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Urinary Parameters as Predictors of Primary Hyperparathyroidism in Patients With Nephrolithiasis

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Abbreviations and Acronyms

BMI = body mass index

PTH = parathyroid hormone

SSCaOx = supersaturation calcium oxalate

SSCaPhos = supersaturation calcium phosphate

SSUA = supersaturation uric acid

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For another article on a related topic see page 739.

Purpose: Serum calcium and parathyroid hormone levels are the primary means of evaluating patients for hyperparathyroidism. Whether there are differences in urinary parameters between stone formers with and those without hyperparathyroidism is controversial. In this study we identify urinary parameters that predict primary hyperparathyroidism.

Materials and Methods: From 2001 to 2010 a total of 1,190 adult, noncystine stone forming patients underwent urinary metabolic stone evaluation. Of these patients 34 (3%) underwent parathyroidectomy for primary hyperparathyroidism. Urinary parameters were evaluated as predictors of primary hyperparathyroidism. The most accurate combination of serum and urinary tests and their cutoffs were determined.

Results: Stone forming patients with primary hyperparathyroidism were more likely to be women and had higher urinary calcium excretion. Hypercalciuria (aOR 4.38), supersaturation calcium oxalate greater than 10 (aOR 4.27), supersaturation calcium phosphate greater than 2 (aOR 3.64), calcium per kg greater than 4 mg/kg (aOR 8.03) and calcium-to-creatinine ratio greater than 150 mg/gm (aOR 7.07) were significant predictors of primary hyperparathyroidism in separate multivariate models after adjustment. The best accuracy was determined using serum calcium and parathyroid hormone levels with our laboratory cutoffs (AUC 0.984) with a sensitivity of 87%, specificity of 99%, positive predictive value of 79% and negative predictive value of 99.5%. No other factor(s) improved diagnostic accuracy or could replace parathyroid hormone level.

Conclusions: Greater urinary calcium excretion predicted primary hyperparathyroidism. Serum calcium with parathyroid hormone level was the most accurate test for primary hyperparathyroidism. No other serum or urinary parameter improved diagnostic accuracy or could replace parathyroid hormone. There were no obvious cutoffs for any of the urinary parameters that reliably differentiated cases of hyperparathyroidism.

Key Words: hyperparathyroidism, nephrolithiasis, kidney calculi, parathyroidectomy, urinalysis

In large metabolic stone clinics only 2% to 8% of patients have primary hyperparathyroidism.[1] Correctly making the diagnosis of primary hyperparathyroidism is one of the rare opportunities to potentially cure urinary stone disease.[2,3] Thus, despite the infrequency of this diagnosis, a complete metabolic stone evaluation is typically performed in all recurrent stone formers, and typically involves serum calcium and parathyroid hormone levels

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in addition to serum electrolytes, uric acid and a complete 24-hour urinary metabolic evaluation.

Nephrolithiasis in patients with primary hyperparathyroidism is largely attributed to hypercalciuria.[2,4] Increased PTH levels increase serum calcium due to increased intestinal absorption, bone resorption and renal reabsorption of calcium.[5] Despite the increased PTH mediated renal reabsorption of calcium in the distal nephron, the excess serum calcium load overwhelms the ability of the kidney to reclaim calcium, leading to hypercalciuria.

Currently serum calcium and PTH levels are the primary means of evaluating patients for hyperparathyroidism.[4] Whether there are differences in urinary calcium and other urinary parameters between stone formers with and those without primary hyperparathyroidism is currently controversial.[5–11] The identification of other serum or urinary variables that could assist in the diagnosis of primary hyperparathyroidism would be clinically valuable. In this study we evaluated urinary parameters that predict primary hyperparathyroidism and determined the most accurate tests to diagnose primary hyperparathyroidism in patients with nephrolithiasis.

