



Degree of hypercalcemia correlates with parathyroidectomy but not with symptoms

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ABSTRACT

Background: Primary hyperparathyroidism (HPT) is an undertreated disease. This study's purpose is to determine if the calcium levels correlate with prevalence of symptoms and surgical treatment in patients with primary HPT.

Method: Patients treated in 2006–2015 with serum calcium ≥ 10.0 mg/dL and PTH > 65 pg/mL were identified and stratified based on calcium level: 10.0–10.3 (normocalcemia), 10.4–11.2 (moderate), and ≥ 11.3 (severe) mg/dL. Clinical variables and rates of surgery were compared between the three groups.

Results: A total of 2266 patients were identified: 303 with normocalcemia, 1513 with moderate hypercalcemia, and 450 with severe hypercalcemia. All three groups had similar rates of nephrolithiasis ($p = 0.10$), osteoporosis ($p = 0.82$), and reduced GFR ($p = 0.06$). Most patients (85%) had at least one surgical indication, but only 29% underwent parathyroidectomy. Higher calcium levels were correlated with higher surgical rates: 12% for Ca 10.0–10.3, 27% for Ca 10.4–11.2, and 46% for Ca ≥ 11.3 ($p < 0.01$).

Conclusion: Prevalence of symptoms does not correlate with calcium levels. Patients with normocalcemia and moderate hypercalcemia were equally likely to have a surgical indication, but normocalcemic patients are less likely to receive surgery.

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Introduction

Primary hyperparathyroidism (HPT) is a common metabolic condition that predominantly affects older women. It is diagnosed by laboratory testing showing an inappropriately high parathyroid hormone (PTH) level for the serum calcium. The incidence of HPT has increased in recent decades due to the inclusion of serum calcium measurements in standard metabolic assay panels. Recent incidence rates have been as high as 66 for women and 25 for men per 100,000 person-years.¹ Surgery is the most definitive and cost-effective treatment modality.^{2,3} It is indicated when patients have symptoms or signs that meet consensus criteria. The latest consensus guidelines are from the 2013 Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.⁴ They are divided into 4 categories: patient age (less than 50 years), calcium level (> 1.0 mg/dL above reference range), skeletal (bone mineral density T-score < -2.5), and renal issues including creatinine clearance < 60 mL/min, nephrolithiasis,

or 24-h urinary calcium > 400 mg/day.

Typical patients will have both elevated calcium and PTH levels. Normocalcemic hyperparathyroidism is a relatively new diagnosis, and it is thought of as an early manifestation of the condition. Although conventional wisdom would predict that patients with this variant are less likely to develop symptoms or complications, several small institutional studies have shown that the prevalence of symptoms can be just as high compared to patients with hypercalcemic hyperparathyroidism.^{5–7} This casts doubt on the assumption that more severe hypercalcemia will cause more numerous and serious symptoms. The purpose of this study is to determine if the degree of hypercalcemia correlates with prevalence of symptoms and rates of surgical treatment in patients with primary HPT. We hypothesize that patients with higher serum calcium levels will have more symptoms of the condition and be more likely to receive surgery.

Methods

Approval was obtained from the NorthShore University Health System Institutional Review Board for this retrospective review. Patients receiving care at Northshore University HealthSystem

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between 2006 and 2015 were identified from the electronic medical record system using the following criteria: at least one serum calcium (Ca) measurement ≥ 10.0 mg/dL and an elevated intact parathyroid hormone (PTH) level (≥ 66 pg/mL) within 6 months of the Ca measurement. Variables obtained for each patient included: age, gender, race, baseline serum creatinine level, baseline Vitamin D 25-OH level, and history of parathyroidectomy or re-exploration for parathyroidectomy. Medical history was taken from each patient's problem list and included the presence of: nephrolithiasis, osteoporosis, osteopenia, depression, gastroesophageal reflux (GERD), fatigue, type II diabetes mellitus (DM), hypertension (HTN), coronary artery disease (CAD), stroke, chronic renal disease (CKD), and end stage renal disease (ESRD). Patients with ESRD were excluded to avoid grouping patients with secondary hyperparathyroidism. Estimated GFR was calculated for each patient using the Modification of Diet in Renal Disease Equation: $GFR = 186 \times (\text{Creatinine}-1.154) \times (\text{age}-0.203) \times (1.212 \text{ if patient is black}) \times (0.742 \text{ if female})$.⁸ The equation for non-black and male patients is: $GFR = 186 \times (\text{Creatinine}-1.154) \times (\text{age}-0.203) \times (1 \text{ if non-black}) \times (1 \text{ if male})$. Patients with estimated GFR < 15 mL/min were also excluded from the analysis.

