World Journal of Nephrology

Online Submissions: http://www.wjgnet.com/esps/
wjnephrol@wjgnet.com
doi:10.5527/wjn.v1.i2.54

World J Nephrol 2012 April 6; 1(2): 54-62
ISSN 2220-6124 (online)
© 2012 Baishideng. All rights reserved.

REVIEW

Bone disease in pediatric idiopathic hypercalciuria

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares, Department of Pediatrics, Pediatric Nephrology Unit, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Belo Horizonte, CEP 30130100, Minas Gerais, Brazil
Author contributions: Moreira Guimarães Penido MG and de Sousa Tavares M contributed equally to the conception and design of the study, the acquisition, analysis and interpretation of data, and the drafting and critical revision of the article.
Correspondence to: Maria Goretti Moreira Guimarães Penido, MD, PhD, Department of Pediatrics, Pediatric Nephrology Unit, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Belo Horizonte, CEP 30130100, Minas Gerais, Brazil. mariagorettipenido@yahoo.com.br
Telephone: +55-31-92991595 Fax: +55-31-32414466
Received: October 9, 2011 Revised: November 11, 2011
Accepted: February 10, 2012
Published online: April 6, 2012

Abstract

Idiopathic hypercalciuria (IH) is the leading metabolic risk factor for urolithiasis and affects all age groups without gender or race predominance. IH has a high morbidity with or without lithiasis and reduced bone mineral density (BMD), as described previously in pediatric patients as well as in adults. The pathogenesis of IH is complex and not completely understood, given that urinary excretion of calcium is the end result of an interplay between three organs (gut, bone and kidney), which is further orchestrated by hormones, such as 1,25 dihydroxyvitamin D, parathyroid hormone, calcitonin and fosfatonins (i.e., fibroblast growth-factor-23). Usually, a primary defect in one organ induces compensatory mechanisms in the remaining two organs, such as increased absorption of calcium in the gut secondary to a primary renal loss. Thus, IH is a systemic abnormality of calcium homeostasis with changes in cellular transport of this ion in intestines, kidneys and bones. Reduced BMD has been demonstrated in pediatric patients diagnosed with IH. However, the precise mechanisms of bone loss or failure of adequate bone mass gain are still unknown. The largest accumulation of bone mass occurs during childhood and adolescence, peaking at the end of the second decade of life. This accumulation should occur without interference to achieve the peak of optimal bone mass. Any interference may be a risk factor for the reduction of bone mass with increased risk of fractures in adulthood. This review will address the pathogenesis of IH and its consequence in bone mass.

© 2012 Baishideng. All rights reserved.

Key words: Bone mineral disease; Bone mineral density; Hypercalciuria; Children; Urine

Peer reviewer: Sinee Disthabanchong, MD, Assistant Professor, 270 Rama VI Rd, 7th floor, Building 1, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Phayathai, Bangkok 10400, Thailand

Moreira Guimarães Penido MG, de Sousa Tavares M. Bone disease in pediatric idiopathic hypercalciuria. *World J Nephrol* 2012; 1(2): 54-62 Available from: URL: http://www.wjgnet.com/2220-6124/full/v1/i2/54.htm DOI: http://dx.doi.org/10.5527/wjn.v1.i2.54

INTRODUCTION

Idiopathic hypercalciuria (IH) is a metabolic alteration of high prevalence and affects all age groups without gender or race predominance[1,2]. It is considered a risk factor for urolithiasis and is the major metabolic disorder found in children[1,3,4] and adults who have urinary stones[5-7].

The clinical presentation of IH includes gross or microscopic hematuria, voiding symptoms (urinary urgency, pollakiuria, dysuria, incontinence, enuresis and suprapubic pain), urinary tract infection, as well as back, flank, or abdominal pain in the absence of urolithiasis and, less frequently, acute renal colic[3,8-12]. The suggested role of IH in enuresis at present is controversial[13-17].

Two consecutive 24-h urine collections without dietetic manipulations are recommended to confirm the presence of hypercalciuria. Because dietetic factors can

widely influence urinary calcium excretion, "true" IH is considered the form of urinary calcium excess that does not depend on known conditions and in which possible dietetic disturbances have been eliminated by keeping patients on a daily diet with 1000-1200 mg of calcium and no more than 1-1.5 g of protein per kg body weight per day[18]. Depending on age group, excess of dietary calcium (more than 1500 mg/d) can be associated with the development of hypercalciuria[18].

IH is defined as urinary calcium excretion greater than or equal to 4 mg/kg per 24 h (0.1 mmol/kg body weight) for any sex or age[19-22]. It is also defined as calcium excretion in relation to creatinine in fasting urine samples higher than 0.80 for infants, 0.40 for preschool children, and 0.21 for children and adolescents (0.6 mmol/mmol calcium/creatinine ratio)[19]. These values can be temporarily higher during adolescence, coinciding with the rapid growth, which is characteristic of this age. Another definition of hypercalciuria is based on calcium urinary excretion per deciliter of glomerular filtration rate of creatinine in fasting morning urine samples (mg/100 mL of glomerular filtration rate), where values below 0.10 are considered normal, according to the formula proposed by Simkin *et al*[23]. These random urine samples are particularly useful for children who do not have urinary sphincter control.

Recently, several studies have demonstrated reductions in bone mineral density (BMD) in adults with IH as compared to non-hypercalciuric controls, suggesting that persistent hypercalciuria may lead to decreased bone mass and increased risk for fracture. Emerging clinical evidence now points to a similar association between IH and bone loss in children with or without hematuria or nephrolithiasis. Although studies in children with IH have not been as numerous or detailed as those in adults, they raise concern that life-long hypercalciuria might be an important contributor to diminished bone mass. This review discusses the evidence for an association between reduced bone mass and IH in children and possible causes for such an association.

PATHOPHYSIOLOGY

Pak and colleagues[24] classified IH into three distinct pathogenetic pathways, according to three independent primary metabolic defects: (1) absorptive hypercalciuria type I , when primary intestinal hyperabsorption of calcium is involved; (2) absorptive hypercalciuria type Ⅲ, when a primary renal leak of phosphate is present, thus inducing hypophosphatemia and secondarily 1,25 $(OH)_2$ vitamin D-mediated intestinal hyperabsorption of calcium; and (3) renal hypercalciuria, when a primary renal leak of calcium with secondary compensatory hyperparathyroidism is present. These authors also distinguished a form of so-called "resorptive hypercalciuria", when hypercalciuria is induced by an excessive output of calcium from bone, for example in patients with Primary Hyperparathyroidism. In many cases, classification into one of these groups has proved difficult and most individuals appear to have a more generalized acceleration of calcium transport, which affects all these processes, and the clinical value of the classification appears limited. This classification has been widely revised over the years on the basis of new pathophysiological observations. We currently know that the pathophysiology of IH is complex and not completely understood, given that urinary excretion of calcium is the end result of an interplay between three organs - namely, the gastrointestinal tract, bone, and kidney. This is further orchestrated by hormones, such as 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], parathyroid hormone (PTH), calcitonin, fibroblast growth factor (FGF-23), and probably others unknown. Often, a primary defect in one organ induces compensatory mechanisms in the remaining two organs, such as increased absorption of calcium in the gut secondary to a primary renal loss. Thus, IH is a systemic abnormality of calcium homeostasis with changes in cellular transport of this ion in intestines, kidneys and bones[18,25-28]. These three organs possibly act together as a single system.

