IDIOPATHIC HYPERCALCIURIA AMONG CHILDREN WITH URINARY SYSTEM RELATED SYMPTOMS

By

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ABSTRACT

Background: *Idiopathic hypercalciuria (IH) is characterized by the excess excretion of calcium, despite normal levels of calcium in the blood and no apparent cause. In recent years, this metabolic disorder is become more common to diagnose in children and can cause various urinary symptoms.*

Objective: *To determine the prevalence of idiopathic hypercalciuria in children with different urinary symptoms, recurrent unexplained fever, or abdominal pain and to explore the risk factors and symptoms associated with childhood idiopathic hypercalciuria.*

Methods: *This descriptive cross-sectional study that was conducted from May to November 2022 in a Pediatric Nephrology and General Pediatric Clinic at Bab Al-sharia Hospital Al-Azhar University Hospital on 100 children aged between 2 months to 14 years with urinary symptoms, recurrent unexplained fever, or abdominal pain. All Participants provided two urine samples for the calcium-to-creatinine ratio measured. Venous blood samples were collected to analyze creatinine, urea, uric acid, calcium, sodium, and potassium.*

Results: *The prevalence of idiopathic hypercalciuria in children was 20 % at a cutoff point of 0.14 mg/mg ca/ creatinine ratio. Serum ca, creatinine, urine ca excretion, and Ca/creatinine ratio was significantly higher in idiopathic hypercalciuria children than in those with normal ratios but lower urinary creatinine. The Ca/creatinine ratio showed a significant negative correlation with age and urine creatinine, while a positive correlation with serum ca and urinary ca excretion. According to multiple linear regression, serum calcium is a significant predictor for ca/creatinine ratio change in those with idiopathic hypercalciuria.*

Conclusion: *Hypercalciuria may present different symptoms associated with urinary symptoms, recurrent unexplained fever, and abdominal pain. Therefore, checking the urinary calcium level in children with urinary symptoms with no definite etiology is recommended.*

Keywords: *Idiopathic hypercalciuria, Urinary symptoms, Ca/creatinine ratio.*

INTRODUCTION

Idiopathic Hypercalciuria (IH) is characterized by the excess excretion of calcium, despite normal serum calcium levels and an unknown etiology **(Cuellar et al., 2020)**. This metabolic disorder is quite common and may cause various symptoms related to the urinary system in both children (40–80%) and adults (30–60%) **(Milart et al., 2020) (Esteghamati et al., 2017)**. Urinary calcium excretion in children is increased when above 4 mg/kg body weight/24 h. The calcium-creatinine (Ca/Cr) ratio, calculated from the second-morning urine sample, can also estimate hypercalciuria. The reference values of this indicator depend on age and range from 0.8 in infants to 0.2 in adults **(Zerwekh, 2010)**.

A recent study has linked hypercalciuric pediatric kidney stone patients with increased urinary excretion of lipid metabolism/transport-related proteins. This suggests that abnormalities in lipid metabolism may be responsible or connected in some way to pediatric hypercalciuria and nephrolithiasis **(Vieira et al., 2020)**. The prevalence of IH varies among different countries and is associated with a higher risk of renal stones in affected children **(Coe et al., 2016)**. Additionally, recurrent fever may occur as a cyclical fever with apparent periods of remission and fever-free intervals of at least two weeks **(Statler & Marshall, 2016)**.

Initially, the primary method of treatment for hypercalciuria in children is dietary. Calcium intake should not be limited unless it exceeds the usual recommended quantity. Vitamin D supplementation should be avoided, and dietary animal protein intake should be limited to within normal limits. A three to six-month trial of dietary measures alone is reasonable before resorting to thiazide medications **(Doizi et al., 2018)**. Diagnosing and treating hypercalciuria can be challenging and requires input from primary care, nurse practitioners, nephrologists, or urologists.

This study aimed to determine:

1. The prevalence of idiopathic hypercalciuria in children presented with different urinary symptoms, recurrent unexplained fever, or recurrent unexplained abdominal pain and,

2. The different risk factors and symptoms associated with childhood idiopathic hypercalciuria.

Our studied patients will be classified into 2 groups:

a. Group 1: normal ca\cr ratio

b. Group 2: high ca\cr ratio.

