AM E21, E210, E211, E212, and E213. Secondary and tertiary hyperparathyroidism, as well as familial hypocalciuric hypercalcemia, were excluded, and the diagnosis of PHPT was verified by a review of the medical records. PHPT was diagnosed by the presence of hypercalcemia and an elevated/inappropriately normal intact PTH (iPTH) level. In total, 121 patients who presented between July 2002 and December 2013, with a median (interquartile range) follow-up period of 18.0 months (4.5–46.8 months), were reviewed.

Clinical and biochemical data were obtained from case notes and electronic records. Medical history including history of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, osteoporosis, fractures, renal stones, and medications were collected at both baseline and follow-up. Biochemical analysis for serum calcium, phosphate, creatinine, low-density lipoprotein (LDL) and, 24-h urinary calcium was assayed on the standard autoanalyzer Beckman Coulter UniCel® DxC 800 immunoassay system (Beckman Coulter, Inc.). Albumin-corrected calcium in mg/dL was calculated using the formula: Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]).

Creatinine level at baseline and at last follow-up were obtained, and eGFR was calculated using the modification of diet in renal disease (MDRD) study equation: GFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$ × (0.742 if women). CKD was defined by eGFR <60 mL/min/1.73 m^2 which is the threshold of concern in the third International Workshop on the Management of Asymptomatic PHPT.[3] The patients were further divided into five groups according to National Kidney Foundation Disease Outcomes Quality Initiative guidelines with stage 1 (eGFR ≥ 90), stage 2 (eGFR 60–89), stage 3 (eGFR 30–59), stage 4 (15–29), and stage 5 (eGFR < 15).[25]

Serum 25(OH) D was measured by radioimmunoassay (Diasorin, Inc., Stillwater Minn, USA). The sensitivity of the assay is 1.5 ng/mL and the intra-assay coefficient of variation (CV) of 11.7% at 8.6 ng/mL, 10.5% at 22.7 ng/mL, 8.6% at 33 ng/mL, and 12.5% at 49 ng/mL. The total imprecision CV was 9.4%, 8.2%, 9.1%, and 11% at these 4 serum concentrations.

Serum iPTH was measured on the Beckman Dxl 800 analyzer by using a two-site sandwich immunoenzymatic chemiluminescent assay. The CV of the assay is <3% for iPTH levels between 19 and 622 pg/ml, and the inter-assay CV is <7% for iPTH between 19 and 754 pg/mL.

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry using QDR 4500 Elite (Hologic, Waltham, MA, USA). Male and female local reference databases were used to calculate the T-scores in men and women, respectively.[26,27]

Statistical analysis was performed using SPSS 21.0 for Macintosh (IBM Corp., Armonk, NY, USA). All values are given as mean ± standard deviation unless stated otherwise. Comparison between groups for categorical variables was evaluated with Chi-square test or a Fisher's exact test (where appropriate) while between groups comparison for continuous variables was evaluated with one-way analysis of variance (ANOVA). Log-transformation of parameters found to be non-normally distributed such as 24-h urine calcium, duration of follow-up, iPTH, and serum creatinine levels was performed to convert them to a normal distribution before utilizing parametric statistics. In the case of statistically significant difference in ANOVA, Bonferroni *post-hoc* adjustment was used. ANOVA was used to compare paired means of log-transformed PTH values among the CKD stages. Repeated measures one-way analysis of covariance was used to adjust within group comparisons for potential cofounders. All statistical tests were 2-tailed, and a $P < 0.05$ was considered as significant.

Results

The mean age of the patient population was 70 ± 16 years, and the majority (73%) was asymptomatic at presentation. Thirty-four patients (28.1%) subsequently underwent parathyroidectomy, 42 patients (34.7%) were treated with bisphosphonates (1 patient was treated with cinacalcet) while 45 patients (37.2%) were observed without any medical or surgical therapy.

Effect of therapy on renal function

Baseline characteristics of the three groups are presented in Table 1. There were no significant differences in gender, ethnicity, BMD at any axial site, 25(OH) D_3 levels, serum iPTH level, history of DM, dyslipidemia or HTN, HbA1c levels, fasting LDL levels, use of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and blood pressure between the three groups. Neither was there any difference in the proportion of asymptomatic patients between the 3 groups.

