Urol Res (2010) 38:453–457
DOI 10.1007/s00240-010-0327-9

SYMPOSIUM PAPER

Epidemiologic insights into pediatric kidney stone disease

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Received: 29 September 2010 / Accepted: 1 October 2010 / Published online: 22 October 2010

Abstract The epidemiology of pediatric kidney stone has not yet been as rigorously defined as that of adult kidney stone disease. Herein, we review our recent epidemiologic works characterizing pediatric stone disease using the Kids' Inpatient Database (KID). Specifically we investigated the age and gender distribution of pediatric kidney stone disease, changes in disease prevalence over time, and medical comorbidities associated with this disorder. We identified patients by International Classification of Disease 9th Edition (ICD-9) codes for renal and ureteral calculi as the primary diagnosis. Medical comorbidities were identified using specific comorbidity software. Statistical comparisons between children with and without stone disease were performed. In the first decade of life, stone disease was more prevalent among males than females; however, in the second decade of life females were more commonly affected. Of note, there was a significant increase in treated stone disease across both genders between 1997 and 2003. We also found that the risk of kidney stone diagnosis in children younger than 6 years of age was significantly associated with hypertension and diabetes mellitus. The gender distribution among pediatric stone formers varies significantly by age, although overall females have a greater prevalence than males. There is also a strong association of stone disease and both diabetes and hypertension, although this was only observed in children less than 6 years of age. Taken all together, these findings suggest that urolithiasis in the young child is a complex systemic disease process.

Keywords Kidney · Calculi · Pediatric · Epidemiology

Proceedings paper from the 3rd International Urolithiasis Research Symposium, Indianapolis, Indiana, USA, December 3–4, 2009.

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Introduction

Classically, the epidemiology of kidney stone disease, a disease affecting the adult population, is rapidly changing. Recent years have witnessed a marked increase in the prevalence of this disorder; Stamatelou and associates [1] reported a 37% increase between 1980 and 1994. The gender distribution of adult stone formers is also evolving. Once reported to be approximately 12% for men and 6% for women, Scales and associates [2] have reported that these numbers may be moving closer toward parity. These increasing numbers are of particular concern, given the cost of treating of stone disease: Pearle and associates, [3] as part of the Urologic Diseases in America project, reported that kidney stones cost over two billion dollars per year in the USA. This figure underestimates the burden of the disease on society when one considers metrics such as quality of life.

The epidemiology of pediatric kidney stone disease has not yet been as rigorously defined as that of adult kidney stone disease. Such epidemiologic investigations are of great importance, though, as they allow an objective assessment of the burden of disease, and how this burden may change over time. In addition, an understanding of the epidemiology of disease may allow the identification of risk factors associated with disease progression or severity. Importantly, epidemiologic studies may provide unique insights into disease pathophysiology. Herein, we review

our recent studies characterizing the epidemiology of pediatric kidney stone disease using the Kids' Inpatient Database (KID), a large-scale national data set that captures childrens' use of hospital services. Specifically, we investigated the age and gender distributions of pediatric kidney stone disease, changes in disease prevalence over time, and medical comorbidities associated with kidney stone disease in children.

Methods

The KID is a part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). This is a sample of discharges from all community, non-rehabilitation hospitals in states participating in the HCUP. The KID contains information on all patients, regardless of payer, including persons covered by private insurance, Medicaid, Medicare, and the uninsured. The KID includes a core set of patient data found in a typical discharge abstract, such as demographics (e.g., age, gender), diagnostic codes, procedure codes, payer and financial data, and discharge disposition. The KID does not contain physiologic or laboratory patient data. KID data are collected and compiled in a uniform manner from all participating states. We evaluated three iterations of the KID: 1997, 2000, and 2003. The 1997 version contains 1,905,797 total discharges from 22 states; the 2000 version contains 2,516,833 total discharges from 27 states; and the 2003 version contains 2,984,129 total discharges from 36 states.

For the studies reviewed herein, we identified patients by International Classification of Disease 9th Edition, Clinical Modification (ICD-9-CM) codes for renal calculus (592.0) and ureteral calculus (592.1) as the primary diagnosis. Medical comorbidities were identified using the AHRQ Comorbidity Software, which is a tool that assigns variables to ICD-9-CM comorbidities found in hospital discharge records. The Comorbidity Software was used to identify the variables for diabetes mellitus (DM), hypertension (HTN), and obesity among those children admitted for a renal or ureteral stone. Race data was not available for one-third of the included states; thus, this variable was not included in our analyses. Comparisons between children with and without pediatric stone disease were based on the *t* test for comparison of continuous variables, and Chi-square test for comparison of categorical variables. The risk of stone disease was evaluated with univariate and multivariable logistic regression models. Cross-product terms were entered into the models to evaluate interactions between age and comorbidities, and was evaluated using the likelihood ratio test.

Results

Our initial analysis was to define the prevalence of stone disease in the pediatric population. In the first decade of life, stone disease was more prevalent among males than among females. However, in the second decade of life, females were more commonly affected than males. Within a single sex, the distribution by age group changed from 1997 to 2000, but remained constant in the 2000 and 2003 data sets. Of note, there was a dramatic increase in treated stone disease across both genders. The rate of increase was greater among the female gender, 365%, than among the male gender, 274%. These data are presented as Table 1.