Ethical consideration:

- Approval by the ethical committee of the Pediatrics department at the Faculty of Medicine at Al-Azhar University under the registration number: 000458 was obtained before the study.
- There was no conflict-of-interest regarding the study or publication.
- Patients were enrolled in the study after taking informed oral and written consent from their parents.
- Patient data confidentiality was preserved during all study procedures.
- We ensure that the participants are not physically or psychologically harmed during the study.
- There are no any financial support or sponsorship.
- The patient and parents were informed that they have the right to withdrawal at any time of from the study.

Sample size:

The sample size calculation was based on the Prevalence of Idiopathic Hypercalciuria in Children retrieved from previous research **(Al Ghwass et al., 2021)**. Using Epi info version 7.2.4.0 to calculate sample size based on 7%, 95% CL with an acceptable margin of error =5, the total sample size was 100 cases at least.

Inclusion criteria:

- Both sex with the age from 2 months to 14 years old.
- Patients with urinary symptoms including dysuria, frequency, urinary tract infection, macroscopic and microscopic hematuria, nocturnal and daily urinary incontinence, and kidney stones confirmed with sonography.
- Patients with recurrent unexplained fever.
- Patients with recurrent unexplained abdominal pain.

Exclusion criteria:

- Patients used nephrotoxic drugs, corticosteroids, vitamin D, or methylxanthines.

- Patients with associated systemic diseases, e.g., kidney, liver, and biliary tract diseases
- Children with secondary forms of hypercalciuria.

Study design:

The study was conducted between May to November 2022 at Pediatric Nephrology and General Pediatric Clinic at Bab Al-sharia Hospital Al-Azhar University Hospital on 100 children who had urinary symptoms, recurrent unexplained fever and abdominal pain using convenience sampling during a 7 months period.

Study procedure:

All included patients were subjected to:

I. Full history: including age, sex, family history of any urinary problems. symptoms such as dysuria, frequency hematuria, nocturnal and daily urinary incontinence, recurrent unexplained fever, and recurrent unexplained abdominal pain.

II. Full clinical examination including:

a. General examination including: angular stomatitis, Nail (brittle and spooning),

b. Systemic examination including: CNS (decreased alertness, learning, and concentration span), Heart (palpitation and hemic-murmur),), abdominal examination for tenderness, renal fullness, and distention.

III. Laboratory investigations including,

- Kidney functions (creatinine, urea, and uric acid) and electrolytes (Na,K,Ca) venous blood sample were analyzed by COBAS 8000 ANALYSER.
- Urine analysis was analyzed by COBAS INTEGRA.
- Urinary ca/ creatinine ratio, by NM-BAPTA.

IV. Pelvi-abdominal U/S for positive cases (elevated ca/creatinine ratio).

Method:

Two 24-h urine samples were obtained, followed by two single fasting urine samples (which were kept refrigerated). The 24-h urine samples analysis included calcium and creatinine. Random morning urine samples were collected from all patients for measurement of the Calcium/Creatinine ratio. A complete urinalysis was performed on the two single fasting urine samples Urine sample was analyzed by Cobas

Integra (Cobas Integra, Germany). Then, six ml of venous blood sample was drawn from all participants after collecting the urine samples. Blood samples were analyzed for creatinine, urea, uric acid, calcium, sodium, and potassium. Urinary calcium was measured by NM-BAPTA. Hypercalciuria is a urinary calcium excretion rate of more than 4 mg/kg per 24 hours in a child older than two years **(Esteghamati et al., 2017)**.

Statistical analysis:

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software (Version 24 for Windows; SPSS Inc., Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. Quantitative data were described using mean± Standard deviation for normally distributed data and median (minimum and maximum) for non-normally distributed data after testing normality using the Kolmogrov-Smirnov test. The chi-Square test was used to compare qualitative data between groups as appropriate. The independent t-test compared two independent groups for normally distributed data, whereas the Mann-Whitney U test was used for non-normally distributed data. Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship. Multiple linear regression was used to assess predictors of continuous normally distributed outcomes. A P-value<0.05 was considered to be statistically significant.

