

Clinical, demographic, and laboratory characteristics of children with nephrolithiasis

David J. Sas¹ · Lauren J. Becton² · Jeffrey Tutman³ · Laura A. Lindsay⁴ · Amy H. Wahlquist⁵

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Abstract While the incidence of pediatric kidney stones appears to be increasing, little is known about the demographic, clinical, laboratory, imaging, and management variables in this patient population. We sought to describe various characteristics of our stone-forming pediatric population. To that end, we retrospectively reviewed the charts of pediatric patients with nephrolithiasis confirmed by imaging. Data were collected on multiple variables from each patient and analyzed for trends. For body mass index (BMI) controls, data from the general pediatrics population similar to our nephrolithiasis population were used. Data on 155 pediatric nephrolithiasis patients were analyzed. Of the 54 calculi available for analysis, 98 % were calcium based. Low urine volume, elevated supersaturation of calcium phosphate, elevated supersaturation of calcium oxalate, and hypercalciuria were the most commonly identified abnormalities on analysis of 24-h urine collections.

Our stone-forming population did not have a higher BMI than our general pediatrics population, making it unlikely that obesity is a risk factor for nephrolithiasis in children. More girls presented with their first stone during adolescence, suggesting a role for reproductive hormones contributing to stone risk, while boys tended to present more commonly at a younger age, though this did not reach statistical significance. These intriguing findings warrant further investigation.

Keywords Nephrolithiasis · Urolithiasis · Kidney stones · Pediatrics · Obesity · Adolescents

Introduction

Nephrolithiasis in children is increasingly more common and accounts for a growing proportion of pediatric hospitalizations and cost [1–4]. It is associated with considerable pain in all age groups, and elevated blood pressure and decreased renal function in studies of adult cohorts [5–8].

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✉ David J. Sas
sas.david@mayo.edu

Lauren J. Becton
lauren.becton@gmail.com

Jeffrey Tutman
Jeffrey.Tutman@hsc.utah.edu

Laura A. Lindsay
lindsayl@childrensdayton.org

Amy H. Wahlquist
herrin@muscc.edu

² Division of Pediatric Nephrology, Department of Pediatrics, Albert Einstein School of Medicine, 1300 Morris Park Ave, Bronx, NY 10461, USA

³ University of Utah Department of Radiology, 30 North 1900 East #1A071, Salt Lake City, UT 84132, USA

⁴ Children's Emergency Services, Dayton Children's Hospital, 1 Children's Plaza, Dayton, OH 45404, USA

⁵ Division of Biostatistics and Epidemiology, Department of Medicine, Medical University of South Carolina, 96 Jonathan Lucas St., Suite 803 MSC 623, Charleston, SC 29425, USA

¹ Division of Pediatric Nephrology and Hypertension, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA

Additionally, younger patients may have a lower rate of spontaneous passage for calculi and may be more likely to require invasive and costly surgical intervention [9].

While there has been much speculation regarding the cause of the increasing incidence of pediatric nephrolithiasis, there have not yet been any conclusive answers. Possible reasons for the increasing incidence have included obesity, increased sodium intake, decreased calcium intake, decreased water intake, and increased antibiotic usage [10].

We set forth to analyze data from our growing population of pediatric stone formers from our single institution in the so-called “stone belt” to look for patterns related to clinical, demographic or laboratory data. We specifically sought to compare our stone-forming population to our general pediatric population with regard to obesity.

Materials and methods

This study was approved by the institutional review board of the Medical University of South Carolina (MUSC). We identified patients in our electronic medical record with International Classification of Diseases, 9th Edition (ICD-9) code 592.0 (nephrolithiasis) or 592.9 (urolithiasis) between the ages of 0 and 18 years. Of the 200 patients identified, 155 had kidney stones confirmed by imaging studies (CT, ultrasound, or abdominal X-ray). We retrospectively reviewed the charts of these 155 patients and collected data on demographic, clinical, laboratory, evaluation, management, and follow-up variables on each patient. Data regarding 24-h urine chemistry analysis were based on pediatric norms established by Litholink or other reference ranges (see Supplemental Table 1) [11–15]. Collection adequacy for 24-h urine collections was validated by urine creatinine excretion rate.