The genetic background is also involved in the pathogenesis of IH. Studies have shown an increased incidence of nephrolithiasis and hypercalciuria among first degree relatives of stone formers, indicating that this disorder has a genetic basis[29]. The precise gene or genes that contribute to IH are still unknown. The trait is most probably polygenic in origin, with contributions from several genes which may differ from one individual with IH to another.

Increased intestinal absorption of calcium

Increased gut absorption of calcium is a feature noted in essentially all patients with IH. Studies have shown increased calcium uptake in IH compared to normal subjects[27,30]. One potential mechanism for increased absorption may be the higher levels of serum calcitriol found in patients with IH compared to normal subjects. Calcitriol upregulates expression of calcium transport proteins in the intestine, including the apical calcium channel, the transient receptor potential cation channel, subfamily V, member 6 (TRPV6)[31]. Calcium absorption is directly related to calcitriol levels, although in some hypercalciuric subjects intestinal calcium absorption appears to be increased out of proportion to the calcitriol level[32]. Patients with IH maintain normal fasting serum calcium levels and normal or slightly low PTH levels.

Urinary calcium rises in normal subjects as net intestinal calcium absorption increases. However, in patients with IH, urinary calcium is higher than normal at any level of net calcium absorption, Balance studies using controlled diets, demonstrate that urinary calcium is often higher than net absorption, meaning that some of the urinary calcium must be derived from bone[33]. IH patients will lose bone mineral more readily than normal when challenged by an extremely low calcium diet[33]. The loss of calcium in urine in excess of dietary intake is a definitive proof of abnormal bone mineral wasting in

IH, and again suggests that alterations in renal calcium handling that limit calcium conservation may be a common feature of IH. It is notable that those patients did not show a drop in serum calcium or increase in serum PTH while on low calcium diet compared to levels seen on a free-choice diet. Serum PTH levels were lower in IH than in normal subjects on both diets. Overall, it appears that renal mineral conservation must be abnormal in IH, and that bone mineral loss is somehow facilitated, so that despite the absence of dietary calcium to balance renal losses, serum calcium can remain normal and serum PTH suppressed[30].

A possible mechanism that could explain bone mineral lability and abnormal renal tubule conservation of calcium, as well as increased gut absorption of this ion, would be an altered tissue vitamin D response. Studies have supported the idea that high tissue vitamin D response can produce all the manifestations of IH: increased gut calcium absorption, decreased renal reabsorption, and increased mobilization of calcium from bone[34,35]. Several possible mechanisms could account for an increased tissue vitamin D response: serum calcitriol itself, the vitamin D receptor, or other factors.

A rat model of hypercalciuria has been generated by breeding rats for increased urine calcium excretion, and has been called the genetic hypercalciuric stone-forming (GHS) rat[36]. Like humans with IH, GHS rats have increased gut absorption of calcium, decreased renal calcium reabsorption, and a tendency to bone demineralization. When placed on low-calcium diet, they excrete more calcium than is absorbed, indicating a loss of mineral bone[36]. Overall, they have a systemic abnormality in calcium homeostasis, which appears to be similar to that found in human stone formers with IH. Unlike many humans with IH, $1,25(OH)_2D_3$ levels are normal in those rats. However, significantly higher levels of vitamin D receptors (VDR) have been found in bone, kidney and intestine, compared to normal rats, which would explain the increased sensitivity to $1,25(OH)_2D_3$ found in tissue samples[37]. In the gut, vitamin D-responsive genes are expressed at increased levels in response to small doses of $1,25(OH)_2D_3$[38], with consequent increase in expression of proteins related to calcium homeostasis, such as epithelial calcium channels (TRPV6 in gut), and calbindins. The calcium sensing receptor (CaSR) is another $1,25(OH)_2D_3$ responsive gene, and increased levels of CaSR protein and mRNA have also been found in the kidneys of GHS rats compared to control rats fed the same diet[39].

Humans with IH frequently have high $1,25(OH)_2D_3$ levels, and administration of calcitriol to normal men can replicate much of the picture seen in IH. The importance of $1,25(OH)_2D_3$ in IH was further demonstrated by a study of 19 hypercalciuric subjects treated with the CYP450 inhibitor ketoconazole, which suppresses $1,25(OH)_2D_3$ levels by 30%-40%[40]. This is consistent with the abnormalities seen in the GHS rat.

Whether VDR levels are increased in some patients with IH is unclear. One study has looked at VDR in peripheral blood monocytes from 10 male stone formers with IH, compared with age-matched normal controls[41]. The VDR levels were twice as high in patients with IH, while $1,25(OH)_2D_3$ levels did not differ. Increased levels of VDR could lead to an increased tissue effect of $1,25(OH)_2D_3$, despite comparable serum levels of the hormone. However, whether monocyte VDR expression reflects tissue levels of VDR is not known.

Renal mineral handling

Renal calcium handling in most patients with IH differs from normal. When hypercalciuric patients are placed on a very low calcium diet, most are unable to reabsorb calcium with the same efficiency as normal subjects. Even on diets that provide normal or increased amounts of calcium, many subjects excrete calcium in excess of absorption. Patients with IH have an increased fasting fractional excretion of calcium, and many have fasting hypercalciuria, suggesting a role for decreased tubule calcium reabsorption[42]. Alternatively, the increased absorption of calcium with meals could lead to a post-absorptive rise in blood calcium that increases the filtered load[43]. Theoretically, PTH could also be suppressed, thereby decreasing tubule calcium reabsorption. Worcester *et al*[44] studied ten stone formers with IH (5 female) and seven normal subjects (4 female) during a 3-meal day, while on diets composed of whole foods containing equivalent amounts of daily calcium (1160 mg), phosphorus (1240 mg), sodium (2141 mg) and potassium (2427 mg). They found that neither ultrafiltrable calcium nor filtered load of calcium differed between the normal subjects and those hypercalciuric, either while fasting or after meals. However, urinary calcium excretion was significantly higher after meals in subjects with IH, and fractional reabsorption was lower both during the fasting and the post-absorptive periods. Therefore, the increased calcium absorbed with meals in IH is removed into the urine mainly *via* decreased tubule reabsorption and this occurred despite the fact that PTH levels did not differ between normal subjects and those with IH, either fasting or with meals. Although PTH levels fell with meals in both groups, PTH levels overlapped in the two groups, and at any given level of PTH, calcium reabsorption was significantly lower in subjects with IH[44]. Recently, Worcester *at al*[45] showed that stone-forming patients with IH, eating fixed and identical high-calcium and normal diets, reduce distal and proximal tubule calcium reabsorption more than matched controls with each meal. Then, at identical serum calcium levels and calcium-filtered loads they excrete more calcium[45]. Studies in the genetic hypercalciuric rat demonstrated alterations in both proximal tubule and thick ascending limb calcium reabsorption, with more calcium delivery to distal tubules. Similar studies in humans have begun to provide evidence about the corresponding abnormalities in stone formers with IH[45-47]. Studies provide evidence for a defect in renal phosphate reabsorption in some hypercalciuric patients[48]. Although levels of phosphate are within the normal range, fractional reabsorption of

