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Metabolic risk factors and the role of prophylaxis in pediatric urolithiasis

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Summary
Suppose that the recurrence in pediatric urolithiasis has a close relationship with metabolic abnormalities and is affected by residual burden and prophylaxis. If so, the recurrence rates could be reduced with effective surgery and appropriate prophylaxis. Here we retrospectively evaluate the metabolic risk factors data of 148 children who were operated on between January 2005 and March 2013 due to kidney stones. All patients underwent percutaneous nephrolithotomy (PCNL), and all were children. Thirteen children had a history of surgery performed to treat urological anomalies. Twenty-four-hour urine analysis, the residual status of surgery, BMI levels, and the number of metabolic abnormalities were noted. Only 18 (15%) of 122 patients without residual stones after PCNL had recurrence at follow-up whereas; nine (26%) of 26 patients with residual stones developed recurrence ($p = 0.017$). Recurrence was observed in 14 (16%) of 89 patients with a metabolic abnormality, and 13 (30%) of 44 patients with two or more metabolic abnormalities had recurrence at follow-up ($p = 0.024$). Those patients with no metabolic abnormalities did not develop recurrence. Stone recurrence was seen in six (8%) of 78 children who were given metabolic prophylaxis, compared to 21 (30%) of 70 patients who did not receive metabolic prophylaxis ($p = 0.02$). No stone recurrence was seen in nine children who were given Shohl's, whereas four (67%) of six patients who did not take Shohl's had recurrence ($p = 0.022$). Complete removal of stones by a suitable surgical method is essential to avoid recurrences. Detailed clinical and laboratory evaluations should be performed in children with urolithiasis. Appropriate specific prophylactic treatment (e.g., potassium citrate and Shohl's) and non-specific prophylactic treatment (e.g., avoiding animal proteins, salt, simple sugars, and increased water intake) should be given to prevent reformation of stones in patients with pediatric urolithiasis.

reccurrence	PCNL result		number of metabolic abnormalities			prophylaxis		Shohl's	
	stone-free	CIRF	none	one	two or more	given	not given	given	not given
none	104 (85%)	17 (65%)	15 (100%)	74 (84%)	31 (70%)	72 (92%)	59 (70%)	9 (100%)	2 (33%)
insignificant	18 (15%)	7 (27%)	0 (0%)	14 (16%)	11 (25%)	6 (8%)	19 (27%)	0 (0%)	3 (50%)
significant	0 (0%)	2 (8%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	2 (3%)	0 (0%)	1 (17%)
p	0.017		0.024			0.02		0.022	

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Introduction

Pediatric urolithiasis is an important health problem in developing and less developed countries [1]. Its prevalence has been reported to be 1—5% in developed countries and 5—15% in developing countries. This difference is based on socioeconomic factors, eating habits, and ethnic, genetic, and geographical changes [2]. In Turkey, it has been reported that the frequency of stone disease in children is 0.8%, but varying among regions [3]. Seventeen percent of children with the urinary stone disease in Turkey are less than 14 years old [4].

Although urinary stone disease is rarely seen in children, it is associated with a higher rate of metabolic abnormalities or urinary system disorders. More than 50% of these patients have metabolic abnormalities, and about 30% have urological anomalies, most commonly ureteropelvic stenosis [5]. Therefore, it is important to determine the risk factors that play a role in the etiology and to prevent stone reformation with proper treatment.

Metabolic abnormalities reported in this age group include hypomagnesuria, hypercalciuria, and cystinuria, and most often, hypocitraturia [6]. Similar studies have shown that medical prophylaxis for the underlying cause reduces the frequency of recurrence of the stones [7]. Anticipating that existing stones will grow over time and metabolic activity will lead to new stone formation are important aspects of treatment [8].

In this study, we aimed to identify the metabolic risk factors of urinary system stones in the pediatric age group and to investigate the effect of metabolic prophylaxis regulated according to these factors on long-term stone recurrence rates.

Material and methods

The study protocol was approved as 2013/172 by the Medical Ethics Committee of Erciyes University (School of Medicine, Kayseri, Turkey). Written informed consent was obtained from patients.

In this study, the data of 148 patients aged 17 and under, who were admitted to our clinic between January 2005 and March 2013 for kidney stones and who remained stone-free or had clinically insignificant residual fragments (CIRF) by the PCNL method, were evaluated retrospectively in terms of metabolic risk factors. In a retrospective scan, patients were evaluated in terms of having underlying urological anomalies. Body mass indexes (BMIs) were also noted for each patient. Patients with metabolic diseases, urinary tract infections, and genetic disorders were excluded from the study.

