Published in final edited form as:

J Surg Res. 2018 December ; 232: 564–569. doi:10.1016/j.jss.2018.07.028.

Timely Evaluation and Management of Primary Hyperparathyroidism in Patients with Kidney Stones

Alberto A. Perez, BE, David F. Schneider, MD, Kristin L. Long, MD, Susan C. Pitt, MD, and Rebecca S. Sippel, MD

Division of Endocrine Surgery, Department of Surgery, University of Wisconsin School of Medicine and Public Health Madison, Wisconsin

Abstract

Background: Nephrolithiasis is a classic, treatable manifestation of primary hyperparathyroidism (PHPT). We examined predictors of kidney stone formation in PHPT patients and determined how efficiently the diagnosis of PHPT is made in patients whose initial presentation is with stones.

Materials and Methods: We performed a retrospective analysis of surgically treated PHPT patients, comparing 247 patients who were kidney stone-formers and 1,047 patients with no kidney stones. We also analyzed 51 stone-forming patients whose stone evaluation and treatment were completed within our health system prior to PHPT diagnosis.

Results: Stone-forming patients had higher 24-hour urinary calcium (342 vs 304 mg/day, $p=0.005$), higher alkaline phosphatase (92 vs. 85 IU/L, $p=0.012$), and were more likely to be normocalcemic (16.9% vs. 26.6%, $p=0.001$). Surprisingly, 47.3% of stone-formers had normal urinary calcium levels (<300 mg/day). Of the 51 stone-forming patients treated at our institution, serum calcium was measured within 6 months of stone diagnosis in 37 (72.5%) patients. Only 16 (31.4%) of these patients had elevated calcium levels, and only 10 (62.5%) of these 16 had a serum PTH ordered within the following 3 months. These patients had a significantly shorter time from their first stone to surgical treatment compared to other patients (median 8.5 vs. 49.1 months, $p=0.001$).

Address for Correspondence: Rebecca S. Sippel, MD, University of Wisconsin, Department of Surgery, Section of Endocrine Surgery, K3/704 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA, Business, Tel.: 608-263-1387, Fax: 608-252-0912, sippel@surgery.wisc.edu.

Summary of Author Contributions:

Perez- Conception/design, Data collection, Analysis/interpretation, Writing

Schneider- Analysis/interpretation, Critical revision

Long- Analysis/interpretation, Critical revision

Pitt- Analysis/interpretation, Critical revision

Sippel- Conception/design, Analysis/interpretation, Critical revision, Funding

Disclosures:

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusion: Elevated serum and urinary calcium levels are not evaluated in the majority of PHPT patients presenting with kidney stones. In nephrolithiasis patients, provider consideration of PHPT with prompt serum calcium and PTH evaluation significantly reduces time to treatment.

Keywords

Primary Hyperparathyroidism; PHPT; Kidney Stones; Nephrolithiasis; Calcium

Introduction:

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disruption impacting calcium homeostasis, with approximately 20–30 new cases per 100,000 people per year in the United States¹. It is the leading cause of chronic hypercalcemia, with long-term consequences for bone, cardiovascular, and kidney health². Nephrolithiasis is a well-known first manifestation of PHPT. Between 7%–20% of PHPT patients ultimately develop kidney stones³. Nephrolithiasis is also costly to patients both financially and through a negative impact on quality of life^{4,5}.

