

Does the Urinary Calcium/Citrate Ratio Help in the Diagnosis of Children at Risk of Urolithiasis?

İdrar Kalsiyum/Sitrat Oranı Ürolitiazis Riski Taşıyan Çocukların Teşhisinde Yardımcı Olur mu?

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Abstract

Introduction: Citrate acts as a stone inhibitor, reducing urinary concentration and thus stone formation. It accounts for 50% of the inhibitory activity against calcium phosphate precipitation in urine. The urinary calcium-citrate ratio is a proposed method for assessing urolithiasis risk. Evaluating high urinary calcium alongside citrate may be more informative than high calcium alone. This study aims to highlight the significance of the calcium/citrate ratio as an additional parameter in assessing urolithiasis risk in children.

Materials and Methods: In this study, patients aged 0-18 years with a prediagnosis of urolithiasis who presented to the Pediatric Nephrology outpatient clinic of Başkent University Ankara Hospital between January 2012 and January 2023 were retrospectively analysed. Patients with calcium and citrate levels in spot or 24-hour urine and urinary system USG at initial presentation were included in the study. Statistical analyses were performed using SPSS version 25.0 software. This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Başkent University Ethics Committee.

Results: In this study, 198 patients (60.9%) had stones detected by the first ultrasound, while 127 (39.1%) did not. We compared urinary metabolic parameters between the two groups. The mean spot urine calcium/citrate (ca/cit) ratio was 0.33 ± 0.49 mg/dl (median 0.18) for patients without stones, and 0.48 ± 0.55 mg/dl (median 0.31) for those with stones. The 24-hour urine ca/cit ratio was 0.38 ± 0.96 mg/mg (median 0.23) for patients without stones and 0.58 ± 1.09 mg/mg (median 0.32) for those with stones. We aimed to establish a threshold for predicting stones based on these measurements, finding the optimal cut-off point for spot urine ca/cit ratio to be 0.23, with the highest sensitivity and selectivity.

Conclusion: Not only hypercalciuria or hypocitraturia alone, but also insufficient citrate for a given urinary calcium concentration may be an important risk factor for stone formation in childhood. This is because stone formation is relatively a joint product of hypocitraturia and hypercalciuria. A calcium to citrate ratio greater than 0.23 in spot urine may be significant in predicting stone formation.

Keywords

Urolithiasis, urinary calcium/citrate ratio, childhood stone disease

Anahtar kelimeler

Üriner sistem taş hastalığı, idrar kalsiyum/sitrat oranı, çocukluk çağı taş hastalığı

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Öz

Giriş: Sitrataş inhibitörlerinden biridir ve idrar konsantrasyonunun azalması taş oluşumunu kolaylaştırır. İdrarda kalsiyum fosfatın çökmesine karşı inhibitör aktivitenin %50'sinden sitrat sorumludur. Ürolitiazis hastalarının risk değerlendirmesi için önerilen yeni yöntemlerden biri de idrar kalsiyum sitrat oranıdır. Kalsiyum taşlarının oluşumunda idrar kalsiyum miktarının yüksek olması tek başına bir kriter olmaktan ziyade yüksek idrar kalsiyumunu eş zamanlı olarak idrar sitrat miktarı ile değerlendirmek daha yararlı olabilir. Biz de çalışmamızda üriner sistem taş hastalığı olan çocuklarda diğer risk faktörlerinin yanı sıra yeni bir parametre olabileceğini düşündüğümüz idrar kalsiyum/sitrat oranının önemini göstermeyi hedefledik.

Gereç ve Yöntem: Bu çalışmada Ocak 2012- Ocak 2023 tarihleri arasında Başkent Üniversitesi Ankara Hastanesi Çocuk Nefrolojisi polikliniğine başvuran ve üriner sistem taş hastalığı ön tanısı konulan 0- 18 yaş aralığındaki hastalar retrospektif olarak incelendi, hastalardan spot idrar ya da 24 saatlik idrarda kalsiyum ve sitrat düzeyi bakılan ve eş zamanlı ilk başvuruda üriner sistem USG'si olan hastalar çalışmaya dahil edildi. İstatistiksel analizler SPSS versiyon 25.0 programı ile gerçekleştirildi. Bu çalışma Helsinki Bildirgesi ilkeleri doğrultusunda gerçekleştirildi. Başkent Üniversitesi Etik Kurulu'ndan onay alındı.

