Idiopathic Hypercalciuria – A Major Metabolic Risk for Calcium Kidney Stone Disease

OLIVE W. TANG, MD, PhD; JIE TANG, MD, MPH

ABSTRACT

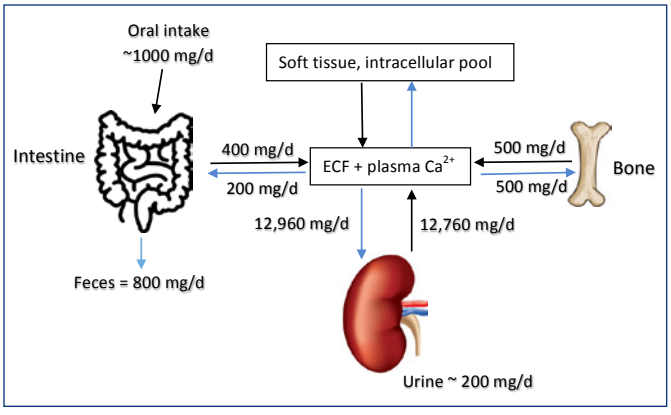
Idiopathic hypercalciuria is defined as excessive urine calcium excretion in the absence of an identifiable cause. It has been strongly associated with the risk of calcium kidney stone formation. Animal and human studies have suggested excessive bone mineral loss or increased gastrointestinal calcium absorption with abnormal renal calcium excretion may contribute to this process. In this article we will review the complex pathophysiology of idiopathic hypercalciuria and discuss clinical management and challenges.

KEYWORDS: hypercalciuria, vitamin D, calcium kidney stone

INTRODUCTION

Kidney stone disease is common in the general population with an estimated prevalence of around 10–15% in males and 3–5% in females.[1] Calcium-based kidney stones are the most common (>80%), with high urinary calcium excretion being the most common metabolic risk factor for stone formation.[2,3] Calcium is tightly regulated through a coordinated interplay between the intestines, bones, and kidneys (**Figure 1**). Any disease processes disturbing the calcium balance can lead to hemodynamic compromise and widespread organ dysfunction, including neurologic, cardiovascular, kidney and bone dysfunction.

Figure 1.



Hypercalciuria is defined as daily urine calcium excretion >300mg in males and >250mg in females. It can be secondary to hypercalcemia caused by a variety of systemic illnesses such as primary hyperparathyroidism, sarcoidosis, and paraneoplastic syndromes. More commonly, blood calcium levels are normal and no primary causes of hypercalciuria can be found. At which point, the etiology is considered idiopathic. Idiopathic hypercalciuria is present in 40–50% of patients with calcium-based kidney stones, and in about 10% of the general population.[4,5] No single cause for this condition has been identified. Three main pathophysiological features have been described: 1) increased gastrointestinal calcium absorption, 2) increased bone mineral loss, and 3) increased renal calcium loss. The clinical presentation is often heterogeneous, and individuals may have multiple pathologic processes occurring simultaneously.

INCREASED INTESTINAL CALCIUM ABSORPTION AND DIETARY FACTORS

The most common cause of increased urinary calcium is increased calcium absorption in the small intestine though both a paracellular passive process, and an active transcellular process in the duodenum and upper jejunum via transient receptor potential vanilloid subfamily member 6 (TRPV6). In a study of 22 patients with idiopathic hypercalciuria, Ca^{2+} absorbed from gut exceeded that excreted in the urine. Reducing intestinal calcium absorption by fasting or cellulose phosphate normalized urinary calcium excretion.[6] In vitro study using jejunal biopsy specimens showed increased intestinal calcium uptake in specimens from patients with idiopathic hypercalciuria compared to those without.[7] The finding has been corroborated by other larger human studies.[6,8]