RESULTS

The results of our study summarized in the following tables and figures:

Table (1): Demographic and symptomatic criteria of the studied cases (n=100)

Variables	Results
Age (years) mean±SD	6.18±3.75
Range	(0.5-14.0)
Gender	
Male	52(52.0%)
Female	48(48.0%)
Family history of renal stones	
Negative	68(68.0%)
Positive	32(32.0%)
Dysuria	55(55.0%)
Hematuria	30(30.0%)
Gross	21(70.0%)
Microscopic	9(30.0%)
Enuresis	23(23.0%)
Recurrent UTI	35(35.0%)
Renal stones	11(11.0%)
Recurrent unexplained fever	12(12.0%)
Recurrent unexplained abdominal pain	36(36.0%)

Data presented as N (%) for Categorical data or mean±SD and range for continuous data.

***** One patient may have more than one symptom.

Table (1) shows that the mean age of the studied children was 6.18±3.75 years, with a range from 2 to 14 years old. More than half were male, and about one-third had a family history of renal stones. Most exhibited dysuria symptoms (55%), followed by recurrent unexplained abdominal pain (36%) and recurrent UTI (35%).

Table (2): Laboratory findings of the studied cases (n=100)

Variables	Results
Serum Calcium (mg/dl)	8.87±1.13
Creatinine (mg/dl)	0.865(0.1-2.6)
Urea (mg/dl)	12.55(8.6-190.6)
Sodium (meq/L)	138.30±7.91
Potassium (meq/L)	4.65±0.98
Calcium in urine	2.5(0.07-41)
Creatinine in urine	50(2.9-608)
Ca/creatinine ratio	0.07(0.0007-2.86)
Ca/creatinine ratio at cut-off point 0.14 Normal High	 80(80%) 20 (20)
Urine analysis Pus RBCS (>1) Crystals	 61(61.0%) 14(14.0%) 25(25.0%)

Data presented as N.& (%) for Categorical data or mean±SD for normal distribution and median (minimum-maximum) for non-normal distribution.

This table show that 20% of the children had an elevated ca/creatinine ratio at the cutoff point of 0.14 ca/ creatinine ratio. The majority also had pus (61.0%).

Table (3): Comparison of sociodemographic characteristics and clinical manifestations between the studied groups

Variables	Ca/creatinine ratio		Test of significance	p-value
	Normal (n=80)	High (n=20)		
Age (Years) Mean±SD	6.63±3.95	4.36±2.02	**t=2.39**	**0.017***
Sex: male Female	43(53.8%) 37(46.2%)	9(45.0%) 11(55.0%)	χ^2=0.491	0.484
Family history of renal stone Negative Positive	57(71.2%) 23(28.8%)	11(55.0%) 9(45.0%)	χ^2=1.94	0.484
Dysuria	22(27.5%)	17(85%)	**χ^2=20.46**	**<0.001***
Hematuria Gross Microscopic	15(18.8%) 15(100.0%) 0(0.0%)	15 (75%) 6(40%) 9(60%)	**χ^2=44.19**	**<0.001***
Enuresis	23(28.8%)	0(0.0%)	**χ^2=7.47**	**0.006***
Recurrent UTI	29(36.2%)	6(30.0%)	χ^2=0.275	0.600
Renal stones	3(3.75%)	13(65.0%)	**χ^2=76.19**	**<0.001***
Recurrent fever	11(33.8%)	1(5.0%)	**χ^2=24.17**	**0.006***
Recurrent abdominal pain	30(37.5%)	6(30%)	χ^2=0.391	0.532

Z: Mann Whitney U test, t: Student t test, χ2: Chi-Square test, *: Statistically significant at p<0.05.

Table (3) shows a statistically significant higher mean age among children with a high Ca/creatinine ratio than those with a normal ratio. However, no statistically significant difference was detected in sex and family history between the two groups.

There was a statistically significantly higher proportion of patients with dysuria and hematuria in high compared to the normal ca/ creatinine ratio. Also, most of the patients with a high ratio had more renal stones and only one case of recurrent fever.

