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Hypercalciuria as a risk Factor For pediatric Urolithiasis in Fayoum.

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Abstract

Introduction: Most cases of calcium kidney stone illness may be traced back to hypercalciuria, or high urine calcium excretion, which affects 5–10% of the population, accounts for 80–90% of kidney stones, and is detected in at least one-third of those who develop calcium kidney stones.

Aim of the study: This case-control study aimed to evaluate children with relevant histories, clinical examinations, and metabolic workups, including a complete urine examination and measurement of the calcium/creatinine ratio in urine.

Subjects and methods: One hundred children below 15 years old who are found to have urolithiasis were evaluated with relevant history, clinical examination, and metabolic workup, which included a complete urine examination and measurement of the calcium/creatinine ratio in urine.

Results: Our results show a statistically significant increase in calcium/creatinine ratio values (*P=0.019*), which means that hypercalciuria is the main metabolic risk factor for pediatric urolithiasis.

Conclusion: We discovered that measuring the urine calcium/creatinine ratio may prove to be a valuable, practical, sensitive, and accurate noninvasive method for the early identification of juvenile urolithiasis.

Key words: Hypercalciuria; Urolithiasis; Urinary calcium; Creatinine.

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1. Introduction

Although symptoms and indicators might be subtle or deceptive, urolithiasis is more common in children than is generally anticipated, yet it is still underdiagnosed or misdiagnosed in a small percentage of patients. Every youngster who experiences colicky stomach pain or macroscopic hematuria needs to have their urolithiasis properly checked [1]. The location of calculi, any anomalies in the urinary system, and any unexpected obstruction brought on by stone disease should then be determined using diagnostic imaging. While an ultrasound check is typically sufficient, there are times when radiological procedures like plain

abdominal films or more delicate, non-enhanced computed tomography are needed [1].

A thorough diagnostic assessment is important to rule out metabolic conditions such as primary hyperoxalurias and others that might cause recurrent urolithiasis or even renal failure because metabolic reasons are frequently present in children [2]. The stone is just one of the scary indications of the illness; it is not the illness itself. Hence, a complete and timely diagnostic evaluation is required for every infant and child who produces their first stone [3]. Missing a diagnosis may have unfavorable effects [4]. For example, the diagnosis of primary hyperoxaluria is frequently delayed until end-stage renal failure manifests years or decades after the onset of the initial nephrolithiasis symptom. According to a 24-hour urine sample collection, children with hypercalciuria are those who have calciuria >4 mg/kg/day (0.1 mmol/kg/day) [5]. If the calcium/creatinine ratio is greater than 0.2 mg/mg (0.6 mmol/mol), hypercalciuria is suspected [6]. Five to ten percent of adults are at risk of acquiring kidney stones due to hypercalciuria, the most common recognized cause of calcium kidney stone disease. At least one-third of people who develop calcium kidney stones also have hypercalciuria since about 80% of kidney stones contain calcium [7]. When a known process generates an excessive number of urine calculi, secondary hypercalciuria develops. When studies using clinical, analytical, and radiographic methods fail to identify the condition's underlying cause, idiopathic hypercalciuria is the diagnosis [8].

Renal phosphate leaks that result from the absorption of hypercalciuria and its subsequent production of hypercalciuria (also known as absorptive hypercalciuria type III) hypercalciuria and resorption indicators are the most prevalent types of clinically severe hypercalciuria.

Hyperparathyroidism is almost always to blame [9]. Hypercalciuria is usually present in kids with hematuria, back or stomach pain, and occasionally voiding symptoms. In children with hypercalciuria, microcrystallization of calcium with urine anions has been linked to uroepithelial damage. When trying to determine urinary tract symptoms from the illness history, concentrate on dysuria, abdominal pain, irritability (in children), urinary frequency, urinary urgency, changes in the appearance of the urine, colic, daytime incontinence, solitary or recurrent urinary tract infections, and vesicourethral reflux [10]. Hypercalciuria has been linked to the development of urolithiasis. In the family of kids with hypercalciuria, urolithiasis is more frequent (46–69%). An autosomal dominant transmission is the most plausible cause of the frequently observed familial clustering of calcium urolithiasis. Excellent evidence of hypercalciuria can be seen in the urine calcium-to-creatinine ratio [11].