MATERIALS AND METHODS

Adult patients presenting to the metabolic urinary stone clinic at the University of California, San Francisco from 2001 to 2010 were evaluated. We identified 1,190 adult, noncystine stone forming patients with a comprehensive stone risk urine collection analyzed by a commercial laboratory (Litholink Corp., Chicago, Illinois). Overall 34 patients (3%) were ultimately determined to have primary hyperparathyroidism and underwent parathyroidectomy. All patients with primary hyperparathyroidism underwent urinary metabolic stone risk evaluation before parathyroidectomy. The first urine collection under our care was selected to minimize the influence of prior dietary, fluid and/or medication interventions. For 99.2% of patients this represented their first urine evaluation by this commercial laboratory. Some patients underwent 48-hour urine collections and for these all urinary parameters were averaged. Overall 67% of patients had an appropriate collection defined as a 24-hour creatinine per kg of 18 to 24 mg/kg daily for males and 15 to 20 mg/kg daily for females. Analyses were repeated and were essentially unchanged by the exclusion of patients with inappropriate collections.

Demographics, serum laboratory and urinary parameters were evaluated. The demographic factors evaluated included age, gender and BMI. Serum sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, uric acid, calcium and PTH levels were evaluated. Serum PTH and calcium levels were evaluated from the same blood draw and the PTH assay did not change during the study period. Serum phosphorous levels were not routinely collected as part of our metabolic evaluation. Confirmatory testing including sestamibi nuclear scan and neck ultrasound was left entirely at the discretion of our endocrine surgery colleagues. Normal serum PTH was defined as less than 65 ng/dl and normal serum calcium as 8.5 to 10.2 mg/dl.

Absolute differences in urinary parameters and the proportion of patients with urinary metabolic defects, defined as urinary levels outside the normal range, were compared between kidney stone formers with and those without primary hyperparathyroidism. Urinary metabolic defects were defined as low urine volume (less than 1,000 ml daily), hypercalciuria (greater than 250 mg daily for men, greater than 200 mg daily for women), hyperoxaluria (greater than 40 mg daily), hypocitraturia (less than 450 mg daily for men, less than 550 mg daily for women), hyperuricosuria (greater than 800 mg daily for men, greater than 750 mg daily for women), pH greater than 6.2, increased SSCaOx (greater than 10), increased SSCaPhos (greater than 2), increased SSUA (greater than 1), hypernatriuria (greater than 150 mmol daily) and hyperphosphaturia (greater than 1.2 gm daily). To normalize excretion for differences in patient size or body weight, urinary calcium excretion was further evaluated for abnormally increased calcium per kg (normal less than 4 mg/kg daily) and increased calcium-to-creatinine (normal less than 140 mg/gm).

Differences in demographics, anthropomorphic data, and initial urinary parameters and urinary metabolic defects were compared between patients with and those without primary hyperparathyroidism. Chi-square analysis was used to compare binary variables and the Wilcoxon rank sum test was used to compare medians. Student's t tests with unequal variance were used to compare continuous variables. Unadjusted logistic regression was used to determine the association of 24-hour metabolic defects with the diagnosis of primary hyperparathyroidism. Multivariate logistic regression analyses with robust standard errors were used to identify variables that were independently associated with or predicted the odds of ultimately being diagnosed with primary hyperparathyroidism, with a priori adjustment for patient age, gender and BMI. In separate models we evaluated the accuracy of demographic factors, serum laboratory values and urinary parameters in the diagnosis of primary hyperparathyroidism by generating individual ROC curves for each variable. The ROC curve, AUC, sensitivity, specificity, positive and negative predictive values, and percent correct classification of patients were evaluated. Each variable was evaluated as a continuous variable, and then the sensitivity and specificity of the laboratory cutoff were evaluated. Ultimately the most accurate combination of serum and laboratory tests and their cutoffs was determined by performing sequential logistic regression analyses using the likelihood ratio test. Significance was set at $p < 0.05$. Analyses were performed using Stata® v10. This study received institutional review board approval from the University of California, San Francisco (10-03525).

