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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Obesity on Metabolic Risk Factors in Children with Urinary Stones

Üriner Sistem Taşı Olan Çocuklarda Obezitenin Metabolik Risk Faktörlerine Etkisi

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ABSTRACT

Aim: Hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia have accepted as metabolic risk factors causing urolithiasis. There are many studies reporting that obesity increases the risk of stone formation by metabolic risk factors. The aim of this study is to evaluate the frequency of metabolic risk factors and the effect of body mass index (BMI) on them.

Material and Method: Children with urolithiasis >3 mm included in the study. Demographic information and biochemistry analyses including urine metabolic screening were recorded.

Results: Of the 155 patients (94 male/61 female) included in the study, with a mean age of 71±57 months, 98 (63%) have a family history of stones. There was at least one metabolic risk factor in 38.7% of the patients, and the most common ones were hyperoxaluria (16.8%) and hypocitraturia (16.8%), respectively. The presence of metabolic risk factors was significantly higher in patients with stone size ≥5 mm and with multiple stones, respectively (p=0.015, p=0.028). Patients with underweight and normal weight were grouped as Group 1 (n=99 patients), and those with overweight and obese as Group 2 (n=56 patients). The frequencies of hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria were similar between groups.

Conclusion: Family history is common in children with urinary system stones. Since the probability of metabolic risk factors is higher in patients with stone size >5 mm and multiple stones, evaluation in this regard would be appropriate, especially in these patients. There was no evidence in this study that obesity increases metabolic risk factors.

Keywords: Urolithiasis, obesity, body mass index, hyperoxaluria, hypocitraturia

ÖZ

Amaç: Hiperkalsiüri, hiperoksalüri, hiperürikozüri, hipositratüri üriner sistem taş hastalığına neden olan metabolik risk faktörleri olarak kabul edilmiştir. Obezitenin metabolik risk faktörlerine bağlı olarak taş oluşum riskini artırdığını bildiren birçok çalışma bulunmaktadır. Bu çalışmanın amacı metabolik risk faktörlerinin sıklığını ve vücut kitle indeksinin (VKİ) ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: 3 mm'nin üzerinde ürolitiazisi olan çocuklar çalışmaya dahil edildi. Demografik bilgiler ve idrar metabolik taramasını da içeren ve biyokimya analizleri kaydedildi.

Bulgular: Ortalama yaşları 71±57 ay olan 155 hastanın (94 erkek/61 kadın) 98'inin (%63) ailesinde taş öyküsü vardı. Hastaların %38,7'sinde en az bir metabolik risk faktörü vardı ve en yaygın olanlar sırasıyla hiperoksalüri (%16,8) ve hipositratüriydi (%16,8). Taş boyutu ≥5 mm olan ve multipl taşı olan hastalarda metabolik risk faktörlerine daha sık rastlanmaktaydı (p=0,015, p=0,028). Hastalar, zayıf ve normal kilolu hastalar Grup 1 (n=99 hasta), fazla kilolu ve obez olanlar Grup 2 (n=56 hasta) olmak üzere gruplandırıldı. Hiperkalsiüri, hiperürikozüri, hiperoksalüri, hipositratüri ve sistinüri sıklıkları gruplar arasında benzer bulundu.

Sonuç: Aile öyküsü üriner sistem taş hastalığında önemli bir uyarıcıdır. Taş boyutu >5 mm ve birden fazla taşı olan hastalarda metabolik risk faktörlerinin görülme olasılığı daha yüksek olduğundan, özellikle bu hastalarda bu açıdan değerlendirme yapılması uygun olacaktır. Bu çalışmada obezitenin metabolik risk faktörlerini arttırdığına dair bir bulguya rastlanmadı.