Patients in the parathyroidectomy group had better baseline renal function (Cr: 0.87 ± 0.24 mg/dL; eGFR: 81 ± 23 ml/min compared to the group on medical therapy (Cr: 1.16 ± 0.63 mg/dL; eGFR: 63 ± 25 ml/min) and the observation group (Cr: 1.58 ± 1.24 mg/dL; eGFR: 56 ± 30 ml/min) ($P < 0.01$). There were no significant differences between the pre- and post-therapy eGFR in the surgical and observation group. However, in the medically managed group, eGFR significantly declined from 63 ± 25 ml/min to 52 ± 32 ml/min ($P = 0.011$). At last follow-up, eGFR in the surgical group (80 ± 30 ml/min) was better as compared with the group on medical therapy (52 ± 32 ml/min) or observation group (48 ± 33 ml/min) ($P < 0.01$) [Table 2]. After adjustments for preintervention eGFR levels, patients in the parathyroidectomy group continued to have better eGFR at last follow-up compared to those in the medical or observation group ($P = 0.010$). This difference also persisted ($P = 0.035$) after adjusting for parameters such as pre-intervention GFR, age, gender, ethnicity, presence of renal stones, serum corrected calcium, serum phosphate, 24-h urinary calcium excretion, and duration of follow-up.

We also repeated the same analysis on patients with eGFR ≥60 ml/min/1.73 m^2 (the threshold for renal impairment as defined earlier[5] and above which the afore-mentioned study had found worsening of eGFR after parathyroidectomy) [13] and obtained the same findings with patients in the parathyroidectomy group having better eGFR at last follow-up compared to the other two groups after adjusting for the same confounders ($P = 0.046$). There was no significant change in pre versus postsurgery eGFR (88 ± 15 ml/min and 84 ± 28 ml/min, respectively, $P = 0.353$). In the medically managed and simply observed groups; however, the eGFR declined from 80 ± 12 ml/min to 63 ± 27 ml/min ($P < 0.01$) and from 82 ± 15 ml/min to 52 ± 35 ml/min ($P < 0.01$), respectively.

Table 1: Baseline characteristics of the study groups

	Reference ranges	Surgery (*n*=34)	Medical (*n*=42)	Observation (*n*=45)
Age (years)		57±16	76±11	74±16
Female (%)		79.4	69.0	68.9
Height (m)		1.56±0.09	1.56±0.11	1.61±0.12
Weight (kg)		58.2±10.1	54.1±13.4	57.6±15.3
BMI (kg/m^2)		23.8±4.2	24.4±4.8	24.5±6.6
Ethnicity				
Chinese (%)		64.7	66.7	73.3
Malay (%)		17.6	23.8	11.1
Indian (%)		8.8	9.5	13.3
Eurasian (%)		8.8	0	2.2
Asymptomatic (%)		64.7	71.4	80.0
Renal Stone (%)		17.6	7.1	2.2
Osteoporosis (%)		47.1	57.1	40.0
History of fracture (%)		8.8	31.0	24.4
25 (OH) D (ng/mL)	30-100	19.7±16.9	22.6±18.9	16.7±10.4
Serum corrected calcium (mg/dL)	8.4-10.4	11.5±1.3	11.9±1.2	11.0±1.1
PTH (pg/mL)*	12.4-72.4	150.3 (105.8-202.7)	105.8 (78.3-163.4)	132.0 (97.5-184.2)
Phosphate (mg/dL)	2.0-5.1	2.9±1.1	2.5±0.8	3.3±1.2
HbA1c (%)	4.4-6.4	6.6±1.3	6.8±1.3	6.7±2.0
LDL (mg/dL)	0-186	122±57	106±37	107±39
24 h urine calcium (mg/24 h)*	10-40	282 (200-418)	194 (95-427)	108 (68-216)
Creatinine at presentation (mg/dL)*	0.74-1.41	0.81 (0.68-1.04)	0.95 (0.76-1.30)	1.15 (0.79-1.68)
eGFR at presentation (mL/min/1.73 m^2)		81±23	63±25	56±30
BMD (g/cm^2)				
Femoral neck		0.594±0.121	0.522±0.091	0.603±0.109
Total hip		0.633±0.179	0.566±0.128	0.614±0.145
Total spine		0.745±0.147	0.718±0.173	0.805±0.161
T-score				
Femoral neck		−2.14±1.07	−2.93±0.89	−2.10±1.00
Total hip		−2.52±1.53	−3.19±1.10	−2.66±1.27
Total spine		−2.25±1.27	−2.50±1.50	−1.69±1.42
Hypertension (%)		55.9	78.6	68.9
SBP (mmHg)		132±26	131±19	139±27
DBP (mmHg)		73±19	68±11	73±14
ACEi or ARB (%)		20.6	38.1	44.4
Diabetes mellitus (%)		29.4	47.6	48.9
Hyperlipidemia (%)		50.0	52.4	60.0
Duration of follow-up (years)*		3.3 (1.0-6.0)	1.1 (0.4-4.4)	1.3 (0.2-3.3)