phosphate after meals is decreased compared to controls. The ability to conserve phosphorus on a low-phosphorus diet may be compromised, and IH patients show a trend toward negative phosphorus balance, even on normal intakes. Many patients with IH have slightly decreased serum phosphate levels, and perhaps 15%-20% are frankly low. It has been suggested that some of those patients have a defect in phosphate metabolism, which may lead to elevated $1,25(OH)_2D_3$ levels, and increased calcium absorption. Prie *et al*[49] studied 207 calcium stone formers with normal PTH levels and compared them to 105 normal subjects of similar age. The stone formers of both sexes had a significantly decreased renal phosphate threshold (TmPi). The stone formers with low TmPi had lower serum phosphate levels and higher urine calcium excretion than stone formers with TmPi > 0.63 mmol/L, but their $1,25(OH)_2D_3$ levels did not differ, although $1,25(OH)_2D_3$ levels of both groups exceeded that in the normal subjects. An abnormal phosphate excretion may be part of a more general defect in proximal tubule function, although this defect may not explain raised $1,25(OH)_2D_3$ levels in many hypercalciuric patients[7].

Dietary components and urinary calcium excretion

Diet has an effect on urinary calcium excretion, in both normal subjects and those with IH. The increasing sodium intake also is accompanied by increased urinary calcium excretion. In healthy subjects, the urinary calcium increases about 0.6 mmol/d for each 100 mmol/d increment in sodium excretion[50]. Increased dietary protein intake will also raise urinary calcium excretion, by about 0.04 mmol/gram protein intake in healthy men and women[51]. Metabolism of ingested protein creates an acid load, due to the oxidation of organic sulfur in aminoacids to sulfate, leading to increased excretion of net acid and calcium. Administration of alkali reduces both net acid and calcium excretion. The increase in net acid production inhibits renal tubular calcium reabsorption. Studies in mice have shown that induction of acidosis leads to decreased renal tubular expression of the distal tubular apical calcium channel TRPV5. Mice in which the TRPV5 gene was inactivated did not have an increase in calcium excretion with acidosis[52,53]. Decreasing protein intake decreases urine calcium excretion and recurrence of calcium stones[54]. However, urinary calcium is higher in patients with IH than among normals at comparable levels of acid excretion, suggesting that high protein intake worsens but does not usually cause this metabolic abnormality.

Several rapidly metabolized nutrients (glucose, sucrose, ethanol) cause increased excretion of urinary calcium due to diminished tubular calcium and magnesium reabsorption, and patients with IH appear to have an exaggerated calciuric response to a carbohydrate load[55,56]. Urine phosphate excretion may be increased at the same time[31].

Others regulators of urine calcium and phosphate

Other urinary calcium and phosphate regulators have been described. Regulated renal calcium transport involves a calcium channel, TRPV5, found in the distal nephron and it is closely related to the analogous channel, TRPV6, found in the gut[57]. Proximal tubule phosphate transport is primarily conducted by a sodium-phosphate co-transporter, NPT-2a, a member of the type 2 family of phosphate transport proteins[58]. Both transporters are controlled by the PTH-vitamin D axis, although in the last few years new transport regulators have been identified.

Phosphatonins are regulatory factors of phosphate metabolism and the FGF-23 is the best studied of them. FGF-23 is a 251-amino acid factor that differs from other FGF family members by having a 71-amino acid extension at the carboxyl-terminal end of the molecule that is specific for this factor. FGF-23 is produced primarily in bone tissue by osteoblasts and osteocytes[59,60]. Initially related to autosomal dominant hypophosphatemic rickets (DAHR)[60] and tumor-induced osteomalacia (TIO)[61], FGF-23 appears to play an important part in regulating the metabolism of minerals, especially phosphorus[62]. Unlike other components of the family of FGF, FGF-23 has systemic and not only local action. Receptors to FGF-23 are present in many tissues and its actions were recently well described by Gattineni and Baum[63]. However, FGF23 downstream signaling was detected only in a very restricted range of tissues including kidney (the distal convoluted tubules), parathyroid glands and the brain (the epithelium of the choroid plexus)[64]. The reason for this is that in order to exert its effect on its receptor, FGF-23 needs its essential cofactor Klotho present. The latter is a transmembrane protein which is highly expressed in the kidney and, to a lesser extent, in the PTH glands and serves as an obligate co-receptor, enabling FGF-23 to interact with its receptor[65]. Thus, Klotho is the modifier which dictates which tissues will respond to FGF-23.

Klotho that co-localizes in distal convoluted tubules with TRPV5, appears critically important to calcium reabsorption[66]. The effect of Klotho appears to involve its ability to cleave a carbohydrate residue from the calcium channel, which increases TRPV5 activity by trapping it in the plasma membrane[66]. Knockout mice overexpressing the 25(OH) D-1α-hydroxylase, and have high serum $1,25(OH)_2D_3$ levels with consequent hypercalcemia and hypercalciuria. Subtle variations in Klotho could possibly cause a syndrome like IH if $1,25(OH)_2D_3$ increase were not so high as to cause hypercalcemia. Thus, FGF-23 reduces tubule phosphate reabsorption and $1,25(OH)_2D_3$ synthesis. Variations in the Klotho-FGF23 axis could mediate alterations in calcium and phosphate handling by the kidney, and play a role in IH[7].

