Urol Res (2005) 33: 247–253
DOI 10.1007/s00240-005-0498-y

INVITED REVIEW

A. Trinchieri

Bone mineral content in calcium renal stone formers

Received: 25 June 2005 / Accepted: 27 June 2005 / Published online: 3 August 2005

Abstract Idiopathic renal calcium stone disease often presents with reduced bone mineral content. Investigations using non-invasive methods for the measurement of bone mineral content (single and dual-photon absorptiometry, dual-energy x-ray absorptiometry, quantitative computed tomodensitometry) show a slight decrease in skeletal mineral content of idiopathic renal stone formers (RSFs).The alterations in bone mineral content in RSFs have different explanations: prostaglandin-mediated bone resorption, subtle metabolic acidosis and 1–25 vitamin D disorders. Bone mineral content is worsened by insufficient dietary calcium leading to a negative calcium balance.

Keywords Calcium stone disease · Bone mineral density · Hypercalciuria · Dietary calcium · Hyperparathyroidism

Introduction

Recurrent calcium nephrolithiasis is often associated with disorders of calcium phosphate metabolism [32, 53]. For this reason, evaluation of bone mineral content in this group is particularly interesting.

For some pathological conditions correlated to nephrolithiasis, such as hyperparathyroidism [16, 20, 30] or distal renal tubular acidosis [60], the alterations in the bone mineral content are evident and have been known for some time. In other cases, for example idiopathic hypercalciuria, knowledge is limited and incomplete.

A. Trinchieri
Urology Unit, Ospedale A. Manzoni,
Via dell'Eremo 9/11, 23800 Lecco, Italy
E-mail: a.trinchieri@ospedale.lecco.it
Tel.: +39-341-489118
Fax: +39-341-489328

Bone mineral content

Reduction of the bone mineral content is variable and has an ambiguous definition. The loss of bone density has recently been defined as either osteopenia or osteoporosis on the basis of whether the reduction in bone mineral density is either 1 or 2.5 standard deviations, respectively, below the young adult mean [33].

In the adult, a reduced bone mineral density can be due to a low peak bone density or bone loss. Peak bone mass is reached in the third decade, followed thereafter by a decline in total bone density [64, 73]. Genetic and environmental factors, such as race, familial status, diet, physical exercise and hormone balance determine peak bone density. The loss of bone mineral content can be due to reduced bone formation or increased bone resorption and formation [22].

The remodeling cycle of bone consists of three sequential phases: the resorption period, the transitional period, and the formation period. Various types of activating stimuli prime the activity of the osteoclasts that start the resorption process. When the resorption process terminates, bone formation begins. The short interval between bone resorption and formation is defined as the transition period. The time between the end of the formation and the subsequent new activation is called the quiescent period. A reduction in the frequency of activation periods will give an overall positive balance, at the tissue level, until a new steady state is achieved, although the balance at the remodeling site (at the single lacuna) may still be negative. There are many hormonal and non hormonal factors that influence the formation and resorption of bone: 1,25 vitamin D, calcitonin, parathyroid hormone (PTH), dietary calcium intake, etc.

Bone formation and resorption can be studied utilizing plasma and urine markers [15, 72]. Markers of bone formation (osteocalcin, bone alkaline phosphatase, procollagen 1 extension peptides) and bone resorption (urinary pyridinium crosslinks, urinary hydroxyproline) may be used to define the pathophysiology of osteopenia.

Primary hyperparathyroidism

Primary hyperparathyroidism is characterized by an increased bone turnover. PTH acts by increasing the frequency of activation with a subsequent increase in eroded and osteoid covered surfaces in more sites, whereas osteoclastic activity and the resorption depth at the single site may be decreased in hyperparathyroid patients. The action of PTH is reflected by the increased excretion of urinary hydroxyproline.

The presence of bone lesions in patients with hyperparathyroidism was first demonstrated by conventional radiological studies and then by more sophisticated investigations: gamma ray absorption [20], whole body neutron activation analysis [30], and x-ray spectrophotometry [16].

The classical descriptions of primary hyperparathyroidism distinguished between bone and renal clinical forms [1].The introduction and diffusion of reliable methods for the determination of serum calcium has lead to the diagnosis of an increasing number of asymptomatic cases. As a result, the incidence of nephrolithiasis in patients with hyperparathyroidism, which was estimated in 1970–1980 as varying between 30 and 60% [10, 43, 58], is today much less [66].

