HHS Public Access

Author manuscript

Urology. Author manuscript; available in PMC 2015 December 30.

Published in final edited form as:

Urology. 2011 January ; 77(1): 195–199. doi:10.1016/j.urology.2010.06.062.

Medical Comorbidities Associated With Pediatric Kidney Stone Disease

Anthony J. Schaeffer, **Zhaoyong Feng**, **Bruce J. Trock**, **Ranjiv I. Mathews**, **Alicia M. Neu**, **John P. Gearhart**, and **Brian R. Matlaga**

James Buchanan Brady Urological Institute and Division of Pediatric Nephrology, Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

OBJECTIVES—To characterize the relationship between pediatric kidney stone disease and the presence of hypertension (HTN), diabetes mellitus (DM), and obesity. In adults, kidney stone disease has been associated with medical comorbidities such as HTN, DM, and obesity. Similar analyses have never been performed for the pediatric population.

METHODS—The 2003 and 2006 Kids' Inpatient Databases were queried to identify subjects treated for kidney stone disease ("International Classification of Diseases" codes 9592.0 and 592.1). The comorbidities of HTN, DM, and obesity were identified using the provided comorbidity software. The risk of kidney stone disease associated with age, sex, and comorbidity status was evaluated using multivariate logistic regression.

RESULTS—A total of 6 115 443 subjects were evaluated. Of these, 14 245 (0.2%) had a diagnosis of upper tract calculus (4092 boys and 10 045 girls, sex unavailable for 108). Age was the strongest independent predictor of stone risk ($P < .0001$). HTN was associated with a significantly increased risk of stone diagnosis in children ≤10 years old and DM for children ≤5 years old. Stone risk was not affected by obesity in any age group.

CONCLUSIONS—The results of our study have shown that kidney stone disease is significantly associated with age among all children and both HTN and DM for young children. Although exploratory, these findings are novel and suggest that kidney stone disease among young children might be associated with nonrenal, systemic disease states.

Kidney stones are a common and costly disease, affecting both adults and children. Among adults, the epidemiology of kidney stone disease has been well characterized. The lifetime prevalence has been approximately 12% for men and 6% for women, although for both sexes these percentages have recently been increasing.[1–3] The insights gained from epidemiologic investigations of adult patients with stone formation have suggested that certain medical conditions, such as diabetes mellitus (DM), hypertension (HTN), and obesity, are independently associated with kidney stone disease.[4–7]

Reprint requests: Brian R. Matlaga, M.D., M.P.H., James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287. bmatlaga@jhmi.edu.

Our understanding of the epidemiology of pediatric kidney stone disease, however, is limited. It has been reported that the prevalence of stone disease among children varies by age and sex[8]; nonetheless, a paucity of information is available on the systemic medical conditions that might be associated with stone disease. In particular, important comorbidity associations, such as DM, HTN, and obesity, previously characterized among adult patients with stone formation, have not yet been investigated in the pediatric population. Ostensibly, children and adults are physiologically different, and the risk factors associated with stone disease could also vary during a lifetime; therefore, it is of great importance to explore the risk factors for stone disease in the pediatric population. For children, the identification of specific risk factors associated with stone disease could provide unique insights into the pathophysiology of stone formation. Therefore, we performed a study to define the relationship between kidney stone disease and the presence of DM, HTN, and obesity in a pediatric population.

MATERIAL AND METHODS

The Kids' Inpatient Database (KID) is a large-scale, national data set that captures typical discharge information, such as demographics (eg, age, race, sex), diagnostic codes, procedure codes, admitting diagnosis, and discharge disposition from inpatient hospitals. The database contains information for all patients, regardless of payer, and includes children covered by private insurance, Medicaid, and Medicare and the uninsured. The KID is a part of the Healthcare Cost and Utilization Project, which has been sponsored by the Agency for Healthcare Research and Quality. It was developed to enable analyses of hospital use by children across the United States. Systematic random sampling is used to ensure accurate sampling of the KID. The geographic distribution of the KID is diverse, such that no regions of the United States have been overrepresented, which could have skewed the census of patients with stone formation. Although the KID captures a core set of patient data found from a typical discharge abstract, it does not contain physiologic or laboratory data.

