ACCEPTED MANUSCRIPT

The Ability of a Limited Metabolic Assessment to Identify Pediatric Stone-formers with Metabolic Abnormalities

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Extended Summary

Introduction: American Urologic Association (AUA) guidelines recommend a urinary metabolic evaluation after the first stone event in all pediatric stone patients. Prior studies identified hypercalciuria and urine hypovolemia as the most common abnormalities in children with urolithiasis. Recent data suggests that hypocitraturia is most prevalent. We hypothesized that a limited evaluation would detect the majority of clinically significant metabolic abnormalities in pediatric stone-formers.

Material and Methods: We performed a retrospective analysis of all children (<18 years of age) with renal/ureteral calculi evaluated at our institution from 2005-2015. We included those with ≥ one 24-hour urinary metabolic profile after a clinical visit for renal/ureteral calculi. We excluded children with bladder stones and those with under- or over-collections or missing urinary creatinine. We extracted demographics, data from the first urinary metabolic profile and stone analyses. We compared the sensitivity, specificity and positive and negative predictive value (NPV) of a limited urinary metabolic evaluation consisting of four parameters (24-hour calcium, citrate and oxalate and low urinary volume) to a complete urinary metabolic profile. We determined the number and type of metabolic abnormalities that we would have missed with this limited evaluation.

Results: Of 410 patients, we excluded 21 for age ≥18 years, 13 for bladder stones, 248 for over-collections, 38 for under-collections and 10 for missing creatinine. This left 80 patients for inclusion: median age 11.4 years, 60% female, 96.3% white. Of the entire cohort, 69.6% had hypocitraturia, 52.5% had low urine volume and 22.5% had hypercalciuria. Sensitivity was 87.5%. **Specificity could not be calculated because**

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no patients had a normal complete metabolic evaluation. **The NPV was zero and positive predictive value was 100% but these are artifacts resulting from the absence of patients with a normal complete metabolic evaluation.** Of the 80 patients, 10 had at least one abnormality missed by a limited metabolic evaluation (Table 1). The missed abnormalities were high pH (n=6), abnormal 24-hour phosphorus (low in 1 patient, high in 1 patient), low 24-hour magnesium (n=3), low 24-hour potassium (n=3) and high 24-hour sodium (n=4).

Discussion: A limited urinary metabolic evaluation would have detected the vast majority of clinically significant metabolic abnormalities in our sample. Approximately two-thirds of our patients submitted inadequate 24-hour urine specimens.

Conclusions: We propose a simplified approach to metabolic evaluation in first-time stone formers with a stone analysis available. This streamlined approach could simplify the metabolic evaluation and reduce healthcare costs.

Introduction

Nephrolithiasis, once considered an adult disease, is becoming increasingly prevalent in children.[1-6] Data from South Carolina demonstrated an increased stone incidence in children from 7.9 per 100,000 children in 1996 to 18.5 per 100,000 children in 2007.[6] The Pediatric Health Information System database showed an adjusted annual increase of 10.6% between 1999-2008, confirming this trend.[7] The greatest increase in pediatric nephrolithiasis has been amongst adolescents, particularly females.[1, 3] With no known increase in the incidence of anatomical or metabolic

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abnormalities that contribute to the development of stones in children, the exact reason(s) for the increased incidence is unknown.[5, 8] As the largest increase in incidence has been in the adolescent population, many have hypothesized that changes in dietary behaviors that have also led to the obesity epidemic might play a role.[1-5, 8, 9] In adults, there is a clear association between specific dietary factors and urinary stone disease.[10-14] The adult literature has demonstrated an association between nephrolithiasis and increased sodium and fructose consumption and with low dietary calcium and inadequate fluid intake.[10-17] Unlike adults, there is very little data about the association of dietary factors and stone formation in children.[8] There is good evidence, however, that dietary patterns in children have substantially changed in the last 25-30 years.[8]

The growing understanding of nephrolithiasis as a disease that begins in childhood is worrisome for a number of reasons, including implications for future health care spending and services allocation.[2] A growing body of data supports the association of pediatric nephrolithiasis with adult nephrolithiasis, and with significant associated morbidities such as acute myocardial infarction, atherosclerosis, and chronic kidney disease.[3] Acute symptomatic nephrolithiasis is also associated with substantial pain,[2] and younger patients have a low rate of spontaneous calculi passage and are more likely to require surgical intervention.[6] The growing morbidity, financial burden, and concern regarding the long-term sequelae of pediatric nephrolithiasis make a strong case for further investigations into quality improvement and cost reduction for pediatric stone management.

