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Idiopathic hypercalciuria: Association with isolated hematuria and risk for urolithiasis in children

A REPORT OF THE SOUTHWEST PEDIATRIC NEPHROLOGY STUDY GROUP,[1] prepared by
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Idiopathic hypercalciuria: Association with isolated hematuria and risk for urolithiasis in children. A prospective multicenter study was designed to determine the frequency and prognostic importance of hypercalciuria in children with hematuria. Urinary calcium excretion was examined in 215 patients with unexplained isolated hematuria (no proteinuria, urolithiasis, infection or systemic disorder). Hypercalciuria (urinary calcium excretion > 4 mg/kg/day) was identified in 76 patients (35%). Compared to patients with normal urinary calcium excretion, children with hematuria and hypercalciuria were characterized by male preponderance, white race, family history of urolithiasis, gross hematuria and calcium oxalate crystals. Renal biopsies were performed in 10 patients with urinary calcium excretion 0.4 to 2.5 mg/kg/day; three had IgA glomerulonephritis, three had glomerular basement membrane thinning, one had proliferative glomerulonephritis and three were normal. Renal biopsies in three patients with hypercalciuria showed focal segmental glomerulosclerosis, hereditary nephritis or no abnormalities. Oral calcium loading tests showed renal hypercalciuria in 26 patients, absorptive hypercalciuria in 15 patients and were not diagnostic in 35 patients. Serum parathyroid hormone, bicarbonate and phosphorus and urinary cyclic adenosine monophosphate concentrations were similar in the three groups of hypercalciuric patients. Urinary calcium excretion after one week of dietary calcium restriction was higher (5.8 mg/kg/day) in renal hypercalciuria than in other hypercalciuric patients (3.4 mg/kg/day), $P < 0.01$. One to four years follow-up was available for 184 patients. Eight of 60 hypercalciuric patients developed urolithiasis or renal colic compared to 2 of 124 patients with normal urinary calcium excretion ($P < 0.001$). Hypercalciuria is commonly associated with isolated hematuria and represents a risk factor for future urolithiasis in children with hematuria. Oral calcium loading tests offer little diagnostic benefit over 24-hour urinary calcium excretion following dietary calcium restriction.

Hematuria is one of the most common genitourinary abnormalities in children [1, 2]. When urinary bleeding is not associated with red blood cell casts, increased urinary protein excretion or a family history of glomerular disease, extensive evaluation frequently fails to establish a specific etiology [2–4]. In 1981, Moore described eight children in whom microscopic or macroscopic hematuria was associated with increased urinary calcium excretion [5]. Two additional reports described children with idiopathic hypercalciuria in whom painless hematuria preceded formation of calcium oxalate urolithiasis by one to six years [6, 7]. A subsequent study in Memphis identified increased urinary calcium excretion (greater than 4 mg/kg/day) in 23 of 83 children (28%) who were referred for evaluation of hematuria without proteinuria, infection, urolithiasis or systemic disorders [8]. Two of these 23 children with hypercalciuria developed urolithiasis within 18 months of their evaluation for hematuria.

The question of whether increased urinary calcium excretion is often associated with isolated hematuria in children living in geographic locations in addition to Memphis and Chicago remained unanswered. For this reason, the Southwest Pediatric Nephrology Study Group conducted a prospective multicenter study of children who were referred for evaluation of isolated hematuria in order to assess the prevalence of hypercalciuria at member institutions. Additionally, this study examined the clinical characteristics of children with hematuria and hypercalciuria and determined whether children with hypercalciuria and hematuria are at greater risk for subsequent urolithiasis than children with hematuria and normal calcium excretion.

Methods

Patients

During a 30 month period, all children 3 to 18 years of age who were referred to member institutions for evaluation of hematuria were candidates for this study. Hematuria was defined as five or more red blood cells per high power field in a centrifuged urine sample determined on at least two occasions. Children were excluded from the study if they also had proteinuria (≥1+ on a urinary dipstick), previous urolithiasis, urinary infection, sickle cell disease, poststreptococcal glomerulonephritis, biopsy-proven renal parenchymal disorders, systemic

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disease or generalized tubular dysfunction. Children receiving any medications known to affect urinary calcium excretion were also excluded. Either an excretory urogram or renal ultrasound examination was obtained to exclude urolithiasis or urological disorders. The parents of each patient were queried concerning family history of either urolithiasis or hematuria. Informed consent was obtained from each family prior to participating in the study.