Detection and timely treatment of PHPT is critical for preventing recurrent stone disease. The only definitive treatment for PHPT is surgery⁶. Current guidelines⁷ published by the American Association of Endocrine Surgeons (AAES) detail the following indications for surgery: symptomatic PHPT, defined by nephrolithiasis, fragility fractures, and osteoporosis; and asymptomatic PHPT patients with serum calcium greater than 1 mg/dL elevated above normal. Additional factors and symptoms are also included in the evaluation and management of PHPT, and may impact surgical decision-making, including: gout, gastroesophageal reflux, constipation, fatigue, and neurocognitive symptoms. Recent studies show that the majority of PHPT patients are not evaluated or referred for surgery per AAES guidelines⁸. These studies reaffirm that surgical intervention is critical for the management of hyperparathyroidism in both symptomatic and asymptomatic patients⁹. Long-term uncontrolled PHPT poses significant risks to the patient, including recurrent stone disease¹⁰, bone loss^{9,11}, complications from cardiovascular disease (hypertension, stroke, congestive heart failure, and diabetes)¹², psychiatric illness (depression, suicidal ideation, and cognitive impairment)¹³, and hypercalcemic crisis¹⁴. While the presence of kidney stones is a clear indication for surgical treatment, it would be ideal if those patients at greatest risk could be effectively identified early in the disease process so that intervention for their PHPT could proceed prior to the development of stone disease and its associated complications.

The first objective of our study was to identify predictors of kidney stone formation in PHPT patients. The second objective was to determine how effectively the diagnosis of PHPT is made in patients first presenting with stones.

Methods:

We performed a single-institution, retrospective analysis of PHPT patients from a prospectively collected database of patients who underwent parathyroid surgery, with approval from the University of Wisconsin Institutional Review Board for a registry in which there is an approved waiver of consent. A total of 3,103 surgically treated PHPT

patients over 18 years of age were evaluated and treated at our hospital between 2001 and 2017. We compared 247 patients who had a history of kidney stone formation (stone-formers) to 1,047 patients who did not form stones (non-stone-formers); 1,809 patients were excluded due to incomplete data (missing serum calcium, serum PTH, or 24-hour urinary calcium). Of the stone-formers group, we identified 51 patients whose first clinical manifestation of PHPT was a calcium-containing kidney stone, and whose stone evaluation and treatment were completed entirely within our health system. Patient records including PTH and calcium lab work and procedures for evaluation and treatment of their kidney stones were extracted from the electronic health record. Data analysis was performed using SPSS Statistics 24 (IBM Inc; Armonk, NY)

The association of demographic and clinical variables was compared between stone-formers and non-stone-formers. Categorical variables were compared using Pearson chi-squared analysis. Continuous variables were compared using independent samples t-test (if skewness was between -2 and 2) or with a non-parametric, independent samples Mann-Whitney U test (if skewness was not between -2 and 2). Next, multivariable analysis using binary logistic regression models was performed on predictor variables with $p < 0.10$ in univariate analysis (cut-off chosen a priori) to determine the association with stone formation.

For our sub-analysis of patients with stone disease, patients were classified into one of five groups based on time from first stone until a serum calcium measurement, whether the calcium level was elevated, and time from serum calcium study until serum PTH measurement. Time from nephrolithiasis diagnosis to serum calcium measurement and time from serum calcium measurement to serum PTH measurement were treated as categorical variables; serum studies performed within 6 months and 3 months, respectively, were considered reasonable for screening for PHPT. Independent samples Mann-Whitney U test was used to compare the time from first stone until PHPT treatment between these five groups.

Results:

Characteristics of PHPT Patients Who Form Kidney Stones:

Demographic and clinical variables independently compared between stone-formers and nonstone-formers groups are shown in Table 1. Patients in the stone-formers group were more likely to be male ($p = 0.002$) than non-stone-formers. Stone-formers also had higher 24-hour urine calcium ($p = 0.011$) and serum alkaline phosphatase levels ($p = 0.012$) compared to non-stone-formers. In addition, stone-formers were less likely to have an elevated serum calcium ($p = 0.001$), and more likely to have “mild” PHPT disease (defined as having a serum calcium 10.2mg/dL or PTH 65ng/mL ; $p = 0.003$), compared to non-stone-formers. An elevated 24-hour urine calcium level was more likely in stone-formers ($p = 0.011$), but only had a sensitivity of 53% and a positive predictive value of 22%.

Multivariable analysis of sex, age, BMI, PTH, 24-hour urine calcium, and alkaline phosphatase are shown in Table 2. Male sex and having a higher 24-hour urine calcium and alkaline phosphatase were independently associated with a greater risk of kidney stone formation.

