24-Hour Urinary Calcium in Primary Hyperparathyroidism

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Objective: To establish whether urinary and serum calcium levels are correlated in patients with primary hyperparathyroidism (PHPT) and to evaluate related factors including serum levels of parathyroid hormone (PTH) and vitamin D, age, gender and renal function.

Design: Retrospective review on patients undergoing a parathyroidectomy for PHPT from 2000–2008. Data collected included: age, sex, preoperative serum calcium (ionized and total), creatinine, PTH, postoperative ionized calcium, vitamin D, and 24-hour urine calcium and creatinine. Data were evaluated by standard descriptive statistics.

Results: Of the 214 patients evaluated, preoperative 24-hour urinary calcium was available for 150 patients (70%). 24-hour urine calcium levels did not correlate significantly with preoperative total serum or ionized calcium, PTH, vitamin D, or postoperative serum ionized calcium. There were significant correlations ($P < 0.0001$) of 24-hour urinary calcium with age, serum creatinine, and urine creatinine. Secondary analysis grouped subjects by urinary calcium level greater or less than 400 mg/24 hours. Age and urinary creatinine were significantly different between the two groups.

Conclusions: In patients with PHPT who underwent parathyroidectomy, there was little correlation between preoperative 24-hour urine calcium and preoperative serum calcium, PTH, or vitamin D levels. 24-hour urine calcium levels were correlated with renal function and age, but these correlations are likely to occur in the general population and are not specific to this disease group.

Keywords: Hypercalciuria; Primary hyperparathyroidism; 24-hour urine calcium

The normal physiology of calcium metabolism is complex and depends on many factors such as renal function, diet, and age. When this normal metabolism is disrupted, it can acutely lead to hypercalcemia, which causes an increase in urinary calcium excretion through mediation of the calcium sensing receptor (CaSR) in the kidney. Hypercalciuria has been used as a diagnostic marker and indicator for parathyroidectomy in patients with primary hyperparathyroidism (PHPT). Urinary calcium excretion as a function of serum calcium was demonstrated more than 50

years ago.¹ However, it is not clear if 24-hour urine calcium levels correlate with preoperative total serum or ionized calcium, parathyroid hormone (PTH), and vitamin D in patients with primary hyperparathyroidism.

The 24-hour urinary sample, in addition to serologic studies, has historically been part of the standard diagnostic evaluation for patients suspected of PHPT. The use of 24-hour urine studies in PHPT has served two primary functions: elevated urinary calcium was thought to be a risk factor for

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Table 1. Descriptive summary of the laboratory values.

	N	Mean	SD
Serum Calcium (Total), mg/dL	149	10.7	0.66
Serum Calcium (Ionized), mg/dL	133	6.0	0.49
Serum BUN, mg/dL	135	17.7	7.8
Serum Creatinine, mg/dL	146	1.02	0.87
Serum PTH, pg/mL	149	138.1	130.8
Urine Calcium, mg/24hr	150	327.0	182.2
Urine Creatinine, mg/24hr	150	1.25	0.48
Total Serum Vitamin D, ng/mL	101	33.3	12.2
Postoperative Calcium (Ionized), mg/dL	150	5.1	0.40

BUN, blood urea nitrogen; PTH, parathyroid hormone

nephrolithiasis, and 24-hour urine calcium studies have been used to distinguish asymptomatic PHPT from familial hypocalciuric hypercalcemia (FHH). However, guidelines published in the *Journal of Clinical Endocrinology and Metabolism* in 2009 no longer recommend hypercalciuria as a criterion for parathyroid surgery.² The omission of urinary calcium in the updated guidelines for PHPT stems from new perspectives on the pathogenesis of nephrolithiasis. In the absence of nephrolithiasis, hypercalciuria alone is not considered to be an indication for surgery for PHPT; however, other surgeons still regard urinary calcium excretion of >400 mg an indication for surgery.^{2,3}