Calcium excretion studies

A twenty-four hour urine collection documenting calcium excretion and a normal creatinine clearance (greater than 85 ml/min/1.73 m^2) were required for entry into the study. No dietary restrictions were requested during the initial diagnostic urine collection. Urinary calcium excretion was considered to be excessive if it was greater than 4 mg/kg body weight per 24 hour period [9–11]. Each child in whom urinary calcium excretion was greater than 4 mg/kg/day was studied further. Such children ingested a 300 mg calcium, 2000 mg sodium diet for seven days, following which a 24-hour urine collection was then obtained for urinary calcium excretion. On the eighth day a calcium loading test was performed as previously described [12]. In brief, a two-hour fasting urine collection was obtained from 7 to 9 a.m. and a blood sample for serum calcium, phosphorus, bicarbonate and parathyroid hormone concentration was obtained at 9 a.m. Thereafter, each child received a standardized breakfast and an oral calcium dose of 1 g of elemental calcium/1.73 m^2 body surface area as calcium glubionate syrup. Following the oral dose of calcium, a four-hour urine collection was obtained from 9 a.m. to 1 p.m. Urinary concentrations of calcium, creatinine, and cyclic adenosine monophosphate (AMP) were determined in both of the urine collections. Urinary calcium excretion was assessed as the ratio of urinary calcium to creatinine concentration. Normal values for urinary calcium to creatinine are less than 0.21 during fasting and less than 0.27 following the calcium challenge [12]. Aliquots of the 9 a.m. serum sample and both urine samples were sent to a central laboratory where the serum level of immunoreactive parathyroid hormone was determined with an antibody to the mid-region of parathyroid hormone (Immunonuclear Corp., Stillwater, Minnesota, USA). Urine calcium concentration was determined by atomic absorption spectroscopy, creatinine concentration by a modification of the Technicon Autoanalyzer technique, and cyclic AMP by radioimmunoassay (Immunonuclear Corp.).

Twelve months following the conclusion of this study, study centers were surveyed to determine the most recent clinical status of patients included in this study. We determined whether children with either normal or increased urinary calcium excretion had developed urolithiasis or whether a specific diagnosis for the etiology of hematuria other than hypercalciuria had been ascertained.

Statistical analyses were performed by the Data Analysis Center. Data from children with increased urinary calcium excretion were compared with children with normal calcium excretion by Student's *t*-test for unpaired data or chi-square analysis where appropriate. Values are given as mean ± SEM.

Table 1. Patient entry by participating centers

Location	Patients entered *N*	Patients with urinary calcium ≥4 mg/kg/day	
		N	%
Memphis, TN	52	20	38
Dallas, TX	32	12	37.5
Oklahoma City, OK	31	12	39
Little Rock, AR	29	11	38
New Orleans, LA	14	4	28.5
Houston, TX, Baylor	14	4	28.5
Houston, TX, Univ. TX	13	4	31
Denver, CO	13	3	23
San Antonio, TX	10	2	20
Galveston, TX	5	3	60
Salt Lake City, UT	2	1	50
Total	215	76	35

Table 2. Clinical characteristics of 215 children evaluated for hematuria

	Urinary calcium excretion		
	<4 mg/kg/day	>4 mg/kg/day	*P*
N	139	76	
Age (*yr*)[a]	8.4 ± 0.5	7.1 ± 0.6	0.1
Sex *F/M*	66/73	26/50	0.060
Family history of urolithiasis	30 (21.6%)	35 (46.1%)	0.003
Family history of hematuria	25 (18.0%)	23 (30.3%)	0.054
Gross hematuria	30 (21.6%)	33 (43.4%)	0.030
Urinary red blood cell casts	16 (11.5%)	2 (2.6%)	0.049
Calcium oxalate crystalluria	5 (3.6%)	16 (21.1%)	0.0001
Urinary calcium excretion *mg/kg/day*	1.7 ± 0.09	6.46 ± 0.48	0.001

[a] Date are presented as means ± SEM.

Results

The number of patients entered by each of the participating centers is shown in Table 1. Two hundred and fifteen children were enrolled in the study and 76 (35%) of these had urinary calcium excretion ≥4 mg/kg/day while ingesting their routine diets. Patients with increased urinary calcium excretion were identified at each center. The prevalence of hypercalciuria at the individual centers who entered ten or more patients ranged from 20 to 38%.

