

Bone Disease and Idiopathic Hypercalciuria

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Abstract There is sufficient epidemiological and clinical data demonstrating an association between reduced bone mineral density and idiopathic hypercalciuria (IH). There have been relatively few studies that have addressed the underlying defect in bone remodeling. The limited studies to date suggest that increased bone turnover occurs in some forms of IH such as fasting hypercalciuria or renal calcium leak and explains the bone loss observed in these forms of IH. On the other hand, defective bone formation is the major defect observed in patients with IH resulting from intestinal hyperabsorption of calcium. These alterations in bone remodeling have been ascribed to genetic, metabolic, and nutritional causes. Although there are several therapeutic options available for treating such patients and preventing stone recurrence, prevention of future bone loss should also be considered to prevent the increased risk of osteoporotic fracture in patients with IH.

Keywords Nephrolithiasis · Bone biopsy · Bone mineral density · Bone remodeling

Introduction

It has been nearly six decades since Albright and colleagues described the presence of hypercalciuria in normocalcemic patients without any underlying cause of

hypercalciuria such as hyperparathyroidism, Paget's disease, vitamin D intoxication, endogenous or exogenous glucocorticoid excess, sarcoidosis, immobilization or hyperparathyroidism. They termed this idiopathic hypercalciuria (IH) [1]. Today it is known that IH is the most common finding in patients with nephrolithiasis, being present in up to one-half of the subjects who were evaluated [2, 3]. It increases the risk for nephrolithiasis by increasing urine supersaturation with respect to the ionic species of calcium oxalate and calcium phosphate [4–6].

The source of the excess urinary calcium is now known to derive from contributions of the intestine (increased intestinal calcium absorption), kidney (reduced renal calcium reabsorption), and skeleton (increased bone mineral loss). Increased intestinal absorption of calcium is a frequent finding in patients with IH. The cause of the increased intestinal calcium absorption is not fully delineated but may be the result of both genetic and metabolic contributions. Some IH patients may also have excessive fasting urinary calcium [7] or do not reduce urinary calcium excretion during dietary calcium restriction and have been proposed to have a primary renal leak of calcium as the cause of hypercalciuria. However, remaining studies suggest it is unlikely that either of these mechanisms can account for all of the hypercalciuria observed in these patients. Thus, a third contribution from increased skeletal bone resorption has been invoked [3, 7]. As might be anticipated, this loss of calcium from bone could result in a decline in bone mineral density (BMD) if the hypercalciuria is of sufficient magnitude and duration.

This article reviews the evidence supporting the existence of bone loss in patients with IH. It will also consider the nature of the defect in bone remodeling contributing to the bone loss and possible causes for such a loss. Because low BMD is a strong risk factor for fracture [8, 9] it is

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important to better appreciate the causes of bone loss in IH and what measures might be taken to prevent or retard its occurrence.

Patients with Urolithiasis have Reduced Bone Mass

Epidemiological Studies

There are several lines of evidence from epidemiological studies that are consistent with the notion that bone mass is decreased in stone-forming patients. Although epidemiological studies typically employ large subject numbers that provide adequate statistical power, they are limited by the fact that they can only demonstrate association and not a cause and effect relationship. Because reduced bone mass is recognized as a risk factor for fracture, many of these studies have examined whether fracture rates are higher in calcium stone formers than in the general population. A case control study on 367 Swedish men and women [10] indicated that urolithiasis was not associated with the risk of distal forearm fractures (odds ratio, OR = 1.14, CI, 0.41–3.16 for women and OR = 1.00, CI, 0.24–4.1 for men). Association of urolithiasis with vertebral or hip fractures was not assessed in that study. Similar findings for the distal forearm and hip have been reported by Melton and colleagues who conducted a population-based retrospective cohort study on 624 Rochester, Minnesota residents with an initial symptomatic episode of urolithiasis during a 25-year period. Subjects were followed for nearly 12,000 person-years for subsequent age-related fractures. Although they found no association with hip and distal forearm fractures, when vertebral fractures were examined, there was a four-fold increase for stone formers versus the fracture rate in the general population [11]. This observation is consistent with the suggestion that there may be a greater deficit of bone density at the spine than at the hip in patients with urolithiasis. Clinical studies have supported the preferential loss of cancellous bone over cortical bone by bone densitometric techniques (see Clinical Studies below). More recently, Lauderdale and colleagues [12] examined the NHANES III database to determine whether a history of kidney stones was associated with lower femoral neck BMD or prevalent spine or wrist fracture and, if true, whether the finding was true in both men and women. Out of approximately 14,000 with hip BMD measurements reported 793 respondents a history of kidney stones (477 men, 316 women). They found that men with kidney stone history have lower femoral neck BMD than men without kidney stone history after adjusting for age, body mass index, race/ethnicity and other potential confounders ($R = -0.023$, $P = 0.01$ for men and $R = -0.009$, $P = 0.34$ for women). Men with kidney stones were also

