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Association of Urolithiasis With Systemic Conditions Among Pediatric Patients at Children's Hospitals

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Abstract

Introduction—Urolithiasis is associated with systemic medical conditions in adults, but associations have not been well studied in children. We investigated the association of urolithiasis with diabetes mellitus (DM), hypertension (HTN), and obesity among children with and without urolithiasis.

Methods—We performed a matched case-control study using the Pediatric Health Information System (PHIS) database. ICD-9 codes identified urolithiasis cases from 2004–2009. Four randomly selected controls were matched by age, hospital, patient care setting, and year of treatment. Diagnoses from all hospital encounters were ascertained for comorbid conditions. Univariate and multivariable conditional logistic regression were used to assess the associations of urolithiasis with DM, HTN, and obesity.

Results—We identified 9,843 urolithiasis cases and 39,047 controls. On univariate analysis, stone patients had significantly higher odds of obesity (OR 1.44, 95% CI 1.27–1.64) and HTN (OR 2.12, 95% CI 1.88–2.40) compared to controls. The odds of Type I DM was lower among cases compared to controls (OR 0.38, 95% CI 0.30–0.48). After adjusting for gender, race, insurance type, and number of visits using logistic regression, children with urolithiasis still had higher odds of obesity (AOR 1.30, 95% CI 1.12–1.51) and HTN (AOR 1.61, 95% CI 1.40–1.86) and lower odds of Type I DM (AOR 0.32, 95% CI 0.25–0.41) as compared to controls.

Conclusions—Among pediatric patients at freestanding children's hospitals, urolithiasis is associated with higher odds of obesity and hypertension and a lower odds of Type I DM. These findings may be helpful in further elucidating the etiology of pediatric urolithiasis.

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Keywords

Urolithiasis; Kidney stone; Diabetes; Hypertension; Obesity

INTRODUCTION

Urolithiasis is the result of a complex interaction between anatomic and metabolic conditions. Although some of these conditions have a well-defined role in the etiologic pathway to kidney stones (e.g. primary hyperoxaluria), the causative mechanisms for most patients with stones are multifactorial and are poorly understood. This is particularly true for children with urolithiasis.

Studies in adults have demonstrated an association between urolithiasis and specific medical conditions including diabetes mellitus (DM), obesity, and hypertension (HTN).¹ It has been noted that these systemic conditions are associated with perturbations of urine parameters,^{1–5} but the specific mechanisms of these associations are uncertain. Children with urolithiasis represent a distinct subgroup of the urolithiasis population, with a unique range of etiologies and confounding factors. A recent epidemiological study of pediatric inpatient admissions found urolithiasis to be associated with HTN and DM among very young children, with no significant associations with obesity.⁶ However, this study sample was limited to inpatient admissions (a highly selected urolithiasis population).

In this study, we sought to determine if there is a positive correlation between DM, obesity, HTN, and urolithiasis among pediatric patients at US children's hospitals across multiple treatment settings, using a matched case-control study of a national database.

METHODS

Data Source

We used the Pediatric Health Information System (PHIS), a national database of administrative and billing data from >40 freestanding United States children's hospitals affiliated with the Child Health Corporation of America (Shawnee Mission, KS). The PHIS database is composed of over 125 discrete data points drawn from over 1,000,000 pediatric patient encounters including data from inpatient admissions, ambulatory medical and/or surgical short-stay areas, and emergency department visits. PHIS data are screened for accuracy on a quarterly basis through the joint efforts of the Child Health Corporation of America, an independent data manager (Thomson Healthcare, Durham, NC), and each participating hospital. Data are accepted into PHIS only when classified errors occur in less than 2% of a hospital's quarterly data.

Patient Population

We identified cases by screening all hospital visits occurring between January 2003 and December 2009 for patients less than 18 years of age with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) diagnosis codes for calculus of the kidney or ureter (592.0, 592.1). For each urolithiasis patient, we selected the first urolithiasis

visit as the matching encounter, defined as the initial PHIS encounter during which a stone diagnosis code was present. We then selected control patients matched by patient age (± 3 months), treating hospital, calendar year of first visit, and patient care setting. All matching characteristics were based on those of the initial urolithiasis encounter for each case. Up to 4 randomly selected controls were identified for each urolithiasis case. We excluded any cases and controls lacking full data on demographics or diagnosis. We also excluded from the control pool any patients with urolithiasis. To account for possible bias among those with multiple visits, the total number of PHIS hospital visits during the study period was recorded for each case and control.

Demographic information regarding patient gender, race/ethnicity and insurance type were collected. We defined race/ethnicity categories of white, black, Hispanic, or other. Insurance status was defined as public or private payer.