Following at least a 1-month recovery period after the operation, regardless of whether there is a recurrence or not, all patients underwent a complete metabolic evaluation in terms of urinary system stone disease. Twenty-four-hour urine was collected while the patients' normal daily diet and fluid habits continued. Urine samples were preserved in standard plastic bottles containing 10 ml HCl (3.7 mg) and at +4 °C.

Calcium, creatinine, uric acid, and phosphorus levels in serum and urine were analyzed by biochemical methods [9]. Besides, serum levels of magnesium and parathormone were measured via the biochemical analysis of blood. Daily citrate excretion in urine was measured using the citrate lyase technique [10]. Urinary oxalate and magnesium levels were measured using enzymatic methods [11]. The determination of cystine in urine was performed qualitatively by the sodium nitroprusside test. Additionally, pH and urine sediment analysis were performed in spot urine. The stones removed in operation were analyzed in terms of content with the Reflectance Fourier Transform Infrared Spectroscopy method. To identify the metabolic risk factors, previously defined reference values were used in the literature (Table 1) [12]. According to these values, children whose results are within the normal range were considered to have no metabolic abnormalities.

Pediatric nephrology follow-up was recommended to all patients, and patients were directed accordingly. Children without metabolic abnormalities were not prescribed prophylaxis. Appropriate medical prophylaxis was planned for the children with metabolic abnormalities (according to metabolic screening and stone analysis results). Shohl's solution was prescribed to patients with cystinuria and cystine stones in a dose appropriate to their weight [13]. Patients with hypocitraturia, hypercalciuria, hyperoxaluria, hyperuricosuria, or hypomagnesuria were prescribed potassium citrate treatment in a dose appropriate to their weight. Regardless of whether they have metabolic abnormalities or not, sodium restriction and increased water intake (1.5—2 L/m^2) were recommended to all stone patients [14]. Additionally, a diet with limited oxalate and animal proteins was suggested to all stone patients. Yet, in both groups, some did not take prophylaxis because of loss to follow-up. In summary, 78 children followed the prophylaxis schedule; although 133 had been prescribed prophylaxis, the compliance rate was 59%.

The patients were followed up for an average of 2 years, the first two controls every 3 months, and then every 6 months. To evaluate the current situation in terms of stone disease, all patients underwent direct urinary system radiography and total abdominal ultrasonography. Patients were analyzed in two subgroups: stone-free and CIRF, according to the success of PCNL. Stone size $\leq$ 4 mm was accepted as CIRF [15]. Recurrences during follow-up were classified according to stone sizes. Stones sized 3 mm and larger were identified as significant recurrence; stones sized 2 mm and smaller were identified as insignificant recurrence. To avoid inflated recurrence rates, in patients with CIRFs, recurrences were scored by calculating the dimensional substructions of two sequential visits.

Table 1 Reference values of abnormal urine parameters.

abnormality	Value
hypercalciuria	>4 mg/kg/24 h
hypocitraturia	<320 mg/1.73 m^2/24 h
hyperoxaluria	<320 mg/1.73 m^2/24 h
hyperuricosuria	>10.7 mg/kg/24 h
hypomagnesuria	<1.24 mg/kg/24 h
cystinuria	>400 mg/24 h

Statistical analysis

IBM SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.) was used for statistical analysis of the datasets. Categorical measurements were summarized as numbers and percentages, while numerical measurements were summarized as mean and standard deviation (median and minimum—maximum where necessary). The Chi-square test was used to compare categorical measurements between groups. Depending on whether the normality was achieved or not in comparing the numerical data, a t-test or Mann—Whitney U test was used in independent groups. In the general comparison of the numerical measurements of more than two groups, one-way analysis of variance (ANOVA) or the Kruskal Wallis test were used according to whether normality was achieved or not. The variables were integrated into univariate and multivariate regression analysis models to predict the recurrence risk of urolithiasis. While the complementary components of the variables were analyzed, reference analyzes were made for each complementary variable, respectively. The statistical significance level was taken as 0.05 in all tests.

