Diagnosis and management of hypercalciuria in children

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Purpose of review

In this review, recent advances in the epidemiology, genetics, clinical associations and management of idiopathic hypercalciuria will be discussed.

Recent findings

A significant genetic contribution exists in the pathophysiology of hypercalciuria. Although several candidate genes and genetic alterations have been proposed, identification of precise gene(s) responsible remains elusive. Decreased bone density has been increasingly associated with hypercalciuria. Recent publications have suggested that bisphosphonates may play a role in the management in patients in whom both hypercalciuria and decreased bone density are present.

Summary

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. Dietary modifications are often sufficient in the management of hypercalciuria. If the symptoms persist or a rare monogenic disorder is present, consideration should be given to medical treatment with a thiazide diuretic and/or citrate therapy.

Keywords

citrate, hypercalciuria, thiazide, urolithiasis

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Introduction

Idiopathic hypercalciuria, that is elevated urinary calcium excretion without concomitant hypercalcemia, is a common disorder seen in 3–6% of children [1,2]. Hypercalciuria has been defined in children on a 'statistical' basis as urinary calcium excretion of more than 4 mg/kg/day as opposed to the 'outcome'-based value of more than 250 mg/day in women and more than 300 mg/day in men. In children presenting symptoms may include hematuria, voiding dysfunction, flank pain, abdominal pain and urolithiasis. Additionally hypercalciuria has been associated with recurrent urinary tract infections (UTIs) and decreased bone mineral density. In this review, the different aspects of hypercalciuria that are relevant to clinical practice will be discussed.

Genetics of hypercalciuria

Hypercalciuria is linked to development of urolithiasis. In children with hypercalciuria, the prevalence of urolithiasis in the family is 46–69% [3,4•]. A positive family history appears to be the single most important risk factor [5]. The frequently observed familial clustering of calcium urolithiasis is most compatible with an autosomal dominant transmission [6]. A number of candidate genes have been suggested in pathogenesis of hypercalciuria, such as soluble adenylate cyclase, calcium sensing receptor (CASR), vitamin D receptor, chloride channel-5, sodium phosphate cotransporter-2 and claudin-16 [7••]. Reed *et al.* [8,9] mapped the defect in three families with severe absorptive hypercalciuria to 1q23.3–q24 and sequenced a putative gene that increases the relative risk by 2.2–3.5-fold. Vezzoli *et al.* [10] identified a single nucleotide polymorphism, Arg990Gly, in the *CASR* gene, which accounted for 4.1% of total variance in calcium excretion. Imamura *et al.* [11] and Giuffre *et al.* [12] have described three unrelated children with hypercalciuria who have 4q33-qter and 4q31.3-qter deletion, respectively, which raises the potential for a putative gene for hypercalciuria in that region. Currently the hypercalciuric trait is suspected to be polygenic and requires the interaction of genetic and environmental factors [13,14]. The role of environment has been well substantiated by Trinchieri [15], who showed that with change in dietary habits both the incidence and chemical composition of calculi have changed. At the beginning of the last century, bladder calculus from ammonium urate was relatively frequent in Europe. At present, as our diets have become rich in protein, refined carbohydrates and sodium, calcium stones predominate in ureter or kidney.

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Classification of hypercalciuria

The development of hypercalciuria involves interactions between the gastrointestinal tract, bone and kidney, and a complex interplay of hormones, such as parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D. Pak *et al.* [16] introduced a classification of absorptive, renal and resorptive hypercalciuria for idiopathic hypercalciuria. Over the years, investigators have further modified the classification based on urine calcium excretion, serum phosphate, and serum PTH secretion during fasting and after a calcium load [17]. Idiopathic hypercalciuria results from either a combination of increased gastrointestinal calcium absorption from a direct increase in calcium absorption (type 1 absorptive hypercalciuria) or through excess 1,25-dihydroxyvitamin D-mediated calcium absorption (type II absorptive hypercalciuria); decreased renal absorption of either calcium (renal hypercalciuria) or phosphorus (type III absorptive hypercalciuria); or enhanced bone resorption (resorptive hypercalciuria) [18–20]. Renal and absorptive hypercalciuria may not be distinct entities, as indicated by the lack of increased bone turnover in hypercalciuric children [21]. Children initially diagnosed with having either renal or absorptive hypercalciuria had a different result when tested 3–7 years later [22]. Additionally no major alterations in intestinal calcium absorption were identified when children with hypercalciuria were given an oral strontium load [23•]. It is possible that absorptive and renal hypercalciuria may represent a continuum of a single disease [24,25]. Thus, we do not suggest formal assessments for subtypes of hypercalciuria in children on a regular basis, but it can be utilized as a reasonable framework to methodically approach an evaluation of a medically complex child with hypercalciuria.