Evaluation of PHPT Patients Presenting with Kidney Stones:

Of the 51 patients with PHPT who were treated at our institution after an initial presentation with kidney stones, 28 (55%) had their kidney stone worked up by urology, 18 (35%) by their primary care physician, and 5 (10%) by another specialty, such as endocrine, the emergency department, or nephrology (Figure 1). We found that only 21 (41%) of the patients ultimately had their PHPT diagnosed by the provider who evaluated them for their kidney stone. PHPT was most often diagnosed when the evaluation was performed by primary care physicians (61%). Urologists only established a diagnosis of PHPT in 25% of the patients they evaluated.

The timing of evaluation of serum calcium and PTH levels in PHPT patients presenting with kidney stones is shown in Figure 2. The median time from first stone diagnosis to PHPT treatment for each of the end-groups is also shown. A serum calcium was drawn within 6 months of the first stone episode in 37 (72.5%) patients, and 16 (31.4%) of these patients were found to have elevated calcium levels. Median time from stone to PHPT treatment increased as serum calcium decreased. Of the 16 patients with hypercalcemia, only 10 (62.5%) had a serum PTH checked within 3 months following identification of their elevated serum calcium. Patients who were diagnosed with hypercalcemia within 6 months of their initial kidney stone and also had a PTH level checked within the following 3 months had significantly shorter time to surgical treatment of their PHPT than patients did not (median 8.5 months and 49.1 months, respectively; $p = 0.001$). However, if patients were found to be hypercalcemic and the provider did not order a PTH level within the following 3 months, they experienced a 4-year greater delay from the time of first stone presentation to PHPT treatment.

Almost half of the 51 patients (43.1%) required at least 1 intervention for their stone disease ($n = 22$). Eleven patients (21.6%) required 2 or more procedures. These interventions included surgery, lithotripsy, cystoscopy, and ureteral stent placement. The 22 patients who had an intervention directly for their stone had a median time from stone to parathyroidectomy of 23.9 vs 25.8 months for those who did not have a stone intervention. This difference was not statistically significant.

Discussion:

In this study, we found that patients with PHPT who were stone-formers were more likely to be male, have higher urinary calcium excretion (documented by higher 24-hour urine calcium levels), and more extensive mobilizers of mineralized calcium, as evidenced by higher alkaline phosphatase levels. These characteristics, however, were not sensitive or specific enough to be used to screen patients with PHPT for stone formation. In reviewing the diagnostic course of PHPT patients presenting with stones, we found that clinical suspicion of PHPT and timely serum calcium and PTH labs, was a strongly associated with a decreased time to PHPT treatment.

Demographically, male sex was independently associated with stone formation in our study. This finding is consistent with the results of a 2012 study demonstrating that symptomatic male PHPT patients are more likely than women to present with kidney stones, while the

most common symptom of PHPT among female patients is osteoporosis¹⁵. The impact of sex on the clinical presentation of PHPT may be attributed to the observation that background, population-level risk for kidney stones is higher in men than in women¹⁶, and conversely that the risk of osteoporosis in general is higher for women¹⁷.

Biochemical parameters reported in this study demonstrate that stone forming patients are strong calcium mobilizers as well as calcium excretors. This finding is in concordance with the pathophysiology of stone formation in PHPT as described in the primary literature¹⁸. Alkaline phosphatase level was found to be higher in stone-formers than non-stone-formers, indicating a greater rate of bone turnover in stoneforming patients¹⁹ and potentially a more severe phenotype of parathyroid disease. Indeed, stone-forming patients in our study had a higher level of PTH than non-stone-formers, although this difference was not statistically significant. Stone-forming patients also had a significantly higher urinary calcium than nonstone-forming patients without significantly different serum calcium levels, consistent with previous studies^{1,20}. One proposed explanation for this finding is that PHPT patients who develop kidney stones may have accelerated dose-response kinetics of the calcium sensing receptor (CaSR), outweighing the calcium-retaining effect of the PTH receptor in the kidney and creating conditions ideal for stone formation^{1,18}. There may also be a difference in intestinal absorption of calcium in stone-forming compared to non-stone-forming patients; however, we could not evaluate this mechanism in our study. The significance of calcium absorption in kidney stone formation in PHPT patients is supported by one study demonstrating that patients who form stones have higher urinary calcium values after ingestion of a calcium load, than non-stone formers²¹.