Our next analyses were directed toward identifying medical comorbidities associated with a diagnosis of stone disease. In univariate analyses the risk of a kidney stone diagnosis was significantly associated with age, gender, DM, HTN, and obesity (Table 2). In a multivariable logistic regression model, though, only age was significantly associated with the diagnosis of a kidney stone; there was a more than 30-fold increase in risk between the youngest and oldest age groups. Although none of the comorbidities were significantly associated with stone disease in the multivariable model, we performed exploratory analyses to

Table 1 Age and gender distribution among pediatric stone formers

Age quartile (years)	1997		2000		2003	
	Male *n* (%)	Female *n* (%)	Male *n* (%)	Female *n* (%)	Male *n* (%)	Female *n* (%)
0–5	98 (60)	66 (40)	111 (54)	95 (46)	168 (55)	111 (45)
6–10	136 (57)	101 (43)	208 (53)	186 (47)	269 (57)	256 (43)
11–15	213 (44)	275 (56)	327 (45)	401 (55)	452 (49)	589 (51)
16–20	299 (26)	852 (74)	954 (27)	2645 (73)	1153 (23)	3766 (77)
Total	746 (37)	1294 (63)	1600 (32)	3327 (68)	2042 (30)	4722 (70)
p value	<0.0001		<0.0001		<0.0001	

The numbers in parentheses represent the percentages of male and female stone patients in each age group. The *p* value represents the difference in age distribution between males and females for the given year

Table 2 Risk factors for pediatric kidney stone disease based on 2003 Kids' Inpatient Database: univariate and multivariable logistic regression analyses

Variables	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)				
6–10 versus 0–5	15.28 (13.22, 17.66)	<0.0001	15.84 (13.70, 18.32)	<0.0001
11–15 versus 0–5	22.98 (20.14, 26.22)	<0.0001	23.02 (20.17, 26.28)	<0.0001
16–20 versus 0–5	37.60 (33.34, 42.41)	<0.0001	37.28 (32.99, 42.10)	<0.0001
Gender				
Female versus male	1.97 (1.87, 2.07)	<0.0001	1.04 (0.99, 1.10)	0.121
Hypertension				
Yes versus no	1.96 (1.59, 2.41)	<0.0001	1.06 (0.86, 1.31)	0.592
Diabetes				
Yes versus no	2.08 (1.58, 2.73)	<0.0001	0.90 (0.68, 1.19)	0.445
Obesity				
Yes versus no	2.14 (1.77, 2.59)	<0.0001	1.01 (0.83, 1.22)	0.953

Table 3 Interaction between age and either hypertension or diabetes on the risk of pediatric kidney stone disease

Variables	OR (95% CI)	*p* value
Hypertension versus no hypertension		
Age 0–5	13.90 (7.15, 27.03)	<0.0001
Age 6–10	1.79 (0.92, 3.46)	0.085
Age 11–15	0.84 (0.46, 1.52)	0.566
Age 16–20	0.911 (0.71, 1.17)	0.471
Diabetes versus no diabetes		
Age 0–5	22.50 (5.58, 90.66)	<0.0001
Age 6–10	1.02 (0.25, 4.09)	0.980
Age 11–15	0.80 (0.38, 1.69)	0.567
Age 16–20	0.87 (0.64, 1.20)	0.396

consider whether the effects of each of the comorbidities may be modified by age. This was motivated by the known associations of these comorbidities with adult urolithiasis, and the concern that any associations might be masked by the effect of age. We found that the risk of kidney stone diagnosis in children younger than 6 years of age may be significantly associated with HTN and DM, with odds ratios of 13.9 [95% confidence interval (CI) 7.2–27.0] and 22.5 (95% CI 5.6–90.7), respectively (*p* values for interaction < 0.0001 and 0.028, respectively) (Table 3). In contrast, among children aged 6 and older, there was no significant relationship among a diagnosis of stone disease and these comorbidities.

Discussion

The gender distribution of pediatric stone disease differs from adults and appears to change during childhood. While boys are affected more commonly in the first decade, girls predominate in the second. Because of the lack of prior studies such as our present work, it is not known whether this change represents a shift or the natural pattern with adolescence introducing either physiologic or sex-specific environmental changes. In a study of first-degree relatives of stone formers, Bergsland et al. [4] reported that age and gender had a profound influence on calcium oxalate parameters in urine. Among non-stone-forming relatives, younger patients and males demonstrated higher levels of calcium oxalate supersaturation and crystal growth inhibition. The difference in growth inhibition was lost, however, in stone forming patients. These authors hypothesized that the loss of this inhibition might play a role in the rising incidence of nephrolithiasis in young males starting in the third decade. The present data would suggest that this pattern of male inhibition might be even more pronounced during the second decade of life.

