Analysis of Primary Hyperparathyroidism Screening Among US Veterans With Kidney Stones

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IMPORTANCE Approximately 3% to 5% of patients with kidney stones have primary hyperparathyroidism (PHPT), a treatable cause of recurrent stones. However, the rate of screening for PHPT in patients with kidney stones remains unknown.

OBJECTIVES To estimate the prevalence of parathyroid hormone (PTH) testing in veterans with kidney stones and hypercalcemia and to identify the demographic, geographic, and clinical characteristics of veterans who were more or less likely to receive PTH testing.

DESIGN, SETTING, AND PARTICIPANTS This cohort study obtained Veterans Health Administration (VHA) health records from the Corporate Data Warehouse for veterans who received care in 1 of the 130 VHA facilities across the United States from January 1, 2008, through December 31, 2013. Historical encounters, medical codes, and laboratory data were assessed. Included patients had diagnostic or procedural codes for kidney or ureteral stones, and excluded patients were those with a previous serum PTH level measurement. Data were collected from January 1, 2006, to December 31, 2014. Data analysis was conducted from June 1, 2019, to January 31, 2020.

EXPOSURES Elevated serum calcium concentration measurement between 6 months before and 6 months after kidney stone diagnosis.

MAIN OUTCOMES AND MEASURES Proportion of patients with a serum PTH level measurement and proportion of patients with biochemical evidence of PHPT who underwent parathyroidectomy.

RESULTS The final cohort comprised 7561 patients with kidney stones and hypercalcemia and a mean (SD) age of 64.3 (12.3) years. Of these patients, 7139 were men (94.4%) and 5673 were white individuals (75.0%). The proportion of patients who completed a serum PTH level measurement was 24.8% (1873 of 7561). Across the 130 VHA facilities included in the study, testing rates ranged from 4% to 57%. The factors associated with PTH testing included the magnitude of calcium concentration elevation (odds ratio [OR], 1.07 per 0.1 mg/dL >10.5 mg/dL; 95% CI, 1.05-1.08) and the number of elevated serum calcium concentration measurements (OR, 1.08 per measurement >10.5 mg/dL; 95% CI, 1.06-1.10) as well as visits to both a nephrologist and a urologist (OR, 6.57; 95% CI, 5.33-8.10) or an endocrinologist (OR, 4.93; 95% CI, 4.11-5.93). Of the 717 patients with biochemical evidence of PHPT, 189 (26.4%) underwent parathyroidectomy within 2 years of a stone diagnosis.

CONCLUSIONS AND RELEVANCE This cohort study found that only 1 in 4 patients with kidney stones and hypercalcemia were tested for PHPT in VHA facilities and that testing rates varied widely across these facilities. These findings suggest that raising clinician awareness to PHPT screening indications may improve evaluation for parathyroidectomy, increase the rates of detection and treatment of PHPT, and decrease recurrent kidney stone disease.

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Kidney stones affect approximately 1 in 11 persons in the United States, and these persons experience a high likelihood of recurrence, with up to 50% developing a recurrent stone within 10 years of their first stone episode.1–4 One strategy to reduce the recurrence rate is to screen for primary hyperparathyroidism (PHPT), which is evident in approximately 3% to 5% of patients with kidney stones.5–6 Patients with kidney stones and PHPT classically present with hypercalcemia and hypercalciuria, which raise the risk for stones by increasing urine supersaturation for calcium oxalate or phosphate. Guidelines from the American Urological Association and European Association of Urology recommend that clinicians measure the serum calcium concentration in patients with kidney stones followed by the serum parathyroid hormone (PTH) level if there is clinical suspicion for PHPT.7,8 For patients with kidney stones and PHPT, the American Association of Endocrine Surgeons recommends parathyroidectomy. Removal of autonomous parathyroid tissue decreases urine calcium excretion and substantially reduces stone events and recurrence rates.9–13

An unanswered question is whether patients with kidney stones receive guideline-concordant screening for PHPT in clinical practice to prevent recurrent stone episodes and decrease comorbidities associated with PHPT. A recent study by Alore et al14 found that fewer than 1 in 4 veterans with persistent hypercalcemia were screened for PHPT. Alore et al15 examined the proportion of asymptomatic veterans with at least 2 separate high serum calcium values who were screened for PHPT. However, the prevalence of PTH testing in patients with symptomatic disease, such as those with kidney stones, remains unknown. Clinicians may be more likely to screen patients with kidney stones for PHPT because they present with symptoms (eg, renal colic) or complications (eg, urinary tract infection or acute kidney injury) that can be severe or recurrent.

