

## Clinical manifestations of pediatric idiopathic hypercalciuria

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## 1. ABSTRACT

Idiopathic hypercalciuria (IH) is a common metabolic disorder in children with protean manifestations, many of which can mimic other common pediatric diseases. Reports in the medical literature describe children with IH presenting with a wide array of calculi and non-calculi related clinical symptoms such as hematuria, urinary tract infections (UTIs), urgency, urinary incontinence and recurrent abdominal pain. Many of these symptom complexes have been only loosely associated with IH with no definite established causal relationship. Due to the common nature of IH and the varied clinical features attributed to it, it is of utmost importance for health-care professionals to be aware of these; this will facilitate early and appropriate investigations and prompt institution of therapy to avoid long-term morbidity.

## 2. INTRODUCTION

IH is a condition characterized by increased urinary excretion of calcium without hypercalcemia or any other

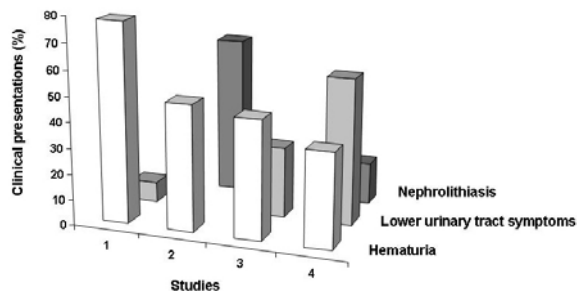
known tubular defects such as renal tubular acidosis or renal insufficiency (1). While most children with IH are asymptomatic and do not have any clinically overt symptoms, a small percentage do present with symptoms that are either a) related directly to the presence of calcium in the urine or b) to bone demineralization (2-5). Whether the latter is a consequence of the negative calcium balance from urinary calcium wasting or in fact a contributor to excess excretion of urinary calcium, or possibly both, is debatable.

## 3. CLINICAL MANIFESTATIONS

### 3.1. Asymptomatic

IH is a frequent disorder in children, the prevalence of which varies considerably by geography (6-10). In a study from Germany, 24-hour urine samples from 507 healthy children and adolescents were analyzed for calcium excretion (10). Among the 1,587 complete 24-hour urine samples collected, calcium excretion of more than 4

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**Figure 1.** Clinical manifestations in children with idiopathic hypercalciuria. Studies: 1 = Penido *et al.* (reference 5); 2 = Polito *et al.* (reference 4); 3 = Escribano *et al.* (reference 3) and 4 = Cervera *et al.* (reference 2).

mg/kg/day (the conventionally accepted definition for IH) was identified in 10.2% of samples. In another population based study in children living in Cimitile, Southern Italy, 24-hour urine samples over 7 consecutive days were collected from 220 children (8). The prevalence of hypercalciuria in this study was found to be 9.1%. Although the reported prevalence of IH in asymptomatic children in one study from the US was noted to be 6.2% (6), very limited data are available on the true prevalence of IH in otherwise healthy children in the US due to the fact that universal screening for hypercalciuria in children is not widely practiced here. The long-term outcome and natural history of these asymptomatic hypercalciuric children is unknown since no epidemiologic studies have been conducted to date to address this issue. All of our current understanding of the long-term morbidity experienced by children with IH has been gained from data obtained from children with IH who came to medical attention due to one of the symptom complexes described below. Whether the information from these studies is applicable to asymptomatic children with IH is not known.

### 3.2. Hematuria

Although the exact mechanism of how hypercalciuria leads to hematuria is unclear, hypercalciuria is a very common cause of both macroscopic and microscopic hematuria in children (Figure 1). Roy *et al.* and Kalia *et al.* were the first 2 groups of investigators to independently describe an association between IH and hematuria in children (11, 12). Since then, several other reports have confirmed the association between IH and isolated hematuria (13, 14). It has been proposed that micro-crystallization of calcium, leading to injury to the urinary tract epithelium, is mechanistically responsible for hematuria and other non-calculi symptoms in patients with IH (7). This hypothesis has been supported by finding calyceal microlithiasis (hyper-echogenic spots < 3 mm in diameter) in hypercalciuric children with hematuria, abdominal pain and/or dysuria (15). Although in a study from Spain only 52/103 (50%) hypercalciuric children had renal calyceal microcalculi at initial presentation, as many as 85% of the studied children developed calyceal microcalculi at different times during the follow-up period (16). Notwithstanding these studies, a cause and effect relationship between the presence of micro-calculi and

clinical symptoms has not been clearly established; however, they do corroborate the above-mentioned hypothesis that micro-crystallization may play a role in the causation of the hematuria and other lower urinary tract symptoms that are commonly seen in children with IH.

