

The relationship between urinary tract infection and calcium excretion in children

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SUMMARY: Altıncık A, Sönmez F, Semerci N, Yenisey Ç. The relationship between urinary tract infection and calcium excretion in children. *Turk J Pediatr* 2012; 54: 387-392.

The aim of this study was to investigate the relationship between urinary tract infection (UTI) and urinary calcium excretion.

A total of 82 children (mean age: 5.41 ± 4.09 years) with UTI and 82 age- and sex-matched children as a control group were enrolled in the study. Urinary calcium excretion was studied in children with UTI before treatment, three days after treatment and six months after remission of UTI. Urine calcium/creatinine ratio ($U_{Ca/cr}$) and 24-hour urinary calcium excretions were studied. $U_{Ca/cr}$ ratios were also evaluated as percentile rates, which was performed in our previous study. The effects of the location of infection, complaints, family history of urolithiasis, and radiological findings on urinary calcium excretion were also investigated.

$U_{Ca/cr}$ ratio before treatment was found higher than in the control group ($p=0.04$). No statistically significant relationship was found between the pre-treatment $U_{Ca/cr}$ and sex, location of infection, family history, or radiological findings.

Key words: hypercalciuria, urinary tract infection, children, nephrolithiasis.

Urinary tract infection (UTI) is one of the most frequent infections in childhood. Due to its long-term complications such as chronic renal failure and hypertension, the significance of treatment and prevention of recurrence is undeniable. The relationship between hypercalciuria and UTI has been reported in a few articles before¹⁻³. These publications speculated that hypercalciuria could damage the urinary epithelium by causing microcrystal formations and facilitate UTI^{1,2}. In addition to this hypothesis, Albright et al.³ mentioned that UTIs could cause impairment in renal tubular functions, such as tubular calcium reabsorption, which would induce hypercalciuria. It has been reported that treatment of hypercalciuria would decrease the frequency of UTI.

The aim of this study was to determine urinary calcium excretion before and after UTI and any factors effective on urinary calcium excretion.

Material and Methods

Totally, 82 children diagnosed as UTI in our outpatient clinic were enrolled in the study. The study group consisted of children who had no

other systemic diseases or medication history that could affect urinary calcium excretion.

Urinary calcium excretion was studied before treatment (BT), three days after treatment (AT) and six months after remission of UTI (Rem) as urine calcium/creatinine ratio ($U_{Ca/cr}$) and 24-hour (h) urinary calcium excretion rate. All patients were followed monthly for urine cultures for at least six months after the treatment of UTI. Children who had a UTI during the follow-up period were excluded from the study. The control group consisted of age- and gender-matched healthy children. $U_{Ca/cr}$ values of the study and control groups were also evaluated as percentile rates as reported in our previous study⁴. In that study, which was a cross-sectional investigation, the study group was determined as 2149 children by using 95% confidence interval and 1% error. Reference $U_{Ca/cr}$ percentile rates of all age groups were calculated from healthy children in our region. Hypercalciuria was defined as a $U_{Ca/cr}$ ratio higher than the 90th percentile.

Urinary tract infection (UTI) was defined as the presence of more than 100,000 bacteria per ml in urine specimens obtained either by mid-stream collection of voided urine or by urine bags. When urine was collected by urine bag, diagnosis required 100,000 colony-forming units per ml. Urethral catheterization or suprapubic aspiration of urine was done when the urine bag results were suspicious for infection. Recurrent UTI was defined as two or more episodes of UTI separated for a period by sterile urine documented with urine culture in the history. All patients were investigated for urinary tract abnormalities by ultrasonography (USG). ^{99m}Tc dimercaptosuccinic acid (DMSA) scan and voiding cystourethrogram (VCUG) were done when indicated. UTI localization was done by using modified Jodal criteria⁵. Vesicoureteral reflux (VUR) classification was done according to the recommendations of the International Vesicoureteral Reflux Study Group⁶. Age at presentation, gender, complaints, family history of urolithiasis, and radiological findings were evaluated.

Urinary calcium and creatinine values were examined on an Abbott C8000 autoanalyzer with photometric method using commercial ILAB kits (catalog no 7D61-20, Germany) from morning urine samples. Calcium values were studied without dilution, and creatinine values were studied by diluting at a 1/10 ratio. Results were given as mg/dl. 24-h urine was collected in 10 ml of 6 mol/L HCL acid-containing cups. 24-h urinary calcium excretion was given as the mg calcium per body weight in kilograms (mg/kg/day).