In this cohort study, we used data from a large national cohort of veterans receiving care within the Veterans Health Administration (VHA) health care system to estimate the prevalence of PTH testing in veterans with kidney stones and hypercalcemia and to identify the demographic, geographic, and clinical characteristics of veterans who were more or less likely to receive PTH testing. We hypothesized that the frequency of PTH testing remains low despite current clinical practice guidelines and that a wide variation in screening practice is not adequately explained by patient-specific or facility-level factors.

Methods

Data and Study Population

The Stanford University School of Medicine Institutional Review Board and the Veterans Administration Research and Development Committee approved this study and waived the requirement for patient informed consent because the data used were deidentified and presented as summary only. Data were collected from January 1, 2006, to December 31, 2014. Data analysis was conducted from June 1, 2019, to January 31, 2020.

We accessed VHA national data stored in the Corporate Data Warehouse, which is hosted by the Veterans Affairs Informatics and Computing Infrastructure, to identify patients with kidney stones and hypercalcemia who received care in 1 of the 130 VHA facilities across the United States from January 1, 2008, through December 31, 2013.15 We defined patients with kidney stones as those with 1 or more inpatient International Classification of Diseases, Ninth Revision codes for kidney or ureteral stones, 2 or more outpatient International Classification of Diseases, Ninth Revision codes for kidney or ureteral stones, or 1 or more Current Procedural Terminology codes for kidney or ureteral stone procedures within 1 year. Each person was counted once at the time of their first qualification as a patient with kidney stones during the observation period. We excluded persons who were previously screened for PHPT, which was defined as those with a PTH level measurement between 6 and 30 months before the index stone diagnosis, to capture how clinicians screened for PHPT around the time of a stone event (eFigure 1 in the Supplement).

Next, we identified patients with kidney stones who had a serum calcium measurement 6 months before or 6 months after their index stone diagnosis. Measured hypercalcemia was defined as a serum calcium concentration greater than 10.5 mg/dL (to convert to millimoles per liter, multiply by 0.25), and albumin-corrected hypercalcemia was defined as a serum calcium concentration greater than 10.5 mg/dL after correction with the nearest serum albumin concentration measurement within 1 month of the serum calcium concentration measurement (Corrected Calcium [in milligrams per deciliter] = Measured Serum Calcium Measurement [in milligrams per deciliter] + 0.8 × (4.0 - Measured Serum Albumin Concentration (in grams per deciliter; to convert to grams per liter, multiply by 10))).16 A serum calcium concentration of 10.5 mg/dL was chosen as a cutoff for hypercalcemia on the basis of the distribution of serum calcium concentrations in the cohort of patients with kidney stones: serum calcium concentrations greater than 10.5 mg/dL represented the highest fifth percentile of serum calcium concentrations measured and were consistent with levels reported in previously published research.17 In the subset of patients with kidney stones and hypercalcemia, we identified those who had a serum PTH level

Key Points

Question What proportion of patients with kidney stones are screened for primary hyperparathyroidism in clinical practice?

Findings In this cohort study of 7561 veterans with kidney stones and hypercalcemia who received care in Veterans Health Administration facilities, only 25% completed a serum parathyroid hormone level measurement around the time of their initial stone diagnosis.

Meaning Findings of this study suggest that improving the rates of screening for primary hyperparathyroidism in patients with kidney stones could increase the rates of detection and treatment of primary hyperparathyroidism and decrease recurrent stone disease.
measurement in the 6 months before or 9 months after their index stone diagnosis.

