Bone Disease and Idiopathic Hypercalciuria

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Summary: Observational and epidemiologic studies alike have shown that idiopathic hypercalciuric (IH) stone-forming patients typically show bone mineral density scores that are significantly lower than those observed for age- and sex-matched normal subjects or those for nonhypercalciuric stone-forming patients. Most of these studies have relied on changes in bone mineral density and have not explored the mechanism(s) involved. There have been a small number of studies that have relied on dynamic bone histomorphometry to ascertain the nature of the bone defect in IH patients. When performed, these studies clearly have shown increased bone resorption and high bone turnover in patients with fasting hypercalciuria whereas suppressed bone formation indices are the most consistent finding in patients with the absorptive variant of IH. The causes of this apparent difference in bone remodeling between the 2 variants of IH still is uncertain. Available evidence suggests that potential mechanisms may be dependent in large part to genetic, metabolic, and nutritional causes of hypercalciuria and bone loss in patients with IH.

Keywords: *Osteopenia, hypercalciuric stone-formers, bone histomorphometry, nutrition, genetics*

It has been 30 years since the first report of reduced bone mineral content in patients with urolithiasis. This was soon followed by a series of studies from several laboratories that were consistent with the notion that patients with calcium urolithiasis typically have lower bone mineral density (BMD) than normocalciuric stone-formers and their non–stone-forming counterparts. Despite the consistency of these early reports in documenting low BMD among stone-formers, these studies suffered from several limitations including various causes for urolithiasis, small patient numbers, differences between instruments used to measure BMD, and other confounders such as body mass and sex. This article reviews the evidence supporting the existence of bone loss in patients with urolithiasis, the nature of the defect in bone remodeling contributing to bone loss, and possible mechanisms for such a loss.

DO PATIENTS WITH UROLITHIASIS HAVE REDUCED BMD?

Clinical Studies

Several of the earliest studies that assessed BMD in patients with idiopathic hypercalciuria (IH) suggested that bone mass or bone mineral content (BMC) was lower than that observed for age- and sex-matched normal subjects. However, most of these studies did not clearly define the underlying mechanism for the hypercalciuria or consistently present urinary calcium data. For example, Alhava et al[1] used single-photon absorptiometry (SPA) to quantitate the BMC of the radius in an unselected population of stone-formers. Compared with normals, the stone-formers' BMD at the distal radius was reduced by 5%. Only 5 patients were hypercalciuric at the time of evaluation and some patients had evidence of subtle hyperparathyroidism, a condition that clearly could

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drive increased bone resorption and decreased BMD, particularly of cortical bone as found in the distal radius. In a study by Fuss et al,[2] SPA of the distal radius in 94 patients with IH showed reduced BMC, especially in patients who had been adhering to a low-calcium diet. Again, this study was somewhat clouded by the inclusion of subjects with fasting hypercalciuria and in whom parathyroid hormone (PTH) concentrations may have been increased. Another set of studies by Casez et al[3] initially reported a mean z-score reduction of −0.55 at the spine by dual-energy x-ray absorptiometry in 94 young calcium stone-formers, but in a subsequent study found normal lumbar vertebral BMD in a second group of 99 patients.[4] Barkin et al,[5] using neutron activation analysis, reported that BMD was reduced by 5% in 109 patients with recurrent urolithiasis. This report is significant in that neutron activation analysis is considered to be one of the most sensitive methods for assessing BMC. Thus, these studies have shown that a bone mass deficit does exist among hypercalciuric stone-formers, although the results probably include patients with mild–moderate hyperparathyroidism.

Several studies also have examined BMD in normocalciuric stone-formers. Again, the findings were mixed, with about half of the studies reporting no significant differences in BMD or BMC as compared with age- and sex-matched normal subjects.[4,6-9] On the other hand, studies that used methods for measuring BMD that were considered to be more sensitive found significant reductions of BMD in normocalciuric calcium stone-formers.[5,10-13] These studies used methods such as neutron activation,[5] dual-energy x-ray absorptiometry,[13] and single-energy quantitative computed tomography. Taken together, these studies suggest that bone loss is present in some normocalciuric stone-forming patients, but not of the magnitude observed for patients with IH.

