Can Fractional Urea Excretion Be a Marker in Pediatric Urinary Stone Disease?

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Abstract

Aim: In the setting of pediatric urolithiasis, it is important to determine the presence of any metabolic disorder to prevent new stone formation and to treat the existing stone. With this aim, the urinary excretions of electrolytes and uric acid are usually obtained. Fractional excretion of urea (FeU) has been demonstrated to be useful in the setting of acute renal injury. The objective of this study is to search the importance of FeU in pediatric stone disease and to compare FeU with other urine electrolyte excretions and uric acid excretion.

Methods: We retrospectively evaluated the laboratory and medical records of 41 pediatric urolithiasis patients whose FeU percentages were studied together with the etiologic work-up. Patients were divided into two groups as microlithiasis and macrolithiasis. Demographic and laboratory data as well as FeU were compared between the two groups.

Results: Twenty-four patients (59%) had stone size less than 3 mms, seventeen patients (41%) had stones larger than 5 mms. Among all patients 20 of them were boys, 21 of them were girls. M/F ratio was 13/11 in microlithiasis and 7/10 in macrolithiasis group. Mean age was 55.8 months in microlithiasis group, whereas 39 months in macrolithiasis group. Among 24 patients with microlithiasis, 20 patients had FeU greater than 35%, and 4 patient had FeU less than 35%. To differentiate microlithiasis from macrolithiasis the sensitivity and specificity of FeU≥35 is 83% and 6% respectively. For FeU<35%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 17% and 94% respectively (p>0.05).

Conclusions: Fractional excretion of urea is not affected from the size of the stone. However, urinary urea excretion is associated with urinary sodium and uric acid excretion. Further studies with larger groups and comparison of the urolithiasis patients with healthy children without urinary stones in the controlled studies will reveal the exact results.

Keywords: *Urea excretion, nephrolithiasis, children*

1. Introduction

Urinary stone disease has become an important problem in the pediatric group, the incidence of which has increased in recent years.[1,2] Turkey is an endemic place for urinary stones affecting 10-20% of the pediatric population.[2-4] Kidney stone formation is multifactorial and metabolic etiological investigation is needed to identify underlying causes such as hypercalciuria, hyperoxaluria, and hypocitraturia, hyperuricosuria and cystinuria etc. In addition, ethnic origin, genetic factors, dietary habits and urinary tract infections, and congenital anomalies of the kidney and urinary tract may be associated with kidney stone formation.[1-3] Identification of risk factors is important for determining treatment and prevention. The most common risk factors detected in urolithiasis patients in Turkey are metabolic abnormalities and anatomical problems.[2,5]

Hypercalciuria and hypocitraturia are the most common metabolic risk factors detected in patients with nephrolithiasis.[1] Normal uric acid and calcium excretion differ in different age groups.

Urea is a fat-soluble molecule that can pass through membranes by passive diffusion, freely filtered in the glomeruli, and reabsorbed in the proximal tubule and 50-60% of the filtered urea is excreted in the urine.[6,7]

Urea is also actively transported in the renal tubules. When per-

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Received: 17.08.2023, Accepted: 31.08.2023, Available Online Date: 02.10.2023
Cite this article as: Aksoy OY, Inozu M, Aydın Z, et al. Can Fractional Urea Excretion Be a Marker in Pediatric Urinary Stone Disease?. J Cukurova Anesth Surg. 2023; 6(3): 382-5.
doi: 10.36516/jocass.1345117

fusion is decreased, urea reabsorption is increased, resulting in decreased urea excretion (usually <35%). If the patient has intrinsic renal failure due to tubular damage, urea reabsorption decreases and fractional excretion of urea (FeU) exceeds 50%.[6-8] However, many conditions such as sepsis, sex, aging, protein infusion, liver disease, and some drugs affect the FeU result by interfering with the active transport of urea.[6,9,10]

There are few studies that mention urea excretion in kidney stone patients. In our study, we wanted to document the relationship between the fractional excretion of urea and the urinary excretions of some other electrolytes, and the associations with the size of the stone.

2. Materials and methods

We evaluated the laboratory and medical records of 41 pediatric urolithiasis patients whose FeU percentages were studied together with other urinary excretions certain electrolytes for the etiologic work-up. The study was conducted in Ankara Bilkent City Hospital in 2019-2020. With the help of radiology records, patients were divided into two groups as microlithiasis and nephrolithiasis according to the size of the stone as less than 3 mms and greater than 5 mms. Demographic and laboratory data as well as FeU percentages were compared between the two groups.

Demographic data, age, serum urea, creatinine, sodium, potassium levels, FeNa, FeU, random urine calcium/creatinine ratio, random urine uric acid/creatinine ratio, tubular reabsorption of phosphorus (TRP), ultrasound results were recorded. Patients were further divided into four subgroups according to their fractional excretion results as FeNa<1%, FeNa≥1% and FeU<35%, FeU≥35%, and the patient numbers were compared, in order to calculate sensitivities and specificities of the tests, between microlithiasis and macrolithiasis groups. Newborns were excluded due to the immaturity of their renal tubular functions.