Data are presented as mean±SD or percentage. *Nonparametric data are presented as median (IQR). IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blocker, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, BMD: Bone mineral density, eGFR: Estimated glomerular filtration rate, LDL: Low density lipoprotein, PTH: Parathyroid hormone, 25(OH) D: 25-hydroxyvitamin D

Table 2: Comparison of the pre- and post-eGFR in the three groups

	eGFR at presentation	eGFR at last follow-up	*P* value within groups
Surgery	81±23[a,b]	80±30[a,b]	0.855
Medical	63±25	52±32	0.011
Observation	56±30	48±33	0.193

Data are presented as mean±SD. Between-groups comparison (Bonferroni *post-hoc* test). [a]*P*<0.01 compared to observation group, [b]*P*<0.01 compared to medical therapy group. SD: Standard deviation, eGFR: Estimated glomerular filtration rate

We explored whether the same factors that could potentially affect renal function and were evaluated at baseline differed between the three groups at last follow-up. There were no significant differences noted in comorbidities such as DM, dyslipidemia, HTN or parameters such as HbA1C, LDL levels, or use of antihypertensives such as ARBs/ACEIs between the 3 groups. eGFR in patients in the parathyroidectomy group continued to be better at last follow-up compared to those in the medical or observation group after adjusting for the factors that significantly different between the three groups in the univariate analysis: Parathyroidectomy: 77 ± 28 ml/min versus medical management: 56 ± 29 ml/min versus simple observation: 44 ± 33 ml/min; (P = 0.033).

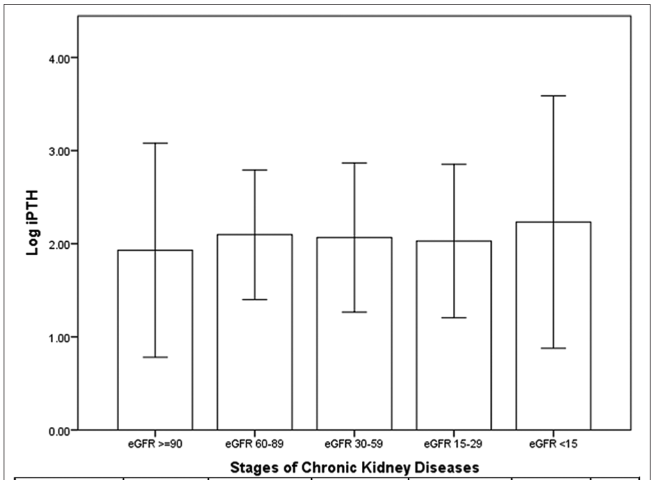
Effect of worsening renal function on parathyroid hormone levels

The number of patients in each stage of CKD and their mean PTH values prior to log transformation are shown in Figure 1. Logarithmically transformed PTH values did not differ between different eGFR groups after adjusting for age, gender, race, serum calcium levels, and 25 (OH) D_3 levels with no threshold of eGFR at which

PTH levels rose [Figure 1]. No correlation was noted between non logarithmically transformed or logarithmically transformed PTH values and eGFR ($r = -0.30$, $P = 0.747$ and $r = -0.55$, $P = 0.555$, respectively) [Figure 2].