According to the classic observations of Albright et al. [1], bone and renal lesions never occur simultaneously in the same patient. The appearance of renal rather than bone problems in primary hyperparathyroidism has been explained on the basis of different mechanisms: dietary calcium intake, intestinal absorption of calcium, different forms of PTH, different levels of 1,25 vitamin D. Albright et al. [1] maintain that a low dietary calcium intake is the origin of the bone form, while a high dietary calcium intake provokes the renal form, but this hypothesis has been refuted by Dent et al. [17] who suggested the presence of two different forms of PTH, one responsible for the bone and the other for the renal form of the disease. Hyperparathyroid patients with nephrolithiasis are said to have an increased intestinal absorption of calcium, whereas it is normal in patients with bone lesions [58]. This hypothesis was supported by the observation of high levels of 1,25 vitamin D in a subgroup of patients with increased intestinal absorption of calcium and renal calculi, and normal 1,25 vitamin D levels in patients with bone lesions and normal intestinal calcium absorption [10]. However, these observations could not be confirmed by others [34, 57].

More recently, Silverberg et al. [66], using bone densitometry, which provides a more accurate measure of demineralization then conventional radiology, demonstrated that bone demineralization is present to the same extent in hyperparathyroid patients both with or without nephrolithiasis. A correlation was observed between 1,25 vitamin D and urinary calcium excretion but there was no difference in 1,25 vitamin D levels in hyperparathyroid patients with or without calculus disease [66].

Higher levels of urinary hydroxyproline in patients with nephrolithiasis have led to the conclusion that urinary calcium excretion is an expression of both vitamin D activity as well as bone resorption.

A reduction of bone mineral content mainly affecting cortical bone has been documented in hyperparathyroidism [46, 62]. These metabolic abnormalities were reversed by parathyroidectomy [46, 50].

Idiopathic calcium nephrolithiasis

Over the last 20 years, the bone mineral content of calcium renal stone formers (RSFs) has been extensively studied in relation to their urinary calcium excretion.

Hypercalciuric patients were classified as ''renal'' or ''absorptive'' according to the proposed cause of hypercalciuria: defective renal tubular calcium reabsorption or intestinal calcium hyperabsorption [56].

Early attempts to study bone mineral content in calcium nephrolithiasis using conventional radiological techniques failed to demonstrate a difference between stone-formers and controls [29].

A more sophisticated photodensitometric method applied to the proximal radius showed that bone mineral content in patients with renal calculi and hypercalciuria was less than 1 standard deviation below the normal average, whereas the difference between hypercalciuric and normocalciuric RSFs was not significant [77]. Similar results were reported by Katayama et al. [35] using microdensitometry.

Calcium kinetic studies have shown an increase in bone turnover with accelerated bone formation and resorption [3, 40].

Barkin et al. [4], using in vivo neutron activation analysis, demonstrated a reduction in calcium content in the middle third of the skeleton in RSFs that was 5.2% less than a control group, together with a negative correlation between fasting calcium excretion and bone calcium content, but there was no significant difference between hypercalciuric and normocalciuric patients.

Other researchers [8, 44, 69] investigated the histological aspects of bone of RSFs. An increase in osteoclast activity and a decrease in osteoblast activity has been observed in some patients with idiopathic hypercalciuria [8, 69], although a reduction in osteoblast activity alone was observed in patients with absorptive hypercalciuria [44].

Recently, reliable and accurate non-invasive methods have become available for the measurement of bone mineral content. Alhava et al. [2], using the americium-241 gamma ray attenuation method, observed a reduced bone mineral content in calcium RSFs without primary hyperparathyroidism. Other studies using 125-I photon absorptiometry of the forearm (single-photon absorptiometry, SPA) demonstrated bone mineral content to be normal in patients with absorptive hypercalciuria, but reduced in those with renal hypercalciuria [38, 41]. Fuss et al. [22] have

shown bone mineral density to be reduced in both hypercalciuric and normocalciuric calcium RSFs compared with controls, but greater than in patients with primary hyperparathyroidism. The lowest levels were present in those with renal hypercalciuria and rose progressively in those with absorptive hypercalciuria and normocalciuria, however, the differences were not statistically significant. Decrease in bone density was found to be aggravated in both hypercalciuric and normocalciuric patients by dietary calcium restriction over a period of 10 years, approaching the levels seen in patients with primary hyperparathyroidism [23].

More recently, computerised dual-photon absorptiometry (DPA) has been used to evaluate the mineral content of the spine, as it allows a more accurate evaluation of the trabecular bone of the lumbar vertebrae and enables detection of early bone loss due to a high turnover and a more sensitive response to metabolic stimuli. This method has been used to confirm that the bone mineral content is reduced in patients who form renal calculi [45] and particularly in those with renal hypercalciuria [71]. Borghi et al. [9] have shown that patients with diet-independent hypercalciuria have a reduced bone mineral content compared with patients with diet-dependent hypercalciuria in whom bone mineral density is normal.

Bataille et al. [6] confirmed these findings with the use of quantitative computed tomodensitometry to the extent of a 30% reduction in some patients with diet-independent hypercalciuria.

