ABSTRACT

Aim: The incidence of pediatric urolithiasis has increased over the last century because of dietary changes, metabolic abnormalities, climate change, and genitourinary abnormalities. Data on pediatric urolithiasis in non-endemic countries are limited. The aim of this study was to evaluate the clinical findings and metabolic etiology of urolithiasis in Korean children.

Material and methods: The medical records of 73 Korean children who were newly diagnosed with urolithiasis from January 2010 to December 2013 were retrospectively analyzed. Evaluation of metabolic risk factors, including hypercalciuria, hyperuricosuria, hypomagnesuria, hyperoxaluria, and hypocitraturia, required analysis of 24-h urine specimens or, alternatively, for infants and toddlers, the solute-creatinine ratio in spot urine.

Results: The male-to-female ratio of the included patients was 1.3:1. The median age at diagnosis was 10.1 years, and the patients were divided into two age groups with pre-school-age children (n = 27, 37.0%) and school-age children (n = 46, 63.0%). While flank pain was more common in school-age children, incidentally detected or urinary tract infection (UTI)-associated urolithiasis was more common in pre-school-age children. Eight patients (11.0%) had renal function deterioration associated with urolithiasis, and three patients (4.1%) progressed to chronic kidney disease. Metabolic abnormalities according to urine chemistry were found in 30 patients (41.1%), including hypercalciuria in 21.9%, hyperuricosuria in 11.0%, hypomagnesuria in 4.1%, hyperoxaluria in 1.4%, hypocitraturia in 1.4%, and cystinuria in 1.4%. Conclusion: We suggest that school-age children with renal colic and pre-school-age children with UTI should be evaluated for urolithiasis. Additionally, the evaluation for metabolic risk factors is important in order to prevent recurrence and renal insufficiency.

Introduction

The characteristics of pediatric urolithiasis are different from those of the adults with regard to the incidence, risk factors, clinical manifestations, and clinical outcomes. Although the incidence of urolithiasis in the pediatric population has been reported to be between 1% and 2.7%, the true incidence has not been reliably estimated. Additionally, the incidence of pediatric urolithiasis varies geographically, and it is more difficult to estimate incidence in non-endemic populations, such as South Korea. Some studies have reported that the annual incidence of pediatric urolithiasis has increased over the last century in response to the risk factors including dietary changes, metabolic abnormalities, climate change, infection patterns, and genitourinary abnormalities. In Tunisia, the dietary habit such as an increase in animal protein intake and increased intake of starchy foods and food with high oxalate content influenced the stone formation. In Thailand, the high prevalence of metabolic disorders such as renal tubular acidosis was associated with the high prevalence of renal stone associated with hypocitraturia. The high prevalence of urolithiasis in the patients with urinary tract infection (UTI) or genitourinary tract abnormalities was also reported. The obesity, prematurity, and hereditary disease such as Dent disease were also reported as the risk factors for pediatric urolithiasis.

Among the risk factors, the metabolic abnormalities have been highlighted in children with urolithiasis because of the association with the recurrence. Some data showed that the recurrence rate in pediatric urolithiasis ranged from 6.5% to 44%, and the associated metabolic abnormalities should be evaluated to prevent the recurrence and morbidity. Additionally, the common metabolic abnormalities in non-endemic areas are different from those in endemic areas because of the underlying genetic and environmental factors, and the metabolic evaluation according to the area is necessary. There is little data for the clinical presentation and renal outcome in pediatric urolithiasis. Herein, we investigated
the clinical characteristics, risk factors including metabolic abnormalities, and renal outcomes in Korean children with urolithiasis.

Patients and methods

Patients

We designed a retrospective study that investigated all children (≤18 years old) who were newly diagnosed as having urolithiasis at Samsung Medical Center in Seoul, South Korea between January 2010 and December 2013. The Institutional Review Board of Samsung Medical Center approved this study. Medical records were reviewed for the patient characteristics, including the gender, age at diagnosis, family history, presenting symptoms during initial episode, accompanying UTI, and genitourinary abnormalities. We also evaluated the laboratory data, including metabolic analysis of urine and stone specimens, imaging results, and treatment modalities. The urolithiasis was diagnosed through a history of stone passage or the imaging studies such as kidney and bladder ultrasonography or computed tomography (CT). The ultrasonography was initially performed in suspicious cases of urolithiasis or UTI. The CT scan was performed in children with gross hematuria with renal colic in whom urolithiasis was not detected by ultrasonography, those in whom the surgical interventions were necessary for urolithiasis, and those visiting the emergency room during nighttime when the ultrasonography was not available. The diagnosis of UTI was performed by the followings: (a) fever higher than 38°C on a tympanic thermometer and not due to other causes; (b) leukocyte esterase- or nitrite-positive on urinalysis or more than five white blood cells per high-power field on urine sediment microscopy; and (c) more than $10^5$ colony forming units (CFU)/mL on urine culture analysis. Urine collection was attempted using a urine catheter in non-toilet-trained children or mid-stream urine at voiding in toilet-trained children.