While stone-formers in our study had higher mean urinary calcium and serum alkaline phosphatase levels, neither value has proven clinically useful in determining which PHPT patients will form kidney stones using current reference range values. In our study, stone-forming patients were not more likely to have an abnormally elevated alkaline phosphatase (>100 IU/L) than non-stone-forming patients. Similarly, abnormally elevated urinary calcium (>300 mg/day) was present in only half of stoneformers, resulting in a very low positive predictive value for either of these metrics as an indicator for the risk of stone formation. Conversely, non-contrast CT has been recommended as an adjunct screening tool for kidney stones in all PHPT patients¹. However, CT imaging would be costly and result in unnecessary radiation for the majority of PHPT patients who do not form kidney stone.

Delays in PTH testing after elevated serum calcium, and normocalcemia in patients with occult PHPT, were two significant risk factors associated with a prolonged time to treatment after an initial clinical presentation of stone disease in our study. The American Urological Association (AUA) guidelines recommend metabolic evaluation, including serum calcium, for patients diagnosed with kidney stones, as well as PTH evaluation if PHPT is suspected. PHPT should be suspected in any patient with high-normal or high serum calcium levels. The results of our study demonstrate a need for improved awareness of PHPT and better adherence to guidelines for the metabolic work-up of kidney stones. Because many of the patients in our study had mild disease, routine testing with both calcium and PTH is probably the best practice for all patients presenting with calcium containing kidney stones.

Normocalcemic hyperparathyroidism presents a challenge in the diagnostic evaluation of PHPT in patients with kidney stones. There is an estimated 8.9%–21% prevalence of normocalcemia among PHPT patients^{22,23}, and the risks associated with unmanaged PHPT are generally equivalent independent of serum calcium status²⁴. Both hypercalcemic and normocalcemic PHPT patients have a significant likelihood of clinical presentation with kidney stones²⁵. However, the current AUA guidelines do not address indications for PTH testing in normocalcemic patients with stone disease, and this remains a gap in evidence-based practice.

These observations highlight the importance of the consideration of possible underlying, undiagnosed parathyroid disease in patients presenting with kidney stones. PHPT should be included in the differential diagnosis for these patients, especially in cases of frank hypercalcemia. PTH and calcium levels are inexpensive, routine serum chemistries that provide rapid guidance toward or away from further consideration of parathyroid disease. Urology and primary care practices are ideal settings in which to address discussion of PHPT in the evaluation of kidney stones.

Diagnostic and treatment delays lead to a higher risk of recurrent stone disease, cardiovascular complications, and fractures in asymptomatic PHPT patients. Thankfully this risk returns to population level risk after parathyroidectomy^{10,11,12}. The incremental cost saved by parathyroidectomy in an average patient with asymptomatic PHPT has been calculated to be \$1,721, demonstrating a modifiable cost to the health care system through appropriate management of these patients⁹.

Given the retrospective nature of this study, there are some inherent limitations. All of the clinical variables of interest, particularly lab test results, were not available on all patients and that limited the number of patients that could be included in our analysis. Despite this limitation we were still able to identify over 1200 patients with complete laboratory data available. Patient records reviewed for this analysis were all surgically treated for parathyroid disease at our institution and may not be representative of all PHPT patients. A larger multi-institutional study could help confirm these conclusions. This focus on surgical patients also creates a selection bias, as those with symptomatic disease are more likely to be referred for surgical intervention. However, this bias offers further support of our findings that clinical parameters alone are not very effective at identifying patients at risk for stone disease, even in the most severe cases.