The other role for urinary calcium studies in the workup of hypercalcemia is to rule out FHH, which is caused by a mutation that inactivates the CaSR, a G protein-coupled receptor expressed in the parathyroid gland and renal tubule. Patients with FHH typically present with hypercalcemia, normal to mildly elevated PTH, and hypocalciuria.⁴⁻⁶ If there is a strong suspicion for FHH, the presence of the mutation in the CaSR gene can be detected using readily available polymerase chain reaction techniques. FHH is an asymptomatic, benign disease; thus, it is important to make the distinction from PHPT, since parathyroidectomy is not indicated in this condition.^{7,8}

For most patients presenting in our practice for evaluation of parathyroidectomy in the setting of primary hyperparathyroidism, a 24-hour urinary calcium level is

obtained during the preoperative workup. Given the changing guidelines, with urinary calcium levels no longer a criterion for parathyroidectomy, we questioned the need for 24-hour calcium levels in patients with PHPT and wondered whether the urine calcium levels could be predicted from the elevated serum calcium levels. Therefore, we sought to determine if there was a correlation between 24-hour urinary calcium levels and serum and urinary laboratory markers relevant in this disease process.

Methods

The study was approved by Institutional Review Board of Marshfield Clinic prior to data collection. Marshfield Clinic is a large multi-specialty, multi-site group practice with regional centers located throughout central and northern Wisconsin. Surgeries for primary hyperparathyroidism performed in the years 2000 through 2008 by one surgeon (ACU) were reviewed. Data were extracted from the Marshfield Clinic electronic medical record and included age, sex, preoperative serum calcium (ionized and total), creatinine, PTH, vitamin D, blood urea nitrogen (BUN), 24-hour urine creatinine, 24-hour urine calcium, and postoperative ionized serum calcium.

Prior to analyses, the electronic data were reviewed, and missing and extreme values were manually reviewed for quality assurance purposes. Standard descriptive statistics were used to summarize the demographic characteristics of the study subjects and their laboratory results. Graphical

Table 2. Correlations with 24-hour urinary calcium.

	N	Spearman correlation	P value
Age	150	-0.393	<0.0001
Serum Calcium (Total), mg/dL	149	0.130	0.114
Serum Calcium (Ionized), mg/dL	133	0.168	0.053
Serum Creatinine, mg/dL	146	-0.357	<0.0001
Serum PTH, pg/mL	149	-0.004	0.960
Urine Creatinine, g/24hr	150	0.457	<0.0001
Total Serum Vitamin D, ng/mL	101	-0.202	0.043

PTH, parathyroid hormone

Figure 1. Age at surgery versus preoperative urine calcium. Older patients had lower urine calcium compared to the younger population.

review showed skewed distributions for laboratory results (particularly serum creatinine, PTH, and BUN), and the primary analyses were based on nonparametric (rank-based) procedures. The Spearman rank correlation was used to evaluate associations among the measures, and the Wilcoxon signed-rank test was used to compare results by level of urinary calcium (less than 400 mg/24 hours or not). Analyses were conducted using SAS version 9.2 statistical software. Results were deemed statistically significant at the 5% level ($P < 0.05$) without adjustments for multiple comparisons.

Results

A total of 214 patients were evaluated, and 24-hour urinary calcium levels were available in 150 patients. Patients with and without urine calcium were found to be similar with respect to demographics and other laboratory results, and the analyses presented here will be limited to those with urine calcium. These patients included 115 females (77%) and 35 males (23%), with ages ranging from 25 to 85 years (median 63 years). The mean preoperative total calcium level was 10.7 mg/dL, and the mean preoperative ionized calcium level was 6.0 mg/dL. The mean postoperative ionized calcium level was 5.1 mg/dL. The mean preoperative 24-hour urinary

calcium level was 327 mg/24 hours, with the upper quartile being 452 mg/24 hours (table 1).

Relatively low correlations were observed for 24-hour urinary calcium levels with preoperative total calcium ($P = 0.11$), ionized calcium ($P = 0.05$), PTH ($P = 0.96$), and vitamin D ($P = 0.04$) (table 2). These correlations were expected, based on known trends with hypercalcemia and related effects. There were highly significant correlations ($P < 0.0001$) of 24-hour urinary calcium with age (figure 1), urine creatinine (figure 2), and serum creatinine levels (figure 3). The correlations were similar in females and males analyzed separately (data not shown).