As controls for body mass index (BMI), we used data collected from well-child checks in general pediatric patients from 14 pediatric primary care clinics in South Carolina, which provide a similar broad geographic representation of children as our stone-forming population. Overweight is defined as BMI between 85th and 94th percentile for age and gender, and obese is defined as BMI >95th percentile for age and gender. Data from 132 subjects with kidney stones with complete weight and height data and 947 controls were included in the analyses. Logistic regression models were used to determine the relationships between variables of interest (gender, BMI, age) and whether someone was a stone former or control patient. Interaction terms with BMI were included (gender by BMI, age by BMI) to determine if these relationships impacted prediction of someone being a stone former. Contrast statements were also used to compare individuals' levels of potential predictor variables between stone formers and controls instead of the overall effect of the variable of

interest. Funding for the statistical analysis was provided by SCTR Grant UL1 RR029882.

Results

We analyzed data from 155 subjects who had kidney stones confirmed by imaging studies between 1993 and 2010. Eight patients were seen prior to the year 2000, 56 from 2000 through 2004, and 91 from 2005 through 2010. Forty-eight percent were girls and 52 % boys. Mean and median follow-up times were 18 and 12 months, respectively (range 0–78 months). Based on zip code of residence, 26.5 % of our subjects live in rural areas vs. 23.6 % of the general pediatric population. Of the 62.5 % who had a positive family history for kidney stones, 58 % had at least one first degree relative with stones.

Regarding relevant medical history, nine subjects were born prematurely (range 23–36 weeks gestation), three had vesicoureteral reflux, three had neurogenic bladder, and two had medullary sponge kidney. Just over half of our subjects presented initially with back/flank pain and 1/3 presented with gross hematuria, vomiting, and/or abdominal pain. At presentation, only 12 % had dysuria and 7 % fever. Boys most commonly presented in the 6- to 11-year age range while girls most commonly presented during adolescence (Fig. 1), though these differences were not statistically different.

The mean (SD) of BMI percentiles (based on age and gender) for the stone formers was 51.4 (34.8), and the mean (SD) of BMI percentiles for the control population was 62.7 (31.1) ($p < 0.001$). Stone formers have a lower BMI than controls in all age groups and are less likely to be overweight than controls (Fig. 2). When divided by gender, girl stone formers are more likely to have a BMI in the normal range than boys (Fig. 3).

Stone analysis was performed on the 54 stones available from 53 different subjects. Analysis revealed that 98 % of stones contained calcium with the majority being predominantly calcium oxalate (Table 1). Adequacy of 24-h urine collection was 76 % overall and 94 % if performed through Litholink vs. 67 % if performed through the hospital lab. The most common metabolic abnormalities found in 24-h urine samples were high calcium phosphate supersaturation (57 %), low urine volume (53 %), high calcium oxalate supersaturation (39 %), and hypercalciuria (34 %). Hyperoxaluria and hypocitraturia were found in 18 and 15 % of subjects, respectively (Fig. 4). Mean 24-h urine sodium excretion was 135.2 mmol/day (3.97 mmol/kg). Potassium excretion was below the reference range (>3 mEq/kg/day) in 24 % of patients and magnesium excretion was below the reference range (>88 mg/1.73m²/day) in 9 % of patients. Selected excretion data are displayed in Table 2.

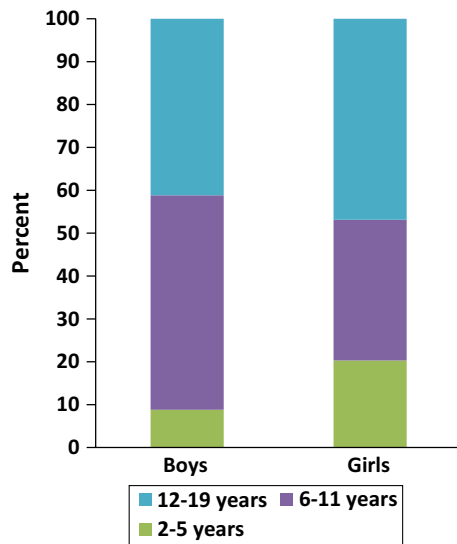


Fig. 1 Age of initial presentation by age range. Boys most commonly present with their first kidney stone during 6–11 years of age while girls most commonly present during adolescence