Conclusions:

Kidney stones are a common presentation of PHPT. While kidney stone forming PHPT patients generally exhibit a certain biochemical profile, markedly elevated serum chemistries or urinary calcium levels do not identify the majority of patients at risk for stone formation. Surveillance for kidney stone formation is recommended for all PHPT patients who are being managed conservatively. This study reaffirms the importance of provider awareness of undiagnosed PHPT as a possible cause of kidney stones. If a diagnosis of PHPT is considered at the initial presentation of kidney stone disease, it can significantly decrease the time to definitive treatment via parathyroidectomy by more than 3 years, in hopes of

minimizing the risks of longstanding PHPT. Evaluating for PHPT is an essential part of the initial treatment and evaluation of patients diagnosed with calcium containing kidney stones.

Acknowledgments:

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number T35DK062709. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Annalisa Chu assisted in data collection.

References:

1. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ, 3rd. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006 1;21(1):171–7. doi: 10.1359/JBMR.050910. [PubMed: 16355286]
2. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, Haigh PI, Adams AL. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab*. 2013 3;98(3):1122–9. doi: 10.1210/jc.2012-4022. [PubMed: 23418315]
3. Rejnmark L, Vestergaard P, Mosekilde L. Nephrolithiasis and renal calcifications in primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2011 8;96(8):2377–85. doi: 10.1210/jc.2011-0569. [PubMed: 21646371]
4. Hyams ES, Matlaga BR. Economic impact of urinary stones. *Transl Androl Urol*. 2014 Sep;3(3):278–83. doi: 10.3978/j.issn.2223-4683.2014.07.02. [PubMed: 26816777]
5. Brito K, Edirimanne S, Eslick GD. The extent of improvement of health-related quality of life as assessed by the SF36 and PASEICA scales after parathyroidectomy in patients with primary hyperparathyroidism--a systematic review and meta-analysis. *Int J Surg*. 2015 1;13:245–9. doi: 10.1016/j.ijsu.2014.12.004. [PubMed: 25542340]
6. Stephen AE, Mannstadt M, Hodin RA. Indications for Surgical Management of Hyperparathyroidism: A Review. *JAMA Surg*. 2017 6 28. doi: 10.1001/jamasurg.2017.1721.
7. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, Doherty GM, Herrera MF, Pasiaka JL, Perrier ND, Silverberg SJ, Solorzano CC, Sturgeon C, Tublin ME, Udelsman R, Carty SE. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg*. 2016 10 1;151(10):959–968. doi: 10.1001/jamasurg.2016.2310. [PubMed: 27532368]
8. Balentine CJ, Xie R, Kirklin JK, Chen H. Failure to Diagnose Hyperparathyroidism in 10,432 Patients With Hypercalcemia: Opportunities for System-level Intervention to Increase Surgical Referrals and Cure. *Ann Surg*. 2017 7 3. doi: 10.1097/SLA.0000000000002370.
9. Zanoeco KA, Wu JX, Yeh MW. Parathyroidectomy for asymptomatic primary hyperparathyroidism: A revised cost-effectiveness analysis incorporating fracture risk reduction. *Surgery*. 2017 1;161(1):16–24. doi: 10.1016/j.surg.2016.06.062. [PubMed: 27836213]
10. Mollerup CL, Vestergaard P, Frøkjaer VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ*. 2002 10 12;325(7368):807. [PubMed: 12376441]
11. Nilsson IL, Norenstedt S, Zedenius J, Pernow Y, Branstrom R. Primary hyperparathyroidism, hypercalciuria, and bone recovery after parathyroidectomy. *Surgery*. 2017 8;162(2):429–436. doi: 10.1016/j.surg.2017.02.017. [PubMed: 28522130]
12. Vestergaard P, Mollerup CL, Frøkjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg*. 2003 2;27(2):216–22. doi: 10.1007/s00268-002-6541-z. [PubMed: 12616440]
13. Weber T, Eberle J, Messelhäuser U, Schiffmann L, Nies C, Schabram J, Zielke A, Holzer K, Rottler E, Henne-Bruns D, Keller M, von Wietersheim J. Parathyroidectomy, elevated depression scores, and suicidal ideation in patients with primary hyperparathyroidism: results of a prospective

