

# Role of High-Dose Hydrochlorothiazide in Idiopathic Hypercalciuric Urolithiasis of Childhood

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**Keywords.** nephrolithiasis, childhood idiopathic hypercalciuria, hydrochlorothiazide, children

**Introduction.** The aim of this study was to evaluate the role of hydrochlorothiazide in pediatric calculus formers with hypercalciuria and define possible factors affecting response to treatment.

**Materials and Methods.** Nineteen pediatric calculus formers, 12 girls and 7 boys, aged 15 days to 60 months, with idiopathic hypercalciuria received high-dose hydrochlorothiazide (1 mg/kg/d to 2 mg/kg/d) and citric acid-potassium citrate (1 mEq/kg/d) and were evaluated in a 2-year period. Avoiding high-salt diets was recommended throughout the study and increasing fluid intake was encouraged.

**Results.** The patients received hydrochlorothiazide for 2.5 to 15 months (mean,  $6 \pm 3$  months), and 10 of them (52.6%) reached normocalciuria. Resolution of hypercalciuria was associated with decreased calculi sizes in 1 (5.3%) and stone-free condition in 4 (21.1%). No significant differences were found between responders and nonresponders with regard to age at presentation, gender, family history of calculus, and size and number of calculi.

**Conclusions.** Our study showed that a combination of diet modification and hydrochlorothiazide has reasonable hypocalciuric effects; however, it is not very efficient in stopping calculus formation process. In addition, clinical and radiological data were not helpful to predict patients with better response to treatment.

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## INTRODUCTION

Urolithiasis has a higher prevalence in hot, arid, and dry climates. Regions with high calculus prevalence include the United States, British Isles, Scandinavian countries, Mediterranean countries, north of India, Pakistan, north of Australia, Central Europe, parts of the Malay Peninsula, and China.<sup>1</sup> Childhood nephrolithiasis remains endemic in certain parts of the world, namely, Turkey and the Far East.<sup>2</sup> Although urinary calculi have been reported in children of any ages with preponderance of boys.<sup>3,4</sup> Some reported male preponderance only in pediatric calculus formers with hypercalciuria and those with genitourinary anomalies.<sup>5</sup> Other studies noted that idiopathic hypercalciuria has

no ethnic, racial, or gender predominance and occurs with equal frequency in boys and girls. The peak incidence of idiopathic hypercalciuria is in children at the ages of 4 to 8 years.<sup>6</sup>

Hypercalciuric nephrolithiasis is a familial disorder in over 35% of patients, and inheritance may occur as a polygenic or monogenic trait with autosomal dominant, autosomal recessive, or X-Linked recessive modes of transmission.<sup>3</sup> Most cases of hypercalciuria are idiopathic, either sporadic or familial.<sup>7</sup> Idiopathic hypercalciuria can be diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause.<sup>6</sup> They are divided into 2 subgroups of absorptive hypercalciuria, which characterized by increased

intestinal calcium absorption and normal serum calcium and parathyroid hormone levels and low bone mineral density,<sup>8</sup> and renal hypercalciuria.

Hypercalciuria has been reported as the most common metabolic abnormality in pediatric calculus formers.<sup>6,9,10</sup> The prevalence of childhood hypercalciuria is 3% to 7% in Eastern Europe and 10% in the United States. Prevalence data from developing countries are lacking.<sup>6</sup> According to some studies, hypercalciuria has been found in 3% to 5.4% of school-age children in Iran.<sup>11-13</sup>

Urinary calcium excretion is affected by sodium, protein, potassium, phosphorus, and calcium in diet.<sup>14</sup> There is a positive correlation between urinary calcium excretion and sodium, protein, and calcium dietary intake.<sup>15-17</sup> In contrast, potassium supplementation decreases calcium excretion.<sup>18</sup> Despite the role of protein and calcium dietary intake in urinary calcium excretion, their restriction is not recommended in children with hypercalciuria, since they can impair growth. In addition, calcium restriction leads to negative calcium balance and poor bone mineralization and also it increases urinary excretion of oxalate.<sup>14</sup> In patients with renal hypercalciuria, urinary calcium excretion is not primarily influenced by dietary calcium intake, is not normalized with dietary calcium restriction, and associates with increased serum parathyroid hormone level.<sup>2</sup>