Despite these inconsistent findings in some studies, there appears to be a general consensus of reduced BMD in patients with IH comprising both fasting and absorptive hypercalciuria variants. Except for 2 studies that used the less-sensitive SPA technique,[14,15] all other studies have shown that BMD is decreased significantly at the spine and moderately at cortical-rich sites[7,10-12,16-20] for stone-forming patients with IH. This observation was found to be true whether patients were considered as a whole or subdivided into those with absorptive hypercalciuria type I (AHI) or fasting hypercalciuria. It should be noted that when this subclassification is made, patients with renal leak or fasting hypercalciuria appear to have a much greater deficit in their BMD as compared with patients with AHI, implicating a role for secondary hyperparathyroidism in contributing to the bone loss. On the other hand, the bone loss in patients with AHI appears to occur despite enhanced intestinal calcium absorption, a fact that underscores a primary defect at the level of the skeleton. In addition, many IH patients are instructed to reduce dietary calcium intake to attenuate their hypercalciuria, but in so doing may contribute to enhanced bone loss. This point has been supported by a recent report from Asplin et al.[21] Their study assessed vertebral and femoral neck BMD among relatives and probands in 22 stone-formers (14 of whom were hypercalciuric) and contrasted the results to 37 patients without stones (10 of whom were hypercalciuric). Several interesting findings emerged from their study. There was no difference in mean BMD z-scores at the spine or at the hip between stone-formers and non–stone-formers. Second, stone-formers reported reduced dietary calcium intakes when factored for body weight, but urinary calcium excretion was comparable among the 2 groups, suggesting that stone-formers were in more negative calcium balance as compared with non–stone-formers. This is consistent with balance studies that have shown that bone of IH patients with stones loses more mineral than normal when dietary calcium becomes limited.[22] BMD z-scores at the hip and spine were correlated inversely with urinary calcium for stone-formers but not non–stone-formers. In addition, 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 sus-

ceptible to bone loss by other mechanisms such as increased dietary acid intake.[23,24]

Epidemiological Studies

Based on the foregoing discussion, it is clear that in a majority of these earlier studies patients with IH are at greater risk of sustaining bone loss than compared with nonhypercalciuric subjects. Although many of these studies were performed in few patients with little attempt to characterize the nature of their hypercalciuria, the consistency of findings of reduced BMD in patients with IH strongly supports an association. The significance of this observation lies in the fact that low BMD is a strong risk factor for osteoporotic fracture.[25,26] However, both fractures and kidney stones are relatively rare events in the general population and demonstration of an association would require large study populations, best obtained by epidemiologic data. Melton et al[27] used a population-based retrospective cohort study design with data from the Rochester Epidemiology Project to determine rates of fracture among 624 persons diagnosed with kidney stones from 1950 to 1974 in Olmstead County, MN. The risk of vertebral fracture was increased greatly among men who formed kidney stones (standardized mortality ratio, 7.0), and was increased mildly among women (standardized mortality ratio, 2.4). This increased risk for fractures was observed only for the spine and not at nonvertebral sites. A second population-based study in 1,309 women failed to disclose any association between BMD and fracture and history of kidney stones.[28] Only 44 women were found to have had a history of kidney stones, suggesting that the study may have had insufficient power to observe an association with BMD or fractures. A cross-sectional study by Lauderdale et al[29] used the National Health and Nutrition Examination Survey (NHANES) III data to determine whether a history of kidney stones was associated with lower femoral neck BMD or prevalent spine or wrist fracture. There were 793 respondents out of approximately 31,000 who reported a history of kidney stones (477 men, 316 women). They found that men with kidney stone history had lower femoral neck BMD than men without kidney stone history

