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Metabolic Abnormalities in Children with Urinary Stone Disease and The Influence of Gender

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ABSTRACT:

Metabolic abnormalities in children with urinary stone disease and the influence of gender

Objective: Urinary stone disease is associated with age, gender, diet, climate, and genetic causes. Infections, anatomic and metabolic abnormalities can lead to stone formation. We aimed to evaluate epidemiologic and metabolic factors in children with urolithiasis.

Material and Methods: A total of 89 patients (46 girls), aged between 0 and 18 years with diagnosis of urolithiasis, microlithiasis and a history of urolithiasis were recruited in this retrospective study. Medical records were assessed for current age, gender, age at diagnosis, presenting symptoms, family history, physical findings, medications, results of laboratory tests (including blood urea nitrogen, serum creatinine, electrolytes, blood gases, urinalysis:urinary calcium, uric acid, oxalate, cystine, citrate, magnesium and creatinine levels) and radiological findings.

Results: The mean age was 6.20±5.27 (range, 0.2-18.2 years). Stones were mostly located in the kidneys (n=52, 58.4%). Microlithiasis, urolithiasis and urolithiasis history were defined in 22 (24.7%), 64 (71.9%), and 3 (3.4%) patients, respectively. Anatomic abnormalities were determined in 17.9% of the patients. Of all patients, 31 (34.8%) had metabolic abnormalities in their urinary analyses. While 26 patients (29.2%) had one metabolic abnormality, five (5.6%) patients had more than one. Metabolic abnormalities were two times more in girls than in boys (p=0.027). The most common metabolic disorder detected was hypocitraturia (n=16, 17.9%), followed by hyperoxaluria (n=8, 8.9%), hypercalciuria (n=6, 6.7%), and hyperuricosuria (n=6, 6.7%).

Conclusions: Metabolic abnormalities were detected frequently in children with urinary stone disease. Hypocitraturia was the most common metabolic abnormality. Detailed evaluation is needed to manage patients with urolithiasis. Female gender may be accepted as a predisposing factor for metabolic abnormality.

Keywords: Childhood, gender, hypercalciuria, hypocitraturia, urolithiasis

ÖZET:

Üriner sistem taşı olan çocuklarda metabolik bozukluklar ve cinsiyetin etkisi

Amaç: Üriner sistemde taş varlığı; yaş, cinsiyet, diyet, iklim ve genetik nedenlerle ilişkilidir. Enfeksiyonlar, anatomik ve metabolik bozukluklar taş oluşuma eğilim yaratan nedenlerdir. Bu çalışmada üriner sistem taşı olan çocuklarda epidemiyolojik ve metabolik faktörlerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Retrospektif olan bu çalışmada, ürolitiazis, mikrolitiazis ve ürolitiazis hikayesi olan 0-18 yaş aralığındaki 89 (46 kız) hastanın dosyası geriye dönük şekilde incelendi. Güncel yaş, cinsiyet, tanı yaşı, başvuru semptomları, ailede taş hikayesi, fizik muayene bulguları, kullandıkları ilaçlar, laboratuvar tetkikleri (kan üre nitrojeni, serum kreatinin, elektrolit, kan gazları; idrarda kalsiyum, ürik asit, okzalat, sistin, sitrat, magnezyum ve kreatinin düzeyleri değerlendirildi) ve radyolojik bulgular kaydedildi.

Bulgular: Yaş ortalaması 6.20±5.27 (minimum-maksimum, 0.2-18.2) yıl idi. Taşlar en sık böbrekte yerleşmekteydi (n=52, %58.4). Yirmi iki hasta (%24.7) mikrolitiazis, 64 hasta (%71.9) ürolitiazis ve üç hasta (%3.4) ürolitiazis hikayesi olan grupta idi. Anatomik sorunlar %17.9 hastada saptandı. Tüm hastaların 31'inde (%34.8) idrar analizlerinde metabolik bozukluk saptandı. Yirmi altı (%29.2) hastada tek metabolik bozukluk saptanırken, birden fazla metabolik bozukluk beş (%5.6) hastada tespit edildi. Kızlarda metabolik bozukluk erkeklerden iki kat fazla idi (p=0.027). En sık metabolik bozukluk hipositratüri (n=16, %17.9) ve sonrasında hiperokzalüri (n=8, %8.9), hiperkalsiüri (n=6, %6.7) ve hiperürikozüri (n=6, %6.7) olarak tespit edildi.