In children with symptomatic hypercalciuria it is important to conduct a formal evaluation for assessment of cause and severity of hypercalciuria, and before hypercalciuria is labeled as idiopathic, one must consider the possibility of a secondary cause. Medical treatment of hypercalciuria should be used once dietary modifications have failed to normalize urinary calcium excretion or when hypercalciuria symptoms persist. Anticalciuric diuretics can be used. Thiazide diuretics stimulate renal calcium handling and are used frequently in the treatment of patients with idiopathic hypercalciuria, especially when it is complicated by nephrolithiasis, osteoporosis, or both.<sup>19</sup>

At present, anticalciuric therapy in children is not based on strong evidence, but more on clinical observation, and it needs to be studied prospectively.<sup>14</sup> The purpose of our study was to assess the role of high-dose hydrochlorothiazide in pediatric calculus formers with hypercalciuric urolithiasis, considering the hypocalciuric action

of this drug, and to determine possible factors affecting response to hydrochlorothiazide.

## MATERIALS AND METHODS

### Study Population

In a 2-year period (2007 to 2008), 19 pediatric calculus formers with hypercalciuric urolithiasis were prospectively evaluated for hypocalciuric effects of hydrochlorothiazide at a single academic center. Kidney-bladder ultrasonography (Adra Model, Siemens, Berlin, Germany) was used for detection of nephrolithiasis or caliceal microlithiasis (hyperechogenic spots which usually devoid of shade cone and are less than 3 mm in diameter).<sup>20-23</sup> Kidney ultrasonography was performed at 5-, 7.5-, and 10-MHz. Bladder ultrasonography was done at 3.5- and 5-MHz.

Hypercalciuria was defined as urinary calcium excretion in excess of 4 mg/kg/24 h<sup>5-7</sup> or a urinary calcium-creatinine ratio greater than 0.8, 0.6, and 0.2 in the first 6 months of life, 7 to 12 months, and after 1 year, respectively.<sup>24</sup> Idiopathic hypercalciuria was defined as hypercalciuria with normal serum electrolytes levels (sodium, potassium, calcium, phosphorus, and magnesium), normal arterial blood gasometry, and absence of any known underlying disease responsible for increased urinary calcium excretion.

Before inclusion of the patients, metabolic evaluations were performed, including serum biochemistry; measurement of daily excretion of urinary calcium, uric acid, oxalate, citrate, and magnesium (in older children); and measurement of calcium, uric acid, oxalate, and creatinine in random urine samples of non-toilet-trained patients. Urinary tests for cystinuria were also performed. Patients with urolithiasis and idiopathic hypercalciuria were enrolled in the study, and those with secondary hypercalciuria (cases secondary to hyperthyroidism, Cushing disease, known bone disorders, immobilization, known malignancies, and distal renal tubular acidosis) and pediatric calculus formers with normal urinary calcium excretion were excluded from the study.

### Design of Study

This study was a noncontrolled clinical trial. The study was funded by a research grant from Mashhad University of Medical Sciences and approved by the local ethics committee. Hydrochlorothiazide was

administered at a dose of 1 mg/kg/d with Polycitra-K (a combination of citric acid and potassium citrate), 1 mEq/kg/d. Polycitra-K was administered to prevent hypocitraturia and hypokalemia due to hydrochlorothiazide treatment and for urine alkalization. The parents were received information about calculus forming and role of diet in controlling calculus forming process. Avoiding high-salt diets (especially high-salt snacks, fast foods, and prepared foods) was recommended and increasing fluid intake was encouraged. They were also instructed about checking and controlling medications.

The children were followed up every 2 to 3 months by checking urine specific gravity, urine pH, and urine calcium and creatinine excretion (in 24-hour or random urine samples) and renal ultrasonography. If they needed to receive hydrochlorothiazide for more than 3 months, arterial blood gas and serum potassium, magnesium, and calcium were checked. If hypercalciuria continued, hydrochlorothiazide dose increased up to 2 mg/kg, and Polycitra-K dose gradually increased to reach a urine pH of 6 to 6.5. Response to hydrochlorothiazide was defined as resolution of hypercalciuria (reaching normal urinary calcium excretion) associated with decreased calculus size (at least 1 mm) or stone-free condition (as a result of calculus dissolution or spontaneous passage). High urinary calcium excretion during the follow-up without considering calculus size and also normal urinary calcium excretion with no change or increased calculus size were defined as failure of treatment (nonresponder).