Table (4): Correlation between Ca\creatinine ratio on the studied groups

	Ca/creatinine ratio		test of significance	p-value
	Group 1 Normal (n=80)	Group 2 High (n=20)		
Serum Calcium (mg/dl)	8.42±0.99	9.61±1.16	**t=4.59**	**<0.001***
Creatinine (mg/dl)	0.885±0.409	1.126±0.47	**Z=2.22**	**0.026***
Urea (mg/dl)	20.85±33.43	44.69±59.38	z=1.39	0.165
Sodium (meq/L)	138.35±7.89	138.10±8.21	t=0.126	0.900
Potassium (meq/L)	4.59±0.94	4.83±1.17	t=0.927	0.356
Urinary ca excretion	5.27±8.63	14.25±14.79	**Z=2.10**	**0.035***
Urinary creatinine	107.81±140.91	51.30±65.05	**Z=2.37**	**0.018***

Z: Mann Whitney U test, t: Student t test, *: Statistically significant at p<0.05.

Table (4) shows a statistically significant increase in the mean value of serum ca, creatinine, urinary ca excretion, and Ca/ creatinine ratio among children with a high Ca/creatinine ratio than cases with a normal ratio. In contrast, there was a statistically significant decrease in urinary creatinine among children with a higher than normal Ca/creatinine ratio.

Table 5. Correlation between Ca/creatinine ratio and age and other laboratory variables of the studied group.

	Ca/ creatinine ratio	
	r	p-value
Age/years	-0.659	**<0.001***
Serum Calcium (mg/dl)	0.323	**0.001***
Creatinine (mg/dl)	0.189	0.06
Urea (mg/dl)	0.031	0.762
Sodium (meq/L)	0.035	0.726
Potassium (meq/L)	0.064	0.530
Urinary ca excretion	0.505	**<0.001***
Urinary creatinine	-0.659	**<0.001***

r: Spearman correlation coefficient, *: Statistically significant at p<0.05.

Table (5) shows Ca/ creatinine ratio had a statistically significant negative correlation with age and Urinary creatinine level while a positive correlation with serum ca and urinary ca excretion.

Table (6): Linear regression for prediction of ca/ creatinine ratio among studied group

Model		Unstandardized Coefficients		Standardized Coefficients	T	p-value
		B	Std. Error	Beta		
1	(Constant)	-0.658	0.283		-2.323	**0.022***
	Age	-.0014	0.009	-0.150	-1.536	0.128
	Serum ca	0.102	0.030	0.331	3.401	**0.001***

*: Statistically significant at p<0.05.

Table (6) shows that serum calcium was a statistically significant predictor of change in the ca / creatinine ratio.

DISCUSSION

Hypercalciuria is the leading cause of stone formation in children, accounting for almost half of all metabolic risk factors identified, followed by hypocitraturia. Notably, a high percentage of children diagnosed with nephrolithiasis or nephrocalcinosis have been found to have hypercalciuria, ranging from 28% to 79 **(Sas, 2011)**.

The current study aimed to evaluate the frequency of IH in children aged 2 to 14 years with different urinary symptoms. Previous studies have focused on children with confirmed IH, reporting the prevalence of various symptoms related to the urinary system, such as recurrent unexplained abdominal pain and fever.

Our study revealed a statistically significant difference in mean age between cases with high calcium/creatinine ratios and those with normal ratios. Various studies have found significant age-related differences in U Ca/Cr. Esbjörner and Jones reported a weak but significant negative association between postprandial U Ca/Cr in 153 children aged between 2 and 18 years **(Esbjorner & Jones, 1995)**. Sargent et al. also observed an age-related decrease in U Ca/Cr in children over the age of 6 years **(Sargent et al., 1993)**, although they did not specify the age at which U Ca/Cr values became stable.

The present study revealed that the prevalence of IH was 20%. According to a recent study in Fayoum University Hospital, IH was found in 32 out of 206 studied children (15.5%) **(Al Ghwass et al., 2021)**. The prevalence of IH varies greatly across different

countries. For instance, in Eastern European countries, it ranges from 3% to 7%, while in Spain it is 3.8%, in Germany 8.6%, in Italy 9.1%, in the United States of America 10%, in Japan 0.6%, and in Brazil 3.2% **(Butani & Kalia, 2004**; **Kalantari et al., 2019**; **Kaneko et al., 2002)**.