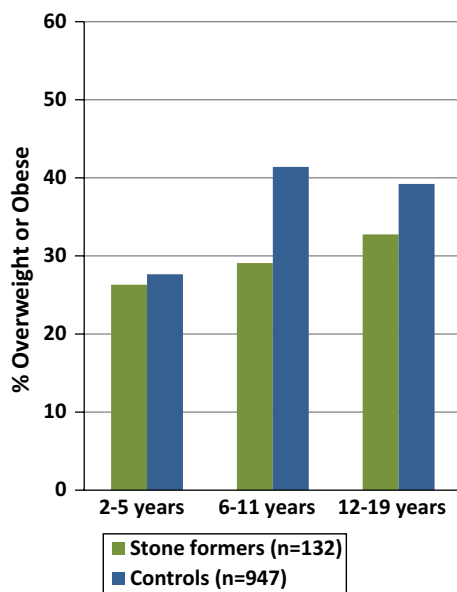


Fig. 2 Percent of stone formers and controls who are overweight or obese by age group. A smaller percentage of stone formers are overweight or obese compared with controls in all age ranges

At initial presentation, 41 % of subjects had a CT scan and 43 % had an ultrasound. Thirty-two percent of subjects had more than one CT scan. Stone sizes based on imaging ranged from 0.5 to 25 mm, though there were also subjects in whom small stones were described as “tiny” or “punctate” with no numerical value given. Twenty (13 %) of our subjects had congenital abnormalities of the urinary

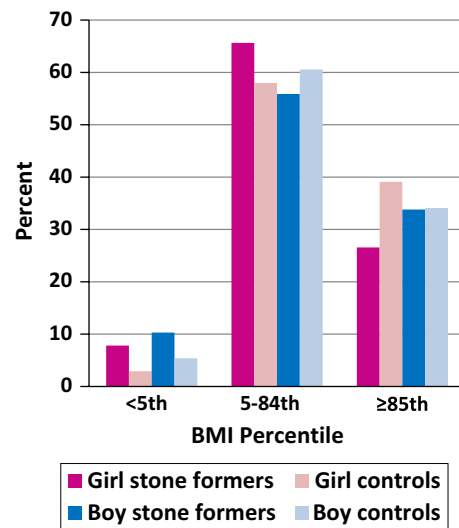


Fig. 3 Percent of girl and boy stone formers and controls who are underweight (<5th percentile BMI), normal (5–84th percentile BMI) and overweight or obese (≥85th percentile BMI). Girl stone formers are less likely to be overweight or obese than boy stone formers

Table 1 Stone composition from 54 kidney stones

	#	%
Calcium oxalate (pure)	31	57.4
Calcium phosphate (pure)	3	5.6
Calcium oxalate–calcium phosphate mix	16	29.6
Calcium oxalate–calcium phosphate–uric acid mix	1	1.9
Ammonium magnesium phosphate–calcium phosphate mix	2	3.7
Cystine	1	1.9
Uric acid (pure)	0	0.0
Total	54	

Calcium was a component of 98 % of stones

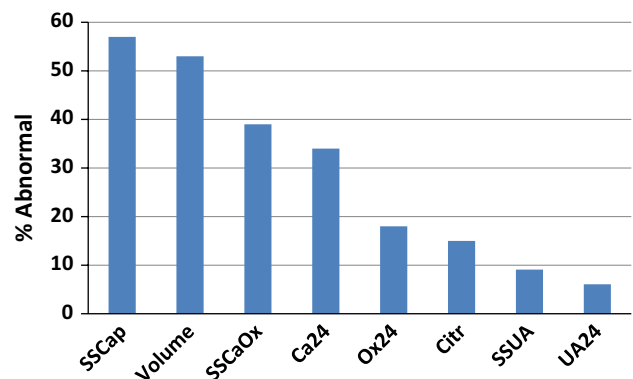


Fig. 4 Percentage of specific abnormalities in 24-h urine chemistry. SS supersaturation, Ca calcium, Ox oxalate, P phosphate, Citr hypocitraturia, UA uric acid