### Statistical Analyses

According to response to hydrochlorothiazide, the patients were divided into 2 groups of responder and nonresponder. To determine clinical and laboratory factors that predict the final outcome (response to treatment or treatment failure) a comparison between these groups was done. Clinical parameters such as age at presentation, gender, positive or negative family history of calculus formation, and ultrasonography findings (size and number of calculi) were compared between the two groups. The chi-square test and the Fisher exact test were used for data analysis and a *P* value less than .05 was considered significant.

## RESULTS

Of the 19 children, 12 (63.2 %) were girls and 7

(36.8%) were boys. Their mean age was  $19.3 \pm 18$  months (range, 15 days to 60 months). Urinary calcium-creatinine ratios were 1.0 to 1.8 (mean, 1.4) for patients aged up to 6 months, 0.6 to 1.2 (mean, 0.9) for those 7 to 12 months, and 0.3 to 0.6 (mean, 0.4) for children older than 1 year. The sizes of the calculi were 1 to 9 mm (mean,  $3.6 \pm 2.2$  mm). The calculi were smaller than 5 mm in 14 children (73.5%) and 5 mm or larger in 5 (26.5%). Calculi locations were the calyces in 16 (84.2%), renal pelvis in 1 (5.3%), and pyelocaliceal system in 2 patients (10.5%), and number of reported calculi were 1, 2, and more than 2 in 5 (26.3%), 2 (10.5%), and 12 (63.2%) patients, respectively.

Four patients (21.1%) were asymptomatic and the calculus was diagnosed during evaluation for microscopic hematuria (1 patient) or doing renal ultrasonography for different reasons (3 patients). The main clinical manifestations were urinary tract infection and dysuria each in 4 children (21.1%); abdominal pain in 2 (10.5%); flank pain, vomiting, and turbid urine each in 1 patients (5.3%). Eleven patients (57.8%) had a positive family history of calculus formation, 4 (21.1%) in their first-degree relatives (parents or siblings) and 7 (36.8%) in their second-degree relatives. In 2 cases, the family history was unknown.

At presentation, urinalysis revealed sterile pyuria in 2 children (10.5%) and microscopic hematuria in 6 (31.5%). Crystalluria was found in 4 (21.1%), while 13 (68.2%) did not have crystalluria and in 2 (10.5%) urine was not checked for crystals. A urine specific gravity of 1020 or less was found in 4 (21.1%) and values higher than 1021, in 6 patients (31.5%). At presentation, urine specific gravity was not checked in 9. Renal ultrasonography showed hydronephrosis in 3 children (15.8%). Table 1 presents clinical and laboratory parameters in our series.

Voiding cysto-urethrography was performed in 9 children, since they had urinary tract infection (at presentation or in the past) or abnormal ultrasonography findings such as hydronephrosis unrelated to calculus. Intravenous urography was performed in case of suspicious about anatomical obstruction (1 patient). These studies revealed vesicoureteral reflux in 4 (21.1%) and ureteropelvic junction obstruction in 1 (5.3%).

The patients received hydrochlorothiazide for 2.5 to 15 months (mean,  $9 \pm 3$  months) and followed

**Table 1.** Clinical and Laboratory Parameters in Children With Calculi

| Variable                                | Number (%) |
|---|------------|
| Age                                     |            |
| < 2 y                                   | 15 (78.9)  |
| ≥ 2 y                                   | 4 (21.1)   |
| Gender                                  |            |
| Male                                    | 7 (36.8)   |
| Female                                  | 12 (63.2)  |
| Family history of calculus              | 11 (57.8)  |
| Calculus size                           |            |
| < 5 mm                                  | 14 (73.5)  |
| ≥ 5 mm                                  | 5 (26.5)   |
| Number of calculi                       |            |
| 1                                       | 5 (26.3)   |
| 2                                       | 2 (10.5)   |
| > 2                                     | 12 (63.2)  |
| History of urinary tract infection      | 3 (15.8)   |
| Urinary tract infection at presentation | 5 (26.2)   |
| Abnormal urinary sediment               | 8 (42.1)   |

