Complications of hypercalciuria

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TABLE OF CONTENTS

1. ABSTRACT

Idiopathic hypercalciuria is a common disorder in children and can present with a range of clinical presentations such as hematuria, voiding dysfunction, flank pain, abdominal pain, nephrolithiasis, urinary tract infection and decreased bone mineral density. In the review below we provide a brief overview of calcium metabolism, types and clinical consequences of hypercalciuria and a brief approach to evaluation and management of hypercalciuria.

2. INRODUCTION

Hypercalciuria is a common condition, with a prevalence of 2-6 % in the pediatric population, and is the most common cause of nephrolithiasis in children from Western society (1, 2). The term idiopathic hypercalciuria was introduced by Albright in 1953 to describe patients with recurrent nephrolithiasis who had elevated urinary calcium excretion without concomitant hypercalcemia (3). The etiology of hypercalciuria is complex and involves interactions between the gastrointestinal tract, bone and

kidney, which is further influenced by hormones, such as parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D3 (1,25 (OH2)D3) (4, 5). Often a primary defect in one organ induces compensatory responses in the remaining two organs. For example, there is an increased intestinal absorption of calcium secondary to a primary renal loss. Hypercalciuria can be either idiopathic or secondary. In this review we will discuss the clinical consequences of hypercalciuria with a brief approach to evaluation and management of idiopathic hypercalciuria in children.

2.1. Overview of calcium metabolism

Calcium exists in three distinct pools in the body. The largest pool is in the skeleton, followed by extracellular calcium, with a minimal amount in the intracellular space. These pools are tightly controlled by known physiological homeostatic mechanisms with >99% of calcium existing as mineral component of bone and <1% in extracellular fluid, and these calcium pool levels deviate <2% under normal conditions (6). The serum calcium consists of three fractions, 50-55% is ionized or free calcium; 35-40% is bound to proteins, mostly albumin; and 10% is complexed to low molecular weight anions (7). Calcium absorption in the gastrointestinal tract occurs via two transport processes, active vitamin D regulated transcellular absorption, and by a passive paracellular absorption that is dependent on the dietary calcium load (8, 9). Currently it is thought that the paracellular pathway predominates when the diet is replete in calcium, while the vitamin D-dependent transcellular pathway becomes critical during periods of limited dietary calcium. The free or ionized calcium (i.e. non-albumin bound calcium) in serum is ultrafiltrated in the glomerulus, which then has to be reabsorbed by the renal tubule to maintain calcium homeostasis. Approximately 70% of calcium retrieval occurs in the proximal tubule and approximately 20% occurs in the thick ascending loop of Henle (TALH), by a paracellular mechanism (10, 11). Solvent drag from salt and water absorption is responsible for calcium absorption in the proximal tubule while the paracellular calcium absorption in the TALH occurs secondary to the lumen-positive potential generated by the sodium absorption from the NKCC2, ROMK and Chloride channel (12). Therefore calcium absorption in the renal tubule is inversely related to sodium absorption. Thus, limiting excessive sodium in diet is extremely important for management of hypercalciuria. The fine tuning of calcium homeostasis occurs at the distal convoluted tubule, connecting tubule, and initial portion of the cortical collecting duct by modulating reabsorption of the remaining ~10% calcium through an active transcellular pathway (10, 11, 13). The active transcellular calcium transport in the distal tubule is regulated by PTH and 1,25 (OH)2D3 (14, 15).

2.2. Regulation of calcium metabolism as it relates to hypercalciuria

The tubular reabsorption of filtered calcium is affected by PTH, 1,25- (OH)2-D, extracellular fluid volume, acid-base status, serum calcium and magnesium concentrations. PTH and 1,25- (OH)2-D play an important role in calcium homeostasis and modulate serum levels of

each other. PTH increases serum calcium through several well characterized mechanisms, including stimulation of renal calcium absorption and phosphate excretion, osteoclast activity and bone resorption, and 1 α-hydroxylase activity and synthesis of 1,25- (OH)2-D by renal proximal tubular cells, which in turn increases intestinal calcium and phosphorous absorption. Thus PTH accrues calcium from bone, kidney and intestinal sources to restore the extracellular calcium. Conversely, when extracellular calcium rises above its setpoint, PTH secretion decreases thus bringing the calcium down toward the setpoint. PTH primarily maintains the serum calcium around its setpoint, while 1,25- (OH)2-D is believed to play a major role in development of hypercalciuria.