Bulgular: Hastalarımızın 198'sinde(%60,9) ilk bakılan USG'de taş gösterilirken 127'sinde(%39,1) taş gösterilemedi. Her iki grubun idrar metabolik parametreleri ve laboratuvar sonuçları karşılaştırıldı. USG'de taş olmayan hastaların spot idrarda ca/sit oranı ortalama $0,33 \pm 0,49$ mg/dl ortanca 0,18 (0,01-3,29) iken USG'de taş olan hastaların spot idrarda ca/sit oranı ortalama $0,48 \pm 0,55$ mg/dl, ortanca 0,31 (0,01-3,47) olarak bulundu. Yirmi dört saatlik idrarda ca/sit oranı ise taşı olmayan hastalarda ortalama $0,38 \pm 0,96$ mg/mg, ortanca 0,23 (0,02-5,73) mg/mg iken taşı olan hastalarda ortalama $0,58 \pm 1,09$ mg/mg, ortanca 0,32 (0,01-6,54) olarak saptandı. Spot idrarda ca/sit ve 24 saatlik idrarda ca/sit ölçümlerinin USG'de taş tahminindeki ayırt edilebilirliği için bir eşik değeri belirlenmesi amaçlandı. Spot idrarda ca/sit ölçümü için duyarlılık ve seçiciliğin en yüksek olduğu kesim noktası 0,23 bulundu.

Sonuç: Çocukluk çağı taş oluşumunda önemli bir risk faktörü olarak yalnız hiperkalsiüri ya da yalnız hipositratüri değil, idrarda belirli bir kalsiyum konsantrasyonu için sitratın yetersiz olması da önemli olabilir. Çünkü taş oluşumu nispeten hipositratüri ve hiperkalsiürinin ortak bir ürünüdür. Spot idrarda 0,23'ten yüksek kalsiyum sitrat oranı taş oluşumunu öngermeye anlamlı olabilir.

Introduction

Urolithiasis is a disease characterised by the formation of stones in the kidneys, ureters and bladder and is caused by many factors including heredity, environmental factors, diet and medication. Urolithiasis is common and its prevalence is increasing in children (1). Studies show that the prevalence of urolithiasis in children in recent years is 5-10% (2,3).

Decreased urinary concentrations of stone inhibitors such as citrate, magnesium, pyrophosphate facilitate stone formation (4). Citrate inhibits spontaneous nucleation of calcium oxalate, crystal growth of calcium oxalate and calcium phosphate, and heterogeneous nucleation of calcium oxalate by monosodium urate (5). Citrate is responsible for 50% of the inhibitory activity against calcium phosphate precipitation in urine (6).

One of the new methods proposed to assess the risk of urolithiasis in patients is the urinary calcium-citrate ratio. In calcium stone formation, it may be more useful to assess high urinary calcium together with the amount of urinary citrate, rather than high urinary calcium alone (7,8).

The calcium-citrate ratio can be analyzed in spot urine or 24-hour urine. However, the number of studies on this topic is limited. In our study, we aimed to determine whether the urinary calcium-citrate ratio, which we believe may be a new parameter in children with a prediagnosis of urolithiasis, can help in the diagnosis of children at risk for urolithiasis.

Materials and Methods

In this study, all patients aged 0-18 years who were admitted to the Pediatric Nephrology Outpatient Clinic of Başkent University Ankara Hospital between January 2012 and January 2023 with a prediagnosis of urolithiasis were retrospectively analysed. For this purpose, all patients who were admitted to our paediatric nephrology outpatient clinic with a prediagnosis of renal calculi (N20.0 ICD (International Classification of Diseases), ureteral calculi, other (N20.0 ICD), renal calculi with ureteral calculi (N20.2 ICD), ureteral calculi, unspecified (N20.9 ICD), bladder calculi (N21.0 ICD), ureteral calculi (N21.1 ICD), lower urinary tract calculi, other (N21.8 ICD), lower urinary tract calculi, unspecified (N21.9 ICD), lower urinary tract calculi, elsewhere classified (N22 ICD), lower urinary tract calculi, schistosomiasis (N22.0 ICD), lower urinary tract calculi, other (N22.8 ICD), lower urinary tract calculi, elsewhere classified (N22.8 ICD), renal colic, unspecified (N23 ICD), the data of all patients aged 0-18 years admitted with diagnosis codes were obtained from the hospital electronic database.

