

## Treatment strategies for pediatric idiopathic hypercalciuria

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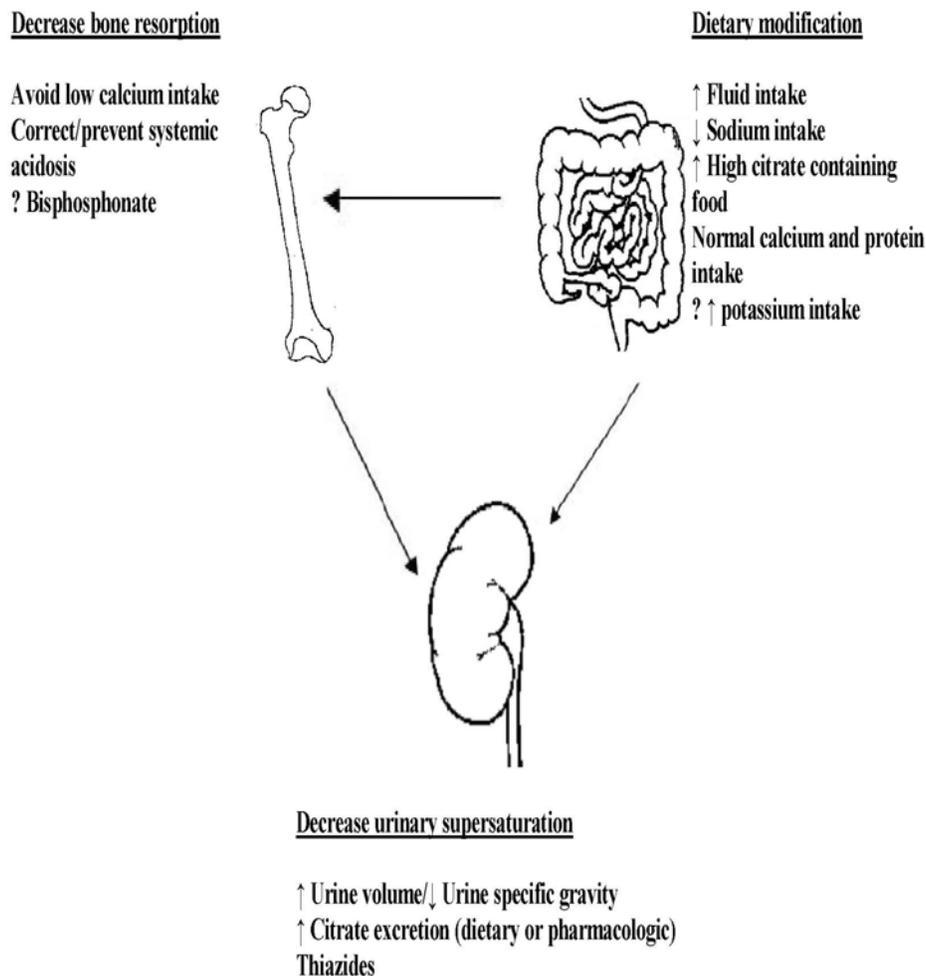
### 1. ABSTRACT

Idiopathic hypercalciuria (IH) is a common metabolic disorder in children and is associated with the development of renal calculi, nephrocalcinosis, hematuria and osteopenia. The effect of various dietary modifications and available pharmacologic therapies on reducing urinary calcium excretion and/or urinary supersaturation is discussed in this article. The importance of a multidisciplinary approach involving the patient, their families, and health-care professionals is also addressed.

### 2. INTRODUCTION

IH was initially thought to be either due to increased intestinal calcium absorption (absorptive hypercalciuria) or from the impairment of renal tubular reabsorption of calcium (renal hypercalciuria) (1). However, it is now apparent that the previously described sub-types of IH are parts of a spectrum of a single disease (2), with an additional contribution of bone demineralization to excessive urinary calcium excretion. Therefore, the management of children with IH of either

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**Figure 1.** Potential sites of action of different treatment modalities in pediatric idiopathic hypercalciuria

sub-type is the same and we will not separate the discussion of treatment strategies into absorptive or renal hypercalciuria. The main goal of treatment in children with IH is to decrease their risk of future stone formation by reducing urinary calcium oxalate supersaturation and to improve/maintain bone mineralization. As depicted in Figure 1, a variety of approaches, often in combination, are necessary to achieve these aims. (Figure 1)

### 3. DIETARY MODIFICATIONS

Dietary modifications are the mainstay of initial therapy for IH in children. Dietary changes alone may not always be successful, but inadequate dietary control will almost always diminish the clinical efficacy of other adjunctive medical therapies.

