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High prevalence of chronic kidney disease in patients with multiple endocrine neoplasia type 1 and improved kidney function after parathyroidectomy[☆,☆☆]

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ABSTRACT

Background: Because chronic kidney disease is an important comorbidity associated with primary hyperparathyroidism, we sought to evaluate the prevalence of chronic kidney disease and effects of parathyroidectomy on kidney function in patients with multiple endocrine neoplasia type 1–associated primary hyperparathyroidism.
Methods: We performed a retrospective analysis of 112 patients with multiple endocrine neoplasia type 1–associated primary hyperparathyroidism who had at least 1 operation for primary hyperparathyroidism at 2 tertiary referral centers. The preoperative and postoperative estimated glomerular filtration rates were compared. The prevalence of chronic kidney disease stage 3 or worse (estimated glomerular filtration rates less than 60 mL/min/1.73m^2) in this cohort was compared to the rates in the US population reported by the Centers for Disease Control and Prevention.
Results: The median age at the time of parathyroidectomy was 36.5 years (range: 12–76 years). A total of 99 patients had biochemical remission. The rate of chronic kidney disease stage 3 or worse in patients with multiple endocrine neoplasia type 1–associated primary hyperparathyroidism was greater than that observed in the US population for ages 20–39 and 40–59 (5% [$n=2/44$] vs 0.39% [$n=18/4565$], $P=.015$ and 10% [$n=4/40$] vs 2.31% ($n=89/3848$), $P=.015$, respectively). We observed improved estimated glomerular filtration rates in those with chronic kidney disease stage 3 or worse postoperatively (48 vs 57 mL/min/1.73m^2, $P=.047$). A successful parathyroidectomy normalized all 24-hour urine calcium excretion.
Conclusion: An indication for early parathyroidectomy should include estimated glomerular filtration rates less than 60mL/min/1.73m^2 in patients with multiple endocrine neoplasia type 1–associated primary hyperparathyroidism.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with an incidence of 65.5 and 24.7 cases per 100,000 person-years in women and men, respectively.[1] Multiple endocrine neoplasia syndrome type 1 (MEN1) is a rare, autosomal dominant, hereditary disorder caused by a germline mutation in the MEN1 gene. MEN1 accounts for 1% to 5% of all PHPT cases and is the most common cause of familial PHPT.[2] PHPT is the most prevalent endocrinopathy that occurs in patients with MEN1. By the age of 50, 70% to 90% of patients with MEN1 present with PHPT.[3] Other common endocrine tumors associated with MEN1 include anterior pituitary, gastrointestinal, thymic, and pancreatic neuroendocrine tumors. Unlike patients with sporadic PHPT, MEN1-associated PHPT (or MEN1-PHPT) typically presents with multigland parathyroid disease characterized by asymmetric and asynchronous enlargement of parathyroid glands.[4] Patients with MEN1 frequently

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Table 1
Clinical characteristics of patient cohorts.

Clinical characteristics	Combined cohort	NIH cohort	MDA* cohort	*P* value
Age at operation	36.5 (24.3–50.0)†	37 (24–49.5)†	34.5 (30–50.25)†	.77
Sex (female)	53.6% (*n* = 60/112)	52% (*n* = 34/66)	56.5% (*n* = 26/46)	.70
Ethnicity (non-Black)	12.1% (*n* = 12/99)	14% (*n* = 9/66)	9% (*n* = 3/33)	.75
Reoperative parathyroidectomy	20.5% (*n* = 23/112)	5% (*n* = 3/66)	44% (*n* = 20/46)	<.0001
Preoperative eGFR	92.3 (76.0–113.0)†	94 (79.0–116.5)†	92 (72.4–110.4)†	.25
Postoperative eGFR	88.0 (72.7–108.7)†	93 (74.8–112.0)†	82.3 (72.4–106.0)†	.31
Preoperative CKD ≥3	9.8% (*n* = 11/112)	11% (*n* = 7/66)	9% (*n* = 4/46)	1.0
Preoperative intact PTH‡	108.7 (79.1–145.3)†	104 (72.3–139.5)†	116 (88.5–160.0)†	.13
Postoperative intact PTH‡	37.2 (22.0–61.3)†	33.7 (23.0–63.5)†	38.5 (15.5–55.8)†	.45
Preoperative highest calcium, corrected	**10.8 (10.3–11.2)**†	10.8 (10.5–11.3)†	10.5 (9.9–11.2)†	.021
Postoperative calcium, corrected	9.1 ± 0.9§	9.6 ± 0.9§	9.0 ± 0.9§	.42
At least 1 comorbidity present	30.4% (*n* = 34/112)	24% (*n* = 16/66)	39% (*n* = 18/46)	.10
Hypertension	17.0% (*n* = 19/112)	14% (*n* = 9/66)	22% (*n* = 10/46)	
Hyperlipidemia	14.3% (*n* = 16/112)	17% (*n* = 11/66)	11% (*n* = 5/46)	
Diabetes mellitus	19.6% (*n* = 22/112)	17% (*n* = 11/66)	24% (*n* = 11/46)	