With the use of dual-energy x-ray absorptiometry (DXA) Pietschmann et al. [59] observed a reduction of 10% in the bone mineral content of the lumbar spine in 74% of patients with absorptive hypercalciuria and in 92% of patients with fasting hypercalciuria, but in only 48% of normocalciuric patients. This difference between the three groups was not evident at the level of the radius. A study of bone mineral content at several skeletal sites [31] demonstrated a tendency to osteopenia but failed to show differences between hypercalciuric and normocalciuric stone formers, which could be influenced by several confounding factors such as weight, height, sex and classification of hypercalciuria.

The degree of bone loss has been usually estimated at 10% or less; more substantial losses have only been observed by Fuss et al. [23] at 20% and Bataille et al. [6] at 30%.

In the last years some population-based epidemiological studies of the link between kidney stones and bone fractures were published.

Melton et al. [48], using data from the Rochester Epidemiology Project, observed that the risk of vertebral fracture was greatly increased among men who formed kidney stones from 1950 to 1974 in Olmstead County, with a standardized morbidity ratio of 7.0. On the contrary, the risk of fracture at the proximal humerus, distal forearm, pelvis, and proximal femur was not increased. In women, the risk of vertebral fracture was lower (standard morbidity ratio = 2.4).

In a second study [67], no association between risk of fractures and a history of kidney stones was observed in a population of 1,309 women by Sowers et al.

Finally, after adjusting for age, body mass index, race/ethnicity and other potential confounders, Lauderdale et al. [37] observed that men with a kidney stone history had lower femoral neck bone mineral density and reported more wrist and spine fractures than men without a kidney stone history. This association was weaker for women.

Pathogenetic mechanisms

An explanation for the loss of bone mineral content can be found in the condition of renal leak hypercalciuria. This defect in the tubular reabsorption of calcium results in a negative calcium balance which leads to secondary hyperparathyroidism with resorption of bone calcium. Lawoyin et al. [38] observed reduced bone mineral content in a group of patients with renal hypercalciuria together with increased levels of PTH and urinary cAMP. Others [22, 41, 71] have also described renal hypercalciuria in association with altered bone mineralization but do not comment on parathyroid function.

Normal or low PTH values (or urinary cAMP) have been reported in patients with hypercalciuria and reduced bone mineral density [9, 77]. On the other hand, the lack of signs of secondary hyperparathyroidism in patients with fasting hypercalciuria has been previously reported [49]. Bataille [6] has not excluded this hypothesis, considering it a rare possibility (2.4% of patients with fasting hypercalciuria).

A subgroup of patients with absorptive hypercalciuria appear to have a defect of tubular phosphate reabsorption and hypophosphataemia that could provide the stimulus for 1,25 vitamin D synthesis [8]. A genetic predisposition for a renal tubular defect in phosphate reabsorption leading to hypophosphataemia has been observed in both humans and animals [68, 74]. Increased osteoclast activity and reduced osteoblast activity in some calcium stone formers correlated with reduced phosphate levels and a reduced renal threshold for phosphate [8], but this was not confirmed by others [9, 22], and Fuss et al. [22] did not find any correlation between bone mineral density, phosphate levels and the indices of tubular phosphate reabsorption (TRP and $TmPO_4/GFR$).

In conclusion a defective tubular reabsorption of calcium with secondary hyperparathyroidism or a defective tubular reabsorption of phosphate with a low serum phosphate stimulating 1,25 vitamin D synthesis could be a possible explanation for the low bone mineral density observed in some patients with calcium nephrolithiasis, but a reduced bone mineral content is also found in calcium renal stone formers without signs of secondary hyperparathyroidism or alterations in phosphate levels.

The earlier classification of hypercalciurias by Pak et al. [56] has been replaced by simpler definitions that make the distinction between diet-dependent or diet-independent hypercalciuria [6,9], based on the investigation of patients on a balanced diet and after a period of calcium restriction with particular attention being paid to sodium intake [9, 27, 51] and natriuresis [6].

It would seem that patients with diet-independent hypercalciuria do not appear to have alterations of PTH or phosphate values [5, 11, 14, 49, 70]. These findings, therefore, do not support the hypothesis of a renal tubular defect as the cause of reduced bone mineral content in RSFs. On the other hand, high levels of urinary hydroxyproline in these patients indicates increased osteoclastic activity [49, 55, 70].

Sutton and Walker [70] and Messa et al. [49] were the first to observe an alteration in urinary hydroxyproline levels and ascribed this to a primary defect of bone metabolism. According to this hypothesis, after extreme calcium deprivation, a strict relation between net calcium flux from bone and fasting calcium urinary excretion occurs [49]. Some authors reported a negative correlation between high levels of urinary hydroxyproline and bone demineralization particularly in the fasting state [6, 9], however, this could not be confirmed by others [22].