- multicenter study. *JAMA Surg.* 2013 2;148(2):109–15. doi: 10.1001/2013.jamasurg.316. [PubMed: 23560281]
14. Lowell AJ, Bushman NM, Wang X, Ma Y, Pitt SC, Sippel RS, Schneider DF, Randle RW. Assessing the risk of hypercalcemic crisis in patients with primary hyperparathyroidism. *J Surg Res.* 2017 7 12;doi: 10.1016/j.jss.2017.06.041.
 15. Mazeh H, Sippel RS, Chen H. The role of gender in primary hyperparathyroidism: same disease, different presentation. *Ann Surg Oncol.* 2012 9;19(9):2958–62. doi: 10.1245/s10434-012-2378-3. [PubMed: 22535262]
 16. Hughes P The CARI guidelines. Kidney stones epidemiology. *Nephrology (Carlton).* 2007;12(Suppl 1):S26–30. doi: 10.1111/j.1440-1797.2006.00724.x. [PubMed: 17316273]
 17. Jordan KM, Cooper C. Epidemiology of osteoporosis. *Best Pract Res Clin Rheumatol.* 2002;16:795–806. doi: 10.1053/berh.2002.0264. [PubMed: 12473274]
 18. Verdelli C, Corbetta S. MECHANISMS IN ENDOCRINOLOGY: Kidney involvement in patients with primary hyperparathyroidism: an update on clinical and molecular aspects. *Eur J Endocrinol.* 2017 1;176(1):R39–R52. doi: 10.1530/EJE-16-0430. [PubMed: 27601015]
 19. Nakaoka D, Sugimoto T, Kobayashi T (2000) Prediction of bone mass change after parathyroidectomy in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 85:1901–1907. doi: 10.1210/jcem.85.5.6604. [PubMed: 10843172]
 20. Castellano E, Attanasio R, Latina A, Visconti GL, Cassibba S, Borretta G. NEPHROLITHIASIS IN PRIMARY HYPERPARATHYROIDISM: A COMPARISON BETWEEN SILENT AND SYMPTOMATIC PATIENTS. *Endocr Pract.* 2017 2;23(2):157–162. doi: 10.4158/EP161476.OR. [PubMed: 27819765]
 21. Odvina CV, Sakhaee K, Heller HJ, Peterson RD, Poindexter JR, Padalino PK, Pak CY. Biochemical characterization of primary hyperparathyroidism with and without kidney stones. *Urol Res.* 2007 6;35(3):123–8. Epub 2007 May 3. doi: 10.1007/s00240-007-0096-2. [PubMed: 17476495]
 22. Lavryk OA, Siperstein AE. Use of Calcium and Parathyroid Hormone Nomogram to Distinguish Between Atypical Primary Hyperparathyroidism and Normal Patients. *World J Surg.* 2017 1;41(1): 122–128. doi: 10.1007/s00268-016-3716-6. [PubMed: 27734082]
 23. Marques TF, Vasconcelos R, Diniz E, Rêgo D, Griz L, Bandeira F. Normocalcemic primary hyperparathyroidism in clinical practice: an indolent condition or a silent threat? *Arq Bras Endocrinol Metabol.* 2011 6;55(5):314–7. doi: 10.1590/S0004-27302011000500003. [PubMed: 21881813]
 24. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014 10;99(10):3570–9. doi: 10.1210/jc.2014-1414. [PubMed: 25162666]
 25. Pawlowska M, Cusano NE. An overview of normocalcemic primary hyperparathyroidism. *Curr Opin Endocrinol Diabetes Obes.* 2015 12;22(6):413–21. doi: 10.1097/MED.0000000000000198. [PubMed: 26512768]

Providers working up 1st Stone

Only 41% of patients were ultimately diagnosed with PHTP by the provider working up the stone

Figure 1.
Breakdown of physicians evaluating kidney stones.