#### 3.1. Fluid: Increasing fluid intake is probably the single most important intervention

As data from adult studies has demonstrated that increasing fluid intake reduces the risk of stone formation (3-6), fluid intake has been viewed as the most crucial component of management of IH in both adults and

children. Although it has been recommended that fluid intake be adjusted to produce a daily urinary volume of at least 2 liters in adults who are at risk of calcium stone recurrence (7), no similar clinical guidelines have been developed or validated for children. In one pediatric study, the authors recommended that children with IH consume fluid to about 1- 1 ½ times their usual maintenance requirement (8). In adolescents, targeting a 24-hour urinary volume of more than 2 liters has also been advocated (9). An alternative approach has been to monitor and keep urinary specific gravity of children with IH below 1.010, as a surrogate marker of determining the adequacy of fluid intake (10). Although increasing the urine volume will not decrease urinary calcium excretion, diluting the urine offers the benefit of decreasing urinary supersaturation and the chance of stone formation.

Specific beverages that may reduce the risk of recurrent nephrolithiasis, based on adult data, include orange juice and lemonade (11-14). Whether there is a benefit to specifically timing and spacing fluid intake through the day or specifically at night is still controversial.

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**Table 1.** Recommendations to reduce sodium (salt) intake include the following

|  |
|--|
| <ul style="list-style-type: none"><li>• Avoid eating out, especially in fast food restaurants.</li><li>• Look at food labels when buying groceries and avoid foods with high salt content.</li><li>• Cook using fresh ingredients whenever possible.</li><li>• If need arises to cook with items having high salt content such as canned foods, drain the water from can and rinse before cooking.</li><li>• Use little or no salt during food preparation. Use less than recipe recommended amount of salt.</li><li>• Use salt alternatives such as pepper, herbs, non-sodium seasonings.</li><li>• Avoid adding extra salt by removing the saltshaker from the dining table.</li></ul> |
|--|

### 3.2. Calcium: Restricting calcium intake in children is not recommended

Avoiding an excessively high-calcium diet has been suggested in adult calcium stone formers in the past (15,16); such recommendations are no longer widely practiced and are, in fact, not advisable. Extensive urinary renal losses of calcium may have already occurred in patients with IH, even children, causing them to become osteopenic (17). Moreover, evidence demonstrates that any theoretical benefit of adopting a severely low calcium diet is countered by the occurrence of absorptive hyperoxaluria (18), actually increasing the risk of stone formation. Patients with IH who have a dietary calcium intake less than the Daily Recommended Intake (DRI) may even need to be on calcium supplementation to counteract the detrimental effects from their being in a state of negative calcium balance (4,19). Interestingly, there is growing epidemiologic evidence that suggests that a higher calcium intake may actually also reduce the risk of stone formation (3-5,20). In a prospective trial involving 45,619 men at risk of nephrolithiasis, dietary calcium intake was inversely associated with the risk of kidney stone formation (3). In another study on the association between intake of dietary and supplemental calcium and the risk of nephrolithiasis in women, high intake of dietary calcium again appeared to have protective effect against stone formation (4). A recent follow up study from the same group suggested that within the adult population, the effects of dietary factors on the risk of stone formation vary with age; hence, whether the results from these adult studies can be extrapolated to children remains to be determined (21). Also, a recent randomized study in healthy men showed that a high calcium diet alone, without concomitant modification of other dietary factors, offered little benefit in reducing stone formation (22).

At our center, we recommend keeping dietary calcium intake for children with IH at or slightly above the DRI (600-800 mg/day in prepubertal children). For children with IH who have low bone mineral density, calcium supplementation with calcium citrate is recommended. This combination has been suggested to be the most effective in limiting the new stone formation rate for those who require calcium supplements (23).

### 3.3. Sodium: Should be restricted in the diet

Increased sodium intake has been observed to be associated with higher urinary calcium excretion in adults with IH (24-26). Conversely, reduction in dietary sodium intake has been shown to decrease urinary calcium excretion (24,26). Renal tubular handling of calcium has been studied in settings of extra-cellular fluid volume

expansion using hypertonic saline (27). In that setting, calcium reabsorption is inhibited in the proximal tubule leading to hypercalciuria. The risk of nephrolithiasis on a high sodium diet was evaluated in 14 normal subjects (28). Increasing dietary sodium intake from 50 mmol/day to 300 mmol/day significantly increased urinary calcium (from  $2.73 \pm 1.03$  to  $3.93 \pm 1.51$  mmol/day) and decreased urinary citrate (from  $3.14 \pm 1.19$  to  $2.52 \pm 0.83$  mmol/day). In another study, daily urinary calcium excretion was shown to increase on average from 110 mg/day to 167 mg/day by daily supplementation of 240 mEq of sodium (29). Hence, excessive salt intake may increase the risk of nephrolithiasis by increasing urinary calcium excretion and decreasing urinary citrate. Although there are no definitive guidelines available on how restrictive to be with dietary sodium intake in children with IH, at our center we recommend that such children limit their daily intake of sodium to less than 2 grams (30). Patients and their families should be made aware that most snacks and fast food items contain a considerable amount of sodium. Similarly, many prepared foods, including canned soups and cold meats, also have large amounts of sodium. Table 1 depicts some dietary recommendations to keep sodium intake low. (Table 1)

