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Prevalence of urinary metabolic disorders and risk factors of kidney stones in Iranian children

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ABSTRACT

Introduction: Nephrolithiasis and urolithiasis, characterized by the formation of calculi in the kidney and lower urinary tract, respectively, pose a significant health concern for millions of children worldwide, particularly in developing countries.**Objectives:** This research aims to explore the prevalence of abnormal concentrations of urinary solutes as potential risk factors for kidney stones in Iranian children under the age of 14 years.**Patients and Methods:** A cross-sectional investigation spanning from January 2021 to January 2022 targeted children diagnosed with nephrolithiasis or urolithiasis through renal sonography, who were subsequently referred to the nephrology outpatient department of our hospital or our private pediatric nephrology office. Laboratory assessments encompassed urine calcium, oxalate, citrate, uric acid, creatinine, and urine cystine. Demographic attributes, stone composition (when available), and urinary metabolic disorders were scrutinized. Data analysis involved SPSS version 24, utilizing descriptive statistics such as mean, standard deviation, and frequency, categorized by variable type. Chi-square tests were employed for statistical analysis, with a significance threshold set at $P < 0.05$.**Results:** The study encompassed 486 children, with a mean age of 55.58 months and a male majority of 50.8%. Among those with kidney stones, 77.2% exhibited unilateral stones, while 22.8% presented with bilateral stones. Predominant urinary metabolic disorders included hypercalciuria (30.2%), hyperuricosuria (22.6%), and hyperoxaluria (20.6%). Notably, 25.7% of the children manifested a combination of multiple metabolic disorders. Significant variations in the prevalence of hyperuricosuria were observed across different age groups. Boys exhibited higher incidences of hypercalcemia and metabolic abnormalities compared to girls, though no statistically significant differences were noted in other disorders.**Conclusion:** In summary, our findings indicate the presence of abnormal urinary metabolic risk factors in over half of children diagnosed with kidney stones. Hypercalciuria was the more frequent risk factor following hyperuricosuria and hyperoxaluria, with prevalence of 30.2%, 22.6%, 20.6%, and (2.1%) respectively.

Implication for health policy/practice/research/medical education:

This research aims to explore the prevalence of abnormal concentrations of urinary solutes as potential risk factors for kidney stones in Iranian children. Our findings indicate the presence of hypercalciuria was the more frequent risk factor following hyperuricosuria and hyperoxaluria.

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Introduction

Nephrolithiasis and urolithiasis, denoting the presence of solid stones in the kidney or lower urinary tract, respectively, are critical medical conditions (1-3). The deposition of

calcium salts within renal tubules, tubular epithelium, or interstitial spaces is termed nephrocalcinosis. The accurate incidence of these conditions in the youth population is believed to be underestimated, given that over 40% of

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children receive diagnoses incidentally, often following a urinary tract infection (4). The prevalence in youngsters is on the rise, mirroring trends observed in the adult population. In the United States, pediatric nephrolithiasis incidence is estimated to range from 36 to 57 cases per 100 000 individuals (5).

Microlithiasis, defined as the ultrasonographic detection of hyperechogenic deposits measuring less than 3 mm in the kidney's calyces, pelvis, or ureters, is indicative of renal urolithiasis (6). Pediatric nephrolithiasis exhibits distinctions from its adult counterpart concerning epidemiology, etiology, symptoms, imaging modalities, and therapeutic approaches. Key risk factors for kidney stones in this demographic include urine metabolic abnormalities such as hypercalciuria (34%), hyperoxaluria (18%), hypocitraturia (15%), and hyperuricosuria (2%), deviating from the prevalence observed in adults, where hyperuricosuria is a common urine chemistry abnormality among stone formers (7).

Objectives

Given the disparate findings in previous investigations regarding the incidence of urine solute abnormalities in pediatric kidney stone formers as compared to adults and variations across different global regions, this study was undertaken in our country. With an expanded sample size, we aim to contribute valuable insights into managing and preventing renal stones in Iranian children under 14 years old.

Patients and Methods

Study design

This study was observational and descriptive cross-sectional. Consecutive individuals under the age of 14 years, diagnosed with urinary stones, and seeking care at Loghman hospital and Mofid pediatric hospital urology and nephrology clinics from January 2021 to January 2022

were considered eligible for inclusion in the study.

Inclusion criteria encompassed ultrasonographic evidence of micro lithiasis exceeding 3 mm, presence of two or more microlithiasis measuring over 2 mm in two ultrasounds with posterior shadow, ureteral stones of any size, bladder stones of any size, and obtaining parental consent. Only patients under the age of 14 were included, and parental participation was contingent upon agreement and the right to withdraw from the research at any point. Exclusion criteria comprised the use of stone-forming medications (e.g., topiramate, allopurinol, acetazolamide, zonisamide), oral citrate consumption, thiazide use, vitamin B6 intake, adherence to a ketogenic diet, urinary infections and glomerular filtration rate <90 cc/min/1.73 m² during the study period.

