Journal of Pediatric Urology (2015) 11, 218–223

National multi-institutional cooperative on urolithiasis in children: Age is a significant predictor of urine abnormalities

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Keywords
Pediatrics; Nephrolithiasis; Metabolic abnormalities; 24-h urine analysis

Received 9 January 2015
Accepted 25 April 2015
Available online 1 June 2015

Summary

Introduction
Pediatric nephrolithiasis is a growing problem and prior studies have shown the greatest increase in nephrolithiasis in the adolescent population. Metabolic abnormalities have historically been cited as the primary cause of pediatric nephrolithiasis; however, dietary and other factors such as obesity have also been studied with mixed results.

Objective
We reviewed the charts of pediatric patients with a history of nephrolithiasis to determine the number and types of metabolic abnormalities present on 24-h urine analysis.

Study design
We retrospectively reviewed the charts of all pediatric patients with a history of nephrolithiasis from 1999–2013 across four different institutions. The subjects were excluded if they had a history of spina bifida, neurogenic bladder, cerebral palsy, isolated bladder stones, or if they were on medical therapy for nephrolithiasis before the first 24-h urine collection.

Results
There were 206 subjects included in the analysis with an average age of 13 (±3.9) years. The patients were stratified into two age groups based on an apparent bimodal distribution of metabolic abnormalities, ≤10 years and >10 years of age. Metabolic abnormalities were present in 130 children (63.1%) and there was a difference between the groups, with children ≤10 years more likely to have a metabolic abnormality compared with those >10 years of age (75% vs. 60.6%, $p = 0.0443$) on univariate analysis. In children ≤10 years hypercalciuria was the most common disorder present (48.4%), and in children >10 years hypocitraturia was the most common disorder present (26.1%). Children ≤10 years of age were more likely to have normal volume ($p = 0.006$), elevated urinary oxalate ($p = 0.0351$), elevated urinary calcium ($p < 0.001$), elevated supersaturation of calcium phosphate ($p < 0.001$), and elevated supersaturation of calcium oxalate ($p = 0.002$). On multivariate analysis, children ≤10 years of age were more likely to have normal volume, hyperoxaluria, elevated supersaturation of calcium phosphate and a trend towards hypercalciuria (Table).

Discussion
Our study reveals that younger children are more likely to have a metabolic abnormality present on 24-h urine analysis. This has important implications when deciding on treatment options, with younger children potentially requiring more aggressive management with medical therapy. Older children were more likely to have low urinary volume and their most common metabolic abnormality was hypocitraturia. Although dietary factors have not been established as the definitive reason behind the rising incidence of nephrolithiasis in the adolescent population, older children may benefit more from diet modification with a strong focus on increasing volume intake.

Conclusion
We found differences in younger compared with older age groups in terms of the number and types of metabolic disorders present. Children ≤10 years of age were more likely to have a metabolic disorder including elevations in calcium, oxalate and supersaturation of calcium phosphate, while children >10 years of age were more likely to have low urinary volume. These differences have important implications for future investigative studies on the rising incidence as well as the best course of treatment for children with nephrolithiasis.

http://dx.doi.org/10.1016/j.jpurol.2015.04.021

Table Multivariate analysis.

Age (≤10 years vs. >10 years)				
	OR	Confidence limits		*p*
Low volume vs. normal volume	0.46	0.215	0.98	0.0443
Oxalate (hyperoxaluria vs. normal)	2.229	1.044	4.758	0.0384
Calcium (hypercalciuria vs. normal)	2.081	0.971	4.461	0.0595
Super saturation calcium phosphate (elevated vs. normal)	3.129	1.457	6.719	0.0034

Introduction

The incidence of pediatric stone disease appears to be rising across the USA, with a 10.6% adjusted annual increase seen across PHIS data from 1999 to 2008 [1]. The causative factors for this rise have not been elucidated; however, two studies have reported the greatest increase in incidence in older children [2,3]. Historically, metabolic abnormalities are the most common cause of urolithiasis in children, although the percentage with an abnormality varies widely in the literature from 16% to 93% [4–9]. The major type of metabolic abnormality present among each institution also differs, with some authors reporting hypercalciuria [2,6,8,10], others hypocitraturia [4,7,11], and still others hyperoxaluria [5] as the most common abnormality present. Mixed metabolic abnormalities also have been noted, with 29% of children in one study having a combination of factors on 24-h urine analysis [11].