more likely to report prevalent wrist and spine fractures (2.32 for men CI, 1.04–5.18, but not for women, 1.75, CI, 0.58–5.29). Unfortunately, lumbar vertebral BMD was not performed in this study but the increased vertebral fracture prevalence indirectly supports greater bone losses at the spine than for cortical-rich bone of the femoral neck. This study also performed an additional provocative analysis. The study examined whether dietary calcium intake modified the association between kidney stone history and the BMD. There was a positive interaction term for kidney stone history and milk consumption for both men and women, but was only significant for men ($P = 0.05$). When men were divided into tertiles based on milk consumption of 0–< 1, <1–1, and >1 servings/day, men who reported the lowest milk consumption were found to have the lowest age-adjusted femoral neck BMD. Men with kidney stones had BMD values that were markedly lower than that for men without stones at all intakes except for >1/d. This observation underscores the concern shared by some investigators over the institution of a low-calcium diet in hypercalciuric stone formers and the potential consequence of increased bone loss [13, 14]. This observation has also been reported for two smaller clinical studies (see below, Clinical Studies).

Lastly, Cauley and colleagues [15] performed a cross-sectional analysis to determine the factors associated with BMD of the lumbar spine and proximal femur in a large population-based sample of older men enrolled in The Osteoporotic Fractures in Men Study, “Mr. Os”. Nearly 6,000 men, 65 years of age or older were enrolled at six US clinical centers. Spine and hip BMD were measured by dual-energy X-ray absorptiometry (DEXA) and medical history and lifestyle information obtained by interviews. Kidney stone history was reported by 13.2% of the men. Both spine and hip BMD values were found to be significantly lower in men who reported a history of kidney stones as compared to men without stones. This association held true after adjustment for age, clinic site, race, weight, height, and several other variables in a multivariable analysis. The loss was equivalent to about a 2 SD decrease in the distribution of the measured BMDs. Women were not a part of this study.

It is interesting to note that most studies have failed to identify an association between BMD and kidney stone history in women. In a much larger study, Sowers et al. [16] studied 1,309 women aged 20–92 and observed no evidence of an association between kidney stone history and lower BMD. This was true for the femoral neck, spine, and radius. In addition, there was no difference in reports of fractures between the two groups. The cause for the lack of association of low BMD and kidney stone history in women is not known. Differences in sex steroid concentrations and their effects on bone or differences between

men and women in excretion of inhibitors of stone formation could be two of many possible reasons. Epidemiological studies such as these are limited by their cross-sectional nature and by the fact that no etiology for the underlying hypercalciuria or stone disease was sought. Thus, it is not clear how many of the stone formers in these studies were truly idiopathic hypercalciuric. Fortunately, this issue has been explored in several clinical studies.

Clinical Studies

The development of technologies that permit rapid and sensitive quantitation of BMD has been useful in numerous clinical studies of bone loss in stone-forming patients. Although early studies relied on the less sensitive single-photon absorptiometry technique and did not discriminate stone-forming patients by their underlying mechanisms for stones, the studies, in general, disclosed lower BMD in stone formers as compared to age- and gender-matched controls [17–21]. The majority (6/10) of studies in normocalciuric stone formers demonstrated normal BMD at both the spine and cortical-rich sites such as proximal radius and femur [17, 20–23]. Even when the nature of the stone-forming patients' hypercalciuria was delineated as to absorptive, fasting, or renal leak hypercalciuria, there is a rather consistent decrease in BMD observed for the stone

formers versus the age- and gender-matched control BMD values. The data are summarized in Table 1, and it can be seen that when more sensitive methods of BMD measurement such as dual photon absorptiometry (DPA), DEXA, and single-energy quantitative computed tomography (SEQCT) are used, lumbar vertebral BMD is consistently reduced [22, 24–30]. It is also interesting to note that a more severe bone involvement is usually seen in patients with fasting hypercalciuria or true renal calcium leak as opposed to patients with absorptive hypercalciuria. This is consistent with the notion that increased bone resorption is a contributing cause to the fasting hypercalciuria. Several causes for such an increased bone resorption have been proposed and are discussed below. For patients with renal calcium leak, parathyroid hormone (PTH)-mediated bone resorption due to secondary hyperparathyroidism is believed to promote increased bone resorption and decreased bone mass, both at cancellous and cortical sites. Thus, the effect of increased bone resorption is manifested as a greater reduction in BMD in these patients as opposed to those with absorptive hypercalciuria where PTH levels are not increased and where the underlying bone defect is one of reduced bone formation [31–33].

