# ROLE OF URINARY CALCIUM/CREATININE RATIO IN DIAGNOSIS OF HYPERCALCIURIA IN CHILDREN WITH UROLITHIASIS IN FAYOUM, EGYPT

## By

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## ABSTRACT

*Background: Early detection of pediatric urolithiasis is important to avoid the associated morbidities that can affect renal function. Hypercalciuria is a common contributing factor to urinary stone formation in children.*

*Aim of the work: To assess the diagnostic performance of urinary calcium/creatinine (UCa/UCr) ratio as a screening test for cases of hypercalciuria with urolithiasis.*

*Subjects and Methods: One hundred children with urolithiasis who attended the Nephrology and Urology Outpatient Clinics in Fayoum University Hospitals, Fayoum Insurance Hospital, and Fayoum General Hospital, during the period from June 2019 to June 2020 selected by simple random method an subjected to history taking, clinical examination, and investigations including blood chemistry, urine analysis, spot urine sample analysis for UCa/UCr ratio, calcium, and creatinine. Thirty age- and sex-matched, healthy children were included as control.*

*Results: The UCa/UCr ratio was significantly higher among the cases (Median: 0.08 vs. 0.04, p-value = 0.019). Twenty-two percent of cases had a high UCa/UCr ratio above 0.2. The UCa/UCr ratio had the highest area under the curve (AUC = 0.641, p = 0.018) compared to urinary calcium (AUC = 0.575, p = 0.216) and creatinine (AUC = 0.625, p = 0.038). The optimal cut-off point for UCa/UCr ratio was 0.06, with 59% sensitivity and 62.3% specificity. Conclusions: UCa/UCr ratio is a potentially early, useful, practical, and non-invasive screening tool for the early detection of urolithiasis*

*in children. We recommend urine microscopy and strict metabolic work-up for all patients who present with symptoms suggestive of urolithiasis.*

**Keywords:** *hypercalciuria; nephrolithiasis; pediatric; risk factor; urolithiasis.*

### INTRODUCTION

Urinary stone formation is more frequent in children than was previously anticipated. The incidence rate of pediatric urolithiasis has increased by approximately 37% over the last two decades (**Bevill et al., 2017**), particularly in teenagers between 14 and 18 years old (**Sas et al., 2010**).

The exact causes underlying the rise in rates of pediatric urolithiasis remain to be identified. Several studies have pointed to the role of some risk factors, such as excess salt intake, inadequate water intake, and obesity (**Valentini and Lakshmanan, 2011** and **Schaeffer et al., 2011**).

Misdiagnosis of urolithiasis in the pediatric population may be attributed to the subtlety of the symptoms and signs. Therefore, pediatricians should consider urolithiasis in the differential diagnosis of all children who present with abdominal colic or macroscopic hematuria. In such cases, a thorough evaluation can rule in or out the diagnosis of urolithiasis (**Bignall and Dixon 2018** and **Hoppe and Kemper, 2010**).

Previous studies reported that approximately 50 to 84% of children with urolithiasis suffer from a metabolic, genetic, or systemic disorder that contributes to the formation of urinary stones (**Bevill et al., 2017** and **Gouru et al., 2018**).

It is important to identify the children who have an underlying disorder contributing to stone development as the risk of recurrent stones is much higher than that of children who have no risk factors (**Üntan et al., 2021**).

Calcium is a component of about 98% of all renal stones (**Sas et al., 2016**). Increased excretion of calcium in the urine has been implicated in the formation of calcium renal stones in a considerable percentage of cases (**Coe et al., 2016**).

Hypercalciuria in children is diagnosed when 24-hour calcium excretion is more than 4 mg/kg/day (0.1 mmol/kg/day) on two or three measurements separated by a few weeks (**Lottmann et al., 2010**). However, it is difficult to obtain 24-hour collections of urine in

young children, and so the urinary calcium/creatinine (UCa/UCr) ratio is measured in a spot urine sample. Levels of UCa/UCr above 0.2 mg/mg (0.6 mmol/mmol) are usually adopted to diagnose hypercalciuria **(Craig, 2004)**.

