Surgery 165 (2019) 99–104

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Parathyroid

End-organ effects of primary hyperparathyroidism: A population-based study ☆

Yasmine Assadipour, MD[a,1,*], Hui Zhou, PhD[b,1], Eric J. Kuo, MD[a], Philip I. Haigh, MD[c], Annette L. Adams, PhD[b], Michael W. Yeh, MD[a]

[a] Section of Endocrine Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA
[b] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA
[c] Department of Surgery, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

ARTICLE INFO

Article history:
Accepted 10 April 2018
Available online 9 November 2018

ABSTRACT

Background: Patients with primary hyperparathyroidism are at risk for skeletal and renal end-organ damage.

Methods: We studied patients with biochemically confirmed primary hyperparathyroidism from 1995–2014 and quantified the frequency of osteoporosis, nephrolithiasis, hypercalciuria, and decrease in renal function.

Results: The cohort comprised 9,485 patients. In total, 3,303 (35%) had preexisting end-organ effects (osteoporosis, 24%; nephrolithiasis, 10%; hypercalciuria, 5%). Of 6,182 remaining patients, 1,769 (29%) exhibited progression to 1 or more end-organ effects over a median 3.7 years. Among patients with classic primary hyperparathyroidism (calcium and parathyroid hormone increased), progression was unrelated to the degree of hypercalcemia (calcium >11.5 mg/dL, hazard ratio 1.03, 95% confidence interval 0.85–1.25; 11.1–11.5 mg/dL, HR 1.07, 95% confidence interval 0.93–1.23; 10.5–11.0 mg/dL = reference). Patients with nonclassic primary hyperparathyroidism (calcium increased, parathyroid hormone 40–65 pg/mL) had a lesser risk of progression (calcium >11.5 mg/dL, hazard ratio 0.68, 95% confidence interval 0.50–0.94; 11.1–11.5 mg/dL, hazard ratio 0.68, 95% confidence interval 0.56–0.82; 10.5–11.0 mg/dL, hazard ratio 0.66, 95% confidence interval 0.59–0.74). End-organ damage developed before or within 5 years of diagnosis for 62% of patients.

Conclusion: End-organ manifestations of primary hyperparathyroidism develop before biochemical diagnosis or within 5 years in most patients. End-organ damage occurred more frequently in patients with classic primary hyperparathyroidism versus nonclassic primary hyperparathyroidism, regardless of severity of hypercalcemia.

Introduction

Patients with primary hyperparathyroidism (PHPT) have increased serum calcium levels and high or inappropriately normal levels of parathyroid hormone (PTH). The prevalence of PHPT has been reported as 1 in 400 women and 1 in 1,200 men in recent studies.[1–3] PHPT predisposes to skeletal and renal end-organ damage.[4] In patients with PHPT, the rate of nephrolithiasis is greater than 4 times that of age-matched controls.[5] PHPT can present in the classic form, with increased serum calcium and a PTH greater than normal; a nonclassic form, with increased calcium and an inappropriately normal (nonsuppressed) PTH; or a normocalcemic form, with high-normal calcium and increased PTH levels. Operative treatment of PHPT decreases the risk of fracture, decreases the incidence of nephrolithiasis, and may halt the decline in renal function.[6,7]

Current consensus guidelines recommend parathyroidectomy (PTX) for all symptomatic patients and asymptomatic patients meeting the following criteria: serum calcium >1 mg/dL above normal, osteoporosis, hypercalciuria, glomerular filtration rate (GFR) <60 mL/min, age <50, or with radiographic evidence of vertebral fracture.[8] These criteria reflect end-organ damage or increased risk for end-organ damage. The prevalence of end-organ damage in patients with PHPT is not well characterized.

☆ Presented at the American Association of Endocrine Surgeons meeting in Durham, North Carolina, May 6–8, 2018.

* Corresponding author: Section of Endocrine Surgery, Department of Surgery, 10833 Le Conte Ave, 72-228 CHS, Los Angeles, CA 90095.
E-mail address: ya@vasurgery.com (Y. Assadipour).

[1] Yasmine Assadipour and Hui Zhou are co-first authors with equal contribution.

https://doi.org/10.1016/j.surg.2018.04.088
0039-6060/

Our aim was to characterize the frequency and timing of clinical progression to end-organ effects in PHPT and to assess for a correlation between clinical progression and biochemical disease severity.

Methods

Study setting and participants

The study population included all active enrollees in Kaiser Permanente Southern California (KPSC), a vertically integrated health care delivery system serving approximately 4.4 million subscribers. The membership closely mirrors the population of the greater Los Angeles metropolitan area demographically and socioeconomically. Because most members receive employer-based insurance benefits, outmigration rates are low, with two thirds of subscribers maintaining membership for at least 5 years.