up for 2.5 to 23 months (mean,  $10.0 \pm 6.6$  months). Ten patients (52.6%) reached normal urine calcium levels. Resolution of hypercalciuria was associated with decreased calculus size in 1 (5.3%) and stone-free condition in 4 children (21.1%). In 5 patients, despite urinary calcium excretion returned to normal range with treatment, calculi sizes did not change. One patient with a large-sized calculus (9 mm) needed calculus removal by extracorporeal shockwave lithotripsy. During the follow-up, 8 patients reached stone-free condition, including 4 who did not respond to hydrochlorothiazide. Table 2 shows urinary calcium excretion rates and ultrasonography findings during follow-up.

Table 3 compares clinical and ultrasonographic parameters in responders and nonresponders.

**Table 2.** Changes in Calculi and Urinary Calcium Excretion After Treatment

| Outcome                   | Number (%) |
|---------------------------|------------|
| Calculus size             |            |
| No change                 | 3 (15.8)   |
| Decreased                 | 7 (36.8)   |
| Increased                 | 4 (21.1)   |
| Stone free                | 4 (21.1)   |
| New calculi               | 1 (5.3)    |
| Urinary calcium excretion |            |
| No change                 | 1 (5.3)    |
| Partially decreased       | 4 (21.1)   |
| Increased                 | 2 (10.5)   |
| Decreased                 | 10 (52.5)  |
| Not checked               | 2 (10.5)   |

**Table 3.** Characteristics of Responders and Nonresponders to Hydrochlorothiazide

| Characteristic            | Responders | Nonresponders | P     |
|---------------------------|------------|---------------|-------|
| Age                       |            |               |       |
| < 2 y                     | 4 (21.1)   | 11 (57.8)     |       |
| ≥ 2 y                     | 1 (5.3)    | 3 (15.8)      | .53   |
| Gender                    |            |               |       |
| Female                    | 5 (26.2)   | 7 (36.8)      |       |
| Male                      | 0          | 7 (36.8)      | .11   |
| Family history of calculi | 3 (15.8)   | 8 (42.4)      | > .99 |
| Calculus size             |            |               |       |
| ≤ 3 mm                    | 3 (15.8)   | 8 (42.4)      |       |
| > 3 mm                    | 2 (10.5)   | 6 (31.5)      | > .99 |
| Number of calculi         |            |               |       |
| ≤ 3                       | 2 (10.5)   | 8 (42.4)      |       |
| > 3                       | 3 (15.8)   | 6 (31.5)      | .47   |

There was not significant correlation between these factors and the final outcome.

## DISCUSSION

When childhood nephrolithiasis happens, parents usually feel anxious and frequently ask about the outcome. Are drugs helpful in controlling or stopping the calculus formation process? How many patients will require nonmedical interventions? Which groups of patients will present the best response to treatment? As hypercalciuria is the most common metabolic abnormalities in pediatric calculus formers and hydrochlorothiazide is the main drug which has been used for correction of hypercalciuria, we assessed response to hydrochlorothiazide in pediatric calculus formers with hypercalciuria. In our series, urinary calcium excretion rates returned to normal range in approximately half of the patients on hydrochlorothiazide; however, only in 5 (26.2%), normocalciuria was accompanied by calculus size reduction or stone-free condition.

The greatest risk factor for nephrolithiasis, after controlling for known dietary determinants, is having an affected family member.<sup>25</sup> In children, 46% to 69% of patients with hypercalciuric nephrolithiasis may have a positive family of the disorder.<sup>26-28</sup> In our series, 57.8% had a positive family history of renal calculi. Although different studies<sup>3-5</sup> have reported a male preponderance in hypercalciuric nephrolithiasis, interestingly our patients revealed a female preponderance (female-male ratio, 1.7:1). Urolithiasis occurs in only 5% of children with hypercalciuria, but microcalculi

(hyperechogenic spots < 3 mm in renal calyces) are much more common (57%).<sup>29</sup> Hypercalciuria can present with voiding symptoms such as urinary urgency, frequency, dysuria, enuresis, or suprapubic pain,<sup>27,29-30</sup> and is linked with urolithiasis and nephrocalcinosis,<sup>31,32</sup> urinary tract infection,<sup>8-24</sup> and hematuria, either microscopic or gross.<sup>29,33-35</sup> In our series, all had urolithiasis (as microlithiasis or nephrolithiasis) either asymptomatic or with different voiding or abdominal symptoms.