Other markers of bone metabolism, such as the bone isoenzymes of alkaline phosphatase and osteocalcin, have been contradictory. Elevation of alkaline phosphatase and normal osteocalcin values in patients with diet-independent calciuria were reported by Borghi et al. [9]. Normal osteocalcin levels were reported earlier by Rico et al. [63]. High levels of alkaline phosphatase have been reported in patients with reduced bone mineral density, both hypercalciuric and normocalciuric [35]. Kuczera et al. [36] found elevated alkaline phosphatase and osteocalcin levels together with raised PTH values in RSFs who were in an active phase of the disease. Osther et al. [54] observed elevated levels of serum osteocalcin and urinary hydroxyproline in patients with calcium nephrolithiasis, but only in the presence of incomplete renal tubular acidosis. Free gamma-carboxyglutamic acid residues derived from bone matrix proteins are considered to be more specific markers of bone metabolism than hydroxyproline. Maruyama et al. [47] reported raised serum, but normal urinary levels of free gamma-carboxyglutamic acid with normal urinary and serum hydroxyproline values in normocalciuric RSFs. No alterations in alkaline phosphatase, urinary hydroxyproline and osteocalcin were observed in patients with hypercalciuria [18], although high levels of 1,25 vitamin D and PTH were present in patients with renal hypercalciuria.

Histology of biopsies from patients with diet-dependent hypercalciuria has shown reduced bone mass and, as osteoid thickness appeared to be reduced, these changes were considered to be due to a reduced velocity of bone formation [7]. These findings do not support the hypothesis that there is increased bone resorption in patients with diet-dependent hypercalciuria; interestingly urinary hydroxyproline was increased in these patients but the more sensitive bone marker, pyridinoline, was not. This, therefore, casts some doubt on the role of increased bone resorption in the pathogenesis of diet-dependent hypercalciuria.

An immunological process has been proposed as the basis for alterations in bone metabolism, as an increase in cytokines (interleukin 1) by monocytes has been observed in patients with idiopathic hypercalciuria [55]. Interleukin 1 (IL-1) is well recognised as a potent stimulus to prostaglandin synthesis and prostaglandins are known to induce bone resorption. The role of prostaglandins is supported by studies demonstrating the hypocalciuric effect of prostaglandin synthetase inhibitors [12, 19, 61]. More recently, Jungers et al. [32] reported an increase in the production of IL-1beta,TNF alfa and IL-6 by monocytes in hypercalciuric stone formers.

Pacifici et al. [55] demonstrated that patients with fasting hypercalciuria have decreased bone mass and increased monocytic production of IL-1 and increased bone resorption.

Weisenger et al. [78] confirmed the correlation between age-normalized bone density values and IL-1 levels and demonstrated that monocytes from hypercalciuric patients have an increased expression of IL-1 mRNA and produce larger amounts of IL-1.

Ghazali et al. [26] reported that bone density was significantly lower in hypercalciuric patients than in age-matched controls. They reported that unstimulated peripheral blood monocytes from stone formers with hypercalciuria secrete larger amounts of IL-1, TNF and GM-CSF than healthy controls.

On the other hand, the observed higher levels of cytokines could be a response to increased bone resorption because the released collagen and other matrix proteins released are known to bind to integrin receptors expressed in monocytes, so stimulating cytokine production.

At the origin of alterations in bone metabolism observed in RSFs, there could also be a defect of vitamin D regulation: high circulating levels of vitamin D or an increased bone tissue sensibility to vitamin D could be responsible for bone mineral loss. Many authors have described high serum levels of vitamin D in hypercalciuric patients [11, 23, 52, 65] and a negative correlation between vitamin D levels and mineral apposition velocity has been described [6]. In fact, 1,25 vitamin D slows down bone formation independently of PTH, inhibiting collagen synthesis; on the other hand it could increase bone resorption in cases of calcium deprivation [42]. Hess et al. [28] formed the hypothesis that in patients with hypercalciuria the synthesis of 1,25 vitamin D is increased due to secondary renal hypertrophy and an excessive protein and sodium dietary intake. Serum levels of 1,25 vitamin D are positively correlated with creatinine clearance which, in turn, is correlated with urinary excretion of sodium, urea and sulphates,

expressing the protein and sodium dietary intake. The wrong regulation of vitamin D synthesis could be responsible for chronic hypoparathyroidism in hypercalciuric patients.

The role of nutrient

The relationship between a high consumption of animal protein and stone formation is well documented. The metabolic acidosis induced by a high protein diet results in bone dissolution secondary to the sacrifice of bicarbonate stores to act as a buffer [39]. There is subsequent hypercalciuria from an increased filtered load and reduced tubular reabsorption. An increase in urea excretion in patients with diet-independent hypercalciuria supports the role of dietary protein [6]. A positive correlation was noted between urinary urea and hydroxyproline excretion and calciuria in fasting patients [6]. Both hypercalciuric or normocalciuric calcium RSFs with a reduced bone mineral content were found to have a high body mass index and raised uric acid excretion [59]. Moreover patients with absorptive hypercalciuria were found to have a positive correlation between bone mineral content and the excretion of sodium, sulphates and urinary pH, evidence of high sodium and protein intake.

