

Research Article

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## Role of Hypercalciuria in Recurrent Urinary Tract Infection in Children

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### Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in children. About 3-5% of girls and %1 of boys experience at least one episode of UTI at childhood and many of them experience recurrent UTI [1,2,3]. Many factors contribute to the occurrence of UTI such as vesicoureteral reflux, obstructive anomalies of the urinary tract, voiding dysfunction, and

**Introduction:** Hypercalciuria has been considered a predisposing factor for recurrent urinary tract infection (UTI) in recent studies. The mechanism may be related to uroepithelial injury by calcium microcrystals. The aim of this study was to evaluate the association of idiopathic hypercalciuria with recurrent UTI in children.

**Materials and Methods:** In this cross-sectional study, the urine calcium/creatinine ratio of 40 children aged 2-16 years with recurrent urinary tract infection (without urinary tract anomalies and voiding dysfunction) was compared with 40 age- and sex-matched healthy children. Hypercalciuria was defined as a calcium/creatinine ratio more than 0.21 in a spot urine test. Recurrent UTI was defined as at least 3 episodes of UTI during 1 year or 2 episodes in 6 months.

**Results:** The mean age of the patients was 5±2.22 years and mean age of the control group was 5.13±1.98 years. The mean calcium/creatinine ratio in the case group (0.21±0.17) was significantly higher than the control group (0.08±0.08) (p<0.05). Hypercalciuria was detected in 47.5% of the patients in the case group and in 7.5% of the participants in the control group (P<0.001). The history of familial urolithiasis was positive in 21% of the hypercalciuric patients. There was no significant difference in the frequency of urinary symptoms between hypercalciuric and normocalciuric patients with recurrent UTI. The episodes of UTI reduced in 12/19 (63.2%) of the patients after the treatment of hypercalciuria.

**Conclusions:** Children who suffer from recurrent UTI in the absence of urinary tract anomalies should be checked for hypercalciuria. Control of hypercalciuria may decrease UTI episodes.

**Keywords:** Hypercalciuria; Child; Urinary Tract Infections.

**Running Title:** Role of Hypercalciuria in Recurrent UTI

constipation [3]. However, more than %50 of the children with recurrent UTI do not have any anatomic malformations and VUR. Recent studies have reported that hypercalciuria may be considered a risk factor for recurrent UTI [4-7]. Heliczer et al as first suggested that recurrent UTI might be a clinical presentation of hypercalciuria [8]. Hypercalciuria can manifest as urolithiasis, microscopic or gross hematuria, abdominal or flank pain, dysuria, frequency, urgency, urinary

incontinence, and UTI [9-11]. Although calcium oxalate microcrystal formation and consequent irritation of the uroepithelial tissue are believed to mediate these symptoms, the precise mechanism by which hypercalciuria causes hematuria, dysuria, or UTI is unknown [3]. It seems that irritation of the uroepithelial tissue deteriorates the normal function of the mucosal barrier against microbial pathogens [4]. Hypercalciuria may be associated with hypercalcemia or normocalcemia. Idiopathic hypercalciuria is the most common cause of normocalcemic hypercalciuria [7], which may be inherited as an autosomal dominant disorder of calcium reabsorption in the distal and collecting tubules of the kidney [12-14]. The prevalence of idiopathic hypercalciuria in children varies from 2.9% to 9% in different studies [15,16]. In some countries, its prevalence is very low and has been reported as low as 0.6% in Japanese children [17]. Since recurrent UTI may result in renal parenchymal damage, hypertension, and renal insufficiency, determination of its predisposing factors is essential for the prevention of recurrent UTI. This study was carried out to evaluate the role of idiopathic hypercalciuria in the occurrence of recurrent UTI in children in East-Azarbaijan, northwest of Iran.

### Materials and Methods

In this cross-sectional and analytic study, 40 patients with recurrent UTI without urogenital anomalies and 40 age- and sex-matched healthy children who were referred to Tabriz Children's Hospital from 2011 to 2012 were studied. Recurrent UTI was defined as 2 episodes of UTI in 6 months or 3 or more episodes within 1 year. Urinalysis, urine culture, and urine Ca/Cr ratio were evaluated in all cases and controls. Hypercalciuria was defined as urine Ca/Cr > 0.21 in two different spot urine samples or 24 hour urine calcium more than 4 mg/kg. In patients who had hypercalciuria, serum calcium, phosphorus, sodium, potassium, blood urea nitrogen, serum creatinine, and blood gas analysis were investigated to differentiate idiopathic hypercalciuria from other causes of hypercalciuria. Patients who had VUR or other anatomic malformations of the urinary tract or neurogenic bladder based on imaging studies (sonography, voiding cystourethrogram, DTPA, and DMSA scan and urodynamic study) were excluded from the study. Moreover, patients with immobilization, urinary stone, renal failure,

history of furosemide and corticosteroid intake, hypercalcemia (Ca>11mg/dl), as well as patients with diseases causing hypercalciuria such as renal tubular acidosis and Bartter syndrome were excluded, as well. Since all patients with recurrent UTI were female, the control group was selected from normal girls without UTI. None of the control cases had a history of urinary symptoms or recurrent UTI in the past history. All demographic, clinical and laboratory findings were collected in organized forms. The research ethics committee of Tabriz University of Medical Sciences approved the study and informed consent was taken from parents.

