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Pediatric urolithiasis: metabolic risk factors and follow-up results in a Turkish region with endemic stone disease

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Abstract The goal of this study was to investigate the metabolic etiology, clinical findings and medical treatment of children with urolithiasis in an endemic region of Turkey. We retrospectively analyzed the medical records of 742 (437 males, 305 females) children with urolithiasis. Physical examination results, serum biochemistry and urine metabolic evaluation, including urinary citrate, oxalate, calcium, uric acid, cystine and magnesium levels were recorded. We obtained follow-up records in 316 patients to evaluate the association between stone recurrence and metabolic risk factors. The mean age at diagnosis was 2.6 ± 3.4 (0.1–17.0) years. Male-to-female ratio was 1.4:1. A family history of stone disease was found in 76.5 % of patients and 41 % of parents had consanguineous marriage. The most common presenting symptoms were urinary tract infection (UTI, 23.9 %) and hematuria (23.6 %). Metabolic abnormalities were found in 588 (79.2 %) patients, including hypercalciuria in 31.5 %, hypocitraturia in 24.2 %, hyperoxaluria in 11.4 %, hyperuricosuria in 9.1 %, hypomagnesuria in 3.9 %, and cystinuria in 3.1 % of patients. The frequency of hyperoxaluria and hypocitraturia were significantly higher in patients with new stone formation. Follow-up records of 316 (42.6 %) patients (192 males, 124 females) were available. Urolithiasis was shown in 135 (42.7 %) of the patients on control ultrasonography, and 61.5 % of these patients had a stone size ≤3 mm. Hyperoxaluria and cystinuria were significantly higher in patients with stone persistence. The main goal of management for children with urolithiasis should be identification of risk factors.

Keywords Urolithiasis · Children · Risk factors · Follow-up

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Introduction

Recent studies have shown an increasing incidence of urolithiasis in both adults and children. Urolithiasis in childhood is different from adults in many aspects, including the etiology, presentation, incidence, and natural history. Although urolithiasis is a common disorder that affects approximately 3–5 % of the population, the true incidence of urolithiasis in the pediatric population is unclear. In a study from South Carolina using data from all pediatric emergency departments, the incidence of urolithiasis for children ≤18 years of age was 18.5 per 100,000 children [1, 2]. The prevalence varies widely depending on geographic location, hereditary and economic factors [3]. Stone formation is a multifactorial process that involves both the patient's underlying metabolic abnormalities and environmental conditions that promote urolithiasis. There is a onefold increase in the prevalence of urolithiasis in the southeast of US when compared with the northwest; this demonstrates the geographic variation in the prevalence of kidney stone disease [4].

Urolithiasis is a painful disease that sometimes necessitates invasive procedures and may lead to harmful effects on kidney. Urolithiasis is associated with significant

morbidity, particularly in children with recurrent stone formation. Urinary stone disease constituted 8 % of the underlying etiological factors for development of chronic kidney disease in Turkish children [5]. Turkey is a country with endemic urinary stone disease, particularly, in the southeast region. Nevertheless, not much information is available regarding children with urolithiasis in our region.

In this study, we evaluated the clinical characteristics, metabolic risk factors and medical treatment results of children with urolithiasis, living in the southeast region of Turkey.

Patients and methods

We reviewed the medical records of 742 children with urolithiasis at Diyarbakır Children's Hospital for clinical and laboratory data, including gender, age at diagnosis, family history of urolithiasis, parental consanguinity, presenting symptoms, accompanying urinary tract infection (UTI), urinary tract abnormalities and metabolic abnormalities. The compositions of spontaneously passed or surgically removed stones were also recorded.

Urolithiasis was diagnosed via a history of stone passage or by ultrasonography (US) and/or in suspicious cases by computed tomography (CT). CT examinations were performed on patients who presented with macroscopic hematuria, renal stones leading to obstructive uropathy and flank pain. All cases were re-evaluated with repeat US examination by a second sonographer to exclude images with artifact. Urinary calculi with an ultrasonographic diameter of ≤3 mm (mm) were defined as microlithiasis and >3 mm in diameter as urolithiasis [6]. However, we evaluated both microlithiasis and urolithiasis as a whole. Voiding cystourethrography (VCUG) and 99m-technetium dimercaptosuccinic acid (^{99m}Tc-DMSA) were performed in patients with history of recurrent UTIs. The diagnosis of a UTI was based on the presence of pyuria (defined as over 5 white blood cells per high-power field), positive urinary nitrites and leukocyte, and a positive urine culture (i.e., $>10^5$ colony-forming units per milliliter of a microorganism).