Clinical data for all children with hematuria who participated in the study are shown in Table 2. Compared to children with normal calcium excretion, a greater number of children with hematuria and hypercalciuria had gross hematuria, calcium oxalate crystalluria, a family history of urolithiasis and/or a family history of hematuria. Urinary calcium excretion in the hypercalciuric patients was 6.46 ± 0.48 mg/kg/day with a range of 4.0 to 19.4 mg/kg/day; calcium excretion in the normocalciuric group was 1.7 ± 0.09 mg/kg/day with a range of 0.02 to 3.9 mg/kg/day ($P < 0.001$). No statistical differences were found between the two groups for systolic or diastolic blood pressure or for the symptom of abdominal or flank pain (not shown). Creatinine clearance was 123 ± 3.64 ml/min/1.73 m^2 in children

Table 3. Race of children evaluated for hematuria

Race	Urinary calcium excretion			
	<4 mg/kg/day		*≥4 mg/kg/day*	
	N	%	*N*	%
White	116	(61%)	71	(39%)
Hispanic	9	(69%)	4	(31%)
Asian	3	(100%)	0	(0%)
Black	11	(92%)	1	(8%)
Total	139	(65%)	76	(35%)

with normal calcium excretion compared to 126 ± 4.16 ml/min/1.73 m^2 in the hypercalciuric group.

The racial mixture of the two groups is shown in Table 3. Only one of 12 black children, and none of three Asian children with hematuria were identified as having increased urinary calcium excretion. Among the 11 black children with normal calcium excretion, urinary calcium was 1.0 ± 0.24 mg/kg/day.

Excretory urography and renal ultrasound examinations were normal, with the exception of one child with a horseshoe kidney, in the 76 children with increased calcium excretion and in all of the 139 children with normal calcium excretion. Voiding cystourethrograms were obtained in 42 children with hypercalciuria and in 67 of the children with normal calcium excretion. All of the voiding cystourethrograms in children with urinary calcium excretion <4 mg/kg/day were normal; however, unilateral grade I to II or grade II vesicoureteral reflux occurred in three patients with increased urinary calcium excretion. Renal biopsies were obtained in three children with increased urinary calcium excretion. One biopsy showed focal segmental glomerular sclerosis, one had hereditary nephritis and one had no pathological findings. Ten children with normal urinary calcium excretion underwent renal biopsy procedures; three had IgA nephropathy, three had thinning of the glomerular basement membranes, one had proliferative glomerulonephritis, and three had no pathological findings.

In children with hypercalciuria, the mean total concentrations of serum calcium was 9.8 ± 0.4 mg/dl, serum phosphorus 4.6 ± 0.1 mg/dl, and serum bicarbonate 23.9 ± 0.3 mEq/liter. Oral calcium loading tests were performed in the 76 patients with hypercalciuria. Renal hypercalciuria was diagnosed in 26 patients in whom the fasting ratio of urinary calcium to creatinine (Ca/Cr) mg/mg, exceeded 0.21. Absorptive hypercalciuria was diagnosed in 15 children with fasting urinary Ca/Cr ratios less than 0.21 (normal) but with values greater than 0.27 following the calcium challenge. In 35 patients, neither the fasting nor post-challenge urinary Ca/Cr ratios were abnormal, and the oral calcium challenge was not helpful in clarifying the pathogenesis of hypercalciuria.

To compare children with renal hypercalciuria and those with absorptive hypercalciuria, patients were grouped on the basis of the fasting Ca/Cr ratio in urines collected from 7 to 9 a.m. after a week of dietary calcium and sodium restriction (Table 4). Serum phosphorus and calcium concentrations were similar in the two groups. Both serum parathyroid hormone and urinary cyclic adenosine monophosphate excretion were higher in children with fasting urinary Ca/Cr ratio > 0.21 but were not statistically different from patients without fasting hypercalciuria. Twenty-four hour urinary calcium excretion after a week of dietary calcium and sodium restriction was greater (5.8 ± 0.7 mg/kg/day) in children with fasting hypercalciuria than in children without fasting hypercalciuria (3.4 ± 0.3 mg/kg/day). In both groups, urinary calcium excretion following dietary calcium restriction was greater than in normal control children who were eating an unrestricted diet (1.6 ± 0.86 mg/kg, N = 123).