The study was approved by the local ethics committee of Adnan Menderes University Faculty of Medicine. An informed consent was obtained from patients and families before the study.

Statistical analysis was performed by using the Statistical Package for the Social Sciences

(SPSS) 13.0 program. Data were expressed as mean \pm standard deviation. The differences in $U_{Ca/cr}$ ratios and 24-h urinary calcium values between BT, AT and Rem periods in the study group were evaluated with one-way ANOVA for repeated measures. McNemar test was used for evaluation of hypercalciuria ratios within the study group, and chi-square test was used for comparison of independent group ratios. Pearson's coefficient of correlation was done for the relation of age with $U_{Ca/cr}$. Since age is a covariant factor for $U_{Ca/cr}$, ANCOVA analysis was used for the comparison of $U_{Ca/cr}$ values between groups. *P* values less than 0.05 were considered statistically significant.

Results

A total of 82 children (68 girls, 14 boys) with UTI were enrolled in the study. The mean age of the study group was 5.42 ± 4.01 years (range: 0.1-14 years). Morning urines were evaluated for $U_{Ca/cr}$ ratio from 82 children. Only 39 children from the study group could collect 24-h urine. Seventy-three children could attend during the remission period of the study, and 24-h urine was obtained from 15 of them in the remission period.

The control group consisted of 82 healthy children (69 girls) with a mean age of 5.41 ± 4.09 years. Only $U_{Ca/cr}$ was evaluated in the control group. The results of $U_{Ca/cr}$ and 24-h urinary calcium are given in Table I.

$U_{Ca/cr}$ ratios were also evaluated as percentile rates, which were reported in our previous study⁴. The results in number and percentage are given in Table II.

Mean $U_{Ca/cr}$ ratio before treatment (BT) was higher in the study group than the control group (0.13 ± 0.13 mg/mg vs. 0.09 ± 0.09 mg/mg; $p=0.04$, $t=1.99$). However, the mean $U_{Ca/cr}$ ratio of the study group after treatment (AT) was not different from that of the control

Table I. Spot Urine $U_{Ca/cr}$ Ratio and 24-h Urinary Calcium Values of the Study Group in Before Treatment (BT), After Treatment (AT) and Remission (Rem) Periods and Mean $U_{Ca/cr}$ Ratio in Controls

(number)	$U_{Ca/cr}$ (mg/mg)			24-h U_{Ca} (mg/kg/day)		
	BT (82)	AT (82)	Rem (73)	BT (39)	AT (39)	Rem (15)
Study group	0.13 ± 0.13^a	0.12 ± 0.15^b	0.12 ± 0.15^c	1.76 ± 1.70	1.72 ± 1.02	2.27 ± 1.44
Control group		0.09 ± 0.09			-	

a: $p=0.04$, $t=1.99$ versus control group, b: $p=0.20$, $t=1.28$ versus control group, c: $p=0.23$, $t=1.18$ versus control group.

Table II. Percentile Rates of $U_{Ca/cr}$ Values of the Study Group in Before Treatment (BT), After Treatment (AT) and Remission (Rem) Periods and the Control Group

$U_{Ca/cr}$ (mg/mg) percentile rates	BT (%)	AT (%)	Rem (%)	Control (%)
3-25p	14.6	17.1	19.2	25.6
26-50p	24.4	32.9	27.4	25.6
51-75p	32.9	28.0	21.9	25.6
76-90p	17.1	12.2	20.5	17.1
>90p	11.0	9.8	11.0	6.1

group (0.12 ± 0.15 mg/mg vs. 0.09 ± 0.09 mg/mg; $p=0.20$, $t=1.28$). The mean $U_{Ca/cr}$ ratio in the remission period (Rem, 0.12 ± 0.15 mg/mg) was also not different from that of the control group ($p=0.23$, $t=1.18$).

In the study group, hypercalciuria was detected in 9 patients (11%) BT, in 8 patients (9.8%) AT, and in 8 patients (11.1%) in the Rem period. The prevalence of hypercalciuria was 6.1% in the control group. The difference in hypercalciuria prevalence was not significant between groups.

There was a negative correlation between age and mean $U_{Ca/cr}$ values of the study group BT ($r=-0.32$).

The $U_{Ca/cr}$ ratio was not different between BT, AT and Rem periods within the study group ($p=0.87$). 24-h urinary calcium values were also not different between BT, AT and Rem periods within the study group ($p=0.43$).