Clinical features of hypercalciuria

The pathological role for hypercalciuria has been attributed in nonglomerular hematuria (gross or microscopic), dysuria, urinary frequency, abdominal pain, back pain or nephrolithiasis as these symptoms improve with normalization of urine calcium. In a retrospective review of 288 hypercalciuric children, presenting symptoms included voiding symptoms and gross hematuria (28%), voiding symptoms and microscopic hematuria (30%), urinary frequency (21%), dysuria (22%) and combined urgency-frequency and dysuria (28%) [26].

Hematuria

Twenty-six to 36% of children have no identifiable basis for hematuria other than hypercalciuria; inversely, 31% of children with hypercalciuria have hematuria [27–30]. The prevalence of hypercalciuria is similar for both gross and microscopic hematuria, with the type of hematuria not related to the severity of hypercalciuria [27–30]. Although the association between hematuria and hypercalciuria has been noted in multiple studies, the underlying mechanism is not known, but likely results from injury to the urinary tract [31].

Voiding symptoms, abdominal pain and flank pain

Hypercalciuria presents in 8–30% of children with voiding symptoms [3,30]. These symptoms can range from urinary urgency, frequency, dysuria, enuresis or suprapubic pain and are believed to occur from injury to urinary epithelium from calcium microcrystals [26]. In addition to voiding symptoms, idiopathic hypercalciuria without nephrolithiasis has been associated with recurrent flank and/or abdominal pain [3,32].

Nephrolithiasis

Hypercalciuria is found in 28–79% of children with urolithiasis and nephrocalcinosis [33,34]. In a recent study, hypercalciuria (40%) and hypocitraturia (38%) were the most common risk factors for the development of urolithiasis in children [4•]. Although urolithiasis occurs in only 5% of children with hypercalciuria, microcalculi (i.e. hyperechogenic spots <3 mm in renal calyces) are much more common (57%) [3]. The risk of urolithiasis in children with idiopathic hypercalciuria has varied between studies from 0/33 (0%) developing stones with a 4–11-year follow-up [35], to 9/58 (16%) with a 1–6-year follow-up [36], to 4/30 (13%) with a 1–3-year follow-up [3] and 8/60 (13%) with a 1–4-year follow-up [28]. The presence of gross hematuria, a family history of urolithiasis and greater levels of hypercalciuria increase the risk for progression to urolithiasis [36,37].

Urinary tract infection

Stojanović *et al.* [38••] found 21% of children with UTI had hypercalciuria compared with 7% in normal children; of these hypercalciuria was seen in 10% of children with first UTI and in 44% with recurrent UTI. Similarly, Biyikli *et al.* [39] found 43% of children with recurrent UTI had hypercalciuria. On the contrary, in children with symptomatic idiopathic hypercalciuria, Vachvanichsanong *et al.* [40] found 40% to have a UTI, of which 78% were recurrent. 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 [40]. In another study of children with recurrent UTIs [41], normal urinary tracts and idiopathic hypercalciuria, no further UTIs occurred in 95% following normalization of urinary calcium excretion.

Decreased bone density

In children, Penido *et al.* [42,43] identified a low bone mineral density in 35% of children with idiopathic hypercalciuria, and this was more marked in hypercalciuric children with hypocitraturia. Schwaderer *et al.* [44••]

recently have shown that children with hypercalciuria have decreased bone mineral content, and this is more marked in children with stones. Gomes *et al.* [45•] found a high expression of receptor activator of nuclear factor κB ligand (RANKL) and a low expression of transforming growth factor-β in transiliac bone biopsies from patients with idiopathic hypercalciuria compared with controls, suggesting a role of increased bone resorption and delayed mineralization in hypercalciuria. Garcia-Nieto *et al.* [46] made the observation of a negative linear correlation between age and bone mineral content in children with idiopathic hypercalciuria. Freundlich *et al.* [47] showed reduced bone mineral density in children with hypercalciuria, and also identified a high incidence of both hypercalciuria and reduced bone mineral density in their asymptomatic mothers. These two studies raise the possibility that adult osteoporosis might have its origin in childhood. The natural course of hypercalciuria-associated low bone density warrants further evaluation.