Anahtar Kelimeler: Ürolitiazis, obezite, vücut kitle indeksi, hiperoksalüri, hipositratüri

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INTRODUCTION

Urinary system stone disease occurring as a result of a process accompanied by infection as well as metabolic and anatomical factor, brings along high morbidity and mortality, causing kidney damage and chronic kidney disease in children (1). The prevalence of kidney stones in childhood is reported to be 2-3% (2). Changes in climate, socioeconomic conditions, increase in welfare level and changes in dietary habits have led to an increase in the incidence of urinary system stones in children. All these have caused changes in etiological factors, stone localization, and chemical content of the stone (3). It has been reported that more than half of the underlying cause of urinary system stone cases is metabolic disorders. Among these disorders, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia have been accepted as metabolic risk factors that increase the risk and recurrence of urolithiasis (2). Obesity is an increasing problem both in western society and in our country. The prevalence of obesity is increasing day by day all over the world, especially in developed countries (4). As in the adult population, there is an increase in the prevalence of childhood and adolescence obesity. In studies conducted with school children in our country, it is observed that the prevalence of obesity exceeds 10% (5). Although there are many studies reporting that obesity increases the risk of stones by increasing hypercalciuria, hyperoxaluria, hyperuricosuria, which are known as metabolic risk factors, there are also studies indicating the opposite. In this study, we evaluated the demographic, clinical and laboratory characteristics of children followed up with the diagnosis of urinary system stones and the effect of body mass index on metabolic risk factors.

MATERIAL AND METHOD

The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.02.2022, Decision No: 1771). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a retrospective cross-sectional study in 155 patients who were followed up with urinary system stones between 10/2019-12/2021 in the Department of Pediatric Nephrology Outpatient Clinic of Adana City Training and Research Hospital. Patients who were followed up and treated with the diagnosis of urinary system stones in the Pediatric Nephrology outpatient clinics of our hospital, between the ages of 2 months and 18 years, with stones >3 mm, and who were screened for metabolic risk factors were included in the study. Demographic information, laboratory data (hemogram, biochemistry, blood gas, urinary electrolytes, and urine metabolic screening) were recorded from patient files. BMI and BMI percentile (BMIp) of the patients were recorded and the effect of BMIp on metabolic risk factors was evaluated. Obesity was evaluated according to BMI, and obese patients were included in the study without distinction between endogenous and exogenous obesity.

Definitions:

BMI is obtained by dividing the body weight in kilograms by the square of the height in meters (BMI= kg/ m2). Patients with BMI <5p were classified as underweight, those with BMI 5–84p as normal weight, those with BMI 85–94 as overweight, and those with BMI ≥95p as obese (6).

The calcium/creatinine excretion in spot urine is >0.53 mg/mg in patients aged 1-3 years, >0.4 mg/mg in patients aged 3-5 years, >0.3 mg/mg in patients aged 5-7 years and >0.2 mg/mg in patients aged 7-18 years was defined as hypercalciuria. Uric acid/creatinine excretion in spot urine >1.9 mg/mg in children 1-3 years old, >1.5 mg/mg in children 3-5 years old, >0.9 mg/mg in children 5-10 years old mg, and >0.6 mg/mg in children aged 10-18 years was defined as hyperuricosuria. Hyperoxaluria was defined as oxalate/creatinine excretion in spot urine>80 mg/g between 2-5 years of age, >65 mg/g between 5-14 years of age and >32 mg/g between 14-18 years of age. Cystinuria was defined as urinary cystine/creatinine excretion above 98 µmol/g at the age of 3-12 years and above 81 µmol/g at the age of 13-18 years. Hypocitraturia was defined as urinary citrate/creatinine excretion ratio below 0.20 g/g between 0-5 years old and 0.14 g/g between 5-18 years old (7).

Statistical Analysis

Statistical analysis of the study was performed using the Statistical Package for Social Sciences" version 20 (IBM Corp., Armonk, NY, USA) program. Descriptive statistics of numerical data were calculated as mean ± standard deviation in parametric data and median (minimum-maximum, interquartile) in non-parametric data. Categorical data were given as percentage (%). Chi-square analysis and Fisher's exact test was used to compare categorical measures between groups. In the comparison of numerical measurements between the groups, the T test was used if the assumptions were met, and the Mann Whitney U test was used if the assumptions were not met. Mann-Whitney U test was used for continuous variables under parametric conditions and Student's t-test under nonparametric conditions. The significance level used for these tests was $p<0.05$.