The KPSC Laboratory Management System was queried to identify patients with a biochemical diagnosis of PHPT from January 1, 1995 through December 31, 2014. Inclusion and exclusion criteria were adapted from prior population-level studies of PHPT, including Wermers, et al[9–11] and Yu et al.[12–14] We included patients with classic PHPT, as defined by hypercalcemia (serum calcium >10.5 mg/dL) and increased (>65 pg/mL) PTH levels, and patients with nonclassic PHPT, as defined by hypercalcemia with an inappropriately increased (nonsuppressed) PTH level within the upper half of the reference range (40–65 pg/mL). PTH levels were measured within 6 months of the initial high serum calcium level. We applied the following exclusions: age <20 years, estimated GFR <30 mL/min within 1 year before or 6 months after biochemical diagnosis, death or disenrollment within the first year of follow-up, and membership term less than 6 months. Any patient with 2 or more tests for immunosuppressant levels was considered a likely kidney transplant recipient with possible tertiary hyperparathyroidism and was excluded.

Study protocol

The biochemical severity of a patient's PHPT was classified into 1 of 6 groups based on the presence of mild (↑Ca, 10.5–11.0 mg/dL), moderate (↑↑Ca, 11.1–11.5 mg/dL), or severe hypercalcemia (↑↑↑Ca, >11.5 mg/dL) and the presence of an increased (↑PTH, >65 pg/mL) or inappropriately normal PTH level (*nl*PTH, 40–65 pg/mL). Patients with classic PHPT were represented with the following notation: ↑↑↑Ca+↑PTH, ↑↑Ca+↑PTH, ↑Ca+↑PTH, whereas patients with nonclassic PHPT were represented by the following: ↑↑↑Ca+*nl*PTH, ↑↑Ca+*nl*PTH, ↑Ca+*nl*PTH.

We initially assessed for the existence of osteoporosis, nephrolithiasis, or hypercalciuria before the biochemical diagnosis of PHPT. After identification of patients with these preexisting, end-organ effects, the remaining patients were studied further. Although GFR <60 mL/min does reflect end-organ damage, we decided to follow patients with GFR 30–60 mL/min to assess for progressive declines in renal function that may be attributable to PHPT.

The primary outcome of this study was progression to end-organ effects of PHPT, including osteoporosis, nephrolithiasis, decreasing renal function, or hypercalciuria, whichever was diagnosed earliest (composite endpoint). Osteoporosis was defined by T-score < −2.5. Nephrolithiasis was defined by the *International Classification of Diseases, Ninth Revision* (ICD-9) codes (592.0, 592.1, 592.9, 594.0, 594.1, 594.2, 594.8, 594.9) and Current Procedural Terminology or ICD-9 codes for procedures directed toward urinary tract stones (50590, 50592, 50593, 52317, 52318, 50561, 50580, 52310, 52315, 52325, 52352, 52353, 52356, 50060, 50075, 50080, 50081, 50130, 50980, 51060, 51050, 51065, 59.95, 55.04, 98.5, 98.51, 56.0, 57.0, 55.01, 55.03, 55.04, 55.11, 56.0, 56.2, 57.19, 57.0). Decrease in renal function was defined as a decrease in GFR less than the next threshold value: 60, 45, and 30 mL/min for patients with initial GFRs of >60, 45–60, and 30–45 mL/min, respectively. At least 2 measurements of GFR separated by 90 days were necessary to distinguish between transient and permanent decreases in renal function. Hypercalciuria was defined as 24-hour urine calcium excretion >400 mg. Patients were followed for a period of 5 years and were censored at the time of PTX, death, disenrollment, or study closure, whichever occurred first.

Statistical analysis

Summary statistics were used to describe baseline characteristics. Student's *t*-test and χ^2 tests were used to detect differences in baseline continuous and categorical variables, respectively. The frequencies of preexisting osteoporosis, nephrolithiasis, and hypercalciuria by biochemical severity of PHPT were compared using the χ^2 test. Kaplan-Meier analysis was used to evaluate time to progression to the primary outcome. A multivariable Cox proportional hazards model was used to estimate the risk of progression over time to the primary outcome by biochemical severity of PHPT. Because the most common clinical presentation of PHPT is a patient with mild hypercalcemia and an increased PTH, the ↑Ca+↑PTH group was designated as the reference group. Osteoporosis, nephrolithiasis, and a decrease in renal function were also analyzed as individual outcomes. The regression models were adjusted for age, sex, race or ethnicity, and baseline GFR group. When the outcome included a decrease in renal function, the model was additionally adjusted for baseline rates of diabetes and hypertension.

Results

Of 9,485 patients with biochemically confirmed PHPT, 3,303 patients with preexisting osteoporosis, nephrolithiasis, or hypercalciuria were identified initially. The remaining 6,182 patients were then followed forward in time to assess for the new development of end-organ effects (Fig. 1).