Sonuçlar: Üriner sistem taşı olan çocuklarda metabolik bozukluklar sık saptandı. Hipositratüri en sık saptanan bozukluklardan olup hasta yönetimi için kapsamlı değerlendirme gereklidir. Kız cinsiyet metabolik bozukluk için yatkınlık oluşturan bir faktör olarak kabul edilebilir.

Anahtar kelimeler: Çocukluk, cinsiyet, hiperkalsiüri, hipositratüri, ürolitiazis

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INTRODUCTION

Urinary stone disease is an important health problem with increasing frequency, which leads to frequent admission to the hospital, and can lead to major problems such as end-stage renal failure. Presence of stones in urinary system is associated with age, gender, diet, climate, and genetic factors, and is reported to be between 1-15% of frequency at adulthood (1). With increasing incidence in children, it is not known precisely, prevalence is reported to be 1-15% in Turkey and in various countries (2,3).

Although the mechanism of stone formation is not clearly known, there is a hypothesis that crystals begin to form with affected cells at the tubular level (4). Some anatomical problems (such as urinary tract strictures and vesicoureteral reflux), infections, endocrine disorders and some metabolic disorders are known to facilitate stone development in the urinary system. Metabolic disorders in children with urinary tract stones are reported in a wide range of about 30-90% from the world and Turkey (5-10). Metabolic disorders can be divided into two subgroups: 1) Increase in lithogenic factors (such as hypercalciuria, hyperuricosuria, cystinuria and hyperoxaluria), 2) Decrease in factors inhibiting stone formation (such as hypocitraturia and hypomagnesuria) (11). In the presence of metabolic disorder, recurrence of stones in the urinary system is increased and remission can be achieved by appropriate treatment.

The purpose of this study is to contribute to the monitoring of patients by making epidemiological and metabolic evaluation in childhood age group with urinary stone disease.

MATERIAL AND METHODS

Study Design and Patient Group

In this study, the records of 89 children with diagnosis of urolithiasis, microlithiasis and a history of urolithiasis aged between 0 to 18 years, who applied to the Ministry of Health Bağcılar Training and Research Hospital pediatric nephrology clinic between April 2014 and May 2015 were recruited retrospectively. Those with an endocrine or metabolic disease were excluded from the study. Patients' age, gender, age at diagnosis, presenting symptoms, family history, physical examination findings, medications used, laboratory tests [blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), venous blood gas, urine analysis results (complete urine analysis, calcium, uric acid, oxalate, cystine, citrate, magnesium and creatinine levels in spot urine)], and radiological findings (stone placement, size and anatomical problems if any) were assessed and recorded. Metabolites gained from spot urine samples were standardized by being divided to urine creatinine levels.

The diagnosis of urolithiasis was made with having a stone passed at the time of admission or >3 mm stone detected at plain abdominal X-ray or urinary system ultrasonography (US). Microlithiasis is characterized by the appearance of hyperechogenic structures with ≤3 mm diameter in renal calyces. Patients who didn't have stone at the time of admission but who had a spontaneous stone pass or who had a stone removed by surgery prior to admission were evaluated as patients with a history of urolithiasis.

The ethics committee approval was obtained from the Ethics Committee of Bağcılar Training and Research Hospital (Date: 22.04.2014 / No: 04) and the research was conducted in accordance with the Helsinki Declaration. Consents were obtained from the patients and/or their families for participation in the study.