For the present study, we analyzed the 2003 and 2006 KIDs. The 2003 iteration contains 2 984 129 total discharges from 36 states, and the 2006 iteration contains 3 131 324 discharges from 38 states. The 2003 and 2006 data sets were pooled for analysis. The "International Classification of Diseases, 9th revision, Clinical Modification" codes for renal calculus (592.0) and ureteral calculus (592.1) were used to classify the primary diagnosis. Medical comorbidities were identified using the Agency for Healthcare Research and Quality comorbidity software program, a tool that assigns variables to the "International Classification of Diseases, 9th revision, Clinical Modification" comorbidities found in the hospital discharge records. The comorbidity software was used to identify the variables for DM (CM_DM), HTN (CM_HTN_C), and obesity (CM_OBESE) among those children admitted for a renal or ureteral stone. Race data were not available for one third of the included states. Thus, this variable was not included in the analysis.

Comparisons between the children with and without pediatric stone disease were done using the *t* test for continuous variables and the chi-square test for categorical variables. The risk of stone disease was evaluated using univariate and multivariate logistic regression models.

Cross-product terms were entered into the models to evaluate interactions between age and comorbidities and evaluated using the likelihood ratio test.

Our institutional review board found the present study to be exempt from the requirement of review.

RESULTS

Of the total discharges captured in the 2003 and 2006 KIDs, 14 245 (0.2%) were for a primary diagnosis of a renal or ureteral calculus. Children who had been diagnosed with stones were significantly older than those without stones (median age 18 vs 2 years), and the fraction of children with stones, albeit very small, increased strongly with age. Girls (0.31%) were more commonly diagnosed with a stone than were boys (0.15%), by a 2:1 ratio. Children with DM, HTN, or obesity had twice the prevalence of kidney stones (Table 1).

On univariate analysis, the risk of a kidney stone diagnosis was significantly associated with age, sex, DM, HTN, and obesity. When these were entered simultaneously in a multivariate logistic regression model, only age was significantly associated with the diagnosis of a kidney stone, with a >30-fold increase in risk between the youngest and oldest age groups (Table 2). Although only HTN was significantly associated with stone disease in the multivariate model, we performed exploratory analyses to consider whether the effects of DM and obesity could have been modified by age (interaction). This was motivated by the known associations of these comorbidities with adult urolithiasis, and the concern that, given the small numbers of children with both stones and comorbidities, any associations might have been masked by the effect of age. We stratified age into four 5-year age groups. These were represented in the logistic regression models by 3 indicator variables, and the interaction of each of the comorbidities individually with age group were explored in separate models. The results listed in Table 3 demonstrate that the risk of kidney stone diagnosis in children <10 years old might be significantly associated with HTN (model 1; odds ratio 13.74 for age 0–5 years and 2.24 for age 6–10 years; $P < .0001$ for both cohorts). Model 2 (DM) demonstrated that the risk of a kidney stone diagnosis in children <6 years old was significantly associated with DM (odds ratio 11.34; $P = .0006$; Table 4). In contrast, among the other cohorts of children, the 95% confidence intervals for the effect of either HTN or DM included the null value of 1.0. We repeated these analyses, excluding children <1 year from the youngest age group, and the relationships did not change (data not shown). Obesity was not significantly associated with stone disease risk among children in any age group (data not shown). Because of the very small proportions of children with stones and both HTN and DM, we did not evaluate both comorbidities simultaneously in the multivariate model, because this would have required a 3-way interaction and resulted in unstable estimates.

These analyses were also repeated for the 2003 and 2006 data sets separately, and the results were not different from the pooled analyses (data not shown).