Preexisting end-organ effects

The most common preexisting, end-organ effect was osteoporosis ($n = 2{,}302$, 24.3%), followed by nephrolithiasis ($n = 996$, 10.5%) and hypercalciuria ($n = 438$, 4.6%); 215 patients (2.3%) had both osteoporosis and nephrolithiasis, 109 patients (1.1%) had osteoporosis and hypercalciuria, 75 (0.8%) patients had hypercalciuria and nephrolithiasis, and 17 (0.2%) had all 3 conditions. In addition to the patients with osteoporosis, 1,909 patients (20.1%) had preexisting osteopenia. Bone mineral density data were available in 7,505 of 9,485 patients (79%). Compared to patients with nonclassic PHPT, patients with classic PHPT had increased rates of preexisting osteoporosis (26.9% vs. 20.1%, $P < .001$), nephrolithiasis (12.0% vs. 8.1%, $P < .001$), and hypercalciuria (6.5% vs. 1.7%, $P < .001$), whereas no differences were observed with respect to preexisting impaired GFR (GFR 45–59 mL/min, 16.5% vs. 16.1%, not significant; GFR 30–44 mL/min, 9.5% vs. 8.4%, not significant).

Progression to end-organ effects

Baseline characteristics are shown in Table 1. The mean age was 64.1 years, and 79.6% of patients were female. The majority of patients were white (58.5%) with a Charlson Comorbidity Index of 0 (55.9%) and a normal GFR of ≥60 mL/min (75.8%). The median serum calcium and PTH were 10.9 mg/dL and 72 pg/mL, respectively. The PTX rate during the study period was 19% (1,159 of 6,182).

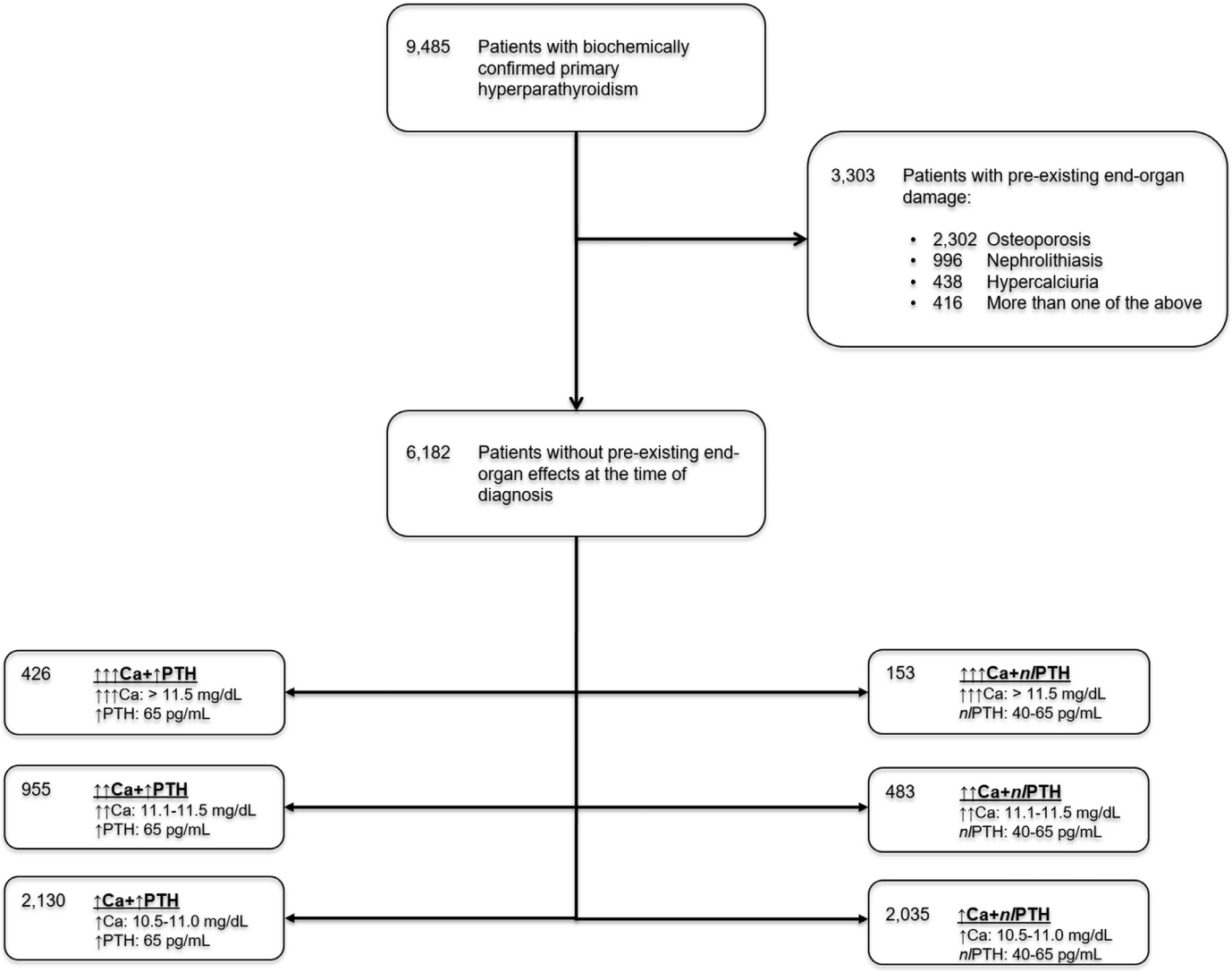

Fig. 1. Cohort derivation from patients with PHPT.