### 3.4. Animal protein: Although restricting animal protein may be beneficial, it is rarely indicated in growing children

Animal proteins have high methionine and cystine content. The sulphur in methionine and cystine generate sulphates when oxidized. The sulphates then increase urinary calcium excretion by complexing with intra-luminal calcium and preventing it from being absorbed. Urinary calcium excretion has been shown to correlate directly with the level of dietary protein intake (31). In a metabolic study, adult men were given a diet that provided either 12 grams or 36 grams of nitrogen per day. All subjects were maintained on approximately 1400 mg of dietary calcium per day. Urinary calcium excretion was significantly higher in subjects receiving the high nitrogen diet (191 mg/day versus 277 mg/day). In a recent randomized trial that was designed to determine the relative efficacy of 2 different diets in preventing recurrence of stone formation in adult men with IH, restricted intake of animal protein and salt, combined with a normal calcium intake, provided greater protection than a traditional low-calcium diet (20). There is also evidence showing that moderate protein restriction in hypercalciuric patients reduces urinary excretion of calcium and bone resorption via a decrease in exogenous acid load (32). In spite of these benefits to animal protein restriction, excessive restriction

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of animal protein in growing children cannot be encouraged due to the potential for growth retardation.

### **3.5. Potassium: May reduce renal calcium excretion but requires further data before it can be recommended**

The role of potassium in the management of IH has been studied both in adults and in children. Hypercalciuric children have been known to have decreased fractional excretion of potassium in the urine (33). Cirillo et al. found a high urine sodium to potassium ratio in adult stone formers compared to healthy non-stone formers (34). Furthermore, administration of potassium supplementation to healthy adults was shown to reduce urinary calcium excretion (35), suggesting that potassium may promote renal calcium retention and reduce hypercalciuria. Observational studies in adults also support a possible protective effect of dietary potassium intake on stone risk (7). Similar observations were noted in 11 children with IH who were treated with potassium supplementation (potassium at 1 mEq/kg/day), in that the urine calcium to creatinine ratio decreased from  $0.31 \pm 0.10$  to  $0.14 \pm 0.07$  (36). These data suggest that diets containing more potassium may rectify a negative calcium balance and thus be beneficial to children with IH. However, randomized controlled trials are still lacking and the optimal dose for potassium supplementation is not known.

## **4. PHARMACOLOGICAL TREATMENTS**

### **4.1. Thiazide diuretics: Useful but not without risks and side effects**

Thiazides are currently the most widely used medical therapy for patients with IH. Although the precise mechanism for the hypocalciuric effect of thiazides is still debatable, recent evidence shows that thiazides induce passive paracellular calcium reabsorption in the proximal tubule via volume contraction (37). In a randomized study of 175 adult patients in Japan, trichloromethiazide treatment significantly reduced hypercalciuria and the rate of stone-formation (38). Thiazides, in addition to their hypocalciuric effect, also reduce intestinal calcium absorption; the net result, however, remains induction of a positive calcium balance (39). Long-term use of thiazides, therefore, as might be expected, is associated with favorable effects on bone mass in hypercalciuric osteoporotic men and reduces the risk of hip fractures (40,41). This hypocalciuric effect is reduced if sodium intake is not limited. Since thiazide diuretics can cause side effects such as weakness, nausea, dyslipidemia and electrolyte abnormalities, especially hypokalemia and hyponatremia, they should be used judiciously. In the authors' practice, thiazide use is restricted to children with IH who have a history of nephrolithiasis, especially if recurrent, or in the setting of recurrent painful hematuria.