COMMENT

Once thought to be a disorder with effects limited to the kidney, recent epidemiologic evidence has suggested that nephrolithiasis among adults is a complex and systemic disease.[5–7,9,10] Our investigation of a large-scale cohort of pediatric patients has similarly demonstrated that pediatric stone disease is a complex entity. Our initial analysis confirmed that the likelihood of an upper urinary tract stone increased most strongly with a child's age, a finding reported previously.[8] From a concern that the profound effect of age on stone risk might mask the effects of the medical comorbidities of interest, we developed an interaction model that explored the effect of the comorbidity of interest within specific age groups to assess the relationship to a stone diagnosis. These analyses demonstrated statistically significant associations between the diagnosis of a kidney stone and both HTN and DM for young children, but not for older children. Although statistically significant associations were observed for both HTN and DM, they must be tempered by the small numbers of children with both stones and comorbidities, the consequently wide confidence intervals, and the exploratory nature of these analyses. Additionally, the KIDs only capture inpatient admissions. Therefore, these results should be viewed as tentative and hypothesis generating. Additional studies are required to confirm or refute the present findings. An examination of the KID, however, found that a large proportion of the 0–5-year-old cohort included children <1 year old. Given that this young cohort might have been overpopulated with children hospitalized in the neonatal intensive care unit, we performed the analysis both including and then excluding children <1 year old. Our findings did not differ between the 2 analyses, suggesting that our results were not affected by the disproportionate representation of children aged <1 year. No significant associations between stone risk and obesity were present for children in any age group.

Among adults, both HTN and DM have been associated with lithogenic changes to the urinary milieu. HTN, DM, and obesity in childhood are likely very different entities, with different etiologies compared with the same disease in adults. Nonetheless, certain similar pathophysiologic features could still be present that affect urinary metabolic stone risk factors. Insulin resistance, the pathognomonic feature of noninsulin-dependent diabetes mellitus, has been implicated in the increased risk of stone formation among patients with DM. In particular, insulin resistance reduces urinary pH, promoting uric acid stone formation.[11,12] Calcium stone risk is also elevated in the setting of insulin resistance, because of reduced citrate excretion and the resultant hypocitraturia.[13] Numerous studies have also demonstrated an association between HTN and stone disease among adults.[4,7] Calcium stone risk might be elevated in the setting of HTN, because hypercalciuria and hypocitraturia have been more commonly encountered in patients with HTN.[14,15] Additional study is needed to more clearly elucidate the lithogenic mechanisms associated with certain medical conditions, especially in the pediatric population for whom such information is very limited.

Our results have further strengthened the finding that age is the most significant predictor of kidney stone risk. Despite the strong association of HTN, DM, and obesity with adult urolithiasis, we did not find similarly strong associations across the entirety of the pediatric population. Future studies with larger numbers of children are required to investigate this

hypothesis further and better define this relationship. At present, it is not clear why the associations we detected were significant only among those children <6 years old. 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 might also be associated with greater systemic effects. Also, HTN and DM in the very young could be markers for overall poor health and systemic disease, which could increase the risk of stone formation. Similarly, conditions that require certain medical therapies that might induce HTN or DM, as well as stone disease, could also have confounded our findings; presumably such conditions would be uncommon. However, the diagnosis codes for specific congenital obstructive uropathies, such as posterior urethral valves and ureteropelvic junction obstruction, known risk factors for both stone disease and HTN in childhood, are not captured in the KID. Finally, given the overall small numbers of children with stones in the present analysis of an extraordinarily large data set, we cannot discount the possibility of a false-positive association. Future prospective studies might be able to examine this question in greater detail, with the benefit of more granular, patient-level data collection.