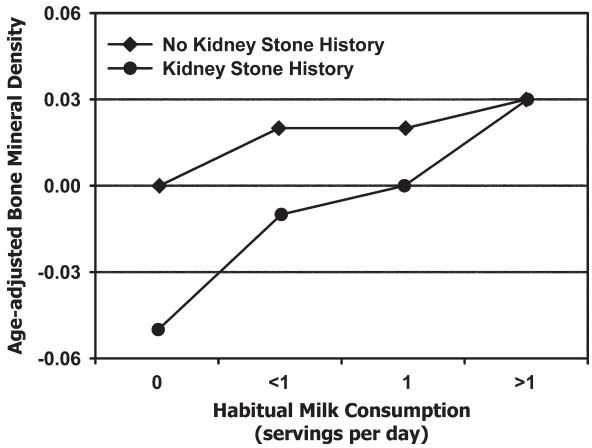

Figure 1. The association between customary dietary calcium intake and age-adjusted femoral neck BMD for men with (●) and without (♦) a history of kidney stones. Customary dietary calcium intake was determined from self-reported habitual milk consumption. Age-adjusted BMD values are relative to men with no kidney stone history and no habitual milk consumption. Reprinted with permission of the American Society for Bone and Mineral Research.[29]

after adjusting for age, body mass index, race/ethnicity, and other potential confounders. This was not true for women who formed kidney stones. Men with kidney stone history were also more likely to report prevalent wrist and spine fractures (prevalence odds ratio for spine fracture, 2.32 for men [95% confidence interval, 1.04-5.18]; but not for women, 1.75 [95% confidence interval, 0.58-5.29]). The study also asked whether dietary calcium modified the association between kidney stone history and BMD. There was a positive interaction term for kidney stone history and milk consumption for both men and women, but was significant only for men ($P = .05$). Figure 1 depicts how the interaction term affects the association between level of milk consumption and age-adjusted BMD for men for each level of milk consumption. Thus, men with a history of kidney stones who reported low milk (calcium) intakes had a much lower age-adjusted BMD than men with no kidney stone history, underscoring an important nutritional consideration in preventing bone loss and increased fracture risk among male kidney stone patients. This observation also was consistent with the results from 2 smaller studies discussed earlier.[2,21]

We can therefore say that there is strong clinical and epidemiologic evidence supporting an association of bone loss in idiopathic hypercalciuric stone-forming patients. Although these studies have used BMD as the marker of bone loss, these studies cannot shed light on the presumed mechanism for bone loss at the tissue level.

WHAT IS THE NATURE OF THE DEFECT IN BONE REMODELING IN IDIOPATHIC HYPERCALCIURIC PATIENTS?

There have been relatively few studies directed at examining bone remodeling dynamics in IH patients. This is probably the result of the need for controlled diets before evaluation, the invasive nature of some procedures such as bone biopsy, and lack of willing patients because of relatively mild asymptomatic bone disease. Two studies have used only biochemical markers of bone turnover. In the study by Jaeger et al,[9] urinary hydroxyproline as well as the collagen cross-links, pyridinoline and deoxypyridinoline, were measured in both fasting and 24-hour urine collections from 29 hypercalciuric and 30 nonhypercalciuric stone-formers. There were no significant differences in the mean values of these markers between hypercalciuric and nonhypercalciuric stone-formers. However, BMD at the tibial diaphysis was correlated negatively with the pyridinoline/creatinine concentration ratio in 24-hour urines and skeletal scores were correlated negatively with fasting hydroxyprolinuria. Although this finding points to increased bone resorption as a cause of the reduced bone mass, subjects were on a free-choice diet during their urine collections, a fact that may have influenced diet-sensitive urinary hydroxyproline excretion. Twenty-four–hour urinary pyridinoline excretion also was correlated inversely with the skeletal score, whereas the more skeleton-specific deoxypyridinoline[30] showed no significant association. More recently, Asplin et al[21] examined 5 bone turnover markers in their study including bone-specific alkaline phosphatase, c-terminal and n-terminal telopeptides of type I collagen in serum, and total pyridinoline and deoxypyridinoline in urine. They found no differences between any of these markers in stone-formers and non–stone-formers. In addition, none were correlated with BMD z-score of the femoral neck or spine to a significant degree. No assessment was made for hypercalciuric versus nonhypercalciuric subjects. Thus, no clear indication of the nature of the bone defect in IH patients has emerged with the use of these biochemical markers.