Management of hypercalciuria

In children with symptomatic hypercalciuria it is important to conduct a formal evaluation for assessment of cause and severity of hypercalciuria, which will guide subsequent dietary and pharmacological therapy.

Evaluation

In clinical situations in which hypercalciuria can be attributed to play a pathological role, a timed urine collection should be obtained for creatinine, calcium, sodium, potassium and citrate. In cases in which it is difficult to collect timed urine samples, random urine samples may be used. The urine samples should ideally be evaluated when the child is free of stones and infection and is on his usual diet. One must be cognizant of two facts: traditional statistical cut-offs of more than 4 mg/kg/day or urine calcium/creatinine ratio more than 0.21 are influenced by diet, ethnicity, age and region, and this has been critically addressed by Butani and Kalia [48], and random urine samples do not always correlate strongly with a 24-h urine collection as shown by Koyun *et al.* [49•]. Before hypercalciuria is labeled as idiopathic, one must consider the possibility of a secondary cause. The rare monogenic disorders and the underlying mechanism for development of secondary hypercalciuria have been recently reviewed in two reviews (Table 1) [13,50••]. An evaluation for secondary disorders should be considered in the presence of positive family history, failure to thrive, growth retardation, rickets, acid–base disturbances, renal dysfunction, proteinuria, electrolyte imbalance, dysmorphic features or poor response to therapy.

Diet in hypercalciuria

Urinary calcium excretion is significantly affected by sodium, protein, potassium, phosphorus and calcium in the diet. There is a reproducible linear positive correlation between urinary sodium and calcium excretion in both stone formers and normal individuals [51]. One excretes ~1 mmol (or 40 mg) calcium for every 100 mmol (or 2.3 g) of sodium [52]. Studies have shown urinary calcium increases when dietary sodium intake is increased from 50 to 300 mmol/day [51]. Breslau *et al.* [53] found mean urinary calcium excretion to increase from 110 to 167 mg/day by daily supplementation of 240 mEq of sodium. In contrast, potassium supplementation at 1 mEq/kg/day has been shown to decrease calcium excretion in children with hypercalciuria [54]. Dietary potassium exists as potassium salts of organic anions in vegetables and fruits [55]. Thus, limiting excessive sodium and supplementing potassium in diet is important in management of hypercalciuria, when normal renal function is present. We recommend a diet that is not

Table 1 Conditions associated with secondary hypercalciuria

Renal hypercalciuria	Absorptive hypercalciuria (GI)	Resorptive hypercalciuria (OS)	Unknown
Proximal tubule	Blue diaper syndrome	Infantile hypophosphatemia	Beckwith–Wiedeman syndrome
Dent's disease	Down's syndrome	McCune–Albright syndrome	β-Thalassemia
Hereditary hypophosphatemic rickets with hypercalciuria	Congenital lactase deficiency	MEN1 syndrome	Cystic fibrosis
Glycogen storage disease type 1a	Congenital sucrase–isomaltase deficiency	Metaphyseal chondrodysplasia Jansen type	Phenylketonuria
Lowe oculocerebrorenal syndrome	Glucose/galactose malabsorption	Neonatal self-limited primary hypoparathyroidism	
Tyrosinemia type 1	Hypophosphatemia and absorptive hypercalciuria		
Wilson's disease	Hypoabsorptive hypercalciuria		
Loop of Henle	Williams–Beuren syndrome		
Bartter syndrome type 1–5			
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis			
Autosomal dominant hypocalcemia			
Distal tubule			
Pseudohypoaldosteronism, type II			
Distal renal tubular acidosis			
Liddle's syndrome			

Adapted from [13,50••].

excessive in salt (2.0–2.4 g sodium/day) and supplemented with at least the recommended daily allowance of five to six servings of fruits and vegetables (3.0–3.5 g potassium/day). Compliance with these dietary recommendations can be assessed by measuring urine Na/K ratio, which should be less than 2.5.