An high protein diet could potentiate the metabolic effects of incomplete renal tubular acidosis [54, 76]. Osteocalcin and urinary excretion of hydroxyproline were increased in patients with an incomplete renal acidification defect.

The negative effect of a low calcium diet in patients with recurrent calcium nephrolithiasis has also been demonstrated. On the other hand, it is still a common practice to recommend a restriction of oxalate and calcium intake to patients with calcium stones. The prolonged adoption of this diet can lead to a negative calcium balance in the presence of various pathological conditions related to calcium stone disease: renal hypercalciuria, hypophosphataemia, and high levels of 1,25 vitamin D. It has been observed that in these patients, following a prolonged reduced calcium intake, an increase in alkaline phosphatase levels and in urinary excretion of hydroxyproline occurs in the presence of normal values of serum PTH and urinary AMPc [23, 24]. On the other hand it has not been possible to show reduced plasma levels or a defect of calcitonin synthesis [25]. Fuss et al. [23] demonstrated that patients with the lowest mineral content in his study had undergone prolonged periods of dietary calcium restriction. This observation has been confirmed by Jaeger et al. [31].

Trinchieri et al. [75] studied the effect of different levels of dietary calcium intake on the bone mineral content of a group of male idiopathic calcium renal stone formers.

Bone mineral density of the lumbar spine, expressed as a Z score, was significantly lower in the group consuming less than 600 mg/day of calcium than in the group consuming more than 1,000 mg/day. No significant difference in calciotropic hormones and in markers of bone resorption was found between patients on a low calcium diet and those consuming a normal calcium diet, although 1,25 vitamin D levels tended to be higher in patients on a low calcium diet. Urinary excretion of pyridinium crosslinks was above the normal range in about 30% of the patients.

They concluded that long-term dietary calcium restriction may lead to negative calcium balance and bone loss in the presence of slightly increased levels of 1–25 vitamin D.

In conclusion studies have revealed that renal stone forming patients have decreased axial and peripheral bone density that can be related, at least in part, to an abnormality in bone remodeling, although chronic calcium deprivation may be a contributing factor.

References

1. Albright F, Aub JC, Bauer W (1934) Hyperparathyroidism: a common and polymorphic condition as illustrated by 17 proven cases from one clinic. JAMA 102: 1276
2. Alhava EM, Juuti M, Karjalainen P (1976) Bone mineral density in patients with urolithiasis. Scand J Urol Nephrol 10: 154
3. Anderson J, Lee HA, Tomlinson RWS (1976) Some metabolic aspects of idiopathic hypercalciuria. Nephron 4: 129
4. Barkin J, Wilson DR, Manuel MA, Bayley A, Murray T, Harrison J (1985) Bone mineral content in idiopathic calcium nephrolithiasis. Miner Electrol Metab 11: 19
5. Bataille P, Bouillon R, Fournier A, Renaud H, Gueris J, Idrissi A (1987) Increased plasma concentrations of total and free 1,25-(OH)2D3 in calcium stone formers with idiopathic hypercalciuria. Contr Nephrol 58: 137
6. Bataille P, Achard JM, Fournier A, Boudail B, Westeel PF, Esper N, Bergot C, Jans I, Lalau JD, Petit J, Henon G, Laval A, Jeantet MA, Bouillon R, Sebert JL (1991) Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. Kidney Int 39: 1193
7. Bataille P, Marie A, Ghazali A, Cohen Solal ME, Steiniche T, Brazier M, Gueris J, Sebert JL, Fournier A (1996) Histological and biochemical study of bone turnover in calcium stone formers (CSF) with fasting hypercalciuria and osteopenia. In: Pak CYC, Resnick MI, Preminger GM (ed) Urolithiasis 1996. Millet, Dallas, p 1
8. Bordier P, Ryckewart A, Gueris J (1977) On the pathogenesis of so-called hypercalciuria. Am J Med 63: 398
9. Borghi L, Meschi T, Guerra A, Maninetti L, Pedrazzoni M, Marcato A, Vescovi P, Novarini A (1991) Vertebral mineral content in diet-dependent and diet-independent hypercalciuria. J Urol 146: 1334
10. Broadus AE, Horst RL, Lang R, Littledike ET, Rasmussen H (1980)The importance of circulating 1,25(OH)2D in the pathogenesis of hypercalciuria and renal stone formation in primary hyperparathyroidism. N Engl J Med 302: 421
11. Broadus AE, Insogna KL, Lang R, Ellison AF, Dreyer BE (1984) Evidence for disordered control of 1,25-dihydroxyvitamin D production in absorptive hypercalciuria. N Engl J Med 311: 73
12. Buck AC, Lote CJ, Sampson WF (1983) The influence of renal prostaglandins on urinary calcium excretion in idiopathic urolithiasis. J Urol 129: 421
13. Coe FL, Kavalach AG (1974) Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. N Engl J Med 291: 1344