Table 1
Characteristics of 6,182 patients without preexisting end-organ effects by biochemical severity of primary hyperparathyroidism.

	↑↑↑Ca+↑PTH $n=426$	↑↑Ca+↑PTH $n=955$	↑Ca+↑PTH $n=2,130$	↑↑↑Ca+*nl*PTH $n=153$	↑↑Ca+*nl*PTH $n=483$	↑Ca+*nl*PTH $n=2,035$
Age	64.1 (12.47)	64.0 (11.97)	65.1 (11.80)	64.6 (13.96)	64.1 (12.23)	63.0 (12.61)
Female	327 (76.8%)	763 (79.9%)	1,714 (80.5%)	115 (75.2%)	372 (77%)	1,628 (80%)
Race/ethnicity						
White	207 (48.6%)	515 (53.9%)	1,203 (56.5%)	97 (63.4%)	298 (61.7%)	1,295 (63.6%)
Asian	15 (3.5%)	33 (3.5%)	69 (3.2%)	7 (4.6%)	26 (5.4%)	103 (5.1%)
Black	120 (28.2%)	239 (25%)	467 (21.9%)	27 (17.6%)	86 (17.8%)	297 (14.6%)
Hispanic	61 (14.3%)	125 (13.1%)	306 (14.4%)	18 (11.8%)	53 (11%)	223 (11%)
Other	23 (5.4%)	43 (4.5%)	85 (4.0%)	4 (2.6%)	20 (4.1%)	117 (5.7%)
Charlson Comorbidity Index						
0	243 (57%)	572 (59.9%)	1,154 (54.2%)	83 (54.2%)	294 (60.9%)	1,173 (57.6%)
1–2	124 (29.1%)	250 (26.2%)	562 (26.4%)	39 (25.5%)	123 (25.5%)	520 (25.6%)
3+	59 (13.8%)	133 (13.9%)	414 (19.4%)	31 (20.3%)	66 (13.7%)	342 (16.8%)
Serum calcium, median mg/dL (IQR)	11.9 (11.7, 12.3)	11.2 (11.1, 11.4)	10.8 (10.7, 10.9)	11.9 (11.7, 12.3)	11.2 (11.1, 11.3)	10.8 (10.6, 10.9)
PTH, median pg/ml (IQR)	132 (96.0, 187.0)	103 (83.0, 138.0)	95 (78.0, 125.0)	50 (44.0, 57.0)	53 (45.0, 58.0)	51 (45.0, 58.0)
GFR (mL/min)						
≥60	325 (76.3%)	742 (77.7%)	1,548 (72.7%)	124 (81%)	377 (78.1%)	1,568 (77.1%)
45–59	62 (14.6%)	145 (15.2%)	342 (16.1%)	21 (13.7%)	73 (15.1%)	297 (14.6%)
30–44	39 (9.2%)	68 (7.1%)	240 (11.3%)	8 (5.2%)	33 (6.8%)	170 (8.4%)
Diabetes	81 (19%)	151 (15.8%)	415 (19.5%)	39 (25.5%)	90 (18.6%)	362 (17.8%)
Hypertension	264 (62%)	531 (55.6%)	1,263 (59.3%)	88 (57.5%)	282 (58.4%)	1,123 (55.2%)

↑↑↑Ca (>11.5 mg/dL), ↑↑Ca (11.1–11.5 mg/dL), ↑Ca (10.5–11.0 mg/dL), ↑PTH (>65 pg/mL), *nl*PTH (40–65 pg/mL)
IQR, interquartile range.

Table 2
HRs of clinical progression among patients with primary hyperparathyroidism.

Group	No. of events	%	Crude HR (95% CI)	Adjusted HR* (95% CI)
↑↑↑Ca+↑PTH	119	27.9	1.01 (0.84–1.23)	1.03 (0.85–1.25)
↑↑Ca+↑PTH	300	31.4	1.02 (0.89–1.17)	1.07 (0.93–1.23)
↑Ca+↑PTH	703	33.0	Reference	
↑↑↑Ca+*nl*PTH	40	26.1	0.69 (0.50–0.95)	0.68 (0.50–0.94)
↑↑Ca+*nl*PTH	120	24.8	0.64 (0.53–0.78)	0.68 (0.56–0.82)
↑Ca+*nl*PTH	487	23.9	0.61 (0.54–0.68)	0.66 (0.59–0.74)

↑↑↑Ca (>11.5 mg/dL), ↑↑Ca (11.1–11.5 mg/dL), ↑Ca (10.5–11.0 mg/dL), ↑PTH (>65 pg/mL), *nl*PTH (40–65 pg/mL)

* Adjusted for age, sex, race or ethnicity, diabetes, hypertension, and base chronic kidney disease (CKD) stage.