The aim of our study was to investigate whether the ratio of calcium to citrate in urine is useful in the diagnosis of stone formation. Patients who did not have urinary calcium and urinary citrate values at the time of initial presentation and who did not undergo US were excluded from the study because we aimed to determine whether urinary calcium citrate ratio is a differential marker for urinary system stones.

Finally, patients who met the criteria were divided into two groups, those with stones and those without stones, based on the urinary tract ultrasound (US) performed at the time of initial presentation. The 127 patients without stones were called group 1 and the 198 patients with stones were called group 2.

The spot urine calcium-citrate ratio was obtained by the ratio of spot urine calcium (mg/dL) to citrate (mg/dL). Twenty-four-hour urinary calcium and citrate levels were expressed as mg/day. The 24-hour urinary ca/cit ratio was obtained by the ratio of calcium (mg/day) to citrate (mg/day) (9,10). In our study, the presence of urolithiasis was defined radiologically as the presence of posterior acoustic shadowing of the stone and a stone larger than 2 mm with a highly echogenic focus (7). This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Başkent University (date: 24.02.2023, approval number: KA23/40).

Statistical Analysis

Statistical analyses were performed with SPSS version 25.0 software. The conformity of the variables to normal distribution was analysed by Shapiro-Wilk test. Mean, standard deviation, median, minimum and maximum values were used for descriptive analyses. Mann Whitney U Test was used to evaluate the variables that did not show normal distribution between two groups. Frequency and percentage values of the variables were used when presenting categorical variables. The relationships between categorical variables were analysed by Fisher-Freeman-Halton Exact Test. Differences between groups were determined by Dunn's

Benferroni Test. p-values below 0.05 were considered as statistically significant results.

Results

Stones were detected on the first US examination in 198 (60.9%) of our patients, respectively. In 127 (39.1%) patients, no stone was detected on the first US examination. The mean age at the time of diagnosis was 56.31 ± 54.1 months in patients without stones and 42.8 ± 49.1 months in patients with stones. The mean weight of the patients was 19.55 ± 14.6 kg in the patients without stones and 15.6 ± 15.2 kg in the patients with stones. In terms of family history of consanguinity and family history of stones, the two groups were not statistically different (Table 1).

Urinary metabolic parameters and laboratory results were compared between the two groups. The mean spot urine ca/cit ratio was $0.33 \pm .49$ mg/dL, median 0.18 (0.01-3.29) in patients without stones on US, whereas the mean spot urine ca/cit ratio was $0.48 \pm .55$ mg/dL, median 0.31 (0.01-3.47) in patients with stones on US. (Figure 1) Twenty-four-hour urine ca/cit ratio was $0.38 \pm .96$ mg/mg, median 0.23 (0.02-5.73) mg/mg in patients without stones, while it was 0.58 ± 1.09 mg/mg, median 0.32 (0.01-6.54) mg/mg in patients with stones. (Figure 2) The detailed results of the other laboratory values of the patients with stones and the patients without stones are shown in Table 2. Spot urine ca/cit and 24-hour urine ca/cit were significantly higher in patients with stones on US than in those without stones. The spot urine ca/cre and uric acid/creatinine ratio were significantly higher in patients with stones on US than in patients without stones. Urine density was lower in patients