Discussion

Our study provides, for the first time, evidence to suggest that among a non-Caucasian multi-ethnic Asian population, patients who undergo parathyroidectomy for PHPT have better renal function compared with other modalities of treatment. This benefit persisted even after adjusting for the higher preintervention eGFR in the parathyroidectomy group. This suggests that even patients with relatively preserved renal function would benefit from parathyroidectomy rather than being medically managed or simply observed. We also found that there was no significant change between pre- and post-eGFR among the surgical group when patients with an eGFR ≥60 ml/min were analyzed separately. Our finding contrasts with that reported recently by an Italian group in which a decrease in creatinine clearance after surgery was observed in patients with a baseline eGFR above 60 ml/min/1.73 m^2.[13] There was no plausible explanation afforded for this finding by the authors. The reasons why parathyroidectomy is superior to medical management and simple observation with regard to renal function and why even in patients with no renal impairment it appeared to maintain renal function as opposed to those patients in whom a nonsurgical approach appeared to cause a significant decline in renal function on follow-up can only be speculated upon. The pathophysiology of the renal manifestations in PHPT is thought to involve a loss of renal concentrating capacity due to hypercalcemia which leads to diuresis.[7] The accompanying hypercalciuria and predisposition for dehydration portends an increased risk for renal stone formation and renal calcifications, all which can lead to impairment of renal function in the long-term though this may not manifest obviously in the short-term on creatinine clearance. This is consistent with the structural changes that have been reported in renal disease associated with PHPT[28] with deposition of calcium salts in fibrosed renal interstitial tissue accompanied by significant destruction of renal parenchyma particularly affecting the renal tubules seen on renal biopsy of patients. Distal renal tubular acidosis due to renal tubular dysfunction secondary to hypercalciuria has been reported in patients with PHPT, and this was found to reverse after parathyroidectomy.[29,30] We are unable to confirm this since parameters such as urine pH, and urine anion gap were not evaluated pre- or post-intervention in our study. Neither are we able to conclusively prove that regression or stabilization of any potential structural changes occurred since renal biopsies were not done.



Stages of Chronic Kidney Disease	Stage 1 eGFR ≥ 90 (n = 26)	Stage 2 60 ≤ eGFR < 90 (n = 50)	Stage 3 30 ≤eGFR <60 (n = 28)	Stage 4 15≤ eGFR < 30 (n = 10)	Stage 5 eGFR <15 (n = 7)	P-value
iPTH (pg/mL)	139 ± 117	161 ± 136	153 ± 99	144 ± 95	389 ± 445	<.05**
Log PTH (pg/mL)	1.93 ± 0.57	2.10 ± 0.35	2.07 ± 0.40	2.03 ± 0.41	2.23 ± 0.68	NS
25OHD (ng/mL)	22.0 ± 21.8	21.6 ± 16.8	14.7 ± 8.8	17.3 ± 9.1	16.0 ± 8.8	NS