Results

Seventy-eight of 148 patients included in the study were boys, and 70 were girls. The mean age of the patients was 7.91 ± 4.66 years. The mean follow-up period of the patients was 23.93 ± 7.16 months. The mean BMI of the children was 22.3 ± 1.9 kg/m^2. Low percentile BMI (L-BMI) was found in 19 (13%), normal percentile BMI (N-BMI) in 118 (80%), and upper percentile BMI (U-BMI) in 11 (7%) of the children. No significant differences were present between N-BMI and U-BMI groups for stone recurrence. In the L-BMI group, recurrence was significantly reduced ($p = 0.04$). No significant differences were present among the BMI groups for the number of metabolic abnormalities. Thirteen (9%) of the 148 patients had a history of surgery for the correction of urological anomalies. Eleven patients had pyeloplasty history, six were ipsilateral, and five were contralateral to the stone formation. Two patients had endoscopic subureteric injection history, one was bilateral, and one was ipsilateral to the stone formation. No significant differences were detected between groups with and without surgical histories for urological anomalies for stone recurrence and the number of metabolic abnormalities.

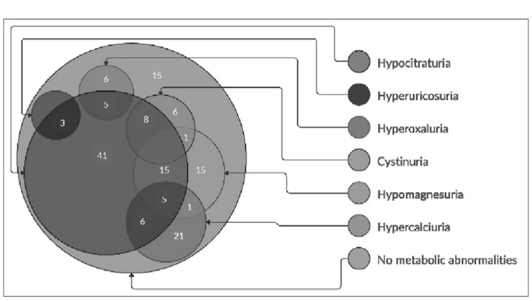

Figure 1 Distribution of metabolic abnormalities.

Table 2 Recurrence according to residual state after surgery.

reccurrence	PCNL result	
	stone-free	CIRF
none	104 (85%)	17 (85%)
insignificant	18 (15%)	7 (27%)
significant	0 (0%)	2 (8%)

One-hundred-twenty-two (83%) of the patients were stone-free, 26 (17%) of them had CIRFs. Stone analysis results of the patients; Calcium Oxalate (CaOX) stone was detected in 130 (88%), cystine stone in 15 (10%) and uric acid stone in three (2%). One or more metabolic abnormalities were determined in 133 (90%) of the patients; 15 (10%) of them were found not to have metabolic abnormalities. The metabolic abnormalities identified were, hypocitraturia in 83 (56%) patients, hypomagnesuria in 37 (25%) patients, hypercalciuria in 33 (22%) patients, cystinuria in 15 (10%) patients, hyperoxaluria in 11 (7%) patients, and hyperuricosuria in three (2%) patients. Fifteen (10%) patients had no metabolic abnormalities. Of the remaining 133 patients with metabolic abnormalities, 89 (60%) had one metabolic abnormality, and 44 (30%) had two or more metabolic abnormalities. The most common isolated metabolic abnormality was hypocitraturia in 41 (28%) patients; the most common dual metabolic abnormality was hypocitraturia and hypomagnesuria in 15 (10%) patients (Fig. 1).

Recurrence occurred in 27 (18%) of 148 patients in the study. Of these, two were significant recurrences. The patients were analyzed according to their residues after surgery; it was seen that stone-free patients developed significantly fewer recurrences. Only 18 (15%) of 122 patients without residual stones had recurrence during follow-up, while nine (35%) of 26 patients with CIRF had a recurrence ($p = 0.017$). As a result, the presence of residual stones after surgical intervention increases the risk of recurrence in children (Table 2).

The number of metabolic abnormalities and recurrence development percentages of the patients are compared; of the 74 patients with a single metabolic abnormality, 14 (16%) revealed an insignificant stone recurrence. Nevertheless, 13 (30%) of the 44 patients with two or more metabolic abnormalities exhibited recurrence, and two (5%) of these were significant recurrence. The set of three metabolic abnormalities consisted of hypocitraturia, hypercalciuria, and hypomagnesuria. Of the five patients in this set, all (100%) displayed recurrence ($p = 0.024$).

Table 3 Number of metabolic abnormalities and recurrence.

reccurrence	number of metabolic abnormalities		
	none	one	two or more
none	15 (100%)	74 (84%)	31 (70%)
insignificant	0 (0%)	14 (16%)	11 (25%)
significant	0 (0%)	0 (0%)	2 (5%)

Table 4 Patients given or not taken prophylaxis according to number of metabolic abnormalities.

prophylaxis	number of metabolic abnormalities		
	none	one	two or more
no	15 (100%)	48 (54%)	7 (16%)
potassium citrate	0 (0%)	39 (44%)	30 (68%)
Shohl's	0 (0%)	2 (2%)	7 (16%)

Moreover, children without metabolic abnormalities showed no recurrences. As the number of metabolic abnormalities increases, the risk of recurrence during follow-up increases (Table 3).