The upper limit of calcium/creatinine ratio in spot urine for hypercalciuria is accepted to be 0.8 mg/mg for 0-12 months of age, 0.53 mg/mg for 1-3 years, 0.4 mg/mg for 3-5 years, 0.3 mg/mg for 5-7 years and 0.2 mg/mg for the age group of 7-18 years. Upper limit of uric acid/creatinine ratio in urine is accepted as 2.2 mg/mg for 0-12 months of age, 1.9 mg/mg for 1-3 years, 1.5 mg/mg for 3-5 years, 0.9 mg/mg for 5-10 years, and 0.6 mg/mg for 10-18 years of age. For the definition of hyperoxaluria, the upper limit of oxalate/creatinine ratio in the urine is accepted as 288 mg/g for 0-6 months of age, 139 mg g for 7-24 months, 80 mg/g for 2-5 years, 65 mg/g for 5-14 years, and 32 mg/g for the age group of 14-18 years (12). Cystinuria

was defined as the ratio of cystine/creatinine in the urine to be over 573 µmol/g at 0-2 months of age, 461 µmol/g at 3-8 months, 186 µmol/g at 9 months-2 years, 98 µmol/g at 3-12 years, 81 µmol/g at 13-18 years of age (13). Hypocitraturia was defined as the ratio of citrate/creatinine in urine to be below 0,20 gr/gr between the age of 0-5 years and 0.14 gr/gr between 5-18 years. Hypomagnesuria is defined as the rate of urinary magnesium/creatinine to be below 0.1 mg/mg between 0-12 months of age, 0.09 mg/mg at 1-2 years, 0.07 mg/mg at 2-5 years, 0.06 mg/mg at 5-7 years and 0.05 mg/mg at 7-18 years of age (12). The normal limit for tubular phosphate reabsorption was accepted as >90% (14).

Table-1: Demographic and clinical features

Male/Female (n, %)	43(%48.3) / 46 (%51.7)
Current age (Mean±SD), (years)	6.20±5.27
Age range (years)	0.2-18.2
Age at first detection of stone (Mean±SD), (years)	4.66±4.96
Weight (Mean±SD), (kg)	23.30±16.60
Boy (Mean±SD), (m)	1.08±0.33
BMI (Mean±SD), (kg/m^2)	17.20±2.88
Blood pressure S/D, (Mean±SD), (mmHg)	98.0±11.8 / 56.5±9.7
Causes of admission	
Pain/discomfort n (%)	62 (69.7)
Urinary tract infection history n (%)	23 (25.8)
Hematuria n (%)	17 (19.1)
Vomiting n (%)	16 (18.0)
Incidental n (%)	12 (13.5)
Acute renal failure n (%)	4 (4.5)
Family history of stone n (%)	51 (57.3)

BMI: Body Mass Index, S: systolic, D: diastolic, SD: standart deviation

If urinary tract stones could be obtained (by self-passing or by operation), they were sent for chemical analysis.

Statistical Analysis

SPSS for Windows, Version 21.0 (IBM Corp., New York) was used for statistical analysis of the data. Of descriptive statistics, continuous variables were stated as mean±standard deviation (SS) if normal distribution was present, and as median (minimum-maximum) if abnormal distribution was present. The

Table-2: Results of radiological evaluation of patients

Radiological findings	n (%)
Stone location	
Right kidney	21 (23.6)
Left kidney	31 (34.8)
Both kidneys	23 (25.8)
Ureter	11 (12.4)
Bladder	3 (3.4)
Evaluation with plain abdominal X-ray	
Radio-opaque stone	16 (18.0)
Non-opaque stone	68 (76.4)
No X-ray	5 (5.6)
Classification	
Microlithiasis	22 (24.7)
Urolithiasis	64 (71.9)
History of urolithiasis	3 (3.4)
Urinary system abnormalities	
Hydronephrosis	12 (13.5)
Neurogenic bladder	1 (1.1)
Atrophic kidney	1 (1.1)
Duplicated collecting system (partial)	1 (1.1)
Ureterocele	1 (1.1)