RESULTS

Clinical Presentation, Family History, and Imaging

Of the 155 patients included in the study, 94 (60.6%) were male and 61 (39.4%) were female, with a mean age of 71±57 months. The mean age of the girls and boys was similar. There was a history of consanguinity in 16 (10.3%) patients. Urinary system stones were present in the family history of 98 patients (63%). Urinary tract stones were found incidentally in 62 (41.3%) patients. The most common complaint of the patients at the time of admission was abdominal pain with 44 patients (29.1 %). Hematuria, vomiting, restlessness, family history of stones and dysuria were among the other complaints of the patients. The urinary system stones of the patients were located in the left kidney in 74 (47.7%) patients, in the right kidney in 65 (41.9%) patients, in both kidneys in 11 (7.1%) patients, and in the bladder in 5 (3.2%) patients.

It was determined that 104 (68%) patients had 1 stone, 49 (32%) patients had 2 or more stones. Staghorn stones were detected in 5 (3.2%) of them. Median stone size was 5 mm (IQR 4mm, min:3mm, max:30 mm). The presence of metabolic risk factors was significantly higher in patients with stone size ≥5 mm and with multiple stones, respectively (p=0.015, p=0.028). There was a weak correlation between stone size and BMIp (p=0.029, r=0.175).

Metabolic Risk Factors

The presence of at least one of the metabolic risk factors was found in 60 patients (38.7%) included in our study. Analyzing the metabolic risk factors causing stone, hyperoxaluria was the most common risk factor in 25 patients (16.8%). This was followed by hypocitraturia in 25 (16.7%) patients, cystinuria in 12 (7.9%) patients, hypercalciuria in 9 (6.2%) patients, and hyperuricosuria in 2%. Metabolic risk factors were shown in **Table 1**.

Table 1: Metabolic risk factors in children with urinary system stone disease

	N (positive/total)	%
Hyperoxaluria	25/150	16.8%
Hypocitraturia	25/149	16.7%
Cystinuria	12 /151	7.9%
Hypercalciuria	9/145	6.2%
Hyperuricosuria	2/100	2.0%

BMI and Effect on Metabolic Risk Factors

The median BMIp of the children included in the study was calculated as 70.0 (IQR 66.0). The median BMIp for girls was 71p (IQR 64.5p), and for boys was 69.9p (IQR 68.2p), and the median BMIp was similar for both sexes. BMIp values of patients with and without positive metabolic risk factors were compared. BMIp values of patients with and without hyperoxaluria, hypocitraturia, cystinuria, hypercalciuria and hyperuricosuria were similar (**Table 2**).

Table 2: Comparison of BMIp values of patients with and without positive metabolic risk factors

		N	BMIp		p *
			Mean+ SD	Median (IQR)	
Hypercalciuria	yes	9	50.7±44.5	52.0 (85.7)	0.752
	no	136	61.0±33.6	71.0 (61.0)	
Hyperuricosuria	yes	2	15.5±0.7	15.5 (NA)	0.087
	no	98	61.5±33.6	75.0 (61.0)	
Hyperoxaluria	yes	25	66.0±36.0	77.6 (64.4)	0.082
	no	124	59.6±33.7	70.0 (61.0)	
Cystinuria	yes	12	53.0±30.8	58.0 (59.5)	0.718
	no	130	61.3±30.8	76.0 (63.5)	
Hypocitraturia	yes	25	53.6±34.9	58.8 (62.0)	0.637
	no	125	61.6±33.9	71.0 (62.0)	