Studies that have used both static and dynamic bone histomorphometry also have shown mixed results, although one aspect of bone turnover has been observed to be a rather consistent finding, namely decreased bone formation in subjects with IH. Bordier et al[31] performed bone biopsy on 47 calcium stone-formers with IH. For the whole group, biopsy findings were within normal limits. However, when patients were divided into those with renal leak hypercalciuria and absorptive hypercalciuria secondary to renal phosphate leak, 2 distinctive patterns of bone turnover emerged. Patients with increases in PTH showed increased osteoclastic and osteoblastic surfaces consistent with high bone turnover. On the other hand, there appeared to be a defect in bone formation for the patients with renal phosphate leak and intestinal hyperabsorption of calcium. Osteoblastic surfaces were decreased, as were osteoid parameters. Although osteoclastic and eroded surfaces were reported as increased, values were within normal age-adjusted limits and may have simply been the result of a failure of the resorbed lacunae to fill in the face of low bone formation. De Vernejoul et al[32] reported static and dynamic parameters for 30 patients with IH. Although immunoreactive PTH was increased in 3 patients, no subclassification of these patients was performed. Trabecular bone volume was decreased mildly whereas osteoid parameters were normal. Despite normal osteoid parameters, osteoblastic surface was decreased significantly in the face of normal mineralization. Resorption parameters were decreased for osteoclastic surface but normal for eroded surfaces. The investigators suggested that cancellous bone volume was decreased owing to decreased bone formation in the face of normal bone resorption. Malluche et al[33] studied 15 patients with IH. These patients were shown to be of the absorptive type by a decrease in the calcium to creatinine ratio after

cellulose phosphate administration, a nonabsorbable calcium binder. Bone biopsy analysis disclosed a defective bone formation as shown by increased osteoid volume and surface and reduced osteoblast numbers. The increased osteoid surface was considered to be inactive because active double-labeled tetracycline surfaces were reduced by nearly half. Bone resorption did not appear to be increased. The investigators concluded that defective bone formation is present in IH patients with AHI. Perhaps the largest series to date is that of Steiniche et al.[34] They performed bone biopsy in 33 calcium stone-formers while on a random diet and compared the values with those obtained in 30 age- and sex-matched control subjects. These patients displayed normal PTH and serum phosphate levels but increased phosphaturia as well as hypercalciuria. Therefore, their hypercalciuria was probably either dietary or idiopathic in origin, but probably not of the renal leak type. Their histomorphometric data showed decreased bone formation rates and increased mineralization lag times. Total resorption surfaces also were increased but again probably were the result of defective refilling of the lacunae in the face of low bone formation.

Two additional studies composed of small numbers of patients used bone density measurements in addition to bone histomorphometry. As expected, BMD was low for the IH patients in both series.[20,35] Although bone formation was low in both series, the 6 men in the Heilberg et al[20] study had fasting hypercalciuria and increased osteoclastic bone resorption, suggesting dissociation between bone resorption and formation. The 5 calcium stone-formers in the Da Silva et al[35] study showed defective mineralization and increased osteoid and resorption surfaces. Another study by Bataille et al[36] studied 24 hypercalciuric calcium stone-formers because BMD of their vertebrae disclosed a mean z-score of −0.5 by single-energy quantitative computed tomography. Twenty-three of the subjects had fasting hypercalciuria and 1 patient had AHI. As a group, trabecular bone volume was decreased on biopsy as well as the osteoid parameters and bone resorption surfaces. Dynamic parameters were consistent with decreased bone formation and mineral apposition rate without a significant increase of mineralization lag time. These findings are somewhat surprising in light of the fasting hypercalciuria present in most of the patients in the Bataille et al[36] study because increased bone resorption would be expected to be found. However, hydroxyprolinuria was shown to be increased in these patients despite relatively normal bone resorption surfaces on bone biopsy. This latter finding serves well to emphasize the discordance that often is seen between histomorphometric indices of bone resorption and that obtained from biochemical markers of bone turnover.