Patients' eligibility for surgery was determined either by meeting consensus criteria or by the presence of symptoms. Patients were deemed to have a surgical indication if they met at least one of the following 2013 consensus criteria: serum Ca > 1.0 mg/dL above the upper limit of normal (≥ 11.3 mg/dL), GFR < 60 mL/min, osteoporosis, age < 50 years, and nephrolithiasis. Patients were also considered eligible for operation if they had any of the following symptoms listed in their problem list: GERD, fatigue, and depression. Patients who fulfilled multiple criteria or had multiple symptoms were counted only once.

Our institution's reference range for serum calcium is 8.5–10.3 mg/dL and for PTH is 15–65 pg/mL. Patients were stratified into 3 groups based on their highest serum calcium level: 10.0–10.3 mg/dL (normocalcemia), 10.4–11.2 mg/dL, and ≥ 11.3 mg/dL. The cut-off of 11.3 mg/dL was chosen because all patients with serum calcium above this threshold met the 2013 consensus criteria for surgery: > 1.0 mg/dL above the reference range. Continuous variables were analyzed using the analysis of variance test (ANOVA) while categorical variables were compared with the Chi-squared test. Statistical analysis was performed using IBM SPSS Statistics Version 22 (IBM Corporation, Armonk, NY).

Results

A total of 2266 patients met study criteria. Their mean age was 63 (± 14) years. Seventy-five percent of the patients were female. Mean serum calcium was 10.9 mg/dL while mean intact parathyroid hormone (PTH) level was 122 pg/mL for the cohort. Overall, 652 patients (29%) underwent parathyroidectomy.

When stratified by calcium levels, 303 patients had normal calcium levels, 1513 patients had calcium levels 10.4–11.2 mg/dL, and 450 patients had $\text{Ca} \geq 11.3$ mg/dL (Table 1). The three groups were similar with regards to age. Patients with $\text{Ca} \geq 11.3$ mg/dL were less likely to be female (75% vs. 76% vs. 70%, $p = 0.04$) and had significantly higher mean PTH levels (115 vs. 112 vs. 163 pg/mL, $p < 0.01$) than the other 2 calcium groups. The $\text{Ca} \geq 11.3$ mg/dL group also had significantly lower Vitamin D 25-OH levels than the other 2 groups (31 vs. 29 vs. 25 ng/mL, $p < 0.01$). With regards to comorbidities, the three groups had similar prevalence of hypertension ($p = 0.78$), diabetes mellitus ($p = 0.36$), and stroke (0.88). Coronary artery disease was more common in the normocalcemia group than the other two (16% vs. 11% vs. 11%, $p = 0.04$).

Comparison of symptoms and complications of HPT showed there was no direct correlation with the degree of hypercalcemia

(Table 1). The prevalence of renal manifestations (nephrolithiasis and GFR < 60 mL/min) were not significantly different across the three groups (Table 1). Rates of osteoporosis were also similar across all three groups. The moderate hypercalcemia patients were more likely than the other two groups to have osteopenia, fatigue, and depression. The normocalcemic group was most likely to have GERD compared to the other two. All patients with severe hypercalcemia (≥ 11.3 mg/dL) met criteria for surgery because of their elevated calcium levels, but the normocalcemic and moderate hypercalcemia groups had similar proportions of patients who had at least 1 indication for surgery (84% vs. 85%).

Examination rates of surgery for patients at each calcium level demonstrated a direct correlation for parathyroidectomy with serum calcium levels (Fig. 1a). Rates of surgery increased along with rising calcium levels. Surgical rates were consistently less than 20% among the normocalcemic patients, peaked above 20% in patients with serum calcium levels ≥ 10.7 mg/dL, and reached 40% once serum calcium rose above 11.0 mg/dL. In Fig. 1b, no correlation was demonstrated between the serum calcium level and whether patients had at least 1 symptom of hyperparathyroidism. At every calcium level from 10.0 to 12.0 mg/dL, between 75 and 90% of patients had at least one symptom, and the differences were not significant on analysis of variance test ($p = 0.06$).