14. Coe FL, Favus MJ, Crockett T, Strauss AL, Parks JH, Porat A, Gantt CL, Sherwood LM (1982) Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1,25(OH)2D3 levels in patients with idiopathic hypercalciuria and in normal subjects. Am J Med 72: 25
15. Cormier C (1995) Markers of bone metabolism. Curr Opin Rheumatol 7: 243
16. Dalen N, Hjern B (1974) Bone mineral content in patients with primary hyperparathyroidism without radiological evidences of skeletal changes. Acta Endocrinol 75: 297
17. Dent CE, Hartland BV, Hicks J, Sykes ED (1961) Calcium intake with primary hyperparathyroidism. Lancet 2: 336
18. Diaz Perez de Madrid J, Munoz Torres M, Garcia de Vinuesa MJ, Mijan JL, Escobar Jimenez F, Zuluaga A (1989) Parathormone, cyclic AMP, 1,25 dihydroxyvitamin D and osteocalcin in hypercalciuric renal lithiasis. Arch Esp Urol 42: 129
19. Filipponi P, Mannarelli C, Pacifici R, Grossi E, Moretti I, Tini S, Carloni C, Blass A, Morucci P, Hruska KA, Avioli LV (1988) Evidence for a prostaglandin-mediated bone resorptive mechanism in subjects with fasting hypercalciuria. Calcif Tissue Int 43: 61
20. Forland M, Strandjord NM, Paloyan E, Cox A (1968) Bone density studies in primary hyperparathyroidism. Arch Intern Med 122: 236
21. Frost HM (1983) The skeletal intermediary organization: a review. Metab Bone Dis Rel Res 4: 281
22. Fuss M, Gillet C, Simom J, Vandewalle J-C, Schoutens A, Bergmann P (1983) Bone mineral content in idiopathic renal stone disease and in primary hyperparathyroidism. Eur Urol 9: 32
23. Fuss M, Pepersack T, Bergman P, Hurard T, Simon J, Corvilain J (1990) Low calcium diet in idiopathic urolithiasis: a risk factor for osteopenia as great as in primary hyperparathyroidism. Br J Urol 65: 560
24. Fuss M, Pepersack T, Van Geel J, Corvilain J, Vandewalle JC, Bergmann P, Simon J (1990) Involvement of low-calcium diet in the reduced bone mineral content of idiopathic renal stone formers. Calcif Tissue Int 46: 9
25. Fuss M, Pepersack T, Corvilain J, Bergmann P, Simon J, Body JJ (1991) Calcitonin secretion in idiopathic renal stone formers. J Bone Miner Res 6: 35
26. Ghazali A, Fuentes V, Deisaint C, Westeel A, Brazier M, Prin L, Fournier A (1997) Low bone mineral density and peripheral monocyte activation profile in calcium stone formers with idiopathic hypercalciuria. J Clin Endocrinol Metab 82: 32
27. Goldfarb S (1988) Dietary factors in the pathogenesis and prophylaxis of nephrolithiasis. Kidney Int 34: 544
28. Hess B, Casez J-P, Takkinen R, Ackermann D, Jaeger P (1993) Relative hypoparathyroidism and calcitriol up-regulation in hypercalciuric calcium renal stone formers. Impact of nutrition. Am J Nephrol 13: 18
29. Hisazumi H, Katsumi T (1970) A study of the mineral contents of the bone by x-rays in patients with urolithiasis. Jpn J Urol 61: 266
30. Hosgkin DJ, Chamberlain MJ, Fremlin JH (1972) Changes in total body calcium content in primary hyperparathyroidism. Clin Sci 43: 627
31. Jaeger P, Lippuner K, Casez J-P, Hess B, Ackermann D, Hug C (1994) Low bone mass in idiopathic renal stone formers: magnitude and significance. J Bone Miner Res 9: 1525
32. Jungers P, Houillier P, Liote F, De Groote D, Labrunie M, Daudon M, Descamps-Latscha B (1996) Imbalance between monocyte-derived cytokines and their specific inhibitors in idiopathic hypercalciuria. In: Pak CYC, Resnick MI, Preminger GM (eds) Urolithiasis 1996.. Millet, Dallas, p 68
33. Kanis JA, Melton LJIII, Christiansen C, Johnson CC, Khaltaev N (1994) The diagnosis of osteoporosis. J Bone Miner Res 9: 1137
