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Unilateral Hypercalciuria: A Stealth Culprit in Recurrent Ipsilateral Urolithiasis in Children

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Abstract

Purpose—Hypercalciuria is a risk factor for nephrolithiasis. We hypothesized that children with recurrent stones in 1 but not both kidneys and a normal 24-hour bladder urine calcium-to-creatinine ratio might exhibit isolated hypercalciuria of the affected kidney.

Materials and Methods—Patients 18 years or younger with symptomatic urolithiasis who had undergone ureteroscopic stone removal were included. All subjects underwent 24-hour bladder urinalysis. Subjects with an increased urine calcium-to-creatinine ratio from the 24-hour urine collection were excluded. The 4 subject cohorts defined were 1) single stone episode in 1 kidney, 2) single stone episode in both kidneys, 3) recurrent stone episodes on 1 side and 4) recurrent stone episodes on both sides. All urine collections were obtained at ureteroscopy. Urine was obtained from the bladder and from the renal pelvis of the kidney forming the stone. Spot urine calcium-to-creatinine ratio was determined from these samples.

Results—A total of 329 patients were included. Nine of 74 subjects (12%) with recurrent stone episodes on 1 side had increased spot urine calcium-to-creatinine ratio from the affected kidney. No patients in the other cohorts had increased spot urine calcium-to-creatinine ratio. Patients who formed recurrent stones in 1 kidney had increased spot urine calcium-to-creatinine ratio in the affected kidney vs other stone formers (ANOVA $p < 0.001$).

Conclusions—Unilateral hypercalciuria can occur in children with normal calcium levels in bladder urine. Unilateral hypercalciuria should be considered as a risk factor for nephrolithiasis in children with recurrent stone episodes in 1 kidney only.

Keywords

hypercalciuria; nephrolithiasis; pediatrics

The risk factors for nephrolithiasis are multifactorial and include metabolic, anatomical and as yet undefined causes.¹ In children hypercalciuria has been shown to be a risk factor for nephrolithiasis.² Hypercalciuria is defined by a urinary calcium excretion of greater than 4 mg/kg during 24 hours while ingesting a routine diet.^{3,4} Due to the difficulty in obtaining 24-hour urine collections in children, a spot sample, from which the ratio of urinary calcium to urinary creatinine is calculated, has been used to diagnose hypercalciuria.^{5,6} Hypercalciuria promotes nephrolithiasis by increasing the likelihood of calcium supersaturation in the urine, which can progress to form calcium based kidney stones or

noncalcium based stones (eg uric acid) through heterogeneous nucleation. Presumably hypercalciuria reflects a metabolic derangement that affects both kidneys.

We have noted in clinical practice that some patients have recurrent episodes of symptomatic nephrolithiasis in 1 kidney but not in the contralateral kidney. Other investigators have noted similar findings in patients with severe hypocitraturia and cystinuria, both of which are presumed to be global metabolic defects that increase the risk of nephrolithiasis.^{7,8} Proposed hypotheses to account for unilateral stone disease include sleep position associated renal perfusion and unilateral renal vascular injury.^{9,10} We hypothesize that, similar to anatomical anomalies such as UPJO and renal cysts, metabolic derangements could occur in 1 but not both kidneys. Such unilateral metabolic abnormalities could predispose children to recurrent stones in the affected kidney. This study was designed to determine the urine calcium levels excreted by kidneys that form kidney stones in children with normal UCa levels in the bladder urine. We further sought to determine if children who form recurrent stones in 1 kidney manifest unilateral hypercalciuria of the affected kidney.

MATERIALS AND METHODS

Data Source and Outcomes

CHOP maintains a database of all children 1 day to 18 years old with nephrolithiasis (ICD-9 592). Age, gender, race, ethnicity, serum calcium, spot UCa and UCr, and 24-hour urinary parameters were prospectively collected, as well as stone laterality, size and composition. A retrospective review of this database was performed, and all children who underwent ureteroscopy between July 2004 and September 2011 were included. Children with previously diagnosed anatomical abnormalities (eg neuropathic bladder, ureteropelvic junction obstruction, posterior urethral valves), hypercalciuria on 24-hour urine collection (defined as more than 4 mg/kg/24 hours) or comorbid conditions known to contribute to stone formation (eg cystinuria) were excluded. A total of 329 patients met inclusion criteria (see figure).