Serum sodium, potassium, calcium, magnesium, phosphate, uric acid and parathyroid hormone levels were measured by standard methods. After treatment of the symptomatic stone episode and UTI, the levels of urinary calcium, oxalate, citrate, uric acid, cystine, magnesium, and creatinine were measured for metabolic evaluation from a 24-h urine in older children who were able to cooperate; spot urine mineral-to-creatinine ratio was used in younger patients. A ≥25 mL/kg/day collection of 24-h urine was considered adequate. We obtained one urine sample from 350 (48.1 %) patients for evaluation and more than one sample from 377 (51.9 %). Absolute urine concentrations of metabolic variables in 24-h urine sample and/or spot urinary mineral-to-creatinine ratios were determined and compared with age-appropriate reference values to define metabolic abnormalities (Table 1) [7, 8]. The X-ray diffraction method was used for stone analysis of spontaneously passed or surgically removed stones.

Table 1 Normal values for urinary solute excretion

Metabolite	Age	Random (mg/mg)	24 h (all ages)
Calcium	<12 months	<0.81	<4 mg/kg
	1–3 years	<0.53	
	3–5 years	<0.40	
	5–7 years	<0.30	
	>7 years	<0.21	
Oxalate	0–6 months	<0.28–0.26	<45 mg/1.73 m^2
	7–24 months	<0.11–0.14	
	2–5 years	<0.08	
	5–14 years	<0.06–0.065	
	>16 years	<0.032	
Citrate	0–5 years	>0.20–0.42	>0.14 g/1.73 m^2
	>5 years	>0.14–0.25	
Cystine	1–6 months	<0.112	<50 mg/1.73 m^2
Uric acid	>2 years	<0.56 mg/dl per GFR	<815 mg/1.73 m^2
Magnesium	>2 years	>0.13	>0.8 mg/kg

GFR glomerular filtration rate

The patients with metabolic risk factors were managed according to the underlying metabolic abnormality [9]. Vitamin D usage was questioned in infants especially receiving formula to avoid over-dosage, because formulas in Turkey consists vitamin D. Increased fluid intake was recommended to infants receiving formulas. High fluid intake and restriction of sodium intake were recommended to all patients. Protein restriction and low-oxalate diet were recommended to selected patients such as those with hyperoxaluria and cystinuria. Conservative treatment (high fluid intake, dietary sodium restriction) was initiated when microcalculi were detected. If the size and/or number of calculi increased during follow-up, medical treatment was added. In patients who had stone formation (>3 mm) and metabolic abnormalities, medical treatment was started immediately after diagnosis. We treated patients with idiopathic hypercalciuria with 2 mEq/kg day of potassium citrate solution (potassium citrate 100 mg, sodium citrate 100 mg in each 1,000 mL water) or potassium citrate pill. Hydrochlorothiazide (1–1.5 mg/kg day) was added to the treatment regimen in patients who were resistant to dietary modifications and potassium citrate. Patients with hypocitraturia received potassium citrate. Infants with hyperoxaluria also received pyridoxine (3–5 mg/kg day) in addition to potassium citrate. Older children followed a diet consisting of high calcium and low oxalate. Potassium citrate

was administered to alkalinize the urine in children with hyperuricosuria and cystinuria. Thiopronin (15 mg/kg day) was used in patients with cystinuria who were unresponsive to potassium citrate and dietary modifications. The dosage of potassium citrate was decreased in noncompliant patients due to taste. Patients who received thiazide diuretic were followed-up for the development of potential side effects including electrolyte imbalance (i.e., hyponatremia, hypokalemia), and hyperglycemia.

We utilized descriptive statistics for statistical analyses. Student's *t* test, Mann–Whitney *U* test and Chi square test were performed for comparisons of groups, using the statistical software package SPSS version 13.0 (SPSS, Chicago IL, Ca, USA). A $p < 0.05$ was accepted as significant.