34. Kaplan RA, Haussler MR, Deftos LJ, Bone H, Pak CYC (1977) The role of 1,25(OH)2D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J Clin Invest 59: 756
35. Katayama Y, Umekawa T, Ishikawa Y, Kodama M, Takada M, Katoh Y, Kataoka K, Kohri K, Iguchi M, Kurita T (1990) Calcium urolithiasis and bone change. Nippon Hinyokika Gakkai Zasshi 81: 89
36. Kuczera M, Wiecek A, Kokot F (1993) Estimation of selected markers of bone metabolism in patients with nephrolithiasis. Pol Arch Med Wewn 89:385
37. Lauderdale DS, Thisted RA, Wen M, Favus MJ (2001) Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey. J Bone Miner Res 16: 1893
38. Lawoyin S, Sismilich S, Browne B, Pak CYC (1979) Bone mineral content in patients with calcium urolithiasis. Metabolism 28: 1250
39. Lemann JJr, Litzow JR, Lennon EJ (1966) The effects of chronic acid loads in normal man: further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Invest 45: 1608
40. Liberman UA, Sperling O, Atsmon A (1969) Metabolic and calcium kinetic studies in idiopathic hypercalciuria. J Clin Invest 47: 2580
41. Lindergard B, Colleen S, Mansson W, Rademark C, Rogland B (1983) Calcium loading test and bone disease in patients with urolithiasis. Proc EDTA 20: 460
42. Maierhofer WF, Gray RW, Cheung HS, Lemann J (1984) Dietary calcium and serum $1,25(OH)_2$-vitamin D concentrations as determinants of calcium balance in healthy men. Kidney Int 26: 752
43. Mallette LE, Bilezikian JP, Heath H, Auerbach GD (1974) Primary hyperparathyroidism: clinical and biochemical features. Medicine 53: 127
44. Malluche HH, Tschope W, Ritz E, Meyer-Sabellek W, Massry SG (1980) Abnormal bone histology in idiopathic hypercalciuria. J Clin Endocrinol Metab 50: 654
45. Malvasi L, Sartori I, Giannini S, Al Awady M, Musaio F, Varotto S, D'Angelo A (1988) Mineral metabolism and bone mineral content in calcium nephrolithiasis with and without hyperparathyroidism. Urol Res 16: 190
46. Martin P, Bergmann P, Gillet C (1986) Partially reversible osteopenia after surgery for primary hyperparathyroidism. Arch Intern Med 146: 689
47. Maruyama Y, Hirata N, Yamada H, Sasaki K, Motomiya Y, Hirao Y, Okajima E (1993) A study on markers of bone metabolism in patients with non hypercalciuric calcium stone: measurement of gamma-carboxyglutamic acid and hydroxyproline. Nippon Hinyokika Gakkai Zasshi 84: 541
48. Melton LJ III, Crowson CS, Khosla S, Wolson DM, O'Fallon WM (1998) Fracture risk among patients with urolithiasis: a population-based cohort study. Kidney Int 53: 459
49. Messa P, Mioni G, Montanaro D, Adorati M, Antonucci F, Favazza A, Messa A, Enzmann G, Paganin L, Nardini R (1987) About a primitive osseous origin of the so-called "renal hypercalciuria". Contr Nephrol 58: 106
50. Minisola S, Rosso R, Romagnoli E, Pacitti MT, Scarnecchia L, Carnevale V, Mazzuoli G (1993) Trabecular bone mineral density in primary hyperparathyroidism: relationship to clinical presentation and biomarkers of skeletal turnover. Bone Miner 20: 113
51. Muldowney FP, Freaney R, Moloney MF (1982) Importance of dietary sodium in the hypercalciuria syndrome. Kidney Int 22: 292
52. Netelenbos JC, Jongen MJM, Van der Vijgh WJF, Lips P, Van Ginkel FC (1985) Vitamin D status in urinary calcium stone formation. Arch Intern Med 145: 681
53. Nordin BEC, Peacock M, Wilkinson R (1972) Hypercalciuria and calcium stone disease. Clin Endocrinol Metab J 1: 169
54. Osther PJ, Bollerslev J, Hansen AB, Engel K, Kildeberg (1993) Pathophysiology of incomplete renal tubular acidosis in recurrent renal stone formers: evidence of disturbed calcium, bone and citrate metabolism. Urol Res 21: 169