Enhanced vitamin D activity is an important mechanism modulating calcium hyperabsorption.[2,9] Vitamin D regulates TRPV6, intracellular calbindin expressions, and facilitates calcium exit through the basolateral side, playing a key role in calcium absorption (**Figure 1**).[10,11] The majority of patients with idiopathic hypercalciuria have normal blood 1,25-dihydroxy-vitamin D (1,25 $(OH)_2D$) levels, with the increased intestinal calcium absorption out of proportion to the measured 1,25 $(OH)_2D$.[11] A similar phenotype has been observed in a rat model with increased vitamin D receptor activity

in the GI tract.[12,13] In humans, there are no direct measurements of vitamin D receptor expression in the GI tract. Favus et al showed a two-fold increase in peripheral blood monocyte vitamin D receptor expression in patients with kidney stones with idiopathic hypercalciuria compared to age-matched controls.[14] The molecular or genetic basis of this increased receptor expression remains unclear. In a study of 33 patients with hypercalciuria and 36 matched normal controls, investigators failed to find any differences in the distribution of variant alleles in the vitamin D receptor gene or in the coding region of vitamin D receptor messenger RNA.[15] Like other nuclear receptors, the vitamin D receptor may undergo significant post-translational modification, altering its metabolism leading to an enhanced activity.

While increased intestinal calcium absorption is a primary process in some patients with idiopathic hypercalciuria, others consuming controlled diets have urine calcium level exceeding the amount absorbed from GI tract, suggesting bone turnover may be an important additional source of hypercalciuria.[16]

INCREASED BONE MINERAL LOSS

Bones contain 99% of the total body calcium and serves as the primary storage site. Normal bone turnover involves 5–10 mmol of calcium with flux of calcium between bone and the systemic circulation. This process is predominantly regulated by parathyroid hormone.

"Resorptive hypercalciuria" is a well-recognized process among patients with stone formers who are found to have idiopathic hypercalciuria.[17,18] Increased bone resorption results in fasting hypercalciuria, with elevated markers of bone turnover. Multiple studies have demonstrated a lower bone mineral density among those with idiopathic hypercalciuria due to sustained bone loss, regardless of an underlying primary absorptive hypercalciuria or fasting hypercalciuria.[19-21] There have been few studies directly examining bone remodeling dynamics in idiopathic hypercalciuria patients. A histomorphometric analysis of iliac crest bone biopsies revealed that patients with calcium stone and idiopathic hypercalciuria had both reduced bone formation and increased bone resorption, compared with their matched controls. A short course of alendronate treatment corrected fasting urinary calcium, which confirmed that for some patients, there is a primary resorptive physiology.[22] Bone turnover in idiopathic hypercalciuria is more complex with the exact phenotype varying based on the underlying causes of hypercalciuria, i.e., resorptive or renal leak vs. absorptive hypercalciuria.[23]

The mechanistic cause of abnormal bone turnover remains unclear. Despite enhanced intestinal calcium absorption, there remains a net bone loss in patients with absorptive hypercalciuria, indicating a primary defect in the bone itself to maintain calcium balance. Exposure to high doses of $1,25(OH)_2$-vitamin-D has been shown to be potent in stimulating bone resorption and decreasing collagen synthesis in studies using organ cultures.[24] Furthermore, increasing doses of calcitriol was able to promote calcium efflux from cultured calvariae of inbred genetic hypercalciuric rats but not from those of normal wild-type controls.[25] Future human studies are needed to examine the action of vitamin D on bone mineral loss in patients with idiopathic hypercalciuria.

INCREASED RENAL CALCIUM WASTING

The kidneys are key regulators of calcium homeostasis. On average, 10–12 grams of calcium are filtered daily, with 98% being re-absorbed, resulting in a net loss of 200mg. Calcium reabsorption occurs paracellularly in the proximal tubule and thick ascending limb, and transcellularly in the distal segment. The renal excretion of calcium is regulated by several proteins including parathyroid hormone (PTH), vitamin D, and calcium sensing receptor (CaSR). It is also driven by intravascular volume status, acid-base balance, and serum concentrations of several electrolytes including calcium, magnesium and potassium.