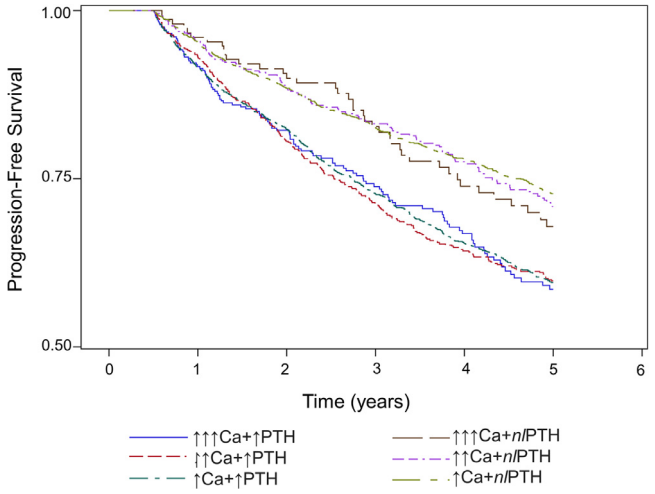

Fig. 2. Kaplan-Meier analysis of probability to progression by patient biochemical profile. [↑↑↑Ca (>11.5 mg/dL), ↑↑Ca (11.1–11.5 mg/dL), ↑Ca (10.5–11.0 mg/dL), ↑PTH (>65 pg/mL), *nl*PTH (40–65 pg/mL)]. *HR*, hazard ratio; *CI*, confidence interval.

After a median follow-up of 3.7 years (interquartile range: 2–5 years), 1,769 of 6,182 (28.6%) patients progressed to the composite endpoint of osteoporosis, nephrolithiasis, decreases in renal function, or hypercalciuria. The most frequent first cause of progression was a decrease in renal function ($n = 866$, 14.0%), followed by osteoporosis ($n = 637$, 10.3%), nephrolithiasis ($n = 163$, 2.6%), and hypercalciuria ($n = 103$, 1.7%). Osteopenia newly developed in 530 of 4,568 patients (11.6%). Multiple manifestations developed in 35 (0.6%) patients with both osteoporosis and nephrolithiasis, 30 (0.5%) patients with osteoporosis and hypercalciuria, 4 patients with hypercalciuria and nephrolithiasis, and 3 had all 3 conditions. A decrease in renal function was accompanied by the development of osteoporosis, nephrolithiasis, and hypercalciuria in 158 (2.5%), 36 (0.6%), and 9 (0.1%) patients, respectively.

In Kaplan-Meier analysis, the probability of progression from baseline to the end of 5 years in groups ↑↑↑Ca+↑PTH, ↑↑Ca+↑PTH, and ↑Ca+↑PTH were 41.5%, 40.4%, and 40.4%, respectively, and in groups ↑↑↑Ca+*nl*PTH, ↑↑Ca+*nl*PTH, and ↑Ca+*nl*PTH the rates were 32.1%, 29.2%, and 27.3%, respectively (Fig. 2). After adjustment for age, sex, race or ethnicity, diabetes, hypertension, and baseline GFR, patients with classic PHPT had a similar risk of progression to end-organ effects regardless of the severity of hypercalcemia (↑↑↑Ca+↑PTH, hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.85–1.25; ↑↑Ca+↑PTH, HR 1.07, 95% CI 0.93–1.23; ↑Ca+↑PTH, reference). In comparison, patients with nonclassic PHPT had a decreased risk of progression that also did not vary with the severity of hypercalcemia (↑↑↑Ca+*nl*PTH, HR 0.68, 95% CI 0.50–0.94; ↑↑Ca+*nl*PTH, HR 0.68, 95% CI 0.56–0.82; ↑Ca+*nl*PTH, HR 0.66, 95% CI 0.59–0.74; ↑Ca+↑PTH, reference; Table 2).