1,25- (OH)2-D appears to be important in development of hypercalciuria through its action on gastrointestinal tract and bone as suggested by (a) NPT 2a[-/-] gene knockout mouse models and genetic hypercalciuric stone-forming rats, (b) clinical observation in subjects with X-linked hypophosphatemic rickets who develop hypercalciuria only after therapy is initiated with calcitriol, (c) the administration of 1,25 (OH)2D3 in healthy subjects on a normal-calcium diet led to an increase in intestinal calcium absorption and an increase in urinary calcium excretion (16), (d) in subjects on a calcium restricted diet that receive calcitriol develop a negative calcium balance from increased urinary calcium loss mediated through increased bone resorption (17), (e) intoxication with vitamin D gives rise to hypercalcemia and hypercalciuria by stimulating intestinal calcium absorption; of note, hypercalciuria usually precedes hypercalcemia as indicator of vitamin D overdose (18) and (f) cross sectional clinical studies in patients with hypercalciuria where it has been observed that serum calcitriol levels are, on average, either inappropriately normal for the clinical scenario or higher in patients with idiopathic hypercalciuria compared to healthy controls (19).

It is possible that cytokines may play a role in the rare "resorptive hypercalciuria" where a primary bone disorder is believed to be the inciting defect, and the less common renal hypercalciuria may arise from "renal leak" of calcium. Cytokines are known to induce bone resorption and inhibit bone formation. Cytokines such as interleukin-1β, interleukin-6, tumor necrosis factor-α, and granulocyte, macrophage stimulating factor have been found to be increased in hypercalciuric calcium stone forming subjects with increased bone loss (20, 21). Metabolic bone diseases that are associated with a primary increased bone turnover, independent of PTH or vitamin D, which are associated with hypercalciuria are osteogenesis imperfecta, hypophosphatasia and metaphyseal chondrodysplasia (Jansen type) (22-25)

2.3. Subtypes of idiopathic hypercalciuria

Idiopathic hypercalciuria has traditionally been divided into three subtypes; absorptive, renal and resorptive hypercalciuria (26). The classification has been further modified over the years, based on urine calcium excretion, serum phosphate, and serum PTH secretion during fasting and after a calcium load (27). Idiopathic hypercalciuria

results from either or a combination of (1) increased gastrointestinal calcium absorption from a direct increase in calcium absorption (Type 1 absorptive hypercalciuria) or through excess 1,25-dihydroxyvitamin D3 (1,25 (OH)2D3)-mediated calcium absorption (Type II absorptive hypercalciuria); (2) decreased renal absorption of either calcium (renal hypercalciuria) or phosphorus (Type III absorptive hypercalciuria); (3) enhanced bone resorption (resorptive hypercalciuria) (12, 28, 29). Patients with renal and absorptive hypercalciuria normalize urine calcium excretion when treated with thiazides, but only the renal hypercalciuric group showed a decrease in intestinal hyperabsorption, PTH and calcitriol levels (30). The aforementioned results suggest that calcium leak is the inciting event in renal hypercalciuria and abnormal 1,25- $(OH)_2$-D metabolism is the inciting event in absorptive hypercalciuria. Hypercalciuria appears to be a complex trait, and it is possible that absorptive and renal forms of hypercalciuria may represent a continuum of a single disease (31, 32). Renal and absorptive hypercalciuria may not be distinct physiologic entities as indicated by the lack of increased bone turnover in hypercalciuric children (33). When children initially diagnosed with having either renal or absorptive hypercalciuria received a calcium loading tests after an interval of 3-7 years, a different result was obtained in more than half of the children studied (34). Although the classification of hypercalciuria subtypes has been questioned, it still provides a reasonable framework to methodically approach an evaluation of a difficult child with hypercalciuria.

