Article

Bone metabolism in primary hypercalciuria

Sandro Giannini
Stefania Sella
Luca Dalle Carbonare

Department of Medical and Surgical Sciences, University of Padova, Italy

Address for correspondence:
Sandro Giannini, M.D.
Department of Medical and Surgical Sciences
Clinica Medica 1, University of Padua
Via Giustiniani, 2
35128 Padua, Italy
Ph. +39 049 8212169
Fax +39 049 8212151
E-mail: sandro.giannini@unipd.it

Summary

Primary Hypercalciuria (PH) is very frequently accompanied by some degrees of bone demineralization. The most frequent clinical condition in which this association has been studied is calcium nephrolithiasis. In these patients bone density has been reported to be very frequently low and increased susceptibility to fragility fractures has been described. One of the most important aspects is the very poor definition of this bone disease from a histomorphometric point of view. At present, the most common findings seem to range from those of a low bone turnover condition to an osteomalacic trait. Many factors are involved in the complex relationships between bone loss and PH. Since bone loss has been mainly reported in patients with fasting hypercalciuria, a primary alteration in bone metabolism has been proposed as a cause of both hypercalciuria and bone demineralization. This hypothesis has been strengthened by the observation that some bone resorbing-cytokines, such as IL-1, IL-6, and TNF-α are elevated in hypercalciuric patients. The effect of an excessive response to the acid load induced by dietary protein intake seems an additional factor explaining a primitive alteration of bone. The intestine plays a major role in the clinical course of bone disease in PH. Patients with absorptive hypercalciuria less frequently show bone disease and a reduction in dietary calcium greatly increases the probability of bone loss in PH subjects. It has recently been reported that greater bone loss is associated with a larger increase in intestinal calcium absorption in PH patients. Considering the absence of PTH alterations, it has been proposed that this is not a compensatory phenomenon, but probably the marker of disturbed cell calcium transport, involving both intestinal and bone tissue. While renal hypercalciuria is rather uncommon, the kidney still seems to play a role in the pathogenesis of bone loss of PH patients, possibly via the effect of mild to moderate urinary phosphate loss, with secondary hypophosphatemia. In conclusion, bone loss is very common among PH patients. Even if most of the factors involved in this process have been identified, many aspects of this intriguing clinical condition remain to be elucidated.

KEY WORDS: bone metabolism, BMD, hypercalciuria.

Primary (or idiopathic) hypercalciuria (PH) is the most frequent metabolic abnormality in patients with nephrolithiasis (1) and it is believed to be present in up to 10% of the general population (2). Several hypotheses have been made to explain its pathogenesis and clinical consequences. It has recently become clear that bone is one of the most important involved tissues in patients with PH. Our paper will focus on the role of bone in hypercalciuric patients.

The size of the problem

Since the seventies the hypothesis that a continuous elevation in urine calcium excretion could be associated with some degree of bone loss has been more clearly defined. Due to the fact that idiopathic hypercalciuria is one of the most common phenotypes in patients with kidney stones, the large majority of the studies undertaken to assess bone status in hypercalciuric patients were conducted in patient with calcium nephrolithiasis. These studies demonstrated that while bone density is substantially normal or only slightly reduced in patients with calcium nephrolithiasis without hypercalciuria, significant bone loss is present in patients with kidney stones and primary hypercalciuria (Table I). Bone loss seems to mainly involve those skeletal sites where trabecular bone is more represented, such as vertebral bodies (5-14,16,17). However, a reduction in femoral density was reported by several authors (9,10,12-14,16,17). There are no data available on the number of hypercalciuric patients who suffer from an established osteoporotic bone disease, as defined by WHO classification (18). Yet, the rate of demineralization is generally substantial, ranging from 10 to 15% as compared to age and sex-matched normal subjects (5,7-9,12,14). Some authors reported even more significant decreases in bone density (6). These results seem to be of clinical importance, in view of the relatively young age (approximately 50 years) and of the large proportion of males in the populations studied. There are no data on hypercalciuria as a risk factor for fractures. However, an increased fracture risk was reported in patients with renal calculi (19). Since bone loss was predominantly, if not exclusively, reported in patients with kidney stones and hypercalciuria, exaggerated urine calcium excretion is likely to increase the probability of developing fractures.