Statistical analyses were performed using IBM SPSS for Windows (SPSS version 17.0). Distribution of the data for normality was tested by the Shapiro-Wilk test. Student t test was performed for normally distributed data, and Mann-Whitney U test for non-normally distributed data. Frequencies and percentages were used as descriptive values in the categorical data. Arithmetical mean ± standard deviation was used for the normally distributed data, and median and interquartile range (IQR) were used for the non-normally distributed data. Chi square test was used for fractional excretion analysis. Sensitivities and specificities were calculated. Spearman Rank Correlation analysis and Kruskal-Wallis tests were used for the relations of the electrolyte excretions. Statistical significance was accepted as 0.05.

The study was approved by the Local Ethics Committee (Ankara City Hospital, Clinical Studies E2-21-329) and the study was conducted by the Declaration of Helsinki. All data were collected and checked by two researchers.

3. Results

The relevant data regarding the urinary stone patients having the etiological work-up, including random urine urea and creatinine as well as serum urea and creatinine at the same time to calculate the fractional excretion of urea, were obtained from the medical records of the hospital. Total 41 patients were found with available data. The data regarding 41 patients were evaluated. Twenty-four patients (59%) had stone size less than 3 mms, seventeen patients (41%) had stones larger than 5 mms. Mean serum urea, creatinine, sodium, potassium, phosphorus levels and FeNa, FeU and TRP percentages were similar between the two groups (p>0.05).

Table 1

Demographic and Laboratory Data of the Groups

	Microlithiasis (≤3mm)	Nephrolithiasis (≥5 mm)	P value
n	24	17	
m/f	13/11	7/10	0.41
Mean age (months)	55.8	39.0	0.07
Serum urea (mg/dL)	23.1	21.6	>0.05
Serum creatinine (mg/dL)	0.5	0.5	>0.05
Serum potassium (mmol/L)	4.3	4.3	>0.05
Serum sodium (mmol/L)	136.6	135.2	>0.05
FeU (%)	56.9	62.9	>0.05
TRP (%)	86.8	91.9	>0.05
Random urine uric acid/creatinine ratio	1.2	1.1	>0.05
Random urine calcium/creatinine ratio	0.3	0.4	>0.05
Urine urea (mg/dL)	1108.0	835.0	
Urine sodium (mmol/L)	80.0	81.0	>0.05
Urine potassium (mmol/L)	37.0	35.0	>0.05
Urine phosphorus (mg/dL)	34.0	17.0	
FeNa(%)	1.1	1.3	>0.05

FeU: Fractional Excretion of Urea, FeNa: Fractional Excretion of Sodium, TRP: Tubular reabsorption of Phosphate

Table 2
Fractional Urea and Sodium Excretion Between the Groups

		Microlithiasis (≤3mm), n	Nephrolithiasis (>5 mm), n	n(%)
FeU (%)	≥35	20	16	36(87.8)
	<35	4	1	5(12.2)
Total p=0.299		24	17	41(100)
FeNa (%)	≥1	7	3	10(37)
	<1	8	9	17(63)
Total p=0.247		15	12	27(100)

FeU: Fractional Excretion of Urea, FeNa: Fractional Excretion of Sodium

Among all patients 20 of them were boys, 21 of them were girls. Male/female (M/F) ratio was 13/11 in microlithiasis and 7/10 in macrolithiasis group. Microlithiasis was more prevalent in boys, however the difference is not significant (p=0.41). Mean age was 55.8 months in microlithiasis group, whereas 39 months in macrolithiasis group (p=0.07) (Table 1).

We divided the patients according to their FeU percentages as FeU<35% and FeU ≥35%, and compared the microlithiasis and macrolithiasis groups. Among 24 patients with microlithiasis, 20 patients had FeU greater than 35%, and 4 patient had FeU less than 35%. To differentiate microlithiasis from macrolithiasis the sensitivity and specificity of FeU≥35 is 83% and 6% respectively. For FeU<35%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 17% and 94% respectively (p>0.05). When we analyze FeNa, among the two groups, for FeNa<1%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 53% and 25% respectively. In addition, for FeNa ≥1% the sensitivity and the specificity of the test is 47% and 75% respectively (p>0.05) (Table 2).

The urinary calcium excretion of the patients (random urine calcium/creatinine ratios) are correlated with random urine uric acid/creatinine ratios in both microlithiasis and macrolithiasis groups (p=0.001). Random urine calcium/creatinine ratio also correlates with the tubular phosphorus reabsorption (p=0.023), as well as random urine uric acid excretion correlates with tubular phosphorus reabsorption (p=0.024).

Urine calcium excretion correlates with urine sodium excretions (p= 0.04), urine calcium excretion does not significantly correlate with urea excretion (p=0.08). Urea excretion significantly correlates with sodium and uric acid excretions (p= 0.001 and p=0.01 respectively).