Patient records from nephrolithiasis cases at Mofid children's hospital and Loghman hospital's nephrology clinics provided the requisite results, supplemented by survey-based data collection. Random urine samples were collected from children below the age of four, while those older than four underwent 24-hour urine sample collection. Meanwhile calcium, oxalate, uric acid, and citrate concentrations were assessed in the urine sample, where received by the laboratory within two hours:

Metabolic risk factors were diagnosed based on established criterias for 24-hour urine—idiopathic hypercalciuria >4 mg/kg/d, hyperoxaluria > 50 mg/1.73 m² body surface area (BSA) per day, hypocitraturia < 400 mg/g creatinine, hyperuricosuria >815 mg/1.73m² BSA per day(8-11).The cut-off values for these variables in random urine were delineated, as presented in Table 1 (12). Demographic information, including age, sex, weight, and height, was systematically collected and documented.

Statistical analysis

The collected data underwent analysis using SPSS version 24 software, employing descriptive statistics such as mean,

Table 1. Definition of urinary disorders in the current study

	Age	Random	Timed	Notes
Calcium	0-6 mon	<0.8 mg/mg creatinine	<4 mg/kg/24 h	Prandial variation
	7-12 mon	<0.6 mg/mg creatinine	-	Sodium-dependent
	≥ 2 y	<0.21 mg/mg creatinine	-	-
Oxalate	<1 y	0.15-0.26 mmol/mmol creatinine	≥ 2 y: <0.5 mmol/1.73 m ² /24 h	Highly age-dependent
	≥ 1 and <5 y	0.11-0.12 mmol/mmol creatinine	-	
	≥ 5 and <12 y	0.006-0.15 mmol/mmol creatinine	-	
	≥ 12 y	0.002-0.083 mmol/mmol creatinine	-	Excretion rate/1.73 m ² constant though childhood and adulthood
Uric acid	Term infant	3.3 mg/dL GFR	<815 mmol/1.73 m ² /24 h	
	>3 y	<0.53 mg/dL GFR		
Magnesium	>2 y	<0.12 mg/mg creatinine	<88 mmol/1.73 m ² /24 h	
Citrate	-	> 400 mg/g creatinine	-	-
Cystine	-	<75 mg/g creatinine	<60 mg/1.73 m ² /24 h	If > 250 mg/g creatinine means homozygosis cystinuria

standard deviation, and frequency, stratified by variable type. The chi-square test was utilized for statistical analysis, with a significance threshold set at $P < 0.05$.

Results

Following rigorous consideration of the inclusion criteria, a total of 530 patients met the eligibility criteria. Subsequent application of exclusion criteria and accounting for the loss of follow-up led to the final inclusion of 486 children for study purposes. The mean age of the participants was 55.58 months, with a standard deviation of 40.96 months. Of the study cohort, 247 participants (50.8%) were male, and the remainder were female.

Table 2 presents a descriptive analysis of the study participants. Notably, 41 individuals (8.6%) had a history of surgery, while 55 patients (11.3%) reported a history of urinary tract infections, and 36 (7.4%) had a history of urinary tract abnormalities. Concurrent medical conditions were identified in 13 subjects (2.7%).

The prevalent urinary metabolic disorders among the patients included hypercalciuria (30.2%), hyperuricosuria (22.6%), and hyperoxaluria (20.6%). Conversely, the least frequent urinary metabolic disorder observed was cystinuria (2.1%). Additionally, 46 patients (9.6%) exhibited obesity (BMI $>85^{\text{th}}$ percentile for age and gender). More than half of the patients presented with at least one metabolic disorder, and over a quarter

manifested two or more. Examining urinary stone types when were available revealed the following prevalences: calcium oxalate (40 cases), calcium phosphate (8 cases), cystine (7 cases), triple sulfate (6 cases), and uric acid (6 cases). Notably, calcium oxalate, with a prevalence of 8.2% (40 cases), emerged as the most common urinary stone, followed by calcium phosphate and cystine.

Comparative analysis of the prevalence of past medical diseases across different age groups showed a noteworthy age-related difference in hyperuricosuria, with rates of 12.5% in infants under one month, 32.3% in infants, 26.2% in toddlers, 22.6% in preschoolers, 16.0% in primary school children, and none in adolescents ($P = 0.031$). However, this age-related variation was not statistically significant for other parameters, including hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, metabolic acidosis, metabolic problems, stone types, history of surgery, urinary tract abnormalities, urinary infections, and comorbidities.

Metabolic abnormalities were more prevalent in males (63.3%) compared to females (53.1%), representing a significant difference ($P = 0.020$). Gender-based analysis revealed a significant difference in hypercalcemia, with rates of 34.8% in boys and 25.5% in girls ($P = 0.016$). No statistically significant differences were observed in the context of other underlying disorders.