Before starting medical treatment, we encouraged parents to increase fluid intake and avoid high-salt foods in their children's diets. Increased fluid intake is difficult especially in infants and small children, and control of random urine specific gravity during follow-up in most patients revealed that changing dietary habits in children frequently needs long time. Normal values for urinary calcium-creatinine, sodium-creatinine, potassium-creatinine, and sodium-potassium ratios in healthy children have been studied.<sup>36</sup> We did not measure these parameters before and during the treatment with hydrochlorothiazide. Although Polycitra-K was added to treatment in order to increase potassium intake and prevent hypokalemic effects of hydrochlorothiazide, we are not sure about appropriate sodium and potassium intake and urinary excretion during follow-up. We suppose that in our series, hypocalciuric responses might be related to the drug, diet modification, or both. No study has addressed whether low doses of thiazides have a hypocalciuric effect, especially in children. Despite common use of thiazides, no long-term clinical trials have been performed documenting their efficacy and safety in children.<sup>6</sup> In our series, we used a combination of high-dose hydrochlorothiazide and Polycitra-K. This combined regimen led to normocalciuria in about half of the patients, and partial decrease in urinary calcium excretion in 21.1%.

Using higher doses of hydrochlorothiazide (> 0.4 mg/kg/d) in Dent disease does not affect daily urinary calcium excretion measured in a free calcium diet.<sup>37</sup> Raja and coworkers showed a 50% decrease in daily calcium excretion after 15 days of treatment with 25 mg of chlortalidone.<sup>37</sup> Seikaly and Baum studied the effect of hydrochlorothiazide in patients with X-linked hypophosphatemia. With a long-term follow-up, they showed that high doses of hydrochlorothiazide slowed the progression

of nephrocalcinosis without affecting glomerular filtration rate.<sup>38</sup>

A meta-analysis of randomized trials for medical prevention of calcium-oxalate nephrolithiasis showed that thiazide diuretics significantly reduced calculus recurrence.<sup>39</sup> This Cochrane review analyzed 4 studies that compared the effect of thiazides (including one study on indapamide) with the standard control of the disease (periodic clinical follow-up and general recommendations for increasing water intake) or specific dietary recommendations. In all these studies, the association of thiazide diuretics with strategies for the dietary control of the recurrence of calculi improved results in randomized controlled studies.

Potassium citrate therapy has been shown to be beneficial in adults with urinary calculi,<sup>40-43</sup> and in children, citrate therapy decreases recurrence of new calculus and growth of residual calculi fragments following lithotripsy in children with hypocitraturia.<sup>44,45</sup> Neutral phosphate salts have been used in children with hypercalciuria secondary to severe tubular phosphate leak.<sup>46</sup>

The strength of our study was that we tried to find an association between hypocalciuric effect of the drug (hydrochlorothiazide) and decreased calculus size or stone-free condition. The main limitation of our study was that we did not have any control group. Selecting a group of patients as control group was difficult because of ethical issues (hydrochlorothiazide is the current standard of care recommended for hypercalciuric nephrolithiasis), and also most of the parents expected that we start treatment as soon as possible.

## CONCLUSIONS

According to our results, we conclude that a combination of diet modification and treatment with hydrochlorothiazide and Polycitra-K has reasonable hypocalciuric effects, but it is not efficient enough in stopping calculus formation process. As nowadays there is no alternative treatment with better hypocalciuric effects, combination of treatment with hydrochlorothiazide and diet modification is a reasonable choice regarding to its good effect in controlling hypercalciuria. In our series, we failed to show any significant correlation between age, gender, family history of urinary calculi, or calculi sizes and number with final outcome. Concerning that all of 5 responder patients were girls, for

better judgment about relation between gender and response to hydrochlorothiazide, studying larger groups of patients is required. In addition, clinical and radiological details were not helpful to predict patients with better response to treatment. Doing multicenter studies in larger groups of pediatric calculus formers is warranted.

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### CONFLICT OF INTEREST

None declared.

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