Our study had several limitations that merit mention. Some of these limitations are inherent to the use of an administrative claims database. Erroneous and incomplete coding (ie, failing to list the codes for all diagnoses relevant to a given admission) could have limited our ability to capture all events. The specific criteria for, or definitions of, HTN, DM, and obesity might vary among practice settings. Additionally, the KID cannot discriminate between noninsulin-dependent DM and insulin-dependent DM. Finally, granular laboratory data were not available; in particular, stone composition data would have been welcome and could have provided important insights into the relationship of medical comorbidity and stone disease. Race information was not provided for more than one quarter of the included states and thus was not included in our analysis. The KID includes only inpatient admissions, and one could argue that most stone removal procedures are performed on an outpatient basis. To that end, however, our study might have underestimated the true magnitude of the disease burden, because many patients would not have been included in the present data set. Additionally, our results might reflect a selection bias if children with stones and more severe comorbidities were hospitalized preferentially to those with stones who were otherwise healthy. Despite these limitations, the present hypothesis-generating work strengthens the known association of increasing age as a risk factor for stone disease. It also raises the possibility that stone disease could be more prevalent in young children with HTN or DM.

CONCLUSIONS

The risk of a diagnosis of an upper urinary tract calculus among children was most significantly associated with the child’s age. Also, a strong association was seen between the primary diagnosis of a kidney stone and both HTN and DM, although this association was confined to children <6 years old and resulted from an exploratory analysis. Future studies with larger numbers of affected children are needed to further explore whether children with DM and HTN have a greater risk of stone formation. If this finding is supported, it could suggest that urolithiasis in the young child is a unique and complex systemic disease

process. Clinicians treating the young patients with stone formation would need to be aware of these associated disease states as they pursue the evaluation and treatment of this unique group of patients.

Acknowledgments

This study was supported in part by Award T32DK007552 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.

References

1. Johnson CM, Wilson DM, O'Fallon WM, et al. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979; 16:624–631. [PubMed: 548606]
2. Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–94. Kidney Int. 2003; 63:1817–1823. [PubMed: 12675858]
3. Scales CD Jr, Curtis LH, Norris RD, et al. Changing gender prevalence of stone disease. J Urol. 2007; 177:979–982. [PubMed: 17296391]
4. Borghi L, Meschi T, Guerra A, et al. Essential arterial hypertension and stone disease. Kidney Int. 1999; 55:2397–2406. [PubMed: 10354288]
5. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005; 293:455–462. [PubMed: 15671430]
6. Daudon M, Jungers P. Diabetes and nephrolithiasis. Curr Diab Rep. 2007; 7:443–448. [PubMed: 18255008]
7. Cappuccio FP, Siani A, Barba G, et al. A prospective study of hypertension and the incidence of kidney stones in men. J Hypertens. 1999; 17:1017–1022. [PubMed: 10419076]
8. Novak, TN.; Trock, BJ.; Lakshmanan, Y., et al. Gender distribution of pediatric Stone formers. In: Evan, AP.; Lingeman, JE.; McAteer, JA., et al., editors. Renal Stone Disease 2. 2nd International Urolithiasis Research Symposium. Vol. 1049. Melville, NY: American Institute of Physics; 2008. p. 338-341.
9. Sakhaee K. Nephrolithiasis as a systemic disorder. Curr Opin Nephrol Hypertens. 2008; 17:304–309. [PubMed: 18408483]
10. Obligado SH, Goldfarb DS. The association of nephrolithiasis with hypertension and obesity: a review. Am J Hypertens. 2008; 21:257–264. [PubMed: 18219300]
11. Pak CY, Sakhaee K, Moe O, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology. 2003; 61:523–527. [PubMed: 12639639]
12. Daudon M, Traxer O, Conort P, et al. Type 2 diabetes increases the risk for uric acid stones. J Am Soc Nephrol. 2006; 17:2026–2033. [PubMed: 16775030]
13. Cupisti A, Meola M, D'Alessandro C, et al. Insulin resistance and low urinary citrate excretion in calcium stone formers. Biomed Pharmacother. 2007; 61:86–90. [PubMed: 17184967]
14. Strazzullo P, Nunziata V, Cirillo M, et al. Abnormalities of calcium metabolism in essential hypertension. Clin Sci Lond. 1983; 65:137–141. [PubMed: 6305548]
15. Taylor EN, Mount DB, Forman JP, et al. Association of prevalent hypertension with 24-hour urinary excretion of calcium, citrate, and other factors. Am J Kidney Dis. 2006; 47:780–789. [PubMed: 16632016]