2.4. Genetics of hypercalciuria

A genetic contribution to hypercalciuria is suggested by both familial clustering of nephrolithiasis and hypercalciuria. After controlling for known dietary factors, a positive family history appears to be the single most important risk factor for nephrolithiasis (35). Since hypercalcuria is the most common underlying metabolic abnormality associated with nephrolithiasis, increased familial clustering of nephrolithiasis suggest an increased familial clustering of hypercalciuria. In children with hypercalciuria, the prevalence of nephrolithiasis in the family is 69% (36). A genetic defect in three families with severe absorptive hypercalciuria has been mapped to 1q23.3-q24, with a candidate gene subsequently sequenced (37). Eighteen base substitutions in the candidate gene have been identified, four of which increased the relative risk of absorptive hypercalciuria by 2.2-3.5 fold (38). Imamura *et al* (39) and Giuffre *et al* (40) have identified three unrelated children with hypercalciuria with a 4q33-qter and 4q31.3-qter deletion respectively, raising the possibility of a contributing gene for a hypercalcuria phenotype in the region. Currently the hypercalciuria appears to be a complex (polygenic) trait that results from both genetic and environmental factors (41, 42). The expression pattern of idiopathic calcium nephrolithiasis is most compatible with autosomal dominant transmission, but the quantitative genetics of urine calcium excretion remains to be determined.

3. CLINICAL CONSEQUENCES OF IDIOPATHIC HYPERCALCIURIA

3.1 Hypercalciuria and nephrolithiasis

Coe *et al* assessed that 5% of women and 12% of men in USA will develop a kidney stone in their life span (43). Hypercalciuria is the most frequently encountered abnormality in children nephrolithiasis, identified in 28% to 79% of children with kidney stones (44, 45). The majority of stones are composed of calcium with 45-65% consisting of calcium oxalate and 14-30% consisting of calcium phosphate (46). Nephrolithiasis in children can present as acute renal colic, a urinary tract infection, gross or asymptomatic hematuria or as an incidental finding on an imaging study. Nephrolithiasis is the primary pathology associated with hypercalciuria since it associated with severe pain and recurrent stones can lead to progressive renal failure (47, 48). The risk of developing kidney stones in patients with idiopathic hypercalciuria has varied between studies from 0/33 (0%) developing stones with a 4-11 year follow-up (49), to 9/58 (16%) with a 1-6 year follow-up (50), to 4/30 (13%) with a 1-3 year follow-up (36) and 8/60 (13%) with a 1-4 year follow-up (51). The presence of gross hematuria, a family history of nephrolithiasis and greater levels of hypercalciuria in a dose-effect association increase the likelihood of progression from hypercalciuria to nephrolithiasis (50, 52). The recurrence risk of nephrolithiasis is 27% to 50% for adults within 10 years of the first stone episode (53, 54). Noe HN on follow up of 27 of 44 children with nephrolithiasis associated with hypercalciuria, found 9/27 (33%) to develop a recurrence of stone 3-15 years (mean 7.2 years) from the first presentation (55).

3.2 Hypercalciuria and hematuria

Hematuria is frequently encountered in children in the primary care setting with an incidence of 1.3 per 1000 for gross hematuria and 41 per 1000 for microscopic hematuria (56, 57). Hematuria may be caused by injury to the glomeruli, renal interstitium, renal vasculature or the urinary tract (58). Hematuria in hypercalciuria is thought to result from injury to the urinary tract (58). The association between hematuria and hypercalciuria has been demonstrated in multiple studies. Twenty six to thirty six percent of patients with hematuria have no identifiable basis for hematuria other than hypercalciuria (51- 60). On the other hand 31% of patients with hypercalciuria have hematuria (61). The incidence of hypercalciuria is similar in children with gross and microscopic hematuria (60). The subtype of absorptive and renal hypercalciuria is evenly distributed in children with hematuria (59). Hematuria in idiopathic hypercalciuria patients is characterized by calcium oxalate crystalluria, a family history of hypercalciuria, and the absence of red blood cell cast in the urine (51). Although the mechanism for hematuria in hypercalciuria is not known, the hematuria resolves with anticalciuric therapy in the vast majority of cases (59, 60).