Besides the wide overlap between the pathophysiology of absorptive and fasting hypercalciuria, there is some doubt about the differences in bone involvement in patients with both forms of hypercalciuria. While most authors specifically observed a significant proportion of bone loss in patients with fasting hypercalciuria but not in those with the absorptive form (5-7,12,14), others reported a decrease in bone density irrespective of the type of primary hypercalciuria (8,10,11), that is, even in patients classified as having absorptive hypercalciuria (8-10). These data could appear rather surprising, if one considers that patients with the absorptive form of hypercalciuria should be theoretically protected from bone loss by the same mechanism generating hypercalciuria, that is, increased intestinal calcium absorption, which in turn induces positive calcium balance. However, several explanations can be proposed. For

one thing, some studies focusing on this issue were carried out on too small population samples to properly differentiate the effect on bone of the two forms of hypercalciuria (10). Pietschmann et al. (8) found that their patients with absorptive hypercalciuria had low bone density, although its prevalence was limited as compared to patients with fasting hypercalciuria. They speculated on the hypothesis that a low calcium diet, aimed to prevent stone recurrence, and a high consumption of dietary protein may be additional risk factors for bone loss in absorptive hypercalciuria. Moreover, increased serum levels of calcitriol or increased sensitivity to this hormone may stimulate bone resorption in these patients. More recently, it has been found that hypercalciuric patients with the largest proportion of bone loss also present the highest levels of intestinal calcium absorption (17). These intriguing findings suggest that a unique disorder may account for both bone and intestinal alterations, thus explaining the reason why bone loss can be observed in both forms of hypercalciuria.

The type of bone disease

One of the most puzzling aspects of bone disease in patients with PH is its nature. As a matter of fact, bone histomorphometric studies are rare in this setting and have yielded non-homogeneous results. Bone resorption activity seems to be increased (31,32,34) or even normal (33), while the most common histological alteration is a reduction in bone formation function, as observed by most authors (31-36). These results tend to be in contrast with those reported for bone turnover markers. Most authors observed increased levels of both bone formation and resorption markers in hypercalciuric patients (5-7,12,14,21). Additional uncertainness may arise from the observation of a moderate to severe mineralization defect associated with a prolonged mineralization lag (31,33,34-36). An increased osteoid thickness was also reported by Thomas and coworkers (35). Because of the differences in the populations studied (type of PH, sex, age, dietetic conditions, and so on) these findings cannot be univocally interpreted. However, taken as a whole, these data seem to refer to a type of skeletal alteration ranging from a moderately low-turnover osteoporosis to an osteomalacic trait.

Pathophysiology

That primary hypercalciuria and bone disease are not a chance association, but are strictly linked, is a well-established fact based on several observations. The rate of urine calcium excretion was found to correlate with bone loss (10,17,20) and elevation in bone turnover markers (6,12,14,21). In addition, several retrospective and prospective studies showed that thiazide use is associated with a reduction in fracture incidence (22-27) and an increase in bone density [28-30]. Although thiazides may directly act on bone resorption [29,30], the reduction in renal calcium excretion remains the most important contributing factor to the improvement in bone density detected in thiazide-treated subjects (28-30).
Understanding the relationships between PH and bone loss and the pathogenetic factors shared by the two conditions is even more difficult.
We will briefly review the role of bone, kidney, and intestine in the pathogenesis of skeletal alteration of PH.

Bone

Since the revision of the types of PH proposed by Levy and colleagues (37), the term “fasting hypercalciuria” has been used to identify patients who could not lower or normalize their urine calcium excretion appropriately after a restriction in dietary calcium consumption. As low bone density was more frequently reported in these patients, the presence of some conditions causing hypercalciuria and bone demineralization at the same time was suggested.

Table I - Bone mineral density (BMD) in patients with primary hypercalciuria.

Author (reference), year	Measurement method	Measurement site	Result of BMD
Lawoyin et al. (3), 1979	SPA	Radius	↓ N
Fuss et al. (4), 1983	SPA	Radius	↓
Pacifici et al. (5), 1990	QCT	Spine	↓
Bataille et al. (6), 1991	QCT	Spine	↓
Borghi et al. (7), 1991	DPA	Spine	↓
Pietschmann et al. (8), 1992	DEXA, SPA	Spine, radius	↓
Jaeger et al. (9), 1994	DEXA	Spine, femur	↓
Weisinger et al. (10), 1996	DEXA	Spine, femur	↓
Ghazali et al. (11), 1997	QCT	Spine	↓
Giannini et al. (12), 1998	DEXA	Spine, femur	↓
Nisael da Silva et al. (13), 2002	DEXA	Spine, femur	↓
Tasca et al. (14), 2002	DEXA	Spine, femur	↓
Caudarella et al. (15), 2003	DEXA, QUS	Radius, finger	↓
Asplin et al. (16), 2003	DEXA	Spine, femur	↓
Vezzoli et al. (17), 2003	DEXA	Spine, femur	↓

DEXA: Dual Energy X-ray Absorptiometry; *DPA:* Dual Photon Absorptiometry; *QCT:* Quantitative Computed Tomography; *QUS:* Quantitative ultrasound; *SPA:* Single Photon Absorptiometry.