*Mann Whitney-U test, NA: Not applicable

According to BMIp values, 13 (8.4%) of the patients were underweight, 86 (55.5%) were normal weight, 21 (13.5%) were overweight, 35 (22.6%) were obese. Patients with underweight and normal weight were grouped as Group 1 (n=99 patients), and those with overweight and obese were grouped as Group 2 (n=56 patients). Group 1 and Group 2 were similar in terms of age and gender (p=0.170, p=0.722). There was no difference between the two groups in terms of urine pH and serum biochemical analyzes. The frequencies of hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria were also similar in patients in group 1 and group 2. Comparison of underweight and normal weight patients with overweight and obese patients in terms of metabolic risk factors was shown in **Table 3**. When the patients were grouped as obese and non-obese, the groups were also similar in terms of each metabolic risk factors. Besides, the presence of any of the (at least one) metabolic risk factors was also not associated with obesity (p>0.05)

Table 3: Comparison of underweight and normal weight patients with overweight and obese patients

	Patients with Underweight and Normal weight	Patients with Overweight and Obese	p *
Laboratory analysis	**Median (IQR)**	**Median (IQR)**	
Urea (mg/dl)	21.0 (10.5)	22.0 (11.0)	0.583
Creatinine (mg/dl)	0.3 (0.2)	0.4 (0.2)	0.506
Uric acid (mg/dl)	3.6 (1.1)	3.7 (1.6)	0.958
Calcium (mg/dl)	10.0 (0.5)	10.0 (0.5)	0.880
Phosphorus (mg/dl)	5.1 (1.3)	4.9 (0.9)	0.753
Potassium (mg/dl)	4.4 (0.8)	4.4 (0.9)	0.697
Magnesium (mg/dl)	2.0 (0.2)	2.0 (0.1)	0.740
Urine pH	7.40	7.39	0.986
Metabolic risk factors	**n (%)**	**n (%)**	**p †**
Hypercalciuria	6 (6.4)	3 (5.9)	0.905
Hyperuricosuria	2 (3.1)	2 (0)	0.295
Hyperoxaluria	13 (14.0)	12 (21.4)	0.239
Cystinuria	8 (8.2)	4 (7.4)	0.741
Hypocitraturia	16 (16.8)	9 (16.4)	0.940

* Mann Whitney-U test, †Chi-square analysis

DISCUSSION

Urinary system stones may be detected between 0.2-15 years of age in childhood. In a study performed by Shahta et al. on children aged 0-18 years, the mean age was found to be 54.3 months; Sas et al. in another study found that boys were usually diagnosed between the ages of 6-11 and girls were diagnosed in adolescence (8,9). In the study of Karabacak et al. from our country, the mean patient age was found to be 9.35 years (10). The gender distribution of childhood urinary system stone disease varies according to age. The prevalence of boys was higher in the first decade of life, and the prevalence was higher in girls in the second decade of life. In the studies carried out, the male/female ratio can vary from 1.14 to 4 (11). In our study, similar to the literature, the male/female ratio was found to be 1.54.

Presence of urinary system stone disease among family members may indicate the relative risk for urinary system stone formation. The rate of those with a family history of childhood urinary system stone disease is reported between 3.15% and 78.7% in different series (1,2,12,13). In a study conducted by Erbağcı et al. in our country, a positive family history was found at a rate of 54% (14). This rate is similar to the family history rate of 63% in our study. Nowadays, there are studies pointed out monogenetic causes to be reason for stone formation in pediatric population (15). Genetic research is not recommended because of the high cost. However, the presence of nephrocalcinosis and recurrence of stone within year should be warning (16). Although the presence of a family history of urinary system stone disease is mostly associated with an underlying genetic cause, it should not be forgotten that shared environmental factors and dietary habits may also contribute to familial predisposition of idiopathic urolithiasis.

Apart from genetic factors, many epidemiological factors such as race, geographical region, climate, socioeconomic level, dietary habits play a role in the pathogenesis of urinary system stone. Regardless of epidemiological differences, the obvious situation is that the incidence of urinary system stone disease is increasing all over the world (17). Urinary system anomalies increased urinary excretion of some metabolites and ions that cause crystal formation, urinary supersaturation, urinary pH and tubular flow rate are seen as the most important risk factors (18).

