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Metabolic Factors Associated With Urinary Calculi in Children

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Introduction. We aimed to identify metabolic and anatomical abnormalities present in children with urinary calculi.
Materials and Methods. Metabolic evaluation was done in 142 pediatric calculus formers. Evaluation included serum biochemistry; measurement of daily excretion of urinary calcium, uric acid, oxalate, citrate, and magnesium (in older children); and measurement of calcium, uric acid, oxalate, and creatinine in random urine samples in nontoilet-trained patients. Urinary tests for cystinuria were also performed. All of the patients underwent renal ultrasonography.
Results. Sixty-one patients (42.7%) had metabolic abnormalities. Anatomical abnormalities were found in 12 patients (8.4%). Three children (2.1%) had infectious calculi, and 3(2.1%) had a combination of metabolic and anatomic abnormalities. In 66 children (46.2 %) we did not find any reasons for calculus formation (idiopathic). Urinalysis revealed hypercalciuria in 25 (17.6%), hyperuricosuria in 23 (16.1%), hyperoxaluria in 17 (11.9%), cystinuria in 9 (6.3%), hypocitraturia in 3 (2.1%), and low urinary magnesium level in 1 (0.7%) patients. Sixteen patients (11.2%) had mixed metabolic abnormalities.
Conclusions. Metabolic abnormalities are common in pediatric patients with urinary calculi. In our study, calcium and uric acid abnormalities were the most common, and vesicoureteral reflux seemed to be the most common urological abnormality which led to urinary stasis and calculus formation.

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INTRODUCTION

Although pediatric urinary calculi are rare in western countries, it remains a common health problem in some parts of the world.[1-3] Some epidemiological studies have shown that the annual incidence of urolithiasis is 1% in asymptomatic primary school children.[4] Metabolic and genitourinary anomalies which predispose to urolithiasis often coexist in pediatric patients. Various anatomical abnormalities such as ureteropelvic junction obstruction, ureterocele, vesicoureteral reflux, horseshoe kidney, and tubular ectasia (medullary spongy kidney) promote urine stasis and increase the risk of calculus formation.[5] Natural inhibitors and promoters of crystal and calculus formation exist in the urine. Natural inhibitors consist of magnesium, citrate, and especially, glycoproteins (nephrocalcin and Tamm-Horsfall proteins).[6] Urinary supersaturation indexes which are considered lithogenic and calculus inhibitory substances in the urine were recently suggested as more precise predictors of calculus recurrence than traditional metabolic parameters.[5-7] Some of known metabolic risk factors of calcium calculi are increased excretion of calcium, oxalate, and uric acid or decreased excretion of citrate.[6,8] The majority of hypercalciurias are idiopathic, either sporadic or familial.[9] Calcium calculi in childhood may occur due to certain enzymes defects, such as primary hyperoxaluria types 1 and 2 and also in 4

conditions previously described as separate entities: X-linked nephrolithiasis with kidney failure, Dent's disease, X-linked recessive hypophosphatemic rickets, and low-molecular-weight proteinuria with hypercalciuria and nephrolithiasis.[10] Cystinuria—an inborn error in transport of cystine, ornithine, lysine, and arginine amino acids—accounts for 1% to 3% of metabolic urolithiasis cases among children in industrialized countries.[11]

All calculus formers may benefit from increasing fluid intake and some advocate drinking at night. Many researchers have analyzed the relationship between dietary intake of various nutrients and excretion of lithogenic and inhibitory substances in urine.[12] Dietary habits like high animal protein diet or excessive vitamin C or D supplements, low fluid consumption, and certain medications contribute to calculus disease.[13-15] Finally, body weight is considered as a risk factor of calculus formation in adults.[16] However, risk factors in children need to be investigated more in different populations. This study was conducted to identify metabolic abnormalities present in children with urinary calculi.

MATERIALS AND METHODS

We prospectively analyzed 142 consecutive patients with urinary calculi referred to the pediatric nephrology clinic of Dr Sheikh Children Hospital of Mashhad, Iran, between 2005 and 2007. Patients were included into the study if at least preliminary evaluations were done (biochemistry analyses including measurement of blood urea nitrogen concentrations; serum levels of creatinine, sodium, potassium, chloride, calcium, phosphorous, alkaline phosphatase, uric acid, and magnesium; arterial blood gas; urinary excretion of calcium, creatinine, uric acid, and oxalate, urine sodium nitroprusside test; and urine amino acid chromatography.