The initial 24-hour bladder urinalysis obtained at presentation to the urology clinic was used to exclude patients with hypercalciuria. Other parameters evaluated on the 24-hour urinalysis were urine volume, citrate and oxalate. The primary outcome of this study was an increased spot UCa/UCr ratio of the kidney with nephrolithiasis. Normal UCa/UCr values were adjusted for age as defined by Sargent et al.⁵ Hypercalciuria for patients older than 5 years was defined as UCa/UCr ratio greater than 0.21 mg/mg.

Study Design

All surgeries and specimen collections were performed by a single surgeon (PC). All children who underwent surgery had orders for nothing by mouth for solids for at least 8 hours and for clear liquids 2 hours preoperatively. All spot urine samples were obtained at ureteroscopy or at placement of a ureteral stent if ureteroscopy could not be safely performed without pre-stenting.

A 4Fr or 5Fr open-ended catheter was placed cystoscopically under fluoroscopic guidance into the renal pelvis of the kidney affected by nephrolithiasis before instillation of iodinated contrast medium. A minimum of 1.5 ml urine was collected by gravity drainage and sent for analysis. Spot samples of urine collected from the bladder, which represented pooled urine from both kidneys, and urine samples from the renal pelvis of the affected kidney(s) were obtained and analyzed by the CHOP chemistry laboratory. Spot UCa and UCr levels (mg/ml) obtained in patients with bilateral nephrolithiasis were collected and analyzed individually. Based on these values, spot urinary calcium-to-creatinine ratios were obtained.

The 4 subject cohorts defined were 1) single stone episode in 1 kidney, 2) single stone episode in both kidneys, 3) recurrent stone episodes on 1 side and 4) recurrent stone episodes on both sides. All patients were unique to their respective cohort. Urine samples were collected at presentation with a recurrent stone for cohort 3, which is the point at which the hypothesis was developed. All urine samples for the other cohorts were collected at initial presentation.

All patients were followed for at least 1 year. As per our protocol for stone management, all children were followed with renal bladder ultrasound 1 month after intervention and again at 6 months. If patients had hypercalciuria, they were routinely referred to nephrology for medical stone treatment.

Statistical analysis was performed with SPSS®, version 18. Variances in mean values were analyzed using ANOVA. Proportions were analyzed using the Pearson chi-square test. Variables were checked for normal distribution before statistical analysis. All tests were 2-sided and results were considered statistically significant if $p < 0.05$. This study was approved by the CHOP institutional review board.

RESULTS

Search of the stone database at CHOP yielded 1,120 patients who were diagnosed with nephrolithiasis between 2004 and 2011. Of these patients 329 met inclusion criteria (see figure). Of the patients 200 had a single stone episode in 1 kidney, 36 had single stone episodes in both kidneys, 74 had recurrent stone episodes on 1 side and 19 had recurrent stone episodes on both sides. Mean patient age was 8 years (range 7 months to 18 years). There were no statistically significant differences in age between cohorts ($p = 0.23$). The standard deviation of the ages was similar between cohorts. Girls were affected by stone disease in this study more than boys. Mean followup after last ureteroscopy was 2.8 years. Length of followup was similar between cohorts ($p = 0.76$).

The only patients with increased spot UCa/UCr levels were those with recurrent unilateral stones (table 1). Nine of 74 patients (12.2%) with recurrent stone episodes in a single kidney had a significantly increased spot UCa/UCr ratio in the affected kidney, which was a significantly higher proportion compared to the other cohorts ($p = 0.02$). The spot bladder UCa/UCr ratio taken at the initial stone intervention and the 24-hour bladder UCa/UCr ratio were normal in these patients. This group also tended to form stones containing CaPhos.