2. Subjects and methods

2.1. Subjects

The nephrology and urology clinics of the Fayoum University Hospitals, the Fayoum Insurance Hospital, and the Fayoum General Hospital are included in the current case-control study. Evaluations of 100 urolithiasis patients under the age of 15 included pertinent histories, clinical checks, metabolic workups that included thorough urine investigations, and measurements of the calcium/creatinine ratio in urine. 30 children from age-matched homes who were the controls did not have any additional diseases.

2.2. Study Design

The participants were divided into two groups:

- Patient group: 100 children below 15 years old who are found to have urolithiasis were evaluated with relevant history, clinical examination, and metabolic workup, which includes a complete urine examination and measurement of the calcium/creatinine ratio in urine.
- Control group: 30 children from age-matched group with no other disease.

Inclusion criteria

All children at the ages of 1-15 years and with renal radio opaque stones were eligible for the current study.

2.3. Methods

2.3.1. Full medical history reports

That included the previous history of recurrent urinary tract infections, hematuria, stomach aches, ancestry, water intake, salt intake, and water supply source, in addition to the history of the current stone, history of prior stones, etc.

2.3.2. Full clinical examination

That included general examination, anthropometric measurement (BP and cardiac examination), and chest examination.

2.3.3. Abdominal examination

That included investigations of the serum and urine calcium levels, creatinine in urine, urine analysis, and calcium/creatinine ratio (CA\C). Imaging included pelviabdominal ultrasound (PUT) and C.T. The stone analysis was performed when available. Oral consent was obtained from the parents of the participating children.

3. Statistical methods

The data were organized, tabulated, and statistically analyzed using the SPSS statistical computer program, version 18 (SPSS Inc., USA). To define numerical variables, the mean, standard deviation (SD), median, and range were employed. To compare the two groups, an independent t-test or Mann-Whitney-U test was applied. Numbers and percentages were used to express data that could be categorized. To determine the discrimination value of Ca, Creatinine, and the Ca/Creatinine ratio for separating cases from controls, the optimal cut-points for sensitivity and specificity were calculated using the receiver operating characteristic (ROC) curve. *P<0.05* was used as the significance level for analyzing test results.

3. Results

This case-control study was carried out in the pediatric department's outpatient nephrology and urology clinic at El Fayoum University's General Hospital and Insurance Hospital in Egypt. **Table 1.** illustrated comparison between case and control group regarding Socio- demographic characteristics which were statistically insignificant.

Table 1: Demographic data of the study population.

Variables		**Cases (N=100)**	**Control (N=30)**	***P-value***
Age (mean ±SD)		5.5 ±2.8	6.5 ±3.6	0.124
Sex	Male	46 (46%)	15 (50%)	0.7
	Female	54 (54%)	15 (50%)	

Investigation of the medical history revealed that participants in Group 1 suffered from variable symptoms included the abdominal pain (34%), dehydration (1.0%), dysuria (33.0%), enuresis (7.0%), fever (2.0%), hematuria (21.0%), lion pain (1.0%), and vomiting (1.0%) (**Figure 1**).

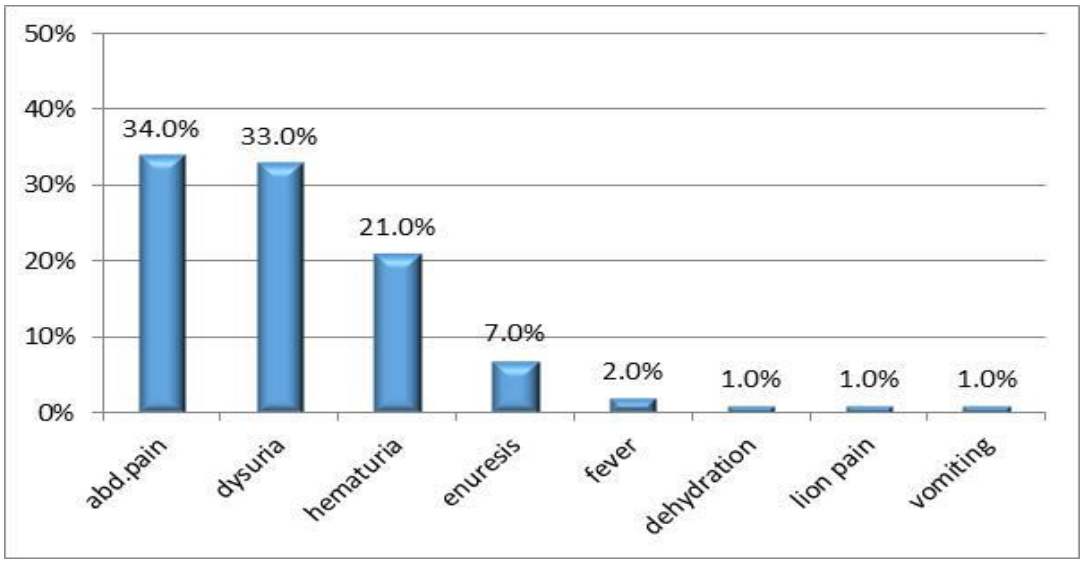

Figure 1: Frequency of main complains among study group.