Table 1

Demographic characteristics

	Kidney Stone Diagnosis		
Characteristic	**No (n)**	**Yes (n)**	***P* Value**
Children	6 101 208 (99.8)	14 245 (0.2)	NA
Age (y)			<.0001
0–5	3 478 200 (99.98)	605 (0.02)	
6–10	411 486 (99.7)	1077 (0.3)	
11–15	538 927 (99.6)	2182 (0.4)	
16–20	1 637 088 (99.4)	10 331 (0.6)	
Sex			<.0001
Male	2 766 204 (99.85)	4092 (0.15)	
Female	3 264 349 (99.69)	10 045 (0.31)	
HTN			<.0001
No	6 052 728 (99.77)	14 004 (0.23)	
Yes	48 480 (99.51)	241 (0.49)	
DM			<.0001
No	6 077 311 (99.77)	14 113 (0.23)	
Yes	23 897 (99.45)	132 (0.55)	
Obesity			<.0001
No	6 046 958 (99.77)	13 951 (0.23)	
Yes	54 250 (99.46)	294 (0.54)	

HTN, hypertension; DM, diabetes mellitus.
Data in parentheses are percentages.

Table 2

Risk factors for pediatric kidney stone disease

	Univariate Analysis		Multivariate Analysis	
Variable	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age (y)				
6–10 vs 0–5	15.04 (13.61–16.61)	<.0001	15.48 (14.01–17.11)	<.0001
11–15 vs 0–5	23.26 (21.26–25.45)	<.0001	23.10 (21.10–25.28)	<.0001
16–20 vs 0–5	36.26 (33.40–39.35)	<.0001	34.98 (32.19–38.00)	<.0001
Sex (female vs male)	2.08 (2.01–2.16)	<.0001	1.12 (1.08–1.16)	<.0001
HTN (yes vs no)	2.15 (1.90–2.44)	<.0001	1.17 (1.02–1.33)	.020
DM (yes vs no)	2.38 (2.00–2.82)	<.0001	1.02 (0.85–1.21)	.858
Obesity (yes vs no)	2.35 (2.09–2.64)	<.0001	1.06 (0.94–1.19)	.335

OR, odds ratio; CI, confidence interval; other abbreviations as in Table 1.

Table 3

Multivariate models of risk of pediatric kidney stone disease, with interaction between age and hypertension

Variable	OR (95% CI)	*P* Value
Female vs male	1.12 (1.08–1.16)	<.0001
HTN vs no HTN		
Age 0–5 y	13.74 (9.06–20.85)	<.0001
Age 6–10 y	2.24 (1.52–3.32)	<.0001
Age 11–15 y	0.86 (0.59–1.25)	.437
Age 16–20 y	1.02 (0.88–1.19)	.767

HTN, hypertension; other abbreviations as in Table 2.

Table 4

Multivariate models of risk of pediatric kidney stone disease, with interaction between age and diabetes

Variable	OR (95% CI)	*P* Value
Female vs male	1.12 (1.08–1.16)	<.0001
DM vs no DM		
Age 0–5 y*	11.34 (2.82–45.49)	.0006
Age 6–10 y	1.16 (0.48–2.79)	.747
Age 11–15 y	1.18 (0.79–1.77)	.416
Age 16–20 y	0.98 (0.81–1.20)	.874

DM, diabetes mellitus; other abbreviations as in Table 2.

*Only 2 children in 0–5 age group had DM and kidney stone.