Complete information about family history of urinary calculi in close relatives including first- and second-degree relatives was obtained. In all of the patients, kidney ultrasonography was used for detection of the calculi (Adra model, Siemens, Berlin, Germany). Kidney ultrasonography was performed using 5-, 7.5-, and 10-MHz probes. Bladder ultrasonography was done using 3.5- and 5-MHz probes. The proximal and distal ureters were checked for calculus, and if there was any dilatation in the ureters, the entire ureter would be checked.

In infants and nontoilet-trained patients, a random urine sample was checked for creatinine, calcium, uric acid, and oxalate levels. In toilet-trained patients, 24-hour urine was collected for the measurements. Patients whose sodium

Table 1. Criteria for Abnormal Urine Parameters

Abnormality	Definition
Random urine	
Hypercalciuria	
0 to 6 months	Calcium/creatinine > 0.8 mg/mg
7 to 12 months	Calcium/creatinine > 0.6 mg/mg
> 1 year	Calcium/creatinine > 0.2 mg/mg
Hyperuricosuria	
Term infant	Uric acid > 3.3 mg/dL GFR
> 3 years	Uric acid > 0.53 mg/dL GFR
Hyperoxaluria	
< 1 year	Oxalate/creatinine > 0.26 mmol/mmol
1 to 5 years	Oxalate/creatinine > 0.12 mmol/mmol
Cystinuria	Positive urine sodium nitroprusside test and abnormal bands on cystine, ornithine, lysine, and arginine regions in urine amino acid chromatography
24-hour urine	
Hypercalciuria	Calcium ≥ 4mg/kg/d
Hypocitraturia	Citrate < 2 mg/kg/d
Low magnesium level	Magnesium < 1.2 mg/kg/d
Hyperuricosuria	Urine uric acid > 10.7 mg/kg/d
Hyperoxaluria	Urine Oxalate ≥ 0.57 mg/kg/d
Cystinuria	Urine cystine level > 5.7 mg/kg/d + positive urine sodium nitroproside test and abnormal bands on cystine, ornithine, lysine, and arginine regions in urine amino acid chromatography

nitroprusside tests were positive underwent 24-hour urine cystine level measurement, as well. Urinalysis and urine culture were also performed for all of the patients. Urine samples were collected in special bottles containing hydrochloride as preservative in the 24-hour period. After collection, urine was centrifuged and analyzed. We defined hypercalcemia as a serum calcium level greater than 10.2 mg/dL (serum calcium levels were checked by the methyl tymolol blue method), and hypomagnesemia as a serum magnesium level lower than 1.2 mg/dL in infants and lower than 1.9 mg/dL in older children. Table 1 shows the utilized criteria for abnormal urine parameters.[17,18]

We determined anatomical and metabolic abnormalities in our cohort, and compared those in symptomatic and asymptomatic patients, as well as patients with and without a family history of urinary calculi. The independent *t* test, the Fisher exact test, and the chi-square test were comparisons, and *P* value less than .05 was considered significant.

RESULTS

The studied patients were 76 girls (53.5%) and 66 boys (46.5%) with ages ranged from 1 month to 13 years (mean, 2.85 ± 2.84 years). Sixty-four of the children (45.1%) were 2 years or younger. The mean age was 3.10 ± 3.01years and 2.50 ± 3.01 years for the girls and boys, respectively ($P = .24$). Thirty children (21.1%) were asymptomatic and the urinary calculus was diagnosed when ultrasonography was performed for other reasons. Table 2 shows details of clinical manifestations and Table 3 presents urinary parameters in the patients. A total of 61 patients (43.6%) had urine metabolite levels beyond the reference ranges.

In 107 patients (75.4%) the calculus size was 5 mm or less. A single calculus was seen in 77 patients (54.2%), while 22 (15.4%) had 2 calculi, 22 (15.4%) had 3 to 7 calculi, and 21 (14.7%) had more than 7 calculi. In 3 patients, the calculus was diagnosed after spontaneous calculus passage and ultrasonography did not show any other calculi. Six patients (4.2%) had nephrocalcinosis, and in 4 (2.8%), the calculi were limited to the bladder. Fifty-three children (37.3%) had no family history of nephrolithiasis, whereas 89 (62.7%) had a positive family history, including 34 (23.9%) cases in the parents, 5 (3.5%) in the siblings, and 50 (35.2%) in close relatives (grand parents, uncles, or aunts).