Another possible contributing factor to decreased BMD in hypercalciuric stone-forming patients is the practice of reducing dietary calcium intake. This is typically done in

Table 1 Bone mineral density (BMD) values in calcium stone formers with idiopathic hypercalciuria

Authors, year	Measurement method	Measurement site	Type of IH	BMD findings ^a
Lawoyin et al. [24]	SPA	Distal radius	AHI (<i>n</i> = 117) Renal (<i>n</i> = 44)	Normal Slightly ↓
Lindergard et al. [26]	SPA	Distal radius	AHI Renal	Normal Slightly ↓
Fuss et al. [25]	SPA	Distal and proximal radius	AHI (<i>n</i> = 53)	↓ (85% of normal BMD)
Bataille et al. [112]	SEQCT	L3 lumbar vertebra	Idiopathic (<i>n</i> = 24)	Δ VMD ^b = −37 mg/cm ³
Malvasi et al. [111]	DPA	Lumbar vertebra	Idiopathic (<i>n</i> = 20)	↓ to 88% of normal
Pacifici et al. [41]	SEQCT	Lumbar vertebra	AH, I and II (<i>n</i> = 18) Fasting (<i>n</i> = 15)	z-score ↓ −0.43 z-score ↓ −1.07
Bataille et al. [27]	SEQCT	L3 lumbar vertebra	Idiopathic (<i>n</i> = 24) AHI (<i>n</i> = 8) Renal (<i>n</i> = 1) Undetermined (<i>n</i> = 15)	↓ to 69% of normal ↓ to 71% of normal ↓ to 54% of normal ↓ to 68% of normal
Borghi et al. [28]	DPA	Lumbar vertebra	Idiopathic (<i>n</i> = 21)	z-score < −2 in 1/3 of cases
Audran et al. [29]	SEQCT	Lumbar vertebra	Idiopathic (<i>n</i> = 17)	↓ to 66% of normal
Heilberg et al. [30]	DPA	L3 lumbar vertebra	Absorptive type (<i>n</i> = 35) Renal (<i>n</i> = 20)	↓ in 11% of cases ↓ in 35% of cases
Pietschmann et al. [22]	DXA SPA	Lumbar vertebra Radius	Absorptive type I (<i>n</i> = 62) Fasting (<i>n</i> = 27)	↓ in 74% of cases ↓ in 92% of cases

^a BMD compared to age and gender-matched control subjects

^b Δ VMD = measured vertebral mineral density − normal BMD

an effort to decrease urinary calcium concentration and the state of saturation of urine with respect to the calcium salts. Although both epidemiological [34] and clinical studies [35] have indicated an increased risk for stone formation with low-calcium intake, there is concern that a low-calcium intake may also promote increased bone resorption leading to bone mineral losses and decreased BMD in these patients. Indeed, the epidemiological study described above [12] demonstrated a direct association between reported customary dietary calcium intake and age-adjusted femoral neck BMD for men with and without kidney stones. This observation has also been observed in a recent study by Asplin and colleagues [36] who studied vertebral and femoral neck BMD among relatives of hypercalciuric stone formers, and contrasted those with stones to those without stones. There were 22 stone formers (14 of whom were hypercalciuric) and 37 patients without stones (10 of whom were hypercalciuric). The findings are of interest in several aspects. First, there was no difference in mean BMD z-scores at the spine or at the hip between stone formers and non-stone formers, a result clearly at odds with the majority of previous studies using bone densitometry. Second, stone formers reported reduced dietary calcium intakes when factored for body weight, but urinary calcium excretion was comparable between the two groups. The finding of reduced calcium intake and urinary calcium losses equal to that in non-stone formers suggests that the stone formers were in a much greater negative calcium balance than the non-stone formers. This observation is also consistent with balance studies that have shown that bone of IH patients with stones loses more minerals than normal when dietary calcium becomes limited [37]. BMD z-scores at the hip and spine were inversely correlated with urinary calcium for stone formers but not for non-stone formers. Third the BMD z-scores of the femoral neck and spine varied significantly with ammonium excretion for stone formers but not for non-stone formers. These findings suggest that a low calcium intake may exaggerate bone loss in hypercalciuric patients and render the skeleton more susceptible to bone loss by other mechanisms such as increased dietary acid intake [38, 39]. It is interesting to note that Jaeger et al. [21] also observed a significant negative correlation between BMD and urinary sulfate supporting a possible role of excessive dietary acid in augmenting bone resorption. Although the nature of the hypercalciuria in these studies was not alluded to, there is no firm evidence to indicate that patients with intestinal hyper-absorption of calcium do better on a low-calcium diet with respect to their skeletal status than do stone-forming patients with normal intestinal calcium absorption.

On the basis of the foregoing epidemiological and clinical evidence, there is clear indication of a deficit in BMD in patients with IH. This loss may be more extensive

and involve both cortical and cancellous bone in patients with fasting hypercalciuria or renal calcium leak. Despite increased intestinal calcium absorption in up to 50% of the patients with hypercalciuria, bone loss is still prevalent in this group and may reflect years of consuming a low-calcium diet as a prophylaxis against renal stone formation. Unfortunately, many of the foregoing studies only demonstrate an association between low BMD and urolithiasis. To better understand the mechanisms involved, an assessment of bone metabolism and remodeling is required.