Puberty marks a time of great growth and hormonal changes, which can plausibly affect stone pathogenesis. Heller et al. [5] have investigated hormonal effects on calcium oxalate stone formation, comparing the urine chemistries of post-menopausal women with and without estrogen replacement. These authors noted that estrogen treatment resulted in a lowering of urinary calcium excretion and calcium oxalate saturation. The predominance of female stone formers in the second decade of life could represent a lithogenic effect of estrogen in females or a protective effect of testosterone in males. It is also possible that the primary effect of the hormones on stone formation is not directly on urine chemistry, but on body habitus and such an effect on stone pathogenesis may be secondary. The impact of estrogen stimulated adiposity and enhanced bone mineralization in young females after puberty on urine chemistry and stone formation is not known.

Our analysis of the KID databases suggests that the prevalence of stone disease appears to be increasing in the pediatric population [6]. VanDervoort et al. [7] originally proposed such a rise in the pediatric patient population when they reported a 4.6-fold increase in outpatient pediatric stone encounters at a single institution between two time points (1994–1996 and 2003–2005). Sas and associates [8] reported that the incidence of kidney stone disease has risen in the state of South Carolina between 1996 and 2007. Our report lends support to this claim, as we provide a statistically robust analysis of the pediatric population. In fact, our data may even underestimate the true prevalence of pediatric stone disease, as the KID database captures only inpatient visits. The question of why pediatric stone disease may be increasing is a complicated one that will require prospective hypothesis-testing trials to answer. The coincident rise in obesity during this same time period may have a causative role. The prevalence in adult obesity doubled between 1980 and 2002; however, in children aged 6–19 years, it nearly tripled in the same time period [9]. In a prospective, epidemiologic study of three large cohorts, Taylor et al. [10] noted an increased risk of nephrolithiasis in adult patients who were overweight or obese. A cross-sectional analysis of adults over the age of 20 from NHANES III reported that metabolic syndrome traits are associated with a self-reported history of kidney stones [11].

Our investigation of a large-scale cohort of pediatric patients demonstrates that pediatric stone disease is a complex systemic disorder. Our analyses demonstrated statistically significant associations between the diagnosis of a kidney stone and both HTN and DM for children at 5 years of age or younger, but not for older children. Although statistically significant associations were observed for both HTN and DM, any interpretation of these findings must be tempered by the small numbers of children with both stones and comorbidities. These results, although provocative, should be viewed as tentative and hypothesis-generating, and further studies are required to confirm or refute these findings.

Among adults, both HTN and DM have been associated with lithogenic changes to the urinary milieu [10, 12]. Hypertension, diabetes, and obesity in childhood are likely very different entities, with different etiologies, compared to the same disease in adults; but nonetheless there may still be certain similar pathophysiologies which affect urinary metabolic stone risk factors. Insulin resistance, the pathognomonic feature of non-insulin dependent DM, has been implicated in the increased risk of stone formation among diabetics. In particular, insulin resistance reduces urinary pH, which promotes uric acid stone formation [13]. An association between HTN and stone disease among adults has also been reported [14]. Calcium stone risk may be elevated in the setting of hypertension, as hypercalciuria and hypocitraturia have been more commonly encountered in hypertensive subjects [15]. Further study is needed to more clearly elucidate the lithogenic mechanisms associated with certain medical conditions, especially in the pediatric population where such information is very limited.

Despite the strong association of hypertension, obesity, and diabetes with adult urolithiasis, we did not find similarly strong associations across the entire pediatric population. Future studies with larger numbers of children are required to further investigate this hypothesis, and better define this relationship. At present, it is not clear why the associations we detected were significant only among those children younger than 6 years of age. Although one would expect that the relationship between stone diagnosis and comorbidity would be constant throughout childhood, several possibilities could explain our findings. Stone disease among the very young may also be associated with greater systemic effects. One might also consider that HTN and DM in the very young may be markers for overall poor health and systemic disease, which could also increase the risk for stone formation. Future prospective studies may be able to examine this question in greater detail, with the benefit of more granular, patient-level data collection.

It is worth considering that the histopathology of stone formation varies among the stone forming phenotypes [16]. Certain pathophysiologies are associated with renal tubular damage and plugging, whereas others are not. One might suspect that if the underlying pathology in children is associated with tubular damage and plugging, there may be more severe long-term effects on renal function. Conversely, for phenotypes not associated with tubular injury, long-term consequences may be less severe. Future efforts, making use of granular, patient-specific data, may better address these important questions.

Conclusions

The gender distribution among pediatric stone formers varies significantly by age; in the first decade of life, males predominate, whereas in the second decade of life, females predominate. Overall, females in the pediatric population have a greater prevalence of treated stone disease than do males. There is also a strong association between the primary diagnosis of a kidney stone and both DM and HTN, although we only observed the association in those children under the age of 6 years. Our study suggests that urolithiasis in the young child may be a unique and complex systemic disease process. Clinicians treating the young stone-former, then, should be aware of these associated disease states, as they pursue the evaluation and treatment of this unique group of patients. Future efforts, which incorporate

both ambulatory treatment settings as well as patient-specific laboratory data, should build upon our novel findings and continue to define the relationship between medical comorbidity and stone disease, as has already been done in the adult population.

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