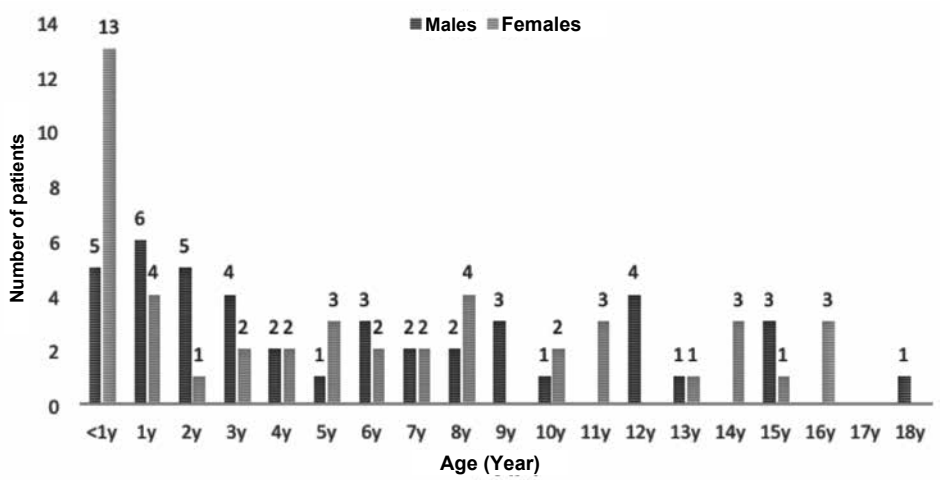

Figure-1: Age distribution according to gender in children with urinary tract stones

Table-3: Urine analysis results in terms of metabolic disorders of patients

	n (%)
Number of patients	89 (100.0)
Metabolic disorder	31 (34.8)
Single metabolic risk factor	26 (29.2)
Hypocitraturia	13 (14.6)
Hyperoxaluria	4 (4.5)
Hypercalciuria	4 (4.5)
Hyperuricosuria	4 (4.5)
Hypomagnesiuria	1 (1.1)
Multiple metabolic risk factor	5 (5.6)
HipoS + HO	2 (2.2)
HO + HK	1 (1.1)
HipoS + HU +S	1 (1.1)
HK + HO + HU	1 (1.1)

HC: hypercalciuria, HO: hyperoxaluria, HU: hyperuricosuria, HypoC: hypocitraturia, C: cystinuria

frequencies are given in terms of number (n) and percentage (%). p value ≤0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of 89 patients (43 males/46 females) evaluated in the study are shown in Table 1. The mean age was 6.20±5.27 (minimum-maximum, 0.2-18.2) years. Age distribution by gender is presented in Figure-1. The age at detection of stone was between 1 month-16 years. The most common presenting complaints were pain or discomfort (n=62, 69.7%), urinary tract infection (n=23, 25.8%) followed by hematuria (n=17, 19.1%). Twelve patients without symptoms (13.5%) had a coincidental urinary tract stone. In addition, four patients (4.5%) admitted with an acute renal failure condition. Physical examination findings were normal except costovertebral angle tenderness in four patients. Radiological evaluation data are presented in Table-2. Stone settement was most common in the kidney (n=52, 58.4%). On plain abdominal X-ray, only 18% of the stones (n=16) could be seen (radio-opaque). According to ultrasonographic evaluation, median stone size was 5.4 mm (minimum-maximum, 1-24 mm). Microlithiasis was detected in 22 patients (24.7%) and urolithiasis in 64 patients (71.9%). Three patients (3.4%) had a history of stone passage prior to application. The urinary system examination revealed anatomical problems in 16 (17.9%) patients and the most common anomaly was hydronephrosis (n=12, 13.5%).

Examination of blood samples showed biochemical anomalies [hypercalcemia (n=6, 6.7%), hyperuricemia (n=4, 4.5%), metabolic acidosis (n=6, 6.7%) and metabolic alkalosis (n=2, 2%)].