#### 3.2.1. Macroscopic hematuria

Macroscopic hematuria has been strongly associated with IH in children. In a recent study from Northern United States, among the 228 children investigated for causes of asymptomatic macroscopic hematuria, 22% had IH as the primary cause of their hematuria (17); 24% of them had a family history of nephrolithiasis. Similarly in another report from the Southwest Pediatric Nephrology Study Group, 75 of 215 (35%) children with isolated hematuria were found to be hypercalciuric (18). Children with hypercalciuria, when compared to those with normocalciuria, were more likely to have: 1) macroscopic instead of microscopic hematuria, 2) presence of calcium oxalate crystals in urine, and 3) a positive family history of nephrolithiasis. Follow up data was available in 60 hypercalciuric children. Eight of the 60 (13%) hypercalciuric children developed renal calculi or colic during a 1-4 year follow up, significantly higher than the incidence of calculi in the non-hypercalciuric children with hematuria.

While most of the hypercalciuric patients with macroscopic hematuria are otherwise asymptomatic and pain-free, some patients do present with abdominal pain. In a study from South America (5), 471 hypercalciuric children were brought to medical attention for various symptoms, included hematuria, abdominal pain, UTI and lower urinary tract symptoms. Among these 471 children, 146 had painless hematuria, while 221 had concomitant abdominal pain at presentation.

#### 3.2.2. Microscopic hematuria

Similar to what is seen in children with macroscopic hematuria, IH is also prevalent in children with isolated microscopic hematuria. In the aforementioned study from the Northern United States (17), 342 children with asymptomatic isolated microscopic hematuria were studied. After comprehensive and extensive investigations, no etiology could be found in 80% of the children. In the 20% of the children with an identifiable cause, IH without coexistence of nephrolithiasis was the most common diagnosis, accounting for 16% of the studied population (17). Similar findings were seen in another study from the Northern United States. Of the 263 children referred to 2 tertiary care centers for the management of asymptomatic microscopic hematuria, 11% were noted to have IH (13). Notably, the incidence of a positive family history for nephrolithiasis in that studied population was 16% and 14% in the normocalciuric and hypercalciuric groups respectively, which was not significantly different.

Therefore, in most of the available studies, hypercalciuria is detected in a substantial proportion of children with unexplained macroscopic or microscopic hematuria, although a direct cause and effect relationship has not been established between the 2, and the exact

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pathogenic basis for hematuria remains unclear. While evaluation for IH in patients with unexplained hematuria is justified (18, 19), the presence of hypercalciuria in these children should not exclude consideration of other etiologies, especially with the coexistence of other abnormal urinary findings such as proteinuria or dysmorphic red cells.