The patients in each calcium category were then separated into three groups based on their clinical status: had surgery, did not have surgery but had ≥ 1 surgical indication, and did not have surgery and had no surgical indication. In the normocalcemic group ($N = 303$), 37 (12%) patients underwent surgery; 227 (75%) patients did not have surgery but had at least 1 surgical indication; and only 39 (13%) did not have any indication for surgery. Among the 1513 patients with Ca 10.4–11.2 mg/dL, 408 (27%) patients had surgery, 923 (61%) did not have surgery but had a surgical indication, and the remaining 182 (12%) did not have an indication and appropriately did not have surgery. In the $\text{Ca} \geq 11.3$ mg/dL group (all of whom met criteria for surgery by definition), only 207 (46%) of the 450 patients underwent surgery for hyperparathyroidism. Overall, 1393 patients (61%) in the entire cohort did not have surgery even though they had at least 1 symptom or 2013 criteria for surgery.

Discussion

This retrospective study shows that the majority of patients with HPT do not undergo parathyroidectomy. Although HPT patients with higher serum calcium levels were more likely to receive surgery, there is no direct correlation between serum calcium levels and prevalence of disease symptoms and signs. Prevalence of nephrolithiasis, reduced GFR, and osteoporosis are similar between patients with hyperparathyroidism who had normal calcium, mildly elevated calcium, and calcium greater than 1 mg/dL above normal. Osteopenia, fatigue, depression, and GERD were more likely to be present in the normocalcemia or Ca 10.4–11.2 mg/dL patients. In fact, Fig. 1b shows nearly no change in the proportion of patients with symptoms with respect to calcium level. This implies that referral and subsequent treatment of these patients is dependent on having higher calcium levels and not on whether the condition is causing adverse effects. Our results are similar to the findings by Boone et al.'s¹⁵ study of 20,081 patients with hyperparathyroidism. Their study stratified patients into 2 groups based on serum calcium: > 11.0 mg/dL or ≤ 11.0 mg/dL and found nearly identical rates of fatigue, GERD, osteoporosis, nephrolithiasis, reduced GFR, and hypertension between the two groups.

Normocalcemic hyperparathyroidism is often considered an earlier manifestation of this disease process with fewer and less severe symptoms. However, our results are consistent with previous studies that have shown normocalcemic patients are just as

Table 1
Comparison of patient characteristics and symptoms.

Calcium	10.0–10.3	10.4–11.2	≥11.3	p-value
N (%)	303 (13%)	1513 (67%)	450 (20%)	
Mean Age, years (SD)	64 (±14)	63 (±13)	63 (±16)	0.39
Female (%)	228 (75%)	1154 (76%)	317 (70%)	0.04
Mean PTH, pg/mL (SD)	115 (±72)	112 (±58)	163 (±96)	<0.01
Mean Vitamin D 25-OH, ng/mL	31 (±14)	29 (±13)	25 (±14)	<0.01
Nephrolithiasis	46 (16%)	195 (13%)	77 (17%)	0.10
GFR<60	130 (46%)	564 (39%)	163 (38%)	0.06
Osteoporosis	12 (4%)	50 (3%)	17 (4%)	0.82
Osteopenia	99 (34%)	634 (43%)	154 (35%)	<0.01
Fatigue	120 (41%)	667 (46%)	160 (36%)	<0.01
Depression	47 (16%)	242 (17%)	52 (12%)	0.04
GERD	117 (40%)	532 (36%)	129 (29%)	<0.01
Has ≥1 surgical Indication ^a	247 (84%)	1233 (85%)	450 (100%)	<0.01

^a Surgical indication defined as having any of the 2013 consensus criteria or at least one symptom (fatigue, depression, GERD).

likely to have symptoms. In their comparison of 33 patients with normocalcemic HPT and 37 patients with classic HPT, Amaral et al. found nearly identical rates of nephrolithiasis (18.2 vs. 18.6%).⁵ They also found no significant differences in rates of fractures or bone mineral density (BMD) in the lumbar spine or femoral neck. However, the normocalcemic group did have higher BMD in the distal radius than the hypercalcemic patients (0.54 vs. 0.45 g/cm², respectively, p = 0.046). In Lowe et al.'s cohort of 37 patients with normocalcemic HPT, 57% had osteoporosis and 14% had history of kidney stones.⁶ Although Lowe's study did not make a comparison with patients with hypercalcemic HPT, one of the co-authors Bilezikian commented in a subsequent review that their department's observation was that patients with normocalcemic HPT were more likely to have symptoms of the disease.⁷

