



**LEARNING OBJECTIVE:** Readers will evaluate hypercalciuria in the context of bone health

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# Idiopathic hypercalciuria: Can we prevent stones and protect bones?

## ABSTRACT

Idiopathic hypercalciuria increases the risk of urinary stones and osteoporosis. The aim of this review is to delineate our current understanding of idiopathic hypercalciuria in the context of bone health, specifically its definition, causes, epidemiology, laboratory evaluation, and potential treatments.

## KEY POINTS

Idiopathic hypercalciuria is common in patients with kidney stones and is also present in up to 20% of postmenopausal women with osteoporosis but no history of kidney stones.

Idiopathic hypercalciuria has been directly implicated as a cause of loss of trabecular bone, especially in men. But reversing the hypercalciuria in this condition has not been definitively shown to diminish fracture incidence.

Patients with kidney stones who have low bone mass and idiopathic hypercalciuria should increase their daily fluid intake, follow a diet low in salt and animal protein, and take thiazide diuretics to reduce the risk of further calcium stone formation. Whether this approach also improves bone mass and strength and reduces fracture risk in this patient group requires further study.

A 65-YEAR-OLD WOMAN WAS recently diagnosed with osteoporosis after a screening bone mineral density test. She has hypertension (treated with lisinopril), and she had an episode of passing a kidney stone 10 years ago. A 24-hour urine study reveals an elevated urinary calcium level.

What should the physician keep in mind in managing this patient?

## ■ IDIOPATHIC HYPERCALCIURIA

Many potential causes of secondary hypercalciuria must be ruled out before deciding that a patient has idiopathic hypercalciuria, which was first noted as a distinct entity by Albright et al in 1953.<sup>1</sup> Causes of secondary hypercalciuria include primary hyperparathyroidism, hyperthyroidism, Paget disease, myeloma, malignancy, immobility, accelerated osteoporosis, sarcoidosis, renal tubular acidosis, and drug-induced urinary calcium loss such as that seen with loop diuretics.

Idiopathic hypercalciuria is identified by the following:

- Persistent hypercalciuria despite normal or restricted calcium intake<sup>2,3</sup>
- Normal levels of parathyroid hormone (PTH), phosphorus, and 1,25-dihydroxyvitamin D (the active form of vitamin D, also called calcitriol) in the presence of hypercalciuria; serum calcium levels are also normal.

An alias for idiopathic hypercalciuria is “fasting hypercalciuria,” as increased urinary calcium persists and sometimes worsens while fasting or on a low-calcium diet, with in-

creased bone turnover, reduced bone density, and normal serum PTH levels.<sup>4,5</sup>

Mineral loss from bone predominates in idiopathic hypercalciuria, but there is also a minor component of intestinal hyperabsorption of calcium and reduced renal calcium reabsorption.<sup>6</sup> Distinguishing among intestinal hyperabsorptive hypercalciuria, renal leak hypercalciuria, and idiopathic or fasting hypercalciuria can be difficult and subtle. It has been argued that differentiating among hypercalciuric subtypes (hyperabsorptive, renal leak, idiopathic) is not useful; in general clinical practice, it is impractical to collect multiple 24-hour urine samples in the setting of controlled high- vs low-calcium diets.

### ■ COMPLICATIONS OF IDIOPATHIC HYPERCALCIURIA

Calcium is an important component in many physiologic processes, including coagulation, cell membrane transfer, hormone release, neuromuscular activation, and myocardial contraction. A sophisticated system of hormonally mediated interactions normally maintains stable extracellular calcium levels. Calcium is vital for bone strength, but the bones are the body's calcium "bank," and withdrawals from this bank are made at the expense of bone strength and integrity.

