Chapter 5
Medical Management of Hypercalciuria

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Introduction

Nearly 80 % patients with nephrolithiasis have calcium-based stones. Hypercalciuria is the most common metabolic abnormality in calcium stone formers, with about 50 % of patients with stone disease demonstrating the trait. It may be defined as >250 mg/day of urine calcium in females and >300 mg/day in males. However, the risk of stones increases as urine calcium excretion increases even at values below these thresholds, suggesting that urine calcium should be considered a linear function, rather than a binary "normal" vs. "high." Increasing urine calcium concentration alters the urinary supersaturation of calcium oxalate and calcium phosphate and is thus directly linked to increased risk of calcium stone disease [1].

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Etiology

The most common etiology of hypercalciuria is genetic hypercalciuria, often termed idiopathic hypercalciuria. Approximately 50 % of first degree relatives of a patient with hypercalciuria without an apparent systemic cause will also demonstrate hypercalciuria, suggesting an autosomal dominant pattern of inheritance, though the trait appears to be polygenic. A careful history and a high index of suspicion may help guide further evaluation or will help eliminate secondary causes of increased urinary calcium excretion including:

- Primary hyperparathyroidism—a normal serum calcium generally excludes this diagnosis, but a high index of suspicion is necessary for subtle cases.
- Vitamin D excess—exogenous vitamin D, granulomatous disease (sarcoidosis, lymphoma, tuberculosis).
- Hyperthyroidism—it is also important to make sure that in the setting of thyroid replacement therapy, the doses remain appropriate over time.
- Renal Tubular Acidosis—the diagnosis is suggested by a low serum bicarbonate concentration.
- Vitamin A toxicity
- Medication use
  - Corticosteroids, acetazolamide, topiramate
- Immobility
- Paget's disease
- Genetic/congenital abnormalities [2]
  - Calcium sensing receptor (CaSR) mutations
  - Dent's disease (chloride channel 5 mutations)
  - Bartter's syndrome (mutations in multiple genes affecting ion transport in the ascending limb of the loop of Henle)
  - Liddle's syndrome (ENaC mutations)
  - Hereditary hypophosphatemic rickets with hypercalciuria
  - Medullary sponge kidney
  - Beckwith—Weidmann syndrome
  - Familial hypomagnesemia (claudin 16, claudin 19 mutations)
  - Osteogenesis imperfecta type 1

Diagnosis

The diagnosis of hypercalciuria is established with at least one 24-h urine collection demonstrating excess calcium excretion [1] as defined by at least one of the following:

- An absolute value of greater than 250 mg of calcium per day in females or >300 mg of calcium per day in males. Even values significantly below these "thresholds" however may be worth lowering in patients with recurrent stones.
- Urinary calcium excretion of greater than 4 mg/kg of body weight.
- Urinary calcium excretion of greater than 140 mg/g creatinine.

Definitions based on factoring calcium excretion for body weight or creatinine excretion may be useful in children and older people or others with reduced muscle mass.

Complications

In addition to risk of stone disease, hypercalciuria carries with it a risk of bone demineralization and osteoporosis [3].

- Hypercalciuric patients often excrete more calcium than they absorb leading to a negative calcium balance and bone loss.
- Bone mineral density is inversely correlated with degree of hypercalciuria in both male and female hypercalciuric stone formers (but not non-stone formers).
- Stone formers have a higher incidence of both vertebral and long bone fracture compared to non-stone formers in multiple epidemiological studies.
- Consider performing Dual Emission X-ray Absorptiometry (DEXA) in patients with hypercalciuria, particularly post-menopausal women and either gender with a family history of osteoporosis or bone fracture.

Treatment

General Considerations

Hypercalciuria portends a risk of kidney stone formation. General kidney stone prevention guidelines apply to patients with hypercalciuria including

- High fluid intake to yield at least 2–2.5 L of urine volume.
- Sodium restricted diet of less than 2,000–2,300 mg per day.
- Moderation of animal protein intake to 0.8–1 g/kg per day.
- Avoidance of calcium supplements and age-appropriate intake of dietary calcium (1,000 mg of elemental calcium between the ages of 19 and 50, 1,200 mg in patients older than 50 years).