### 3.3. Lower urinary tract symptoms

#### 3.3.1. Urinary frequency-urgency

IH has been inferred to be the cause of a variety of lower urinary tract complaints in children, including urinary frequency, urgency, and/or dysuria, often, but not always associated with macroscopic or microscopic hematuria. Alon *et al.* reported 13 children with persistent or recurrent frequency/dysuria associated with increased urinary calcium excretion (20). All of the patients had dysuria and a variable association with other symptoms, including urinary frequency (8 patients), enuresis (6 patients) and back/abdominal pain (4 patients). A family history of nephrolithiasis was present in 2 children. One child reported a history of macroscopic hematuria while microscopic hematuria was identified in 5. UTI was documented in 4 children. Treatment consisted of increased fluid intake and a reduced salt diet, supplemented with chlorothiazide if there was failure to achieve normocalciuria with dietary changes. Nine children became symptom free after achievement of normal urinary calcium excretion. Some of the patients had reappearance of symptoms when hypercalciuria recurred; these patients again became symptom-free after re-initiation of therapy for hypercalciuria. In a recent study in children (21), data from 288 children with voiding disorders were retrospectively reviewed. After excluding those children with UTI, patients were divided into 5 groups for analysis: a) children with macroscopic hematuria plus dysfunctional voiding; b) children with microscopic hematuria and dysfunctional voiding; c) children with only daytime urinary frequency; d) children with isolated dysuria syndrome; and e) children with combined frequency-urgency-dysuria syndrome. Hypercalciuria was prevalent in all 4 groups, the frequency ranging from 21 to 30%. In another study, urinary screening for IH was performed in 30 patients with isolated urinary frequency and in 39 patients with both frequency and dysuria (22). Three of the 30 (10%) children with frequency and 5 of the 39 (13%) children with frequency/dysuria were hypercalciuric. All the patients, both normocalciuric and hypercalciuric, had symptom resolution within 8 weeks after the initial visit without any specific intervention. Although no data were supplied by the author on whether the urinary calcium excretion normalized upon follow up, the author concluded that both the frequency and frequency/dysuria syndromes (in both normocalciuric and hypercalciuric children), are benign and transient conditions. No cause and effect relationship of their clinical symptoms to hypercalciuria could be identified in these two groups.

To summarize, IH has been associated with functional voiding disorders in children, although the exact mechanism remains unknown. Moreover, even though a significant number of patients with voiding dysfunction

have an elevated urine calcium-to-creatinine ratio, the majority of these children have symptom resolution without treatment directed towards hypercalciuria. Therefore, there is absence of cogent data in the current literature to support the cause effect relationship between dysfunctional voiding and IH in children (22).

#### 3.3.2. Incontinence/nocturnal enuresis

IH has also been recognized in children with various forms of urinary incontinence. Among 124 children that were evaluated for IH, 28 (23%) had different types of urinary incontinence (23). After dietary modifications targeting IH, 9 of the 28 (32%) patients had complete remission. Another 10 patients (36%) had greater than 50% improvement in their incontinence. However, the authors did not provide details on the correlation between the clinical response and the urinary calcium excretion. In a study from Italy, 406 patients with primary monosymptomatic nocturnal enuresis were studied (24). The authors noted that 21 of the 406 patients with nocturnal enuresis had IH. After 3 months of dietary management for IH, nocturnal enuresis had ceased completely in 4 patients (19%) while episodes had diminished in the remaining 17 children. Similarly, in a study that attempted to determine the etiology and pathogenesis of enuresis among primary school children (25), 66 enuretic children aged 6-12 years of age were studied and hypercalciuria was identified in 9.2% of the patients. These studies suggested that enuresis may be a clinical manifestation of IH in children. However, without data on the population prevalence of IH in the local community being studied, the significance of an elevated urinary calcium excretion in the symptomatic children cannot be ascertained.

#### 3.3.3. Recurrent colicky abdominal pain

Recurrent colicky abdominal pain concomitant with IH has been reported in the past. Polito *et al* described one hundred and eighty children with hypercalciuria or hyperuricosuria who had recurrent central/diffuse abdominal pain and/or lumbar/flank pain as their initial presenting features (26). Although the significance is not clear, micro-calculi and calculi were detected by ultrasound in 93 (52%) of the children with IH. Over half of the children also had dysuria together with either macroscopic or microscopic hematuria at presentation. The authors observed a significant and progressive shift in the site of the abdominal pain from a central location to the flank with increasing age. However, no information on the therapy and clinical outcomes was provided by the authors. Similarly, 52 out of 124 (64%) hypercalciuric children from East Tennessee also had recurrent abdominal pain at presentation (27); 12% of those hypercalciuric children with recurrent abdominal pain were identified to have nephrolithiasis. All these children were treated with increased fluid intake and a reduction in dietary sodium and oxalate, while 38 of them also required treatment with thiazide diuretics and antispasmodics. As a result, 45/52 (87%) had either complete resolution or significant relief of their abdominal pain following initiation of the intervention.