#### Renal stones

Patients with idiopathic hypercalciuria have a high incidence of renal stones. Conversely, 40% to 50% of patients with recurrent kidney stones have evidence of idiopathic hypercalciuria, the most common metabolic abnormality in "stone-formers."<sup>7,8</sup> Further, 35% to 40% of first- and second-degree relatives of stone-formers who have idiopathic hypercalciuria also have the condition.<sup>9</sup> In the general population without kidney stones and without first-degree relatives with stones, the prevalence is approximately 5% to 10%.<sup>10,11</sup>

#### Bone loss

People with idiopathic hypercalciuria have lower bone density and a higher incidence of fracture than their normocalciuric peers. This relationship has been observed in both sexes and all ages. Idiopathic hypercalciuria has been noted in 10% to 19% of otherwise healthy men

with low bone mass, in postmenopausal women with osteoporosis,<sup>10-12</sup> and in up to 40% of postmenopausal women with osteoporotic fractures and no history of kidney stones.<sup>13</sup>

### ■ LABORATORY DEFINITION

#### Urinary calcium excretion

Heaney et al<sup>14</sup> measured 24-hour urinary calcium excretion in a group of early postmenopausal women, whom he divided into 3 groups by dietary calcium intake:

- Low intake (< 500 mg/day)
- Moderate intake (500–1,000 mg/day)
- High intake (> 1,000 mg/day).

In the women who were estrogen-deprived (ie, postmenopausal and not on estrogen replacement therapy), the 95% probability ranges for urinary calcium excretion were:

- 32–252 mg/day (0.51–4.06 mg/kg/day) with low calcium intake
- 36–286 mg/day (0.57–4.52 mg/kg/day) with moderate calcium intake
- 45–357 mg/day (0.69–5.47 mg/kg/day) with high calcium intake.

For estrogen-replete women (perimenopausal or postmenopausal on estrogen replacement), using the same categories of dietary calcium intake, calcium excretion was:

- 39–194 mg/day (0.65–3.23 mg/kg/day) with low calcium intake
- 54–269 mg/day (0.77–3.84 mg/kg/day) with moderate calcium intake
- 66–237 mg/day (0.98–4.89 mg/kg/day) with high calcium intake.

In the estrogen-deprived group, urinary calcium excretion increased by only 55 mg/day per 1,000-mg increase in dietary intake, though there was individual variability. These data suggest that hypercalciuria should be defined as:

- Greater than 250 mg/day (> 4.1 mg/kg/day) in estrogen-replete women
- Greater than 300 mg/day (> 5.0 mg/kg/day) in estrogen-deprived women.

#### Urinary calcium-to-creatinine ratio

Use of a spot urinary calcium-to-creatinine ratio has been advocated as an alternative to the more labor-intensive 24-hour urine collection.<sup>15</sup> However, the spot urine calcium-to-creatinine ratio correlates poorly with 24-hour urine criteria for hypercalciuria whether

**40%–50% of patients with kidney stones have evidence of idiopathic hypercalciuria**

by absolute, weight-based, or menopausal and calcium-adjusted definitions.

Importantly, spot urine measurements show poor sensitivity and specificity for hypercalciuria. Spot urine samples underestimate the 24-hour urinary calcium (Bland-Altman bias  $-71$  mg/24 hours), and postprandial sampling overestimates it (Bland-Altman bias  $+61$  mg/24 hours).<sup>15</sup>

■ **WHAT IS THE MECHANISM OF IDIOPATHIC HYPERCALCIURIA?**

The pathophysiology of idiopathic hypercalciuria has been difficult to establish.

**Increased sensitivity to vitamin D?** In the hyperabsorbing population, activated vitamin D levels are often robust, but a few studies of rats with hyperabsorbing, hyperexcreting physiology have shown normal calcitriol levels, suggesting an increased sensitivity to the actions of 1,25-dihydroxyvitamin D.<sup>16</sup>

Another study found that hypercalciuric stone-forming rats have more 1,25-dihydroxyvitamin D receptors than do controls.<sup>17</sup>

These changes have not been demonstrated in patients with idiopathic hypercalciuria.

