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Journal

Journal of Pediatric Urology, 16(3)

ISSN

1477-5131

Authors

Li, Yi
Bayne, David
Wiener, Scott
et al.

Publication Date

2020-06-01

DOI

10.1016/j.jpurol.2020.03.014

Peer reviewed

Journal of Pediatric Urology (2020) **16**, 373.e1–373.e6

Stone formation in patients less than 20 years of age is associated with higher rates of stone recurrence: Results from the Registry for Stones of the Kidney and Ureter (ReSKU)

Yi Li *, David Bayne, Scott Wiener, Justin Ahn, Marshall Stoller, Thomas Chi

University of California, San Francisco, Department of Urology, 400 Parnassus Ave., A610, San Francisco, CA 94143, USA

* Corresponding author.
yi.li3@ucsf.edu (Y. Li)
David.bayne@ucsf.edu (D. Bayne)
wienersc@upstate.edu (S. Wiener)
Justin.ahn@ucsf.edu (J. Ahn)
Marshall.stoller@ucsf.edu (M. Stoller)
Tom.chi@ucsf.edu (T. Chi)

Keywords
Nephrolithiasis; Stone Recurrence; Stone disease; Kidney stone; Pediatric nephrolithiasis; Pediatric stone disease

Received 9 September 2019
Accepted 17 March 2020
Available online 25 March 2020

Summary

Introduction
Nephrolithiasis is a major source of morbidity in the United States. In recent decades, there has been a notable increase in stone incidence in the pediatric population. We investigate whether recurrent stone formers who had their initial stone episode earlier in life are at risk for more frequent stone recurrences, compared to those with initial episodes later in life. We also examine possible risk factors that might change our approach to treatment of these patients.

Methods
A review of prospectively collected data from the Registry for Stones of the Kidney and Ureter (ReSKU) from September 2015 to July 2018 was conducted to compare stone recurrence and other patient factors in patients who reported an initial stone episode prior to 20 years of age versus patients who reported an initial stone episode after age 20. Data on patient age, gender, BMI, family history, race, income, infectious symptoms, and number of prior stone episodes was analyzed. We excluded patients with a history of cystinuria stones. Univariate analysis was performed using Fisher's exact test and student's T test. Multivariate analysis was performed using logistic regression.

Results
Of the 1140 patients enrolled during this study period, 472 patients were recurrent stone formers, and of these, 66 had their first stone episode prior to the age of 20. On univariate analysis, early stone formers were more likely to be female, present at a younger age, and have more prior stone episodes on enrollment. Using multivariate modelling to control for age, gender, race, BMI, family history, and number of stone episodes, early stone formers were more likely to be female (CI 1.17 – 3.54) and have more than one prior stone episode (CI 1.13 – 3.78). Late stone formers were more likely to have BMI > 30 (CI 0.26 – 0.94).

Conclusion
Recurrent stone formers who have their first episodes prior to age 20 are more likely to present to stone clinics with multiple prior recurrences and hence more aggressive stone disease. Female gender seems to be a risk factor. Earlier stone formers should be encouraged to have close follow up and surveillance due to the increased rate of recurrence. Adult stone databases focusing on early presentations can improve understanding of pediatric stone disease.

Summary Table

Patient Variables Associated with Early Versus Late Stone Formation

	Odds Ratio	Confidence Interval (2.5–97.5%)
Gender (Female)	2.03	**1.17–3.54**
Race (Non-caucasian)	0.83	0.46–1.47
BMI > 30	0.51	**0.26–0.94**
Family History of Nephrolithiasis	0.94	0.54–1.63
Infectious symptoms on Presentation	1.46	0.68–2.97
More than 1 prior stone episode	2.02	1.13–3.78

Patient variable associated with early stone formation. Multivariate analysis of associated patient factors comparing early vs late recurrent stone formers. Increased odds ratio indicates association with early stone former group. Statistically significant confidence intervals ($p < 0.05$) noted in bold.

https://doi.org/10.1016/j.jpurol.2020.03.014

Introduction

Nephrolithiasis is a common disease with high associated morbidity and healthcare costs. A major source of morbidity and cost in treating this systemic disease is due to its high recurrence rate. Adults who experience a first episode of a symptomatic stone have a 50% chance of radiological or symptomatic recurrence in the next 5–10 years [1]. Patients with recurrent nephrolithiasis account for increased emergency room visits, hospital costs, and procedural costs. These patients also have an associated increased risk of cardiovascular disease, chronic kidney disease, and fractures [2–6].