The Nature of the Bone Defect in IH

There have been very few studies that have undertaken a close examination of the nature of the bone defect in stone-forming patients. Possible reasons for such limited information include the need for dietary control when assessing urinary hydroxyproline excretion, the lack of suitable patients to study due to their perceived notion of relatively asymptomatic bone disease, and the invasive nature of some procedures such as trans-iliac crest bone biopsy. Although various biochemical markers of bone turnover are now widely used, few studies have taken advantage of their usefulness, perhaps because of the large analytical and biological variability associated with some of these bone marker assays. In addition, many of these bone turnover markers are known to undergo a significant circadian variation necessitating 24-h urine collections or procurement of blood and a spot urine collection at the same time of day for each patient [40]. Despite these limitations, five studies have reported an increased urinary concentration of hydroxyproline in patients with IH [21, 27, 41–43]. Hydroxyproline is a major constituent of type I collagen, and its release into urine is generally regarded to be a good indicator of bone resorption. However, it is readily influenced by dietary intake of gelatin-containing food products requiring careful dietary control for accurate assessment of bone resorption. The advent of newer markers of both bone resorption and formation heralded a new approach to measuring the rate of bone turnover without the previous concerns over diet. Two of the resorption markers are deoxypyridinoline (DPD) and pyridinoline (PYR), both of which are found in type I collagen where they act as cross-linking molecules and serve to stabilize the triple helix. During osteoclastic bone resorption, they are released into the circulation and cleared by the kidney. Two studies have employed these markers. In the study by Jaeger et al. [21] there were no significant differences in the mean values of either PYD or DPD between hypercalciuric and normocalciuric stone formers suggesting that bone resorption was not increased in the hypercalciuric stone formers at the time of collection. However, BMD at the tibial diaphysis

was correlated negatively with fasting hydroxyprolinuria. Unfortunately, subjects were on a free-choice diet which may have influenced the diet-sensitive urinary hydroxyproline excretion. Twenty-four hour urinary PYD excretion also correlated negatively with tibial diaphysis BMD ($r = 0.37$, $P = 0.02$) but the more bone-specific DPD showed no significant association. In the study of Asplin et al. [36], biochemical markers of both bone resorption and formation were measured. They found no differences for the mean values of any of these markers between stone formers and non-stone formers. In addition, none of the markers correlated with BMD z-score of the femoral neck or spine in a significant manner. Another study in 48 male calcium stone formers observed no significant differences in vertebral and hip BMD between hypercalciuric and normocalciuric stone formers [44]. However, hypercalciuric stone formers had significant increases in 2 h PYD excretion and in serum total alkaline phosphatase consistent with an increase in bone turnover. In addition, this study disclosed that dietary calcium intake was significantly lower in the stone formers with osteopenia as compared with those with normal BMD and suggests that calcium restriction may have served to increase bone

turnover. Taken together, these findings with biochemical markers of bone turnover have not given any clear indication of the nature of the bone remodeling defect in IH patients with bone loss. This may be the result of small patient numbers in these studies and the inherent analytical and biological variability associated with some of these assays.

A more direct and accurate approach to examine bone remodeling is through the use of static and dynamic bone histomorphometry. Bone histomorphometry is considered to be the gold standard for determining the nature of bone remodeling defects under various disease conditions. Its invasive nature however, has limited its widespread application in patients with IH and decreased BMD. There have been eight studies to date in calcium stone formers that have utilized static bone histomorphometry [19, 30–33, 45–48]. Of these eight, six have also examined dynamic indices of bone remodeling after tetracycline labeling [19, 30–33, 47]. Table 2 summarizes the major findings from each of these studies for the static parameters and for mineralizing surface. Because of methodical differences in analysis and in the various control populations, it is difficult to directly compare the studies with each other. Rather,

Table 2 Static and dynamic bone histomorphometric findings for cancellous bone in calcium stone-forming patients

Author and type of hypercalciuria ^b	Histomorphometric parameter ^a								
	BV/TV (%)	OV/TV (%)	OS/BS (%)	O.Th (μm)	Ob.S/BS (%)	Oc.S/BS (%)	ES/BS (%)	MS/BS (%)	BFR
<i>Bordier et al.</i> [45]									
Renal ($n = 22$)	–	–	–	–	↑	–	↑		
AH III ($n = 25$)	–	↓	–	–	↓	↑?	↑?		
<i>De Vernejoul et al.</i> [46]									
IH ($n = 30$)	17 (↓)	2 (N)	12 (N)	–	2.9 (↓)	1.7 (↓)	15 (N)		
<i>Malluche et al.</i> [32]									
AH I and II ($n = 15$)	N	↑	17 (↑↑)	–	1.5 (↓)	0.8 (N)	5.5 (N)	(↓)	(↓)
<i>Steiniche et al.</i> [47]									
IH ($n = 33$)	21 (N)	–	19 (N)	10 (N)	–	–	4.7 (↑)	N	N
<i>Da Silva et al.</i> [19]									
IH ($n = 5$)	–	–	15 (↑)	–	–	–	7 (↑)	–	(↓)
<i>Heilberg et al.</i> [30]									
Renal HC ($n = 6$)	13 (↓)	–	10 (N)	–	–	–	24 (↑↑)	(↓)	?
<i>Fournier et al.</i> [48]									
IH ($n = 26$)	20 (N)	1.6 (N)	12 (↓)	9 (↓)	1.6 (N)	0.4 (N)	2.2 (↓)	N	(↓)
<i>Heller et al.</i> [33]									
AHI ($n = 9$)	15 (N)	–	6 (N)	8 (↓)	1.8 (↓)	N	N	(↓)	(↓)