**High sodium intake** has been proposed as the cause of idiopathic hypercalciuria. High sodium intake leads to increased urinary sodium excretion, and the increased tubular sodium load can decrease tubular calcium reabsorption, possibly favoring a reduction in bone mineral density over time.<sup>18-20</sup>

In healthy people, urine calcium excretion increases by about 0.6 mmol/day (20–40 mg/day) for each 100-mmol (2,300 mg) increment in daily sodium ingestion.<sup>21,22</sup> But high sodium intake is seldom the principal cause of idiopathic hypercalciuria.

**High protein intake**, often observed in patients with nephrolithiasis, increases dietary acid load, stimulating release of calcium from bone and inhibiting renal reabsorption of calcium.<sup>23,24</sup> Increasing dietary protein from 0.5 to 2.0 mg/kg/day can double the urinary calcium output.<sup>25</sup>

In mice, induction of metabolic acidosis, thought to mimic a high-protein diet, inhibits osteoblastic alkaline phosphatase activity while stimulating prostaglandin E2 production.<sup>26</sup> This in turn increases osteoblastic

expression of receptor activator for nuclear factor kappa b (RANK) ligand, thereby potentially contributing to osteoclastogenesis and osteoclast activity.<sup>26</sup>

Decreasing dietary protein decreases the recurrence of nephrolithiasis in established stone-formers.<sup>27</sup> Still, urine calcium levels are higher in those with idiopathic hypercalciuria than in normal controls at comparable levels of acid excretion, so while protein ingestion could potentially exacerbate the hypercalciuria, it is unlikely to be the sole cause.

**Renal calcium leak?** The frequent finding of low to low-normal PTH levels in patients with idiopathic hypercalciuria contradicts the potential etiologic mechanism of renal calcium “leak.” In idiopathic hypercalciuria, the PTH response to an oral calcium load is abnormal. If given an oral calcium load, the PTH level should decline if this were due to renal leak, but in the setting of idiopathic hypercalciuria, no clinically meaningful change in PTH occurs. This lack of response of PTH to oral calcium load has been seen in both rat and human studies. Patients also excrete normal to high amounts of urine calcium after prolonged fasting or a low-calcium diet. Low-calcium diets do not induce hyperparathyroidism in these patients, and so the source of the elevated calcium in the urine must be primarily from bone. Increased levels of 1,25-dihydroxyvitamin D in patients with idiopathic hypercalciuria have been noted.<sup>28,29</sup>

Whether the cytokine milieu also contributes to the calcitriol levels is unclear, but the high or high-normal plasma level of 1,25-dihydroxyvitamin D may be the reason that the PTH is unperturbed.

■ **IMPACT ON BONE HEALTH**

Nephrolithiasis is strongly linked to fracture risk.

The bone mineral density of trabecular bone is more affected by calcium excretion than that of cortical bone.<sup>18,20,30</sup> However, lumbar spine bone mineral density has not been consistently found to be lower in patients with hyperabsorptive hypercalciuria. Rather, bone mineral density is correlated inversely with urine calcium excretion in men and women who form stones, but not in patients without nephrolithiasis.

**Spot urine samples underestimate 24-hour calcium, and postprandial samples overestimate it**

### In children

In children, idiopathic hypercalciuria is well known to be linked to osteopenia. This is an important group to study, as adult idiopathic hypercalciuria often begins in childhood. However, the trajectory of bone loss vs gain in children is fraught with variables such as growth, puberty, and body mass index, making this a difficult group from which to extrapolate conclusions to adults.

### In men

There is more information on the relationship between hypercalciuria and osteoporosis in men than in women.

In 1998, Melton et al<sup>31</sup> published the findings of a 25-year population-based cohort study of 624 patients, 442 (71%) of whom were men, referred for new-onset urolithiasis. The incidence of vertebral fracture was 4 times higher in this group than in patients without stone disease, but there was no difference in the rate of hip, forearm, or nonvertebral fractures. This is consistent with earlier data that report a loss of predominantly cancellous bone associated with urolithiasis.