Bone alterations

BMD is often mildly decreased in adults[67-72] and children with IH[73-79]. In hypercalciuric children bone loss can result from increased bone resorption, decreased bone formation, or both. Histological changes due to bone IH are

little known and existing reports are not homogeneous, because histomorphometric studies are rare for this disease. In adults with absorptive IH, findings from bone biopsy analysis are most consistent with a defect in bone formation[80-82], while, in a smaller subset of patients with renal calcium leak, bone loss has been shown to be the result of increased bone resorption[83,84]. A few studies in pediatric hypercalciuric patients have determined the underlying mechanism for the hypercalciuria, although both renal and absorptive subtypes have been reported with a slightly greater prevalence of renal hypercalciuria[85,86]. However, there have been no bone biopsy studies of affected children and only limited data on biochemical markers of bone turnover[74-76]. Since most children with IH demonstrate normal longitudinal growth, it seems less likely that there is an alteration in bone formation. A better explanation for decreased bone mass in those children appear to be increased bone resorption and/or turnover.

Potential causes of deranged bone remodeling in children with IH, which lead to low BMD, have been listed. Aside from genetic influences, nutritional and metabolic causes should be considered.

Interleukin-1 (IL-1) is known to be a potent stimulator of osteoclastic bone resorption. One study suggests that mononuclear cells from patients with fasting hypercalciuria have an increased production of IL-1, explaining the low vertebral BMD in these patients[87,88]. Other bone resorbing cytokines such as IL-6 and tumor necrosis factor (TNF) have also been reported to be increased in patients with IH[88]. However, the expression of IL-1 mRNA by peripheral blood mononuclear cells from IH children did not differ from that of controls[75]. Additional observations in children with IH and in their parents will be necessary to exclude this as a potential cause of reduced bone mass and hypercalciuria.

Prostaglandin E2 (PGE2) is another potent stimulator of bone resorption, but it can also inhibit osteoblastic collagen synthesis. Aside from inflammatory conditions, PGE2 may also be increased during nutritional acid loading, since it may serve as a mediator of the acid-induced increase in bone resorption[89]. It is not known whether a diet high in animal protein in humans can increase systemic PGE2 concentrations sufficiently enough to affect bone remodeling. It is interesting to note that, in the study by Garcia-Nieto *et al*[73], children with IH had higher urinary excretion of PGE2 and lower urinary excretion of citrate. However, urinary excretion of PGE2 for all hypercalciuric patients was significantly correlated with calciuria and not with BMD.

BONE DISEASE IN IDIOPATHIC HYPERCALCIURIA

Life-long hypercalciuria might be an important contributor to diminished bone mass or failure of adequate bone mass gain. Reduced BMD with increased bone remodeling has been described in adult patients with IH since the 1970's[68,81,83,88,90-94]. Studies in children began with Stapleton *et al*[85] in 1982. The authors assessed bone mineralization in children with IH who were divided according to the test of acute oral calcium overload (TAOCaO, currently in disuse) in renal and absorptive hypercalciuria and found linear similar skeleton growth in both patients groups[85,95]. The same authors in 1989 studied BMD of 76 children with IH and a control group. There were no significant differences in BMD between patients and controls or between patients with renal and absorptive hypercalciuria. Similarly, no correlation was found between BMD, PTH and osteocalcin[96]. In early 90's, new studies showed the existence of bone changes in pediatric patients with IH. Perrone and colleagues (1992) in a prospective study of 20 Brazilian children with absorptive hypercalciuria classified according to the TAOCaO test, treated with dietary restriction of calcium and/or rice bran, showed improvement in lumbar spine BMD in those treated compared with those untreated[97]. In 1997, the BMD of the lumbar spine (L2-L4) and bone markers of bone formation and resorption were assessed in 73 white children with IH. The patients had elevated osteocalcin and calcitriol blood levels, as well as magnesium and prostaglandin E_2 urinary levels. In contrast, they had decreased tubular reabsorption of phosphate, ammonium urinary excretion and BMD compared with controls. Osteopenia was present in 30% of the patients with hypercalciuria. BMD was negatively correlated with age, suggesting that children with hypercalciuria have progressive bone loss of unknown etiology[73]. It is possible that increased cytokine activity can explain the pathophysiology of reduced BMD in these patients[98].

Freundlich and colleagues, considering the possibility that peak bone mass and final bone mass of adults may be determined by genotype, studied the BMD (lumbar spine and femur) and bone resorption markers (pyridinoline, deoxypyridinoline and telopeptide) of 21 children with IH and of their premenopausal mothers. The authors found osteopenia in 38% of children and in 33% of their mothers. In 57% of mother-son pairs, osteopenia was found and in 70% of the asymptomatic mothers the diagnosis of IH was made. No correlation was detected between urinary calcium excretion and BMD. The bone resorption markers were increased in 57% of the mothers with osteopenia[74].

García-Nieto *et al*[75], in 2003, evaluated BMD in 40 girls with IH and in their premenopausal mothers from whom they had inherited this disease. A Z-score of < -1 at the lumbar spine was found in 42.5% of the girls, whilst in the mothers, a Z score of < -1 at the lumbar spine and/or femoral neck was observed in 47.5% and a T-score of < -1 at the lumbar spine and/or femoral neck in 62.5%. The Z-score at the lumbar spine was significantly lower in the girls and their mothers compared to controls. Z-scores in the girls of mothers with osteopenia were significantly lower or there was a trend for the score to be lower than in girls of mothers with normal BMD. There was a significant relationship between the Z-score of the girls and the T-score at the lumbar spine in the

mothers (r = 0.32, P < 0.05). The authors suggest that BMD should be measured during the third or fourth decades of life in those individuals with nephrolithiasis or with children diagnosed as having IH[75].

In the same year, Penido *et al*[76] studied a group of 88 children with IH with a median age of 9.4 years at the time of diagnosis of hypercalciuria. As controls, the authors studied 29 children and adolescents (median age 9.7 years) without hypercalciuria. BMD of the lumbar spine, femoral neck, and whole body were all significantly lower for the IH children than for controls. BMD Z-score was significantly reduced at the lumbar spine in 31 (35%) patients. Sixty-three (72%) of the IH patients demonstrated an exaggerated fasting calcium/creatinine ratio, suggesting that fasting hypercalciuria might have been the result of increased bone turnover. Examination of biochemical markers of bone turnover demonstrated increased urinary N-telopeptide excretion in the IH subjects, as well as increased serum osteocalcin. These findings further support the suggestion of low bone mass in children with hypercalciuria and that the decreased bone mass might have been due to increased bone turnover[76].

Skalova *et al*[77] in 2005, examined 15 patients with IH. The values for 24 h urinary calcium and N-acetyl-β-D-glucosaminidase (NAG), a marker of renal tubule impairment, were significantly higher, while lumbar BMD was significantly lower than reference values from a healthy European pediatric population. Forty percent of the patients had BMD Z-scores between -1 and -2 standard deviations (SD) and 20% had BMD Z- scores below -2 SDs. In addition, the authors found an inverse and significant correlation between BMD and 24h calciuria although there was no correlation between urinary NAG/creatinine and 24h calciuria or BMD.