Although clinically overt nephrolithiasis is a recognized cause of abdominal pain, studies have indicated

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that recurrent abdominal pain associated with IH may occur in the absence of nephrolithiasis. While a urological origin for recurrent abdominal pain should not be overlooked in children, the exact mechanism behind the causation of pain in hypercalciuric children has not yet been identified.

### 3.3.4. Recurrent urinary tract infection

The association of IH and UTI has been reported in the past by different groups of investigators (9, 28-30). Biyikli *et al.* observed a high incidence of hypercalciuria in children with recurrent UTI (29). In a group of 75 Turkish children with UTI, hypercalciuria was identified in 32 (43%) children. In another prospective pediatric study that evaluated the association between IH and UTI (30), 75 children with UTI (25 had recurrent UTI and 50 had their first episode of UTI) and a control group of 30 healthy children were studied. Hypercalciuria was identified more frequently in children with UTI than in the controls; twenty-one percent (16/75) of patients with UTI were hypercalciuric, compared to 7% (2/30) of controls. The association was particularly compelling in those that experienced recurrent UTIs. Among the children with UTI, IH was diagnosed in 44% in those with recurrent UTI, and only in 10% of those with single episode of infection. However, it is also possible that those symptoms suggestive of a UTI (such as frequency, urgency and dysuria) may be from IH itself and not necessarily indicate a UTI. No information on the therapeutic responses and clinical outcomes were provided by the authors.

Having stated that, there are a few studies that have provided data on the relationship between the remission of UTI symptoms and the normalization of urinary calcium excretion. From a study on Venezuelan children, 59 hypercalciuric patients with two or more episodes of UTI were studied (9). Clinical manifestations included fever, dysuria, straining with micturition, hematuria, and abdominal pain. Treatment consisted of promotion of fluid intake, avoidance of excessive salt and protein, and adoption of a dietary calcium intake between 900 and 1,200 mg/day. Prophylactic antibiotics were not given during the study. Potassium citrate or hydrochlorothiazide were initiated only if the hypercalciuria persisted in spite of non-pharmacologic therapies. With this, 95% of the children achieved normocalciuria and had no further episodes of UTI. In another study, 124 children with various complaints associated with hypercalciuria were studied (28). Thirty-nine (31%) of them had recurrent UTI episodes. Although all children were managed with increased fluid intake and reduction in dietary sodium and oxalate, about one third of those children with recurrent UTI also required thiazide diuretics to reduce urinary excretion of calcium. Seven children required anti-spasmodics for abdominal pain and 5 children eventually required antibiotic therapy. Long term follow up data were available in 29 of the 39 (74%) children with recurrent UTI. Twenty four of these 29 (83%) children achieved remission without any recurrence of UTI. However, 8 of the children who sustained remission after therapy did not normalize their urinary calcium excretion. Although these studies suggest that IH might be an important contributory factor to recurrent UTI in children, there is a dissociation

between the clinical response and the urine calcium excretion, making a causal link between the 2 unclear.

Mechanistically, it has been speculated that renal calculi and microcrystals that may be present in patients with IH predispose to the development of UTI, as these calculi and crystals may offer shelter to bacteria and hinder their clearance from the urinary tract (7). The microcrystals may also injure the uro-epithelium, thus hindering normal innate defense mechanisms. Furthermore, elevated levels of calcium oxalate crystals may provoke renal cells to increase the synthesis of osteopontin, which is a known inflammatory mediator. Osteopontin may induce a cascade of inflammatory events in the renal tubular epithelium, further reducing immunity to bacterial infection (31). Furthermore, the binding of the calcium oxalate crystals to the tubular epithelium may be facilitated by the osteopontin itself (32).

### 3.4. Nephrolithiasis

Although nephrolithiasis is not the most common presenting feature of IH in children (Figure 1), IH is the most common metabolic abnormality associated with renal calculi both in adults and in children. Roy *et al.* reported five children with painless hematuria secondary to hypercalciuria; renal calculi were subsequently passed or detected in each of the children, 14 to 20 months after initial presentation (11). Stapleton *et al.* reported that 8 of 60 (13%) children with untreated hypercalciuria and hematuria developed nephrolithiasis or renal colic during a 1-4 year follow up (18), compared to 2 of the 124 (2%) normocalciuric children with isolated hematuria. In a recent retrospective study of 85 children with urinary tract calculi, hypercalciuria was found to be the most common metabolic disorder, present in 32% (33).