RESULTS

Of the 1,190 patients evaluated 34 (3%) ultimately underwent parathyroidectomy. Although mean age was similar ($p = 0.34$), no patients in the youngest

and oldest categories were diagnosed with primary hyperparathyroidism (table 1). The distribution of gender and BMI was different between the groups, and serum calcium and serum PTH were higher in patients with primary hyperparathyroidism. All patients were normocalcemic after parathyroidectomy and all had pathologically confirmed parathyroid adenoma (89%) or hyperplasia (11%).

Predictors of Primary Hyperparathyroidism

In unadjusted analyses in kidney stone formers with primary hyperparathyroidism average urinary calcium was 58% higher (mean ± SD 331 ± 161 vs 210 ± 157 mg, absolute difference 121, p = 0.001), SSCaOx was 32% higher (8.7 ± 4.7 vs 6.6 ± 3.8, absolute difference 3.1, p = 0.02), SSCaPhos was 54% higher (1.6 ± 1.4 vs 1.1 ± 0.9, absolute difference 0.5, p = 0.03), urinary calcium per kg excretion was 55% higher (4.2 ± 2.2 vs 2.7 ± 1.9 mg/kg, absolute difference 1.5 mg/kg, p = 0.006) and urinary calcium-to-creatinine excretion was 69% higher (235 ± 121 vs 139 ± 84 mg/gm, absolute difference 96, p <0.001). There was no lower level of calcium excretion that excluded patients with primary hyperparathyroidism as there were 4 such patients (12%) with a urinary calcium between 67 and 115 mg daily. Urinary volume, oxalate, citrate, pH, SSUA, sodium and phosphate were no different between stone formers with and those without primary hyperparathyroidism.

Urinary metabolic defects were common in both groups of patients. However, the types and prevalence of specific metabolic defects differed. The most common urinary metabolic defects in general stone formers were hypernatriuria (57%), hypocitraturia (47%) and hyperoxaluria (44%). In patients with primary hyperparathyroidism increased calcium-to-creatinine ratio (79%), increased calcium per kg (78%) and hypercalciuria (71%) were the most common. In unadjusted analyses patients with primary hyperparathyroidism were almost fourfold more likely to have hypercalciuria (p <0.001), more than threefold more likely to have an increased SSCaOx (p = 0.003), more than 2.5-fold more likely to have an increased SSCaPhos (p = 0.02), more than fivefold more likely to have increased calcium per kg (p <0.001) and almost fivefold more likely to have an increased calcium-to-creatinine ratio (p <0.001). Patients with primary hyperparathyroidism were 67% less likely to have hyperuricosuria (p = 0.04). There were no differences in the odds of having any of the other urinary metabolic defects.

Multivariate logistic regression analyses were performed to identify predictors of primary hyperparathyroidism in separate models adjusting for age, gender and BMI. Hypercalciuria was associated with a 4.38-fold increased risk of primary hyperparathyroidism (95% CI 1.81–10.6, p = 0.001) after adjustment. In a separate model increased SSCaOx was associated with a 4.27-fold increased risk of primary hyperparathyroidism (95% CI 2.02–9.04, p <0.001). In addition, increased SSCaPhos was associated with a 3.64-fold increased risk of primary hyperparathyroidism (95% CI 1.57–8.46, p = 0.003). Increased calcium per kg was associated with an 8.03-fold increased risk of primary hyperparathyroidism (95% CI 3.32–19.4, p <0.001) and increased calcium-to-creatinine ratio was associated with a 7.07-fold increased risk of primary hyperparathyroidism (95% CI 2.46–20.3, p <0.001). Low urine volume, hyperoxaluria, hypocitraturia, hyperuricosuria, urinary pH greater than 6.2, increased SSUA, hypernatriuria and hyperphosphaturia were not associated with primary hyperparathyroidism in adjusted analyses.