Hypocitraturia and low urinary volumes were found in all cohorts. Urinary volume and urine citrate were similar between all cohorts ($p = 0.97$ and $p = 0.75$, respectively). The standard deviation of the mean spot UCa/UCr ratio was also similar between the cohorts. Of the 9 patients with ipsilateral hypercalciuria only 1 was younger than 5 years (table 2). This patient was 4.9 years old, and a reference UCa/UCr value of 0.21 was used as the upper end of normal. The 9 patients with recurrent unilateral stones with ipsilateral hypercalciuria were started on hydrochlorothiazide and potassium citrate. All of these patients remain stone-free after more than 1 year.

DISCUSSION

This is the first known study to identify a metabolic abnormality that could explain recurrent unilateral nephrolithiasis in a subgroup of children with normal 24-hour urine calcium and serum calcium. The etiology of hypercalciuria is multifactorial. Increased renal calcium excretion, intestinal calcium resorption and increased bone resorption can all lead to hypercalciuria.¹¹⁻¹⁴ All of these well described pathophysiological processes should produce increased concentrations of calcium in the urine excreted by both kidneys.

Therefore, hypercalciuria has been thought to be a global metabolic defect. However, in this study of first time and recurrent stone formers we observed that some patients who form recurrent stones in only 1 kidney have increased UCa/UCr ratio in the affected kidney. This finding suggests that differential calcium excretion between kidneys can occur and that a potentially clinically significant risk factor for recurrent nephrolithiasis may be missed on evaluation of bladder urine alone.

Multiple studies have demonstrated that urinary calcium excretion in children is associated with age. Except in neonates, there is an inverse relationship between age and UCa/UCr ratio. At approximately age 5 years UCa/UCr ratio approaches 0.21, which is the upper limit of normal for adults.^{5,15,16} Presumably the differential excretion of urinary calcium is a function of the concentrating ability of the kidney. Mean age for all cohorts was greater than 5 years, so it is unlikely that age would have introduced variability into the urinary calcium levels. Furthermore, all subjects served as their own internal controls given that 1 inclusion criterion was that they had a normal 24-hour bladder urine calcium.

Unilateral renal hypercalciuria in the setting of a normal bladder urine calcium level and recurrent ipsilateral nephrolithiasis has therapeutic implications. Before our observations these children were followed for stone recurrence but could not be offered any specific recommendations for decreasing stone recurrence risk, other than increasing hydration, decreasing salt and decreasing animal protein intake. Our findings suggest that children who exhibit unilateral hypercalciuria and recurrent stones in that kidney may be candidates for medications that decrease renal calcium excretion, such as thiazides. We cannot recommend this approach for all patients with recurrent unilateral stones since the majority of patients in this cohort had normal UCa/UCr ratio in the kidney that formed the stone. However, we recommend obtaining urine from the affected kidney for UCa/UCr ratio determination at stone intervention to ascertain if unilateral hypercalciuria exists and, therefore, if subsequent medical therapy may be indicated.

The other lithogenic factors in the 24-hour bladder urine collection were similar between the 4 cohorts. While this finding suggests that unilateral hypercalciuria could be a significant risk factor for unilateral stone formation, it also illustrates the complex nature of nephrolithiasis. The kidneys affected by nephrolithiasis were not tested for other urinary constituents known to be important in kidney stone formation. Similar to the normal bladder urine calcium levels, it is possible that the urine excreted by each kidney may differ with respect to other components that are known to be prolithogenic (eg hypocitraturia, hypomagnesemia). It would be useful to identify whether citrate, magnesium, oxalate and pH levels differ between kidneys in which recurrent stones form and those that have been stone-free.

Given the differential renal calcium excretion that we observed in this study, it seems plausible that other urine characteristics may vary between kidneys that form and those that do not form recurrent stones. If this is the case, it may explain why patients with recurrent unilateral nephrolithiasis all had either CaPhos or mixed CaPhos and CaOx stones. One hypothesis is that a distal renal tubular acidosis type of physiology exists in these kidneys that form recurrent CaPhos stones. Further studies that analyze differential urine pH and citrate are needed to test this hypothesis. At this point the only conclusion that can be drawn from our observations is that patients with recurrent unilateral nephrolithiasis and ipsilateral hypercalciuria seem to be at risk for forming stones with a CaPhos component. Therefore, caution should be taken with potassium citrate therapy, which could increase urine pH and thereby propagate CaPhos stone formation.