Therefore, **the present study aimed to** assess the diagnostic performance of the UCa/UCr ratio as a screening test for cases of hypercalciuria with urolithiasis

## Ethical considerations:

1. The study was approved by the Ethical Committee of the Faculty of Medicine, Fayoum University, Egypt.

2. Informed, verbal consent was obtained from the participants or their legal guardians after explanation of the aim of the study.

3. All the data of the study is confidential and the patients have the right to keep or withdraw from study at any time,

4. The authors declared that no potential conflict of interest with respect to the research, authorship and /or publication of the article,

5. No financial disclosure regarding the study or publication.

## Sample size:

Sample size was calculated using (G power version 3.1.9.4). sample size of patients was100 in cases and 30 controls needed to get power level of 0.80, alpha level of 0.05 and medium effect size of 0.64 in urinary calcium / creatinine ratio between the two groups.

## Inclusion criteria:

- Children with urinary stones revealed by history of passing stones or operated for stone removal.

- Age from one to 15 years.

## Exclusion criteria:

- Any patient less than one year or more than 15 years.

- Patient has end stage renal disease.

- Any patient refused to participate in the study.

## Study design:

This case-control study was conducted on children who attended the Nephrology and Urology Outpatient Clinics in Fayoum University Hospitals, Fayoum Insurance Hospital, and Fayoum General Hospital, during the period from June 2019 to June 2020. The study enrolled 100 children (of both sexes) whose ages ranged between 1 and 15

years and who had renal radio-opaque stones. For controls, 30 apparently healthy children were selected who were age- and sex-matched to the urolithiasis group. Patients were excluded if their age was below one or above 15 years old or had an end-stage renal disease.

**Procedures:**

**All the study participants were subjected to:**

I. Full history taking was focused on preceding recurrent urinary tract infection, hematuria, abdominal pain, family history, water intake, salt intake, and source of water supply as well as previously passed stones and/or previous stone operation.

II. Clinical examination included general examination, measuring the blood pressure, cardiac examination as well as an examination of the chest and abdomen

III. Laboratory investigations were ordered to assess the levels of calcium and creatinine in serum and urine, and the UCa/UCr ratio in a random spot urine sample (Wu, 2006), besides urine analysis. Imaging investigations included a pelviabdominal ultrasound.

Statistical methods:

The collected data were organized, tabulated, and statistically analyzed using the IBM Statistical Package for Social Sciences version 18 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc., USA). Numerical variables were described as mean ± standard deviation (SD) or median and range. Either an independent samples t-test or Mann-Whitney–U test was used to compare the two groups. Categorical data were presented as numbers and percentages. The receiver operating characteristic (ROC) curve was used to determine the discrimination value of calcium, creatinine, and Ca/C ratio for differentiating cases from controls and to define the optimal cut-off points along with their sensitivities and specificities. The area under the ROC curve (AUC) was graded excellent (0.9-1), good (0.8-0.9), fair (0.7-0.8), or poor (0.6-0.7). For interpretation of the results of statistical tests, significance was adopted at $P \leq 0.05$.

## RESULTS

Our study results are demonstrated in the following tables and figures:

**Table (1):  Sociodemographic data of the two studied groups**

| | | Cases (N=100) | Control(N=30) | P-value |
|---|---|---|---|---|
| **Age (years)** | Mean ± SD | 5.5 ± 2.8 | 6.5 ± 3.6 | 0.124[#] |
| **Sex** | Female | 46 (46.0%) | 15 (50.0%) | 0.700[##] |
| | Male | 54 (54.0%) | 15 (50.0%) | |
| Residence | Rural | 55(55%) | 16 (53.3%) | 0.65[##] |
| | urban | 45 (45%) | 14(46.7%) | |

SD: standard deviation; #: Independent-samples T-test; ##: Pearson's Chi-square test.

This table shows no statistically significant differences between two groups as regard age, sex or residence (p = 0.124, 0.7000. and 0.650 respectively).