Covariates and Study Outcomes

We abstracted patient demographics (age, sex, and race/ethnicity), selected relevant comorbid conditions (osteoporosis, history of fracture, metastatic cancer, and diabetes), laboratory data (serum calcium, PTH, and albumin concentrations; estimated glomerular filtration rate [eGFR]; and 24-hour urine calcium excretion), exposure to specialty care (nephrologist, urologist, and endocrinologist), and geographic region (Midwest, West, Southeast, and Northeast). Patients were stratified by burden of comorbid conditions as measured by the Charlson Comorbidity Index score (range: 0-25, with the lowest score indicating lower burden of comorbidity). We identified the proportion of patients with kidney stones and hypercalcemia in whom PTH level was measured at the time of the stone event (Figure 1). If a patient had more than 1 serum calcium concentration measurement within the observation period, we evaluated the presence of a serum PTH level measurement before and after each serum calcium determination. Biochemically determined PHPT was defined as an elevated serum PTH level (greater than the upper limit of the population reference range of 70 pg/mL [to convert to nanograms per liter, multiply by 1]) in the setting of hypercalcemia (>10.5 mg/dL). We identified the proportion of patients with kidney stones and biochemically determined PHPT as well as the proportion of patients who underwent parathyroidectomy in the 2 years after their index stone diagnosis. To assess whether a patient with kidney stones received specialty stone care, we identified provider codes associated with a clinic visit to a nephrologist, a urologist, or an endocrinologist during the period of ascertainment of PTH testing. To assess whether facility-level factors affected PHPT screening, we used a composite complexity score that included patient and surgical complexity, academic affiliation, and research funding.

Statistical Analysis

To compare groups who underwent screening with those who did not, we used an unpaired, 2-tailed t test to compare continuous variables and the χ² test to compare categorical variables. We performed multivariable logistic regression to identify factors independently associated with receipt of PTH testing. A 2-tailed P < .05 was considered statistically significant. Bonferroni-adjusted α levels were used to compare facility-level variables. All statistical analyses were conducted with SAS, version 9.4 (SAS Institute Inc).

Results

Of the 157,539 unique veterans with kidney stones from January 1, 2008, to December 31, 2013, a total of 139,115 veterans had a serum calcium determination within 6 months of their index stone diagnosis (Figure 1); 7381 patients who were previously screened with a serum PTH level measurement were excluded. After exclusions, the final cohort comprised 7561 patients with kidney stones and measured hypercalcemia (n = 3938) or albumin-corrected hypercalcemia (n = 3623) (eTable 1 in the Supplement). This group had a mean (SD) age of 64.3 (12.3) years, included 7139 men (94.4%) and 422 women (5.6%), and was composed predominantly of white individuals (5673 [75.0%]) (eTable 1 in the Supplement). Patients with hypercalcemia vs those with normocalcemia (n = 124173) were more likely to have diabetes (3013 [39.8%] vs 36 655 [29.5%]), impaired kidney function (eGFR < 45 mL/min/1.73 m²: 2731 [36.1%] vs 18 775 [15.1%]), osteoporosis (331 [4.4%] vs 2626 [2.1%]), and fractures (535 [7.1%] vs 5264 [4.2%]) (eTable 1 in the Supplement).

PTH Testing Rates

Among 7561 patients with kidney stones and hypercalcemia, 1873 (24.8%) completed a serum PTH level measurement around the time of their initial stone diagnosis (Table 1). In the 3938 patients with measured hypercalcemia, 1369 (34.8%) completed a serum PTH level measurement, whereas only 504 of 3623 patients with albumin-corrected hypercalcemia (13.9%) did so. We found that 882 of 2624 patients (33.6%) with a Charlson Comorbidity Index score lower than 3 completed a serum PTH level measurement. Patients with measured hypercalcemia with PTH testing vs those with albumin-corrected hypercalcemia were more likely to have had an elevated PTH level (558 [40.8%] vs 159 [31.5%] above the population reference range; P < .001) and a higher median (interquartile range) level of 24-hour urine calcium excretion (221 [111.0-324.5] mg vs 104.5 [42.5-208.2] mg; P < .001). Among the 1873 veterans with PTH testing, 717 (38.3%) had an elevated PTH level consistent with biochemical PHPT (Table 2).
Patient-Specific Factors Associated With PTH Testing