* MDA = University of Texas MD Anderson Cancer Center
† Data presented as median (range)
‡ PTH = parathyroid hormone
§ Data presented as mean ± standard deviation

have ectopic and supernumerary glands, which are most commonly found in the thymus.[5]

Because nephrocalcinosis and nephrolithiasis are metabolic complications that can lead to decreased kidney function in patients with PHPT, 1 of the indications for the operative intervention in patients with asymptomatic sporadic PHPT includes estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2.[6] Although symptomatic hypercalcemia, osteoporosis, and nephrocalcinosis or nephrolithiasis are indications for parathyroidectomy (PTX) in patients with MEN1-PHPT, the timing for PTX in asymptomatic patients without metabolic complications remains controversial.[7] Unlike patients with sporadic PHPT, patients with MEN1-PHPT usually present with prolonged mild hypercalcemia starting in the second decade of life.[8] Patients with MEN1-PHPT experience greater decreases in bone mineral density compared with those with sporadic disease[9] and greater rates of renal complications.[10] Currently, eGFR less than 60 mL/min/1.73m^2 is not considered an indication for PTX in asymptomatic patients with MEN1-PHPT who have no metabolic complications.

In this study, we hypothesized the following: (1) the prevalence of chronic kidney disease (CKD) in patients with MEN1-PHPT is greater than age-matched population owing to prolonged hypercalcemia and (2) successful PTX can improve kidney function. Thus, we aimed to compare the prevalence of CKD in patients with MEN1-PHPT to that of an age-matched population and to study the effect of PTX on kidney function in patients with MEN1-PHPT.

Methods

We conducted a retrospective analysis of patients with a diagnosis of MEN1 who underwent at least 1 PTX for PHPT at the National Institutes of Health (NIH) Clinical Research Center and the University of Texas MD Anderson Cancer Center between the years 1993 and 2014. The combined cohort included patients who underwent initial PTX and reoperative PTX (Table 1). The study was approved by the Office of Human Subject Research at the NIH and by MD Anderson Cancer Center Institutional Review Board. All patients provided written consent.

The diagnosis of MEN1 was made based on the following: (1) the presence of PHPT combined with anterior pituitary tumor or gastrointestinal and pancreatic neuroendocrine tumor, (2) a diagnosis of PHPT combined with a diagnosis of MEN1 in at least 1 first-degree relative, or (3) a positive germline mutation in the *MEN1* gene. All patients underwent screening and surveillance tests for other manifestations of MEN1, per published guidelines.[11] The diagnosis of PHPT was made based on the presence of hypercalcemia (albumin-corrected total calcium or ionized calcium) and inappropriately increased intact parathyroid hormone in the absence of hypocalciuria. Indications for PTX included symptoms associated with hypercalcemia or metabolic complications such as osteoporosis, nephrocalcinosis, or nephrolithiasis. Patients were considered to have a successful PTX if they achieved biochemical remission and if there was no evidence of PHPT for at least 6 months postoperatively, with or without postoperative hypoparathyroidism. Persistent and recurrent PHPT were defined as PHPT that occurred postoperatively within 6 months and after 6 months, respectively.