As shown in **Table 2,** the risk factors reported in the current study included the family history of stones, food habits, and water intake. Inadequate water intake and salty food were the most reported risk factors of pediatric stones among study group. The urine analysis showed that pyuria and hematuria is common findings, besides calcium crystals (21%) and Urates (18%) were presented, as shown in **Table 3.** Other laboratory findings are shown in **Table 4.**

Table 2: Frequency of risk factors among study group.

Variables		**Cases (N=100)**
Family history of stone	No	71 (71%)
	Yes	29 (29%)
Food habit	Increased salt	14 (14%)
	Ordinary food	86 (86%)
Water intake	Adequate	36 (36%)
	inadequate	64 (64%)

Table 3: Urine analysis findings of the patients group.

Variables		**Cases (N=100)**
Pus cells	0-10	49 (49%)
	>10	51 (51%)
RBC's	0-10	64 (64%)
	>10	36 (36%)
Crystals	Ca oxalate	21 (21%)
	Nil	61 (61%)
	Urates	18 (18%)

RBCs: Red blood cells; **Ca**: calcium.

Table 4: Laboratory findings among study group.

Variables	**Cases (N=100)**
Serum Ca (mg/dl)	9.3 ±0.5
Creatinine (mg/dl)	0.4 ±0.2
Urea (mg/dl)	23.7 ±10.4
Na (mEq/L)	141 ±4.8
K (mEq/L)	4.3 ±0.4

Ca: calcium; **Na:** Sodium; **K:** Potassium.

Ultrasound findings indicated that renal stones were scanned in 46% of cases, followed by Ureter stones (24%), bladder stones (21%), and nephrocalcinosis in 9% of cases (**Figure 2**). In comparison between cases and controls, the calcium/creatinine ratio was significantly higher in cases (8 ±2.2) with stones than in those that didn't (4 ±0.19) (*P= 0.019*) (**Figure 3**).

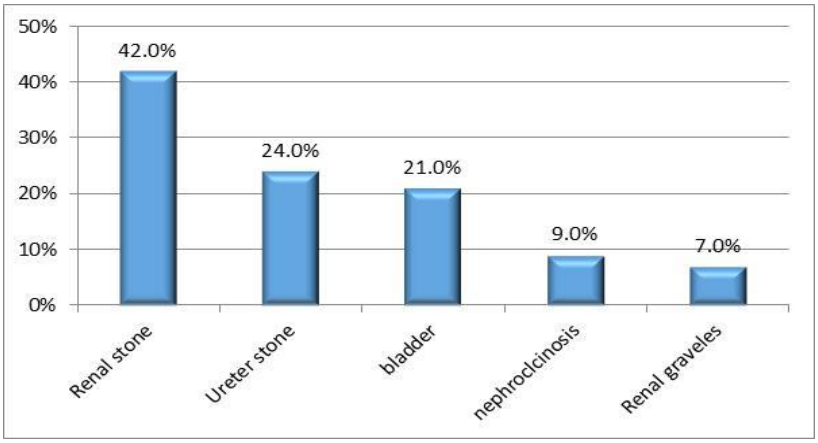

Figure 2: Frequency of ultrasound findings among study group.