The prevalence of idiopathic hypercalciuria varies significantly across different regions of Iran, with Tehran reporting 5.4%, and Bandar Abbas reporting 47.7%. This difference could be attributed to variations in climate, study design, and data collection techniques **(Esfahani et al., 2007**; **Esteghamati et al., 2017)**.

According to **Mori et al. (2006)**, the quantity of creatinine excretion in urine varies based on a child's gender. However, our study didn't show a significant difference in the prevalence of IH between cases with high calcium/creatinine ratios and those with normal ratios regarding gender. A previous study conducted by **Asl et al. (2013)** in Rasht, Iran, found that the prevalence of IH was equal in both males and females, which is consistent with our study.

On the other hand, various studies have shown that the occurrence of IH varies based on gender **(Ahmadzadeh et al., 2008)**.

According to a study conducted by **Safaei et al. in 2013**, 45% of patients with hypercalciuria had a family history of urinary calculi in their first-degree relatives **(Safaei Asl et al., 2013)**. In another study by Vijayakumar et al. in 2014, out of 91 children, 37 had a positive family history of either stone disease or hypercalciurea, suggesting that IH is a complex condition that may be inherited along with various risk factors such as diet, environment, high salt intake, and reduced fluid intake **(Vijayakumar et al., 2014)**. Our research discovered that 45% of patients with hypercalciuria had a family history of renal stones, but this did not have a significant difference.

According to a study by **Neveus et al. 2002**, there is no significant difference in urinary calcium excretion between children with enuresis and those without **(Nevéus et al., 2002)**. Similarly, Kamperis et al. found no notable variation in calcium excretion among children with or without nocturnal enuresis in another study **(Kamperis et al., 2006)**.

It has been observed that around 30-50% of individuals who develop calcium stones suffer

from IH, as stated by **(Coe, 2005)**. The risk of nephrolithiasis is known to increase progressively with higher levels of IH, as noted by Lerolle et al. **(Lerolle et al., 2002)**. Furthermore, follow-up sonographies have indicated that renal calyceal microlithiasis is reported in 85% of children with IH, according to Escribano et al. **(Escribano et al., 2004)**.

According to **Polito et al. (2000)**, 42 children had microcalculi, and 4 had calculi detected through ultrasonography **(Polito et al., 2000)**. Penido et al. found that the prevalence of kidney stones was 56% of participants **(Penido et al., 2001)**, while Esteghamati et al. reported a prevalence of 49.1% **(Esteghamati et al., 2017)**. Our study showed that 16% of participants had kidney stones, with 65% of those children having IH, a statistically significant difference.

The current study demonstrated that serum calcium was a statistically significant predictor of change in the ca / creatinine ratio among patients with IH. Another previous study showed that Ca/Cr ratio differentiated between cases and controls using ROC curve analysis, but its discriminatory power was poor (AUC = 0.641) **(Kamel & Al-gameel, 2022)**. However, age exhibited a statistically significant negative correlation with Ca/ creatinine ratio. Age was not a significant predictor for change in the Ca/creatinine ratio among patients with IH. This may be due to the limited sample size.

CONCLUSIONS

We conclude that I.H. is high among children with urinary symptoms, with a rate of 20 % at a cut-off point of 0.14 mg/mg ca/ creatinine ratio. Our findings are important because IH should be considered an important cause of urinary symptoms in children, even abdominal pain, when other causes are less probable.

RECOMMENDATION

It is essential to establish a reference value for the urinary lack of a group of normal children for calcium excretion in each geographic area comparison. Also, examining the urinary calcium level in children with urinary symptoms with no definite etiology is recommended. Further comprehensive and multicenter studies with a large sample size is an absolute necessity to assess calcium's influence among children with idiopathic hypercalciuria.

LIMITATIONS

Our study has some limitations. The number of patients included

was relatively small, partly due to the restrictive inclusion criteria.

The children in the studied groups have shown difficulty in collecting 24-hour urine samples.

During the clinical examination, some patients, particularly children under the age of 5, may not remain coordinated.

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