Table 1. Demographic data of patients

		US				p-value
		Group 1 n=127		Group 2 n=198		
		Mean ± SD	Med (Min-Max)	Mean ± SD	Med (Min-Max)	
Gender	Female	67	(52.8)	92	(46.5)	0.268
	Male	60	(47.3)	106	(53.5)	
Age (months)		106.8±64.1	89 (19-276)	93.3±56.7	78 (14-252)	0.107
Age at diagnosis (months)		56.31±54.1	36 (1-229)	42.8±49.1	19.5 (0-216)	0.007
Weight (kg)		19.55±14.6	14 (1.9-64.4)	15.6±15.2	9.64 (2.2-102)	0.001
Consanguineous marriage	No	119	(93.7)	184	(92.9)	0.787
	Yes	8	(6.3)	14	(7.1)	
Family history of stones	No	52	(40.9)	85	(42.9)	0.724
	Yes	75	(59.1)	113	(57.1)	

with stones on US than in patients without stones. There were no differences in biochemical tests between the two groups, with the exception of blood urea nitrogen. It was found that the urea nitrogen in the blood was lower in the group with stones than in the group without stones. Calcium and citrate in the 24-hour urine samples did not differ between the two groups, but the ratio of calcium to citrate in the urine was higher in the patients with stones.

The ROC for urine Ca/Cit ratios was constructed to identify potential “cut-off” values to discriminate between groups (Figures 3 and 4). When assessing stone risk between Group 1 and Group 2, the area under the ROC for spot urine was

63.4%. Thus, the urine ca/cit ratio showed good discriminative potential to distinguish between both groups. Based on the above analysis, together with multilevel likelihood analyses, a spot urine ca/cit value of 0.23 was found to be a good cut-off point, providing equal sensitivity and specificity to discriminate between group 1 and group 2 (Figure 3).

When the spot ca/cit value exceeds 0.235, the sensitivity for stone formation is 59.1%, while the specificity is 62.1%. The sensitivity and selectivity for stone formation in individuals with a cut-off value greater than 0.46 in ca/cit measurement in twenty-four-hour urine are 37.8% and 94.1%, respectively. In our study, it can be said that the discriminative power of

Table 2. Laboratory findings in patients with and without Stones

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	US				p-value
	Group 1 n=127		Group 2 n=198		
	Mean ± SD	Med (Min-Max)	Mean ± SD	Med (Min-Max)	
Urine pH	6,22±,84	6 (5-8,5)	6,4±,84	6,5 (5-8,5)	0,053
Urine density	1014,58±8,04	1014 (1001-1031)	1012,39±7,73	1011 (1000-1035)	0,018
Spot ca/cre (mg/dL)	0,18±,22	0,13 (0,01-1,94)	0,36±,39	0,25 (0,01-3,04)	<0,001
Spot urine cit/cre (mg/g creatinine)	1127,79±2743,39	673,63 (11,95-27586)	1148,93±1132,37	871,71 (17,2-8617,65)	0,058
Spot urine ua/cre (mg/dL)	1,14±1,09	1,07 (0,21-11,32)	1,2±,53	1,16 (0,27-4,77)	0,046
Spot urine mg/cre (mg/dL)	0,19±,21	0,15 (0,03-1,6)	0,18±,14	0,16 (0,01-0,82)	0,860
Spot urine ca/cit (mg/dL)	0,33±,49	0,18 (0,01-3,29)	0,48±,55	0,31 (0,01-3,47)	<0,001
24-hour urine calcium (mg)	84,31±71,97	61 (11-411)	106,7±84,08	75 (12-359)	0,327
24-hour urine citrate (mg)	465,56±321,09	432 (124-1261)	420,66±387,13	341,5 (11-2054)	0,429
24-hour urine ca/cit (mg/mg)	0,38±,96	0,23 (0,02-5,73)	0,58±1,09	0,32 (0,01-6,54)	0,041
BUN (mg/dL)	11,3±5,18	10,8 (3-32,9)	9,75±4,56	9,2 (2,4-30)	0,023
Creatinine (mg/dL)	0,51±,12	0,48 (0,24-0,84)	0,5±,14	0,46 (0,3-1,65)	0,074
Na (mg/dL)	137,48±2,42	137 (132-143)	137,72±2,29	138 (130-146)	0,341
K (mg/dL)	4,44±,50	4,35 (3,5-5,7)	4,53±,49	4,45 (3,2-6,2)	0,095
Ca (mg/dL)	10,03±,55	10 (8,9-11,9)	10,11±,91	10,1 (8-19,4)	0,239
P (mg/dL)	5,01±,92	5,1 (2-7)	5,09±,69	5,08 (3,2-7,01)	0,664
Mg (mg/dL)	2,2±,31	2,17 (1,52-3,29)	2,12±,27	2,09 (1,5-3,75)	0,058
Blood pH	7,39±,05	7,39 (7,21-7,54)	7,39±,04	7,39 (7,3-7,56)	0,719
HCO3 (mmol/L)	21,56±2,85	21,9 (13,6-27,1)	22±2,93	22 (16,6-28,8)	0,642
Uric acid (mg/dL)	4,11±1,48	3,9 (1,2-12,8)	3,76±1,20	3,7 (1,2-9)	0,077
ca/cre:calcium/creatinine, cit/rce:citrate/ creatinine, ua/cre: uric acid/ creatinine, mg/cre: magnesium/creatinine, ca/cit: calcium/citrate, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, Ca: Calcium, P: Pospate, Mg: Magnesium, HCO ₃ : Bicarbonate					