GFR is measured in ml/min/ 1.73 m^2

**p= 0.002 stage 1 vs 5, p= 0.004 stage 2 vs 5, p= 0.005 stage3 vs 5, p= 0.017 stage 4 vs 5

Figure 1: Difference in mean PTH subdivided according to eGFR

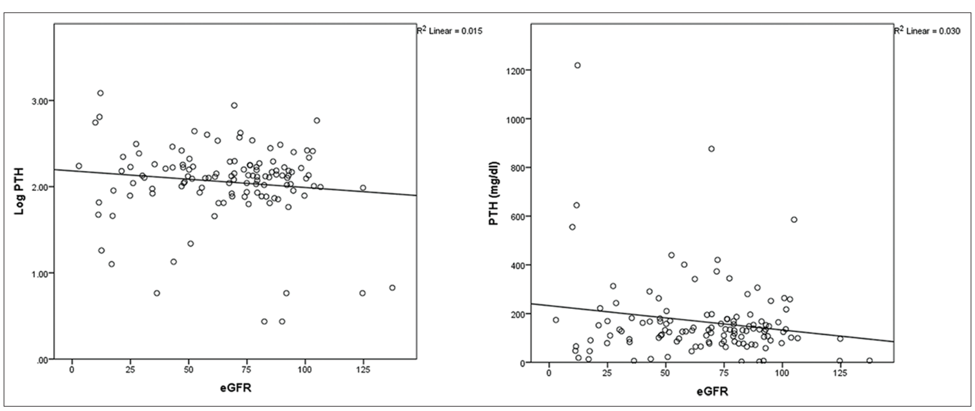


Figure 2: Correlation between PTH levels and eGFR

Our study is limited by its retrospective design. However, we rigorously adjusted for inter-group differences and other potential contributors to worsening of renal function to accurately estimate the treatment effect. Notably, there was no difference in the factors associated with progression of renal disease, including the presence of DM, HTN, hyperlipidemia, use of ACEi or ARB therapy, body mass index, systolic or diastolic blood pressure, LDL, and HbA1c levels. We adjusted for age related decline in renal function and other confounding factors such as gender, ethnicity, presence of renal stones as well as the severity of hypercalcemia and hypercalciuria and still the difference was significant.

Our study is one of the only two that have compared treatment effect in PHPT among all three different treatment modalities, the only one with a defined renal outcome and the first to assess renal outcomes among non-Caucasians in a multi-ethnic Asian population.

Our study showing that parathyroidectomy may be associated with better renal function outcomes compared to medical management, or simple surveillance may help to swing physician and surgeon opinion toward early surgery in patients with PHPT. Recommendations in the guidelines to use renal insufficiency as an indication for surgery may not be widely accepted. In fact, one study reported that impaired renal function was actually significantly predictive of clinicians pursuing non operative management.[31] Indeed, in our series we found that 95.2 and 82.2%, respectively of the asymptomatic patients who were eventually medically managed or simply observed actually had met surgical guidelines. The prevalence of renal impairment (as defined by eGFR <60 ml/min) was 40.5% and 51.1% in these two groups, and this was significantly different to the group that eventually underwent parathyroidectomy. Though we cannot conclusively prove it since information regarding the reasons behind choosing a particular treatment option could not be obtained from our retrospective analysis, it is very likely that the presence of the comorbidity of renal impairment could have influenced the clinician to not proceed with surgery.

The predominant use of bisphosphonates as opposed to the calcimimetic-Cinacalcet for medical management of PHPT in our patients reflects the restrictions (including its significant cost and unclear benefit on long-term bone health) on its use in Singapore as well as in a large part of Asia. It is possible that the decline in renal function with medical management could partly be due to the use of bisphosphonates. Whether this would possibly change with potentially increased use of Cinacalcet in Asian countries for management of hypercalcemia in hyperparathyroidism remains to be seen.

We observed that in our population, there was no significant difference in logarithmically transformed PTH values between the different CKD stages in PHPT and that there was no definite threshold below which PTH levels further rose. Our finding is consistent with and harkens back to the earlier studies that have challenged the notion that a secondary elevation of PTH levels occurs at a threshold of 60 ml/min. It has also to be noted that this is a difficult area of study since considerable overlap between primary and secondary elevations in PTH may occur.[32] Our study methodology does not differ dramatically from the most recent study in which a threshold of <45 ml/min was associated with further elevations of PTH except that the latter study used the CKD- EPI equation to estimate GFR whereas we used the MDRD equation. However, the use of differing equations should not have affected the findings since the authors of the previous study obtained the same results when they used the MDRD equation. It is to be noted that the MDRD formula is still the most widely used to estimate GFR from creatinine. CKD-EPI is more recently established, and its use has not been conclusively validated in a multi-ethnic population. A significant discordance in the prevalence of CKD and the correct assignment of CKD stages has been observed with use of the CKD-EPI formula in South-East Asians.[33] Ethnic differences in the regulation of mineral and parathyroid hormone metabolism have also been described in normal individuals as well as in patients with osteoporosis and CKD.[34,35]

Conclusion

Our study provides compelling evidence to support the premise that surgery for PHPT may be better than a nonsurgical approach with respect to long-term renal function. This has to be confirmed through large randomized controlled trials in other populations also. We also showed that in our population of Asian patients, there was no threshold of eGFR below which further secondary elevations in PTH in PHPT occurred. Ethnic and genetic disparities may contribute to this finding. Further studies should be done to elucidate these differences.

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Conflicts of interest

There are no conflicts of interest.

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