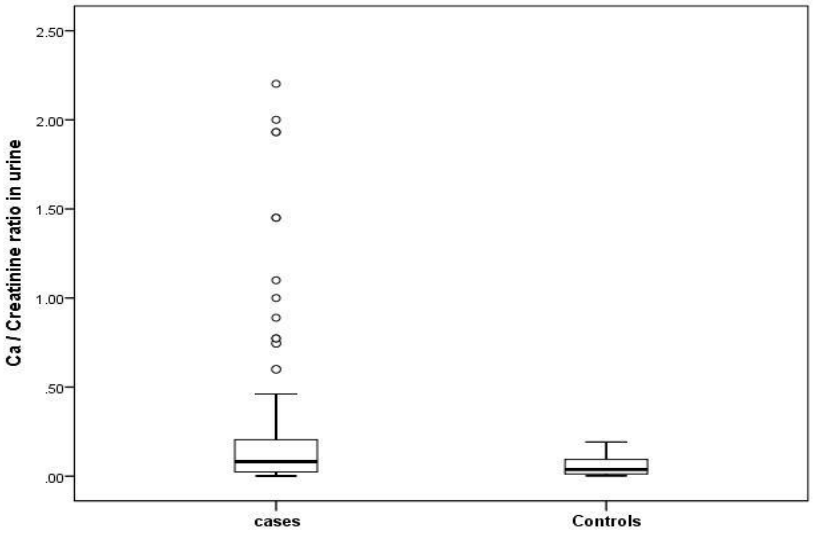

Figure 3: Comparison between cases and control regard ca/creatinine ratio.

The ROC analysis revealed significant values for calcium/creatinine, which indicated that it's a sensitive predictor for Hypercalciuria among the study population (*P=0.018*) (**Figure 4, Table 5**).

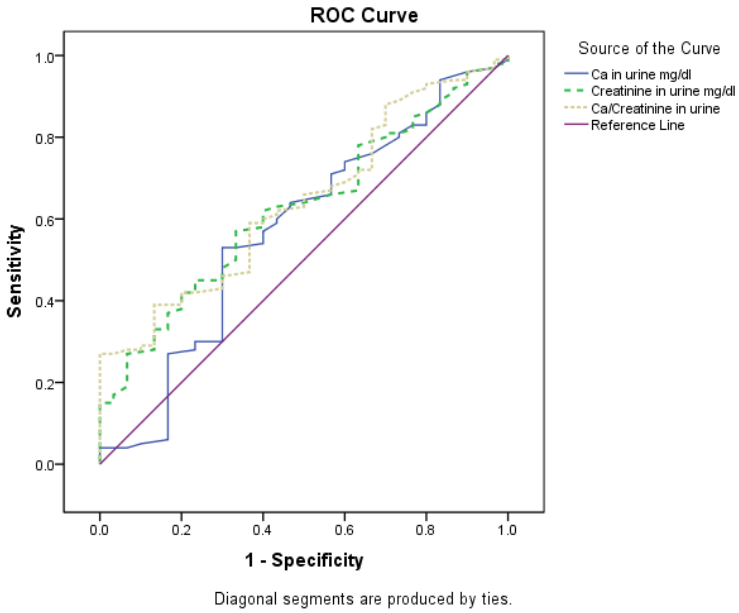

Figure 4: ROC curve Differentiation between the study group.

Table 5: Sensitivity and specificity among study group.

Variables	AUC	*P-value*	Cut-off point	Sensitivity	Specificity
Ca (mg/dl)	0.575	0.216	5.25	53%	70%
Creatinine (mg/dl)	0.625	0.038*	98.75	57%	66.7%
Ca/creatinine	0.641	0.018*	0.06	59%	62.3%

4. Discussion

Although symptoms and indicators might be subtle or deceptive, urolithiasis is more common in children than is generally anticipated, yet it is still underdiagnosed or misdiagnosed in a small percentage of patients. Urolithiasis should be properly investigated in all children who have colicky stomach pain or macroscopic hematuria [12]. As metabolic causes are frequently present in children, a thorough diagnostic evaluation is necessary to rule out metabolic illnesses like primary hyperoxalurias and others that can lead to recurrent urolithiasis or even renal failure [1].

Over one-third of people who develop calcium kidney stones also have hypercalciuria, and calcium makes up about 80% of kidney stones [2]. Hypercalciuria is the most frequently acknowledged cause of calcium kidney stone disease. Around 5–10% of the population is

impacted. According to a 24-hour sample collection, children with hypercalciuria are those who have calcinuria >4 mg/kg/day (0.1 mmol/kg/day) [7]. Typically, a test for hypercalciuria (defined as >0.2 mg/mg or 0.6 mmol/mol) is performed on the urine calcium/creatinine ratio [5]. Hypercalciuria can lead to the development of urolithiasis. In kids with hypercalciuria, urolithiasis occurs 46 to 69% of the time in families. Autosomal dominant transmission is the most plausible cause of the frequently observed familial clustering of calcium urolithiasis. One valid screening method for hypercalciuria is to analyze the urine calcium-to-creatinine ratio [6].