Pacifici et al. (5) firstly reported that some cytokines involved in the mechanisms regulating bone resorption may be involved in the pathogenesis of bone in patients with PH. They found that monocytes from patients with fasting hypercalciuria, but without the absorptive form, produced an exaggerated amount of interleukin-1, a well-known very potent stimulator of bone resorption processes (38), which in turn was correlated with a significant degree of bone demineralization. The role of cytokines in this setting was then confirmed by other reports. Weisinger and coworkers (10) found that the production and mRNA expression of IL-1α from unstimulated peripheral blood mononuclear cells correlated with spinal bone loss in patients with PH and nephrolithiasis. In addition, the same cells produced an increased amount of IL-1α, IL-6, and TNF-α as compared to controls after stimulation with lipopolysaccharide (LPS). Since all these cytokines are considered local mediators of bone resorption (39), the Authors concluded that bone loss may largely depend upon these alterations in hypercalciuric patients with calcium stones. Similar results were obtained by Ghazali et al. (11), who found that IL-1β, IL-6, TNF-α, and GM-CSF from peripheral blood monocytes were involved in the pathogenesis of bone loss in patients with PH. The consistency of all these results undoubtedly strengthens the importance of cytokines as pathogenetic factors of bone loss in PH. However, it remains to be elucidated if an overproduction of these cytokines from bone and bone marrow cells is also present. Indeed, even if it is believed that an altered cytokine secretion from peripheral mononuclear cells may in some way reflect a similar pattern in bone marrow (40), all these bone reabsorbing-substances are mainly considered local regulating factors of cell differentiation and function (39). In addition, no clear explanations were given for such an alteration in cytokine secretion in patients with PH and no differences in IL-1β gene polymorphism were found between patients with or without PH (41).

Other factors are thought to be involved in bone alteration in PH. One of the most studied features is the effect of protein intake in these patients. Excessive protein intake, especially of animal origin, was found to sharply increase urinary calcium excretion and bone resorption and lead to bone loss (42). The main responsible mechanism for these effects is the acid load produced by proteins, especially those rich in sulfur-containing amino acids (42). Accordingly, it was demonstrated that sulfate excretion and some markers of protein intake, such as urinary or serum urea, well correlate with bone turnover markers and density (6,8,9,43). In our study, we also found that a moderate protein restriction was accompanied by a proportional reduction in calcium excretion and bone turnover markers in patients with nephrolithiasis and PH (43). Since dietary protein excess was repeatedly reported in hypercalciuric stone formers (42,43) and hypersensitivity to protein effects on bone was also suggested, normalization of protein intake is highly recommended in hypercalciuric patients.

No consistent data currently support the substantial role of calciotropic hormones in the pathogenesis of bone loss in PH. Calcitriol was reported to be higher in PH patients than in controls and it was observed that this hormone may induce an increase in bone resorption (44). However, the elevation in calcitriol levels was more frequently described in patients with absorptive hypercalciuria, whose bone density levels are generally normal or poorly diminished. In addition, Bataille et al. (6) found that calcitriol levels have a protective rather than a damaging effect on bone mass in patients with PH and kidney stones. Apart from the very small proportion of patients that can be classified as having renal hypercalciuria (37), PTH levels are generally normal in PH patients and are not thought to have a significant role in the pathogenesis of bone loss in this setting.

Intestine

Although the classical distinction of PH in absorptive and fasting hypercalciuria is still maintained, a wide overlap seems to occur between the two forms. Besides, the intestinal function plays a key role both in the pathogenesis of PH and in the development or maintenance of bone disease. Indeed, as mentioned above, some studies also reported a decrease in bone density in patients with absorptive hypercalciuria (8). On the other hand, an increased intestinal calcium absorption is frequently present even in patients with fasting hypercalciuria (45). Vezzoli and coworkers recently reconsidered the complex relationships between intestine and bone in patients with PH in a very interesting study (17). They assessed intestinal calcium absorption in hypercalciuric patients through the method of stable strontium. They found that the greater the loss of bone mineral density, the larger the increase in intestinal calcium absorption, the latter being the best predictor of bone mass in a multiple regression model. Since PTH values were similar in hypercalciuric and normocalciuric stone formers, they speculated that this is not a compensatory phenomenon, but probably the marker of a disturbed cell calcium transport, involving both intestinal and bone tissue (17). This hypothesis would also be in keeping with the view that absorptive and fasting hypercalciuria may be different phenotypes and expressions of the same disorder (46). Although its nature is still poorly understood, some genetic influences might be possible (47).