In multivariable logistic regression models (Table 3), the odds of PTH testing in patients with kidney stones and hypercalcemia was lower with older age (odds ratio [OR], 0.95 per decade; 95% CI, 0.90–1.00) and among patients with a history of metastatic cancer (OR, 0.63; 95% CI, 0.49–0.81). Patients with albumin-corrected hypercalcemia were less likely to complete PTH testing than patients with measured hypercalcemia (OR, 0.32; 95% CI, 0.28–0.37). Conversely, PTH testing was directly associated with the magnitude of calcium concentration elevation (OR, 1.07 per 0.1 mg/dL >10.5 mg/dL; 95% CI, 1.05–1.08) and the number of elevated serum calcium concentration measurements (OR, 1.08 per measurement >10.5 mg/dL; 95% CI, 1.06–1.10). Receipt of PTH testing was not associated with thiazide and thiazide-type prescriptions (OR, 1.05; 95% CI, 0.92–1.20) or a history of osteoporosis (OR, 1.22; 95% CI, 0.93–1.61). Patients located in the Northeast compared with those in the Southeast were more likely to undergo PTH testing (OR, 1.37; 95% CI, 1.17–1.61).

Patients who received care in specialty clinics had different rates of PTH testing (Table 1). The odds of PTH testing were higher for patients who visited either a nephrologist or a urologist (OR, 1.56; 95% CI, 1.35–1.81), and the odds were much higher for those who visited both a nephrologist and a urologist (OR, 6.57; 95% CI, 5.33–8.10) compared with those who visited no stone specialty clinics during the observation period (Table 3). Similarly, patients seen by an endocrinologist were nearly 5-fold more likely to undergo PTH testing (OR, 4.93; 95% CI, 4.11–5.93).

Facility-Level Factors Associated With PTH Testing

The prevalence of PTH testing among veterans with kidney stones varied between 4.0% and 57.0% across the 130 VHA facilities. The prevalence of PTH testing among veterans with kidney stones varied between 4.0% and 57.0% across the 130 VHA facilities. The prevalence of PTH testing among veterans with kidney stones varied between 4.0% and 57.0% across the 130 VHA facilities. The prevalence of PTH testing among veterans with kidney stones varied between 4.0% and 57.0% across the 130 VHA facilities.
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disease. We believe that the present study demonstrated that, even when patients with hypercalcemia had a clinical manifestation of PHPT (ie, presence of kidney stones), screening rates remained surprisingly low. The low prevalence of PTH testing in veterans with kidney stones and hypercalcemia suggests that clinicians are missing an opportunity to prevent recurrent kidney stones by diagnosing and treating PHPT despite guidelines by the American Urological Association and European Association of Urology that recommend PTH testing.7,8

One explanation for the low rate of PTH testing in patients with kidney stones and hypercalcemia is that clinicians do not recognize hypercalcemia unless the level or frequency of hypercalcemia or the manifestation of PHPT becomes severe. In this study, patients with mild hypercalcemia, or hypercalcemia that can be detected only with albumin correction, showed lower rates of PTH testing. Conversely, patients with kidney stones who visited a nephrologist and a urologist or an endocrinologist had higher rates of PTH testing. Specialty care clinics may be more inclined to screen for PHPT in patients with kidney stones and hypercalcemia or may be more aware of the advantages of early detection of symptomatic PHPT.

We found that PTH testing rates varied by 14-fold across the 130 VHA facilities. This wide variation in PTH testing could be partly explained by the presence of kidney stone or endocrine specialty care but not by other facility-level factors (such as composite complexity score) or by access to specialty surgical care (measured by the facility-level volume of parathyroidectomies). These findings suggest that specialists at each facility initiate PTH testing of patients with kidney stones and hypercalcemia. In contrast, general care physicians at different facilities may tend to make decisions on PTH testing on the basis of local experience, culture, or available resources. More awareness about the advantages of PTH testing or wider dissemination of the American Urological Association and European Association of Urology guidelines recommendation for PTH testing may reduce the facility variation observed in the VHA system.

Missing a diagnosis of PHPT in patients with kidney stones is consequential for 2 reasons. First, thiazide and thiazide-type diuretics are commonly used to treat hypercalciuria, but they can increase plasma calcium concentration, particularly in patients with PHPT, and should not be used in this setting. Second, a diagnosis of PHPT is typically associated with parathyroidectomy, the definitive treatment that reduces urinary calcium excretion and risk of stone recurrence. More broadly, parathyroidectomy in PHPT is associated with improved skeletal, cardiovascular, and neuropsychiatric outcomes. These advantages motivated the American Association of Endocrine Surgeons guideline recommendation that patients with kidney stones and biochemical evidence of PHPT be referred for parathyroidectomy. In the present study, the rate of parathyroidectomy in patients with kidney stones and biochemical evidence of PHPT was low at 26.4%, which is only marginally higher than the rate of 23% found in veterans with biochemical evidence of PHPT in the study by Allore et al.14 Findings of the present study suggest that raising awareness of PHPT screening represents a key strategy for secondary prevention of kidney stones and other complications of PHPT.