Results

We evaluated 742 children (male/female = 1.4/1) with the mean age of 2.60 ± 3.43 (median 0.80; range 0.1–17.0) years. Age groups were as follows: 434 (58.5 %) patients were ≤1-year old, and 308 (41.5 %) patients were >1-year old. Consanguineous marriage was found in 304 (41.0 %) of patients and family history of stone disease in 569 (76.5 %). We obtained the medical histories of the children and found that 177 (23.9 %) had a history of UTI, 175 (23.6 %) had prior episodes of macroscopic or microscopic hematuria, 98 (22.6 %) had symptoms of restlessness, 85 (11.5 %) had abdominal pain, and 44 (5.9 %) had dysuria. History of UTI was significantly higher in females than boys ($p < 0.001$) (Table 2).

Stones location varied among the patients. We found that 188 (25.3 %) of patients had left-sided stones, 123 (16.6) had right-sided, and 422 (56.9 %) had bilateral stones. Ureteral stones were found in 37 (5.0 %) patients. The stone size was ≤3 mm in 281 (37.9 %) children and >3 mm in 461 (62.1 %) patients. While microlithiasis was significantly higher in patients under 1 year of age (65.8 %), stone formation over 3 mm was significantly higher in patients older than 1-year old (46 %) ($p = 0.002$). Metabolic abnormalities were found in 588 (79.2 %) patients. The most frequently detected metabolic abnormality was hypercalciuria 31.5 %, followed by hypocitraturia 24.2 %, hyperoxaluria 11.4 %, hyperuricosuria 9.1 %, hypomagnesuria 3.9 %, and cystinuria 3.1 % (Table 3). The frequency of hyperoxaluria and hypocitraturia were significantly higher in patients with stone formation (>3 mm) ($p < 0.001$). No significant difference was observed among age groups for hypercalciuria. Hypocitraturia, hyperuricosuria, hyperoxaluria and cystinuria were significantly higher in patients >1-year old ($p < 0.001$) (Table 4). There were no statistically significant differences in the levels of urinary calcium, oxalate, citrate, magnesium and uric acid between children with or without family history of urolithiasis ($p > 0.05$) (data not shown). Consanguinity was significantly higher in patients with cystinuria (76.2 %) when compared with non-cystinuria patients (40.7 %) ($p = 0.001$).

Table 2 Demographic and clinical characteristics of children with urolithiasis

	≤1 year *n* (%)	>1 year *n* (%)	*p*
Male/female	262/171	175/133	0.314
Family history of urolithiasis	332 (76.9)	237 (76.9)	0.976
Parental consanguinity	173 (39.9)	131 (43.5)	0.466
Hematuria	63 (14.5)	112 (36.4)	<0.001
Urinary tract infection	85 (19.6)	92 (29.9)	0.001
Stone passage	17 (3.9)	34 (11.0)	<0.001
Restlessness	98 (22.6)	–	
Abdominal/flank pain		84 (27.3)	
Dysuria	–	43 (14.0)	

Table 3 Urine chemistry results of children with urolithiasis

Metabolic abnormality	*n*	%
Hypercalciuria	170	22.9
Hypocitraturia	116	15.6
Hyperoxaluria	38	5.1
Hyperuricosuria	33	4.4
Hypomagnesuria	20	2.7
Cystinuria	2	0.3
Hypercalciuria+hypocitraturia	19	2.6
Hypercalciuria+hyperuricosuria	19	2.6
Hyperoxaluria+hypocitraturia	16	2.2
Hypercalciuria+hyperoxaluria	10	1.3
Hypercalciuria+hypomagnesuria	5	0.7
Hypocitraturia+hypomagnesuria	5	0.7
Other abnormality	24	3.2
No abnormality	250	33.7
Not measured	15	2.0
Total	742	100.0

Table 4 Comparison of urinary metabolic abnormalities based on age groups

Metabolic abnormality	≤1 year *n* (%)	>1 year *n* (%)	*p*
Hypercalciuria	129 (30.0)	99 (33.8)	0.282
Hypocitraturia	83 (19.7)	83 (31.4)	<0.001
Hyperoxaluria	28 (6.7)	50 (18.9)	<0.001
Hyperuricosuria	2 (0.5)	64 (21.8)	<0.001
Cystinuria	5 (1.2)	16 (6.1)	<0.001
Hypomagnesuria	7 (1.0)	22 (3.2)	0.035

Spontaneous stone passage was observed in 51 (6.9 %) patients and surgical stone removal was necessary in 33 (4.4 %) patients. Stone analyses revealed calcium oxalate stones in 35 (50.7 %), cystine stones in 13 (18.8 %), uric acid stones in 10 (14.5 %), struvite (magnesium ammonium phosphate) stones in 5 (7.2 %), calcium phosphate stones in 4 (5.8 %), and xanthine stones in 2 (2.9 %) children. In 15 children, stone sizes were not suitable for stone analysis. Surgical operation was performed on 33 (4.4 %) patients and extracorporeal shock wave lithotripsy (ESWL) on 64 (8.6 %) of the children. Vesico-ureteral reflux (VUR) was detected in 19 (2.6 %) of patients and uretero-pelvic junction obstruction in 19 (2.6 %). Seven male patients had a history of a bladder stone operation.