All ICD-9 diagnosis codes used for cases and controls during the study period were abstracted. Our primary outcome was the odds of either DM (ICD-9 249 -250, or subdivided into Type I and Type II/unclassified), obesity (ICD-9 278.00, 278.01) or HTN (ICD-9 401, essential HTN) among cases, compared to the odds of each disease among controls. In addition to the three individual comorbid conditions investigated, we analyzed the association of urolithiasis with multiple simultaneous comorbidities as these represent features associated with metabolic syndrome (MetS).⁷ The American Heart Association and National Heart, Lung, and Blood Institute consensus statement defines MetS as presence of at least 3 out of 5 traits including abdominal obesity (typically measured by waist circumference), increased serum triglyceride, decreased serum high-density lipoprotein cholesterol level, HTN, and impaired glucose tolerance or DM. Although there are no agreed upon diagnostic criterion for MetS in children we used obesity as a proxy measure for abdominal obesity, the presence of HTN and excluded type I DM from the overall DM category for this multiple component analysis, since insulin resistance is not generally seen in type I DM.

Statistical Methods

Univariate tests of association were performed to compare cases to controls with Fisher's exact test, chi square test, or analysis of variance (ANOVA) as appropriate based on data characteristics. Since associations in previous studies did not hold in young and older age groups, stratified Cochran-Mantel-Haenszel analyses were performed for age 13 years or less as compared to greater than 13 years and p-values generated using the Breslow-Day test for homogeneity of the stratified odds ratios. The same tests were used for data stratified by inpatient as compared to non-inpatient patient care settings. Adjusted odds ratios (OR) were generated from multivariable conditional logistic regression models in order to further examine associations after adjusting for possible confounding by gender, insurance type, race/ethnicity and total number of visits for a given patient (categorized as one, two, three, and four or more). The associations between urolithiasis and multiple features of a MetS were examined using the same conditional logistic model to adjust for confounding. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All test statistics were two-sided and p-values of 0.05 or less were considered to be significant.

Institutional review board approval was obtained from Children's Hospital Boston and administrative approval was obtained from PHIS before data extraction and analysis.

Results

Matched Cohort

We identified 19,572 urolithiasis encounters from 15,768,739 overall patient encounters captured by the PHIS database during the study period, comprising 11,554 individual patients (cases). A total of 268 (2.3%) cases were excluded due to missing data and 1,443 due to age 18 years or greater. After exclusions, there were 9,843 pediatric urolithiasis cases matched to 39,047 controls. Overall, 99.4% of cases had at least 3 matched controls. Demographic data for the two groups are presented in Table 1. Cases were more likely to be white, female, privately insured and had a greater number of visits than controls.

Univariate analyses revealed that cases had 44% increased odds of obesity (OR 1.44, 95% CI 1.27–1.64) and a 112% increased odds of HTN (OR 2.12, 95% CI 1.88–2.40). The odds of diabetes mellitus were reduced by 47% in cases as compared to controls (OR 0.53, 95% CI 0.45–0.63). This effect was primarily due to patients with Type I DM (OR 0.38, 95% CI 0.30–0.48) while Type II/unclassified DM was not significantly associated with urolithiasis (OR 1.19, 95% CI 0.89–1.58).

When data were stratified into age 13 years or less and greater than 13 years, odds of HTN among cases was significantly greater in the younger group (OR 2.88, 95% CI 2.41–3.44 vs 1.61, 95% CI 1.35–1.93; $p < 0.01$), odds of obesity and DM were not significantly different ($p = 0.32$ and 0.08 respectively). Similarly, the odds of Type I DM ($p = 0.33$) or Type II DM ($p = 0.97$) among cases were not significantly different in the different age groups.

When data were stratified by encounter type (inpatient versus non-inpatient), odds of obesity among cases was significantly greater in the non-inpatient group (OR 1.84, 95% CI 1.50–2.26 vs 1.25, 95% CI 1.06–1.47; $p < 0.01$) and the increased odds of Type I DM among cases was limited to the inpatient subgroup (OR 0.29, 95% CI 0.21–0.38 versus OR 0.82, 95% CI 0.56–1.21; $p < 0.01$). There was no significant difference in the odds of HTN in cases as compared to controls when stratified by encounter type ($p = 0.97$).