In a secondary analysis, subjects were divided into two groups based on whether or not urinary calcium was less than 400 mg/24 hours (table 3). In the group with urinary calcium ≥ 400 mg/24 hours, the mean age was about 8 years younger than the other group, with a higher percentage male (34.7% vs. 17.8%). Additionally, the urinary creatinine was found to be significantly different between the two groups: the group with urinary calcium ≥ 400 mg/24 hours had a mean urine creatinine of 1.5 g/24 hours, as compared to the other group

Figure 2. Preoperative urine creatinine versus preoperative urine calcium. Characterizes the significant positive correlation between preoperative urine calcium and preoperative urine creatinine.

with a mean urine creatinine of 1.1 g/24 hours. There was no significant difference between the two groups when evaluated for serum calcium, creatinine, BUN, PTH, vitamin D, or postoperative calcium levels. In models with covariates to adjust for age and gender differences, urine creatinine remained as the only laboratory result showing a statistically significant group difference (data not shown).

Discussion

Patients with normal renal function typically excrete approximately 100 mg to 300 mg of urinary calcium per day. Hypercalciuria, defined by the National Institutes of Health guidelines in 1990 and 2002 as 400 mg calcium/24 hours in urine collected at home on a free diet, has been used as both a diagnostic marker and an indication for parathyroidectomy in patients with PHPT.⁸⁻¹⁰ This recommendation stemmed from the assumption that hypercalciuria posed a significant risk for the development of nephrolithiasis. However, a study by Berger and colleagues¹¹ demonstrated that there was no significant correlation between the 24-hour urinary calcium and the serum calcium, in comparing a cohort of PHPT patients who presented with nephrolithiasis to those who did not. Patients with PHPT and stones usually have moderate to

severe hypercalciuria but only mild to moderate increase in serum calcium. Pre- and postoperative 24-hour urine collection between non-stone formers did not show any differences with any variables.^{11,12} In addition, there are mixed results from studies that have tried to demonstrate that hypercalciuria itself promotes nephrolithiasis.¹³ Given this information, the guidelines for the management of asymptomatic PHPT have recently changed. A 24-hour urine calcium is still recommended in the initial evaluation of suspected patients with PHPT, in order to differentiate it from FHH, but is no longer recommended as a criterion for parathyroidectomy.

The urinary studies (24-hour total urine calcium, calcium/creatinine clearance ratio, and fasting urinary calcium excretion [spot urine]) were also historically used to make the distinction between FHH and PHPT. A value of <100 mg/day for total urinary calcium was considered diagnostic for FHH; however, this value was set arbitrarily, and many patients undergoing parathyroidectomy with a confirmed adenoma on exploration have urine calcium excretion values similar to or below this cutoff. Also, the 24-hour urinary calcium study has the potential for inaccuracy due to age, renal function, varied

Figure 3. Preoperative serum creatinine versus preoperative urine calcium. Shows the significant negative correlation between preoperative serum creatinine and preoperative urine calcium.

dietary calcium intake, medications that affect the amount of calcium excreted, and the reliance on patient compliance.³ Because of the difficulty with urine studies in general, some have advocated that rather than 24-hour urinary studies, estimated glomerular filtration rate (eGFR) should be used to determine the level of kidney function in PHPT. An eGFR of less than 60 mL/min should be used as a marker, because at this level of function PTH begins to rise in patients with chronic kidney disease.¹⁴ Also, the National Kidney Foundation no longer recommends the use of 24-hour urinary collections for estimation of renal function, but rather recommends the Modification of Diet in Renal Disease (MDRD) study calculation #7, which is a modification of the Cockcroft-Gault equation that includes race, albumin, and urea nitrogen for a more accurate estimate of GFR.¹⁴ Similarly, the calcium/creatinine (Ca/Cr) clearance ratio, also calculated from 24-hour urine collections, has been found to be relatively non-specific.¹⁵ A ratio less than 0.01 was considered diagnostic for FHH, while a ratio greater than 0.02 was thought to be typical for PHPT.^{6,16} However, in follow-up studies, approximately one-third of patients with confirmed PHPT had a clearance ratio in the range of 0.01-0.02.^{4,5,14,17,18} The Ca/Cr clearance ratio is also used as a marker of hypercalciuria,