Table 2 Excretion rates of calcium, oxalate, citrate, and magnesium

	First quartile	Second quartile	Third quartile	Fourth quartile	Median
Calcium (mg/kg/24 h)	0.6–1.5	1.6–2.3	2.4–4.2	4.3–9.3	2.4
Oxalate (mg/1.73 m ² /24 h)	17.0–28.4	28.5–40.4	40.5–46.8	46.9–121.5	40.5
Citrate (mg/mg _{creat} /24 h)	42.9–452.4	452.5–611.8	611.9–735.3	735.4–1614.2	611.9
Magnesium (mg/1.73 m ² /24 h)	22.3–101.0	101.1–112.5	112.6–128.9	129.0–203.9	112.6

tract (11 males, 9 females). Overall, 29 % of our subjects had a urological procedure performed. Of those, 29 % had extracorporeal shock wave lithotripsy (ESWL), 40 % had ureteroscopic extraction without laser, and 31 % had ureteroscopic extraction with laser. Twenty-seven percent were admitted to the hospital with an average length-of-stay of 4.2 days. Regarding recurrence of kidney stones, 53 % of our patients did not have a recurrence, 27.5 % had 1–3 episodes of recurrence, and 19.5 % had >3 episodes of recurrence.

Discussion

These data representing the largest pediatric stone-forming population published in two decades [16] provide information regarding demographic, clinical, and laboratory characteristics of pediatric kidney stone formers and improve our fund of knowledge regarding the role of obesity and gender, highlighting the need for definitive prospective research. The results suggest that obesity is not a contributing factor to the increasing incidence of kidney stones in children. These data also support the notion that some gender differences may be relevant in determining underlying causes of increasing incidence of pediatric nephrolithiasis.

Our data suggest that obesity is not a risk factor for pediatric nephrolithiasis. In fact, our pediatric stone formers have a lower BMI on average than our general pediatric population. While adult nephrolithiasis literature suggests that higher BMI increases risk for nephrolithiasis [17, 18], pediatric studies examining the relationship between higher BMI and risk for kidney stones in children have been mixed [19, 20]. To further complicate matters, the two studies performed to describe urinary stone risk factors related to BMI in children ended up with widely varying (in the case of oxalate excretion, completely opposite) results [21, 22].

Given the paucity of data, one must rely on the notion of biological plausibility when contemplating a potential increase in risk for nephrolithiasis in pediatric patients who are obese. While there are data showing that obese adults have a lower urine pH [17], the relationship between BMI and pH may be opposite in children [22]. Indeed, in adults higher BMI may be associated with higher risk only for uric acid stones but not calcium-based stones [23]. But uric acid stones are more common in adults than in pediatrics; we

have not had any pure uric acid stone formers in our pediatric population. Our data are consistent with most pediatric literature on obesity and stones showing no direct relationship between higher BMI and pediatric nephrolithiasis.

Perhaps the most compelling finding is related to gender differences in our pediatric stone-forming population. While boys more commonly present prior to adolescence, girls present most commonly during pubertal years. Though our findings regarding the rate of kidney stone formation between genders did not reach statistical significance, it is consistent with other recent publications [2, 3, 24]. This, combined with evidence of a decline in the male predominance of kidney stone disease in the adult population [25], provokes compelling questions regarding hormonal influences vs. some constellation of environmental factors contributing to this intriguing shift.

While Maalouf et al. provided evidence that estrogen supplementation increases the risk for kidney stones in post-menopausal women [26], other studies demonstrate an inhibitory effect of female reproductive hormones [27, 28]. Additionally, data regarding the potential mechanisms are inconsistent [29, 30]. There are no published data regarding the effect of reproductive hormones on nephrolithiasis risk or risk factors in adolescents, but the increase in kidney stones in our adolescent female population suggests that investigation is warranted.

The urine chemistry results from our population were comparable to other previously reported populations [13, 31, 32]. Like most stone-forming children, our population demonstrates a combination of low urinary volume, hypercalciuria, hyperoxaluria, and hypocitraturia leading to elevated supersaturation of calcium phosphate and/or calcium oxalate.

The primary limitation of our study is that it is retrospective in nature, resulting in a lack of uniform data. Additionally, like all pediatric kidney stone studies to date, we have a relatively small sample size. Last, because these data come from one geographic area, it is not certain that our findings can be extrapolated to the entire US Pediatric population. These limitations support the formation of a national kidney stone registry which will allow for uniform collection of data from multiple institutions, which may provide more insight into the risk factors contributing to pediatric nephrolithiasis and provide a matrix to test potential therapeutic interventions.

Conclusions

While the causes related to the increasing incidence of kidney stone in children are not yet known, obesity is not a likely contributor. The increasing incidence in the adolescent female population suggests a role for reproductive hormones contributing to stone risk which warrants further investigation.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare.

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