National Health and Nutrition Examination Survey III data in 2001 focused on a potential relationship between kidney stones and bone mineral density or prevalent spine or wrist fracture.<sup>32</sup> More than 14,000 people had hip bone mineral density measurements, of whom 793 (477 men, 316 women) had kidney stones. Men with previous nephrolithiasis had lower femoral neck bone mineral density than those without. Men with kidney stones were also more likely to report prevalent wrist and spine fractures. In women, no difference was noted between those with or without stone disease with respect to femoral neck bone mineral density or fracture incidence.

Cauley et al<sup>33</sup> also evaluated a relationship between kidney stones and bone mineral density in the Osteoporotic Fractures in Men (MrOS) study. Of approximately 6,000 men, 13.2% reported a history of kidney stones. These men had lower spine and total hip bone mineral density than controls who had not had kidney stones, and the difference persisted after adjusting for age, race, weight, and other variables. However, further data from this cohort revealed that so few men with os-

teoporosis had hypercalciuria that its routine measurement was not recommended.<sup>34</sup>

### In women

The relationship between idiopathic hypercalciuria and fractures has been more difficult to establish in women.

Sowers et al<sup>35</sup> performed an observational study of 1,309 women ages 20 to 92 with a history of nephrolithiasis. No association was noted between stone disease and reduced bone mineral density in the femoral neck, lumbar spine, or radius.

These epidemiologic studies did not include the cause of the kidney stones (eg, whether or not there was associated hypercalciuria or primary hyperparathyroidism), and typically a diagnosis of idiopathic hypercalciuria was not established.

The difference in association between low bone mineral density or fracture with nephrolithiasis between men and women is not well understood, but the most consistent hypothesis is that the influence of hypoestrogenemia in women is much stronger than that of the hypercalciuria.<sup>20</sup>

### Does the degree of hypercalciuria influence the amount of bone loss?

A few trials have tried to determine whether the amount of calcium in the urine influences the magnitude of bone loss.

In 2003, Asplin et al<sup>36</sup> reported that bone mineral density Z-scores differed significantly by urinary calcium excretion, but only in stone-formers. In patients without stone disease, there was no difference in Z-scores according to the absolute value of hypercalciuria. This may be due to a self-selection bias in which stone-formers avoid calcium in the diet and those without stone disease do not.

Three studies looking solely at men with idiopathic hypercalciuria also did not detect a significant difference in bone mineral loss according to degree of hypercalciuria.<sup>20,30,37</sup>

### ■ A POLYGENIC DISORDER?

The potential contribution of genetic changes to the development of idiopathic hypercalciuria has been studied. While there is an increased risk of idiopathic hypercalciuria in first-degree relatives of patients with nephro-

**Bone mineral density is inversely correlated with urine calcium excretion in patients with kidney stones, but not in those without stone disease**



lithiasis, most experts believe that idiopathic hypercalciuria is likely a polygenic disorder.<sup>9,38</sup>

**EVALUATION AND TREATMENT**

The 2014 revised version of the National Osteoporosis Foundation’s “Clinician’s guide to prevention and treatment of osteoporosis”<sup>39</sup> noted that hypercalciuria is a risk factor that contributes to the development of osteoporosis and possibly osteoporotic fractures, and that consideration should be given to evaluating for hypercalciuria, but only in selected cases. In patients with kidney stones, the link between hypercalciuria and bone loss and fracture is recognized and should be explored in both women and men at risk of osteoporosis, as 45% to 50% of patients who form calcium stones have hypercalciuria.

Patients with kidney stones who have low bone mass and idiopathic hypercalciuria should increase their daily fluid intake, follow a low-salt and low-animal-protein diet, and take thiazide diuretics to reduce the incidence of further calcium stones. Whether this approach also improves bone mass and strength and reduces the risk of fractures within this cohort requires further study.