the spot urine ca/cit ratio was higher than the 24-hour urine ca/cit ratio (Figure 3, Figure 4).

Discussion

Pediatric urolithiasis is becoming more common in Türkiye and worldwide (1,11). Although pediatric urolithiasis is more common than in the past, children have less urinary stone disease than adults. The prevalence of urolithiasis is lower in children than in adults. This difference may be attributed to higher urinary citrate and magnesium levels in children compared to adults. The most common

predisposing factors for kidney stone formation in children are hypercalciuria and hypocitraturia (7). It is not only the concentration of calcium and citrate in the urine that determines the risk of stone formation, but also the relative excess of calcium to citrate in the urine (12). Normal values for the urinary calcium/citrate ratio according to age are given in Table 3. (13).

In this study, the mean urinary ca/cit ratio was significantly higher in those who presented with a history of urolithiasis and had stones at the time of initial diagnosis compared to those without stones ($p<0.001$).

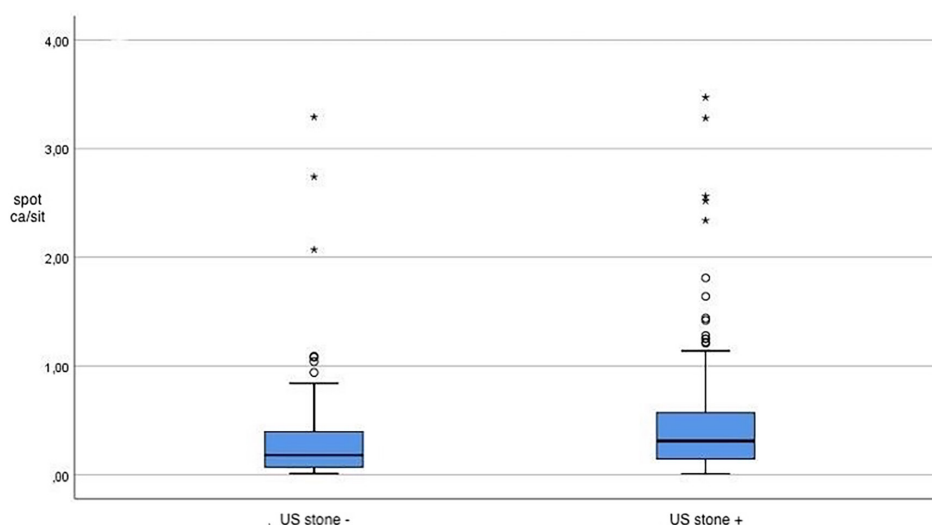


Figure 1. Ca/cit ratios in spot urine of patients with and without stones on US