When we examined whether the category of hypercalcemia (measured vs albumin-corrected) was associated with the likelihood of PTH testing in patients with kidney stones, we found that 34.8% of patients with measured hypercalcemia and 13.9% of patients with albumin-corrected hypercalcemia had a serum PTH level measurement. Patients with kidney stones and albumin-corrected hypercalcemia appeared to be clinically distinct from those with measured hypercalcemia: they had more comorbid illnesses such as diabetes, chronic kidney disease, and metastatic cancer. Testing for PTH level may be lower in patients with kidney stones and albumin-corrected hypercalcemia for several reasons. These reasons include having alternative diagnoses for hypercalcemia (eg, cancer or immobilization) or having poor functional status so that patients prefer not to be screened or clinicians prefer not to screen for PHPT.

Figure 2. Rate of Parathyroid Hormone (PTH) Testing in Patients With Kidney Stones and Hypercalcemia at Each Veterans Health Administration (VHA) Facility

Each bar indicates the SE of the PTH testing percent estimate for each VHA facility, and each diamond indicates the percent estimate for each facility.
Strengths and Limitations
This study has several strengths. First, we identified a sizeable cohort of patients with kidney stones from the largest integrated national health care system in the US, and we had access to both inpatient and outpatient diagnostic claims that interfaced with laboratory results. The cohort was diverse in age, race/ethnicity, geographic location, and presence or absence of comorbid conditions. Second, veterans who receive care in VHA facilities may experience fewer financial restrictions in obtaining laboratory tests and procedures, which allows them to have similar access to medical care across the country. Third, to our knowledge, this study is the first to include patients with an eGFR lower than 45 mL/min/1.73 m² in the estimation of PTH testing prevalence in patients with hypercalcemia. Serum PTH levels may be elevated in patients with an eGFR lower than 45 mL/min/1.73 m² if they have secondary HPT, but serum calcium concentration tends to be normal or low rather than high in secondary HPT. Patients with an eGFR lower than 45 mL/min/1.73 m² and hypercalcemia, such as those in this cohort, should be screened with a PTH level measurement to assess the presence of PHPT, especially given that hypercalcemia may be associated with hypertension and progression of chronic kidney disease.

This study has some limitations. First, the study population comprised mostly male veterans, which may limit the generalizability of these results to women. Women are 3 times more likely than men to develop PHPT, but it is unclear from the results whether the rate of PTH testing might be higher if more women were part of the present study. Second, we defined PHPT as presence of an elevated serum calcium concentration with an elevated serum PTH level measurement. We did not consider alternative criteria for diagnosing PHPT, such as the presence of an inappropriately normal PTH level (ie, non-suppressed) measurement in the setting of hypercalcemia. Third, we could not ascertain whether patients with chronic kidney disease and HPT had primary or secondary HPT with overzealous treatment using oral calcium (often as a phosphate binder) and/or calcitriol or active vitamin D analogs. Fourth, we could not capture medical care for veterans with kidney stones who received care outside of the VHA system. However, we inferred that PTH testing that occurred outside the VHA system might be limited given that Alore et al. reported that the rate of parathyroidectomy in veterans with only VHA coverage was similar to that in veterans with additional Medicare, Medicaid, or private insurance (12.6% had VHA coverage only, and 12.8% had overall coverage).

Conclusions
In this cohort study, a generally low rate of PTH testing was found in veterans with kidney stones and hypercalcemia, and extensive variation in PTH testing rates was found across VHA facilities in the US. More awareness of the level or frequency of elevated serum calcium concentration may be associated with higher rates of PTH testing in patients with kidney stones. Improved screening for PHPT could increase the rates of detection and treatment of PHPT and decrease stone recurrence associated with missed or untreated PHPT.

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