Table 2. Clinical Features of Urinary Calculi in Studied Children

Presentation	Patient (%)
Symptomatic children	
Urinary infection	24 (16.9)
Abdominal pain	21 (14.8)
Gross hematuria	11 (7.7)
Nausea and vomiting	10 (7.0)
Flank pain	9 (6.3)
Ab normal urine color	9 (6.3)
Dysuria	8 (5.6)
Lower urinary tract symptoms (dribbling and difficult voiding)	8 (5.6)
Frequency	4 (2.8)
Growth retardation	3 (2.1)
Urinary retention	1 (0.7)
Asymptomatic children	
Diagnosed by ultrasonography for different reasons	19 (13.4)
Microscopic hematuria or crystal on urine analysis	11 (7.7)
Others	4 (2.8)

Table 3. Data on 24-Hour and Random Urine Studies in Studied Children*

Urinary Findings	Patient (%)
Hypercalciuria	19 (13.5)
Hyperoxaluria + hyperuricosuria	9 (6.3)
Hyperoxaluria	8 (5.6)
Cystinuria	8 (5.6)
Hyperuricosuria	7 (4.9)
Hyperuricosuria + hypercalciuria	5 (3.5)
Hypocitratiuria	2 (1.4)
Hypomagnesuria	1 (0.7)
Hypocotriaturia + hyperuricosuria + hypercalciuria	1 (0.7)
Hyperuricosuria + cystinuria	1 (0.7)

*Values in parentheses are percents.

There were no significant differences regarding the frequency and types of metabolic abnormalities between the children with and without a positive family history of urinary calculi (Table 4).

Three of 6 patients with nephrocalcinosis had hypercalciuria. Hypercalciuria was also found in 22 of 136 children (16.1%) who did not have nephrocalcinosis ($P = .04$). Two of 13 children (15.4%) who had hypercalcemia were also hypercalciuric. This was also found in 23 of 129 (17.8%) who had normal serum calcium levels ($P = .82$). None of the patients with nephrocalcinosis had hypercalcemia. Of 19 patients with hypercalciuria, a clinical cause for hypercalciuria was found just in 1 patient and others were diagnosed with idiopathic hypercalciuria.

Table 4. Urine Parameters in Patients With a Positive Family History of Calculus Versus Those With a Negative Family History*

Urine Parameters	Children With Urinary Calculi		*P*
	Positive Family History	Negative Family History	
Normal	52 (58.5)	28 (53.2)	.51
Hypercalciuria	12 (13.6)	7 (13.5)	.96
Hyperuricosuria	4 (4.5)	3 (5.8)	.99
Hyperoxaluria	5 (5.6)	3 (5.8)	.99
Hypocitraturia	2 (2.3)	0	.52
Hypomagnesuria	1 (1.1)	0	…
Cystinuria	3 (3.4)	5 (9.6)	.13
Mixed abnormalities	11 (12.5)	5 (9.6)	.59

*Values in parentheses are percents.

Urinalysis revealed gross hematuria in 11 children (7.7%), microscopic hematuria in 22 (15.4%), and sterile pyuria in 26 (18.3%). No abnormal findings were reported in the urine of 83 patients (58.4%). Twenty-four children (16.9%) had a history of urinary tract infection (UTI), and urinary calculus was diagnosed during imaging studies for UTI follow-up. In addition, in 6 children (4.2%) ,UTI was diagnosed during laboratory evaluation for urinary calculi. In the first group, the causative agents for UTI were urease-negative bacteria (mostly *Escherichia coli*), but in the second group, it included *Escherichia coli* in 3, and *Proteus vulgaris*, *Kelebsiella*, and enterococci in the others.

Serologic tests revealed hypercalcemia in 13 (9.1%) and hypomagnesaemia in 9 children (6.3%). One patient had hyperchloremic metabolic acidosis with alkaline urine pH. Some patients underwent additional imaging studies to exclude associated anatomical abnormalities. Voiding cystourethrography was performed for patients with a history of UTI or those in whom renal ultrasonography revealed hydronephrosis or hydroureteronephrosis in the kidney-ureter units which did not have a calculus or unexplainable dilatation with a small calculus. Totally, in 34 patients, voiding cystourethrography was done which revealed vesicoureteral reflux in 9 (26.5%). Renal ultrasonography revealed moderate to severe hydronephrosis or hydroureteronephrosis unrelated to the calculus in 7 children (4.9%). Intravenous urography revealed anatomical ureteropelvic junction obstruction and ureterovesical junction obstruction in 1 (0.7%) and 2 (1.4%) patients, respectively. We performed intravenous urography in order to differentiate anatomical obstruction from urinary obstruction secondary to a calculus. Of 10 patients (7.0%) for whom calculus analyses were available, 7 had pure and 3 had mixed calcium calculi (including a combination of calcium and oxalate with uric acid in 2, and calcium-oxalate with uric acid and calcium-phosphate in 1). Half of the calcium calculus formers had normal urine parameters. Interestingly, hyperuricosuria and hyperoxaluria were the most common abnormal urine parameters in calcium calculus formers (hyperoxaluria, hyperuricosuria, and mixed abnormalities were reported each in 3 patients). Nine children (6.3%) needed nonmedical interventions, including extracorporeal shockwave lithotripsy in 7 and open surgery in 2. One patient needed shockwave lithotripsy twice.