Our observations raise the possibility that hypercalciuria associated with conditions other than nephrolithiasis may be isolated to 1 kidney. Hypercalciuria has been observed to occur in children with UPJO, which is usually a unilateral condition.¹⁷ Additionally preliminary studies have revealed an increased incidence of hypercalciuria in children with VUR.^{18,19} This association between VUR and hypercalciuria was strengthened by a more recent report in which Madani et al observed the incidence of hypercalciuria was 21.3% in children with VUR and only 3.6% in controls without VUR.²⁰ It is plausible that a subset of patients with unilateral UPJO or VUR may have occult ipsilateral hypercalciuria that would be masked by the normal contralateral kidney and thereby missed on analysis of a bladder urine sample.

The hypothesis that ipsilateral hypercalciuria is associated with unilateral anatomical anomalies such as VUR and UPJO should be addressed in future studies. Children with VUR and UPJO have increased rates of hypercalciuria and may be at greater risk for nephrolithiasis.^{20–23} Therefore, determining if children with unilateral VUR or UPJO have occult ipsilateral hypercalciuria could provide an opportunity to begin medical therapy or at least make an early referral to nephrology for counseling and nephrolithiasis risk reduction strategies.

The strengths of this study include using multiple comparative cohorts and a followup of longer than 1 year. All subjects underwent 24-hour urine collection and serum calcium analysis. Study limitations include the fact that only urine calcium and creatinine were collected from the affected kidney. Also we have not reassessed the UCa/UCr ratio of the hypercalciuric kidney after medical intervention was started due to the ethical considerations of subjecting an asymptomatic patient to anesthetic and operative risk to collect urine from the affected kidney. If recurrent stone develops in these patients, then urine will be collected intraoperatively and evaluated. Additionally those patients who underwent extracorporeal SWL, percutaneous nephrolithotomy or active surveillance were excluded from this study. There could certainly be patients treated with these modalities who may have unilateral hypercalciuria. It would also be interesting to determine how SWL changes urine parameters, as Parks et al have shown that extracorporeal SWL is associated with an increase in formation of CaPhos stones.²⁴

As noted previously, other lithogenic urine constituents found in the kidney affected by nephrolithiasis may differ between these cohorts, which may have contributed to the development of solitary or recurrent nephrolithiasis. Additionally although the length of followup was similar between the cohorts, it is possible that patients who present with a single stone in either 1 or both kidneys may evolve into recurrent stone formers. Long-term followup and complete metabolic evaluation are needed in all children who form kidney stones. If recurrent stones develop, it may be useful to repeat urine sampling from the affected kidney to determine if UCa has changed. Finally, urine was collected at stone intervention. It is possible that instrumentation of the urinary tract changes the dynamic equilibrium of the urine. However, the same surgical technique was used in all patients and, therefore, all urine profiles should have been affected equally.

We cannot assign a cause to the finding of unilateral hypercalciuria. It is possible that the vascular and renal perfusion hypotheses proposed by Le et al⁷, and Purohit and Stoller⁸ are consistent with unilateral hypercalciuria. It would be worthwhile to investigate whether renal diseases that predispose to recurrent nephrolithiasis, such as type 1 renal tubular acidosis, which is believed to affect both kidneys, could occur in only 1 kidney. Studies that analyze lateralized urine pH, citrate and oxalate are needed to advance our understanding of the mechanisms underlying unilateral hypercalciuria.

CONCLUSIONS

Unilateral hypercalciuria can occur in children with normal calcium levels in bladder urine. Unilateral hypercalciuria should be considered as a risk factor for nephrolithiasis in children with recurrent stone episodes in 1 kidney only.

Abbreviations and Acronyms

CaOx	calcium oxalate
CaPhos	calcium phosphate
CHOP	Children's Hospital of Philadelphia
SWL	shock wave lithotripsy
UCa	urine calcium
UCr	urine creatinine
UPJO	ureteropelvic junction obstruction
VUR	vesicoureteral reflux

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Figure 1.