3.3 Hypercalciuria and voiding symptoms and abdominal pain

Between 8 and 30 % of patients diagnosed with hypercalciuria present secondary to voiding symptoms (36,

61). The diurnal voiding symptoms described in patients with idiopathic hypercalciuria include urinary urgency, frequency, dysuria, enuresis and suprapubic pain and are hypothesized to occur from injury to the urinary epithelium secondary to calcium microcrystallization (62). A retrospective review of 288 children that presented secondary to functional voiding disorders reported hypercalciuria in 28% who presented with gross hematuria and voiding symptoms, 30% with microscopic hematuria and voiding symptoms, 21% with urinary frequency, 22% with dysuria, and 28% with combined urgency frequency and dysuria (62). In addition to voiding symptoms, idiopathic hypercalciuria has been associated with recurrent flank and/or abdominal pain (in the absence of nephrolithiasis) that improves or resolves with increased fluids, reduction of dietary sodium and oxalates and in some cases thiazide therapy (36, 63). Hypercalciuria decreases the effect of vasopressin mediated water reabsorption in the distal tubule leading to polyuria, and thus has been proposed to be a potential risk factor in development of nocturnal enuresis with conflicting results in reported studies. The findings of Valenti *et al* (59) and Pace *et al* (60) support a role for hypercalciuria in nocturnal enuresis (64-66). This was not found to be true in two other studies in children with nocturnal enuresis where no significant difference was observed compared to controls for either daytime or nighttime urinary calcium excretion (67, 68). A study of 450 children identified a significant incidence of nighttime, but not daytime, hypercalciuria and low vasopressin levels in enuretic children (69). The role of hypercalciuria in the evaluation and treatment of nocturnal enuresis remains uncertain.

3.4 Hypercalciuria and urinary tract infection

Urinary tract infections (UTI) occur frequently in infants and children with an incidence of 5% in febrile patients between 2 and 24 months of age (70). In addition, by 6 years of age, 7% of girls and 2% of boys will have had at least one urinary tract infection (71). The long term morbidity from urinary tract infections is from renal scarring which can lead to hypertension and reduced renal function (72). In order to limit the morbidity associated with urinary tract infections, identification and treatment of predisposing factors with the goal of preventing recurrent urinary tract infections is desirable. Urinary tract infections are a well known complication of nephrolithiasis, presumably secondary to the renal stones serving as a nidus where bacteria can congregate without being flushed from the urinary tract during voiding and/or increased susceptibility to urinary tract epithelium secondary to physical damage (73, 74). Akil *et al* demonstrated in rat model that hypercalciuria produces an adverse effect on the cell architecture of uroepithelum and disruption in the epithelial barrier of bladder and ureter which would predispose to urinary tract infection (75). Stojanović *et al* found 21% of children with UTI had hypercalciuria compared to 7% in normal children; of which hypercalciuria was seen in 10% of children with first UTI and in 44% with recurrent UTI (76). Similarly Biyikli *et al* found 43% of children with recurrent UTI had hypercalciuria (77). On the other hand, in children with symptomatic idiopathic hypercalciuria Vachvanichsanong

et al found 40% to have a UTI of which 78% were recurrent (78). A reduction in urinary calcium excretion with increased fluid intake, reduction of dietary sodium and oxalate, and thiazide diuretic (in 36%) resulted in no further UTIs in 61% of children with recurrent UTIs (78). In another study children with recurrent UTI, normal urinary tract and idiopathic hypercalciuria no further UTIs occurred in 95% following normalization of urinary calcium excretion with treatment of hypercalciuria (79). Hypercalciuria as a contributing factor should be a consideration in the evaluation and management of children with recurrent urinary tract infections.

3.5 Hypercalciuria and bone mineral density

Rapid bone formation typically occurs in children and adolescent with the peak bone mineral density obtained in late adolescence (80). There is a gradual loss of bone mineral density starting in the third decade of life and any disturbance to obtain the peak bone density as a young adult is a preventable risk factor for osteoporosis later in life (81). Thus acquiring an optimal bone mass during childhood is a major determinant of future adult bone health (82). Additionally, osteoporosis in childhood is being increasingly recognized as a clinical problem in high risk patient populations (81).