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American Urological Association (AUA) guidelines recommend a complete urinary metabolic evaluation in all pediatric stone patients after the first stone event due to a historically high incidence of metabolic abnormalities. [18] The goal of this complete metabolic evaluation is to screen children for treatable metabolic disorders, reduce calculi recurrence and detect any rare genetic abnormalities. Prior studies demonstrated that hypercalciuria was the most common metabolic abnormality in pediatric stone formers.[19-21] Several recent studies, however, noted that hypocitraturia was more common than hypercalciuria, accounting for the majority of metabolic abnormalities.[22, 23] Hypocitraturia corresponds to a low consumption of potassium and magnesium suggesting a dietary origin for the changing composition of urinary metabolic profiles in children.

Given the predominance of diet-related issues, it may be feasible to use a more streamlined approach to screen for metabolic abnormalities. Potential benefits of this approach include reduced healthcare costs and avoidance of low-yield testing. Therefore, the purpose of this study was to assess the sensitivity and specificity of a hypothetical, limited metabolic evaluation in pediatric stone formers extrapolated from the complete urinary metabolic evaluation. The limited evaluation includes low urine volume and 24-hour calcium, oxalate and citrate. We hypothesized that a limited metabolic evaluation would detect the majority of clinically significant metabolic abnormalities in pediatric stone-formers.

Materials and Methods

We performed a retrospective analysis of all children (<18 years of age) with renal and/or ureteral calculi evaluated at our institution between 2005 and 2015. In

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order to build a comprehensive stone database, we performed a query of our billing system for all pediatric patients with a stone-related ICD-9 or ICD-10 diagnosis code associated with a clinical visit at our institution during the study period. **We included ICD-9 codes for kidney stones, bladder stones and calculus of the ureter. We also included ICD-10 codes for calculus of the kidney, calculus of the ureter, calculus of the kidney with calculus of the ureter, urinary calculus unspecified, calculus in bladder, calculus in urethra, other lower urinary tract calculus and calculus of lower urinary tract unspecified.**

We also requested Litholink data for all pediatric patients from our institution during the study period. The billing data and Litholink data were then merged based on name and date of birth. We only included those who had at least one 24-hour urinary metabolic profile after a clinical visit for kidney/ureteral calculi. **A pediatric nephrologist evaluated all of the patients. Litholink distributed 24-hour urine collection instructions to all families prior to specimen collection consisting of an 11-step process with detailed illustrations.**

We excluded patients who had their first clinical visit prior to 2005 and patients who had a Litholink study performed prior to their first clinical visit for renal/ureteral calculi. We also excluded children with bladder stones and those with under- or over-collections on their metabolic evaluation (normal Cr in pre-pubertal patients: 10-15 mg/kg/24 hours).[24]

Demographics and the data from the first urinary metabolic profile were extracted. We classified patients with 85th to <95th body mass index (BMI) percentile as overweight and those with ≥95th percentile BMI as obese. We included BMI percentile

data because of the proposed association between obesity and stone risk factors in children.[25] Low urine volume was defined as <1ml/kg/hour, elevated 24-hour calcium as >4.0 mg/kg/24 hours and elevated 24-hour oxalate as <52 mg/1.73m^2/24 hours.[26-29] Low 24-hour citrate was defined by age and gender criteria as previously described in the literature.[30, 31] We compared the **sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)** of a limited urinary metabolic evaluation consisting of four parameters (24-hour calcium, 24-hour citrate, 24-hour oxalate and low urinary volume) compared to a complete urinary metabolic profile. The number and type of metabolic abnormalities that we would have missed with this limited evaluation was then determined.

Results

Of 410 patients identified, we excluded 21 for age ≥18 years, 13 for bladder stones, 248 for over-collections, 38 for under-collections and 10 for missing creatinine thus leaving 80 patients for analysis. Median age was 11.4 years (interquartile range 8.2, 15.5), 60% were female, 96.3% were white, 19.5% were obese and 13.0% were overweight. All patients underwent a complete evaluation. **All of them had at least one abnormality identified on the complete profile and so were classified as "abnormal" on complete metabolic assessment.** The most common abnormalities were low 24-hour citrate (69.6%), low urine volume (52.5%) and elevated 24-hour calcium (22.5%) (Table 1). Most patients had more than one abnormality (Table 2). **The sensitivity of the limited metabolic evaluation was 87.5%. Specificity could not be calculated because no patients had a normal complete metabolic evaluation (i.e. all patients in the cohort had the abnormality being tested for) which results in a**

