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ORIGINAL PAPER

# Osteopenia/osteoporosis in patients with calcium nephrolithiasis

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**Abstract** The objective of this study is to analyze the alterations in bone mineral density and bone and calcium–phosphorus metabolism in patients with calcium nephrolithiasis. We designed a study with 182 patients who were distributed among three groups: group O, 56 patients without nephrolithiasis; group A, 67 patients with calcium nephrolithiasis and mild lithogenic activity; and group B, 59 patients with calcium nephrolithiasis and severe lithogenic activity. Metabolic parameters of blood and urine that were related to calcium–phosphorous and bone metabolism and bone densitometry were assessed in all patients. A comparative study was performed on the variables of bone and calcium–phosphorus metabolism and bone densitometry as well as the presence or absence of osteopenia/osteoporosis. The patients in group B had a greater loss of bone mineral density, measured by the T-score, than the patients in groups O and A. Moreover, the proportion of patients in group B with osteopenia/osteoporosis was statistically significantly higher than the proportion of patients in groups O and A. We observed higher values of calciuria, fasting calcium/creatinine ratio, and 24-h calcium/creatinine among the patients in group B compared to the other two groups. Calciuria, citraturia, and fasting calcium/creatinine were independent factors that showed a relationship with severe lithogenic activity compared to the control group, and $\beta$-crosslaps is an independent factor that has a relationship with severe lithogenic activity as compared to mild lithogenic activity. Patients with calcium lithiasis and severe lithogenic activity have a greater loss in bone mineral density and therefore a greater risk of osteopenia/osteoporosis.

**Keywords** Calcium stones · Bone mineral density · Osteoporosis · Osteopenia · Bone remodeling markers

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## Introduction

Oxalate and calcium phosphate lithiasis has been detected in 70–75 % of cases, and lithiasis is related to alterations in calcium–phosphorus metabolism, hyperoxaluria, hyperuricosuria, a deficiency of inhibitors of crystal precipitation, alterations in urinary pH, and anatomical factors [1]. Biochemical alterations in the urine can be of renal or prerenal origin, as a consequence of exogenous agents (e.g., dietary habits, pharmaceuticals, bacteria, and viruses) or endogenous agents (e.g., endocrine, metabolic, and immunologic factors and tubulopathies), which can be integrated under the designation of systemic diseases related to urinary lithiasis including endocrine and metabolic alterations, immunological problems and tubulopathies, bone and

digestive system diseases, dietary issues, intoxication, and lithogenic pharmaceuticals [1].

Regarding these systemic diseases, some authors have observed relationships among loss of bone mineral density, hypercalciuria, hypocitraturia, and nephrolithiasis [2, 3]; these relationships are the most significant in patients with recurrent calcium nephrolithiasis [4, 5], but osteopenia has also been found in patients with normal urine calcium levels [5, 6]. Tugcu et al. observed a severe loss of bone mineral density in patients with normal urine calcium and recurrent calcium nephrolithiasis [7]. Asplin et al. demonstrated that patients who are stone formers would consume less calcium for fear of new lithiasis episodes, which were related to a greater loss of bone calcium to maintain stable serum calcium levels and was therefore related to a greater loss of bone mineral density [8]; these results highlighted the importance of dietary habits. These same observations were highlighted by other authors, who have suggested that bone alterations in these patients could be mediated by cytokines such as IL-1 [9]. This important relationship between nephrolithiasis and bone metabolism and the loss of bone mineral density leads us to consider, similar to Stoermann et al. [10], whether calcium urinary lithiasis is a bone disease.

The objective of this study is to analyze the alterations in bone mineral density and bone and calcium–phosphorus metabolism that occur in patients with calcium nephrolithiasis.

## Materials and methods

### Study subjects

We conducted a cross-sectional study with a control group for a total of 182 patients from eastern Andalucia (Spain), who were distributed into three groups:

*Group O*: 56 patients between 25 and 60 years of age without nephrolithiasis.
*Group A*: 67 patients between 25 and 60 years of age with calcium nephrolithiasis and mild lithogenic activity.
*Group B*: 59 patients between 25 and 60 years of age with calcium nephrolithiasis and severe lithogenic activity.

We consider severe lithogenic activity to be lithiasis >2 cm, more than two calculi, bilateral lithiasis, or severe recurrence (2 episodes in 1 year or three in 3 years). Mild lithogenic activity is considered as nephrolithiasis <2 cm (1–2 calculi) with healthy contralateral kidney and without recurrence or with mild recurrence. The control group was composed of patients without lithiasis or urologic pathologies related to lithiasis.

*Inclusion criteria*: Men and women who were between 25 and 60 years of age and had no nephrolithiasis or who had calcium nephrolithiasis and mild or severe lithogenic activity.