To help resolve the contribution of bone to fasting hypercalciuria in patients with AHI, Heller et al[37] obtained bone biopsy specimens on 9 stone-formers with AHI and on 9 matched control subjects. Patients then were studied after stabilization on a low-calcium (400 mg/d) diet in an inpatient setting at the General Clinical Research Center for evaluation of calcium homeostasis before and after blockade of bone resorption with alendronate (10 mg/d for 17 days). Bone biopsy analysis disclosed that compared with controls, stone-formers had decreased indices of bone formation (osteoblast surface/bone surface, 1.8% ± 2.1% vs 3.0% ± 1.5%, $P = .04$; mean wall thickness, 36 ± 7 μm vs 47 ± 8 μm, $P = .001$) and relatively higher bone resorption, although the mean value was well within normal limits (osteoclastic surface, 0.4% ± 0.2% vs 0.2% ± 0.2%, $P = .05$). A short-term course of alendronate treatment corrected fasting hypercalciuria and reduced 24-hour urinary calcium by 48 mg/d. However, increased intestinal calcium absorption persisted and calcium balance improved significantly. These studies not only support the persistent finding of reduced bone formation observed in other studies, but also suggest that the hypercalciuria of AHI originates primarily from intestinal hyperabsorption of calcium, but bone resorption in excess of bone formation may contribute. Indeed, Weisinger et al[38] reported a mean decrease in urinary calcium of 75 to 202 mg/d with an identical dose of alendronate to IH patients. Bushinsky et al[39] also found that the urinary calcium of hypercalciuric rats decreased toward the range of wild-type

rats after treatment with subcutaneous alendronate, correcting the estimated negative calcium balance. Urinary calcium did not change in normal subjects or normal rats after alendronate in either of these studies.

Thus, a majority of the studies that have used bone histomorphometry in IH patients support the notion that the low BMD principally is owing to a suppression of bone formation in the face of relatively normal bone resorption. There are exceptions to this, particularly in the face of fasting hypercalciuria and secondary hyperparathyroidism where bone resorption and formation may be increased.

WHAT MECHANISMS ARE RESPONSIBLE FOR BONE LOSS IN IH?

From the foregoing discussion, it is apparent that 2 general types of bone remodeling defects are present in patients with IH and are dependent on the nature of the hypercalciuria. For those with a clear picture of renal hypercalciuria resulting from either renal calcium leak or from increased filter load of calcium, the remodeling defect is consistent with one of increased bone turnover, whereas in those with the absorptive form of hypercalciuria the defect appears to be more consistent with defective bone formation in the presence of normal or inappropriately increased bone resorption. Several possible mechanisms have been proposed to explain these differing responses in bone turnover.

In renal hypercalciuria, there is an increase in bone turnover believed to be secondary to an increase in PTH secretion to maintain serum ionized calcium concentration. Bone biopsy analysis in osteoporotic patients with renal calcium leak and secondary hyperparathyroidism has disclosed increased bone turnover that resolves with hydrochlorothiazide treatment.[40] However, there are additional circumstances under which a renal hypercalciuric picture might emerge associated with increased skeletal turnover.