Idiopathic hypercalciuria, by definition, is characterized by excessive urinary calcium excretion. A subtle increase in glomerular filtration rate of 5% or a small 0.25 mg % increase in ultrafilterable calcium over 24 hours would be enough to raise urinary calcium excretion significantly, indicating the possibility of subtle undetectable increases in the filtered calcium load as a contributor to idiopathic hypercalciuria.[26] However, most patients with idiopathic hypercalciuria have abnormal renal calcium handling resulting in a phenomenon known as "renal leak hypercalciuria". These patients can have normal blood concentrations of calcium and other key regulators of calcium balance (PTH, vitamin D and other metabolic factors). In a study conducted by Worcester et al, 10 patients with idiopathic hypercalciuria and 7 control patients ingested a controlled diet for three days after fasting. Neither ultrafilterable calcium, nor filtered calcium load differed between the two groups during fasting or after meals. But urine fractional reabsorption of calcium was significantly lower during fasting or after meals in subjects with idiopathic hypercalciuria, suggesting a defect in kidney to conserve calcium.[27] However, other investigators failed to show significant differences in the renal tubular reabsorption of calcium between normocalciuric and hypercalciuric subjects when calcium was injected intravenously.[26] These conflicting findings highlight the likelihood that patients with idiopathic hypercalciuria are a heterogeneous population with differing underlying pathophysiology.

The underlying cause of "renal leak" remains unknown. PTH, a key regulator of renal calcium handling, does not appear to play a role.[27] Among those with "renal calcium leak", the dissociation between urinary calcium and sodium

excretions implicated the distal nephron as the culprit site.[27] In some patients experiencing subtle rise in blood calcium load, CaSR may play a role.[27] However, in most cases of idiopathic hypercalciuria, which exist without changes in blood calcium concentration, excessive vitamin D action may have a direct effect on renal calcium loss. Initial evidence came from a retrospective study which showed a strong positive correlation between serum $1,25(OH)_2D$ concentration and urinary calcium excretion in fasting patients with idiopathic hypercalciuria.[28] In a genetic hypercalciuric stone-forming (GHS) rat model mimicking human idiopathic hypercalciuria, vitamin D receptor (VDR) expression is significantly enhanced at basal state in both the kidney cortex and intestines without any alterations in binding affinity. A small dose of intra-peritoneal 1,25(OH)2D3 injection can further increase VDR gene expression in GHS rats but not in normocalciuric control rats.[13] Normally, vitamin D enhances calcium reabsorption in distal nephron, where vitamin D receptor and vitamin D dependent proteins (luminal epithelial calcium channel, calbindins, and basolateral Ca-ATPase) are expressed.[29] In calcium and vitamin D replete states, excessive vitamin D action can lead to calcium wasting, likely through a CaSR-related mechanism. In the kidney, activation of CaSR is important in reducing paracellular calcium reabsorption in the thick ascending limb of the loop of Henle.[30] CaSR expression is regulated by activated 1,25-OH-vitamin D, and is PTH-independent.[31] Furthermore, CaSR is able to up-regulate VDR gene expression, which can create a self-amplifying process to potentiate vitamin D action on renal calcium handling.[32]

GENETICS

A genetic contribution to idiopathic hypercalciuria has long been suspected. In a study of 40 children with idiopathic hypercalciuria, 47.5% had one or more affected first-degree relatives with likely an autosomal dominant transmission.[33] In a study of adult patients with kidney stones and idiopathic hypercalciuria, hypercalciuria was also found in 43% of first-degree relatives, with a higher incidence of hypercalciuria seen in the second and third generations, strongly suggestive of a genetic basis of idiopathic hypercalciuria.[34]

Known rare monogenetic disorders such as Dent disease typically present with familial hypercalciuria and kidney stone disease, and can be distinguished from idiopathic hypercalciuria by their unique disease features (**Table 1**).