Pharmacological Treatment of Hypercalciuria

Treatment of hypercalciuria to decrease supersaturation for calcium oxalate and calcium phosphate decreases the risk of recurrent nephrolithiasis. Given the linear nature of urine calcium excretion, applying these therapies only to patients meeting the threshold definitions of hypercalciuria discussed above may be too restrictive and will preclude giving effective therapy to all those who may benefit. As discussed below, thiazides have been shown to prevent stones even in patients who do not meet these threshold definitions of hypercalciuria.

General Indications for Pharmacological Treatment

- Clinical or radiological evaluation showing worsening stone disease on conservative treatment after first episode of symptomatic stone and evidence of hypercalciuria on metabolic evaluation.
- Multiple stones detected on imaging with evidence of hypercalciuria with or without clinical symptoms.

- Can be strongly considered in first time stone former with evidence of higher magnitudes of hypercalciuria on metabolic evaluation.
- Osteopenia or osteoporosis.

Pharmacotherapy

Thiazide Diuretics

Mechanism of Action

- Thiazides block sodium reabsorption in distal convoluted tubule leading to natriuresis, mild extracellular volume depletion, and a consequent upregulation of calcium absorption in proximal tubule. In addition there might be a component of direct enhancement of calcium absorption in the distal nephron.
- Thiazides cause increased excretion of certain inhibitors of crystallization like magnesium, zinc, and pyrophosphate. In addition, long-term use may reduce urine oxalate levels.

Efficacy

1. Reducing Hypercalciuria:
   - In experimental studies, indapamide and hydrochlorothiazide (HCTZ) were shown to result in up to 50 % reduction in 24-h calcium levels in patients with idiopathic hypercalciuria [4, 5].
   - Indapamide caused a 48 % reduction in 24-h calciuria in a larger clinical trial.
2. Reducing Stone recurrence:
   - Current evidence indicates that HCTZ in doses of 50 mg/day [6], chlorthalidone 25–50 mg/day, and indapamide 2.5 mg/day are effective in reducing stone recurrences in patients with or without hypercalciuria at baseline [7].

Individual Medications

1. Hydrochlorthiazide
   - Starting dose may be 25 mg but goal dose for treatment with HCTZ is 50 mg/day or 25 mg bid. Note that it is higher than doses used commonly for treatment of hypertension.
   - The hypocalciuric effect of HCTZ is dose dependent. Though doses up to 200 mg/day have been used in the clinical trials, these are limited by metabolic abnormalities associated with thiazides like hypokalemia, hypomagnesemia, and metabolic alkalosis.
   - HCTZ is also available as a combination tablet with amiloride: 50 mg HCTZ with 5 mg amiloride. An effective dose is often ½ tablet twice a day.
2. Chlorthalidone
   - Chlorthalidone has significantly longer half-life allowing for once daily dosing. It can be used in doses of 25–50 mg/day and is equivalent in hypocalciuric efficacy to HCTZ.
   - May have greater hypokalemic effect than HCTZ and require increased potassium supplementation.
3. Indapamide
   - Indapamide is typically used in doses of 2.5 mg per day. Limited data from smaller studies have shown a trend towards better metabolic profile (less hyperuricemia, hypokalemia) and lesser effect on urine citrate reduction than HCTZ.

Adverse Effects

Well-recognized dose dependent adverse effects include metabolic abnormalities such as hypokalemia, mild increases in blood glucose, hyperlipidemia, hyperuricemia, and hypomagnesemia. Mild increases in serum calcium have also been noted. By causing potassium depletion, thiazides cause a reduction in urine citrate levels, and thus the effect

on supersaturation of calcium salts may not parallel the hypocalciuric effect [8]. Supplementation with potassium citrate therefore is usually recommended, as citrate excretion is corrected, and hyperglycemia may be prevented. Even potassium chloride supplementation will help maintain citrate excretion. The systemic blood pressure lowering is generally a welcome effect, but can be dose limiting in the healthy young person.