DISCUSSION

Pediatric urolithiasis is an endemic disease, especially in certain developing countries such as the Far East, Middle East, and Turkey.[19] This prospective study provided information on pediatric urolithiasis in a developing country. Although the true incidence of urolithiasis in Iranian children has not been identified, considering the large number of referred patients with nephrolithiasis to pediatric nephrology clinic in our province (Khorasan province, which is the largest and the most populated province of Iran), pediatric urolithiasis seems to be common in Iran.

In the United States, hypersecretion of calcium has been reported as an important risk factor of pediatric calculus disease. Significant association of idiopathic hypercalciuria with the risk of future urolithiasis in children with hematuria has been reported.[20] In developing countries, children may have uric acid calculi which are often found in the bladder.[21] Lama and colleagues also documented higher urinary calcium excretion in children with urolithiasis than in controls.[22] Scheinman

reported hypercalciuria in as many as 66% of pediatric calculus cases.[23] Battino and colleagues reported calcium-related abnormality as the most common metabolic derangement in children with nephrolithiasis.[24] A study performed in Pakistan showed low urinary citrate and magnesium levels (in half of the patients), hyperoxaluria, and hyperuricosuria as common findings. Hypocitraturia has been reported as the most common risk factor in patients with calcium calculus disease among Turkish children.[25] Tekin and colleagues found hypocitraturia as the most important metabolic risk factor of calculus formation and hyperoxaluria as a common etiologic factor which accompanies hypocitraturia in Turkish pediatric calculus formers. They also reported calcium calculi in the absence of any predisposing factor.[26] In a study on 72 pediatric Turkish patients with urolithiasis, metabolic, anatomic, infectious, and idiopathic reasons accounted for 33%, 30%, 26%, and 11% of urolithiasis cases. In addition, all patients with a family history of calculus had a metabolic etiology which considered being the reason of calculus formation. The most common metabolic abnormality was hypercalciuria.[19] In our series, metabolic and anatomic abnormalities were found in 61 (42.7%) and 12 (8.4%) patients, respectively. Thirty patients had UTI when urolithiasis was diagnosed, while in only 3 children (2.1%), we found infection with urease-positive organisms (infectious calculi). Three patients had a combination of metabolic and anatomic abnormalities, while in 66 patients (46.2 %), we did not find any reasons for calculus formation (idiopathic).

Some studies suggested that determination of urinary supersaturation for calcium-oxalate, calcium-phosphate, and urate may be helpful, but a recent study revealed that in children, these studies do not offer much additional information than consideration of 24-hour urine volume.[27] Most children with elevated supersaturation had a urine volume less than 1 mL/kg/h.[27] Although metabolic defects, urinary stasis, and infection seem to be the major causes of urinary calculi in many western countries,[28] in countries where pediatric urinary calculus is considered to be endemic, the etiology remains idiopathic in the majority of cases.[29] Metabolic abnormalities have been reported in 30% to 86% of children with urolithiasis, depending on the location of the studies.[23,30] When pediatric patients form calculi, they usually do so in recurrent fashion (65% lifelong risk of recurrence), and because of potential morbidity of the disease, metabolic evaluation is indicated in all children with urolithiasis.[10] Metabolic evaluation can lead to identification of metabolic abnormalities present in patients and help one to establish effective therapy. Type and extent of evaluation depends on the severity and type of calculus, presence and absence of systemic diseases, risk factors of recurrent calculus formation, and family history of nephrolithiasis (considered as a significant risk factor of relapse).[12] Evaluating first-degree relatives of patients who have hypercalciuria and urolithiasis, more than 40% had urolithiasis.[27] In our study, 12 of 19 patients with isolated hypercalciuria and nephrolithiasis had a positive family history of urinary calculus in their close relatives. Evaluating first-degree relatives of patients, 6 (31.5%) had urolithiasis.