Only 29% of the patients in this study had surgery for their hyperparathyroidism. This number is likely similar to the number of patients referred to surgery based on our institutional data showing 92% of patients referred to a surgeon for hyperparathyroidism ultimately undergo parathyroidectomy. Over 60% of the entire cohort had at least 1 indication for surgery but did not receive it. Similarly low rates of referral and treatment have been shown in previous studies. In Yeh et al.'s study of 3388 PHPT patients in the Kaiser Health System, only 28% underwent surgery for hyperparathyroidism, and the rates of parathyroidectomy were only 39–51% among patients who had symptoms or met consensus criteria.⁹ In a similar study from the University of Alabama, Balentine et al. showed that only 31% of 10,432 patients with hypercalcemia had PTH levels measured and that only 22% of the 2666 patients diagnosed with PHPT patients were referred to a surgeon.¹⁰ They found

that older age and more comorbidities were negatively associated with surgical referral while higher calcium levels, nephrolithiasis, and osteoporosis were predictors of surgical referral. A smaller study of 102 HPT patients in Worcestshire, England by Shapey et al. documented the highest referral rate in these types of studies: 37%.¹¹

Recognition of PHPT is the most obvious barrier to treatment with patients waiting an average of 2 years for surgery,¹⁴ but several patient related factors have also been shown to affect treatment. Increasing age is one of most common barriers. This has also been demonstrated by Wu et al. among 3388 PHPT patients in the Kaiser Health System in whom the likelihood of surgery decreased linearly with increasing years after the age of 60. While 40% of patients below age 60 received surgery, only 17% of 70–79 year olds and 5% of patients ≥80 years received surgery.¹² This barrier is likely due to several factors, including patient reluctance, perception of high surgical risk and limited benefit, and difficulty in distinguishing the symptoms of hypercalcemia from the normal aging process. However, a study by Kebebew et al.¹³ showed that the surgery can still be safely done in the elderly provided that it is performed at high-volume centers. In their analysis of 54 octogenarians and nonagenarians, Kebebew et al. had no perioperative mortalities and only 5 complications: 1 urinary tract infection, 1 bladder perforation from urinary catheter placement, and 3 cases of transient hypoparathyroidism. Yeh et al. also found renal impairment to predict against surgery in their analysis of 3388 patients in the Kaiser Health System.⁹

This study is limited by its retrospective nature. Patients who had hypercalcemia but no intact PTH measurements were excluded

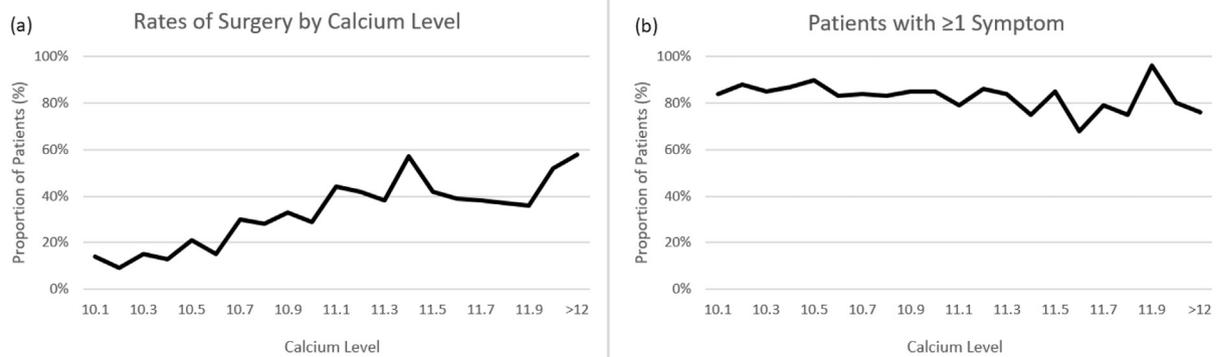


Fig. 1. Patients who had (a) surgery and (b) ≥1 symptom by serum calcium levels.

since the diagnosis of PHPT could not be confirmed. Surgical status was based on chart documentation, and it is possible that some patients who underwent surgery at other institutions were misclassified if this history was not properly charted. It is probable that not all patient symptoms were captured in the medical records system, and an even higher proportion of patients would have had a surgical indication. For example, the presence of osteoporosis and osteopenia was based on the diagnosis being present in the patients' problem lists and not based on bone density measurements because bone density measurements for many patients were performed at outside institutions. Finally, the reasons for non-referral to a surgeon could not be determined due to the retrospective nature.

Conclusion

Primary hyperparathyroidism remains an under treated condition due to its nonspecific symptoms and insidious onset. Although patients with higher calcium levels are more likely to have parathyroidectomy, the majority of patients who have an indication for surgery do not have it. Patients with normal serum calcium levels were just as likely to exhibit symptoms as those with hypercalcemia. Normocalcemic hyperparathyroidism does not seem to represent a milder form of this disease.

Disclosures

None.

Conflicts of interest statement

We have no conflicts of interest or disclosures.

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