In 2006, Penido *et al*[99] evaluating 88 children and adolescents with IH, 44 with idiopathic hypocitraturia (IHC) and 44 without, found that those with IHC had greater reduction in BMD in the absence of metabolic acidosis. The authors also identified a significant reduction in blood pH and bicarbonate in the group with IHC, although venous blood gases were normal in all patients. It was postulated that lower blood pH and bicarbonate in patients with IHC could indicate that the primary event would be an intracellular acidification defect present in all patients with IH, but more severe in those patients with IHC. The more acidic intracellular environment in patients with IHC would stimulate bone buffering, leading to loss of bone calcium into the urine, and could result in reduced bone mass with decreased BMD. In this study, although age did not differ between patients with and without IHC, patients with IHC had significantly lower weight, height, body mass index (BMI) and bone age, suggesting an effect of IHC on growth[99]. These results also allowed the authors to consider whether IHC in the absence of systemic acidosis could alter bone metabolism of patients with IH, thereby interfering with growth. This hypotheses was not proved and requires further investigation with prolonged clinical monitoring of patients with IH and IHC[99].

BMD was studied in 104 children with IH (43 M, 60 F) on two occasions. Densitometry (ZDMO1) was first performed at 10.7 ± 2.6 years and again (ZDMO-2) at 14.4 ± 2.7 years. At the first densitometry, 64 children (62.1%) had osteopenia and an the second, 54 (52.4%). Sixty-two patients (60.2%) improved their ZBMD value (Group A) and 41 (39.8%) worsened (Group B). Compared to children in Group B, Group A had significantly higher BMI as well as creatinine, uric acid and sodium levels. Among these groups, there were no differences in the values of calciuria, citraturia or age or time elapsed between two densitometries. The value of ZDMO-2 was related to the IMC2 (r = 0.42, P < 0001). In patients who remained with osteopenia, hypercalciuria persisted in 17.6% and those with ZDMO-2 and normal calciuria, remained high at 35.4% (P = 0.02). The authors concluded that there is a certain tendency to spontaneously improve BMD in children with IH. The improvement in BMD is associated with increased body mass. They also concluded that calciuria is normalized in a high percentage of cases and they believe that, except in case of fractures, drug treatment with bisphosphonates or thiazides is not indicated initially[78].

Moreira Guimarães Penido *et al*[79] (2012) studied the bone mass of 80 pediatric patients with IH. Bone densitometry was carried out by DXA and lumbar-spine BMD (g/cm^2) and BMD Z-scores were evaluated before and after treatment. The patients (43 boys and 37 girls) were followed for a median time of 6.0 years. Median of calcium excretion was 5.0 mg/kg per 24 h before treatment and 2.6 after treatment. BMD before and after treatment with potassium citrate or potassium citrante and thiazides were 0.721 ± 0.175 g/cm^2 and 0.845 ± 0.170 g/cm^2, respectively (P < 0.00001). BMD Z-score also changed significantly from -0.763 ± 0.954 to -0.537 ± 0.898 (P < 0.0001). The authors suggested a beneficial effect and potential value of treatment in these patients[79].

Finally, it is known that reduced BMD and IH are closed entities, although the precise mechanisms of bone loss or failure of normal bone mass gain remain unknown. The largest accumulation of bone mass occurs during childhood and adolescence, peaking at the end of the second decade of life[100,101]. This accumulation should occur without interference in order to achieve the peak of optimal bone mass. However, alterations in childhood bone mass acquisition may not affect bone mass many decades later in late adulthood because it is governed by a homeostatic system that tends to return to a set point after any transient perturbation[102]. A persistent disturbing factor may therefore compromise the final bone mass in adulthood[101,102]. Factors such as irregularities in sun exposure and physical exercise, chronic reduction in calcium intake and continued loss of urinary calcium can be considered risks factors for alterations in bone structure and low bone mass and density throughout life, increasing the risk of osteopenia, osteoporosis and fractures later in life[103-105].

CONCLUSION

Since the seventies, the hypothesis that continuous el-

evation in urinary calcium excretion could be associated with some degree of bone loss has become more clearly defined. Studies in adults have 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 IH. Bone loss seems mainly to involve those skeletal sites where trabecular bone is more represented, such as vertebral bodies[68,69,88,91,94]. Despite the rather limited number of studies to date in children with IH, the majority of results are consistent with the view that there is a decrease in BMD, particularly at the spine, like in adults. The precise mechanisms contributing to bone loss or the failure of adequate bone mass gain remain as yet unknown. Any continuous and persistent interference in bone mass gain may be a determining factor for low BMD, with an increased risk of osteopenia, osteoporosis and fractures in adulthood[103-105].

There are no data on the role of hypercalciuria as a risk factor for fractures. However, low bone mass is a major risk factor for fracture. Therefore, future studies will be important to define the contribution of hypercalciuria in the increased risk of fractures.