Metabolic evaluation

The guidelines by the European Association of Urology (EAU) and the American Urological Association recommended the analysis of 24-h urine and stone composition to prevent recurrence. The EAU recommended the spot urine sampling as an alternative method when a 24-h urine collection is difficult in non-toilet-trained children with urolithiasis. According to the EAU guidelines, the evaluation of metabolic risk factors, including hypercalciuria, hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, and cystinuria, was performed through the analysis of 24-h urine specimens or, alternatively, for infants and toddlers, the solute-creatinine ratio in spot urine. In our study, the spot urine sampling or 24-h urine collection was initially obtained before the surgical interventions. If the surgical interventions were performed before the urine collection, a 24-h urine collection was obtained 2 months later after the interventions. The metabolic analysis of stones obtained by spontaneous passage or surgical intervention was performed using Fourier transform infrared spectroscopy. Serum chemistry using standard methods was employed to measure creatinine, calcium, magnesium, uric acid, and phosphorous levels. In children with UTI, the metabolic evaluation of urine was performed 3 months later after the treatment completion.

The patients were diagnosed with hypercalciuria if the amount of calcium in the 24-h urine was greater than 4 mg/kg/day. Hyperuricosuria was diagnosed if the amount of uric acid in the 24-h urine exceeded 815 mg/1.73 m²/day or if the spot urine uric acid–creatinine ratio was higher than 0.56 mg/dL per glomerular filtration rate. The values used for normalization were adapted from previous publications.13–17

Statistical analysis

We performed descriptive analyses for all variables. Comparisons between groups were performed using Pearson’s correlation coefficient and chi-square test for independent samples. For all statistical analyses, $p < 0.05$ was considered significant. For all statistical analyses, we used SPSS, version 19 (IBM, Armonk, NY).

Results

Demographic data

This study included 73 children and the age at the diagnosis of urolithiasis ranged from 0.6 to 18.0 years. A positive family history for urolithiasis in first-degree relatives was reported in 1.3% of the patients. The most common presenting symptoms were renal colic. Seven patients were diagnosed as having urolithiasis during a UTI episode. In 13 patients, urolithiasis was incidentally detected without specific symptom through kidney and bladder ultrasonography for the primary disease. Seven patients had one or more genitourinary tract abnormalities, including duplex kidney ($n=2$), calyceal diverticulum ($n=2$), ureterocele with hydronephrosis ($n=2$), and renal cyst ($n=1$) (Table 1). The most common location was the kidney, and in the kidney stones, unilateral location was more common (76%). Four stones in the two patients were obtained by spontaneous passage, and it
was difficult to determine the location. For the associated medical conditions, four patients had a history of premature birth and furosemide use, and one patient was diagnosed as having glycogen-storage disease. One patient with proteinuria was diagnosed with Dent disease through the genetic study and two patients with Turner syndrome had stones in the renal pelvis without structural abnormality.

**Clinical manifestations according to the age**

Patients were divided into two age groups: pre-school-age children \((n=27, 37.0\%)\) and school-age children \((n=46, 63.0\%)\). The median age in pre-school-age children was 3-year-old and in school-age-children was 14-year-old. While flank pain was more common in school-age children, incidentally detected or UTI-associated urolithiasis was more common in pre-school-age children. Three patients with UTI-associated urolithiasis had hypercalciuria. The relationship between presenting symptoms and age group was significant (Pearson coefficient \(=0.296, \ p=0.046\); Table 2).

All patients received initially conservative treatment, such as oral hydration or a low-salt diet even though we could not assess the amount of water and sodium intake. Two patients with hypercalciuria were treated with hydrochlorothiazide, and three patients with hyperuricosuria were treated with potassium citrate. Spontaneous stone passage occurred in four (5.4%) patients. There was no difference in the modality of surgical management and renal outcomes between two groups.