Figure 2.

Clinical history of Primary Hyperparathyroidism (PHPT) evaluation in patients with initial clinical presentation of kidney stones. t_{surgery} is time from first stone to parathyroid surgery. Ca²⁺ is calcium. PTH is parathyroid hormone.

Table 1.
Comparison of Stone-Formers (SF) to Non-Stone-Formers (NS)

Values reported as mean $\pm$ SD, median [Interquartile range (IQR)], or %, as appropriate. In the case of missing data, we have described the total number of SF and NS patients with complete data as follows: n = SF/NS. Data for alkaline phosphatase value was available for 147 SF and 675 NS patients; data for Vitamin D status was available for 177 SF and 867 NS patients. Elevated lab values defined as: calcium >10.2 mg/dL, PTH >65 ng/mL, 24-hour urine calcium >300 mg, alkaline phosphatase >100 IU/L, creatinine >1.2 mg/mL. Deficiency in 25-hydroxyvitamin D defined as <25 ng/mL. "Mild" PHPT is defined as not having both elevated PTH and serum calcium. PTH is parathyroid hormone. BMI is body mass index.

	SF (n = 241)	NS (n = 1,053)	P value
Sex			0.002
Male (%)	28.6	19.7	
Female (%)	71.4	80.3	
Age (years)	58.5 $\pm$ 12.7	60.3 $\pm$ 12.9	0.054
Height (meters)	1.65 $\pm$ 0.09	1.65 $\pm$ 0.09	0.295
BMI (kg/m²)	31.6 $\pm$ 8.2	30.5 $\pm$ 7.7	0.056
Systolic Blood Pressure (mmHg)	128 $\pm$ 17	129 $\pm$ 17	0.165
Diastolic Blood Pressure (mmHg)	76 $\pm$ 11	75 $\pm$ 11	0.108
Pulse (bpm)	72 $\pm$ 11	73 $\pm$ 12	0.350
Weight (kg)	85 $\pm$ 22	83 $\pm$ 23	0.110
Regular Alcohol Consumption (%)	29.9	30.3	0.898
Smoker (%)	16.6	17.7	0.694
Family History of Parathyroid Disease (%)	7.1	6.5	0.736
Serum Calcium Level (mg/dL)	10.8 $\pm$ 0.9	10.9 $\pm$ 0.8	0.197
Elevated Calcium (%)	73.4	83.1	0.001
PTH Level (pg/mL)	100 [69]	96 [60]	0.068
Elevated PTH (%)	90.5	90.2	0.910
"Mild" PHPT (%)	34.9	26.5	0.003
24-hour Urine Calcium (mg/24hr)	313 [210]	280 [217]	0.011
Elevated 24-hour Urine Calcium (%)	52.7	43.8	0.013
Phosphorus Level (mg/dL)	2.80 [0.85]	2.90 [0.70]	0.136
Alkaline Phosphatase Level (IU/L) n = 147/675	92 [43]	85 [34]	0.012
Elevated Alkaline Phosphatase (%) n = 147/675	36.1	28.8	0.082
25-OH Vitamin D Deficiency (%) n = 177/867	31.6	26.2	0.137
Elevated Creatinine Level (%)	14.2	13.5	0.790

Table 2.
Multivariable comparison of Stone Formers to Non-Stone Formers

Values reported as odds ratio (OR) with 95% confidence intervals (CI). PTH is parathyroid hormone. BMI is body mass index.

	OR (95% CI)	P value
Sex		0.044
Female	reference	
Male	1.565 (1.011–2.420)	
Age (years)	1.005 (0.990–1.020)	0.505
BMI (kg/m²)	1.007 (0.983–1.033)	0.565
PTH (pg/mL)	1.000 (0.998–1.002)	0.812
24-hour Urine Calcium (mg/24hr)	1.001 (1.000–1.002)	0.035
Alkaline Phosphatase (IU/L)	1.006 (1.002–1.010)	0.007