Metabolic disorders were detected in 31 (34.8%) of all patients in urine analysis (Table-3). Twenty-six (29.2%) patients had only one metabolic disorder while more than one metabolic disorder was detected in five (5.6%) patients. Metabolic disorders in females were twice more than that in males (p=0.027)

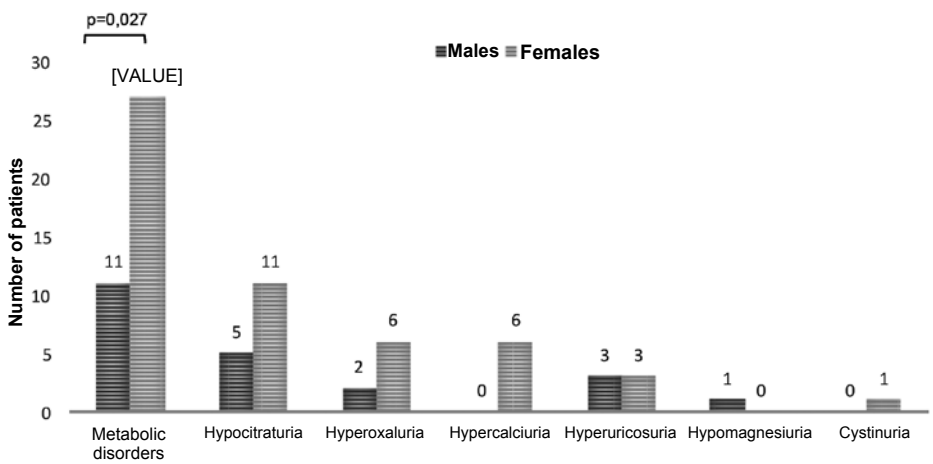

Figure-2: The frequency and distribution of metabolic disorders according to gender (single and multiple metabolic disorders were considered together and counted as two separate cases when there were two metabolic disorders in a patient).

(Figure-2). When single and multiple metabolic disorders were considered together, hypocitraturia was the most common metabolic disorder (n=16, 17.9%), follwed by hyperoxaluria (n=8, 8.9%), hypercalciuria (n=6, 6.7%), hyperuricosuria (n=6, 6.7%) and cystinuria (n=1, 1.1%). Patients with hypercalciuria had normal serum calcium levels (idiopathic hypercalciuria).

Family history of stone was present in more than half of the patients (n=51, 57.3%). In addition, 31% (16/51) of children with a family history of stone had metabolic disorders.

The chemical analysis of the stone was performed in 13 of the 89 patients, and calcium oxalate stone (CaC_2O_4) was detected in nine patients. The stone analysis of the remaining four patients revealed uricite (n=2), silicium dioxide (n=1) and fluorapatite (n=1).

Prior to the admission, 14 patients (n=15.7) underwent "Extracorporeal Shock Wave Lithotripsy (ESWL)", two patients underwent percutaneous nephrolithotomy and one patient underwent cystolithotomy.

DISCUSSION

Although the frequency of urinary tract stones, which is relatively low compared to the adults in children, is not known precisely, it takes an important place in the reasons for application to the hospital. Incidence and etiology are associated with the geography in which they live (9). Most of these children have a family history of stone with a frequency of 40-55% of cases (8,9,15,16). In this study, the family history was found to be 57.3%, consistent with the literature.

Stone placement in urinary system is related to variables such as anatomical problems, chemical content of the stone, and infection. Bladder-located stones (ammonium urate) in countries in which carbohydrate intake is rich (such as Southeast Asian countries) are more commonly reported, while upper urinary tract stones (calcium oxalate and phosphate) are more commonly reported in developed countries in which protein intake is high (17,18). Upper urinary tract stones are commonly mentioned in publications reported in recent years from Turkey (8,19).