^a BV/TV, trabecular bone volume; OV/TV, osteoid volume, tissue referent; OS/BS, osteoid surface, bone surface referent; O.Th, osteoid thickness, Ob.S/BS, osteoblastic surface; Oc.S/BS, osteoclastic surface; ES/BS, eroded surface; MS/BS, total mineralizing surface; BFR, bone formation rate, surface referent

^b Hypercalciuria classified according to Pak et al. [110]. N—Normal, ↓—decreased, ↑—increased as compared to age- and gender-matched control population

it is important to note general trends that emerge from this data. Most of these studies did not divide patients into their respective hypercalciuric classifications. When performed, patients with renal hypercalciuria invariably demonstrated increased bone resorption activity as assessed from osteoclastic and total eroded surfaces. This is not unexpected in light of the secondary hyperparathyroidism these patients usually manifest. The mild but chronic elevation in parathyroid hormone will stimulate osteoclastic bone resorption leading to increased levels of markers of bone resorption and increased osteoclastic activity on bone biopsy examination. Secondly, patients classified as IH, and in whom there was intestinal hyperabsorption of calcium, typically demonstrated reduced bone formation parameters as typified by reduced osteoblastic numbers, and, when performed, reduced tetracycline uptake supporting decreased bone mineralizing activity. Bone resorption parameters are generally in the normal-to-low normal range but could be considered to be inappropriately elevated in light of the low bone formation. In cases where eroded surface is increased but bone formation is diminished, it is possible that the increased eroded surface may be due to the decreased refilling of the Howship's lacunae and not due to a true uncoupling of bone resorption from bone formation. Taken together, these bone histomorphometric findings in patients with IH support the notion that low BMD in this patient population is the result of suppression of bone formation in the face of relatively normal bone resorption. There are, of course, exceptions to this general observation as seen in IH patients with fasting hypercalciuria and secondary hyperparathyroidism where both bone resorption and formation may be increased. The question now remains as to what mechanisms are contributing to the derangements in bone remodeling.

Mechanisms that May Contribute to Bone Loss in IH

From the foregoing discussion, it can be said that there are two types of bone remodeling defects present in patients with IH that appear to be dependent on the type of the hypercalciuria. In patients with renal hypercalciuria resulting from renal calcium leak or from increased filtered load of calcium, the remodeling defect appears to be one of high turnover, possibly as the result of increased serum parathyroid hormone. In addition to the bone biopsy findings, treatment of postmenopausal women with renal leak of calcium and secondary hyperparathyroidism with hydrochlorothiazide, results in correction of the hypercalciuria, resolution of the secondary hyperparathyroidism, and a decline in bone turnover [49]. There are several mechanisms that can contribute to such a high turnover bone remodeling picture.

Role of Cytokines

As discussed above, Pacifici et al. [41] have shown that mononuclear cells from patients with fasting hypercalciuria had an increased constitutive production of interleukin-1 (IL-1). IL-1 is known to be a potent *in vitro* and *in vivo* stimulator of osteoclastic bone resorption [50, 51] and this action of this cytokine may help to explain the lower vertebral BMD observed in these patients. Other bone resorbing cytokines such as IL-6 and tumor necrosis factor (TNF) have also been reported to be increased in patients with IH and that the *in vitro* production of these cytokines was inversely correlated with vertebral BMD [52]. While being attractive, there has not been demonstration of increased cytokine production and simultaneous assessment of bone turnover in the same patients with renal calcium leak. Although this observation was not found to be true for patients with absorptive hypercalciuria [41], there have been no additional studies in patients divided into renal leak and absorptive hypercalciuric groups. Based on previous histomorphometric findings, it is unlikely that this mechanism is operative in absorptive hypercalciuria because the primary defect appears to be the reduced bone formation in the face of normal bone resorption.

High Animal Protein Intake

A high animal protein diet is known to promote hypercalciuria [53]. This diet is typically high in methionine containing amino acids which ultimately are metabolized to sulfate and sulfuric acid. This acid load is eliminated from the body by renal mechanisms and by the involvement of bone buffering under high or chronic metabolic acidosis. This may result from two possible mechanisms that involve both bone and kidney. High dietary protein intake promotes glomerular hyperfiltration, which results in increased filtered load of calcium and hypercalciuria. In addition, metabolic acidosis can directly impair the renal reabsorption of calcium and contribute to a renal calcium leak [54]. Recent studies have disclosed that this action is via direct inhibition of the apical calcium channel in the renal distal tubule cell [55]. However, the magnitude of the hypercalciuria suggests that it cannot be the result of only renal loss. Rather there is another source of calcium contributing to the hypercalciuria which is of skeletal origin. The initial calcium loss from bone under acidotic conditions is due to physicochemical dissolution of bone mineral [56]. However, with continued exposure there is an increase in osteoclastic-mediated bone resorption [57, 58]. Most of these studies have been performed in bone cell culture systems or in animal models. Clinical studies have also supported this notion of acidosis-mediated bone resorption. Reddy and colleagues assessed the effects of a