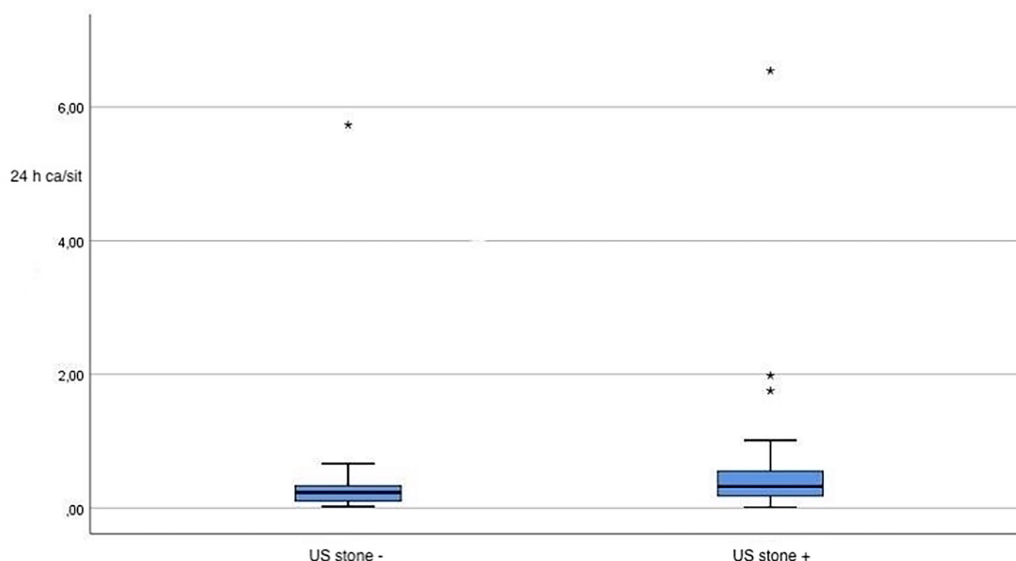


Figure 2. Ca/cit ratios in 24-hour urine of patients with and without stones on US

In the study, there was no significant difference between men and women in either the spot urine ca/cit ratio or the 24-hour urine ca/cit ratio. As creatinine is removed from the equation when calculating urinary calcium and urinary citrate, the urinary Ca/Cit ratio is not affected by muscle mass. Previous studies in children have shown that the urinary calcium/citrate ratio is not affected by age or sex (10,14,15). There are many studies showing that the urinary ca/cit ratio can discriminate between normal children and children with urinary calculi.

Srivastava et al. (10) conducted an evaluation of random urine calcium, citrate, and creatinine levels in 78 hypercalciuric non-stone formers, 34 hypercalciuric children with stones, and 149 controls. Their findings indicated that the urine calcium/citrate ratio (mg/mg) is a valuable tool for differentiating between healthy children and those who develop kidney stones.

Kompani et al. (7) evaluated in children aged 2-12 years, the urinary ca/cit ratio (mg/mg) was 0.19 in controls, 0.39 in children with hypercalciuria without stones and 0.44 in