Plain abdominal X-ray was reported to be sensitive in 45-58% of the patients in detection of the stone, and it provided positive results in 16/84 (19%) patients in this study (20). Although most of the stones have radio-opaque content, plain abdominal X-ray alone is insufficient to evaluate the patient with a probable stone. Ultrasonography can detect 90% of kidney-located stones, but it is difficult to detect <5 mm stones (21). In this study, it was seen that <3 mm small stones (microlithiasis) could be detected in a significant part of the patients (24.7%). When performed carefully, anatomical evaluation is also an advantage by ultrasonography, which has an important place in the diagnosis. Because children with urinary tract stones can have genitourinary anomalies of 30% (such as hydronephrosis, duplicated collecting system, posterior urethral valve and bladder anomalies) (22). Structural or functional obstructions let to tendecy to stone formation by causing urine stasis and infection. It is stated that only 1-5% of children with urinary anomalies form stones and the accompanying metabolic disorders increase this rate (17,23). Also, in this study genitourinary anomalies were detected in 17.9% of patients.

Although the coexistence of urinary tract infection and urinary tract stones are common, formation of stones other than the struvite stones has not been shown (9,15). In this study, there was a history of urinary tract infection in a quarter of the patients but there was no patient identified with struvite stones.

In studies involving urinary tract stone cases in childhood age group, stone formation has been associated with various metabolic disorders and reported in 30-90% of cases (5-7,10,18). A comprehensive screening in mandatory, regarding possible permanent damage to renal functions by these disorders. Metabolic disorders should be assessed by examining blood and urine specimens. Hypercalcemia, hyperuricacidemia, metabolic acidosis or alkalosis can be suggestive in terms of possible diseases. Hypercalcemia was observed in six patients, hyperuricemia in four patients, metabolic acidosis in six patients and metabolic alkalosis in two patients, and these results were accepted as a guide for diagnosis (such as renal tubular disease) and

treatment (diet or drug therapy). Hypercalciuria and hypocitraturia are reported as the most common metabolic disorders, although their frequency varies in the studies. In addition, hyperoxaluria, hyperuricosuria and cystinuria are the other known metabolic disorders (8,10,17). In this study, metabolic disorder was detected in approximately one-third (34.8%) of the patients, and hypocitraturia, hyperoxaluria, hypercalciuria, and hyperuricosuria, respectivel, were the significant metabolic risk factors. Similar to other studies, hypocitraturia was detected fairly frequently, whereas hypercalciuria was less frequent than expected. Tefekli et al. (24) reported that the most common metabolic disorder was hypocitraturia, while Alpay et al. (5) have found that hypocitraturia and hypercalciuria are equally the two most common metabolic disorders. In addition, the frequency of hypocitraturia in children followed between 2003 and 2005 was reported as 52% (25). While hypocitraturia is often idiopathic, nutrition rich in animal proteins and poor from potassium and plant foods contributes to the reduction of citrate excretion (26,27).

Oxalate is the final product of glyoxylate and ascorbic acid metabolism and is primarily excreted through the kidneys. 80-90% of daily oxalate excretion occurs at the end of normal metabolic process and 10-15% is related to diet. The increase in oxalate levels in the urine may be secondary to a genetic-metabolic disease (primary hyperoxaluria) or, more commonly, to an increase in oxalate absorption or increased intake. In our study, there were eight patients with hyperoxaluria and there was no case with proven primary hyperoxaluria.

Hypercalciuria is reported to have a frequency of 30-50% in children with urolithiasis, and mostly the most common metabolic disorder (5,7,8,10,18). It is usually idiopathic and may be associated with endocrine (such as hyperparathyroidism and D hypervitaminosis), rheumatologic (such as juvenile rheumatoid arthritis and sarcoidosis), nephrological (such as tubular diseases) and genetic problems (such as Williams syndrome and familial hypercalciuria) (17). Idiopathic cases are defined as presence of hypercalciuria without hypercalcemia. In this study, different than in the literature, hypercalciuria was found less frequently (n=6, 6.7%). Serum calcium was normal in patients diagnosed with hypercalciuria but the serum calcium level was slightly elevated according to the age of six different patients. For this reason hypercalciuria was defined as idiopathic.