**Table (2):  Frequencies of the main complaint and risk factors in the cases group**

| variable | | N | % |
|---|---|---|---|
| **Main Complaint** | Abdominal pain | 34 | 34.0% |
| | Dysuria | 33 | 33.0% |
| | Hematuria | 21 | 21.0% |
| | Enuresis | 7 | 7.0% |
| | Fever | 2 | 2.0% |
| | Dehydration | 1 | 1.0% |
| | Lion Pain | 1 | 1.0% |
| | Vomiting | 1 | 1.0% |
| **Risk factors** | Inadequate water intake | 64 | 64.0% |
| | Family history of stone | 29 | 29.0% |
| | Increased salt in food | 14 | 14.0% |

This table illustrated that the most frequent presenting main complaints of the patients (study groups) were abdominal pain (34%) and dysuria (33%), followed by hematuria (21.0%). The most common clinical presentations were dysuria (55%), recurrent UTI (45%), and hematuria (32%), while enuresis was less frequently recorded (6%). Inadequate water intake (64%) was the main risk factor in the studied patients, followed by positive family history of renal stones (29%) and salty food intake (14%) as.

## Table (3):  laboratory and ultrasound findings in the cases group

| | | | |
|---|---|---|---|
| **Laboratory investigations** | **Serum calcium** mg/dl | Mean ± SD (range) | 9.3 ± 0.5 8.3-10.4) |
| | **Creatinine** mg/dl | Mean ± SD (range) | 0.4 ± 0.2 (0.1-2.6) |
| | **Urea** mg/dl | Mean ± SD (range) | 23.7 ± 10.4 (9-190) |
| | **Sodium** meq/L | Mean ± SD (range) | 141 ± 4.8 (128-151) |
| | **Potassium** meq/L | Mean ± SD (range) | 4.3 ± 0.4 (3.2-5.1) |
| **Urine analysis** | **Pus cell** / (HPF) | 0-10 | 49 (49.0%) |
| | | >10 / HPF | 51 (51.0%) |
| | **RBCs** / (HPF) | 0-10 / HPF | 64 (64.0%) |
| | | >10 / HPF | 36 (36.0%) |
| | **Crystals** | Nil | 61 (61.0%) |
| | | Ca Oxalate | 21 (21.0%) |
| | | Urates | 18 (18.0%) |
| **Ultrasound findings** | **Renal stone** | | 46 (46.0%) |
| | **Ureteric stone** | | 24 (24.0%) |
| | **Bladder stone** | | 21 (21.0%) |
| | **Nephrocalcinosis** | | 9 (9.0%) |

This table shows that Serum calcium, sodium, and potassium were nearly within the normal laboratory ranges in the studied patients. The results of urine analysis of the studied patients showed that pyuria and hematuria were common findings (51% and 36%, respectively). Sixty-one percent of the patients had no crystals in urine analysis, while 21% and 18% had calcium oxalate and urates crystals, respectively. Examination with ultrasonography revealed renal stones in 46% of patients, followed by ureteric stones in 24%, bladder stones in 21%, and nephrocalcinosis in 9% as shown in **table 3**.

## Table (4):  Comparison of urinary calcium/creatinine ratio between the cases and control groups

| | | Cases (N=100) | Control (N=30) | P-value[#] |
|---|---|---|---|---|
| **Ca/creatinine in urine** | Median (range) | 0.08 (0.0 – 2.20) | 0.04 (0.0 – 0.19) | 0.019* |

Max: maximum; Min: minimum; *: significant; #: Mann-Whitney U test
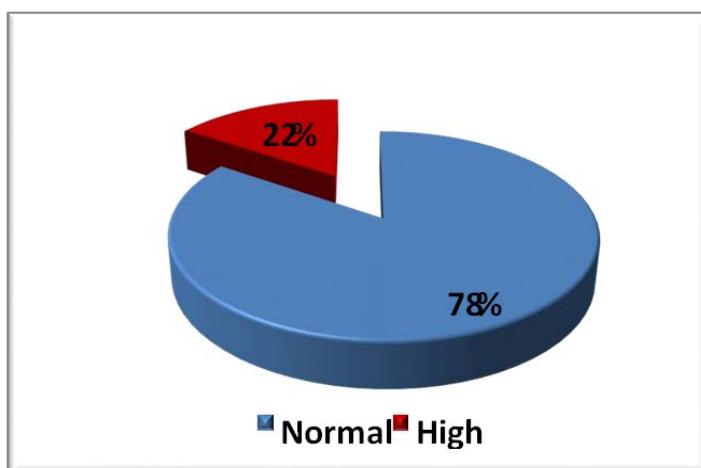
**Figure (1): Frequency of high urinary calcium creatinine ratio among the study group**