Pediatric urolithiasis is not as well understood as adult urolithiasis and this is partly because of the increased presence of structural abnormalities that may be present and predispose to stones, as well as difficulty in obtaining 24-h urine analyses. Normative values for what constitutes an abnormality also vary within the literature making interpretation difficult. This underscores the difficulty in providing the best treatment for children with urolithiasis in the face of a rising incidence, of which many factors, such as diet and obesity are thought to contribute, but conflicting data exist on whether these factors are truly causative. Herein, we examine 24-h urinary parameters in stone-forming children to determine if there are major differences between younger and older children to help guide future treatment.

Materials and methods

We reviewed retrospectively the charts of all pediatric patients with a history of nephrolithiasis across four institutions from 1999 to 2013. Data collected at initial presentation included age at presentation, height, weight, stone location and size, treatment rendered for the stone, family history, comorbidities, and stone analysis where available. All children in the study underwent 24-h urine analysis with Litholink. Exclusion criteria included patients with a history of spina bifida, neurogenic bladder, cerebral palsy, patients with isolated bladder stones, and patients on treatment medications before the first 24-h urine analysis.

The first 24-h urine analysis was included, unless two analyses were done within a 48-h period in which case they were averaged. The 24-h urine collection was obtained while the child was on regular diet and fluid intake, prior to dietary recommendations and before the initiation of medical treatment. Importantly, some children had stone fragments present within the collecting system at the time of 24-h urine collection. Some of the patients, regardless of whether they spontaneously passed stones, were observed or had surgical intervention, had small upper tract fragments that were not aggressively managed unless they became symptomatic. These patients were not precluded from a 24-h urine profile. Urinalysis and urine culture were not routinely checked on patients prior to 24-h urine collection because of the time lag between last office visit and the start of the collection. To prevent bacterial overgrowth that could potentially affect the citrate concentration, all patients were provided with an antibacterial preservative and were instructed to add it at the beginning of the urine collection.

Urine collections were considered adequate if creatinine excretion was greater than 12 mg/kg/day [12]. All 24-h urinary values were adjusted for weight or body surface area. Abnormal values were considered if calcium excretion was greater than 4 mg/kg/day, oxalate greater than 40 mg/1.73 m^2, citrate less than 310 mg/1.73 m^2 per day in girls and 365 mg/1.73 m^2 per day in boys, and uric acid greater than 0.815 g/1.73 m^2 [13]. Urinary volume was considered low if it was less than 20 mL/kg/day. Supersaturation of calcium oxalate, phosphate, and uric acid also were included in the analysis.

Statistical analysis included Chi-square, independent *t* test, and logistic regression. Multivariate models were adjusted. All tests were two-sided with significance considered at $p < 0.05$. The 95% CI was calculated for all odds ratios. All analysis was done with SAS, version 9.2.

Results

We analyzed 206 children who met inclusion criteria with a mean age of 13 years (±3.9). Females comprised 51.9% of the cohort. A bimodal distribution based on age was recognized from the data and the cohort was split into two groups. Group 1 children defined as aged ≤10 years represented 31.1% of the cohort ($n = 64$), and Group 2 children were aged >10 years and represented 68.9% ($n = 142$) of the cohort. Metabolic abnormalities were present in 130 children (63.1%), with 75% of children ≤10 years having a metabolic abnormality compared with 60.6% of children >10 years ($p = 0.044$). The institutions were well matched with respect to the types of metabolic disorders present (Table 1), with hypercalciuria present on 24-h urine analysis