We found metabolic abnormalities in 42.7% of our patients; the most common etiologic factors of calculus formation were hypercalciuria (17.6%) and hyperuricosuria (16.1%). Interestingly, most of the patients with hyperuricosuria had mixed abnormalities, including concurrent hyperoxaluria (9 of 23) and hypercalciuria (6 of 23). Cystinuria accounted for 6.3% (9 patients) of nephrolithiasis cases in our patients. Compared to the childhood nephrolithiasis in industrialized countries,[11] cystinuria was twice more common in our series. Although we found metabolic abnormalities in 42.7% of patients, the true incidence of metabolic abnormalities in our series might be more, since 24-hour urine samples were checked for citrate and magnesium only in 44 patients (30.8%) who were toilet trained. Of these patients, 3 (6.8%) had hypocitraturia and low urine magnesium level was found in 1 (2.2%). For correct judgment regarding the true incidence of hypocitraturia and hypomagnesuria, we need to check 24-hour urine samples in all patients. Magnesium is a well-documented inhibitor of urinary calcium oxalate supersaturation, and thus, the nucleation of calcium oxalate crystals. In our series, 9 patients (6.3%) had hypomagnesemia. In 8 of them, 24-hour urine magnesium level was measured and only 1 patient had low urinary magnesium level, but 4 patients had hyperoxaluria and another 4 had hyperuricosuria. We also found hypercalciuria in 1 patient.

Mild and transient hypercalcemia (serum calcium level, 10.3 mg/dL to 11 mg/dL) was found in 13 patients (9.1%), which accompanied by hypercalciuria, Hyperoxaluria, and hyperuricosuria, each in 2 patients. Serum phosphorous and alkaline phosphates levels were normal in all. Most of hypercalcemic patients were infants. We did not find any reason for hypercalcemia and low serum magnesium levels in our patients. Serum calcium levels returned to normal by vitamin D withdrawal. In 3 patients, parathyroid hormone level was checked, which revealed normal results. Thiry patients (21%) had UTI at the time of urinary calculus diagnosis. The rate of UTI in our patients seems to be much lower than other reported series which have reported UTI in 47% of patients with urolithiasis.[28] Two of 30 patients with UTI (6.6%) had infection with urea-splitting organisms (*Proteus* and *Kelebsiella*). This finding reflects the low incidence of struvite calculi in our series, and infection in our patients appeared to be secondary to the calculi.

We found urological abnormalities in 12 patients (8.4%), consisting of vesicoureteral reflux in 9 (6.3%) and obstructive uropathies in 3 (2.1%). The occurrence of primary vesicoureteral reflux and urinary calculi in infants and children has been reported infrequently.[31] Regarding some studies, the incidence of vesicoureteral reflux in patients with urolithiasis is approximately 8%.[32] Although we found vesicoureteral reflux in 9 of 142 patients (6.3%), the true incidence of urological abnormalities like vesicoureteral reflux in our patients may be more, since urinary tract imaging studies including voiding cystourethrography were not done in all patients. The incidence of vesicoureteral reflux in our series is compatible with our previous study which revealed nephrolithiasis in 6 of 87 pediatric patients (6.8%) with vesicoureteral reflux.[33] Compared with Robert and Atwell's study,[34] it seems that association of vesicoureteral reflux with nephrolithiasis is significantly more common in our series.

CONCLUSIONS

Hypercalciuria and hyperuricosuria seemed to be the most important metabolic factors of calculus forming in our pediatric series. Hyperoxaluria is also a common etiologic factor which accompanies hyperuricosuria in half of the patients, and it seems that association of vesicoureteral reflux and nephrolithiasis in our patients is more frequent than other series. We proved presence of vesicoureteral reflux at least in 9 of 142 pediatric patients (6.3%) with nephrolithiasis. In our series, reflux was the most common urological abnormality resulting in urinary stasis and calculus formation. Urolithiasis can lead to UTI by urinary stasis or obstruction. However, it seems logical to rule out urological abnormalities, especially vesicoureteral reflux, when UTI happens in children with nephrolithiasis. Regarding the significant incidence of vesicoureteral reflux in patients with nephrolithiasis who have UTI, we recommend voiding cystourethrography in this group.

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CONFLICT OF INTEREST

None declared.

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