This table shows Comparison between the cases and control groups regarding the UCa/UCr ratio and revealed a significantly higher ratio in cases (Median: 0.08 vs. 0.04, p-value = 0.019). Twenty-two percent of patients in the cases group had a high UCa/UCr ratio above 0.2 as illustrated in **Figure 1**.

**Table (5): The analysis of the receiver operating characteristics curve for urinary calcium, creatinine, and calcium/creatinine among cases**

|  | AUC | P-value | Cut-off point | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Ca in urine mg/dl** | 0.575 | 0.216 | 5.25 | 53% | 70% |
| **Creatinine in urine mg/dl** | 0.625 | 0.038* | 98.75 | 57% | 66.7% |
| **UCa/UCr ratio** | 0.641 | 0.018* | 0.06 | 59% | 62.3% |

AUC: area under the curve; UCa/UCr: urinary calcium/creatinine; *: significant

Diagonal segments are produced by ties.
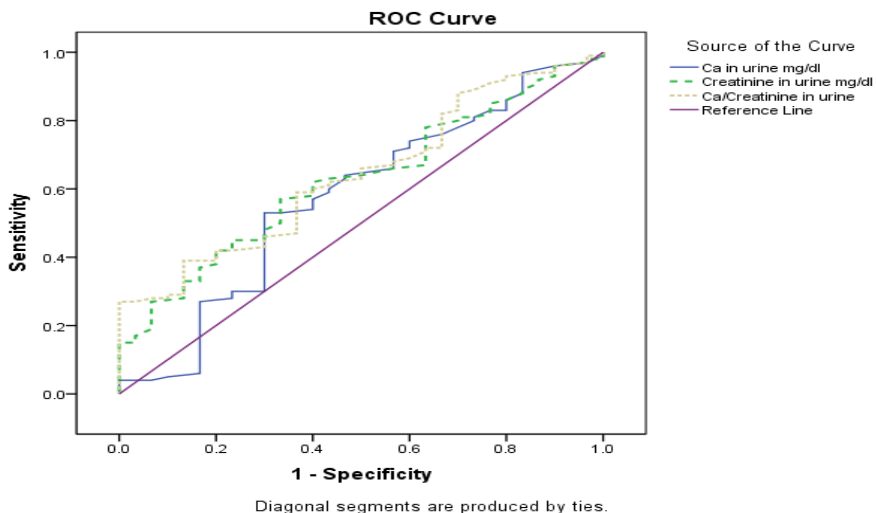
**Figure (2):** **The receiver operating characteristics curve of the UCa/UCr ratio for differentiating between cases and controls. The area under the curve (AUC) = 0.641; with 59% sensitivity and 62.3% specificity at a cut-off value 0.06**

The previous Table and Figure show analysis of the ROC curve and showed that UCa/UCr ratio had the highest area under the curve (AUC = 0.641, p = 0.018). Meanwhile, its discriminatory power is considered poor to fair. The optimal cut-off point for UCa/UCr ratio was 0.06 which achieved a sensitivity of 59% and a specificity of 62.3%. The least discriminatory power was that of calcium in the urine (AUC = 0.575, p = 0.216) and was not significantly better than random chance in identifying the patients. The discriminatory power of urinary creatinine was mid-way between the two markers (AUC = 0.625, p = 0.038).