high-protein-low-carbohydrate weight-reducing diet in 10 overweight subjects [59]. The diet increased net acid excretion by 54 mEq/d and reduced urinary pH by 0.5 units. Urinary calcium increased by nearly 2.5 mmol/d. Biochemical markers of bone resorption tended to rise upward during the diet. There is also epidemiological evidence that individuals in the highest quartile of net acid production or in the lowest quartile of potassium intake, indicative of alkali ingestion, have significantly lower BMD values than for subjects in the other quartiles [60, 61]. There is also suggestive evidence that this mechanism could be operative in some IH patients from the studies of Pietschmann et al. [22], and Jaeger et al. [21] who reported an inverse association between vertebral BMD and 24 h urinary sulfate excretion. In the study of Asplin et al. [36], no significant relation was seen between BMD z-scores of the femoral neck or spine with urinary sulfate or titratable acid. However, an inverse significant correlation was found for total urinary ammonium excretion versus femoral neck and vertebral BMD z-score in stone formers. No such association was observed in non-stone-formers. Sakhaee et al. [62] reported that potassium alkali administration (as potassium citrate) to postmenopausal women significantly decreased urinary calcium without changing serum PTH levels or intestinal calcium absorption. In this study, potassium alkali alone had little effect on bone turnover markers suggesting that the principal effect of alkali is to reduce urinary calcium loss at the kidney. Because increasing alkali intake should reduce or prevent the acid-mediated increase in bone turnover, we evaluated the effect of potassium alkali administration on the bone histological findings in rats placed on high- or low-casein diets (animal protein) and treated with either potassium chloride or potassium alkali. Potassium citrate effectively reduced the acid load and prevented hypercalciuria, cancellous bone loss, and the marked increase in bone resorption seen in the high-casein/KCL-treated group [63]. Although this mechanism could contribute to fasting hypercalciuria seen in some patients with IH, it may not be applicable to the majority of patients with the absorptive hypercalciuric variant of IH because bone biopsy analysis has failed to consistently demonstrate increased bone resorption activity.

Prostaglandin E₂ Excess

Intra-arterial administration of prostaglandin (PG)E₂ in experimental animals has been shown to increase urinary calcium excretion without changes in glomerular filtration [64]. Prostaglandins may act to exacerbate the acid-load-induced hypercalciuria by sensitizing the epithelial calcium channel to inhibition by acid. Prostaglandins also have potent skeletal effects. Their effect on osteoclastic-

mediated bone resorption and osteoblastic bone formation has been reported to be varied and dependent, in part, on the model system used to explore their actions. In general, most studies suggest that PGE₂ is a potent stimulator of bone resorption [65] while inhibiting osteoblastic collagen synthesis [66]. Studies by Krieger et al. [67] have nicely demonstrated that PGE₂ may serve as a mediator of the acid-induced increase in bone resorption. PGE₂ production by mouse calvarial cell cultures is mediated by the inducible cyclooxygenase 2 enzyme. PGE₂ could then promote hypercalciuria by increasing bone loss through increased osteoclastic differentiation and activity and by inhibiting osteoblastic bone formation. Histomorphometric analysis of femurs from rats placed on a high-sulfur-containing diet demonstrated changes consistent with this proposal [57]. However, PGE₂ was not quantitated in that study. Nor has it been established whether a high animal protein diet in humans can increase systemic PGE₂ concentrations sufficiently to affect bone remodeling. Its applicability to patients with absorptive hypercalciuria is again questioned by the limited biochemical and histological evidence not supporting increased bone resorption. Despite these remaining questions, PGE₂ excess could mediate some of the bone loss observed in IH patients with renal calcium leak or fasting hypercalciuria (Fig. 1).

Increased Vitamin D Sensitivity

Many of the biochemical and physiological abnormalities observed for IH patients can be explained by an excess of 1,25-dihydroxyvitamin D (1,25[OH]₂D). Patients with renal leak hypercalciuria have been shown to have increased circulating 1,25[OH]₂D concentrations that can act to mediate increased intestinal calcium absorption and increased bone resorption [68]. On the other hand, the majority of patients with absorptive hypercalciuria have been shown to have normal serum 1,25[OH]₂D concentrations but their hypercalciuria may be mediated by an increased end organ sensitivity to the actions of 1,25[OH]₂D. This notion stems from recent studies in the genetic hypercalciuric stone-forming rat created by Bushinsky and colleagues [69]. These rats have a systemic phenotype in calcium homeostasis that closely mimics that observed in IH patients with the absorptive variant. They absorb more intestinal calcium, and they resorb more bone, particularly on a low-calcium diet, than non-affected littermates. Because serum 1,25[OH]₂D concentration is not increased in these rats, it suggests that there may be increased sensitivity to the actions of 1,25[OH]₂D. Indeed, it has been shown that these hypercalciuric rats have a fourfold increase in the level of 1,25[OH]₂D receptor (VDR) in cultured calvariae compared to control calvariae and similar to the finding of increased intestinal VDRs