**Dietary interventions**

**Don’t restrict calcium intake.** Despite the connection between hypercalciuria and nephrolithiasis, restriction of dietary calcium to prevent relapse of nephrolithiasis is a risk factor for negative calcium balance and bone demineralization. Observational studies and prospective clinical trials have demonstrated an increased risk of stone formation with low calcium intake.<sup>27,30</sup> Nevertheless, this practice seems logical to many patients with kidney stones, and this process may independently contribute to lower bone mineral density.

**A low-sodium, low-animal-protein diet** is beneficial. Though increased intake of sodium or protein is not the main cause of idiopathic hypercalciuria, pharmacologic therapy, especially with thiazide diuretics, is more likely to be successful in the setting of a low-sodium, low-protein diet.

Borghi et al<sup>27</sup> studied 2 diets in men with nephrolithiasis and idiopathic hypercalciuria: a low-calcium diet and a low-salt, low-animal-protein, normal-calcium diet. Men on the

latter diet experienced a greater reduction in urinary calcium excretion than those on the low-calcium diet.

Breslau et al<sup>40</sup> found that urinary calcium excretion fell by 50% in 15 people when they switched from an animal-based to a plant-based protein diet.

**Thiazide diuretics**

Several epidemiologic and randomized studies<sup>41-45</sup> found that thiazide therapy decreased the likelihood of hip fracture in postmenopausal women, men, and premenopausal women. Doses ranged from 12.5 to 50 mg of hydrochlorothiazide. Bone density increased in the radius, total body, total hip, and lumbar spine. One prospective trial noted that fracture risk declined with longer duration of thiazide use, with the largest reduction in those who used thiazides for 8 or more years.<sup>46</sup>

Thiazides have anticalciuric actions.<sup>47</sup> In addition, they have positive effects on osteoblastic cell proliferation and activity, inhibiting osteocalcin expression by osteoblasts, thereby possibly improving bone formation and mineralization.<sup>48</sup> The effects of thiazides on bone was reviewed by Sakhaee et al.<sup>49</sup>

However, fewer studies have looked at thiazides in patients with idiopathic hypercalciuria.

García-Nieto et al<sup>50</sup> looked retrospectively at 22 children (average age 11.7) with idiopathic hypercalciuria and osteopenia who had received thiazides (19 received chlorthalidone 25 mg daily, and 3 received hydrochlorothiazide 25 mg daily) for an average of 2.4 years, and at 32 similar patients who had not received thiazides. Twelve (55%) of the patients receiving thiazides had an improvement in bone mineral density Z-scores, compared with 23 (72%) of the controls. This finding is confounded by growth that occurred during the study, and both groups demonstrated a significantly increased body mass index and bone mineral apparent density at the end of the trial.

Bushinsky and Favus<sup>51</sup> evaluated whether chlorthalidone improved bone quality or structure in rats that were genetically prone to hypercalciuric stones. These rats are uniformly stone-formers, and while they have components of calcium hyperabsorption, they also demonstrate renal hyperexcretion (leak)

**Many patients with kidney stones may self-limit their calcium intake, harming their bones**

and enhanced bone mineral resorption.<sup>51</sup> When fed a high-calcium diet, they maintain a reduction in bone mineral density and bone strength. Study rats were given chlorthalidone 4 to 5 mg/kg/day. After 18 weeks of therapy, significant improvements were observed in trabecular thickness and connectivity as well as increased vertebral compressive strength.<sup>52</sup> No difference in cortical bone was noted.

No randomized, blinded, placebo-controlled trial has yet been done to study the impact of thiazides on bone mineral density or fracture risk in patients with idiopathic hypercalciuria.

In practice, many physicians choose chlorthalidone over hydrochlorothiazide because of chlorthalidone's longer half-life. Combinations of a thiazide diuretic and potassium-sparing medications are also employed, such as hydrochlorothiazide plus either triamterene or spironolactone to reduce the number of pills the patient has to take.