Genetic testing to identify monogenic mutations and risk associated polymorphisms has implicated CaSR activation in the pathogenesis of idiopathic hypercalciuria.[35] The R990G polymorphism of CaSR is a gain-of-function mutation that predisposes to primary hypercalciuria.[36] However, the exact genes or gene panels involved in idiopathic hypercalciuria remains incompletely understood as the trait is likely polygenic and involves both genetic and environmental factors.

Table 1. Monogenic forms of hypercalciuric nephrolithiasis

Disease	Inheritance	Genes	Clinical features
Dent's disease	X-linked	CLC-5	Hypercalciuria, low-molecular-weight proteinuria
Lowe's syndrome	X-linked	OCRL1	Hypercalciuria, congenital cataracts, severely impaired intellectual development, and renal tubular dysfunction
Bartter syndrome			Hypercalciuria, hypokalemia, volume depletion
Type 1	AR	NKCC2	
Type 2	AR	ROMK	
Type 3	AR	CLC-Kb	
Type 4	AR	Barttin	
Type 5	X-linked	CaSR	
ADHH	AD	CaSR	Hypercalciuria, hypocalcemia
HHRH	AR	NaPi-2c	Hypercalciuria, hypophosphatemia, phosphaturia, elevated calcitriol, rickets
FHH	AR	CLDN16	Hypercalciuria, hypomagnesemia
		CLDN19	Hypercalciuria, hypomagnesemia, severe ocular abnormalities
Distal RTA	AD	SLC4A1	Hypercalciuria, dRTA-1
	AR	ATP6N1B	Hypercalciuria, dRTA-1
	AR	ATP6B1	Hypercalciuria, dRTA-1, sensorineural deafness

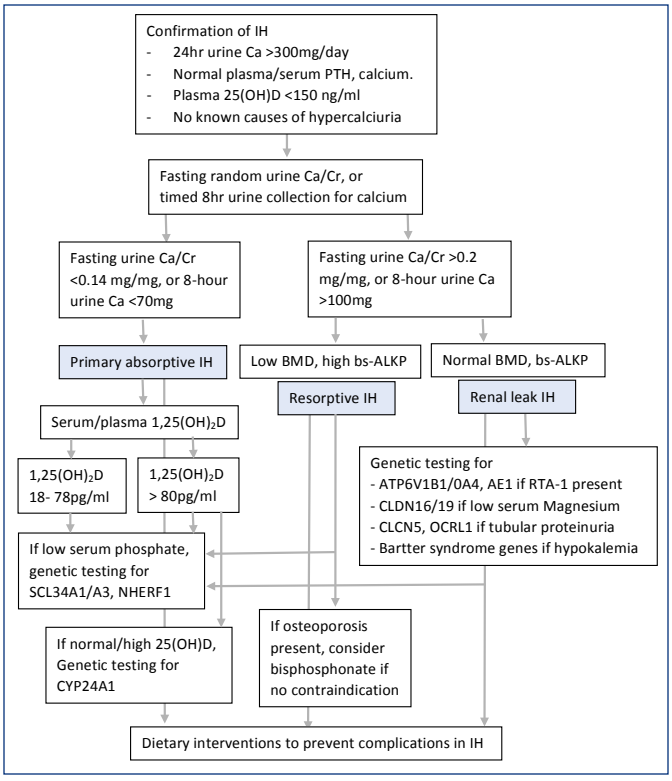
ADHH: autosomal dominant hypocalcemic hypercalciuria. HHRH: hereditary hypophosphatemic rickets with hypercalciuria. FHH: familial hypomagnesemia with hypercalciuria. AD: autosomal dominant. AR: autosomal recessive. CLC-5: chloride/proton antiporter 5. OCRL1: oculocerebrorenal-1 gene. NKCC2: Na–K–Cl co-transporter. ROMK: renal outer-medullary potassium channel. CLC-Kb: chloride channel. Barttin: CLC-Kb beta subunit. CaSR: calcium-sensing receptor. NaPi-2c: Na-phosphate cotransporter 2c. CLDN: claudin. SLC4A1: solute carrier family 4 member 1. ATP6N1B/ATP6B1: encoding proton pump. dRTA: distal renal tubular acidosis.