Over the last three decades, an association between decreased bone density and hypercalciuric kidney stones has been identified in several studies in adults (83-86). Lower bone density has been observed in hypercalcuric compared to normocalciuric stone formers (85, 87). Factors associated with decreased bone density in hypercalciuria patients include the male gender and increasing severity of hypercalciuria (84, 88-89). Adults with renal hypercalcuria have a trend towards higher rates of decreased bone density than those with absorptive hypercalciuria (84, 86, 90). Few studies have reported no reduction in bone mineral density in adults with absorptive hypercalciuria (83, 91). Nephrolithiasis has been associated with a higher rate of vertebral fractures in men, with a potential male predominance (89, 92). Histomorphometric evaluation of hypercalcuria patients with low bone density has revealed severe mineralization defect and decreased bone formation (86, 93). The fracture risk in idiopathic hypercalciuria patients has not yet been evaluated.

In children, Penido *et al* identified a low bone mineral density in 35% of children with idiopathic hypercalciuria, and in a subsequent study they found that these findings were more marked in hypercalciuric children with hypocitraturia (94, 95). Garcia-Neto *et al* also identified a decrease in bone mineral density in 30% of children with hypercalciuria but made the observation of a negative linear correlation between age and bone mineral content in children with idiopathic hypercalciuria (96). This raises the possibility in the hypercalciuric children that the decrease in bone density progresses over time and the origin of adult osteoporosis may occur in childhood (96). Similarly, Freundlich *et al* showed that reduced bone mineral density was present in 38% of children with hypercalciuria, and also identified a high incidence of both hypercalciuria and reduced bone mineral density in their

asymptomatic mothers (97). The data in both children and adults indicate that the risk for low bone mineral density is present in patients with hypercalciuria. Although it is not done conventionally the data in literature would support that clinicians should consider monitoring bone mineral density as a proxy for calcium balance in children. The present pharmacological treatments of hypercalciuria and/or nephrolithiasis such as citrate and thiazide diuretics have been shown in adults to increase bone mineral density (98-100). It should be noted that the effect of anti-hypercalciuric therapy on bone mineral density in hypercalciuric children has not been systematically evaluated.

3.6 Hypercalciuria and Hypertension

A relationship between hypercalciuria and hypertension has been suggested (101, 102). Hypercalcuria has been identified in 35% of 112 adult patients with essential hypertension compared to 2% of controls (103). The association between hypercalciuria and hypertension is controversial and other studies have failed to detect increased urinary calcium excretion in hypertensive patients when compared to normotensive controls (104). The possibility exist that a subset of hypercalcuria patients are at risk for hypertension. In adult patients with kidney stones, hypertension is associated with patients that have both hyperuricosuria and hypercalciuria, but not in patients with either of the aforementioned urinary abnormalities in isolation (105). The presence of other variables such as the dietary sodium intake and body habitus make the potential association between hypercalciuria and hypertension difficult to elucidate.

4. APPROACH AND MANAGEMENT OF HYPERCALCIURIA

Hypercalciuria in children can present as hematuria (gross or microscopic), dysuria, voiding dysfunction, abdominal pain and flank pain, or with nephrolithiasis (59, 106). It can be intermittent or persistent, occur in isolation or associated with a family history of nephrolithiasis. Once hypercalciuria is detected in a child before it is labeled as idiopathic hypercalciuria, one must consider the possibility of a secondary etiology causing hypercalciuria, for successful treatment of hypercalciuria in such cases depends on accurate diagnosis and management of the primary cause. An increase in urinary calcium excretion can occur from: (a) increased intestinal calcium absorption (vitamin D excess, increased calcium intake, congenital lactase deficiency, congenital sucrase-isomaltase deficiency and glucose/ galactose malabsorption and blue diaper syndrome), (b) impaired renal tubular calcium reabsorption (distal renal tubular acidosis, Dent's disease, activating mutations in calcium sensing receptor gene, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, loop diuretics), (c) bone resorption (immobilization, hyperparathyroidism, steroid use, neoplasm, metabolic bone diseases), (d) renal tubular phosphate leak (hereditary hypophosphatemic rickets with hypercalciuria), (e) increased 1,25 dihydroxy vitamin D synthesis (sarcoidosis, neoplasm) and (f) increased renal prostaglandin E2 production (Bartter syndrome), (g) too high dietary salt intake and too low potassium intake. Although these secondary forms of hypercalciuria are rare, a comprehensive evaluation for an underlying metabolic disorder should be undertaken in the presence, failure to thrive, growth retardation, rickets, acid-base disturbances, renal dysfunction, proteinuria, electrolyte imbalance, dysmorphic features or poor response to therapy.