Studies have shown that childhood urinary system stone disease is associated with underlying metabolic risk factors at a rate of 26-88% (2,8,19,20). In this study we detected at least one metabolic risk factor in 60 (38.7%) of the patients included in our study. Metabolic factors that have the greatest effect on the formation of calcium stones have been reported as hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and hypomagnesemia (18). Hypercalciuria is reported as the most common metabolic disorder with a frequency of 30-50% in children with urinary system stones (2, 21).

In some studies, hypocitraturia with hypocalciuria was reported as the most common metabolic risk factors (22, 23). In our study, unlike those reported in the literature, hypercalciuria was detected less frequently (6.2%), and hypocitraturia with a frequency of 16.7%, was the second most common metabolic risk factor after hyperoxaluria. The reason for these differences may be associated with the fact that in our study, urine metabolites were studied from spot urine samples, not from collected urine for 24 hours.

The relationship between obesity and urolithiasis is well established among adult population (24,25). Ekeruo et al. reported that hypercalciuria, hyperuricosuria and hyperoxaluria were more common in obese patients compared to the non-obese patient group (25). Daudon found that the incidence of uric acid stones was 4 times higher in obese patients than in normal-weight patients, and there was an inversely proportional relationship between BMI and urine pH. (26).

Beside adult population, several studies has been conducted in pediatric population to determine the association between obesity and urolithiasis. Roddy et al. reported that both obesity and hypocitraturia, as the most common metabolic risk factor. However, there was no significant difference between obese and non-obese patients in terms of metabolic risk factors for urinary system stone formation (27). Bandari et al. showed that the incidence of hypercalciuria is increased in 110 stone forming overweight/obese children. Also, in contrast to findings in adults, no association reported between urine pH and BMI (28). Fang et al. in their study evaluated 243 pediatric stone patients retrospectively; non-overweight patients found to be more likely to have hyperoxaluria and hyperuricosuria, while overweight patients were more likely to have hypocitraturia (11). Cambareri et al. determined that stone-forming children who are overweight or obese to have low urinary volume and elevated uric acid compared to normal-weight stone-forming children (29). A systematic review from Italy evaluated studies reporting association between renal stones and obesity. In this paper, it was stated that hyperuricosuria, hypercalciuria and hyperoxaluria are more common metabolic risk factors in obese patients, respectively (30). In our study, no significant difference was found between the obese and non-obese groups in terms of hypercalciuria, hyperuricosuria and hyperoxaluria and no relationship was found between obesity and urine pH. As it is seen, although there are publications in the literature showing that obesity is a risk factor for stone formation, there are also contradictory publications.

The fact that stone formation is multifactorial and affected not only by BMI but also by the nutritional characteristics of the patient may explain these different results in the literature.

The retrospective nature of our study is one of the most important limitations. Another limitation of the study is that 24-hour urine collection in children is difficult and often not possible, so spot urinalysis is requested, and metabolic characteristics are evaluated based on these results. Another limitation of the study is the relatively low number of patients. Our patient group, which is a very good number for a single center, may be insufficient in comparing metabolic risk factors and nutritional status. In addition, no distinction was made between endogenous and exogenous obesity in the obese patients included in the study.

CONCLUSION

The important information obtained from this study; Family history is common in children with urinary system stones. Since the probability of metabolic risk factors is higher in patients with stone size >5 mm and multiple stones, evaluation in this regard would be appropriate, especially in these patients. The most common metabolic disorders were found to be hyperoxaluria and hypocitraturia. In this study, the relationship between obesity and urinary calcium, oxalate, cystine, and citrate excretion could not be demonstrated. Metabolic risk factors that increase the risk of urinary system stone formation in patients with a family history of urinary system stone disease should be investigated and treated. There is a need for more comprehensive, prospective multicenter studies that include patients' nutritional status and metabolic risk factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.02.2022, Decision No: 1771).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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