Table 1. *Patient demographics*

	Primary Hyperparathyroid Stone Formers		General Stone Formers		p Value
No. pt age (%):					
1–20	—		8	(1)	0.007
21–40	5	(15)	260	(22)	
41–60	20	(59)	569	(49)	
61–80	9	(26)	309	(27)	
81+	—		10	(1)	
Mean pt age (SD)	54	(12)	52	(14)	0.34
No. gender (%):					
F	23	(68)	457	(40)	
M	11	(32)	699	(60)	0.002
No. kg/m^2 BMI (%):					
Less than 25	8	(24)	399	(35)	0.02
25–30	14	(42)	350	(30)	
30–35	2	(6)	159	(14)	
35+	5	(15)	107	(9)	
Mean kg/m^2 BMI (SD)	28	(5)	27	(6)	0.46
Mean mg/dl serum calcium (SD)	10.9	(0.8)	9.4	(0.5)	<0.001
Mean ng/dl serum PTH (SD)	120	(66)	51	(32)	<0.001

Testing for Primary Hyperparathyroidism

Of the serum laboratory values evaluated alone serum calcium (AUC 0.964) and serum PTH (AUC 0.914) were the most accurate single tests for diagnosing primary hyperparathyroidism when evaluated as continuous variables (fig. 1, *A*). Using our laboratory cutoffs a serum calcium greater than 10.2 mg/dl had a sensitivity of 93% and a specificity of 95% with more than 95% of patients classified accurately, while a PTH greater than 65 ng/dl had a sensitivity of 90% and a specificity of 77%, with 78% classified correctly. All other serum laboratory measures had an AUC with 95% CI that overlapped with 0.500 and were excluded from further consideration.

Of the urinary parameters evaluated urinary calcium-to-creatinine excretion (AUC 0.750), urinary calcium (AUC 0.712) and urinary calcium per

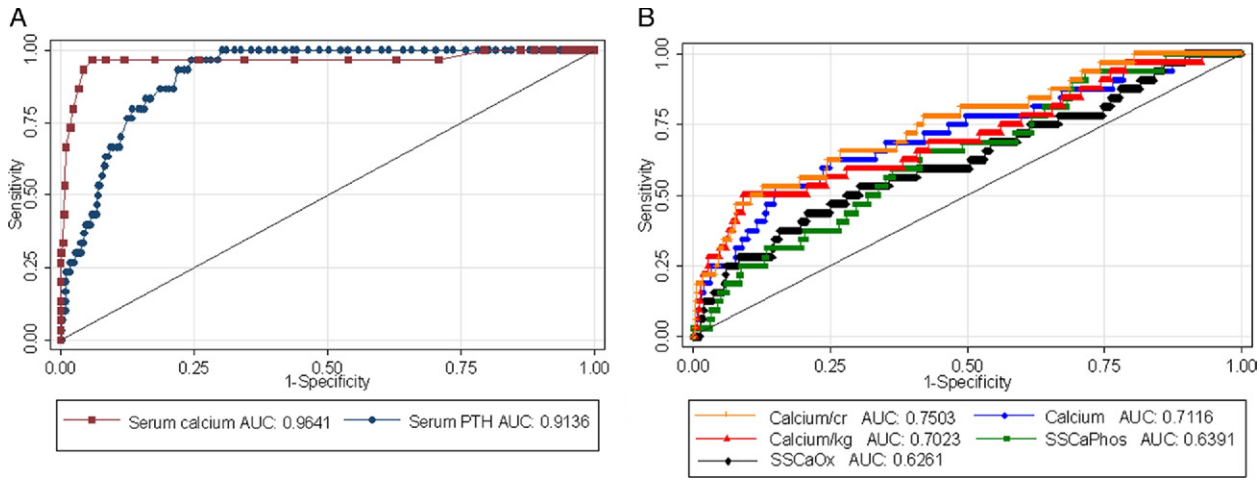

Figure 1. ROC curve for serum (*A*) and urine (*B*) laboratory tests with AUC greater than 0.500. *cr,* creatinine.

kg (AUC 0.702) were the most accurate single tests for diagnosing primary hyperparathyroidism (fig. 1, *B*). In addition, SSCaOx (AUC 0.626) and SSCaPhos (AUC 0.639) provided some diagnostic accuracy and, thus, were considered. All remaining urinary parameters had an AUC with 95% CIs that overlapped with 0.500 and were excluded from further analyses.