The association of a positive family history and the detection of IH vary based on geographical location. Stapleton *et al.* reported that as many as 70% of children with IH have a strong family history of nephrolithiasis (14), although other pediatric studies do not support such a high familial incidence (13). Polito *et al.* studied the prevalence of a history of nephrolithiasis in first- and second-degree relatives of children with hypercalciuria and/or hyperuricosuria (HU), and in a control population of children with other diseases (34). A strong family history of nephrolithiasis (69 to 78%) was found in children with hypercalciuria, hyperuricosuria or both, compared to the controls (22%). In spite of the data suggesting that there is a strong familial prevalence of nephrolithiasis and hypercalciuria in children, neither a family history of nephrolithiasis nor the amount of urinary calcium excretion are predictors of future stone formation. This observation points to the significant contribution of a number of additional factors to the risk of nephrolithiasis, such as urinary volume and dilution and the balance between a variety of other stone promoting and inhibiting constituents in urine, which include oxalate and citrate.

### 3.5. Nephrocalcinosis

Nephrocalcinosis has also been described in patients with hypercalciuria. Eggert *et al.* described 3

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siblings with IH and nephrocalcinosis (35). The index patient, a 4.5-year-old girl was identified to have both IH and nephrocalcinosis during her work up for recurrent dysuria and microscopic hematuria. Surveillance in other family members revealed IH and nephrocalcinosis in her 14-year old sister and a 19-year old brother. Neither of the siblings had any symptoms at the time of diagnosis. In a retrospective survey on 152 German children with nephrocalcinosis, IH was the most frequently identified coexisting condition and was noted in 34% of the children (36).

### 3.6. Bone demineralization

Decreased bone mineral density (BMD) has been recognized in both children and adults with IH and nephrolithiasis (37). BMD in 88 children with IH, at the time of diagnosis, was compared to a group of 29 normal children. Lumbar spine BMD was significantly reduced in 35% of the hypercalciuric children compared to only 7% of the controls. In another study, lumbar BMD was measured by dual X-ray absorptiometry (DEXA) in fifteen pediatric patients with IH who presented with either hematuria or abdominal pain (38). There was a significant negative correlation between the 24-hour urine calcium excretion and the BMD of the lumbar spine. In yet another study on young Brazilian adults, 40 (22 with IH and 18 with normocalciuria) patients with nephrolithiasis and 10 controls were studied (39). Almost half (45%) of the hypercalciuric patients were found to be osteopenic with decreased BMD at the femur neck. Moreover, 91% of the hypercalciuric patients had eroded bony surfaces and 36% had a mineralization defect. Therefore, measurement of bone density may aid in the identification of those children with IH that are at risk of future serious consequences such as osteoporosis and bone fractures. Besides hypercalciuria, nephrolithiasis has also been associated with decreased BMD. In a cross-sectional study that used data from Third National Health and Nutrition Examination Survey (NHANES III), investigators found that men with a history of kidney stones had lower femoral neck BMD than men without nephrolithiasis after adjusting for other potential confounders (40). Wrist and spinal fractures were also more prevalent among men with a history of nephrolithiasis. These studies suggested that bone involvement can be detected in individuals with nephrolithiasis, even at a young age.

Furthermore, a high prevalence of decreased BMD has been observed in both hypercalciuric children and their mothers. Garcia-Nieto *et al.* studied BMD in girls with IH and in their hypercalciuric mothers, in order to evaluate the genetic influence on bone mass (41). In the study, BMD was measured in 40 hypercalciuric girls together with their pre-menopausal hypercalciuric mothers. BMD was determined by DEXA scanning of the lumbar spine and the femoral neck, and values were expressed as z-scores. The z-scores for BMD at the lumbar spine were significantly lower in girls and their mothers compared to controls. Z-scores in the girls with mothers suffering from osteopenia were also significantly lower than in the girls of mothers with normal BMD. The authors concluded that BMD should be measured or followed in middle aged