The most observed clinical manifestations of the children with UTI included fever (56%), abdominal pain (29.3%) and dysuria (28%). The relationship between complaints and $U_{Ca/cr}$ and 24-h urinary calcium excretion is given in Table III. Only the difference in $U_{Ca/cr}$ between the children with and without restlessness was significant ($p=0.04$).

Thirty-one of the children (37.8%) with UTI were evaluated as cystitis and 62.2% as pyelonephritis. $U_{Ca/cr}$ ratio of the children with cystitis (0.13 ± 0.12 mg/mg) was not different from the $U_{Ca/cr}$ ratio of the children with pyelonephritis (0.12 ± 0.14 mg/mg) ($p=0.79$). 24-h urinary calcium value of the children with cystitis (1.93 ± 1.82 mg/kg/d) was also not different from the 24-h urinary calcium value of the pyelonephritis group (1.60 ± 1.61 mg/kg/d) ($p=0.55$).

Hypercalciuria incidence was 16.1% in the cystitis group and 7.8% in the pyelonephritis group; however, the difference was not significant ($p=0.28$).

Nephrolithiasis was present in the family history of 23 (28%) children. The $U_{Ca/cr}$ ratio of the children with positive family history (0.08 ± 0.07 mg/mg) was not different from that of the children with negative family history (0.14 ± 0.15 mg/mg) ($p=0.08$). 24-h urinary calcium value of the children with positive family history (1.47 ± 1.93 mg/kg/d) was also not different from that of the children with negative family history (1.92 ± 1.48 mg/kg/d) ($p=0.43$). The incidence of hypercalciuria was 13.5% in children with negative family history and 4.3% in children with positive family history, and the difference was not significant ($p=0.43$).

Thirty-eight of the 82 children (46.3%) had single UTI, while the remaining had recurrent UTI. The $U_{Ca/cr}$ ratio BT of the children with single UTI was 0.17 ± 0.17 mg/mg and of those with recurrent UTI was 0.09 ± 0.08 mg/mg, and the difference between groups was not statistically significant ($p=0.11$). The difference between 24-h urinary calcium value of the children with single UTI (1.41 ± 0.87 mg/kg/d) and recurrent UTI (1.88 ± 1.91 mg/kg/d) was also not significant ($p=0.41$). The incidence of hypercalciuria was 13.1% in the children with single UTI and 9.1% in the children with recurrent UTI, and the difference between them was not significant ($p=0.72$).

All patients underwent renal ultrasonography; 79.3% had normal sonography, 78% had DMSA and 23.4% of these had renal scar. VCUUG was done in 63% of the patients, and 15.3% of them had VUR. A comparison of $U_{Ca/cr}$ and 24-h urinary calcium according to the radiological findings is given in Table IV.

Table III. The Relationship between Complaints and UCa/cr and 24-h Urinary Calcium Excretion of the Study Group in Before Treatment (BT), After Treatment (AT) and Remission (Rem) Periods