Serum creatinine levels were measured before PTX and during follow-up in the postoperative period. Serum creatinine levels, patient age, sex, and ethnicity were used with the Modification of Diet in Renal Disease (MDRD) equation to calculate preoperative and postoperative eGFR for each patient.[12] These eGFR values were used to characterize the renal function based on the classification of CKD by the 2012 Kidney Disease Improving Global Outcomes clinical practice guideline. CKD stage 3 or worse (CKD ≥3) was defined as eGFR less than 60 mL/min/1.73 m^2. The preoperative and postoperative eGFR values for patients were compared to determine the impact of successful PTX on kidney function.

To assess if patients with MEN1-PHPT have a greater rate of CKD than the general population, the prevalence of CKD ≥3 in patients with MEN1-PHPT was compared to that of the age-matched US population from 1999 to 2004 as reported by the Centers for Disease Control and Prevention.[13]

Statistical analysis

The Fisher's exact test and chi-squared test were used to analyze differences in categorical variables. The Student's *t*-test and Mann-Whitney U test were used to assess the differences in parametric and nonparametric continuous variables, respectively. The paired *t*-test was used to analyze differences between preoperative and postoperative eGFR and 24-h urinary calcium levels (available in NIH cohort only). A 2-tailed *P* value less than .05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 7.01 (GraphPad Software, La Jolla, CA).

Results

We identified a cohort of 112 patients with MEN1-PHPT who underwent PTX at either of the 2 tertiary referral centers. The com-

Table 2
eGFR values for patients with preoperative CKD ≥3.

Patient ID	Age	Sex	Biochemical remission	Preoperative eGFR	Postoperative eGFR	Diabetes mellitus	Hypertension	Hyperlipidemia
NIH002	52	F	Y	32.00	25.00			
NIH005	54	F	Y	58.00	65.00			
NIH016	48	F	N	54.00	54.00			
NIH019	65	F	Y	45.00	41.00	•		•
NIH045	72	F	Y	49.00	70.00	•		•
NIH049	59	M	Y	50.00	61.00		•	•
NIH063	60	F	Y	41.00	56.00	•		•
MDA011	64	M	N	43.73	46.97			•
MDA021	57	F	Y	57.15	73.93	•		
MDA023	64	F	N	14.07	11.92	•	•	•
MDA036	61	F	Y	52.70	59.80	•		

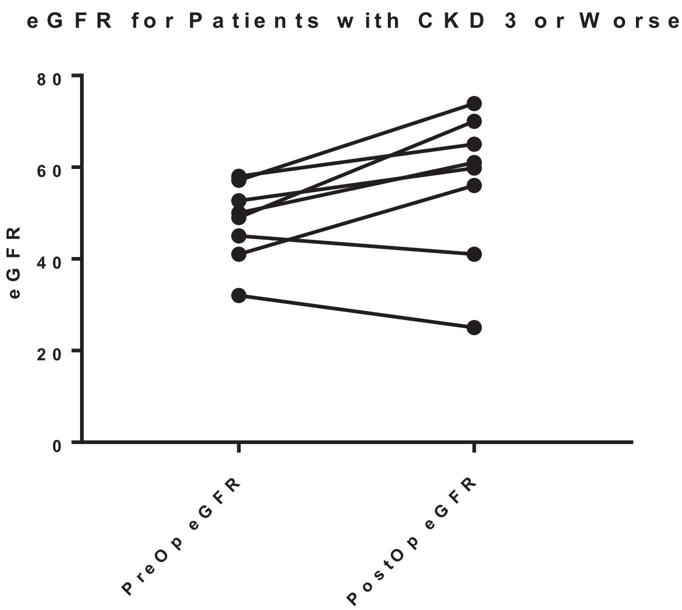

Fig. 1. Comparison of preoperative and postoperative estimated glomerular filtration rate(eGFR)(ml/min/1.73m^2) for patients with CKD 3 or worse who achieved biochemical remission.