4. Discussion

Kidney stones are a common nephrological problem in childhood. Diagnostic procedures and follow-up in children are different from adults and metabolic study is usually expected. In parts of the Near/Middle East and North Africa (Turkey, Saudi Arabia, Egypt and Pakistan) nephrolithiasis is an endemic disease affecting 10-20% of the population.[11]

In this study, we compared the urinary electrolytes and kidney function tests of patients with microlithiasis, which can be considered as a more benign condition, and patients with stones of 5 mm or larger. Consistent with the literature we did not find any difference. Most of the microlithiasis patients were male, although not statistically significant. Microlithiasis can be considered as a more benign condition according to many studies, patients can be followed without medical treatment if there is no metabolic and/or anatomical risk factor. Medical treatment should be reserved in cases with metabolic risk factors.[2]

In a large series, it was found that the rate of microlithiasis was higher in infants (40.6%) and 64.5% of patients with microlithiasis were infants.[2] However, in our patient group, the mean age was higher in the microlithiasis group, but the difference was not significant. This can be attributed to the design of our study.

In infants or young children, microliths are sometimes not thoroughly searched for due to the presence of transient echogenicity on ultrasound. Metabolic risk factors play an important role in kidney stone formation. Calcium excretion, oxalate and citrate excretion and uric acid excretion are important in the etiological work-up of kidney stones.[5]

Urea and ammonia are the main determinants in nitrogen metabolism. Urea is transported via specific transport proteins that play an important role in concentrating urine.[12] Urea excretion is mostly the result of glomerular filtration and less tubular reabsorption. A low urea excretion indicates increased tubular reabsorption.[13]

Renal ammonia metabolism requires intrarenal ammonia formation from glutamine. Changes in factors regulating renal ammonia metabolism may have significant effects on glutamine in addition to nitrogen balance. Clinical conditions associated with altered urine concentration ability or water homeostasis can cause changes in urea excretion and urea transporters.[14]

When we examined whether there was a difference between fractionated urea excretion and urinary sodium excretion in differentiating microlithiasis from larger stones, we could not find a significant difference. In the case of low urea excretion (<35%), the probability of the stone being microlithiasis was higher, but it was not statistically significant. At the same time, the probability of detecting microlithiasis was higher in cases where the fractional sodium excretion was above 1% (sensitivity: 47%, specificity: 75%).

Clinical conditions associated with altered ammonia excretion can have significant effects on nitrogen balance. In a study, 24-hour urinary urea excretion, calculated as a reflection of protein intake, was evaluated in a study evaluating 65 children with idiopathic hypercalciuria and 76 normocalciuric control children. Urinary urea excretion was higher in patients with idiopathic hypercalciuria compared to controls. Urinary urea excretion decreases significantly with age, body weight, and height increase.[14]

Calcium and uric acid excretion were correlated in both groups. Both random urinary calcium/creatinine and uric acid/creatinine

excretion rates are associated with tubular phosphorus reabsorption. Polito et al.[14] showed that calcium excretion increases significantly with increased sodium and urea excretion. A significant interaction between urinary sodium and urea excretion has been demonstrated in increased calciuria in patients with idiopathic hypercalciuria in their study.[14] In our study, we found a correlation between calcium excretion and sodium and uric acid excretion. Urea excretion was significantly associated with sodium and uric acid excretion, but the correlation with calcium excretion was not significant in our study. In another study, urea excretion was found to be significantly higher in hypercalciuria and hyperuricosuria patients when compared with the controls.[15]

In a different study, it is demonstrated that variations in urinary urea explained 11.4% of the overall variability of urinary calcium excretion, when the urinary sodium effect is added this association rises to 16%[16]. Children with hypercalciuria have a higher dietary protein intake than children with normocalciuria. The decrease in urea excretion with increasing age and body mass may reflect the relatively higher protein intake of young growing individuals. Salt and protein have a cumulative effect on increased calcium excretion. A significant positive correlation was found between the 24-hour urinary sodium creatinine ratio and the urinary calcium creatinine ratio.[16]

Urea excretion has also been studied by other researchers; 24-hour urea excretion has been shown to increase with both potassium and sodium supplementation.[17] Potassium supplementation causes a decrease in fractional calcium excretion, while sodium supplementation causes an increase in urinary calcium excretion.[17]

The limitations of this study are that it is retrospective and the sample size is small. Urea excretion is not routinely requested in the etiological examination of patients with urinary tract stones, therefore prospective studies with sufficient number of patients will elucidate its definite benefits.

5. Conclusions

Fractional urea excretion is not affected by the size of the stone. However, urinary urea excretion is associated with urinary sodium and uric acid excretion. In daily clinical practice, urea excretion may not be beneficial in the diagnostic work-up of kidney stone patients, but it may be associated with high urinary sodium (which may imply high sodium intake, a risk for stone formation) and high uric acid excretion. Further studies with larger groups and comparison of urolithiasis patients with healthy children without urinary stones in controlled studies will reveal definitive results.

Acknowledgements

None.

Statement of ethics

This study was approved the approval of the Local Ethical Committee was obtained (Ankara City Hospital). (07/04/2021-E2-21-329)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Funding source

No financial support has been received for this study.

Author contributions

OYA is the major contributor in writing the manuscript. OYA and USB are involved in the design and conception of the study. OYA, Mİ, ZA, BA, FSC, and USB were involved in the collection of the data and the clinical follow-up of the patients. All authors read and approved the final manuscript.

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