### **4.2. Citrate: Provides protection by reducing urinary supersaturation**

Citrate is a useful alternative therapy in children with IH. It decreases the risk of stone recurrence by binding to urinary calcium and forming soluble calcium-citrate complexes. Various preparations containing citrate are available such as potassium citrate or potassium-

magnesium citrate; the sodium salt of citrate should be avoided due to salt load that is associated with it. Also, potassium rich citrus fruits and juices, such as oranges, grapefruit, and cranberries, are recommended. Orange juice, for example, has high content of natural potassium citrate. Lemon juice also has very high citrate content, so lemonade made from real lemon juice is recommended. Long-term use of potassium citrate also increases bone mineral density (42), and may prevent age-related bone loss in adult patients (43). Those effects may be due to its alkaline effect, preventing acid-related bone resorption. Due to its safety and lack of side effects, citrate supplementation may become the first line therapy in children with IH who are deemed candidates for pharmacological intervention. However, some children continue to have recurrence of renal stones after correction of hypercalciuria with potassium citrate. It has been hypothesized that citrate therapy, by elevating the urine pH, may predispose patients to develop calcium-phosphate stones, which precipitate in an alkaline environment. Researchers have just finished recruiting hypercalciuric children to study the effect of citrate on urine chemistries and acid-base balance (44).

### **4.3. Bisphosphonates: Very limited data available to date**

Bisphosphonates are analogues of pyrophosphate with a high affinity for the hydroxyapatite matrix in bone, especially in areas of rapid turnover and bone resorption. Data on the use of bisphosphonates, which reduce bone resorption via inhibition of osteoclast activation, for the treatment of IH are still very limited. Animal studies have shown that alendronate decreases urinary calcium excretion in genetic hypercalciuric rats, supporting the role of bone as a major contributor to urinary calcium excretion in IH (45). To our knowledge, the only 2 published human studies of bisphosphonates in patients with IH are in adults and both have shown a decrease in urinary calcium excretion and increase in bone mineral density (BMD) in the treated subjects (46,47). In 7 young adult men, mean lumbar spine BMD increased significantly by  $2.6 \pm 1.0\%$  in the first year after treatment with etidronate (46). Using a model of bed rest immobilization in 16 male subjects, alendronate significantly inhibited bone mineral loss and averted the hypercalciuria in the treatment group (47). However, due to lack of adequate experience with bisphosphonates in children, and their possible side effects such as osteonecrosis of jaw (48,49), the use of bisphosphonates in children with IH needs to be studied before their use becomes more widespread.

## **5. MANAGEMENT ISSUES: TEAM APPROACH**

### **5.1. Dietitian**

Since dietary modification is a crucial and mandatory part of a successful management strategy, children with IH should be referred to a dietitian to accurately assess dietary intake of calcium and sodium. Because of the concerns regarding bone growth, no child should receive less than the DRI of calcium. Reduction of sodium intake and judicious animal protein restriction also

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facilitates lowering of urinary calcium excretion and goes long ways in preventing recurrent stone formation.

### 5.2. Pediatric nephrologist

Children with IH should be followed at regular intervals by a pediatric nephrologist. Growth parameters should be followed in all children and BMD should be measured if there is any suspicion of demineralization. Random urine calcium to creatinine ratio or timed 24-hour urinary collections for calcium excretion should be monitored at 6-month intervals. If dietary control, by itself, is not able to induce symptomatic relief and reduce recurrent stone formation, pharmacotherapy should strongly be considered. As pharmacological treatments are not without side effects, serum electrolytes and lipid panels should be followed closely in children on therapy with thiazides.

### 5.3. Patients and families

Patient involvement is very important in the treatment of IH. Children and their families should be encouraged to be an intrinsic part of the team. The patient should be educated on the nature of the disorder including the associated symptoms, complications and prognosis. The rationale behind the dietary modifications and the indications for pharmacologic interventions should also be explained. Motivated patients who understand the significance of prolonged treatment are more likely to adhere in the long run to the individualized preventive program designed.

## 6. PROGNOSIS

Children with IH are at increased risk of developing urinary stones. The vast majority of children diagnosed with IH do extremely well. They normally have preserved renal function and can have symptom-free lives with appropriate management. However, in some cases, life-long therapy is required.

## 7. SUMMARY AND PERSPECTIVES

Treatment goals in IH are to decrease urinary supersaturation and to promote a positive calcium balance with the ultimate goal of decreasing the risk of stone formation and improving bone mineral density. This can best be accomplished by an increased fluid intake and low-salt diet; pharmacotherapy consisting of thiazides diuretics and/or potassium citrate may be necessary in some cases. However, since none of the medications are without side effects, in view of the additional benefits offered by high fluid and low sodium in the diet of children, it seems reasonable to emphasize dietary modification as the primary treatment.

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**Abbreviations:** IH: idiopathic hypercalciuria; DRI: daily recommended intake; BMD: bone mineral density

**Key Words** Idiopathic hypercalciuria, Children, Dietary modifications, Pharmacological treatment, Bone demineralization

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