After adjusting for confounding in a multivariable conditional logistic model, cases had a 30% increased odds of obesity (adjusted odds ratio (AOR) 1.30, 95% CI 1.12–1.51) and 61% increased odds of HTN (AOR 1.61, 95% CI 1.40–1.86). The adjusted odds of DM were 55% lower in cases as compared to controls (AOR 0.45, 95% CI 0.37–0.54). Again, this effect was primarily due to Type I DM (AOR 0.32, 95% CI 0.25–0.41) while Type II/unclassified DM remained non-significant (AOR 1.18, 95% CI 0.87–1.60).

The two or more features of MetS (Type II DM, HTN, and obesity) had a stronger association with urolithiasis when present simultaneously than with any component individually (Table 2). The AOR (from the same conditional logistic model) of having urolithiasis among those with one and two or more of these three diagnoses was 1.26 (95% CI 1.13–1.40) and 1.62 (95% CI 1.24–2.12) respectively.

Discussion

There is a keen interest among researchers to unravel the associations between urolithiasis and comorbid medical conditions, particularly HTN, obesity and DM. Studies in adult patients demonstrate clear associations between these conditions,^{1, 7-9} however there are few data in pediatric patients. Since there is evidence that pediatric urolithiasis incidence is increasing,¹⁰ such information is of increasing importance.

Multiple adult studies describe lithogenic urine parameters in association with HTN,^{1, 3, 4} obesity^{5, 11} and DM.^{2, 12, 13} Specifically, HTN has been found in association with low pH, low citrate, and high calcium excretion in stone formers. Obesity is linked to low urinary pH and higher urinary sodium, phosphate, and oxalate. Interestingly, insulin resistance has similarly been implicated in metabolic alterations related to stone formation including a lower pH and hypocitraturia.^{13, 14} Type I DM is not related to insulin resistance and individuals typically have higher than average insulin sensitivity. The inverse association of Type I DM with urolithiasis found in this data set has not been previously reported; however, this association was only significant among inpatients, suggesting that this finding may reflect characteristics of the inpatient population rather than a true biological effect. One retrospective review of pediatric urolithiasis patients at a single institution found that a low BMI (but not a high BMI) was associated with an earlier age at presentation with stone disease.¹⁵ These results discounted the association between obesity and urolithiasis in the pediatric age group. However, this study was limited by small sample size, and a true association between obesity and urolithiasis could have been obscured by multiple other risk factors.

One recent large epidemiological study of pediatric patients analyzed the associations between DM, obesity, HTN and pediatric urolithiasis.⁶ Using the Kids' Inpatient Database (KID), Schaeffer *et al.* examined 14,245 inpatient stone hospitalizations and compared them to >6 million non-urolithiasis hospitalizations. They observed significant associations between urolithiasis and HTN and between urolithiasis and DM in young children. These associations were not found in older children nor was any significant relation demonstrated between urolithiasis and obesity. However, certain limitations of the source data require further confirmation of their findings. Only inpatient encounters are captured by KID; however, urolithiasis is commonly managed on an outpatient basis (clinic, emergency room, ambulatory surgery),¹⁶ and one recent report found that the rate of hospitalization for urolithiasis is decreasing while the use of ambulatory treatment is increasing.¹⁷ Therefore, children with urolithiasis who require inpatient admission may represent a selected (and presumably sicker) subset of all children with urolithiasis, and conclusions based on analysis of these groups should be made cautiously. Additionally, since KID does not contain unique patient identifiers, it cannot distinguish multiple encounters of an individual child from encounters of multiple different children. This, too, would tend to bias the KID sample toward a sicker (or at least more frequently admitted) urolithiasis population, since children with multiple admissions would be counted multiple times.

In the current study, we sought to expand upon the findings of Schaeffer *et al.* using a more flexible database which allows longitudinal tracking of individual patients, thus avoiding the

problem of counting individuals multiple times. Furthermore, the PHIS dataset includes large numbers of outpatient encounters (emergency department, ambulatory surgery, and other settings), which provides a more representative balance of urolithiasis patient acuity and comorbidity. Finally, we were able to individually match our cases and controls by a variety of key characteristics, obviating the need for complex multiple regression interaction terms.

The results of our analysis should be considered in light of its limitations. First, this study is from tertiary children's hospitals and is not truly population-based. Even though this large, well-matched sample allows sufficient power for a robust multivariable analysis, characteristics of this control population differ in significant ways from those of truly healthy, community-dwelling controls. Thus, the unique characteristics of this control population may result in associations that differ to greater or lesser degrees from those that would be noted in a comparison with healthy controls. For example, it is likely that children with diabetes are overrepresented among the control group, since such children are often quite ill and may be seen in substantial numbers at these tertiary referral centers. This overrepresentation (compared to a healthy control population) could contribute to the lower odds of DM in our cases, not because DM is actually protective for urolithiasis, but because so many children with DM are included among the control group. Conversely, the finding that HTN and obesity remain positively correlated with urolithiasis in such a tertiary care setting suggests that these effects may be even more pronounced in the community setting, if urolithiasis patients were compared with truly healthy controls (whose rates of HTN and obesity would presumably be lower than those seen in our control group).