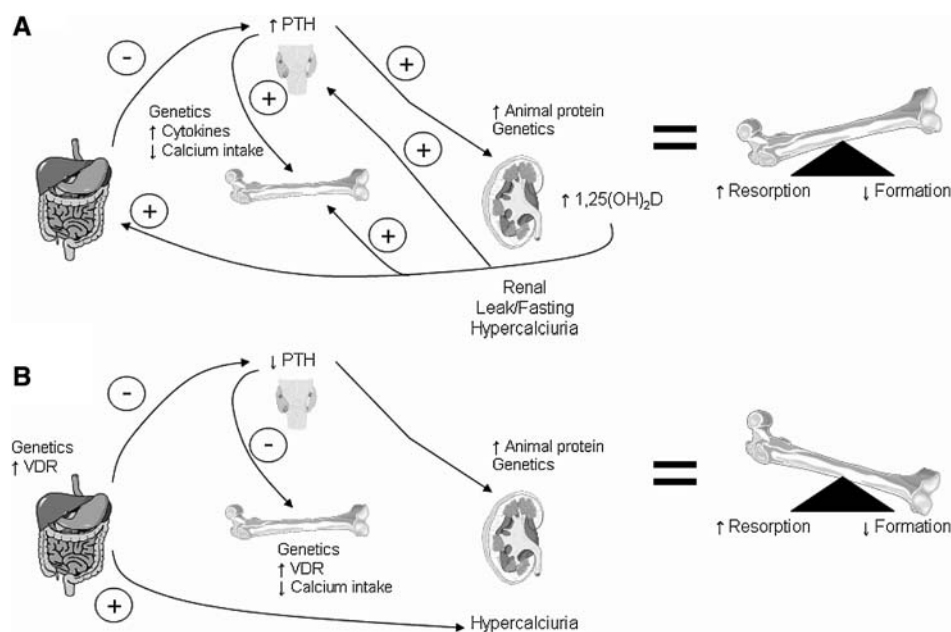


Fig. 1 Pathogenetic mechanisms for concomitant hypercalciuria and bone disease in idiopathic hypercalciuria. **a** Renal leak of calcium or fasting hypercalciuria may result from dietary indiscretions (e.g. high animal protein intake) or from genetic causes (e.g. mutations in TRPV5). This in turn stimulates PTH secretion which increases the renal synthesis of 1,25(OH)₂D. Both of these calcitropic hormones can act directly at bone to stimulate osteoclastic bone resorption. Increased serum 1,25(OH)₂D can also stimulate gastrointestinal absorption of calcium which can help to minimize excessive PTH secretion. Despite the rise in bone mineralizing activity due to the high turnover state of bone remodeling, osteoclastic bone resorption

outpaces osteoblastic bone formation yielding a net loss of bone. **b** Under conditions of increased intestinal vitamin D receptor number, intestinal calcium absorption is augmented in the face of normal serum 1,25(OH)₂D. The increased calcium absorption serves to suppress PTH secretion but at the same time promotes hypercalciuria due to an increased filter load. Dietary indiscretions as well as genetics may play roles at both the gut and kidney. Decreased PTH keeps osteoclastic bone resorption within normal limits but defective osteoblastic bone formation seems to predominate by an unknown mechanism. The end result is loss of bone mass due to reduced bone formation in the face of relatively normal bone resorption

[70, 71]. In a recent clinical study, circulating monocytes from humans with IH were shown to have an increased number of VDRs [72]. Although it will require additional studies before it can be said that this observation is true for the majority of stone-forming IH patients with intestinal hyperabsorption of calcium, it offers a plausible mechanism for explaining the increased bone resorption and reduced bone formation reported in most biopsy studies for this group of patients.

Genetic

The IH appears to be inherited in an autosomal dominant fashion with approximately 40% of patients demonstrating a family history of nephrolithiasis [73, 74]. Attempts to identify the responsible gene(s) have been difficult as we now know that IH does not fit into classical Mendelian genetics but is more closely approximated by a polygenic entity [75–77]. In addition, it is well established that up to 75% of the variation in BMD can be explained by genetics [78]. Thus, it seems logical that studies have attempted to look for common allelic variations or polymorphisms in

genes that link IH and decreased BMD. As mentioned above, the epithelial calcium channels are important gatekeepers of transcellular calcium transport and primary targets for regulation of renal calcium handling by calcitropic hormones, dietary factors, and acid-base status. Whereas these would represent ideal targets for assessment of mutations, studies in nine families with IH disclosed no mutations in the exons for the epithelial calcium channel 1 (TRPV5). Haplotype analysis did not implicate a role of the locus on chromosome 1 (see below). Single nucleotide polymorphisms were noted in the 5'-flanking region. No genotype–phenotype association was identified [79, 80]. Due to the likelihood of loci heterogeneity, TRPV5 and TRPV6 cannot be totally ruled out yet as candidate genes for renal hypercalciuria. Others have looked for association with the VDR gene. Heilberg et al. [81] did not observe an association between BsmI VDR polymorphism and BMD in patients with IH despite previous reports suggesting strong association of the BsmI polymorphism with BMD in osteoporotic patients [82]. In a recent study, a higher prevalence of the “b” rather than the “B” allele was found in stone formers with fasting hypercalciuria and reduced