bined cohort was slightly female predominant (53.6%), the median age at the time of PTX was 36.5 years (range: 12–76 years), and 99 patients (88.4%) achieved biochemical remission after PTX. The median follow-up time was 20.3 months (range: 10.2–42.7). Of 112 patients, 34 patients (30%) had at least 1 risk factor associated with CKD. The cohorts from the 2 referral centers differed only by preoperative corrected calcium values and the rate of reoperative PTX. Risk factors included a history of hyperlipidemia, hypertension, and diabetes mellitus. The clinical characteristics of patients are summarized in Table 1.

Patients with MEN1-PHPT had a greater prevalence of CKD ≥3 when compared with the age-matched US population for the age range of 20–39 (5% [$n = 2/44$] vs 0.39% [$n = 18/4565$], $P = .015$) and 40–59 (10% [$n = 4/40$] vs 2.31% [$n = 89/3848$), $P = .015$). There was no difference in the prevalence of CKD ≥3 in patients with MEN1-PHPT who were 60 years of age or older compared with the US population (32% [$n = 6/19$] vs 21.6% [$n = 944/4372$], $P = .273$).

There was no difference between preoperative and postoperative eGFR in the 99 patients who had biochemical remission (97 vs 95 mL/min/1.73 m^2, $P = .40$) after successful PTX; however, successful PTX improved eGFR (48 vs 57, $P = .047$) in patients with MEN1-PHPT and CKD ≥3 ($n = 8/99$). Of 8 patients with MEN1-PHPT and CKD ≥3 who achieved biochemical remission, 5 of the 8 patients had stabilized or improved eGFR (Table 2, Fig 1). Successful PTX also decreased and normalized all 24-hour urine calcium excretion (306 ± 192 mg/24 h to 177 ± 110 mg/24 h, $P < .001$) in a subset of 31 patients from the NIH cohort for which this information was available. We found no statistically significant difference between preoperative and postoperative eGFR after successful PTX in patients with MEN1-PHPT who had at least 1 risk factor for CKD (83 vs 89 mL/min/1.73 m^2 [$P = .18$]).

Discussion

The high prevalence of CKD ≥3 (up to 17%) was observed in patients with sporadic mild or asymptomatic PHPT.[14] It is not known, however, if the prevalence of CKD ≥3 is greater than the general population as no comparison has been made previously. In this study, we demonstrate a greater prevalence of CKD ≥3 in patients with MEN1-PHPT compared with the age-matched US population 60 years of age or older. In addition, we show that PTX improved eGFR in patients with MEN1-PHPT and CKD ≥3. Because MEN1-PHPT starts commonly in the second or third decade of life, it is possible a greater prevalence of CKD ≥3 was observed in patients with MEN1-PHPT younger than 60 years of age because of prolonged exposure of hypercalcemia. Compared to our cohort, the median age of patients in sporadic cohorts was older (59.1–68.0 vs 36.5 years) as expected.[14,15] The lack of difference in prevalence of CKD ≥3 between patients in our cohort and the US population aged 60 years or older may be due to high rates of comorbidities associated with CKD in this population in both groups and the possibility of a type-2 statistical error from the small sample size. The causal relationship between hyperparathyroidism and renal impairment has not been demonstrated definitively in a population-based or a large cohort study.[16] The recent population-based study by Kalla et al was not age matched, and patients in the PHPT group were significantly older.[16] Because patients with MEN1 frequently have prolonged PHPT before developing metabolic complications followed by PTX, we believe the MEN1 cohort can demonstrate a natural history of delayed PTX in patients with PHPT. Thus, we chose this cohort to compare with the age-matched US population.