REFERENCES

1 **Stapleton FB**. Idiopathic hypercalciuria: association with isolated hematuria and risk for urolithiasis in children. The Southwest Pediatric Nephrology Study Group. *Kidney Int* 1990; **37**: 807-811
2 **Stapleton FB**, Miller LA. Renal function in children with idiopathic hypercalciuria. *Pediatr Nephrol* 1988; **2**: 229-235
3 **Penido MG**, Diniz JS, Moreira ML, Tupinambá AL, França A, Andrade BH, Souto MF. [Idiopathic hypercalciuria: presentation of 471 cases] *J Pediatr* (Rio J) 2001; **77**: 101-104
4 **van't Hoff WG**. Aetiological factors in paediatric urolithiasis. *Nephron Clin Pract* 2004; **98**: c45-c48
5 **Lemann J**, Worcester EM, Gray RW. Hypercalciuria and stones. *Am J Kidney Dis* 1991; **17**: 386-391
6 **Pak CY**. Etiology and treatment of urolithiasis. *Am J Kidney Dis* 1991; **18**: 624-637
7 **Worcester EM**, Coe FL. New insights into the pathogenesis of idiopathic hypercalciuria. *Semin Nephrol* 2008; **28**: 120-132
8 **Alon US**, Berenbom A. Idiopathic hypercalciuria of childhood: 4- to 11-year outcome. *Pediatr Nephrol* 2000; **14**: 1011-1015
9 **Polito C**, La Manna A, Cioce F, Villani J, Nappi B, Di Toro R. Clinical presentation and natural course of idiopathic hypercalciuria in children. *Pediatr Nephrol* 2000; **15**: 211-214
10 **Vachvanichsanong P**, Malagon M, Moore ES. Urinary tract infection in children associated with idiopathic hypercalciuria. *Scand J Urol Nephrol* 2001; **35**: 112-116
11 **Alon US**, Zimmerman H, Alon M. Evaluation and treatment of pediatric idiopathic urolithiasis-revisited. *Pediatr Nephrol* 2004; **19**: 516-520
12 **Srivastava T**, Schwaderer A. Diagnosis and management of hypercalciuria in children. *Curr Opin Pediatr* 2009; **21**: 214-219
13 **Valenti G**, Laera A, Pace G, Aceto G, Lospalluti ML, Penza R, Selvaggi FP, Chiozza ML, Svelto M. Urinary aquaporin 2 and calciuria correlate with the severity of enuresis in children. *J Am Soc Nephrol* 2000; **11**: 1873-1881
14 **Pace G**, Aceto G, Cormio L, Traficante A, Tempesta A, Lospalluti ML, Selvaggi FP, Penza R. Nocturnal enuresis can be caused by absorptive hypercalciuria. *Scand J Urol Nephrol* 1999; **33**: 111-114
15 **Kamperis K**, Hagstroem S, Rittig S, Djurhuus JC. Urinary calcium excretion in healthy children and children with primary monosymptomatic nocturnal enuresis. *J Urol* 2006; **176**: 770-773
16 **Nevéus T**, Hansell P, Stenberg A. Vasopressin and hypercalciuria in enuresis: a reappraisal. *BJU Int* 2002; **90**: 725-729
17 **Aceto G**, Penza R, Coccioli MS, Palumbo F, Cresta L, Cimador M, Chiozza ML, Caione P. Enuresis subtypes based on nocturnal hypercalciuria: a multicenter study. *J Urol* 2003; **170**: 1670-1673
18 **Kerstetter JE**, O'Brien KO, Insogna KL. Low protein intake: the impact on calcium and bone homeostasis in humans. *J Nutr* 2003; **133**: 855S-861S
19 **Sargent JD**, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr* 1993; **123**: 393-397
20 **Stapleton FB**. Hematuria associated with hypercalciuria and hyperuricosuria: a practical approach. *Pediatr Nephrol* 1994; **8**: 756-761
21 **Chen YH**, Lee AJ, Chen CH, Chesney RW, Stapleton FB, Roy S. Urinary mineral excretion among normal Taiwanese children. *Pediatr Nephrol* 1994; **8**: 36-39
22 **Penido MG**, Diniz JS, Guimarães MM, Cardoso RB, Souto MF, Penido MG. [Urinary excretion of calcium, uric acid and citrate in healthy children and adolescents]. *J Pediatr* (Rio J) 2002; **78**: 153-160
23 **Simkin PA**, Hoover PL, Paxson CS, Wilson WF. Uric acid excretion: quantitative assessment from spot, midmorning serum and urine samples. *Ann Intern Med* 1979; **91**: 44-47
24 **Pak CY**, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, McGuire J, Sakhaee K, Bush S, Nicar M, Norman DA, Peters P. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. *Am J Med* 1980; **69**: 19-30
25 **Kerstetter JE**, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. *Am J Clin Nutr* 2003; **78**: 584S-592S
26 **Bushinsky DA**. Genetic hypercalciuric stone-forming rats. *Curr Opin Nephrol Hypertens* 1999; **8**: 479-488
27 **Vezzoli G**, Tanini A, Ferrucci L, Soldati L, Bianchin C, Franceschelli F, Malentacchi C, Porfirio B, Adamo D, Terranegra A, Falchetti A, Cusi D, Bianchi G, Brandi ML. Influence of calcium-sensing receptor gene on urinary calcium excretion in stone-forming patients. *J Am Soc Nephrol* 2002; **13**: 2517-2523
28 **Heilberg IP**, Weisinger JR. Bone disease in idiopathic hypercalciuria. *Curr Opin Nephrol Hypertens* 2006; **15**: 394-402
29 **Coe FL**, Parks JH, Moore ES. Familial idiopathic hypercalciuria. *N Engl J Med* 1979; **300**: 337-340
30 **Liberman UA**, Sperling O, Atsmon A, Frank M, Modan M, Vries AD. Metabolic and calcium kinetic studies in idiopathic hypercalciuria. *J Clin Invest* 1968; **47**: 2580-2590
31 **Hoenderop JG**, Nilius B, Bindels RJ. Calcium absorption across epithelia. *Physiol Rev* 2005; **85**: 373-422
32 **Kaplan RA**, Haussler MR, Deftos LJ, Bone H, Pak CY. The role of 1 alpha, 25-dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. *J Clin Invest* 1977; **59**: 756-760
33 **Coe FL**, Favus MJ, Crockett T, Strauss AL, Parks JH, Porat A, Gantt CL, Sherwood LM. 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* 1982; **72**: 25-32
34 **Maierhofer WJ**, Gray RW, Cheung HS, Lemann J. Bone resorption stimulated by elevated serum 1,25-(OH)2-vitamin D concentrations in healthy men. *Kidney Int* 1983; **24**: 555-560
35 **Adams ND**, Gray RW, Lemann J, Cheung HS. Effects of calcitriol administration on calcium metabolism healthy men. *Kidney Int* 1982; **21**: 90-97
36 **Bushinsky DA**, Frick KK, Nehrke K. Genetic hypercalciuric