In the last few decades, incidence of nephrolithiasis in the pediatric population has grown approximately 4–10% annually and now affects upwards of 50 per 100,000 children per year [7]. Recurrent stone disease in the pediatric population brings additional complications as they are less likely to spontaneously pass similar sized distal ureteral stones[8,9] and are more likely to have monogenic causes of disease [10]. Other complicating factors include the need to limit radiation exposure in this population, and the need for repeat intervention due to re-treatments. Pediatric stone patients often need pre-stenting, as well as sedation for stent removal resulting in an increased exposure to anesthesia [11]. Recent studies have shown that pediatric patients tend to have a shorter time period to first recurrence and that patients who obtain a 24 hour urine sample after first stone episode have marked decrease in recurrence risk [12].

Pediatric stone formers appear to be a growing patient population with limited literature regarding population specific stone outcomes. This is partially due to limited number of patient databases available for retrospective and prospective analysis. There is an especially notable lack of data with regards to long-term follow-up in these patients as they age into adulthood. Given the limited data in this area of growing need, we use our prospectively collected adult stone database to retrospectively evaluate patients who had an initial stone episode in childhood. We hypothesize that recurrent stone patients who had an initial stone episode in childhood have a higher risk of multiple recurrences relative to recurrent stone formers who had an initial stone episode in adulthood.

Methods

Since November 2015, new patients presenting to the University of California San Francisco (UCSF) Urology Clinic for urinary stone disease management have been prospectively enrolled into the Registry for Stones of the Kidney and Ureter (ReSKU). Integrated with the electronic medical record (EMR), this registry collects and stores patient data

Table 1 Patient characteristics of recurrent stone formers who report initial stone episode prior to age 20 compared to recurrent stone formers with initial episode after age 20.

Patient Characteristics by Age of Initial Stone Episode			
	Initial stone before age 20 (n = 66)	Initial stone after age 20 (n = 406)	p value
Average age at enrollment	35	57	$p < 0.001$
Gender	41%	58%	$p = 0.011$
Male	59%	42%	
Female			
Race	71%	67%	$p = 0.572$
Caucasian	29%	33%	
Other			
BMI	23%	34%	$p = 0.088$
>30	77%	66%	
<30			
Family History	45%	42%	$p = 0.688$
Yes	55%	58%	
No			
Infectious symptoms	18%	13%	$p = 0.252$
Present	82%	87%	
Absent			
Stone recurrences	26%	40%	$p = 0.028$
1 prior episode	74%	60%	
>1 prior episodes			
Comorbidities	6.5%	16.6%	$p = 0.004$
Hypertension	14.4%	13.9%	$p = 0.773$
Chronic Kidney Disease	6.0%	15.3%	$p = 0.054$
Diabetes mellitus, type 2	2.0%	13.0%	$p = 0.451$
Diabetes mellitus, type 1			

Table 2 Prior stone procedures reported by patients at initial clinic presentation compared to age of first reported stone episode.

Prior Reported Stone Surgeries on Initial Presentation			
	Initial stone before age 20 (n = 66)	Initial stone after age 20 (n = 406)	p value
No prior stone procedures	36.4%	48.3%	p = 0.084
Ureteral stent placement	16.7%	12.3%	p = 0.325
Nephrostomy tube placement	1.5%	3.0%	p = 1.000
Ureteroscopy	54.5%	35.2%	p = 0.004
Percutaneous Nephrolithotomy	9.1%	7.9%	p = 0.807
Shock Wave Lithotripsy	45.5%	39.7%	p = 0.418
Open or Laparoscopic Stone Surgery	6.1%	2.5%	p = 0.118

specific to kidney stone disease. Data points are generated from the EMR notes providers create at clinic visits, surgical encounters, and follow up visits as a part of routine care. These data are automatically integrated and stored into this registry database. Included are 60 new patient visit variables, 80 perioperative variables, 64 postoperative care variables, and 64 follow up visit variables. The methodology and organization of this registry have been previously described [13]. All subjects enrolled in ReSKU provide written consent, and the study was approved by the Committee on Human Research (Protocol 14—14533).

We selected patients from the ReSKU database who presented to the clinic between November 2015 through July 2018 with at least one prior stone episode. Patients with a history of cystinuria and primary hyperoxaluria were excluded. As a part of the new patient intake data in the RESKu database, age of first stone episode (0—10 years, 10—20 years, 20—30 years, etc.) is recorded. For this study, we included only patients who reported at least one prior stone event that occurred before the stone episode that led to their initial presentation to our clinic. These recurrent stone formers were then split into two cohorts: patients with a reported initial stone episode prior to 20 years of age, and those who had an initial stone episode after age 20. Data on patient age, gender, BMI, family history, infectious symptoms at presentation, and number of prior stone episodes were analyzed. Multivariate analysis was performed using in R Statistical Software version 3.5.2.