The most recent 2 iterations of the management guidelines from the Third and Fourth International Workshops recommended operative intervention for patients with sporadic PHPT and eGFR <60 mL/min/1.73 m^2.[6] These recommendations are based on the perceived deterioration of CKD in these patients with sporadic PHPT and the concern for worsening of PHPT secondary to CKD. The ideal timing for PTX in MEN1-PHPT remains controversial. It is unclear as to whether PTX should be performed early on or late in the disease course. For example, a recent study suggested earlier PTX in patients with MEN1-PHPT and low bone mineral density because the bone density recoverability after PTX was not as effective as patients with sporadic PHPT.[17] At our institutions, asymptomatic mild PHPT in patients with MEN1 may be observed even in patients younger than 50 years of age,[6] reserving operative intervention for those who develop symptoms associated with hypercalcemia or metabolic complications, consistent with the recent guidelines.[7] To date, there have been little data to support the recommendation to perform PTX in patients with sporadic PHPT who have eGFR <60 mL/min/1.73 m^2. No improvement in kidney function was seen in 3 randomized controlled trials comparing PTX to active surveillance in asymptomatic patients with mild, sporadic PHPT,[18–20] but kidney function was not the primary outcome measure. It is likely that these patients with sporadic PHPT experienced a lesser duration of hypercalcemia at a much older age of onset compared to patients with MEN1-PHPT. One recent study of a cohort in India demonstrated improvement in CKD stages for 13 of 44 patients (30%) with sporadic PHPT and preoperative eGFR <60 mL/min/1.73 m^2.[21] Another retrospective study demonstrated arrest of further decline in renal function after PTX in patients with PHPT and CKD ≥3. It is unclear how many, if any, patients with MEN1 were included.[14] Because eGFR naturally decreases with age, our data support the role of PTX in patients with MEN1-PHPT and CKD ≥3 because 5 of 8 patients in our cohort had stabilized or improved eGFR after successful PTX.

The results from our study represent the first data to suggest the benefit of PYX for patients with MEN1-PHPT and CKD ≥3. The findings from this study are potentially important because this study provides evidence to support PTX in this patient population. We demonstrated that these patients suffer from CKD at rates greater than the age-matched US population at the younger age. This has great implication for the future management of these patients in terms of health care expenditure and quality of life. By intervening, we may prevent or delay the progression of CKD and subsequent complications associated with CKD such as dialysis-dependent, end-stage renal disease. Because CKD promotes hypertension and dyslipidemia and accelerated cardiovascular disease, which in turn can contribute to the progression of renal failure,[22] we believe that early PTX is indicated in patients with MEN1-PHPT and CKD ≥3. Although the use of proton pump inhibitors, such as in patients with MEN1 and Zollinger-Ellison syndrome, is associated with acute interstitial nephritis and increased risk of CKD,[23] the improvement after successful PTX suggests that chronic hypercalcemia contributed to the decreased eGFR.

The limitations of this study include the incomplete data on risk factors associated with CKD such as obesity, smoking, or family history of kidney disease. Because of the retrospective nature of the analysis, the timing of eGFR assessment was not standardized. Likewise, because the sample size of MEN1-PHPT is small, the high rate of CKD ≥3 may be overestimated. This study utilized the MDRD equation to calculate eGFR instead of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation has been shown to be more accurate in estimating GFR >60 mL/min/1.73m^2 and predicting the risk of end-stage renal disease and mortality[24]; however, the CKD-EPI equation and the MDRD equation were equally accurate in a subgroup with eGFR less than 60 mL/min/1.73 m^2.[25] We chose the MDRD equation to be consistent with the US population study for direct comparison. There are additional confounding factors that may affect the renal functions such as other treatments or additional procedures these patients may have undergone for other manifestations of MEN1. The differences in management of comorbid conditions may have had an impact on renal function. A short follow-up may be a limitation of the study; however, because the primary outcome measure of the study was the effect of PTX on postoperative eGFR, which naturally declines over time, we expected the eGFR improvement within a short follow-up. In addition, the age-related decline in eGFR would have more effect in the longer follow-up.