Uric acid excretion is highest in the newborn period and reaches to more stable levels after two years of age. In the presence of hyperuricosuria, low urine pH forms a serious predisposition for the formation of uric acid stones. If accompanied by hyperuricemia, genetic diseases related to purine metabolism, lymphoproliferative diseases and polycythemia should be investigated. The frequency of hyperuricosuria ranges from 6% to 25% (5,7,8,19). The frequency of hyperuricosuria in this study was found to be consistent with the frequency reported in the literature.

The stone formation in the urinary system starts with the crystallization of some ions (supersaturation) in the urine. The most important parameters for crystallization can be counted as the total urine volume, density of ions predisposing to stone formation, presence of sufficient levels of inhibitors and urine pH. The frequency of all stone types is reduced in urine with low density (diluted). In addition, citrate, magnesium, pyrophosphate and glycosaminoglycans have reducing effects on the crystallization of calcium oxalate and calcium phosphate. In this study, hypocitraturia was the most common metabolic disorder, and hypomagnesuria was seen in one patient. Several studies have reported multiple metabolic disorders together, and results consistent with the literature have been obtained in this study (5,7,10). Increased ions in such cases may increase the crystallization of each other. For example, increase in uric acid concentration in urine increases calcium oxalate crystallization.

There are different reports about the relation between stone and gender and it is stated that they are more frequent in males, whereas there are studies reporting equal frequency (8,15,28). In our study, the incidence of stone presence was not statistically different between males and females for all ages, consistent with the literature, but the was found to be significantly increased in females at first age. In

addition, when all ages were considered, the rate of metabolic disorders was twice as high in girls. Hypocitraturia, hyperoxaluria and hypercalciuria were more common in females. There is limited data in the literature about this subject, and Alpay et al. (15) reported that cystinuria was seen more in boys in children under one year of age.

In conclusion, important information obtained from this study, which retrospectively evaluated patients who were seen at a period of about one year included that the family story is common in children with urinary tract stones, the stones are usually located in the upper urinary tract, microlithiasis is present at significant rates, anatomical problems are not uncommon and the most important predisposing factor is the metabolic disorders. It was also shown that other disorders, especially hypocitraturia, can be detected as frequently as hypercalciuria. Adequate metabolic assessment should be performed in children with urinary tract stones and a treatment plan should be planned if risk factors are present. Although female gender seems to be a predisposing factor for metabolic disorders, further studies are needed involving larger number of cases in this regard.