Whatever the explanation for this increased intestinal calcium absorption in patients with PH, the importance of this observation is further strengthened by considering that in the absence of a proportional intestinal calcium hyperabsorption, the negative calcium balance observed in patients with fasting hypercalciuria should be much larger than it actually is, with a tremendous impact in terms of bone loss and fracture risk. Even if intestinal calcium absorption may largely vary, depending on dietary calcium intake, food quality, intestinal function, serum calcitriol, and so forth, approximately 4-5 mmol of calcium are absorbed daily through the gut and the same amount is eliminated with the urines (47). In the presence of hypercalciuria, calcium balance may be maintained only at the expenses of skeletal tissue or by an increase in intestinal calcium absorption, which may in turn limit bone loss. The restriction in dietary calcium intake, which many hypercalciuric patients tend to do by themselves or after medical prescription, is therefore a major risk factor for bone loss in this setting. Indeed, it was clearly seen that a reduction in calcium intake is associated with negative calcium balance and bone loss in hypercalciuric patients (9,48,49). Some authors (48,49) reported this negative effect after a calcium-restricted diet of 2-8 years, while Jaeger et al. observed a significant reduction in bone density in hypercalciuric patients already after the first year of low calcium diet (9). In addition, Curhan et al. (50) reported that dietary calcium restriction does not reduce the incidence of new kidney stones but, in fact, it increases the risk of developing new symptomatic renal calculi, at least in males. This seems to occur because of the increase in intestinal oxalate absorption with a secondary increase in its urinary excretion in the absence of calcium in the colon. All these observations suggest that hypercalciuric patients need to maintain an appropriate dietary calcium intake.

Kidney

The presence of renal calcium leak is the basis for the so-called renal hypercalciuria, which is characterized by increased urine calcium, a tendency toward hypocalcemia, and a secondary increase in parathyroid hormone secretion. The latter is

considered the main cause of bone loss in these patients (48). However, the large revision of the pathogenetic aspects of patients with PH led to the observation that less than 5% of hypercalciuric patients suffer from a renal form of PH (37). As a consequence, the importance of renal calcium leak as a pathogenetic factor for bone loss in these patients was completely reconsidered.

However, some other aspects seem to link the kidney to the complex relationships occurring between hypercalciuria and bone. Increased urinary phosphate excretion was found in hypercalciuric patients as compared to normal subjects, irrespective of the presence of a true form of absorptive hypercalciuria with renal calcium leak (51). It was suggested that an excessive excretion of phosphate may be present in the majority of patients with PH, then concurring to the development of the hypercalciuric state in the whole population of PH patients. Similar findings were reported by Prié et al. (52) in hypercalciuric stone formers. They observed that the distribution of renal phosphate threshold normalized for glomerular filtration rate (TmPi) was quite different between patients and controls, with hypercalciuric patients showing a decreased value of TmPi in approximately 20% of cases. No assessment of bone status was made in the two papers. However, it could be hypothesized that the alteration in phosphate metabolism seen in these patients may play a role also in the pathogenesis of bone damage in hypercalciuric patients. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a paradigm of this pathophysiology (53). This disease shares some clinical aspects with the disorder seen in the Npt2 knockout mice, carrying the deletion of the gene of kidney-specific Na-Pi cotransporter, in which a delay in bone mineralization is seen 21 days after birth. These bone alterations may resemble those observed in hypercalciuric patients by histomorphometric studies (31-36), in which an alteration in bone mineralization process was reported. Accordingly, a mutation of NPT2 gene was found in nephrolithiasic patients with decreased bone density by Prié and coworkers (54). In conclusion, even if no clear evidence supports the hypothesis that renal phosphate leak may be at least in part responsible for bone disease in PH patients, this research field appears as one of the most promising to better elucidate the role of kidney in the pathogenesis of bone loss in PH.

Conclusions

Bone disease is one of the most common clinical findings in patients with PH, even though its importance seems to be currently underestimated. Most of the organs and tissues normally involved in the control of calcium and phosphate metabolism seem to take an active part in the pathogenesis of skeletal alterations. New insights in molecular medicine as well as larger clinical studies will be helpful for a better understanding of this very complex matter.

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