Follow-up records were obtained for 316 (192 male, 124 female) patients (42.6 %) and 292 (92 %) of them had received medical treatment. The follow-up period ranged from 6 to 36 months with a mean follow-up duration of 11.8 ± 7.3 months. The mean age of these patients was 2.3 ± 2.9 years [≤1 year, 167 (52.8 %); >1 year, 149 (47.2 %)]. Family history of urolithiasis was seen in 256 (81.0 %) and parental consanguineous marriage was seen in 134 (42.2 %) with regular follow-up. Among followed-up patients, 181 (57.3 %) of them were found stone free at follow-up examinations. The frequency of hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria and cystinuria in these stone-free patients were 39.4, 33.3, 10.0, 4.4, and 2.2 %, respectively. We found that 135 (42.7 %) patients had persistent urolithiasis on control ultrasound examinations. Persistent stone sizes were ≤3 mm in 83 (61.5 %) patients, and >3 mm in 52 (38.5 %). The frequencies of hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria and cystinuria were 32.6, 27.4, 20.7, 9.6, and 6.7 %, respectively, in stone persisted patients. No electrolyte abnormality or hyperglycemia were observed as a result of diuretic use in any patient. No side effects of thiopronin were observed in patients treated for cystinuria. ESWL was performed to 19 patients and 8 patients required surgery.

Decreased renal parenchymal thickness and/or scarring was observed in 48 patients (15.2 %), and 15 (4.7 %) of these patients had VUR. Metabolic abnormalities were found in 251 (79.4 %) patients including hypercalciuria in 36.4 %, hypocitraturia in 30.7 %, hyperoxaluria in 14.6 %, hyperuricosuria in 6.6 %, and cystinuria in 4.4 %. Hyperoxaluria (20.7 vs. 10.0 %) and cystinuria (6.7 vs. 2.2 %) were significantly higher in patients with stone persistence compared with who passed the stone on control ultrasound examinations ($p = 0.008$, $p = 0.05$). Evaluation of the subjects according to gender revealed no significant difference regarding the mean age, mean follow-up duration, parental consanguinity ratio, family history of stone disease, persistent stone in control ultrasound, the ratios of hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, and hyperuricosuria ($p > 0.05$) (data not shown).

Discussion

Pediatric stone disease is a significant health problem that is very common in some parts of the world. Urinary calculi are endemic to certain regions, such as Southeast Asia, the Middle East, India, Turkey and Pakistan. Epidemiologic studies have shown an increasing trend in the incidence of urolithiasis associated with a change in social conditions and eating habits. However, the importance of genetic predisposition, as recognized by racial distribution and family history of urolithiasis, cannot be disregarded [1, 3, 4]. Determining the etiology of urolithiasis plays a key role in planning successful treatment and preventing recurrence. In many countries, the disease affects all age groups, with a male-to-female ratio of approximately 2–1 [3]. Several studies from Turkey reported a male preponderance in children with urolithiasis [10–12]. In our pediatric study population, the male-to-female ratio of urolithiasis was 1.4:1 indicating a slight male predominance.

Generally younger children are more likely to have an underlying metabolic risk factor for pediatric urolithiasis [1]. Metabolic abnormalities have been reported in 33–93 % of the children with urolithiasis [1, 4, 13]. In our study, 79.2 % of the patients had at least one metabolic abnormality. The most frequent stone type in pediatric urolithiasis is calcium-based with the reported incidence of 72–88 % [1, 13]. Children have higher urinary calcium excretion than adults when adjusted for creatinine excretion. It has been also reported that children have higher urinary solute supersaturation of calcium phosphate than adults. In addition, children with stone disease have higher solute supersaturation of calcium oxalate when compared with non-stone-forming children [1]. Similarly, the majority of our patients had calcium oxalate stones. In our region, the most common metabolic disorder was hypercalciuria and hypocitraturia.