female individuals with hypercalciuric children. A similar association has also been observed in another recent study from North America, in which 21 hypercalciuric children and their asymptomatic pre-menopausal mothers were studied (42). Hypercalciuria was diagnosed in 5/21 (24%) of the asymptomatic mothers. Reduced BMD at the lumbar spine or femur neck was observed in 38% and 33% of the children and mothers respectively. The children of osteopenic mothers exhibited significantly reduced bone density at the lumbar spine ( $P < 0.05$ ) when compared with children of mothers with normal BMD. Therefore, reduced BMD has been detected in a large proportion of children with IH and in a substantial number of their otherwise healthy asymptomatic mothers. Interestingly, serum levels of calcitriol and intact parathyroid hormone in children with IH did not correlate with their BMD (43).

Hypocitraturia is also a frequently associated condition among patients with IH and decreased BMD. In a study with 88 children with IH (44), patients were divided into the 3 groups: group 1: patients with associated hypocitraturia, group 2: patients without hypocitraturia and group 3: healthy subjects as the control group. BMD and bone marrow content of the lumbar spine at L2-L4 level and the femur neck were measured. There was no difference in age among the patients, but weight, height, body mass index, and bone age were lower ( $P < 0.01$ ) in group 1. Serum intact parathyroid hormone (PTH) was higher ( $P < 0.05$ ) in children with hypocitraturia. The lumbar spine BMD, as well as femur neck BMD, were significantly lower in group 1 than in groups 2 and 3 ( $P < 0.01$ ). This study suggested that children with IH and associated hypocitraturia may be at an even higher risk of losing bone mass and thus developing subsequent osteopenia.

The pathomechanism of decreased bone mass in patients with IH is still unclear. Cytokines have been studied for their possible role in decreasing BMD in hypercalciuric patients (45). DEXA and cytokine production (by unstimulated and lipopolysaccharide-stimulated peripheral blood mononuclear cells) were measured in 29 patients with recurrent nephrolithiasis (17 hypercalciuric patients and 12 normocalciuric patients), and compared to 12 healthy controls. The hypercalciuric subjects showed lower vertebral BMD than both the normocalciuric individuals with nephrolithiasis and the normal controls. A significant negative correlation was observed between urinary calcium excretion and vertebral BMD ( $P < 0.01$ ). Interestingly, the *in vivo* elevation in interleukin (IL)-1 alpha production correlated inversely with vertebral BMD ( $P < 0.02$ ). This correlation was not seen with IL-1 beta, IL-6 or tumor necrosis factor-alpha production. The results suggested that different cytokines could have different roles in the bone resorption process observed in patients with hypercalciuria. On the other hand, in a rat model that is analogous to humans with IH, Aledronate (a bisphosphonate) was shown to be effective in decreasing both the urinary excretion of calcium and supersaturation (46). These observations further support the possible role of bone in the pathogenesis of IH.

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### 4. SUMMARY AND PERSPECTIVES

IH is a common metabolic disorder in children and may have a wide spectrum of clinical manifestations. Most children with IH are identified during investigations for hematuria and various lower urinary tract symptoms, with a smaller proportion being diagnosed during a work-up for stones or during family screening. Most of these symptoms are transient and may disappear without any therapy. Unlike adults, children with IH are less likely to have renal calculi at presentation.

Available data do suggest that children with IH and hematuria are at risk of developing renal calculi if no interventions are performed; whether the same holds true for asymptomatic children with IH is not known. Available data on BMD also indicate the existence of poor bone health in a substantial proportion of children with IH. Although indiscriminate screening for osteopenia in all children with IH and/or nephrolithiasis cannot be recommended at this point in time, it seems justified to evaluate BMD in a subset of children, especially those with long-term negative calcium balance due to prolonged or recalcitrant hypercalciuria and those with concomitant hypocitraturia. Whether correction of other coexisting metabolic disturbances such as hypocitraturia will alter the outcomes of children with IH has not been studied

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**Abbreviations:** IH: idiopathic hypercalciuria; UTI: urinary tract infection; BMD: bone mineral density; DEXA: dual X-ray absorptiometry; NHANES III: Third National Health and Nutrition Examination Survey; IL-1: interleukin 1

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