stone-forming rats. *Curr Opin Nephrol Hypertens* 2006; **15**: 403-418
37 **Li XQ**, Tembe V, Horwitz GM, Bushinsky DA, Favus MJ. Increased intestinal vitamin D receptor in genetic hypercalciuric rats. A cause of intestinal calcium hyperabsorption. *J Clin Invest* 1993; **91**: 661-667
38 **Yao J**, Kathpalia P, Bushinsky DA, Favus MJ. Hyperresponsiveness of vitamin D receptor gene expression to 1,25-dihydroxyvitamin D3. A new characteristic of genetic hypercalciuric stone-forming rats. *J Clin Invest* 1998; **101**: 2223-2232
39 **Yao JJ**, Bai S, Karnauskas AJ, Bushinsky DA, Favus MJ. Regulation of renal calcium receptor gene expression by 1,25-dihydroxyvitamin D3 in genetic hypercalciuric stone-forming rats. *J Am Soc Nephrol* 2005; **16**: 1300-1308
40 **Breslau NA**, Preminger GM, Adams BV, Otey J, Pak CY. Use of ketoconazole to probe the pathogenetic importance of 1,25-dihydroxyvitamin D in absorptive hypercalciuria. *J Clin Endocrinol Metab* 1992; **75**: 1446-1452
41 **Favus MJ**, Karnauskas AJ, Parks JH, Coe FL. Peripheral blood monocyte vitamin D receptor levels are elevated in patients with idiopathic hypercalciuria. *J Clin Endocrinol Metab* 2004; **89**: 4937-4943
42 **Peacock M**, Nordin BE. Tubular reabsorption of calcium in normal and hypercalciuric subjects. *J Clin Pathol* 1968; **21**: 353-358
43 **Schwille PO**, Rümenapf G, Schmidtler J, Köhler R. Fasting and post-calcium load serum calcium, parathyroid hormone, calcitonin, in male idiopathic calcium urolithiasis--evidence for a basic disturbance in calcium metabolism. *Exp Clin Endocrinol* 1987; **90**: 71-75
44 **Worcester EM**, Gillen DL, Evan AP, Parks JH, Wright K, Trumbore L, Nakagawa Y, Coe FL. Evidence that postprandial reduction of renal calcium reabsorption mediates hypercalciuria of patients with calcium nephrolithiasis. *Am J Physiol Renal Physiol* 2007; **292**: F66-F75
45 **Worcester EM**, Coe FL. Evidence for altered renal tubule function in idiopathic calcium stone formers. *Urol Res* 2010; **38**: 263-269
46 **Coe FL**, Evan A, Worcester E. Pathophysiology-based treatment of idiopathic calcium kidney stones. *Clin J Am Soc Nephrol* 2011; **6**: 2083-2092
47 **Worcester EM**, Coe FL, Evan AP, Bergsland KJ, Parks JH, Willis LR, Clark DL, Gillen DL. Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. *Am J Physiol Renal Physiol* 2008; **295**: F1286-F1294
48 **Levy FL**, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. *Am J Med* 1995; **98**: 50-59
49 **Prié D**, Ravery V, Boccon-Gibod L, Friedlander G. Frequency of renal phosphate leak among patients with calcium nephrolithiasis. *Kidney Int* 2001; **60**: 272-276
50 **Borghi L**, Meschi T, Maggiore U, Prati B. Dietary therapy in idiopathic nephrolithiasis. *Nutr Rev* 2006; **64**: 301-312
51 **Kok DJ**, Iestra JA, Doorenbos CJ, Papapoulos SE. The effects of dietary excesses in animal protein and in sodium on the composition and the crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. *J Clin Endocrinol Metab* 1990; **71**: 861-867
52 **Nijenhuis T**, Renkema KY, Hoenderop JG, Bindels RJ. Acid-base status determines the renal expression of Ca2+ and Mg2+ transport proteins. *J Am Soc Nephrol* 2006; **17**: 617-626
53 **Borghi L**, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002; **346**: 77-84
54 **Lemann J**, Lennon EJ, Piering WR, Prien EL, Ricanati ES. Evidence that glucose ingestion inhibits net renal tubular reabsorption of calcium and magnesium in man. *J Lab Clin Med* 1970; **75**: 578-585
55 **Lemann J**, Piering WF, Lennon EJ. Possible role of carbohydrate-induced calciuria in calcium oxalate kidney-stone formation. *N Engl J Med* 1969; **280**: 232-237
56 **Lennon EJ**, Lemann J, Piering WF, Larson LS. The effect of glucose on urinary cation excretion during chronic extracellular volume expansion in normal man. *J Clin Invest* 1974; **53**: 1424-1433
57 **Murer H**, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: molecular mechanisms. *Physiol Rev* 2000; **80**: 1373-1409
58 **Sommer S**, Berndt T, Craig T, Kumar R. The phosphatonins and the regulation of phosphate transport and vitamin D metabolism. *J Steroid Biochem Mol Biol* 2007; **103**: 497-503
59 **Alon US**. Clinical practice. Fibroblast growth factor (FGF)23: a new hormone. *Eur J Pediatr* 2011; **170**: 545-554
60 **ADHR Consortium**. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet* 2000; **26**: 345-348
61 **Shimada T**, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA* 2001; **98**: 6500-6505
62 **Urakawa I**, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature* 2006; **444**: 770-774
63 **Gattineni J**, Baum M. Regulation of phosphate transport by fibroblast growth factor 23 (FGF23): implications for disorders of phosphate metabolism. *Pediatr Nephrol* 2010; **25**: 591-601
64 **Ramon I**, Kleynen P, Body JJ, Karmali R. Fibroblast growth factor 23 and its role in phosphate homeostasis. *Eur J Endocrinol* 2010; **162**: 1-10
65 **Torres PU**, Prié D, Molina-Blétry V, Beck L, Silve C, Friedlander G. Klotho: an antiaging protein involved in mineral and vitamin D metabolism. *Kidney Int* 2007; **71**: 730-737
66 **Chang Q**, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG. The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science* 2005; **310**: 490-493
67 **Weisinger JR**. New insights into the pathogenesis of idiopathic hypercalciuria: the role of bone. *Kidney Int* 1996; **49**: 1507-1518
68 **Giannini S**, Nobile M, Sartori L, Calò L, Tasca A, Dalle Carbonare L, Ciuffreda M, D'Angelo A, Pagano F, Crepaldi G. Bone density and skeletal metabolism are altered in idiopathic hypercalciuria. *Clin Nephrol* 1998; **50**: 94-100
69 **Caudarella R**, Vescini F, Buffa A, Sinicropi G, Rizzoli E, La Manna G, Stefoni S. Bone mass loss in calcium stone disease: focus on hypercalciuria and metabolic factors. *J Nephrol* 2003; **16**: 260-266
70 **Giannini S**, Nobile M, Sella S, Dalle Carbonare L. Bone disease in primary hypercalciuria. *Crit Rev Clin Lab Sci* 2005; **42**: 229-248
71 **Asplin JR**, Donahue S, Kinder J, Coe FL. Urine calcium excretion predicts bone loss in idiopathic hypercalciuria. *Kidney Int* 2006; **70**: 1463-1467
72 **Zerwekh JE**. Bone disease and idiopathic hypercalciuria. *Semin Nephrol* 2008; **28**: 133-142
73 **García-Nieto V**, Ferrández C, Monge M, de Sequera M, Rodrigo MD. Bone mineral density in pediatric patients with idiopathic hypercalciuria. *Pediatr Nephrol* 1997; **11**: 578-583
74 **Freundlich M**, Alonzo E, Bellorin-Font E, Weisinger JR. Reduced bone mass in children with idiopathic hypercalciuria and in their asymptomatic mothers. *Nephrol Dial Transplant* 2002; **17**: 1396-1401
75 **García-Nieto V**, Navarro JF, Monge M, García-Rodríguez VE. Bone mineral density in girls and their mothers with idiopathic hypercalciuria. *Nephron Clin Pract* 2003; **94**: c89-c93