High Animal Protein Intake

A high animal protein diet is known to cause hypercalciuria. Several mechanisms have been invoked to explain the hypercalciuria but it appears to be derived mainly from both bone and renal loss mechanisms resulting from a systemic acid load.[41] High dietary protein intake causes glomerular hyperfiltration, which results in increased filtered load of calcium and hypercalciuria. However, the hypercalciuria seen under high dietary protein intake is much greater than that predicted to occur only from increased filter load to the kidney.[42] This suggests that there may be a direct acid-mediated inhibition of renal tubule calcium reabsorption. Recent studies have confirmed that an acid load inhibits the renal reabsorption of calcium[43] and promotes a sharp increase in bone turnover in an animal model.[42] Furthermore, in a recent clinical study,[44] a high-protein–low-carbohydrate weight-reducing diet increased net acid excretion by 54 mEq/d and reduced urinary pH by 0.5 units. Although urinary calcium increased by 90 mg/d, intestinal calcium absorption was not altered, suggesting that the hypercalciuria was of skeletal origin. We recently reported on the deleterious effects of high protein intake on the skeleton using static and dynamic-based bone histomorphometry.[42] Protein excess was produced in rats by feeding a high-casein diet. Compared with a low-casein diet, urinary calcium was 3- to 4-fold greater on a high-casein diet that was high in acid ash content. The increase in bone resorption as assessed by eroded surfaces and active osteoclastic surfaces was quite dramatic, with each of these parameters being increased 3-fold or better (Fig. 2). In a preliminary study, Zerwekh et al[45] showed that neutralization of the acid load by co-administration of potassium citrate completely prevented hypercalciuria, cancellous bone loss, and the increase in bone resorption parameters. It is interesting to also note that in 3 previous studies mentioned earlier, in which it was asked whether an association between acid intake and BMD existed, that those results were consistent with such an association. Pietschmann et al[7] found an inverse association between vertebral BMD and 24-hour urinary sulfate and pH. Jaeger et al[9] also showed an inverse association between these biochemical markers of increased acid load and corrected BMD at the tibia and femur. In the study

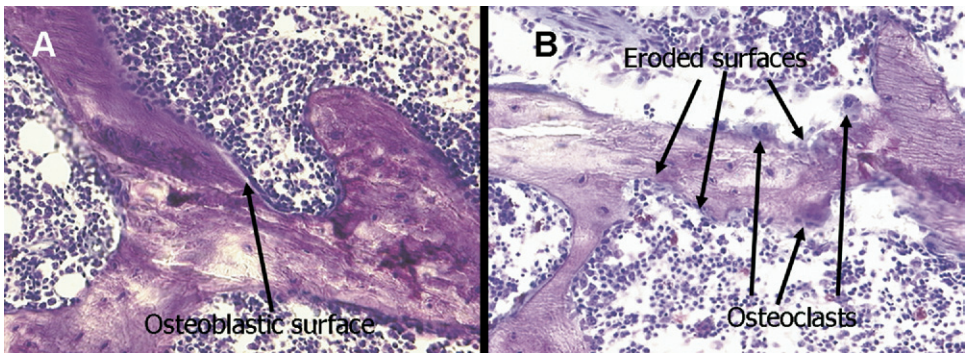

Figure 2. Microphotographs of cancellous bone from rat femur. (A) Trabecular bone from a rat that had been on a low-casein diet for 2 months showing osteoid and osteoblasts (arrow) and normal bone formation. (B) Trabecular bone from a rat that had been on a high-casein diet showing a marked increase in the number of active osteoclasts and extent of eroded surface (arrows). Final magnification, 160×.

by Asplin et al,[21] no significant relation was seen between BMD z-scores of the femoral neck or spine with urinary sulfate or titratable acid, but an inverse significant correlation was found for total ammonium versus femoral neck and vertebral BMD z-score in stone-formers. Non–stone-formers did not show such an association. Finally, Sakhaee et al[46] reported that potassium alkali administration (40 mmol/d) to postmenopausal women significantly decreased urinary calcium without changing serum PTH levels. In this study potassium alkali alone had little effect on bone turnover markers, although it did reduce the serum carboxyterminal extension peptide of type I collagen (a marker of bone resorption) by about 10%.