Several studies from Turkey reported that hypocitraturia and hypercalciuria were the most common metabolic abnormalities [10–12, 14]. Hypocitraturia has also been shown to be a risk factor for recurrent stone disease in children [1]. Our study also demonstrated that hypocitraturia was the most common metabolic risk factor in children older than 1 year. It is also known that the probability of hypocitraturia is higher in the younger children with urolithiasis [13]. In our study, hypocitraturia did not correlate with a family history of urolithiasis. We speculate that environmental factors and dietary habits can be greater contributors to development of stone disease due to hypocitraturia, than the hereditary risk factors.

A family history of urolithiasis has been suggested to increase the risk of stone formation and recurrence [15]. About 40 % of the children with urolithiasis have a positive family history of kidney stones [7]. Curhan et al. [16] reported that approximately 60 % of the enhanced risk of stone formation among relatives of patients with idiopathic urolithiasis might be related to genetic inheritance. In our study population, the rate of a positive family history of urinary stone disease was 76.5 %. No association was determined between positive family history and metabolic abnormalities. This finding suggests that familial recurrence does not necessarily imply an inherited transmission for a metabolic abnormality, instead environmental factors shared by family members, mainly those related to dietary habits.

Urinary stone disease is associated with significant morbidity, particularly in children with recurrent stone formation. If not treated, metabolic abnormalities may lead to recurrent stone formation, with a potential rate as high as 50 % at 5 years [2]. Stone recurrence rate has been reported to be 40 % in children with hypocitraturia and hypercalciuria [17]. In our study, recurrence rate was 42.7 % after medical treatment. DeFoor et al. [18] reported a 2.3- and 3.5-fold increase in hypercalciuria and hypocitraturia in patients with recurrent stone disease, respectively. Tekin et al. [14] found low-citrate levels to be the most important risk factor for developing idiopathic calcium oxalate stones in their patient population from central Turkey. The frequencies of hypocitraturia and hyperoxaluria were reportedly increased 4.3- and 4-fold, respectively, when compared with the control group, in the aforementioned study. We also observed significantly increased frequencies of hypocitraturia and hyperoxaluria in patients with stone formation (>3 mm), suggesting that earlier diagnosis and treatment of metabolic disorders, such as hypocitraturia and hyperoxaluria is essential to prevent stone formation and associated morbidity.

In recent reports, factors including obesity, and changes in nutritional habits (increased sodium intake, decreased calcium intake, increased fructose intake) are noted to be responsible from the worldwide increasing incidence of pediatric stone disease [1]. However, metabolic disorders are also potential risk factors especially in countries with endemic stone disease where consanguineous marriages prevail [10–12, 14]. With regard to stone prevention, risk factors should be determined and appropriate treatment modalities should be initiated in pediatric patients [14, 19, 20]. Pietrow et al. [20] reported that children with an underlying metabolic disorder had an up to 50 % risk of recurrent stone formation; this was contrasted with a 10 % recurrence risk in those without an identifiable metabolic risk factor. The study conducted in Turkey by Tekin et al. [14] showed that potassium citrate therapy has a preventive effect for recurrent calcium stone disease in children with hypocitraturia and calcium stones. Medical treatment compatible with the metabolic disorder was adjusted to the patients in our study. Among the 316 patients with available follow-up data, 57.3 % were stone free. Stone size was reduced (≤3 mm) with medical therapy in 61.5 % of these patients. Our data support the recommendation that children with stone disease should be evaluated carefully for potential metabolic abnormalities, and treated appropriately during the first stone episode. In addition, hyperoxaluria and cystinuria were significantly higher in patients with stone persistence. The rate of consanguineous marriages in our region is as high as 41 %. This may be a contributing factor in the genetic tendency toward urolithiasis in our study group.

This study had some limitations. We did not obtain repeated 24-h urine collections for each variable for urinary mineral excretions and it was not determined whether hyperoxaluria was due to genetics or absorption.

In conclusion, hyperoxaluria and hypocitraturia are important risk factors for stone formation in pediatric urolithiasis cases. Persistence of urolithiasis is common in patients with hyperoxaluria and cystinuria. Diagnostic investigation for high-risk patients should be applied to all children with urolithiasis. Appropriate treatment of associated metabolic abnormality is essential to reduce recurrent stone disease and to avoid invasive surgical procedures.

Conflict of interest The authors declare that they have no conflict of interest.

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