76 **Penido MG**, Lima EM, Marino VS, Tupinambá AL, França A, Souto MF. Bone alterations in children with idiopathic hypercalciuria at the time of diagnosis. *Pediatr Nephrol* 2003; **18**: 133-139

77 **Skalova S**, Palicka V, Kutilek S. Bone mineral density and urinary N-acetyl-beta-D-glucosaminidase activity in paediatric patients with idiopathic hypercalciuria. *Nephrology* (Carlton) 2005; **10**: 99-102

78 **García-Nieto V**, Sánchez Almeida E, Monge M, Luis Yanes MI, Hernández González MJ, Ibáñez A. Longitudinal study, bone mineral density in children diagnosed with idiopathic hipercalciuria (IH). *Pediatr Nephrol* 2009; **24**: 2083

79 **Moreira Guimarães Penido MG**, de Sousa Tavares M, Campos Linhares M, Silva Barbosa AC, Cunha M. Longitudinal study of bone mineral density in children with idiopathic hypercalciuria. *Pediatr Nephrol* 2012; **27**: 123-130

80 **Malluche HH**, Tschoepe W, Ritz E, Meyer-Sabellek W, Massry SG. Abnormal bone histology in idiopathic hypercalciuria. *J Clin Endocrinol Metab* 1980; **50**: 654-658

81 **Heller HJ**, Zerwekh JE, Gottschalk FA, Pak CY. Reduced bone formation and relatively increased bone resorption in absorptive hypercalciuria. *Kidney Int* 2007; **71**: 808-815

82 **Heilberg IP**, Martini LA, Szejnfeld VL, Carvalho AB, Draibe SA, Ajzen H, Ramos OL, Schor N. Bone disease in calcium stone forming patients. *Clin Nephrol* 1994; **42**: 175-182

83 **Bordier P**, Ryckewart A, Gueris J, Rasmussen H. On the pathogenesis of so-called idiopathic hypercalciuria. *Am J Med* 1977; **63**: 398-409

84 **Steiniche T**, Mosekilde L, Christensen MS, Melsen F. A histomorphometric determination of iliac bone remodeling in patients with recurrent renal stone formation and idiopathic hypercalciuria. *APMIS* 1989; **97**: 309-316

85 **Stapleton FB**, Noe HN, Roy S, Jerkins G. Hypercalciuria in children with urolithiasis. *Am J Dis Child* 1982; **136**: 675-678

86 **Hymes LC**, Warshaw BL. Idiopathic hypercalciuria. Renal and absorptive subtypes in children. *Am J Dis Child* 1984; **138**: 176-180

87 **Pacifici R**, Rothstein M, Rifas L, Lau KH, Baylink DJ, Avioli LV, Hruska K. Increased monocyte interleukin-1 activity and decreased vertebral bone density in patients with fasting idiopathic hypercalciuria. *J Clin Endocrinol Metab* 1990; **71**: 138-145

88 **Weisinger JR**, Alonzo E, Bellorín-Font E, Blasini AM, Rodriguez MA, Paz-Martínez V, Martinis R. Possible role of cytokines on the bone mineral loss in idiopathic hypercalciuria. *Kidney Int* 1996; **49**: 244-250

89 **Krieger NS**, Frick KK, LaPlante Strutz K, Michalenka A, Bushinsky DA. Regulation of COX-2 mediates acid-induced bone calcium efflux in vitro. *J Bone Miner Res* 2007; **22**: 907-917

90 **Misael da Silva AM**, dos Reis LM, Pereira RC, Futata E, Branco-Martins CT, Noronha IL, Wajchemberg BL, Jorgetti V. Bone involvement in idiopathic hypercalciuria. *Clin Nephrol* 2002; **57**: 183-191

91 **Lawoyin S**, Sismilich S, Browne R, Pak CY. Bone mineral content in patients with calcium urolithiasis. *Metabolism* 1979; **28**: 1250-1254

92 **Zanchetta JR**, Rodriguez G, Negri AL, del Valle E, Spivacow FR. Bone mineral density in patients with hypercalciuric nephrolithiasis. *Nephron* 1996; **73**: 557-560

93 **Alhava EM**, Juuti M, Karjalainen P. Bone mineral density in patients with urolithiasis. A preliminary report. *Scand J Urol Nephrol* 1976; **10**: 154-156

94 **Bataille P**, Achard JM, Fournier A, Boudailliez B, Westeel PF, el Esper N, Bergot C, Jans I, Lalau JD, Petit J. Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. *Kidney Int* 1991; **39**: 1193-1205

95 **Stapleton FB**, McKay CP, Noe HN. Urolithiasis in children: the role of hypercalciuria. *Pediatr Ann* 1987; **16**: 980-1,984-92

96 **Stapleton FB**, Jones DP, Miller LA. Evaluation of bone metabolism in children with hypercalciuria. *Semin Nephrol* 1989; **9**: 75-78

97 **Perrone HC**, Lewin S, Langman CB, Toporovski J, Marone M, Schor N. Bone effects of the treatment of children with absorptive hypercalciuria. *Pediatr Nephrol* 1992; **6**: C115

98 **García-Nieto V**, Navarro JF, Ferrández C. Bone loss in children with idiopathic hypercalciuria. *Nephron* 1998; **78**: 341-342

99 **Penido MG**, Lima EM, Souto MF, Marino VS, Tupinambá AL, França A. Hypocitraturia: a risk factor for reduced bone mineral density in idiopathic hypercalciuria? *Pediatr Nephrol* 2006; **21**: 74-78

100 **Saggese G**, Baroncelli GI, Bertelloni S. Osteoporosis in children and adolescents: diagnosis, risk factors, and prevention. *J Pediatr Endocrinol Metab* 2001; **14**: 833-859

101 **Baroncelli GI**, Bertelloni S, Sodini F, Saggese G. Osteoporosis in children and adolescents: etiology and management. *Paediatr Drugs* 2005; **7**: 295-323

102 **Gafni RI**, Baron J. Childhood bone mass acquisition and peak bone mass may not be important determinants of bone mass in late adulthood. *Pediatrics* 2007; **119** Suppl 2: S131-S136

103 **Schalamon J**, Singer G, Schwantzer G, Nietosvaara Y. Quantitative ultrasound assessment in children with fractures. *J Bone Miner Res* 2004; **19**: 1276-1279

104 **Clark EM**, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. *Pediatrics* 2006; **117**: e291-e297

105 **Loro ML**, Sayre J, Roe TF, Goran MI, Kaufman FR, Gilsanz V. Early identification of children predisposed to low peak bone mass and osteoporosis later in life. *J Clin Endocrinol Metab* 2000; **85**: 3908-3918

S- Editor Zhang DN **L- Editor** A **E- Editor** Zheng XM