**Metabolic evaluation**

Metabolic abnormalities according to urine chemistry were found in 30 patients (Table 3). The most frequently detected metabolic abnormality was hypercalciuria (21.9%), followed by hyperuricosuria (11.0%), hypomagnesuria (4.1%), hyperoxaluria (1.4%), hypocitraturia (1.4%), and cystinuria (1.4%) (Table 3). There was no difference in metabolic abnormality according to age group. Additionally, stone analysis was completed for 14 patients. These analyses revealed calcium oxalate stones in nine patients (12.3%), a calcium apatite stone in three patients (4.1%), a carbonate apatite stone in one patient (1.4%), and cystine stone in one patient (1.4%). Infection-associated stones, such as carbonate apatites and calcium apatites, were detected in pre-school-age children who suffered from recurrent UTI episodes without congenital genitourinary abnormalities.

**Renal outcomes**

Eight patients showed the renal insufficiency when urolithiasis was initially diagnosed, and three patients with urolithiasis progressed to chronic kidney disease during follow-up. Case 1 with cystinuria was treated with tioxon and extracorporeal shock wave lithotripsy. Case 2 had the incidentally detected staghorn stones associated with hypercalciuria and was treated with hydrochlorothiazide and extracorporeal shock wave lithotripsy. Case 3 was diagnosed as having cystine stone after retrograde intrarenal surgery. Although they received the appropriate medical and surgical management, their renal function was not completely improved during follow-up (Table 4).

**Discussion**

There were some reports that boys were more commonly affected in the first decade and girls were more susceptible to pediatric urolithiasis in the second
decade because of the pubertal hormonal change.\textsuperscript{5,18} However, there were the other reports that there was no evidence of hormonal effects on the incidence of pediatric urolithiasis.\textsuperscript{19,20} In our study, there was no significant difference in the onset age of urolithiasis between boys and girls. Our study included the small number of patients, and further evaluation was necessary.

The clinical presentation of urolithiasis in children is different from that in adults.\textsuperscript{21} While flank pain is the most common symptom in adults, the symptoms in children are highly variable and can include a combination of vague abdominal pain, gross hematuria, and UTI. In our study, the most common symptom varied by age group. While the school-aged children had symptom patterns that were similar to those of adults, younger children tended to be asymptomatic or have UTI. UTI is thought to be a predisposing factor for development and recurrence of urolithiasis and can also occur as a complication of urolithiasis. We found the infection-associated stones in pre-school-age children with recurrent UTI, suggesting that asymptomatic urolithiasis is common in younger children with recurrent UTI. In a previous study, Alpay et al. reported that renal scarring developed in up to 8% of children with urolithiasis who experienced a UTI during follow-up, indicating that screening and awareness of stone formation are important for pediatric patients with recurrent UTI.\textsuperscript{22}

Underlying anatomic abnormalities might cause urinary stasis and have been thought to be predisposing factors of urolithiasis. In our study, the prevalence of urinary tract abnormalities was relatively low, and the features of abnormalities were similar with those in other reports.\textsuperscript{10,19} It is possible that the extensive prenatal ultrasonography can cause early correction of significant genitourinary abnormalities. The majority of stones in this study were found in the kidney or the proximal ureter. Stone location varies according to region. Reilin et al. reported that, in The Netherlands, a non-endemic country, renal stones and ureter stones were identified in 52% and 33% of patients, respectively.\textsuperscript{23} In a UK study, Coward et al. found 90% of stones in the upper urinary tract of patients and 4% in the lower urinary tract.\textsuperscript{20} In Turkey and Tunisia, both of which are endemic countries, about 80% of stones were found in the upper urinary tract and 20% in the lower urinary tract.\textsuperscript{24,25} While it has been reported that the bladder stones are the most common type in endemic areas, recent data suggest that the majority of stones in children occur in the upper urinary tract, regardless of endemicity.\textsuperscript{10,19,20,23–25} There were a few explanations that the majority of pediatric urolithiasis was upper urinary tract stones. Previously, a nutritionally poor diet that is low in animal protein, calcium, and phosphate, but high in cereal and poor drinking water or dehydration caused by chronic diarrhea in the tropics can lead to decreased urinary volume and increased urinary concentration of ammonium and urate in bladder, which increase the likelihood of bladder stone.\textsuperscript{26,27} As nutrition improved in this area, upper urinary tract stone consisting of calcium oxalate might replace the bladder stone, such as in most Western countries.\textsuperscript{27} The change of diet is supposed to be responsible of the majority of upper urinary tract stone in endemic and non-endemic area.