Discussion

The study in question has provided valuable insights into the prevalence and risk factors associated with kidney stone formation in a pediatric Iranian population. The study investigated prevalence of metabolic risk factors of kidney stones in children under 14 years of age, with 486 children with nephrolithiasis included in the study. The mean age of the patients was 55.58 months, and 50.8% of the patients were boys.

The most common urinary metabolic disorders in our survey included hypercalciuria, hyperuricosuria and hyperoxaluria, with prevalence of 30.2%, 22.6% and 20.6% and cystinuria (2.1%) respectively. This discussion will contextualize these findings within the broader research landscape on pediatric urolithiasis and metabolic disorders.

The finding of hypercalciuria as the most prevalent metabolic disorder (30.2%) is in line with Bergsland et al (13) who noted hypercalciuria as a leading risk factor for kidney stones in children. Notably, the rate of hyperuricosuria (22.6%) and hyperoxaluria (20.6%) observed is noteworthy as these conditions are also significant contributing factors to stone formation. These findings mirror the reports by Spivacow et al (14,15), who emphasized the role of these metabolic abnormalities in pediatric kidney stone disease.

The identified history of urinary tract infection in 11.3% of cases raises a point of consideration given that

Table 2. Descriptive analysis of study participants

	Number	Percent
History of surgery (yes)	41	8.4
Comorbidity (yes)	13	2.7
Urinary tract infection (yes)	55	11.3
Anomaly of the urinary tract (yes)	36	7.4
Metabolic disorder		
Hypercalciuria (yes)	147	30.2
Hyperoxaluria (yes)	100	20.6
Hyperuricosuria (yes)	110	22.6
Hypocitraturia (yes)	57	18.7
Cystinuria (yes)	10	2.1
Metabolic cidosis (yes)	28	5.8
Number of metabolic disorders		
0	202	41.6
1	154	31.7
≥ 2	130	26.7
Nephrolithiasis type		
Calcium oxalate	40	8.2%
Calcium phosphate	8	1.6%
Cysteine	7	1.4%
Triple sulfate	6	1.2%
Uric acid	6	1.2%

urinary tract infections can contribute to stone formation, particularly struvite stones. This is supported by another study (16).

Boys demonstrating higher incidences of hypercalcemia and metabolic abnormalities is a gender-specific finding that has been corroborated by Spivacow et al (14,15), highlighting a potential sex-related predisposition that warrants further investigation. Another essential aspect of this study is the significant variation in hyperuricosuria across different age groups which may reflect the changing metabolic profiles throughout childhood development, as discussed in a research by Sas et al (17).

However, this study did not find statistically significant differences in other disorders, a finding that contrasts with the work of DeFoor et al (18), which revealed various metabolic differences between solitary and recurrent stone formers in children. The absence of such differences in this study may suggest a need for larger sample sizes or highlight the potential influence of genetic, dietary, and environmental factors that were not necessarily accounted for in the research design.

Lastly, the increasing prevalence of obesity and its association with kidney stone disease (2,19,20) was not directly addressed in the study. Hence, the incorporation of body mass index data could offer additional insights into the relationship between obesity and pediatric urolithiasis, helping to elucidate further the complex interplay of risk factors as discussed in the literature (4).

In the study, Stamatelou showed that in contrast to adults, obesity does not appear to be a risk factor for stones in children (21).

In summary, the findings of this study add to the existing body of literature on pediatric kidney stones, highlighting metabolic disorders and their associated risk factors (2,13,14,22,23).

Conclusion

In summary, our findings indicate the presence of abnormal urinary metabolic risk factors in over half of children diagnosed with kidney stones. Hypercalciuria emerged as the predominant risk factor, surpassing hyperuricosuria and hyperoxaluria, with respective prevalence rates of 30.2%, 22.6%, and 20.6%. Cystinuria, with a prevalence of 2.1%, exhibited the lowest frequency among the observed metabolic abnormalities.

Limitations of the study

Generalizability is constrained by the single-center focus within Tehran. Additionally, the study did not explore factors such as dietary habits, family history, and environmental influences, which may contribute to a more comprehensive understanding of pediatric nephrolithiasis. Further research is warranted to extend our understanding of these relationships, especially involving longitudinal and multi-center studies to validate and expand upon these results.

Study Highlights

What is the current knowledge?

- Contribute valuable insights into managing and preventing renal stones in Iranian children under 14 years old.

What is new here?

Findings indicate hypercalciuria was the more frequent risk factor following hyperuricosuria and hyperoxaluria

Authors' contribution

Conceptualization: Zahra Pournasiri.

Data curation: Zahra Pournasiri, Paniz Pourpashang.

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Writing—original draft: Zahra Pournasiri, Paniz Pourpashang.

Writing—review & editing: Zahra Pournasiri, Paniz Pourpashang.

Conflicts of interest

The authors have no conflict of interest.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Shahid Beheshti University of Medical Science, with the (Ethical code#SBMU.MSP.REC.1402.078). For this study, the parents of the children provide consent for participation in this research. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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