Alkali Therapy in Hypercalciuria

Mechanism of Action

- An alkali load reliably increases urine pH by increasing excretion of the bicarbonate ion. Citrate is converted to bicarbonate by the liver and ultimately the increased serum bicarbonate concentration decreases reabsorption of citrate by the proximal tubule.
- An alkali load may also have an independent mechanism in lowering urine calcium excretion by lowering bone turnover.

Individual Medications

Potassium Citrate

Use

Potassium citrate should be used in situations where thiazide treatment is compounded by hypokalemia or if hypocitraturia is also present. Patients with concurrent hypocitraturia with hypercalciuria should be started on combined therapy at the beginning of treatment.

The initial dose of potassium citrate can be 10 meq 2 or 3 times a day with up to 60 meq/day. Dose can be titrated based on serum potassium concentration and urine pH. Doses up to 100 meq may be required in certain situations particularly with high doses of thiazides, or resistant hypokalemia.

Sodium Potassium Citrate

While the alkali loading effect of a mixed sodium/potassium citrate is similar, the sodium load may blunt the beneficial antilithogenic response of therapy.

Potassium Magnesium Citrate

Potassium magnesium citrate has been shown to be effective in decreasing the rate of calcium oxalate stone formation, as well as in the treatment of thiazide-induced hypokalemia, hypocitraturia, and concomitant hypomagnesemia. Trial data suggest an initial dose equivalent to 14 meq of potassium, 6 meq of magnesium, and 18 meq of citrate three times daily.

Adverse Effects

Gastrointestinal upset is common. If urine pH > 6.5, potentially increased risk for calcium phosphate stone formation may result. However, the effect of citrate to inhibit calcium stone formation makes this a rare event.

Neutral Phosphates

Mechanism of Action

Neutral phosphates can lower the calcitriol levels and reduce absorption of calcium from the gut, reducing urinary calcium excretion. Levels of urinary pyrophosphate, an inhibitor of calcium crystallization may also increase with therapy.

Efficacy

Potassium phosphate (elemental phosphate of about 600 mg) in divided doses can cause a 30–35 % sustainable reduction in 24 h urine calcium. While no long-term clinical trial data on preventing stone recurrence exist, neutral phosphates can be

considered as an alternative in case of thiazide ineffectiveness or intolerance, or in particularly recalcitrant cases. It is used infrequently.

Adverse Effects

Gastrointestinal symptoms limit widespread use.

Amiloride

Amiloride augments the hypocalciuric effect of thiazides [9] though there are no long-term data on stone recurrence rates. Combination therapy with thiazide may limit the hypokalemic and hypocitraturia effects of thiazides. Use of amiloride can also be considered in situations where clinical situation dictates the need for further natriuresis.

Management Issues

Duration of Treatment

- Generally treatment for hypercalciuria is lifelong as risks of stone formation and bone loss return to baseline with cessation of therapy. Trials off therapy with measurement of urine calcium excretion might be worthwhile in patients who have effectively reduced their sodium intake.
- If renal function declines during therapy, typically hypercalciuria will abate due to secondary hyperparathyroidism leading to reduced urine calcium excretion. Ongoing treatment can then be reconsidered.

Monitoring

- Periodic monitoring of serum electrolytes, creatinine, and 24-h urinary parameters is necessary to assure stability of both risk factors and the effects of therapy.

A 50 % reduction in urine calcium excretion is desirable but even lesser degrees of reduction are useful, especially when combined with increased urinary volume and citrate excretion. Our practice is to perform a 24-urine collection and a serum panel with creatinine and electrolytes every 12–24 months in all patients.

Bisphosphonates for Hypercalciuria

Mechanism of Action

Reduction of osteoclast resorption of bone may reduce release of calcium and reduce the kidneys' filtered load.

Use

Some data suggest that bisphosphonates are associated with reductions in urine calcium excretion in patients with hypercalciuria and might therefore reduce calcium stone incidence. Convincing evidence that stone formation is prevented is lacking. They may be useful adjuncts to therapy with or without thiazides, when low bone mineral density is present. They may be useful especially if thiazides are not well tolerated.

Individual Medications

Alendronate, risedronate, ibandronate, and zoledronic acid may all be useful and have not been compared for efficacy in reducing urine calcium excretion or preventing stones.

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