Table 4. Study results in children with initial urinary calcium excretion greater than 4 mg/kg/day

	Fasting urinary calcium/creatinine *mg/mg*		
	<0.21	>0.21	*P*
N	50	26	
Serum calcium *mg/dl*	9.9 ± 0.6	9.9 ± 0.5	0.99
Serum phosphorus *mg/dl*	4.7 ± 0.01	4.6 ± 0.13	0.5
Serum parathyroid hormone *pmol/ml*	68.9 ± 3.5	76.8 ± 6.2	0.3
Urinary cyclic AMP *mg/g creat*	6.0 ± 0.3	8.4 ± 2.0	0.3
24-hour urine calcium *mg/kg/day* after dietary Ca restriction	3.4 ± 0.3	5.8 ± 0.7	0.005

All results were obtained after one week of ingesting a 300 mg calcium, 2.0 g sodium diet. Groups are divided on the basis of the fasting ratio of urinary calcium to creatinine (mg/mg), normal <0.21. Normal values for serum parathyroid hormone − 64 ± 8.0 pmol/ml, urinary cyclic AMP = 5.6 ± 0.6 mg/g creatinine, urinary calcium (unrestricted diet) = 1.6 ± 0.8 mg/kg/d. Data are means ± SEM.

Follow-up data were available for 124 children with normal urinary calcium excretion and 60 children with hypercalciuria. Six additional children with hypercalciuria were receiving hydrochlorothiazide therapy and were excluded from the analysis. Eight of 60 children (6 boys, 2 girls) with untreated hypercalciuria developed urolithiasis or renal colic during the one to four year follow-up period. Six of these patients either spontaneously passed a calculus, required surgery or were treated with extracorporeal shockwave lithotripsy. One of the children has had recurrent stone episodes. Although two children had recurrent incapacitating renal colic with macroscopic hematuria that required therapy with analgesic, no calculi have been recovered. Seven of the eight patients initially presented with macroscopic hematuria; however, calcium oxalate crystals were not observed in the initial urinalysis in any of these patients. Six had a family history of urolithiasis. Urinary calcium excretion decreased to values less than 4 mg/kg/day when dietary calcium and sodium were restricted in three of the eight patients. Oral calcium loading tests were performed in six of these eight patients. In three of the children, the results were consistent with absorptive hypercalciuria, while two were diagnosed as having renal hypercalciuria. The oral calcium loading test was not diagnostic in one child.

In addition, two of the 124 children with normal calcium excretion developed urolithiasis. Both patients with normal calcium excretion who developed urolithiasis were girls and had a family history of urolithiasis; urinary calcium excretion was 1.9 and 3.1 mg/kg/day. Neither had calcium oxalate crystals in their initial urinalysis when referred for evaluation of hematuria. Both have spontaneously passed at least two calculi.

Discussion

In this prospective multicenter study, urinary calcium excretion exceeded 4 mg/kg/day in 35% of 215 children with hema-

turia in the absence of proteinuria, urinary tract infection, previous urolithiasis or systemic disorders. These data are consistent with previous reports [5–8]. In a prospective study, 23 of 83 children (28%) with unexplained hematuria had hypercalciuria (urinary calcium excretion ≥4 mg/kg/day) [8]. The somewhat greater percentage of children with hypercalciuria in the present study may reflect the attention given to this association following the previous reports as well as increased numbers of children specifically referred to the study centers for the evaluation of hypercalciuria. Patients with increased urinary calcium excretion and hematuria were identified in each of the participating centers. A relatively consistent incidence of hypercalciuria (20 to 38%) was observed in centers who entered more than 10 patients.

Similar to previous reports, a family history of urolithiasis and macroscopic hematuria was more common in hypercalciuric patients. Calcium oxalate crystals in the urine sediment were observed infrequently in either group but were observed more commonly in children with hypercalciuria. In contrast, red blood cell casts were observed in only two children with hypercalciuria; both of these patients had glomerular disease documented by renal biopsy. Urinary calcium excretion in the group of children with normal calcium excretion (1.7 ± 0.09 mg/kg/day) is very similar to normal children in Memphis, Tennessee (1.6 ± 0.86 mg/kg/day). Mean urinary calcium was significantly above the upper limits of normal in the hypercalciuric group (6.4 ± 0.48 mg/kg/day). Unfortunately, the overlap of clinical manifestations associated with hematuria between patients with hypercalciuria and patients with normal calcium excretion is sufficiently great that sensitive and specific predictive criteria for the presence of hypercalciuria could not be established.

Although the number of black children with hematuria was small, there was a paucity of black patients with hypercalciuria and hematuria. Urinary calcium excretion is less in black adults than in white adults [13]. It is not known whether normal values for urinary calcium excretion are the same for both white and black children, although preliminary reports have not documented racial differences in healthy children [14]. On the other hand, Moore and associates found 6.2% of 273 black children who were examined in an acute care setting to have hypercalciuria (>2 SD) by ascertaining the ratio of urinary calcium to creatinine [15]. Moore and associates have subsequently suggested that urinary calcium greater than 2 mg/kg/day in healthy children should be considered excessive [16]. Had this lower value been applied to this study, none of the black children would have been reclassified as being hypercalciuric.