Many candidate genes have been screened for their potential associations with idiopathic hypercalciuria, including genes coding for vitamin D metabolism, *VDR*, renal epithelial calcium channel *TRPV5*, and renal sodium-phosphate co-transporter *NPT2a*. Thus far, results have been mostly negative or inconclusive.[15,37-41] Since idiopathic hypercalciuria is a heterogeneous process, larger scale studies are needed to examine genetic variances in well-defined subpopulations, i.e., patients with primary absorptive hypercalciuria. The target genetic panel likely needs to be expanded to include more genes involved in the control of calcium homeostasis. A recent genome-wide association study uncovered a novel nucleotide polymorphism associated with fibroblast growth factor 23 (*FGF23*) that achieved genome-wide significance for calcium excretion.[42] Further work is needed to define the roles of these genetics in idiopathic hypercalciuria.

MANAGEMENT OF ADULTS WITH IDIOPATHIC HYPERCALCIURIA

Currently, there are no consensus guidelines for the management of idiopathic hypercalciuria. The approach presented is based on expert opinion. For patients with kidney stones with or without nephrocalcinosis, laboratory studies should be pursued to examine disturbances in calcium homeostasis. **Figure 2** outlines the general approach for the clinical management of patients with idiopathic hypercalciuria. All patients will need dietary interventions to prevent complications from idiopathic hypercalciuria. A kidney stone prevention diet should be pursued. Ideally, oral fluid intake should be enough to maintain a daily urine output of more than 2 liters. Potassium intake should be maintained at a minimum of 1.6–2.0 grams per day, unless there are conditions predisposing patients to hyperkalemia. Sodium should be restricted to less than 6 grams per day. Animal protein and grain intake should also be restricted to avoid excessive dietary acid load. In some cases, additional alkali therapy using citrate containing drugs or supplements will be used to prevent kidney stone formation and bone loss.[43] With regard to calcium intake, for those with primary absorptive hypercalciuria, dietary calcium intake should be restricted to 1 gram per day for ages ≤70, and to 1.2 grams per day for ages>70, regardless of sex. For patients with other subtypes of idiopathic hypercalciuria (± absorptive hypercalciuria), no dietary calcium restriction is recommended, and the optimal intake should be individualized based on the degree of bone loss or net calcium balance and whether there is enteric hyperoxaluria present. A thiazide diuretic is often prescribed to reduce renal calcium loss and to improve bone mineralization,[43] but may result in hypokalemia which needs close monitoring and aggressive supplementation of potassium. In cases of nutritional vitamin D deficiency, vitamin D supplementation is indicated to prevent bone demineralization and is not associated with worsening hypercalciuria among patients with idiopathic hypercalciuria who have calcium-based kidney stones.[44] However, vitamin D supplementation should be avoided in patients carrying *CYP24A1* mutations or having conditions associated with an enhanced vitamin D 1α-hydroxylase activity.

Figure 2. Management approach of idiopathic hypercalciuria (IH)



SUMMARY

Idiopathic hypercalciuria is a complicated multifactorial metabolic abnormality determined by both genetic and environmental factors, with strong associations with kidney stone formation and bone loss. Although progress has been made, the clinical diversity, pathophysiological mechanisms, and effective management for this condition remains incompletely understood.

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Authors

Olive W. Tang, MD, PhD, Department of Medicine,The Johns Hopkins University School of Medicine, Baltimore, MD.

Jie Tang, MD, MPH, Division of Kidney Diseases and Hypertension, Alpert Medical School of Brown University, Providence, RI.

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Correspondence

Olive W. Tang, MD, PhD
Department of Medicine
The Johns Hopkins University School of Medicine
1830 E. Monument St, Suite 2-300
Baltimore, MD 21287
Otang@jhmi.edu