*Exclusion criteria*: Patients older than 60 years or younger than 25 years and patients with congenital bone pathologies, congenital renal pathologies, hyperparathyroidism, intestinal inflammatory diseases, renal tubular acidosis, treatment with bisphosphonates, hormone replacement therapy, and treatment with thiazides, potassium citrate, corticosteroids, and supplements of calcium and vitamin D.

We recommended a daily intake of 1,000 mg calcium in the diet. Patients took supplements of calcium or vitamin D independently of the diet.

### Study variables

Patient histories and physical examinations were performed on all patients, and measurements of weight, height, body mass index, and blood pressure of the patients were recorded. At the beginning of the study, plain film radiographs of the abdomen and/or intravenous urograms and ultrasound were obtained with the objective of classifying the patients into one of the three study groups.

Then, each patient underwent a biochemical analysis of blood and urine and an analysis of the bone density of the femur and lumbar spine.

*Serology*: Creatinine (mg/dl), urea (mg/dl), uric acid (mg/dl), triglycerides (mg/dl), HDL cholesterol (mg/dl), total cholesterol (mg/dl), protein (g/dl), sodium (mEq/l), potassium (mEq/l), chloride (mEq/l), calcium (mg/dl), phosphorus (mg/dl), alkaline phosphatase (U/l), iPTH (pg/ml), osteocalcin (ng/ml),[1] beta-crosslaps (ng/ml),[2] beta-crosslaps/osteocalcin, (25) OH Vitamin D (ng/ml), and chloride/phosphorus ratio.

Twenty-four-hour urine study: Diuresis (ml), creatinine clearance (ml/min), creatinine (mg/dl), urea (mg/dl), sodium (mEq/l), potassium (mEq/l), calcium (mg/dl), phosphorus (mg/dl), microalbuminuria (mg/dl), microalbuminuria/creatinine (mg/gCr), urate (mg/dl), chloride (mEq/l), oxalate (mg/dl), citrate (mg/dl), tubular reabsorption of phosphate (RTP), and calcium/creatinine, calcium/citrate, oxalate/creatinine, oxalate/citrate, and calcium/oxalate ratios.

Post-fasting urine study: Calcium/creatinine ratio.

[1] Determined by chemiluminescence methods in a LIAISON-Osteocalcin (DIASORIN) automatic analyzer.

[2] Determined by the "ECLIA" method, or electrochemiluminescence immunoassay, in an Elecsys MODULATOR ANALYTICS E170 automatic analyzer (Roche Diagnostics).

**Table 1** Bone density results for dual energy X-ray absorptiometry

Analysis of the three groups of patients. Values are expressed as mean ± standard deviation

| | Group O | Group A | Group B | *p* |
|---|---|---|---|---|
| BD Hip (T-score) | −0.2 ± 1.1 | −0.6 ± 0.8 | −1 ± 0.8 | 0.0001 |
| BD Femoral neck (T-score) | −0.5 ± 1 | −0.6 ± 0.8 | −1.2 ± 0.8 | 0.0001 |
| BD Lumbar spine (T-score) | −0.5 ± 1.1 | −0.8 ± 0.9 | −1.5 ± 1.1 | 0.0001 |

Bone mineral densitometry (BMD) was obtained using dual energy X-ray absorptiometry with Hologic QDR 4,500 equipment.

Stone composition: Infrared spectroscopy.

We followed the WHO criterion and classified the loss of bone mineral density according to standard deviations (T-score) as follows: normal, BMD greater than −1 SD on the T scale; osteopenia, BMD between −1 and −2.5 SD on the T scale; and osteoporosis, BMD less than −2.5 SD on the T scale [11].

### Statistical analysis

A statistical analysis of the results was performed by applying the Student's *t* test and ANOVA for the analysis of qualitative–quantitative variables, the Chi-squared test for the analysis of qualitative variables, and binary logistic regression, obtaining results through the OR and a 95 % confidence interval. The Pearson correlation test was applied or, if the Pearson correlation test could not be applied, the Spearman rho test was applied for the analysis of linear correlations between quantitative variables. The normality of the variables was checked by applying the Kolmogorov–Smirnov test, and the analysis of variance was checked with the Levene test. We established statistical significance when $p \leq 0.05$. The statistical analyses were performed with the program SPSS 17.0 for Windows.

### Limitations of the study

The daily salt, calcium, and protein intake were not determined. Also, smoking and alcohol were not investigated in our study.

### Ethics

The study was approved by the hospital's ethics committee, and the study patients received information about the analytical study prior to the start of the study.

## Results

The mean age of the patients who participated in the study was 48.9 ± 10.1 years in group O, 45.5 ± 13.1 years in group A, and 45.9 ± 12.1 years in group B, with no significant differences among the three groups ($p = 0.13$). In addition, no significant gender differences existed among the three groups (group O: 31 men and 25 women; group A: 34 men and 33 women; group B: 36 men and 23 women; $p = 0.51$). There were no significant differences in the composition of the calculi in the patients with calcium lithiasis in groups A and B among the two groups.