### DISCUSSION

Pediatric patients are at high risk of having recurrent urinary stones, particularly those who suffer from metabolic disorders. Hypercalciuria is considered among the common metabolic disorders that are identified in children with urolithiasis. In infants and young children, the urinary calcium/creatinine ratio is used for diagnosis. However, this ratio is strongly age-dependent and decreases considerably during

the first year of life. Our study aimed to assess the diagnostic performance of the UCa/UCr ratio as a screening test for cases of hypercalciuria with urolithiasis.

In the present study, male patients represented about 54 % and females represented 46%. Likewise, several recent studies reported a predominance of male over female gender in patients with urinary stones as **Bacallao et al., 2021**, **Lee et al., 2019** and **Ramya et al., 2021**. In contrast, **Sas et al., 2010** found a higher percentage of female patients among children hospitalized for urolithiasis2. The disparity in the predominant gender in pediatric urolithiasis may be explained by variations in the inclusion criteria employed in the studies and the proportions of male and female children in the populations from which the studied samples were withdrawn.

We found that the most common complaint among pediatric patients was abdominal pain (34%), followed by dysuria (33%), hematuria (21%), and enuresis (7%). The reported commonest complaints agree with similar studies, but with varying frequencies across the studies as **Amancio et al., 2016** found the most common presenting symptoms to be non-specific abdominal pain (56.7%), classic renal colic (44.2%), urinary tract infection (37.5%), and gross hematuria (31.9%), while urinary symptoms, including dysuria, suprapubic/urethral pain, urge/incontinence, and enuresis were recorded in 24% of the patients. While **Sas et al., 2016** stated that more than half of their patients presented with back or flank pain, one-third presented with gross hematuria, vomiting, and/or abdominal pain, and 12% had dysuria. **Issler et al., 2017** found that 36% of patients presented with urinary tract infections, whereas pain and gross hematuria were the presenting symptoms in 32% and 13% of patients, respectively.

Urinary symptoms, particularly dysuria, were more frequently reported in our sample. The variations of frequencies of the presenting complaints among the studies can be partially explained by the inclusion of children of different ages, as the symptoms in young children and infants tend to be non-specific and more subtle **Hoppe and Kemper 2010**. The non-specificity of most complaints and the lower prevalence of urinary symptoms warrant increased alertness of clinicians to identify those patients early and to develop effective tools for screening patients for urolithiasis.

Diagnosis of nephrolithiasis in pediatrics relies on clinical acumen in combination with imaging and selective laboratory testing. Common presenting signs and symptoms include abdominal or flank pain, dysuria, nausea or vomiting, as well as hematuria (**Bowen and Tasian, 2018**).

Risk factors for urolithiasis should be identified. Known risk factors include anatomical anomalies and metabolic disorders. Therefore, the evaluation of patients with urolithiasis requires analysis of their dietary habits, family history of metabolic diseases, the composition of passed/extracted stones, and radiologic examination of the urinary tract. We found that inadequate water intake was prevalent in most patients (64%), while family history and salty food consumption were recorded in 29% and 14% of cases, respectively and this is in agreement with **Bowen and Tasian, 2018** and **Cogswell et al., 2014** who found drinking less water than required and consumption of sodium in amounts exceeding the recommended daily intake. In addition, the administration of greater amounts of animal protein and sodium represents independent risk factors for hypercalciuria, which is a metabolic risk factor for calcium urinary stones as reported by **Tasian and Copelovitch, 2014**.

In our study positive family history of urolithiasis is reported in about 29% comparable to previous studies rates which is varying from 40% as in **Hoppe and Kemper, 2010**, **VanDervoort et al., 2007** and **Alemzadeh-Ansari et al., 2014** up to 85% as **Amancio et al., 2016** reported.

The results of urine analysis in our sample revealed the presence of pyuria in half the patients and hematuria in nearly one-third. Also, calcium and urate crystals appeared in 21% and 18%, respectively of the cases. In partial agreement with these findings, **Amancio et al., 2016** found that the most common abnormalities in urine analysis were hematuria (58.3%) and pyuria (57.3%). However, the prevalence of oxalate and urate crystals (3.1% and 2.1%, respectively) was much lower than our findings. We found no significant deviation from normal ranges in the patients' biochemical blood tests, which are in agreement with **Amancio et al., 2016**.