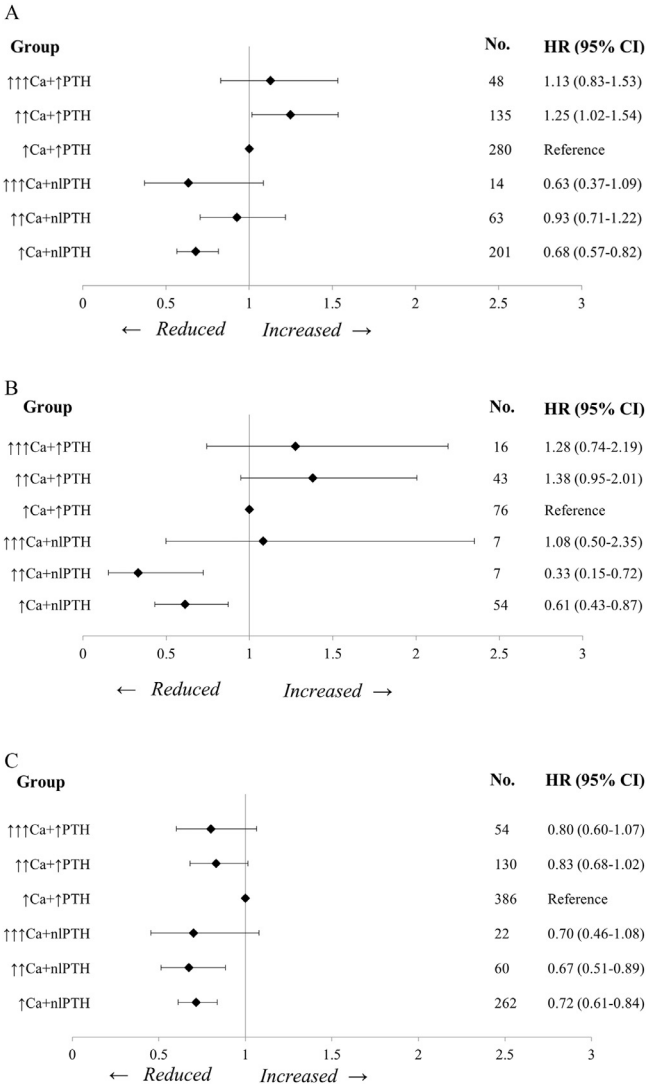

Fig. 3. Hazard ratios for progression to: (A) osteoporosis, (B) nephrolithiasis, (C) decrease in renal function.

Frequencies and risk of progression to osteoporosis, nephrolithiasis, and decreasing renal function as individual outcomes are shown in Table 3 and Fig. 3, respectively. With respect to osteoporosis (Fig. 3, *A*) and nephrolithiasis (Fig. 3, *B*), a trend toward an increased risk of progression in patients with classic versus nonclassic PHPT was observed. With respect to decreasing renal function, the ↑Ca+*nl*PTH group was less likely to progress compared to the reference group (Fig 3, *C*). Age ≥50 years was associated with the development of osteoporosis (HR 2.26, 95% CI 1.59–3.21) and

Table 3
Number of patients developing end-organ damage within 5 years.

	Total $n = 6,182$	↑↑↑Ca+↑PTH $n = 426$	↑↑Ca+↑PTH $n = 955$	↑Ca+↑PTH $n = 2,130$	↑↑↑Ca+*nl*PTH $n = 153$	↑↑Ca+*nl*PTH $n = 483$	↑Ca+*nl*PTH $n = 2,035$	*P* value
Osteoporosis	741 (12.0%)	48 (11.3%)	135 (14.1%)	280 (13.1%)	14 (9.2%)	63 (13.0%)	201 (9.9%)	.004
Nephrolithiasis	203 (3.3%)	16 (3.8%)	43 (4.5%)	76 (3.6%)	7 (4.6%)	7 (1.4%)	54 (2.7%)	.020
Decrease in renal function	914 (14.8%)	54 (12.7%)	130 (13.6%)	386 (18.1%)	22 (14.4%)	60 (12.4%)	262 (12.9%)	<.001
Hypercalciuria	116 (1.9%)	9 (2.1%)	31 (3.2%)	61 (2.9%)	1 (0.7%)	2 (0.4%)	12 (0.6%)	<.001

↑↑↑Ca (>11.5 mg/dL), ↑↑Ca (11.1–11.5 mg/dL), ↑Ca (10.5–11.0 mg/dL), ↑PTH (>65 pg/mL), *nl*PTH (40–65 pg/mL)

a decrease in renal function (HR 2.46, 95% CI 1.64–3.68), but not nephrolithiasis (HR 0.70, 95% CI 0.47–1.03). The risk of progression to hypercalciuria was not estimated because of the low number of events.

Considering both preexisting and developed end-organ effects, 5,876 patients (62%) developed end-organ damage before or within 5 years of diagnosis.

Discussion

Our results show that most patients with PHPT exhibit end-organ damage within 5 years of diagnosis. Disease progression did not correlate with severity of hypercalcemia. Newly incident osteoporosis and impaired renal function occurred at high rates among the different biochemical profiles, regardless of the calcium level. Although patients with nonclassic PHPT displayed a lesser level of end-organ damage compared with those with classic PHPT, we still observed a high rate of osteoporosis, impaired renal function, and nephrolithiasis in the nonclassic group.