Results

We identified 1140 patients in our stone database. 25 cystinuric patients were excluded. 472 remaining patients reported experiencing more than one stone episode prior to clinic presentation. Within this subset, 66 patients had their first stone episode prior to the age of 20. On univariate analysis, stone formers prior to age 20 were younger, more likely to be female, less likely to have hypertension, and have greater than two prior stone episodes before presenting (Table 1). Earlier stone formers were more likely to report prior ureteroscopic stone removal surgery at initial clinic presentation (Table 2). On multivariate analysis, recurrent stone formers who had an initial stone episode prior to age 20 were more likely to be female (CI 1.17—3.54) and have more than two prior stone episodes (p = 0.028). There was a significant association between BMI>30 and the late stone former group (CI 0.26—0.94) (Table 3).

Table 3 Patient variable associated with early stone formation. Multivariate analysis of associated patient factors comparing early vs late recurrent stone formers.

Patient Variables Associated with Early Versus Late Stone Formation		
	Odds Ratio	Confidence Interval (2.5—97.5%)
Gender (Female)	2.03	**1.17—3.54**
Race (Non-Caucasian)	0.83	0.46—1.47
BMI > 30	0.51	**0.26—0.94**
Family History of Nephrolithiasis	0.94	0.54—1.63
Infectious symptoms on Presentation	1.46	0.68—2.97
More than 1 prior stone episode	2.02	**1.13—3.78**

Increased odds ratio indicates association with early stone former group. Statistically significant confidence intervals (p < 0.05) noted in bold.

Discussion

Pediatric stone disease is morbid and understudied. Our results demonstrate that patients whose first stone episode occurred prior to age 20 were more likely to suffer stone recurrence over their lifetime compared to those whose first episode occurred later in life. To our knowledge, these data represent a first use of prospectively collected data specific to urinary stone disease to understand urinary stones in pediatric patients. Very few prospective registries for nephrolithiasis exist. Although we performed a retrospective review of data to understand how urinary stones presenting earlier in life can affect natural history later on, the data source was prospectively collected patient data from our ReSKU database. Our approach demonstrates one way in which registries can be applied to study pediatric diseases, even if their design was primarily for the study of adult diseases.

On univariate analysis, we found that patients who reported an earlier initial stone occurrence were younger in age at the time of presentation to the stone clinic. This is an expected finding given the study design and serves as confirmation for the validity of the data. We also found a significant association with the presence of hypertension ($p = 0.004$), as well as a trend towards significance with Type 2 diabetes ($p = 0.054$) in the older stone cohort, which we attribute to the differences in patient age (Table 1). Interestingly, there was no notable difference between rates of chronic kidney disease at presentation despite the difference in age between the two groups, which suggests that the younger cohort may be more prone to developing CKD at this earlier age. This finding is consistent with the known association between nephrolithiasis and worsening renal function, and suggests a need for prospective long term follow up in this earlier stone former group [10].

Gender discrepancies warrant discussion from our data. Among the younger patient cohort, the majority of recurrent stone formers were female. Gender remained a significant association after controlling for the other evaluated variables, including infectious symptoms. While nephrolithiasis has historically been a male dominated disease, this finding is consistent with recent trends in the pediatric population that have shown an increasing incidence of female nephrolithiasis over the last two decades [7,14]. There has been some conjecture that hormonal changes in puberty in combination with other environmental factors may play a role in this changing gender demographic, but a clear mechanism or pathology for this change in gender has yet to be elucidated [10]. Our findings indicate that young female patients who present with a stone episode are at higher risk for going on to develop recurrent stone disease compared to their older male counterparts.

Interestingly, our findings show that BMI greater that 30 was significantly associated with the late stone former group when controlling for other factors (CI 0.26—0.94) (Table 3). In our study, the significance of this finding may be confounded by lack of power, as only 18 patients in the early stone former group had BMI greater than 30 and were a significantly younger cohort. We also do not have the data regarding actual BMI in childhood for these patients, and therefore the BMI at clinic presentation may not be an accurate model for BMI at time of initial stone episode. Obesity has been shown to be a risk factor for stone disease in the adult population [15]. Prior studies indicate that obese adult patients have lower urine pH and increased sodium and uric acid secretion [15]. This finding has been shown in pediatric patients as well [16]. It has been theorized that the increase in obesity in the pediatric population has been one of the driving factors influencing the increased incidence of pediatric stone disease. However, individual studies have not shown association between increased BMI and increased stone incidence in the pediatric population [16].

In our study, we found early stone formation to be significantly associated with multiple stone recurrences. Tasian et al. recently published a retrospective cohort study of pediatric patients evaluating time to first recurrence in this population. They found that in patients aged 3—18 years old, there was a 50% recurrence rate at 3 years after first episode [12]. They also found that obtaining a 24 hour urine specimen significantly decreased risk of stone recurrence [12]. Unfortunately, due to the retrospective nature of the study, only a third of the patients in this cohort had any data on 24 hour urine specimens. Therefore, we were unable to replicate Tasian et al. findings, or comment on any significant differences in urine metabolites between the groups. Our data does demonstrate that early stone formers were more likely to have had more than one recurrence versus later stone formers when controlled for age and other factors. This further emphasizes the severity of the disease in patients who present in childhood. In this cohort, stone recurrence happens at an earlier interval and with higher frequency.