Prostaglandin E_2 Excess

Another potential sequela of high protein intake is increased renal production of prostaglandin (PG)E_2. Intra-arterial administration of PGE_2 in experimental animals has been shown to increase urinary calcium excretion without changes in glomerular filtration rate.[47] Under conditions of high animal protein intake (increased acid load), PGE_2 may serve to exacerbate the acid-load–induced hypercalciuria by increasing the sensitivity of the epithelial calcium channel to inhibition by acid. Prostaglandins also have potent skeletal effects. Their actions on osteoclasts and osteoblasts have been shown to be mixed, depending on the model used (cell culture, organ culture, whole animal). Most studies have suggested that PGE_2 is a potent stimulator of bone resorption[48] while inhibiting osteoblastic collagen synthesis.[49] Whether a high animal protein diet can increase systemic PGE_2 concentrations sufficiently to affect the bone remodeling process is currently unknown.

Other Potential Causes

Other reports have suggested that the bone loss seen in IH patients with stones may be intrinsic to the underlying cause of the hypercalciuria. Several factors, including interleukin-1, interleukin-6, tumor necrosis factor-α, granulocyte macrophage colony stimulation factor, and fatty acids have been intimated to promote hypercalciuria and bone loss, the latter through increased bone resorption and turnover.[12,47,50-52] Although these potential mechanisms are consistent with increased bone turnover, they may not explain the low bone formation that has been reported for a majority of patients with AHI.

Potential Causes of Low Bone Formation in AHI

As discussed previously, bone biopsy specimens from patients with AHI have shown a picture compatible with low bone formation and turnover whereas features suggestive of increased bone resorption are less common. At the cellular level, decreased bone formation may result from reduced osteoblast numbers, decreased work function per osteoblast, and/or

increased osteoblast apoptosis. To date, there has not been an assessment of osteoblast apoptosis in bone biopsy specimens from patients with AHI. Malluche et al[33] suggested that in patients with nephrolithiasis and stones, the bone biopsy was consistent with decreased work function per osteoblast, whereas in the study by Heller et al[37] it was more consistent with decreased osteoblast numbers. At the molecular level, the number of base changes in the absorptive hypercalciuria-related adenylyl cyclase (AHRAC) has been shown to be well correlated with reduced spinal bone density.[53] Among AH patients with intestinal hyperabsorption of calcium, patients harboring AHRAC base substitutions had much lower bone density than those with wild-type AHRAC genotypes. AHRAC is expressed in bone but its current function in bone cells is currently not known. It is conceivable that dysfunction of AHRAC can alter the rate of bone formation that produces an inappropriately high bone resorption in AHI.[37]

Another potential cause is increased serum 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) or increased sensitivity to its actions. At high doses, this hormonal regulator of intestinal calcium absorption may increase bone resorption and decrease collagen synthesis.[54] Administration of $1,25(OH)_2D$ to normal volunteers mimics the AHI phenotype.[55] Some 30% to 80% of patients with AHI have increases in this vitamin D metabolite because of disordered regulation.[56,57] Vitamin D receptor concentrations have been reported to be increased in IH patients in some studies[58] but not in another study.[59] Increased vitamin D receptor concentration and increased sensitivity of bone[60,61] also have been shown in an animal model of hypercalciuric nephrolithiasis, namely the genetic hypercalciuric stone-forming rat. Thus, in patients with high $1,25(OH)_2D$ or increased receptor number, there may be increased bone resorption compared with normal subjects and possibly reduced collagen synthesis similar to the reduced bone formation observed in AHI stone-forming patients. Additional studies with both human and animal models of AHI will be needed to further explore what mechanisms may be contributing to the bone loss observed for this group of stone-forming patients.

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