Sequential logistic regression analyses were performed to evaluate the diagnostic accuracy gained by the addition of other variables. The best diagnostic accuracy (AUC 0.984) for the diagnosis of primary hyperparathyroidism was with serum calcium and PTH levels (table 2, fig. 2). The addition of serum PTH to the model improved the positive predictive value from 48% to 79% in exchange for only a slight decrease in negative predictive value (99.8% to 99.5%, likelihood ratio p <0.001). No other demographic, serum or urinary variable improved diagnostic accuracy. Additional analyses were performed to evaluate if any variable could replace PTH level, but all of the remaining diagnostic tests in any combination had inferior accuracy.

Table 2. *Diagnostic accuracy of serum calcium alone compared to serum calcium and PTH levels*

	Serum Calcium Greater Than 10.2 mg/dl	Serum Calcium Greater Than 10.2 mg/dl + Serum PTH Greater Than 65 ng/dl
AUC	0.949	0.984
Sensitivity (%)	94	87
Specificity (%)	96	99
Pos predictive value (%)	48	79
Neg predictive value (%)	99.8	99.5
Correctly classified (%)	96	99
p Value (likelihood ratio test)	Ref	<0.001

DISCUSSION

Among patients with kidney stones those with primary hyperparathyroidism were more likely to be female and had excess urinary calcium excretion. This excess calcium excretion was manifested as increased urinary calcium, SSCaOx and SSCaPhos, calcium per kg and calcium-to-creatinine ratio, although there was considerable overlap between the 2 groups. This pattern was similar when urinary metabolic defects were evaluated in univariate and multivariate adjusted analyses.

In this cohort the most accurate single test for diagnosing primary hyperparathyroidism was serum calcium. Used alone, this test was excellent at excluding primary hyperparathyroidism, but on further evaluation almost half of the patients with se-

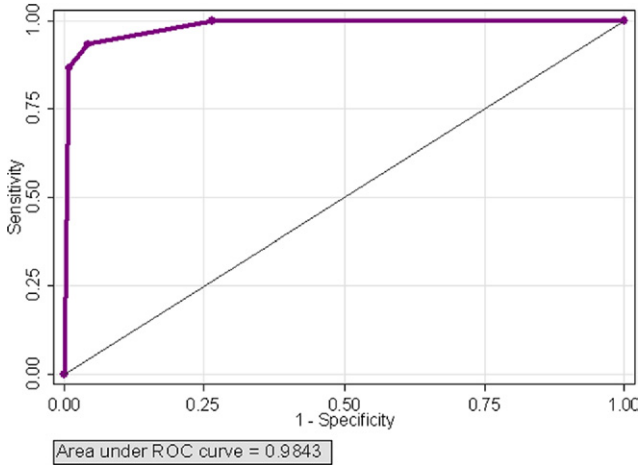

Figure 2. Serum calcium and PTH provided best diagnostic accuracy by ROC curve to diagnose primary hyperparathyroidism using standard laboratory cutoffs for abnormal calcium and PTH levels.

rum calcium greater than 10.2 mg/dl did not have primary hyperparathyroidism. With the addition of PTH level (greater than 65 ng/dl) the diagnostic accuracy improved primarily by improving the specificity and the positive predictive value. Despite the differences in absolute urinary parameters and the prevalence of urinary metabolic defects, none of these factors improved diagnostic accuracy or could successfully replace PTH testing.