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calculation with zero in the denominator. **The negative predictive value was calculated as zero, and positive predictive value as 100% but these are artifacts resulting from the absence from the cohort of any patients with normal complete metabolic evaluation and are not reflective of any actual test characteristics.** Of the 80 patients, 10 (12.5%) had at least one abnormality missed by a limited metabolic evaluation (Table 3). Of these 10, 7 had detailed clinical notes available. The missed abnormalities were high pH (n=6), abnormal 24-hour phosphorus (low in 1 patient, high in 1 patient), low 24-hour magnesium (n=3), low 24-hour potassium (n=3) and high 24-hour sodium (n=4).

Metabolic treatment for the 80 patients with an appropriate evaluation were as follows. One patient was diagnosed with cystinuria based on stone analysis and was started on potassium thiazide. One patient with a history of congenital heart disease was on furosemide at the time of the metabolic evaluation. The nephrologist switched them to a thiazide diuretic to minimize the risk of hypercalciuria. The remainder of the patients received counseling about increasing their fluid intake and restricting sodium intake. No patient had a missed abnormality that was clinically significant or would have changed the prescribed therapeutic regimen. No specific treatment was necessary for any of the following: high pH, high phosphorus, low magnesium, low potassium or high sodium. Our institution **charges $182 for a** limited evaluation **and $430 for a complete evaluation.**

Discussion

In this study, we found that a hypothetical limited metabolic evaluation would have detected almost all clinically significant metabolic abnormalities in our sample.

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Hypocitraturia was the most common metabolic abnormality, noted in 70% of the patients in our sample. This reflects the findings of two recent pediatric studies that each noted hypocitraturia in 58% of their respective samples.[22, 23] They also noted hypercalciuria in 48% and 27% of their patients respectively.[22, 23] In addition, approximately half of our sample had low urine volume, a risk factor that prior authors have not emphasized in their analyses of metabolic evaluations. Although dehydration is a well-established risk factor for stone formation in adults, no prior studies have conclusively established this association in children.[15, 16] One flaw with a limited metabolic evaluation is that we would have missed the patient with cystinuria since we did not include the cystine screen in our limited approach; however, we made the diagnosis based on the stone analysis. Therefore, we would recommend doing a limited evaluation only when a stone sample is available.

One noteworthy finding of our study was that approximately two-thirds of patients submitted inadequate 24-hour urine specimens due to either under- or over-collection of the sample as determined by the ratio of creatinine to weight in kilograms adjusted by gender and age. **If a patient collects urine for more than 24 hours (i.e. over collection), the daily calcium normalized to weight would overestimate the daily calcium excretion in the urine. The calcium to creatinine ratio would still be accurate but, in our experience, the value normalized to weight is more often used for 24-hour samples. This could potentially lead to the incorrect diagnosis of hypercalciuria and erroneous prescription of diuretics.**

Several studies have demonstrated that approximately 50% of adult stone formers submit inadequate 24-hour urine specimens.[32, 33] To our knowledge, no

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prior studies have determined predictors of inadequate specimen collection in pediatric patients. **There are likely a variety of factors that contribute to inadequate specimen collection in children including parental factors such as education, employment and marital status and child factors such as difficulty with specimen collection at school.** This finding highlights a potential area for future exploration to determine barriers to proper collection of 24-hour urine specimens in pediatric patients **and develop an intervention to address this issue**.

There are several notable differences between a complete metabolic evaluation and our proposed limited metabolic evaluation for first-time stone formers. **First, we did not include a cystine screen in our limited evaluation. The probability of a missed diagnosis of cystinuria is quite low given that the prevalence is 1 in 7,000.[34]** Cystinuric patients typically have unique clinical characteristics such as larger stone size at diagnosis and a higher probability of bilateral and/or recurrent stone disease that would suggest a genetic cause.[35] Patients with primary hyperoxaluria typically have associated clinical features such as nephrocalcinosis and calcium oxalate monohydrate stones.[36] Therefore, we would consider a complete metabolic profile in a patient with recurrent urolithiasis who had a negative limited evaluation after the incident stone. Second, we did not include urine electrolytes such as magnesium, phosphorus, potassium or sodium since most providers do not use these measures in tailoring their second prevention strategies. Finally, we not include uric acid since the stone analysis is usually diagnostic in these cases.