We elected to include patients with initial GFR 30–60 in long-term follow-up analyses to assess for further decreases in renal function attributable to PHPT. Based on the 2014 guidelines for the management of asymptomatic hyperparathyroidism, however, these patients already met consensus criteria for intervention at the time of diagnosis.[8] If these patients with a GFR 30–60 were categorized with the cohort of patients with preexisting, end-organ damage, 4,801 patients met consensus criteria for intervention at the time of diagnosis and an additional 1,075 clinically progressed to meet criteria; this yields 5,876 patients (62%) who developed end-organ damage and an indication for surgical intervention within 5 years. When considering both clinical progression and a calcium level 1 mg/dL greater than the normal range, 6,220 patients (66%) presented with or developed an indication for PTX within 5 years.

We investigated the relationship between biochemical profile and clinical manifestations to confirm or dispel the intuitive notion that severity of hypercalcemia dictates the likelihood of end-organ damage. We found no dose-response relationship between mild, moderate, and severe hypercalcemia. PHPT is frequently undertreated both in the community and academic settings, and previous studies have shown that patients with mild or moderate hypercalcemia are less likely to undergo PTX.[1,15] Aforementioned consensus guidelines list calcium 1 mg/dL greater than normal as an indication for intervention, but we did not find a clinical difference between patients with calcium levels greater than or less than 11.5 mg/dL. Extreme hypercalcemia is inherently dangerous with risk of neurologic events, including seizure and coma, and cardiac events, but very few patients experience this level of hypercalcemia.[16,17] In our cohort only 933 of 9,485 patients (10%) had a calcium greater than 11.5 mg/dL. We found the duration of disease to be an important factor because the rate of progression to end-organ effects was cumulative over time. Patients with PHPT and a life expectancy greater than 5 years can be expected to develop end-organ damage more often than not. The median age of presentation in our cohort was 64. Based on actuarial life tables, average life expectancy at age 64 is 19 years for men and 21 years in women in the United States.[18] Therefore, the overall rate of eventual clinical progression in patients with PHPT is very high.

One limitation of this study is the lack of a healthy control group with normal parathyroid physiology. Compared to historic controls, the prevalence of osteoporosis, chronic kidney disease, and nephrolithiasis were increased in our cohort of patients with PHPT. A total of 42% of study subjects had osteoporosis at the time of enrollment or developed it within 5 years of diagnosis. This incidence is greater than the current osteoporosis rates in the United States: 7% for women aged 50–59 years, 12% for ages 60–69, 26% for ages 70–79, and 3% for men aged 50–59, 3% for ages 60–69, and 5% for ages 70–79.[19] At the time of enrollment, 39% of study subjects had a GFR less than 60mL/min or experienced a decrease in renal function within 5 years. This figure is also greater than the current rates of chronic kidney disease in the United States: 8% for those under 60 and 22% for those over 60.[20] Of the study subjects, 15% developed nephrolithiasis, which is greater than the current rate of nephrolithiasis in the United States, which is 9%.[21] Because both bone mineral density and GFR decrease with normal aging, we are unable to parse the independent contribution of PHPT to these conditions without a matched control group. Although the KPSC membership represents approximately 20% of the insured population within the ethnically diverse region of Southern California, this may not be representative of other communities in the United States and worldwide.[2]

Conclusion

Despite these constraints, we demonstrated that the majority of patients with PHPT experience at least 1 manifestation of end-organ damage and often have multiple manifestations. The probability of progression to end-organ damage correlated most closely with the duration of PHPT and not with the severity of hypercalcemia. Patients with nonclassic PHPT (increased serum calcium levels and inappropriately normal PTH levels) exhibited a comparatively lesser risk of developing end-organ effects. The mechanism underlying this difference is unclear. Clinicians armed with this knowledge may be better poised to counsel and manage patients with PHPT.

Conflicts of interest

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

References

1. Yeh MW, Wiseman JE, Ituarte PH, et al. Surgery for primary hyperparathyroidism: are the consensus guidelines being followed. *Ann Surg*. 2012;255:1179–1183.
2. Yeh MW, Ituarte PH, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab*. 2013;98:1122–1129.
3. Press DM, Siperstein AE, Berber E, et al. The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery*. 2013;154:1232–1237 discussion 7–8.
4. Zanocco KA, Yeh MW. Primary hyperparathyroidism: effects on bone health. *Endocrinol Metab Clin North Am*. 2017;46:87–104.