On univariate analysis, we found that patients with earlier stone disease self-reported higher rates of prior ureteroscopy on first presentation to our clinic (Table 2). Only 36.4% of early stone formers reported no prior stone procedures, compared to 48.3% of later stone formers when they first present. The higher rates of past surgical interventions correlate with higher number of prior stone episodes, and may indicate more aggressive disease as well. Further prospective studies are needed in order to determine if this cohort requires more surgical interventions over time, which increases both patient morbidity and financial burden.

Guerra et al. compared family history of stones with stone recurrence and found no association, which is also reproduced in our study [17]. We included infectious symptoms on presentation in our clinic as a surrogate to evaluate for presence of infectious stones, which historically is more prevalent in pediatrics and in female patients [2]. While not a perfect marker for infectious stones, it did not have any significant effect on our findings when this variable was included in the multivariate analysis. Of note, calcium-based stones remain the most common stone type even in the pediatric population, and this finding is confirmed in our limited stone analysis data [18]. Caucasian race is also historically a risk factor for increased prevalence of nephrolithiasis [2]. In our study, race did not play a significant role in age of initial stone presentation.

This study is limited by potential recall bias as data on prior stone episodes and surgeries are completely based on patient memory. Patients who form stones earlier may be biased towards recalling more stone events than actual. Prior studies by Curhan et al. investigated ascertainment bias and showed that patients recall stone episode dates with great accuracy (89/90 patients with accurate survey recall when checked against the medical record) [19,20]. This supports patient recall as an accurate representation of initial stone event timing. This bias would also not explain a higher incidence in female patients.

Another limitation of our study is the retrospective analysis of a prospectively collected data set. The data was not initially collected with this study in mind. As a result, we do not have the specific age at initial stone episode (only the decade), nor the timing of recurrent events. This limits our ability to characterize the number of recurrences over time for each patient. We are only able to describe the total number of stone episodes overall when discussing stone recurrence in this group.

The single institution nature of this study represents a possible source of selection bias, as subjects were recruited from a tertiary stone referral center. In addition, there was an overall relatively small number of subjects available for analysis, lowering the power of the study compared to larger claims-based database studies. However, with the exception of BMI, the relative proportions of each clinical characteristic within our study population were large, supporting that our findings represent true statistical significance. Additional larger, multi-institutional studies are under way incorporating other clinical sites where ReSKU registries have been implemented to validate the current findings.

Additionally, there may be some variation comparing patients under age 20 with the general pediatric literature, which is often variable in its definition of pediatric patients. In our experience, patient recall is much clearer regarding decade of life versus before or after age 18. ReSKU therefore divides patients into these categories. However, the ability to retrospectively evaluate prospectively collected adult stone database patients serves as an excellent resource for investigating this patient population, which otherwise has limited patient databases from which to extrapolate data. This method of looking at pediatric patients in our adult ReSKU database affords us an avenue for further investigation, which can include metabolic workup of these patients and stone composition to evaluate any differences in metabolic state between these cohorts. Use of combined adult-pediatric registries would be valuable to further understand this question as well. The younger group's higher rates of recurrence places them at risk for more procedures, imaging, and other health services. This could also be evaluated further to better elucidate long term patient outcomes in this pediatric stone forming group.

Conclusion

Nephrolithiasis is a difficult disease to treat due to its high recurrence rate. Patients with nephrolithiasis are at higher risk for recurrence if they are female and present with an initial stone episode prior to age 20. Patients who have an early initial stone episode are more likely to have more than one prior stone episode on presentation to our clinic. Obesity was found to be significantly associated with a later initial presentation. Young patients presenting with an initial stone episode should be closely followed, referred early to a stone specialist, and transitioned carefully to an adult urologist as they mature to help mitigate increased risk of stone recurrence in this vulnerable population. Female patients in particular appear to be at increased risk and should be counselled and risk stratified as such by a stone specialist. Longitudinal databases than span both pediatric and adult care are needed to fully understand the natural history of the disease.

Conflicts of interest

There are no conflicts of interests associated with this publication.

Disclosures

Dr. Marshall Stoller and Dr. Thomas Chi are consultants for Bard and Boston Scientific.

Ethical approval for this study was not required. All subjects enrolled in ReSKU provide written consent, and the study was approved by the Committee on Human Research (Protocol 14—14533).

Funding

This study was funded through the NIH NIDDK Grant.
Grant P20DK116193.

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