Complaints		U _{Ca/cr} BT	U _{Ca/cr} AT	U _{Ca/cr} Rem	24-h UCa BT	24-h UCa AT	24-h UCa Rem
Dysuria	(+)	0.10± 0.11	0.10±0.15	0.09±0.09	1.39±0.74	1.61±1.15	2.19±2.34
	(-)	0.14 ± 0.14	0.12±0.15	0.12±0.17	1.95±2.01	1.74±0.97	1.58±1.01
	p	0.68	0.90	0.62	0.34	0.77	0.37
Nocturia	(+)	0.09±0.16	0.12±0.23	0.06±0.05	1.34±0.07	2.22±2.17	1.45±1.44
	(-)	0.13±0.13	0.11±0.14	0.12±0.17	1.79±1.75	1.65±0.92	1.80±1.47
	p	0.47	0.73	0.41	0.71	0.42	0.97
Lumbar pain	(+)	0.13±0.14	0.06±0.04	0.16±0.13	1.24±0.92	1.74±1.25	
	(-)	0.12±0.73	0.12±0.15	0.11±0.15	1.84±1.79	1.69±1.01	
	p	0.89	0.52	0.50	0.47	0.96	
Fever	(+)	0.13± 0.14	0.12±0.16	0.11±0.15	2.05±2.20	1.59±1.04	1.36±1.04
	(-)	0.12±0.12	0.11±0.14	0.12±0.16	1.54±1.22	1.77±1.03	2.03±1.66
	p	0.31	0.45	0.38	0.36	0.52	0.55
Vomiting	(+)	0.14±0.17	0.09±0.07	0.08±0.06	1.88±2.55	2.12±0.99	2.50±0.98
	(-)	0.13±0.13	0.12±0.16	0.12±0.16	1.74±1.52	1.60±1.02	1.67±1.47
	p	0.45	0.77	0.58	0.82	0.16	0.48
Abdominal pain	(+)	0.11±0.07	0.07±0.05	0.09±0.11	2.04±2.11	1.66±0.94	2.68±1.95
	(-)	0.14±0.15	0.13±0.17	0.12±0.16	1.52±1.26	1.72±1.11	1.41±1.09
	p	0.77	0.64	0.86	0.35	0.89	0.11
Restlessness	(+)	0.23±0.22	0.20±0.22	0.17±0.21			0.45±0.63
	(-)	0.11±0.10	0.10±0.13	0.10±0.14			1.86±1.44
	p	0.04	0.09	0.27			0.19
Odor in urine	(+)	0.17±0.20	0.15±0.15	0.13±0.08	1.35±1.14	1.10±0.27	
	(-)	0.12±0.13	0.11±0.15	0.11±0.16	1.79±1.74	1.72±1.04	
	p	0.72	0.84	0.88	0.73	0.44	
Dark color in urine	(+)	0.22±0.23	0.18±0.17	0.14±0.14			
	(-)	0.12±0.12	0.11±0.15	0.11±1.15			
	p	0.36	0.79	0.92			
Urgency-enuresis	(+)	0.06±0.05	0.07±0.29	0.06±0.05	3.27±3.24	1.45±0.85	1.72±0.91
	(-)	0.13±0.14	0.12±0.15	0.12±0.16	1.60±1.42	1.72±1.05	1.74±1.49
	p	0.38	0.72	0.48	0.07	0.57	0.93

Discussion

Urinary tract infection (UTI) is one of the most common infectious diseases in childhood. Many predisposing factors have been involved as a risk for UTI. The laboratory investigation of a child with single UTI is controversial. However, recurrent UTI requires diagnostic studies about host and urinary tract anatomic structure (7-9). A few studies have been reported about the association of hypercalciuria with UTI¹⁻³. One of the hypotheses is that hypercalciuria may predispose to UTI by formation of calcium oxalate microcrystals, which would damage the epithelial cells of the urinary tract. Additionally, it is reported that adherence of microcrystals

to uroepithelial cells may influence the cellular defense mechanism^{1,10}. Evaluation of histologic changes in the urinary tract of hypercalciuric rats revealed that hypercalciuria was observed to have adverse effects on the cell architecture of the uroepithelium and to disrupt the epithelial barrier of the bladder and ureters and all kidney structures. The damage of uroepithelial cells, which play an important role in antibacterial response, could promote UTI¹¹. We observed that the U_{Ca/cr} ratio of the study group BT was significantly higher than in the control group. However, the mean U_{Ca/cr} ratio of the study group (in both AT and Rem periods) was not different from that of the control group. This data supported Albright's³ speculation that

UTIs could cause impairment in renal tubular functions, such as tubular calcium reabsorption, and induce hypercalciuria. Treatment of UTI could improve the tubular functions.

The incidence of hypercalciuria in the control group was 6.1% in our study, and the result was similar to the incidence of hypercalciuria reported in other studies (3.8-12.7%) among healthy children^{12,13}.

In our study, the incidence of hypercalciuria in the study group BT was 11%, and this ratio was lower than Stojanovic's and Mahmoodzadeh's studies^{14,15}. In Stojanovic's study, the cut-off level for hypercalciuria was 0.21 mg/mg and incidence of hypercalciuria was reported as 21%¹⁴. Mahmoodzadeh et al. reported the incidence of hypercalciuria as 17.8% in children with UTI. In that study, the cut-off level for definition of hypercalciuria was 0.8 mg/mg for infants younger than one year and 0.2 mg for older children, and the age of the study group was 41.14±22.1 months, which was younger than our study population¹⁵. The cut-off level for definition of hypercalciuria was 0.46 mg/mg for infants in our study.

In our study, we observed that the localization of the infection did not change the $U_{Ca/cr}$ ratio or hypercalciuria incidence. There were no similar data for comparison in the literature.

Family history was positive for nephrolithiasis in 28% of the children in our study, although higher ratios of 34%, 44% and 59% were reported in other studies^{2,10,16}. However, in those studies, the study population consisted of children with idiopathic hypercalciuria and/or

recurrent UTIs. The lower incidence of positive family history in our study might be explained by selection of the study group.