We would suggest utilization of the limited metabolic profile in select first-time stone formers with small-volume stone disease who have a urinalysis and stone

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analysis available. This approach would decrease the likelihood of missing rare, genetic causes of nephrolithiasis. Limitations of this study include possible selection bias due to the exclusion of inadequate collections. It is possible, although unlikely, that patients who collected their 24-hour urine samples incorrectly had different types of metabolic abnormalities than those who submitted adequate collections. We acknowledge that the sample size is small, but given the infrequent nature of stone disease in children and difficulties in obtaining an acceptable 24-hour specimen our study size is a reasonable number of patients to analyze. **We acknowledge that there is no difference from the patient perspective in terms of the burden of a 24-hour urine collection with a limited versus complete approach. Unfortunately there is poor correlation between early morning spot urine and 24-hour urine samples for metabolic evaluation. A recent study showed strong correlation between 12-hour nighttime collection and 24-hour urine collection in adults.[37] This technique has not yet been validated in the pediatric population, however, and the 24-hour collection remains the standard of care. There still may be significant savings with this approach, however, given that the charge for a complete evaluation is more than twice that of a limited evaluation.**

To our knowledge, this is the first study to demonstrate the feasibility of a limited urinary metabolic evaluation in pediatric stone formers. We confirmed our hypothesis that a limited urinary metabolic evaluation would detect the majority of clinically significant abnormalities in children with urolithiasis.

Conclusions

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We recommend a limited metabolic evaluation in first-time pediatric stone formers who have a stone analysis available. The combination of a limited metabolic evaluation and a stone analysis should detect all clinically significant metabolic abnormalities in this population. This streamlined approach could simplify the metabolic evaluation and reduce healthcare costs, particularly for providers that do not used bundled services for their 24-hour metabolic evaluations. Future directions include a cost-effectiveness analysis of limited versus complete metabolic evaluations.

Conflict of Interest

The authors have no conflicts of interest to declare.

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None

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Table 2: Number of abnormalities per patient on metabolic evaluation

Total Abnormalities	N (%)
1	4 (5.0%)
2	7 (8.8%)
3	11 (13.8%)
4	26 (32.5%)
5	18 (22.5%)
6	8 (10.0%)
7	4 (5.0%)
8	2 (2.5%)

Extended Summary Table: Abnormalities missed by limited evaluation

Total Count of Abnormalities	Frequency	Percent
1	4	40%
2	4	40%
3	2	20%

Table 1: Types of metabolic abnormalities (n=80 patients)

Abnormality	N (%)
potassium (low)	61 (76.3%)
magnesium (low)	57 (71.3%)
*citrate (low)	55 (69.6%)
low urine volume	42 (52.5%)
pH (high)	27 (33.8%)
sodium (high)	20 (25.0%)
calcium (high)	18 (22.5%)
phosphorus (low)	14 (17.5%)
oxalate (high)	12 (15.0%)
pH (low)	12 (15.0%)
phosphorus (high)	7 (8.8%)
oxalate (low)	5 (6.3%)
sodium (low)	2 (2.5%)
uric acid (high)	2 (2.5%)
magnesium (high)	1 (1.3%)

*One patient had a missing value for citrate.

Table 3: Characteristics of patients with abnormalities missed by limited evaluation

*Pt #	Stone location	Stone analysis	Total abn.	Missed abn.	Secondary prevention	Notes
1	ureter	none	1	High pH	Increase fluid; limit Na	
2	kidney	100% cystine	2	Low Mg, High P	Potassium citrate	
3	ureter	none	2	Low Mg, Low K	Increase fluid; limit Na	
4	kidneys and ureter	100% Ca Ox dihydrate	2	High Na, High pH	Increase fluid; limit Na	
5	**unknown	none	3	Low Mg, Low K, High Na	Switched to HCTZ to minimize hypercalciuria risk	History of congenital heart disease; on furosemide
6	kidney	none	3	High Na, Low SS Ca Ox, High pH	Increase fluid; limit Na	

*4 patients did not have detailed clinical notes available

**patient passed the stone spontaneously and did not save the specimen; no radiographic evidence of stones

Na=sodium; Mg=magnesium; P=phosphorus; K=potassium; SS=supersaturation; Ca Ox=calcium oxalate; HCTZ=hydrochlorothiazide