Furthermore, although we examined visits from a variety of patient care settings, there may still have been selection bias due to the use of hospital encounter-level data. An analysis of community level outpatient pediatric clinic visits may lead to different conclusions. However, since children interacting with tertiary care centers are likely to be 'sicker' than the average child, it is likely that the focus on hospital level encounters would bias our results toward greater comorbidity in the control group. Since HTN and obesity were more common in the stone population (cases), these biases are likely to result in underestimates of true associations. In addition, although we controlled for variability of patient care settings by matching on this variable, the analysis is nonetheless limited to the distribution of encounter settings present in PHIS.

It is important to recognize that these data cannot assess the timing of onset of urolithiasis in relation to those of the comorbid conditions (urolithiasis may have preceded or followed the onset of comorbid diagnoses). We are only able to assess for presence or absence of comorbid conditions, not severity (eg. without BMI data we cannot quantify the severity obesity). Additionally, the observational nature of our study cannot exclude the possibility of some unmeasured confounding factor related to both urolithiasis and the associated comorbid conditions. Despite these limitations, our results provide corroborating evidence of direct associations between specific medical conditions and urolithiasis in the pediatric population.

Conclusions

Among pediatric patients seen at free-standing, tertiary care children's hospitals, urolithiasis is associated with increased odds of obesity and HTN compared to controls without urolithiasis. Conversely, pediatric urolithiasis is inversely associated with Type I DM, though this is limited to inpatients. Overall, these findings may help elucidate metabolic causes and effects of stone disease in this population.

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Abbreviations

ICD-9	International Classification of Disease, 9th Edition, Clinical Modification
DM	Diabetes Mellitus
HTN	Hypertension

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Table 1

Characteristics of Pediatric Urolithiasis Cases and Matched Controls

	Cases (Urolithiasis) n=9,843	Controls (No Urolithiasis) n=39,047
Age	12.1±4.7	12.1±4.7
<1yr	321 (3.3%)	1268 (3.3%)
1–5yr	643 (6.5%)	2548 (6.5%)
5–13yr	3,856 (39.2%)	15,301 (39.2%)
13–18yr	5,023 (51.0%)	19,930 (51.0%)
Gender (%)		
Male	4,481 (45.5%)	20,562 (52.7%)
Female	5,362 (54.5%)	23,887 (47.3%)
Race/Ethnicity		
White	6,668 (67.7%)	19,610 (50.2%)
Black	701 (7.1%)	8,423 (21.6%)
Hispanic	1,266 (12.9%)	5,463 (14.0%)
Other	471 (4.8%)	2,631 (6.7%)
Missing	737 (7.5%)	2,920 (7.5%)
Insurance		
Private	6,603 (67.0%)	23,887 (61.2%)
Public	3,133 (33.0%)	14,674 (38.8%)
Total Number of Visits to PHIS hospital		
One	3,159 (32%)	19,780 (51%)
Two	1,900 (19%)	7,819 (20%)
Three	1,240 (13%)	3,883 (10%)
Four or more	3,544 (36%)	7,565 (19%)
Year		
2004	1495 (15%)	5963 (15%)
2005	1474 (15%)	5878 (15%)
2006	1621 (16%)	6451 (17%)
2007	1689 (17%)	6717 (17%)
2008	1641 (17%)	6530 (17%)
2009	1923 (20%)	7508 (19%)
Encounter type		
Inpatient	4230 (43%)	16769 (43%)
Emergency Room	3888 (39.5%)	15441 (39.5%)
Ambulatory Surgery	1137 (11.5%)	4504 (11.5%)
Other (Observation, Clinic, Other)	588 (6%)	2333 (6%)

Table 2

Distribution of urolithiasis cases and controls by the number of metabolic syndrome components including obesity, essential hypertension, and type II diabetes mellitus. (Univariate $p < 0.01$ for trend)

	Cases (n=9,920)	Controls (n=39,433)	Odds Ratio (95% CI)
None (No HTN, obesity, Type II DM)	9,131 (92.8%)	37,288 (95.5%)	Ref -
One Component	615 (6.25%)	1,548 (3.96%)	1.62 (1.47–1.79)
Two or More Components	97 (0.98%)	211 (0.54%)	1.88 (1.47–2.39)