Hypercalciuria, is defined on a 'statistical' basis in children as urinary calcium excretion of >4 mg/kg/day or a calcium/ creatinine ratio >0.21 mg/mg (107). Urinary calcium excretion is affected by both ethnicity and age, with much higher excretion in Caucasian compared to African-American children and in infants and young children compared to older children (108). It is our belief that pharmacologic agents should be reserved for children with symptomatic hypercalcuria.

When idiopathic hypercalciuria is confirmed in symptomatic children, the initial management is to assess whether dietary manipulation and increased fluid intake can normalize calcium excretion and/or eliminate the associated symptoms. We recommend a diet that contains the United States recommended daily allowance (RDA) of protein, calcium and potassium, and avoids excessive sodium and oxalates. A list of foods high and low in oxalates can be found in Table 1. Contrary to past practice, dietary restriction of calcium is not recommended in children with hypercalciuria as it puts the growing child at risk for negative calcium balance, poor bone mineralization and an increase in urinary oxalate excretion. Compliance with these dietary recommendation can be assessed in part by measuring urine Na/K ratio which should be <2.5 meq/meq. Some children may not respond or fully comply with such dietary manipulations nor with the traditional recommendation of high fluid intake and may benefit from pharmacological treatment (45) with potassium citrate at 0.5 to 1 mEq HCO_3^-/kg/dose given orally two times daily (2) and/ or a thiazide diuretic such as hydrochlorothiazide at 0.5 to 1 mg/kg/dose given orally twice daily or chlorothiazide 7.5 to 12.5 mg/dose given orally twice daily (2, 109). Children on long term thiazide diuretics need to be monitored for dyselectrolytemia, hyperlipidemia, hyperglycemia and hypotension. One can consider under special circumstances to add amiloride as it further increases the hypocalciuric effect and decreases potassium loss (2).

5. SUMMARY

Hypercalciuria, while a common disorder may be responsible for a range of clinical symptoms and presentations that range from hematuria, voiding dysfunction, flank pain, abdominal pain, nephrolithiasis, urinary tract infection and decreased bone mineral density. Its role in hypertension and nocturnal enuresis at present is controversial. The more common idiopathic hypercalciuria can be controlled in most cases with dietary modifications and/ or drug therapy with potassium citrate or thiazides. The rare secondary hypercalciuria has to be addressed on a case by case basis and by the nature of metabolic disorder.

Complications of hypercalciuria

Table 1. Foods that are high and low in oxalate

High oxalate foods
• Chocolate / Cocoa
• Tea
• Nuts
• Leafy greens: collard greens, dandelion greens, swiss chard, spinach, escarole, mustard greens, sorrel, kale, rhubarb
• Sweet potatoes
• Pepper
• Beets
• Orange juice/ Cranberry juice/ Grape juice
• Gelatin
• Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries
• Okra
• Celery
• Grits
Low oxalate foods
• Dairy products
• Meat
• Fish
• Eggs
• Cereals
• Apples
• Peaches
• Pears
• Pineapple
• Lettuce
• Cabbage
• Asparagus
• Peas
• Banana
• White potatoes
• Spaghetti

It has been shown clinically that control of elevated urinary calcium excretion allays the common symptoms of dysuria, dysfunctional voiding, hematuria and abdominal pain. Anti-hypercalciuric treatment has been found to be effective in decreasing urinary tract infections in hypercalciuric children with recurrent UTIs and in delaying the recurrence of new stone and/ or growth of a pre-existing stone. Its role in prevention or treatment of low bone mineral density in children is not known. The issues related to need for anti-calciuric therapy, nature of therapy (dietary, citrate or thiazides) or duration of therapy in hypercalciuria children as evidence based therapy remains to be determined. Although not known at the present time, research is definitely needed to address the questions such as: Is it possible to identify children with hypercalciuria who are at risk for nephrolithiasis or for low bone mineral density as an adult, and if interventions done during childhood will have an impact on development of nephrolithiasis and/ or osteoporosis as an adult. Future studies designed to address these complex issues associated with hypercalciuria will allow the pediatric community to treat this condition as evidenced based therapies rather than anecdotal experiences.

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