In our study, the most frequently reported clinical manifestations of UTI were fever (56%), abdominal pain (29.3%) and dysuria (28%). Fever was also the most frequently reported (100%) complaint in Lopez's study¹⁰, while lumbar pain was found in 50% in Bıyıklı's study¹⁶ and in 2% in Lopez's study¹⁰. The existence or absence of complaints did not alter the $U_{Ca/cr}$ in our study. Only the $U_{Ca/cr}$ of the children with restlessness was higher than in those without restlessness. Dysuria, lumbar pain, urgency, and nocturia were also the complaints associated with hypercalciuria. We compared the $U_{Ca/cr}$ of the children with and without these complaints, and there was no statistically significant difference.

In our study, the incidence of hypercalciuria and the mean $U_{Ca/cr}$ ratio did not differ between children with single versus recurrent UTI. In Stojanovic's study¹⁴, 33% of the children had recurrent UTI, and recurrence of UTI was significantly more in children with idiopathic hypercalciuria. In Vachvanichsanong's study², the study group consisted of children with idiopathic hypercalciuria; 40% of the patients had UTI and 78% of these had recurrent UTI. After the treatment of hypercalciuria, 83% of the children had no recurrence of UTI. In Lopez's study¹⁰, patients were selected for having recurrent UTI and hypercalciuria, and treatment of the hypercalciuria reduced the recurrence of UTI in 95% of the children.

Table IV. Comparison of the Radiological Findings and $U_{Ca/cr}$ and 24-h Urinary Calcium Ratios

		$U_{Ca/cr}$ BT	$U_{Ca/cr}$ AT	$U_{Ca/cr}$ Rem	24-h U_{Ca} BT	24-h U_{Ca} AT	24-h U_{Ca} Rem
DMSA	Scar	0.09±0.07	0.13±0.17	0.12±0.17	2.40±2.62	1.78±0.90	2.21±1.80
	No Scar	0.14±0.14	0.12±0.15	0.10±0.13	1.52±1.11	1.71±1.08	1.39±1.22
	p	0.36	0.48	0.59	0.20	0.68	0.47
VUR	VUR (+)	0.12±0.04	0.12±0.08	0.12±0.11	1.66±1.60	1.43±1.01	0.51±0.75
	VUR (-)	0.11±0.01	0.11±0.17	0.11±0.17	1.65±1.73	1.60±0.86	2.01±1.49
	p	0.32	0.80	0.90	0.98	0.71	0.10
USG	Normal	0.14±0.15	0.15±0.17	0.08±0.08	1.33±0.93	1.95±0.94	2.80±0.43
	Urinary tract abnormality	0.12±0.14	0.11±0.15	0.12±0.16	1.84±1.81	1.65±1.04	1.58±1.47
	p	0.97	0.62	0.28	0.48	0.62	0.39

BT: Before treatment. AT: After treatment. Rem: Remission. DMSA: 99mTc dimercaptosuccinic acid. VUR: Vesicoureteral reflux. USG: Ultrasonography.

These authors proposed that hypercalciuria could be a contributing factor to recurrent UTI. Regarding this data, we had also expected a higher incidence of hypercalciuria or $U_{Ca/cr}$ ratio in the recurrent UTI group; however, our data were different from the literature. This difference might be attributed to the shorter follow-up period in our study. Also, in our study, the definition of recurrent UTI was made regarding the presence of UTI in the children's history. A higher rate of recurrent UTI would have been detected in our study if the observation period was longer.

Urinary tract abnormality detected with USG was 20.7% in our study. We observed that urinary tract abnormality did not change the $U_{Ca/cr}$ ratio. Higher incidence of urinary tract abnormality was reported in Biyikli's study¹⁶, but their study group consisted of children with recurrent UTI. The incidence of urinary tract abnormality was similar in hypercalciuric and normocalciuric patients in our study. Mahmoodzadeh¹⁵ reported that the hypercalciuria incidence in children with UTI and VUR was similar to that in healthy children. Similar findings were reported in our study for the relation of VUR and hypercalciuria.

In conclusion, we observed that the $U_{Ca/cr}$ ratio was higher in the pre-treatment period of the UTI. Regarding this data, we thought that transient tubular dysfunction due to UTI might induce hypercalciuria. We did not observe a relationship between $U_{Ca/cr}$ and localization of the UTI, family history of nephrolithiasis, clinical manifestations of UTI, or radiological findings. Further studies are needed to examine the association between urinary calcium excretion and UTI.

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