As regarding risk factors for renal stones, we found that family history, inadequate water intake, and salty food were risk factors for pediatric stones among the study group. As there were 29% of cases with a positive family history, we also found that salty food intake and inadequate water intake represent 14% and 64%, respectively. A previous study discovered that over 40% of kids with urolithiasis have a confirmed family history of kidney stones [11]. The outcomes of our study indicate that pyuria and hematuria are frequent findings and that calcium crystals were detected in 21% and urates in 18% of the study group. Similar to our findings, a previous study reported that casts, crystals, hematuria, and pyuria may be visible using urine microscopy [12]. While clean suprapubic or catheterization may be required to prevent contamination in some younger patients, clean midstream urine can be collected from older people [13]. According to the study's ultrasound results, renal stones were found to be 46% common, followed closely by urinary tract stones (24%), bladder stones (21%), and nephrocalcinosis (9%). Moreover, it was hypothesized that a deficiency in dietary phosphates, particularly during infancy, may have contributed to the difference in the rarity of bladder stones in wealthy nations and their prevalence in some underdeveloped nations [14]. Another study found that urethral stones in older children are more common than renal stones in younger children [14]. Some of the clinical signs of the prevalent disease hypercalciuria in children include hematuria, flank discomfort, nephrolithiasis, and urinary tract infections [15]. Using the urine calcium-creatinine ratio, diagnoses can be made on newborns and young children. Throughout the first year of life, this ratio rapidly decreases and is notably age-dependent [16].

In the current study, there were 130 kids and teens in each of the two groups that were formed. They were divided into a patients' group (with a history of urolithiasis, N = 100) and a control group (seemingly healthy people, matched for age and sex to the sick group, N = 30). The age range of the participants in our study was 1 to 15, with a mean age of 5.5 years. Around 54% of patients were male, compared to 46% of patients who were female. like the investigation we carried out. According to Dogan and colleagues, 2011, most men develop urinary calculi in children of all ages [17]. In contrast to the current findings, Sas, 2011, argued that current evidence indicated pediatric nephrolithiasis was more frequent in females [18]. Inpatient care for nephrolithiasis is 1.5 times more common in females than in males. We discovered that, after dysuria, hematuria, enuresis, and fever, stomach discomfort (reported by 34% of patients) was the second most typical adolescent urolithiasis complaint. This was in line with what was reported by Bowen et al., 2018, who discovered the typical symptoms of pediatric urolithiasis, which include hematuria, dysuria, stomach or flank pain, nausea, and vomiting [19]. The symptoms were generally vague and poorly localized in younger children. In addition, another study indicated that colicky stomach discomfort, which is reported in roughly 50–80% of cases, is the most prevalent presenting sign of renal

stones [20]. Considering the clinical manifestation of urolithiasis as well, our study shows that dysuria was the main presentation by a percentage of 55%, followed by 45% with recurrence urinary tract infection, 32% with gross hematuria, and 6% with enuresis. Similar to our study, the study done by Hoppe and colleagues, 2010, they established that the first sign of stones is difficulty passing urine in babies, especially where stones may become lodged and therefore perceptible in the urethra (dysuria) [21], whereas Alon (2018) reported that just 5.6% of patients had dysuria [22].

In our study, the calcium-to-creatinine ratio increased statistically significantly in 22.0% of the participants. This indicates that hypercalciuria is the main discernible metabolic risk factor for juvenile urolithiasis, which is similar to a previous study by Pak et al., 2011, which revealed that hypercalciuria is likely to be the most prevalent risk factor for calcium nephrolithiasis [23]. The urine ca/creatinine ratio in our investigation exhibited an area under the curve (AUC) of 0.641, 59% sensitivity, and 62.3% specificity for discriminating between cases and controls using a threshold value of 0.06 mg/dL. Odvina *et al.* (2006) found that, on a restricted diet, the urine calcium-creatinine ratio was a reliable predictor of the development of stones. (95% confidence interval: 0.83-0.91; ROC area under ROC curves: 140.87) [24]. The ROC curve produced by logistic regression using the stone-forming group as the dependent variable served as evidence. The specificity, positive predictive value, and negative predictive value were all 0.90, with a 95% confidence interval [CI] of 0.84-0.94.

Conclusion

For early detection of pediatric urolithiasis in children and teenagers and to enable early intervention and therapy, urine calcium/creatinine assays may prove to be a helpful, practical, accurate, and noninvasive method. This study convincingly established that children with renal stones had greater urine calcium and creatinine levels compared to controls.

Ethical approval: The Ethics Committee of Research at Fayoum University's School of Medicine approved the current study.

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Conflicts of Interest: None declared.

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