The first-line diagnostic imaging modality in pediatric urolithiasis is ultrasound imaging (**Türk et al., 2016**).

Ultrasonography is preferred in children to avoid exposure to ionizing radiation, besides its utility due to the relatively low body fat content in children and its lower cost compared to compute tomography (**Colleran et al., 2017**). Although the US is less sensitive (70%) than computed tomography, it is effective in diagnosing most clinically significant stones that require surgical intervention (**Passerotti et al., 2009** and **Johnson et al., 2011**).

The most common US finding in the current study were renal stones (46%), followed by ureteric stones (24%), bladder stones (21%), and finally nephrocalcinosis (9%). This finding is in line with **Amancio et al., 2016**, **Spivacow et al., 2008** and **Alpay et al., 2009** who found most stones to be in the upper urinary tract. On the contrary, **Penido and Tavares, 2021** reported that bladder stones are more frequently reported in their study.

The spot urine analysis for UCa/UCr ratio is frequently used for the diagnosis of hypercalciuria as obtaining 24-hour urine collection presents some problems in children. In children above the age of seven months, a UCa/UCr ratio ≥ 0.21 is used to diagnose hypercalciuria as stated by **Craig,**

**2004**. Meanwhile, some studies have assessed different cut-off values of the UCa/UCr ratio as **Choi et al., 2013** and **Matos et al., 1997**.

In our study, there was a statistically significant increase in the values of the UCa/UCr ratio in 22% of the cases this is in agreement with: **Elmacı et al., 2014** (21.7%) in Turkey, **Imran et al., 2017**, (20.4%) in **Iran and Ramya et al., 2021** (29.2%) in South Eastern India. The prevalence of hypercalciuria varied across the different studies, presumably due to variations in the children's age, ethnic origin, geographic location, and the calcium content in their diet as reported by **Matos et al., 1997**. However, much higher rates were reported by other studies, ranging from 33.9% up to 74.6% as **Sas et al., 2016**, **Bacallao et al., 2021**, **Amancio et al., 2016** and **Cetin et al., 2020**. On the other hand, a much lower rate of 11% was reported by one study **Bevill et al., 2017**.

The ROC curve analysis in the present study showed that UCa/UCr ratio differentiated between cases and controls, but its discriminatory power was poor (AUC = 0.641). The optimal cut-off value was 0.06 mg/mg, with a sensitivity of 59% and a specificity of 62.3%. Meanwhile,

other studies showed a slightly better discriminatory power of the UCa/UCr ratio. **Choi et al., 2013** reported that the discriminatory power was fair (AUC = 0.778) and identified the optimal cut-off value of the random UCa/UCr ratio as 0.075 mg/mg. Nevertheless, the associated sensitivity and specificity (77.8% and 64.3%, respectively) are relatively low. **Lee et al., 2019** determined the ROC area for UCa/UCr as 0.736 (fair discriminatory power), with a sensitivity of 53% and a specificity of 78% while at a cut-off value > 0.60 mmol/mmol.

The present study showed several merits being one of the few studies conducted in Egyptian children to detect the prevalence of hypercalciuria among pediatric patients with urolithiasis. In addition, the study assessed the utility of spot urine sample UCa/UCr ratio as a screening test to identify cases of hypercalciuria.

## CONCLUSION

The present study has demonstrated that high UCa/UCr levels have been found in children with renal stones compared to controls. So, UCa/UCr measurement might become an early, useful, sensitive, practical, and non-invasive screening tool for the early detection of urolithiasis in children and adolescents, which allows early intervention and treatment.

## RECOMMENDATIONS

We recommend that urine microscopy should be done at least once for all stone patients to screen for urinary crystals. In addition, strict metabolic work-up should be done for children with pediatric urolithiasis. Further studies with larger samples are needed to confirm the utility of the UCa/UCr ratio as a screening test for hypercalciuria as a risk factor of pediatric urolithiasis

## LIMITATION

Main limitations of the study were the non-analysis of other common metabolic disorders that contribute to urolithiasis. In addition, the composition of the stones was not analyzed and relatively small number of the patients.

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