In previous reports of urinary calcium excretion in children with hematuria, the oral calcium loading test has successfully distinguished patients with renal (fasting) hypercalciuria and absorptive hypercalciuria [8]. In the present study, this oral calcium loading test was unsuccessful in classifying the majority of hypercalciuric patients into these two diagnostic categories. The reason for these differences are unknown. It is possible that the initial screening 24-hour urine collections identified children in whom dietary or other exogenous factors might have resulted in an uncharacteristically high calcium excretion during the initial screening. Examples of such confounding factors are dietary sodium and physical exercise, both of which might increase urinary calcium excretion [16–18].

The usefulness (and importance) of the oral calcium loading test in classifying patients with hypercalciuria has been challenged by a number of investigators [19–21]. This study further questions the value of the oral calcium loading test in the routine evaluation of children with hematuria and suggests that either the fasting ratio of urinary calcium to creatinine or the 24-hour urinary calcium excretion following dietary calcium and sodium restriction may be more useful in characterizing children with increased urinary calcium excretion.

Unfortunately, only a single 24-hour screening urine collection was possible before entry into the study due to the distances that many patients travelled to the referral centers. Excessive dietary sodium is an attractive putative explanation for the lack of correlation between the initial urine and oral calcium challenge test, since the follow-up diagnostic studies were conducted after a week of dietary sodium restriction. Unfortunately, urinary sodium excretion was not measured in the screening urines. Etiologies for hypercalciuria other than idiopathic hypercalciuria such as acidosis, hypophosphatemia and hyperparathyroidism were not identified.

Clearly, the finding of hypercalciuria in a child with otherwise unexplained hematuria identifies a patient at risk for developing urolithiasis. Recently in a retrospective review of 68 Hungarian children with hematuria associated with hypercalciuria, 49 children (72%) developed urolithiasis during 2 to 15 years of follow-up [22]. In our patients during a short period of follow-up (1 to 4 yrs), 13% of the hypercalciuric patients developed urolithiasis or stone-like episodes. Considering the relative infrequency with which children develop urolithiasis, this occurrence rate is an important finding. It is possible that the risk for urinary calculi in untreated hypercalciuric patients may be even greater as many of the centers routinely recommended a reduction in dietary calcium and sodium intake if a patient's evaluation suggested absorptive hypercalciuria. Furthermore, at least one center (whose patients were excluded from follow-up analysis) routinely prescribed hydrochlorothiazide for patients with renal (fasting) hypercalciuria and macroscopic hematuria after one such patient was untreated and developed a urinary calculus.

Many important questions concerning the association of hypercalciuria and idiopathic hematuria in children remain unanswered. This study does not clarify the pathogenetic basis of urinary tract bleeding in patients with hypercalciuria. In order to rationally consider therapies and to counsel families of children with this association, a greater understanding of the mechanism of hematuria is essential. Similarly, although the risk of urolithiasis in children with hematuria and hypercalciuria is significant, the benefit and safety of long-term anticalciuric therapies in such children remains unknown. Long-term surveillance of patients identified in this study may provide greater insights into the natural history of hypercalciuria in children.

In addition to the questions concerning the association of urinary calcium excretion with hematuria, this study provides additional insights concerning the evaluation of children with hematuria. The routine application of the voiding cystourethrogram in the initial evaluation of childhood hematuria does not appear to be warranted. Furthermore, the mere presence of hypercalciuria in a child with hematuria should not exclude consideration of other etiologies of hematuria. Recently, an example of factitious hematuria in a child with hypercalciuria

has been published [23]. Two of the hypercalciuric children in this study had red blood cell casts and evidence of glomerular pathology by renal biopsy examination. Three additional children had minor vesicoureteral reflux which may have contributed to hematuria. Renal biopsies in children with hematuria and normal urinary calcium excretion provided a pathological diagnosis in six of ten patients. The two most common diagnoses were IgA nephropathy and thin glomerular basement membrane disease.

Increased urinary calcium excretion is frequently associated with unexplained hematuria in children within the geographic region served by the centers in this collaborative study group. Based upon these results, routine evaluation of urinary calcium excretion in children with unexplained hematuria certainly is justified. Encouraging ample water intake to prevent highly concentrated urines and avoiding both high dietary sodium intake and foods rich in oxalate would appear to be prudent in an effort to minimize the risk for subsequent urolithiasis in children found to have increased urinary calcium excretion. Surveillance for early signs of urinary calculi should be maintained in children with hypercalciuria and hematuria.

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