Children without metabolic abnormalities were not planned to recieve prophylaxis. Of the 74 patients with a single metabolic abnormality, 39 (53%) were given potassium citrate, and two (3%) were given Shohl's. Of the 44 patients with two or more metabolic abnormalities, 30 (68%) were given potassium citrate, and seven (16%) were given Shohl's (Table 4). Groups were evaluated for recurrence according to whether or not they received prophylaxis; stone recurrence was seen in six (8%) of 78 children who were given prophylaxis. In the no prophylaxis group, 21 (30%) of 70 children developed recurrence, and two (3%) of them were significant recurrences ($p = 0.02$). Furthermore, no recurrence was observed in nine cystinuric children given Shohl's. Otherwise, of the six cystinuric children who did not use Shohl's, four (67%) developed recurrence, and one of them was a significant recurrence ($p = 0.022$). Based on these findings, metabolic prophylaxis significantly reduces stone recurrence (Fig. 2). This effect is also pronounced in cystinuria patients (Fig. 3).

History of urological anomalies, BMI, and receiving prophylaxis subjected to multivariate analysis. The risk of stone recurrence was almost three times lower in the children with U-BMI compared with the children who have L-BMI and N-BMI ($p = 0.041$). The risk of stone recurrence was 13-times higher in the children not receiving prophylaxis compared with the children received prophylaxis ($p < 0.001$) (Table 5).

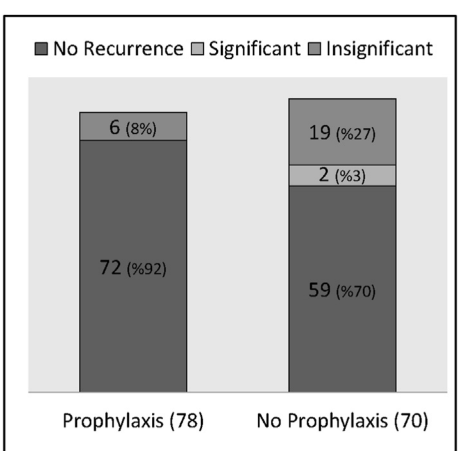

Figure 2 The effect of prophylaxis on stone recurrence.

Discussion

Management of urolithiasis in pediatric patients can be examined under two main titles, complete removal of existing stones and prevention of new stone formation. A suitable surgical option should be planned for removing the stones, and if metabolic abnormalities are detected, prophylaxis should be given accordingly. In this study, metabolic evaluation has been performed in patients who have been operated on for pediatric stone disease. We examed the usefulness of prophylaxis and the factors associated with recurrence during follow-up.

In our study, the patients were analyzed according to their residuals after surgery; it has been seen that stone-free patients developed less recurrence ($p = 0.017$). In the literature, a significant relationship has been reported between residual size and recurrence development after PCNL or alternative surgeries [16—18]. The relationship between our study and the literature highlights the importance of the complete removal of stones by an appropriate surgical method for preventing recurrence.

To prevent new stone formation, metabolic abnormalities must be revealed, and prophylaxis should be given accordingly. In our study, the most common metabolic abnormality was hypocitraturia, followed by hypercalciuria. In the literature, the most common isolated metabolic abnormality in children has been reported as hypocitraturia in some series, whereas in some publications, it has been reported as hypercalciuria [19]. In line with the literature [20], CaOX was the most common stone analysis result in our study. In our study, the most common dual metabolic abnormality was hypocitraturia plus hypomagnesuria. Contrary to our study, the most common dual metabolic disorder has been reported in the literature as hypocitraturia and hypercalciuria. Moreover, in some other publications, the most common dual metabolic disorder has been reported as hypercalciuria and hyperuricosuria [21]. The stone analyses and stone recurrence were examined according to the given prophylaxis. We found that the stone analysis results are similar, but the presence of stone is affected by prophylaxis. Considering that the most common metabolic abnormality in pediatric patients with urinary

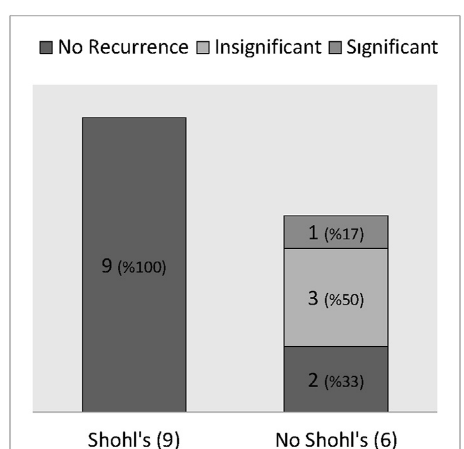

Figure 3 The effect of prophylaxis on stone recurrence in cycstinuric children.