REFERENCES

1. *Pearle MS, Antonelli JA, Lotan Y. Urinary Lithiasis: Etiology, Epidemology, and Pathogenesis. In: Wein AJ (ed) Campbell-Walsh Urology, 17th ed. Philadelphia: Elsevier; 2016. p.1170-99.*
2. *Rizvi SA, Naqvi SA, Hussain Z, Hashmi A, Hussain M, Zafar MN, et al. Pediatric urolithiasis: developing nation perspectives. J Urol 2002; 168: 1522-5.* **[CrossRef]**
3. *Akinci M, Esen T, Tellaloglu S. Urinary stone disease in Turkey: an updated epidemiological study. Eur Urol 1991; 20: 200-3.*
4. *Lieske JC, Toback FG. Renal cell-urinary crystal interactions. Curr Opin Nephrol Hypertens 2000; 9: 349-55.* **[CrossRef]**
5. *Alpay H, Ozen A, Gokce I, Biyikli N. Clinical and metabolic features of urolithiasis and microlithiasis in children. Pediatr Nephrol 2009; 24: 2203-9.* **[CrossRef]**
6. *Bastug F, Dusunsel R. Pediatric urolithiasis: causative factors, diagnosis and medical management. Nat Rev Urol 2012; 9: 138-46.* **[CrossRef]**
7. *Bilge I, Yilmaz A, Kayiran SM, Emre S, Kadioglu A, Yekeler E, et al. Clinical importance of renal calyceal microlithiasis in children. Pediatr Int 2013; 55: 731-6.* **[CrossRef]**
8. *Celiksoy MH, Yilmaz A, Aydogan G, Kiyak A, Topal E, Sander S. Metabolic disorders in Turkish children with urolithiasis. Urology 2015; 85: 909-13.* **[CrossRef]**
9. *Ece A, Ozdemir E, Gurkan F, Dokucu AI, Akdeniz O. Characteristics of pediatric urolithiasis in south-east Anatolia. Int J Urol 2000; 7: 330-4.* **[CrossRef]**
10. *Elmaci AM, Ece A, Akin F. Pediatric urolithiasis: metabolic risk factors and follow-up results in a Turkish region with endemic stone disease. Urolithiasis 2014; 42: 421-6.* **[CrossRef]**
11. *Kok DJ, Papapoulos SE, Bijvoet OL. Excessive crystal agglomeration with low citrate excretion in recurrent stone-formers. Lancet 1986; 1: 1056-8.* **[CrossRef]**
12. *Hoppe B, Leuman E, Milliner DS. Urolithiasis and nephrocalcinosis in childhood. In: Geary DF (ed). Comprehensive Pediatric Nephrology. 1st ed. Philadelphia: Mosby; 2008. p.499-526.* **[CrossRef]**
13. *Cystine Quantitative, Urine. Available from: http://ltd.aruplab.com/Tests/Pub/0081106*
14. *Matos V, Van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr 1997; 131: 252-7.* **[CrossRef]**
15. *Alpay H, Gokce I, Ozen A, Biyikli N. Urinary stone disease in the first year of life: is it dangerous? Pediatr Surg Int 2013; 29: 311-6.* **[CrossRef]**
16. *Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 2010; 25: 403-13.* **[CrossRef]**
17. *Copelovitch L. Urolithiasis in children: medical approach. Pediatr Clin North Am 2012; 59: 881-96.* **[CrossRef]**
18. *Milliner DS, Murphy ME. Urolithiasis in pediatric patients. Mayo Clin Proc 1993; 68: 241-8.* **[CrossRef]**
19. *Elmaci AM, Ece A, Akin F. Clinical characteristics and metabolic abnormalities in preschool-age children with urolithiasis in southeast Anatolia. J Pediatr Urol 2014; 10: 495-9.* **[CrossRef]**
20. *Mandeville JA, Gnessin E, Lingeman JE. Imaging evaluation in the patient with renal stone disease. Semin Nephrol 2011; 31: 254-8.* **[CrossRef]**
21. *Palmer JS, Donaher ER, O'Riordan MA, Dell KM. Diagnosis of pediatric urolithiasis: role of ultrasound and computerized tomography. J Urol 2005; 174: 1413-6.* **[CrossRef]**
22. *McKay CP. Renal stone disease. Pediatr Rev 2010; 31: 179-88.* **[CrossRef]**
23. *Wenzl JE, Burke EC, Stickler GB, Utz DC. Nephrolithiasis and nephrocalcinosis in children. Pediatrics 1968; 41: 57-61.*
24. *Tefekli A, Esen T, Ziylan O, Erol B, Armagan A, Ander H, et al. Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: is there any difference? Urol Int 2003; 70: 273-7.* **[CrossRef]**
25. *VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol 2007; 177: 2300-5.* **[CrossRef]**
26. *Hess B, Michel R, Takkinen R, Ackermann D, Jaeger P. Risk factors for low urinary citrate in calcium nephrolithiasis: low vegetable fibre intake and low urine volume to be added to the list. Nephrol Dial Transplant 1994; 9: 642-9.* **[CrossRef]**
27. *Kok DJ, Iestra JA, Doorenbos CJ, Papapoulos SE. The effects of dietary excesses in animal protein and in sodium on the composition and the crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. J Clin Endocrinol Metab 1990; 71: 861-7.* **[CrossRef]**
28. *Yagisawa T, Hayashi T, Yoshida A, Kobayashi C, Okuda H, Ishikawa N, et al. Comparison of metabolic risk factors in patients with recurrent urolithiasis stratified according to age and gender. Eur Urol 2000; 38: 297-301.* **[CrossRef]**