In summary, we demonstrated a greater prevalence of CKD ≥3 in patients with MEN1-PHPT less than 60 years of age compared with the age-matched US population. Because of the improvement in kidney function after PTX in patients with MEN1-PHPT and CKD ≥3, we recommend that these patients should undergo PTX in an attempt to preserve renal function. Additional prospective studies in larger cohorts are needed to confirm our results and to further examine the role of PTX in patients with MEN1-PHPT and risk factors for CKD.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Discussion

Dr Menno Vriens (Utrecht, Netherlands): Very nice data from great centers.

Your median age for surgery was around 40 years. There was a significant number of patients between the ages of 20 to 39.

Do these data force you now to operate at an earlier age?

Dr Patience Green: At this time our data do not support the use of age alone. However, based on the findings from this study, we are moving forward at NCI to pursue parathyroidectomy for patients with a GFR 60 or below.

Dr Menno Vriens (Utrecht, Netherlands): You mentioned in one of your earlier slides that subtotal or total parathyroidectomy was the operation of choice. Did all patients undergo this kind of operation or did some undergo less than subtotal parathyroidectomy?

Dr Patience Green: Most of these patients underwent a subtotal or a total parathyroidectomy.

Dr Christopher R. McHenry (Cleveland, Ohio): Well done. As I consider your data, you document that there is a higher prevalence of stage 3 chronic kidney disease. And with parathyroidectomy, there's improvement in GFR. I wondered if there is progression or decrease in the GFR that occurs over time with just observing patients that have MEN-1 hyperparathyroidism? I think you are advocating that a GFR that's less than 60 is an indication for an operation. But if a patient has MEN-1 hyperparathyroidism, isn't that alone an indication for parathyroidectomy?

Dr Patience Green: To address your first question, we do not have the data on patients that did not undergo surgery. These patients, once there was an indication, typically underwent surgical intervention. So we don't have a cohort of patients that we followed without operation.

Dr Christopher R McHenry (Cleveland, Ohio): From your conclusion, you say a GFR of less than 60 is an indication for operation. And my sense is, shouldn't they just be operated on whether or not they have a low GFR? Isn't MEN-1 hyperparathyroidism an indication for parathyroidectomy?

Dr Patience Green: In the MEN-1 cohort, there is a high risk of recurrence of disease even after they have undergone surgical intervention, so these patients will typically get a subtotal or a total parathyroidectomy as their index operation. Once one has had that procedure, it's more complicated to do a remedial procedure because of the risk of permanent hypoparathyroidism. So these patients will only undergo surgical intervention once there is an indication such as a metabolic complication. So some of these patients would be followed until they develop a metabolic complication that pushed us to operate.

Dr Cortney Lee (Lexington, Kentucky): Nice paper. I like seeing that what we do helps.

I know that there was some discrepancy between institutions and how far out you measured the GFR, but from your review of the data, about how far out do you need to check to see this improvement? Is it a couple months, a year, two? What was the average, more or less?

Dr Patience Green: For these patients, all of the values that we checked to determine if they achieved their biochemical improvement were within 6 months. So all of the gains that we have seen here were within 6 months of surgery.

Dr Fiemu Nwariaku (Dallas, Texas): I enjoyed your paper as well. I have 2 questions about the GFR. One is how did you account for the potential confounders, such as other interventions that we do for patients with chronic kidney disease over time?

The second question is whether this is really about MEN-1, or is it about hypercalcemia? I couldn't tease that out from the talk. So if you compare these patients to patients with sporadic hyperparathyroidism over a period of time, do you see the same changes in GFR for parathyroidectomy, and does it depend on the time that the kidneys exposed to high calcium levels?

Dr Patience Green: To address the first question, this is primarily for patients with MEN-1 associated primary hyperparathyroidism specifically. For those patients that have sporadic disease, the studies don't consistently suggest an improvement. There can be an improvement, and some suggest it will halt renal disease in sporadic cases. However, the studies are mixed, so there's no firm conclusion that can be drawn about the improvement or the effect on parathyroidectomy in sporadic cases. We were able to demonstrate that for MEN-1 associated primary hyperparathyroidism, so that's primarily what we are addressing with this paper.

Additionally, we do not currently have the data to calculate the trends or rates of change for these patients. That's something that we can definitely look at moving forward.