### Results

The mean age of the cases and controls was 5±2.22 years (range: 2-16 years) and 5.13±1.98 years, respectively (P=0.77). All patients were female; therefore, the control group was selected from age matched girls. The mean calcium/creatinine ratio in the case group (0.21±0.17) was significantly higher than the control group (0.08±0.08) (p<0.05). Hypercalciuria was detected in 19 out of forty patients in the case group (47.5%) and in 7.5% of the participants in the control group (P<0.001). A history of familial urolithiasis was positive in 6 (26.3%) hypercalciuric patients but only in 1 (4%) of normocalciuric patients with recurrent UTI (P=0.03). There was no significant difference in the frequency of clinical symptoms and results of DMSA scanning between hypercalciuric and normocalciuric patients with recurrent UTI (P>0.05) (Table 1). All patients were followed for 11-54 months (32.6±12.5 months). Treatment of hypercalciuria with a high fluid intake and low salt diet resulted in the reduction of UTI episodes in 7 out of 19 patients (36%). In the remaining 12 patients, hydrochlorothiazide was added to the treatment regimen. The episodes of UTI diminished in 5 patients after therapy with hydrochlorothiazide. Therefore, recurrent UTI reduced in 12/19 (63.2%) of the patients after the treatment of hypercalciuria. Seven patients continued to have recurrent UTI in spite of the treatment of hypercalciuria (7/19=36.8%).

### Discussion

In the present study, hypercalciuria was detected in 47.5% of the patients with recurrent UTI that was significantly higher than the control group.

**Table 1.** Comparison of characteristics in two groups of hypercalciuric and normocalciuric patients with recurrent UTI [↑](#)

characteristics	hypercalciuric patients	normocalciuric patients	P. value
Number	19 (47.5%)	21 (52.5%)	
Dysuria	12 (63.2%)	12 (57.1%)	P=0.69
Frequency	14 (73.7%)	15 (71.4%)	P=0.87
Suprapubic pain	7 (36.8%)	6 (28.6%)	P=0.57
Nocturnal enuresis	5 (26.3%)	6 (28.6%)	P=0.87
Urine incontinence	11 (57.9%)	9 (42.9%)	P=0.34
Family history of urolithiasis	5 (26.3%)	1 (4%)	P=0.03
Presence of Scar in DMSA	6 (31.5%)	7 (33.3%)	P=0.73

Similar to our results, studies by Lopez et al in Venezuela and Biyikli et al in Turkey showed that 32% and 43% of the patients with recurrent UTI had hypercalciuria, respectively [5,6]. In a study by Vachvanichsanong et al, recurrent UTI was accompanied by hypercalciuria in 31.4% of the patients [1]. In a study by Stojanovic et al, 44% of the patients with recurrent UTI, 10% of the patients with the first episode of UTI, and 7% of the participants in the control group had hypercalciuria (P<0.05) [13]. In another study in Zahedan, Iran, 30% of the patients with recurrent UTI and 11.4% of the controls had hypercalciuria (P<0.05) [7]. Fallahzadeh et al observed that of 523 children who were referred for at least one of the urinary symptoms (dysuria, frequency, urgency, abdominal or flank pain, incontinence, or enuresis), microscopic hematuria, urinary tract infection, or urolithiasis, 31.3% had hypercalciuria and the urine Ca/Cr ratio was significantly higher in all the subgroups with one or more urinary symptoms (P< 0.001) [18]. In contrast to our study and other researches mentioned above, Nacaroglu et al found idiopathic hypercalciuria in

16.7% of the children who were diagnosed with UTI. They did not find any associations between idiopathic hypercalciuria and the recurrence of UTI and renal scar formation [19]. The different results among the above-mentioned studies may be due to different methods used by different researchers. Similar to Nacaroglu et al, we found no significant difference in scar on DMSA scanning between hypercalciuric and normocalciuric patients with recurrent UTI.

Our study showed no significant difference in the frequency of urinary symptoms between hypercalciuric and normocalciuric patients with recurrent UTI. This finding is similar to the results of the study performed by Biyikli et al in Turkey [6]. Treatment of idiopathic hypercalciuria includes adequate fluid intake and salt restriction in the diet. If hypercalciuria persists in spite of these measures, hydrochlorothiazide may be required. Kaminska et al showed that treatment of hypercalciuria reduced the episodes of UTI in 43.6% of the patients [20]. Moreover, Lopez et al observed that no further episodes of UTI occurred in 95% of the children with recurrent UTI following the treatment of hypercalciuria [5]. Liern et al showed that the treatment of hypercalciuria reduced associated diseases such as hematuria and UTI [21]. In accordance with the mentioned studies, recurrent UTI reduced in 63.2% of our patients after the treatment of hypercalciuria. However, Yousefi et al, in a blind and randomized clinical trial, rejected the hypothesis that treating hypercalciuria was beneficial in preventing repeated UTIs [22]. They divided the patients who had recurrent UTI and idiopathic hypercalciuria into two groups. One group received general preventive instructions for UTI and the other group received hydrochlorothiazide in addition to preventive instructions. They found that the recurrence rate of UTI was 66% in both groups. The beneficial effect of hypercalciuria treatment in reducing the episodes of UTI needs to be more accurately studied and attention should be paid to eliminating other contributing factors.

### Conclusions

This study showed that urine Ca/Cr ratio was significantly increased in children with recurrent UTI and treatment of hypercalciuria reduced the episodes of UTI in 63.2% of the patients. Measuring urinary calcium in all children with recurrent urinary tract infection with a normal anatomy of the urinary tract is recommended.

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## Conflict of Interest

None declared

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