Of the 34 patients ultimately diagnosed with primary hyperparathyroidism only 2 had a serum calcium level within the normal range, including 1 patient with a serum calcium of 9.2 mg/dl (PTH 334 ng/dl) and the other with a high-normal serum calcium of 10.2 mg/dl (PTH 177 ng/dl). Similarly 2 other patients with primary hyperparathyroidism had normal PTH levels of 58 ng/dl (calcium 11.4 mg/dl) and 63 ng/dl (calcium 10.6 mg/dl). The results of these 4 patients were suspicious, and were later confirmed with repeat serum testing and parathyroid scanning. Among general stone forming patients without primary hyperparathyroidism an increased calcium level was rare (less than 4%) but an increased PTH level occurred in 23% (508 patients), possibly due to renal leak, vitamin D deficiency or chronic kidney disease. However, of these patients only 33% had hypercalciuria and only 7% had a creatinine greater than 1.5 mg/dl. Vitamin D testing was performed in only 11% of our cohort. Thus, a low threshold to repeat the serum calcium and PTH level is necessary in patients with borderline results or when either of these serum tests is increased, especially among stone formers.

It has been our practice to offer metabolic evaluation to all interested stone forming patients with stronger recommendations for those with at least 1 stone recurrence. One could consider the most cost conscious evaluation to include just a serum calcium level given the negative predictive value. Confirmatory PTH testing could then be pursued only in those patients with an increased or high-normal serum calcium. Serum PTH should always be tested simultaneously with a serum calcium test and ionized calcium could be used in borderline cases to help clarify the diagnosis of hypercalcemia. Due to the costs of a missed diagnosis and the potential impact on future stone formation, we have not adopted this practice. Patients with an increased PTH from other causes such as renal insufficiency or vitamin D insufficiency would also be missed. Unfortunately 24-hour urinary parameters, which would be collected in these patients as a part of the metabolic stone evaluation, do not reliably assist in the diagnosis of primary hyperparathyroidism, and no other serum or urinary factor evaluated can replace PTH testing.

Despite the fact that this is 1 of the largest studies of patients with kidney stones to evaluate predictors of primary hyperparathyroidism, it has limitations. It is a retrospective study performed at a tertiary academic referral center and the results may not be generalizable to other populations. Some patients may have collected the 24-hour urine samples incorrectly. However, analyses were unchanged when patients with inappropriate collections were excluded. Patients in both groups may also have altered their diet after the stone event. It is possible that there were additional patients with undiagnosed primary hyperparathyroidism in this cohort, although our threshold is low to repeat the serum and urinary evaluation and/or to refer these patients to our endocrine surgery colleagues for additional confirmatory testing such as sestamibi nuclear scan, neck ultrasound or serum ionized calcium testing. It has recently been proposed that serum phosphorous might replace PTH testing in the evaluation of primary hyperparathyroidism because serum phosphorous testing is generally less expensive than testing PTH levels. Historically serum phosphorous and the chloride-to-phosphorus ratio (normal ratio less than 33) were used to diagnose primary hyperparathyroidism. However, this was largely abandoned with the newer generation of intact PTH assays and because hypophosphatemia is common in patients with idiopathic hypercalciuria, reducing its diagnostic utility in patients with kidney stones.[12–14] Until recently we have not routinely collected serum phosphorous levels as a part of our metabolic stone evaluation and, thus, we were unable to evaluate its performance.

CONCLUSIONS

Urinary calcium excretion is higher in kidney stone formers with primary hyperparathyroidism, although there is considerable overlap with general stone formers. In this cohort the combination of serum calcium and PTH levels provided the best accuracy for diagnosing primary hyperparathyroidism. No other demographic, serum or urinary laboratory test improved the diagnostic accuracy or could replace PTH level. Urinary metabolic evaluation does not reliably differentiate stone forming patients with from those without primary hyperparathyroidism.

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