Selection process for study inclusion. Asterisk indicates anatomical abnormalities including all neuropathic bladders and urinary obstruction of any kind (eg ureteropelvic junction obstruction, ureterovesical junction obstruction, ureteral stricture, posterior urethral valves). Double asterisk indicates metabolic abnormalities including hypercalciuria on 24-hour urinalysis and cystinuria. *ESWL®*, extracorporeal shock wave lithotripsy.

Table 1

Urine and stone parameters

	Single Unilat Stone	Synchronous Bilat Stones	Recurrent Unilat Stones		Recurrent Bilat Stones	p Value
			Hypercalciuric	Nonhypercalciuric		
Mean $\pm$ SD age (yrs)	7.32 $\pm$ 2.30	9.17 $\pm$ 3.1	7.52 $\pm$ 2.9	8.43 $\pm$ 3.3	10.38 $\pm$ 2.6	0.23 (ANOVA)
No. increased spot UCa/UCr ratio in affected kidney/ total No. (%)	0/200 (0)	0/36 (0)	9/74 (12.2)	0/74 (0)	0/19 (0)	0.02 (ANOVA)
Mean spot UCa/UCr ratio in affected kidney (range)	0.04 (0.02–0.11)	0.077 (0.05–0.18)	0.91 (0.47–1.01)	0.06 (0.02–0.13)	0.10 (0.03–0.16)	<0.001 (F = 16.03)
Mean spot UCa/UCr ratio in bladder (range)	0.05 (0.02–0.11)	0.05 (0.02–0.15)	0.04 (0.02–0.14)	0.05 (0.02–0.12)	0.05 (0.02–0.10)	0.39 (ANOVA)
Mean 24-hr UCa/UCr ratio (range)	0.07 (0.03–0.12)	0.08 (0.04–0.13)	0.10 (0.02–0.13)	0.09 (0.03–0.13)	0.07 (0.03–0.12)	0.23 (ANOVA)
Mean serum calcium (range)	9.01 (8.8–9.6)	9.46 (9.2–10.0)	9.42 (8.8–9.7)	9.51 (8.9–10)	9.62 (9.1–10.0)	0.91 (ANOVA)
No. CaOx monohydrate stones (%)	93 (46)	12 (33)	0 (0)	18 (28)	8 (42)	
No. CaOx dihydrate stones (%)	53 (26)	14 (39)	0 (0)	27 (42)	5 (26)	
No. CaOx monohydrate/dihydrate stones (%)	42 (21)	7 (19)	0 (0)	17 (26)	5 (26)	
No. CaPhos stones (%)	2 (2)	0 (0)	5 (56)	1 (1)	0 (0)	
No. CaOx/phosphate stones (%)	10 (5)	3 (8)	4 (44)	2 (3)	1 (5)	

Spot and 24-hour UCa/UCr ratios are measured in mg/mg, with normal values being 0.21 and less than 0.14, respectively, for children older than 5 years. UCa and UCr values for each kidney in patients with bilateral nephrolithiasis were collected and analyzed independently. There were no values greater than 0.21 mg/mg and, therefore, results for each kidney were averaged and values presented represent mean value of both kidneys.

Table 2

Characteristics of patients with unilateral hypercalciuria at first intervention for recurrent stone

Pt No.—Age—Gender	Stone Size (mm)	Spot UCa/UCr Ratio in Bladder	Spot UCa/UCr Ratio in Affected Kidney
1—4.86—M	9	0.02	0.88
2—5.01—F	7	0.03	0.97
3—6.64—F	6	0.07	0.99
4—7.28—M	7	0.02	0.93
5—7.37—F	6	0.02	0.47
6—8.16—M	7	0.03	0.98
7—8.60—F	7	0.14	1.01
8—9.31—F	5	0.02	0.96
9—10.4—F	8	0.05	0.99

First intervention consisted of either pre-stenting or definitive ureteroscopy. Stone size was determined by ultrasound at intervention for recurrent stone. No patient had a urinary tract infection.