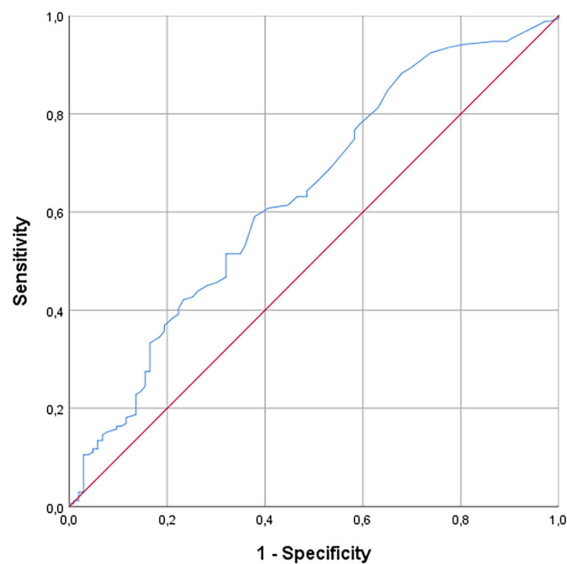


Figure 3. ROC curve in patients with ca/cit measurement in spot urine

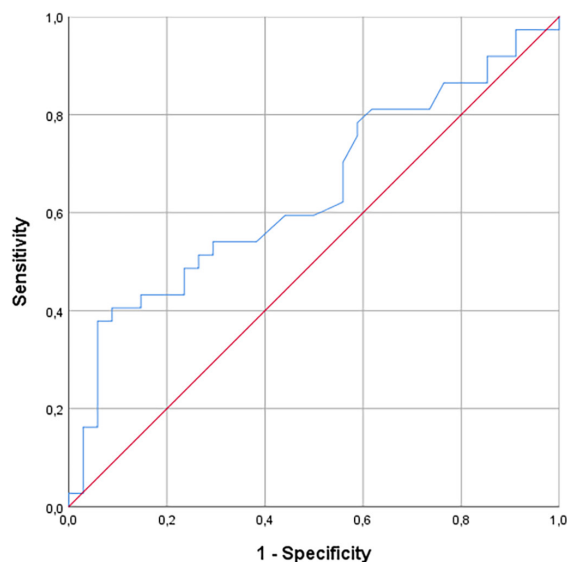


Figure 4. ROC curve for ca/cit measurement in twenty-four-hour urine

Table 3. Normal values of calcium citrate ratio according to age

Calcium/citrate ratio		mmol calcium/mmol citrate		mg calcium/mg citrate	
		Male	Female	Male	Female
	2-6 years	<0,75	<0,65	<0,15	<0,13
	7-12 years	<0,85	<0,60	<0,17	<0,16
	13 years and over	<1,10	<0,8	<0,22	<0,16

children with hypercalciuria with stones. Kompani et al. (7) found a significantly higher ca/cit ratio in children with hypercalciuria compared to the control group. Similar to our study, in a study conducted by Lee et al. (15) on 46 children with unconfirmed urolithiasis and 51 children with confirmed urolithiasis and reporting that spot urine ca/cit ratio was higher in children with confirmed urolithiasis compared to unconfirmed children, spot urine ca/cit ratio (mmol/mmol) was reported as 0.68 in children without stones and 1.30 in children with stones. In a study conducted by Turudic et al. (16) in Croatia on 61 children with urolithiasis and 25 healthy children, the ca/cit ratio (mol/mmol) in 24-hour urine was analysed and reported to be 3.42 and 1.06, respectively (17).

Our ROC data (Figures 3 and 4) show that a urinary Ca/Cit ratio of 0.23 effectively differentiates children with and without stones presenting with urolithiasis who present for evaluation. Consequently, a urinary calcium/citrate ratio of <0.235 may serve as an ideal target value for patients with urolithiasis presenting with stone formation. Another important implication from the data is that complete correction of hypercalciuria in individuals with stone formation may not be necessary, as long as an adequate urinary citrate concentration is maintained that helps to keep the urinary calcium/citrate ratio low enough to prevent stone formation. As the proposed urinary calcium/citrate thresholds are derived from retrospective data, further validation in prospective studies will be required.

Stravistava et al. (10) considered a value greater than 0.33 to be significant for the urinary calcium/citrate ratio threshold for predicting urinary stone formation. Kompani et al. (7) reported a threshold value of 0.25 for the urinary calcium/citrate ratio.

In childhood stone formation, not only hypercalciuria or hypocitraturia but also the insufficiency of citrate for a specific calcium concentration in urine may be an important risk factor. Stone formation is relatively the result of the coexistence of hypocitraturia and hypercalciuria (7,18). In children with hypercalciuria, high citrate excretion in urine may provide a protective role against stone formation (10).

Study Limitations

The main limitation of our study was that it was retrospective and performed in a single centre. Multicentre prospective studies on the urinary calcium-citrate ratio should be performed.

Conclusion

The urine ca/cit ratio is not affected by gender, age or muscle mass. This marker may help us to differentiate stone formation in patients presenting with urolithiasis. In conclusion, our study showed that a spot urine ca/cit ratio higher than 0.23 significantly predicted stone formation. According to this result, it is possible to predict whether a patient will form urinary calculi based on the ca/cit ratio. Therefore, urinary citrate level should be checked as part of the metabolic evaluation in patients presenting to paediatric or paediatric nephrology outpatient clinic with urinary stone disease.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Başkent University (date: 24.02.2023, approval number: KA23/40).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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