where hypercalciuria cannot be excluded if the urinary creatinine concentration exceeds 40 mg/100 mL.^{19,20} In the evaluation of PHPT, it is recommended that FHH be ruled out, even though this condition is very rare. Currently, if there is a strong suspicion for FHH, the presence of the CaSR gene mutation can be detected using readily available polymerase chain reaction techniques. This genetic sequencing provides diagnostic security when the plot of spot urinary calcium excretion to PTH is indicative of FHH. However, this should be reserved for cases in which treatment would be significantly altered based on the diagnosis.^{5,7,14,15,19} Hypercalcemia increases eGFR; however, tubular resorption of calcium is altered by many other factors such as age, medications, and hormones. While the volume of urine collected can affect the urinary creatinine and calcium levels and could be affected by diuretic use, we did not specifically analyze these factors. It could be a contributing factor to explain the correlation between older patients and lower urine calcium levels, particularly if there was a higher use of diuretics in this group. Our mean preoperative 24-hour urinary calcium levels were relatively higher than mean serum calcium levels of 10.2 mg/dL, but, there was little correlation between preoperative 24-hour urine calcium and preoperative serum calcium, PTH,

Table 3. Comparisons of two groups based on level of urine calcium.

	Urine Calcium <400 mg/24hr			Urine Calcium ≥400 mg/24hr			P value
	N	Mean	SD	N	Mean	SD	
Age	101	65.1	11.4	49	57.6	10.3	<0.001
Serum Calcium (Total), mg/dL	101	10.7	0.68	48	10.7	0.63	0.919
Serum Calcium (Ionized), mg/dL	89	5.9	0.48	44	6.1	0.50	0.105
Serum Creatinine, mg/dL	99	1.1	1.04	47	0.9	0.19	0.008
Serum PTH, pg/mL	100	141.1	150.4	49	131.9	77.6	0.819
Urine Creatinine, g/24hr	101	1.1	0.42	49	1.5	0.50	<0.001
Total Serum Vitamin D, ng/mL	70	34.4	13.5	31	30.9	8.6	0.124

PTH, parathyroid hormone

or vitamin D levels. Urinary calcium levels were, however, strongly correlated with age, and also serum and urine creatinine, as demonstrated in figures 1 through 3. Figure 1 shows that older patients had lower urine calcium compared to the younger population; figure 2 characterizes the significant positive correlation between urine calcium and urine creatinine; and figure 3 shows that there is a negative correlation between serum creatinine and urine calcium. The 24-hour urine calcium correlates with serum creatinine and urine creatinine because complexed (calcium bound to phosphate, citrate, carbonate, and other anions) and ionized calcium is freely filterable in the glomerulus as urinary ultrafiltrate, and 98% is reabsorbed along the renal tubule. Increased urinary creatinine (reflected by increased creatinine clearance and GFR) likely explain the increase in calcium excretion. This has been previously demonstrated in pregnant women.²¹ Also, renal insufficiency, reflected by decreased creatinine clearance, decreases renal calcium filtration. We know that age is negatively correlated with GFR, which results in decreased urinary calcium levels, as noted in our study. All of these relationships would be expected in the general population, and are therefore not specific to patients with PHPT. These findings also support the new guidelines for the evaluation of PHPT, where hypercalciuria is no longer regarded as an indication for surgery.²

Conclusion

In patients with PHPT, urinary calcium levels are related to renal function and age, but show no correlation with serum calcium, PTH, or vitamin D levels. These relationships are demonstrated in the general population and are not specific to this disease process.

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