An increase in dietary protein intake increases net acid excretion, which in turn increases urinary calcium excretion [55]. Urinary calcium excretion has been shown to correlate directly with the level of dietary protein intake [56]. The increment in urinary calcium excretion is ~0.04 mmol (~1.6 mg) Ca/g protein. The increase in calcium excretion with dietary protein is more marked in calcium stone formers than in healthy individuals [18,57]. Polito *et al.* [58•] found a significant interaction between urinary urea (protein intake) and sodium (salt intake) in increasing urinary calcium in hypercalciuric children. Protein restriction is not suggested in children as it could impair growth. A dietary restriction of calcium is not recommended in children with hypercalciuria, as it puts the growing child at risk for negative calcium balance and poor bone mineralization, and also increases urinary excretion of oxalate from increased gastrointestinal absorption of oxalate.

Anticalciuric diuretics

Thiazide diuretics that decrease urinary calcium excretion have been widely used in children with hypercalciuria. Medications should be used once dietary modifications have failed to normalize urinary calcium excretion and/or symptoms attributable to hypercalciuria persist. Chlorothiazide 15–25 mg/kg/day or hydrochlorothiazide 1.5–2.5 mg/kg/day can be used. Although the precise mechanism for thiazides is not known, it is proposed that thiazide-induced volume contraction increases paracellular calcium absorption in proximal tubules, though a transcellular calcium transport in distal tubule is also suspected [59]. Recently Jiang *et al.* [60••] showed that WNK4 enhances TRPV5-mediated Ca^{2+} uptake and inhibits thiazide-sensitive Na^{+}–Cl^{-} cotransporter (NCC), and the positive effect of WNK4 on TRPV5 could be blocked by increasing NCC in a dose-dependent fashion. Children on long-term thiazide diuretics need to be monitored for dyselectrolytemia, hyperlipidemia and hyperglycemia. Thiazides are the drug of choice in monogenic disorders associated with severe hypercalciuria such as Dent's disease, Bartter type 5 from activating mutations in *CASR*, pseudohypoaldosteronism type II with *WNK4* gene mutation, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, and others [60••,61–63].

Potassium citrate

Citrate in urine is well known to have an inhibitory role in calcium stone formation [64,65]. In randomized controlled studies, citrate therapy has been shown to be beneficial in adults with stones [66–68]. In children, citrate therapy has been shown to decrease recurrence of new stones, growth of residual stone fragments following lithotripsy and in stone-forming children with hypocitraturia [69,70]. In a preliminary study in nine healthy children, treatment with potassium citrate at 0.5 or 1 mEq K/kg/day resulted in an increase in urinary citrate excretion, but the higher dose also caused a significant increase in urine pH [71]. Indeed there is a concern that the increase in urine pH observed with citrate therapy may promote urinary supersaturation of calcium phosphate, thus defeating the purpose of treatment. It appears that urinary citrate is important in protecting hypercalciuric children from stone formation [72]. Potassium citrate is being used more often as the first line of drugs, given fewer adverse effects, although it has not been examined sufficiently to date, but should be the drug of choice in children with renal tubular acidosis.

Others

Neutral phosphate salts are to be used in children in whom hypercalciuria is secondary to severe tubular phosphate leak in rare disorders involving phosphate reabsorption in the proximal tubule, such as hypophosphatemic rickets with hypercalciuria, Lowe syndrome, and other disorders [73]. Drugs such as sodium cellulose phosphate, a nonabsorbable ion-exchange resin, used for complexing intestinal calcium are not to be used in children as they increase the risk for negative calcium balance. Alendronate, a bisphosphonate drug, decreases urine calcium excretion in genetic hypercalciuric stone-forming rats on a low calcium diet, suggesting a role for bone in development of hypercalciuria [74]. Bisphosphonates were shown to be beneficial in adults with hypercalciuria [75–77]. Freundlich and Alon [78••] published the first case series of seven children with osteopenia and hypercalciuria in whom bisphosphonates normalized urinary calcium excretion, improved bone mineral content and urinary symptoms.

Summary

Our understanding of calcium handling by the kidney and development of hypercalciuria has much improved over the past decade from studying rare inherited renal tubular disorders, and hopefully large population-based genetic studies will allow us to better understand the 'polygenic' trait of idiopathic hypercalciuria. Hypercalciuria can be controlled in most cases with dietary modifications and/or drug therapy with potassium citrate and/or thiazides. It is our belief that for now drug therapy should be reserved for children with symptomatic hypercalcuria and/or rare monogenic disorders. At present anticalciuric therapy in children is not based on strong

evidence-based medicine but more on clinical observation, and needs to be studied prospectively.

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