BMD [83]. Another report identified an Arg990Gly polymorphism of the calcium-sensing receptor gene in patients with IH but its relevance to bone disease is not known because BMD was not measured in that study [84]. Reed and colleagues [85] using linkage analysis in three large stone-forming kindreds, found a linkage to chromosome 1q23-24 and low spinal BMD. The gene was subsequently identified as the soluble adenylyl cyclase gene and subsequent studies disclosed a direct relationship between the number of mutations found in this gene and the severity of the defect in bone formation [86]. Although it is expressed in bone, its function in bone cells is not known. It is hoped that future studies will continue to utilize these molecular biological approaches to fully identify the gene(s) involved with bone loss and IH.

Therapeutic Considerations

Patients with IH represent a particular challenge in the approach to treatment. This is due to the need to not only control their hypercalciuria but also to prevent additional bone loss. In some patients, BMD testing may disclose the need for immediate pharmacological intervention to try and restore lost bone mass. The following represent some useful approaches.

Calcium

Control of calcium intake as a treatment modality is perhaps one of the areas of greatest controversy. Detailed epidemiological studies disclosed an apparent exaggeration of stone formation on low-calcium intake [34]; this effect was attributed, at least in part, to a secondary rise in urinary oxalate (from reduced binding of oxalate by calcium in the bowel, leaving more oxalate available for absorption). Thus, the traditional approach of restricting dietary calcium intake in stone formers has been questioned over the fear that it might exaggerate stone formation. The value of calcium restriction was further questioned when Borghi et al. [35] found that a diet restricted in sodium and animal proteins and rich in fruit products was more effective in preventing stones than a low-calcium diet. A low-calcium diet may produce bone loss. Taylor and Curhan [13] cited the limited effectiveness against stone formation of a low-calcium diet [34] and fear of bone loss from the dietary calcium restriction. In addition, the epidemiological and clinical studies discussed above [12, 17, 44] suggest that reduced calcium intake in stone formers may actually serve to perturb the bone loss. Our approach has been to employ calcium restriction only in hypercalciuric patients [87] in combination with a hypocalciuric agent and potassium citrate [88].

Thiazides

In addition to the calcium-lowering properties of thiazide (TZ) diuretics, several studies have also disclosed that patients treated with TZ display significantly greater BMD, lower rates of bone loss, and fewer hip fractures than those not treated [89–91]. Not all studies have confirmed these findings, however [92]. Although most of the studies were not randomized, two randomized trials assessed the effect of TZ in the prevention of bone loss. Both trials demonstrated significant benefits of TZ on BMD of whole body, as well as at sites that consisted predominantly of cortical bone [93, 94]. Thus, the use of thiazides would seem prudent as it would reduce urinary calcium excretion, prevent kidney stone recurrence, and at the same time exert a positive effect on the skeleton by improving calcium balance.

Bisphosphonates

The genetic hypercalciuric stone-forming rat has been shown to excrete more calcium than available when placed on a low-calcium diet, implying a significant skeletal contribution to the hypercalciuria. When alendronate was added to the diet, there was a significant decrease in both urinary calcium and supersaturation [95]. In addition, it has been shown by others that when IH patients are placed on alendronate, there is a marked decrease in urinary calcium excretion and a fall in bone resorption markers as early as 1 month following treatment [96]. Although these findings would support the use of bisphosphonates in patients with IH, concern has been raised about the possible long-term complication of severely suppressed bone turnover [97]. Because bone biopsy findings in patients with absorptive IH have been consistent with reduced osteoblastic bone formation, caution should be used when initiating bisphosphonate therapy in patients who may already have suppressed bone formation.

Potassium Alkali Therapy

During the use of TZ or indapamide (IND) for the control of hypercalciuria, potassium supplementation is recommended in order to avert hypokalemia, potassium depletion, and attendant neuromuscular and cardiac complications. Moreover, the ensuing hypokalemia may lead to hypocitraturia through intracellular acidification [98, 99], potentially offsetting the beneficial hypocalciuric action on stone formation. Considerable work from our laboratory has shown advantages of potassium citrate over potassium chloride when used with TZ or IND in the management of recurrent stone formation. Overall, potassium citrate is preferred over potassium chloride, because it not only

prevents hypokalemia [98, 100], but also increases urinary citrate [98, 99], an inhibitor of crystallization of calcium salts. Moreover, in short term trials, potassium citrate has been shown to reduce urinary calcium whereas potassium chloride does not [101–104]. Potassium citrate has been shown to be effective in preventing recurrent stone formation in both randomized [105] and non-randomized trials [106]. In addition to its inhibitory action on renal stone recurrence, several reports have shown a possible bone-sparing action of potassium alkali both in vivo [102, 104, 107] and in vitro [108, 109].

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