5. Suh JM, Cronan JJ, Monchik JM. Primary hyperparathyroidism: is there an increased prevalence of renal stone disease? *AJR Am J Roentgenol*. 2008;191:908–911.
6. Zanocco KA, Wu JX, Yeh MW. Parathyroidectomy for asymptomatic primary hyperparathyroidism: a revised cost-effectiveness analysis incorporating fracture risk reduction. *Surgery*. 2017;161:16–24.
7. Nair CG, Babu M, Jacob P, Menon R, Mathew J, Unnikrishnan. Renal dysfunction in primary hyperparathyroidism; effect of parathyroidectomy: a retrospective cohort study. *Int J Surg*. 2016;36:383–387.
8. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99:3561–3569.
9. Wermers RA, Khosla S, Atkinson EJ, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. *The American Journal of Medicine*. 1998;104:115–122.
10. Khosla S, Melton LJ, Wermers RA, Crowson CS, O'Fallon W, Riggs B. Primary hyperparathyroidism and the risk of fracture: a population-based study. *J Bone Miner Res*. 1999;14:1700–1707.
11. Wermers RA, Khosla S, Atkinson EJ, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006;21:171–177.
12. Yu N, Donnan PT, Murphy MJ, Leese GP. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clinical Endocrinology*. 2009;71:485–493.
13. Yu N, Donnan PT, Leese GP. A record linkage study of outcomes in patients with mild primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study (PEARS). *Clinical Endocrinology*. 2011;75:169–176.
14. Yu N, Leese GP, Smith D, Donnan PT. The natural history of treated and untreated primary hyperparathyroidism: the parathyroid epidemiology and audit research study. *QJM*. 2011;104:513–521.
15. Kuo EJ, Al-Alusi MA, Du L, et al. Surgery for primary hyperparathyroidism: adherence to consensus guidelines in an academic health system. *Ann Surg*. 2017. doi:10.1097/SLA.0000000000002474.
16. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. *Cardiol J*. 2011;18:233–245.
17. Bayat-Mokhtari F, Palmieri GM, Moinuddin M, Pourmand R. Parathyroid storm. *Arch Intern Med*. 1980;140:1092–1095.
18. Administration SS. Actuarial Life Table. [cited xxxx]. Available from: https://www.ssa.gov/oact/STATS/table4c6.html2014, Accessed date: February 1, 2018.
19. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29:2520–2526.
20. Castro AF, Coresh J. CKD surveillance using laboratory data from the population-based National Health and Nutrition Examination Survey (NHANES). *Am J Kidney Dis*. 2009;53:S46–S55.
21. Re Assimos D. Prevalence of kidney stones in the United States. *J Urol*. 2012;188:2253–2254.

Discussion

Dr Salley E. Carty (Pittsburgh, PA): Very nice presentation. Very provocative data. Can you clarify how many patients in this series had surgery? Is there any way you can answer whether surgery helped ameliorate or prevent worsening of the conditions that you studied?

Dr Yasmine Assadipour: That's a good question. Only 19% of the patients in this study ultimately underwent parathyroidectomy, and we do have other studies that show that these patients had reduced risk of fracture after parathyroidectomy, although we did not specifically evaluate that in this study.

Dr Mahsa Javid (Charleston, SC): That was a great study and presentation. A quick question about the calcium levels. Does it matter if we use total serum or corrected calcium levels? Do we not need the albumin level to do the corrected calcium, presumably if hypercalcemia isn't the main factor here? And would you recommend following these patients that have a single ionized calcium that's raised rather than a total serum calcium?

Dr Yasmine Assadipour: I think in this particular study, the majority of patients were well nourished, so we assumed the albumin level was within the limits of normal and we used an uncorrected total calcium level. We did not look at ionized calcium in this study. It would be hard to make a conclusion about whether 1 ionized calcium value would be significant for the diagnosis.

Dr Bradford Mitchell (Lansing, MI): I have a question for you about the exclusion of patients that were normocalcemic with elevated PTH. Did you exclude those prior to the initiation of your study?

Dr Yasmine Assadipour: Yes.

Dr Bradford Mitchell (Lansing, MI): In light of the fact that you are defining things as preexisting, I presume that means that their osteoporosis existed before the elevation of calcium, which we think is driven by PTH. Since your study showed that the degree of hypercalcemia didn't affect the progression of end-organ disease, why would you not want to include the normocalcemic hyperparathyroidism patients?

Dr Yasmine Assadipour: I think that from these data, what we can conclude is that an abnormal calcium can lead to progression of the end-organ effects of hyperparathyroidism. We did not directly compare patients with normal calcium and elevated calcium, but I think what we can extrapolate from our data is the degree of hypercalcemia is not indicative of whether patients will progress or not. And why we excluded patients with a normal calcium level is to try to avoid any ambiguity of diagnosis, which would have been more likely if patients had normal calcium levels.

Dr Michael Campbell (Sacramento, CA): Very nice presentation. It seems like 1 of the things you could say from your study is that as the calcium gets higher it begins to progress. What else did you look at? Did you look at PTH levels, alkaline phosphatase, or urinary calcium levels that might be predictors of patients that might get into trouble down the line?

Dr Yasmine Assadipour: In this study, we actually did not (other than the fact that we characterize the patients by a parathyroid level between 44 and 65 and patients with levels greater than that). We did not further stratify abnormally high PTH level but did find that when comparing the patients with an inappropriately high-normal PTH and the patients with a highly elevated PTH, there was more progression among those with the higher PTH levels. We did not have alkaline phosphatase or urinary calcium data to make any conclusions about those relationships. That's a great question.