Table 5 Univariate and multivariate regression analysis on gender, age, urinary anomaly history, BMI, serum, and urinary parameters.

variables	univariate regression OR (95% CI)	multiple regression OR (95% CI)	p value
gender	0.52 (0.19–1.45)	–	
age (years)	1.05 (1.01–1.09)	–	
urinary anomaly history	1.04 (0.58–1.85)	–	
BMI (kg/m$^{2)}$	1.19 (0.37–8.75)	0.37 (0.23–1.97)	0.041
prophylaxis	2.12 (0.71–9.34)	13.12 (4.61–59.45)	<0.001
Serum;		–	
calcium (mg/dL)	0.89 (0.36–2.19)	–	
creatinine (mg/dL)	4.50 (1.55–13.12)	–	
uric acide (mg/dL)	1.42 (1.06–1.89)	–	
phosphorus (mg/dL)	1.05 (0.45–2.42)	–	
magnesium (mg/dL)	2.09 (0.71–6.10)	–	
parathormone (pg/mL)	1.44 (0.53–3.91)	–	
Urinary;		–	
pH	1.01 (0.98–1.03)	–	
creatinine (mg/day)	1.08 (1.01–1.15)	–	
calcium (mg/day)	0.92 (0.60–1.42)	–	
uric acide (mg/day)	0.99 (0.96–1.18)	–	
phosphorus (mg/day)	1.01 (0.99–1.01)	–	
oxalate (mg/day)	1.00 (0.99–1.00)	–	
magnesium (mg/day)	0.77 (0.57–1.03)	–	
cystine (mg/day)	0.62 (0.41–0.93)	–	

system stones is hypocitraturia, it is possible to prevent calcium stone formation in patients by increasing the excretion of citrate in urine with medical prophylaxis.

Cystinuria is a hereditary disease caused by the renal and intestinal involvement defect of cystine, a dibasic amino acid, and the only clinical finding is urinary tract stone disease. Of the 35–40% cystinuria patients represent their initial clinical evidences between 1 and 20 years old [22]. In our study, patients with cystine stones were followed; significantly less stone recurrence was observed in the medical prophylaxis group. Based on these findings, we propose that patients with cystinuria should be given medical prophylaxis.

In our study, in accordance with the literature, all groups of pediatric stone patients that received prophylaxis developed significantly less recurrence than those who did not receive prophylaxis. This relationship suggests that prophylaxis should be given to pediatric patients to prevent possible renal damage. Similar studies have reported that recurrence is less in children receiving prophylaxis [23].

In this study, at least one metabolic abnormality was detected in all patients with stone recurrence. No recurrence has been observed in patients without metabolic abnormality. This relationship between the number of metabolic abnormalities and the development of recurrence makes metabolic assessment an important tool in preventing recurrence. In the literature, compatible with our study, there is a significant relationship between the number of metabolic abnormalities and the development of recurrence [24].

We found that the U-BMI group had significantly less recurrence than the N-BMI and L-BMI groups. Although this is actually new information in terms of the literature and needs more investigations, there are few up to date articles supporting this subject in the literature [25].

The major limitation of our study is its retrospective targeting of pediatric patients who underwent PCNL for stones. Because the underlying urological anomalies that frequently accompany pediatric stone disease had been treated with other surgical methods before, they could not be included in our study strongly enough to show their relationship with the factors discussed here.

Conclusion

In this study, as well as in the published literature, metabolic risk factors are important in children with urinary tract stones. Every pediatric patient who has had stone disease once or nephrocalcinosis should be evaluated in detail (clinical and laboratory terms). Since post-surgical residual stones will increase the risk of recurrence independent of metabolic prophylaxis, applying the most effective surgical option to completely clear the stones is critical. As the number of metabolic abnormalities and the amount of residual after surgery are directly related to recurrence, metabolic analyzes should be performed before or after surgery in pediatric stone patients. It is noteworthy that in all groups, the rate of recurrence is less in those receiving medical prophylaxis.

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Declaration of competing interest

The authors declare no conflict of interest.

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