### Potassium citrate

When prescribing thiazide diuretics, one should also consider prescribing potassium citrate, as this agent not only prevents hypokalemia but also increases urinary citrate excretion, which can help to inhibit crystallization of calcium salts.<sup>6</sup>

In a longitudinal study of 28 patients with hypercalciuria,<sup>53</sup> combined therapy with a thiazide or indapamide and potassium citrate over a mean of 7 years increased bone density of the lumbar spine by 7.1% and of the femoral neck by 4.1%, compared with treatment in age- and sex-matched normocalcemic peers. In the same study, daily urinary calcium excretion decreased and urinary pH and citrate levels increased; urinary saturation of calcium oxalate decreased by 46%, and stone formation was decreased.

Another trial evaluated 120 patients with idiopathic calcium nephrolithiasis, half of whom were given potassium citrate. Those given potassium citrate experienced an increase in distal radius bone mineral density over 2 years.<sup>54</sup> It is theorized that alkalinization may decrease bone turnover in these patients.

### Bisphosphonates

As one of the proposed main mechanisms of bone loss in idiopathic hypercalciuria is direct bone resorption, a potential target for therapy is

the osteoclast, which bisphosphonates inhibit.

Ruml et al<sup>55</sup> studied the impact of alendronate vs placebo in 16 normal men undergoing 3 weeks of strict bedrest. Compared with the placebo group, those who received alendronate had significantly lower 24-hour urine calcium excretion and higher levels of PTH and 1,25-dihydroxyvitamin D.

Weisinger et al<sup>56</sup> evaluated the effects of alendronate 10 mg daily in 10 patients who had stone disease with documented idiopathic hypercalciuria and also in 8 normocalciuric patients without stone disease. Alendronate resulted in a sustained reduction of calcium in the urine in the patients with idiopathic hypercalciuria but not in the normocalciuric patients.

Data are somewhat scant as to the effect of bisphosphonates on bone health in the setting of idiopathic hypercalciuria,<sup>57,58</sup> and therapy with bisphosphonates is not recommended in patients with idiopathic hypercalciuria outside the realm of postmenopausal osteoporosis or other indications for bisphosphonates approved by the US Food and Drug Administration (FDA).

### Calcimimetics

Calcium-sensing receptors are found not only in parathyroid tissue but also in the intestines and kidneys. Locally, elevated plasma calcium in the kidney causes activation of the calcium-sensing receptor, diminishing further calcium reabsorption.<sup>59</sup> Agents that increase the sensitivity of the calcium-sensing receptors are classified as calcimimetics.

Cinacalcet is a calcimimetic approved by the FDA for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, for the treatment of hypercalcemia in patients with parathyroid carcinoma, and for patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy. In an uncontrolled 5-year study of cinacalcet in patients with primary hyperparathyroidism, there was no significant change in bone density.<sup>60</sup>

### Anti-inflammatory drugs

The role of cytokines in stimulating bone resorption in idiopathic hypercalciuria has led to the investigation of several anti-inflammatory drugs (eg, diclofenac, indomethacin) as

**Thiazides have anticalciuric actions and promote osteoblast proliferation and activity**

potential treatments, but studies have been limited in number and scope.<sup>61,62</sup>

### Omega-3 fatty acids

Omega-3 fatty acids are thought to alter prostaglandin metabolism and to potentially reduce stone formation.<sup>63</sup>

A retrospective study of 29 patients with stone disease found that, combined with dietary counseling, omega-3 fatty acids could

potentially reduce urinary calcium and oxalate excretion and increase urinary citrate in hypercalciuric stone-formers.<sup>64</sup>

A review of published randomized controlled trials of omega-3 fatty acids in skeletal health discovered that 4 studies found positive effects on bone mineral density or bone turnover markers, whereas 5 studies reported no differences. All trials were small, and none evaluated fracture outcome.<sup>65</sup>

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