55. Pacifici R, Rothstein M, Rifas L, Lau KHW, Baylink DG, Avioli LV, Hruska K (1990) Increased monocyte interleukin-I activity and decreased vertebral bone density in patients with fasting hypercalciuria. J Clin Endocrinol Metab 71: 138
56. Pak CYC, Kaplan R, Bone H, Towsend J, Waters O (1975) A simple test for the diagnosis of absorptive, resorptive and renal hypercalciuria. N Engl J Med 292: 497
57. Pak CYC, Nicar MJ, Peterson R, Zerwekh JE, Snyder W (1981) Lack of unique pathophysiologic background for nephrolithiasis in primary hyperparathyroidism. J Clin Endocrinol Metab 53: 536
58. Peacock M (1975) Renal stone disease in primary hyperparathyroidism and their relationship to the action of PTH on calcium absorption. In: Talmadge R (ed) Calcium regulating hormones. Excerpta Medica, Amsterdam, p 78
59. Pietschmann F, Breslau NA, Pak CYC (1992) Reduced vertebral bone density in hypercalciuric nephrolithiasis. J Bone Miner Res 7: 1383
60. Pines KL, Mudge GH (1951) Renal tubular acidosis with osteomalacia. Am J Med 11: 302
61. Rao PN, Blacklock NJ (1983) A non-steroidal anti-inflammatory drug (flubiprofen) to control idiopathic hypercalciuria resistant to dietary manipulation. Br J Urol 55: 599
62. Rao DS, Wilson RJ, Kleerkoper M et al. (1988) Lack of biochemical progression of continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for a biphasic course. J Clin Endocrinol Metab 67: 1294
63. Rico H, Paramo P, Perez del Molino J, Nacarino L, Yague M (1988) Osteocalcin, parathormone and hypercalciuria. Eur Urol 15: 239
64. Riggs BL, Wahner HW, Dunn WL, Mazess PB, Offord KP, Melton L (1981) Differential changes in bone mineral density of the appendicular and axial skeleton with ageing. J Clin Invest 67: 328
65. Shen FH, Baylink DJ, Nielsen RL, Sherrard DJ, Ivey JL, Haussler MR (1977) Increased serum 1,25-dihydroxy vitamin D in idiopathic hypercalciuria. J Lab Clin Med 6: 955
66. Silverberg SJ, Shane E, Jacobs TP, Siris ES, Gartenberg F, Seldin D, Clemens TL, Bliezikian JP (1990) Nephrolithiasis and bone involvement in primary hyperparathyroidism. Am J Med 89: 327
67. Sowers MR, Jannausch M, Wood C, Pope SK, Lachance LL, Peterson (1998) Prevalence of renal stones in a population-based study of dietary calcium, oxalate, and medication exposures. Am J Epidemiol 147: 914
68. Sperling O, Weinberger A, Oliver I, Liberman UA, De Vries A (1974) Hypouricemia, hypercalciuria and decreased bone density. A hereditary syndrome. Ann Intern Med 80: 482
69. Steiniche T, Mosekilde L, Christensen MS, Melsen F (1989) A histomorphometric determination of iliac bone remodeling in patients with recurrent renal stone formation and idiopathic hypercalciuria. APMIS 4: 309
70. Sutton RAL, Walker VR (1986) Bone resorption and hypercalciuria in calcium stone-formers. Metabolism 35: 485
71. Takeda M, Katayama Y, Go H, Wakatsuki S, Kawasaki T, Sato S, Odano I (1991) Bone mineral densitometry by dual photon absorptiometry in patients with urolithiasis: on the possibility of the differential diagnosis of idiopathic hypercalciuria. Nippon Hinoyokika Gakkai Zasshi 82: 1954
72. Taylor AK, Lenken SA, Libanati C, Baylink DJ (1994) Biochemical markers of bone turnover for the clinical assessment of bone metabolism. Rheum Dis Clin North Am 20: 589
73. Thomsen K, Gotfredsen A, Christiansen C (1986) Is postmenopausal bone loss an age-related phenomenon? Calcif Tissue Int 39: 123
74. Tieder M, Modai D, Shaked U, Samuel R, Arie R, Halabe A, Maor J, Weissgarten J, Averbukh A, Cohen N, Edelstein S, Liberman U (1987) Idiopathic hypercalciuria and hereditary hypophosphatemic rickets. N Engl J Med 316: 125
75. Trinchieri A, Nespoli R, Ostini F, Rovera F, Zanetti G, Pisani E (1998) A study of dietary calcium and other nutrients in idiopathic renal calcium stone formers with low bone mineral content. J Urol 159: 654
76. Trinchieri A, Zanetti G, Currò A, Lizzano R (2001) Effect of potential renal acid load of foods on calcium metabolism of renal calcium stone formers. Eur Urol 39 [Suppl 2]: 33
77. Velentzas C, Oreopoulos DG, Meema S, Meema HE, Nutsuga T, Alison E, Katirtzoglou A, Crassweller P (1981) Dietary calcium restriction may be good for patients' stones but not for their bones. In: Smith LH, Robertson WG, Finlayson B (eds) Urolithiasis clinical and basic research. Plenum Press, New York. p 847
78. Weisenberg JR, Alonzo E, Bellorinfont E, Blasini AM, Rodriguez MA, Pazmartinez V, Martinis R (1996) Possible role of cytokines on the bone mineral loss in idiopathic hypercalciuria. Kidney Int 49: 244