In our study, the most common metabolic abnormalities associated with urolithiasis were hypercalciuria and hyperuricosuria, different from studies conducted in other countries.\textsuperscript{17,23} Coward et al. found that, in the UK, the most common metabolic abnormality was

### Table 3. The results of metabolic evaluation according to the age group.

|                | Pre-school age (n = 11) number (%) | School age (n = 19) number (%) |
|----------------|-----------------------------------|-------------------------------|
| Hypercalciuria  | 7 (63.6)                          | 9 (47.3)                      |
| Hyperuricosuria | 4 (36.4)                          | 4 (21.0)                      |
| Hypomagnesuria  | 0 (0)                             | 3 (15.8)                      |
| Hyperoxaluria   | 0 (0)                             | 1 (5.2)                       |
| Hypocitraturia  | 0 (0)                             | 1 (5.2)                       |
| Cystinuria      | 0 (0)                             | 1 (5.2)                       |

### Table 4. The clinical features of patients with chronic kidney disease after urolithiasis.

|                      | Case 1 | Case 3 | Case 4 |
|----------------------|--------|--------|--------|
| **Sex**              | Female | Female | Female |
| **Age (years)**      | 18     | 5      | 14     |
| **BMI (kg/m²)**      | 26.0   | 15.7   | 17.7   |
| **Presenting symptom** | Renal colic, GHU | mHU | Renal colic |
| **Location of stone** | Right pelvis, left proximal ureter | Staghorn stones, both | Right pelvis, left proximal ureter |
| **Metabolic evaluation** | Cystinuria | Hypercalciuria (calcium oxalate stone) | Cystine stone |
| **Medical treatment** | Tiopronin | HCT | None |
| **Surgical treatment** | ESWL | ESWL | RIS |
| **eGFR (initial episode)** | 31.5 | 67.5 | 68 |
| **eGFR (final)**     | 61.7   | 85.3   | 65.5   |
| **Follow-up period (years)** | 3 | 2 | 3 |

Notes: BMI: body mass index; GHU: gross hematuria; mHU: microscopic hematuria; HCT: hydrochlorothiazide; eGFR: estimated glomerular filtration rate; ESWL: extracorporeal shock wave lithotripsy; RIS: retrograde intrarenal surgery.
hypercalciuria, followed by cystinuria. In Turkey, Alpay et al. found that hypercalciuria was the most common metabolic abnormality, followed by hypocitraturia, hyperoxaluria, and hyperuricosuria. More recent data from Turkey reported that the most frequent metabolic abnormalities in pre-school-age children with urolithiasis were hyperuricosuria and hypocitraturia. Different dietary habits and hereditary factors might influence differences in urine chemistry results. The recurrence rate of pediatric urolithiasis varies from 20% to 48%, but Kim et al. reported that the recurrence rate in South Korea is 13%. A metabolic evaluation of urine samples in pediatric urolithiasis patients is necessary to prevent stone recurrence. Additionally, stone analyses were performed in available patients, and the most common component was calcium oxalate. In endemic countries, like Turkey and Tunisia, calcium oxalate and phosphate stones account for 77–86% of all stones. Despite the relatively small number of patients enrolled in our study, our results suggest that Korean children with urolithiasis have different stone compositions, according to urine chemistry findings, compared with those in Europe and the Middle East.

In our study, three patients progressed to chronic kidney disease because of urolithiasis. There were little data for the prevalence of renal insufficiency caused by urolithiasis. Eisner et al. reported that kidney stone is associated with an increased risk of chronic kidney disease and end stage renal disease among women. According to our data, the prevalence of renal insufficiency was low and the severity of chronic kidney disease was mild. However, although one patient with renal insufficiency showed no specific symptom, the parenchymal thinning that needed the prompt surgical interventions was observed when urolithiasis was initially detected. These findings suggest that the appropriate imaging study for the pediatric patients with microscopic hematuria might be necessary to evaluate the presence of urolithiasis which could cause the renal insufficiency.

Limitations

There were a few limitations in our study. This study was performed with a retrospective design in a single center, which is located in urban area. The data were not collected from a national database and the results might be deviated. Additionally, the retrospective design of this study might cause incomplete data collection for urine sodium and urine volume. We could not evaluate obesity or overweight as a risk factor for pediatric urolithiasis because of lacking data of body gauges.

Conclusions

School-age children with renal colic and pre-school-age children with UTI should be evaluated for urolithiasis. Additionally, the most common metabolic abnormalities in Korean children with urolithiasis were hypercalciuria and hyperuricosuria, and the evaluation for metabolic risk factors is important in order to prevent recurrence and permanent renal damage from pediatric urolithiasis.

Disclosure statement

The authors report no conflict of interest.

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