We compared the bone densitometry data (T-score) among the three groups, observing that patients with calcium nephrolithiasis and severe lithogenic activity (group B) had a greater loss of bone mineral density than the other two groups (groups O and A). The mean T-score for hip densitometry was −0.2 in group O, −0.6 in group A, and −1 in group B ($p = 0.0001$); at the neck of the femur, the mean score was −0.5 in group O, −0.6 in group A, and −1.2 in group B ($p = 0.0001$); and in the lumbar spine, the mean score was −0.5 in group O, −0.8 in group A, and −1.5 in group B ($p = 0.0001$) (Table 1).

According to the WHO criteria, in the bone densitometry of the hip, a loss of bone mineral density was observed in 26.8 % of the cases in group O (osteopenia, 25 % and osteoporosis, 1.8 %), 32.8 % of the cases in group A (osteopenia, 32.8 % and osteoporosis, 0 %), and 49.2 % of the cases in group B (osteopenia, 45.8 % and osteoporosis, 3.4 %); these differences were statistically significant ($p = 0.03$) between group B and groups O and A (Table 2). In the bone densitometry of the spine, a loss of bone mineral density was observed in 26.8 % of the cases in group O (23.2 % osteopenia and 3.6 % osteoporosis), 43.3 % of group A (37.3 % osteopenia and 6 % osteoporosis), and 71.2 % of group B (55.9 % osteopenia and 15.3 % osteoporosis); these differences were statistically significant ($p = 0.0001$) for group B compared to groups O

**Table 2** Comparison among distinct groups (O, A, B) of the prevalence of hip osteopenia–osteoporosis (T-score less than −1 standard deviation in bone densitometry)

| | Osteopenia–osteoporosis | No osteopenia–osteoporosis | Total |
|---|---|---|---|
| Group O | 15 (26.8 %) | 41 (73.2 %) | 56 |
| Group A | 22 (32.8 %) | 45 (67.2 %) | 67 |
| Group B | 29 (49.2 %) | 30 (50.8 %) | 59 |

After applying the Chi-squared test, we observed statistically significant differences ($p = 0.03$) in group B, where standardized residuals were the most elevated (1.6)

**Table 3** Comparison among distinct groups (O, A, B) of the prevalence of lumbar spine osteopenia–osteoporosis (T-score less than −1 standard deviations in bone densitometry)

| | Osteopenia–osteoporosis | No osteopenia–osteoporosis | Total |
|---|---|---|---|
| Group O | 15 (26.8 %) | 41 (73.2 %) | 56 |
| Group A | 29 (43.3 %) | 38 (56.7 %) | 67 |
| Group B | 42 (71.2 %) | 17 (28.8 %) | 59 |

After applying the Chi-squared test, we observe statistically significant differences ($p = 0.0001$) in group B, where standardized residuals were the most elevated (2.7)

and A (Table 3). The cases with osteopenia/osteoporosis of the hip had a stronger correlation with severe lithogenic activity than those without osteopenia ($\chi^2 = 26.048$; $p = 0.000$); there were no significant differences between cases without lithiasis and those with mild lithogenic activity. The cases with osteopenia/osteoporosis of the lumbar spine had a greater correlation with severe lithogenic activity than the cases without osteopenia ($\chi^2 = 21.899$; $p = 0.000$); there were no significant differences between cases without lithiasis and those with mild lithogenic activity. No differences in age and gender were found comparing patients of three groups with osteopenia/osteoporosis in the hip and lumbar spine. In the hip (age: group 0: 51.3 years vs. group A: 46.3 years vs. group B: 48.9 years; $p = 0.6$; gender [men/women]: group 0: 53.3/46.7 % vs. group A: 40.9/59.1 % vs. group B: 65.5/35.5 %; $p = 0.2$) and in the lumbar spine (age: group 0: 53.9 years vs. group A: 47 years vs. group B: 46.1 years; $p = 0.16$; gender [men/women]: group 0: 60/40 % vs. group A: 55.2/44.8 % vs. group B: 61.9/38.1 %; $p = 0.2$).

After analyzing the principal serum and urine parameters in the three groups, we obtained statistically significant differences for the serum values of alkaline phosphatase, iPTH, osteocalcin, and beta-crosslaps. With regard to urinary values, the calcium/creatinine ratio in post-fasting urine, and calcium, citrate, and calcium/creatinine, calcium/citrate, and calcium/oxalate ratios in 24-h urine were also statistically significantly different (Table 4).

**Table 4** Results and analysis of the variables of demography, calcium–phosphorus, bone, and mineral metabolism in patients without lithiasis or with calcium lithiasis and mild or severe lithogenic activity

| | Group O | Group A | Group B | *p* |
|---|---|---|---|---|
| Age (years) | 48.9 ± 10.1 | 45.4 ± 13.1 | 45.8 ± 12.1 | 0.132 |
| Weight (kg) | 76.3 ± 16.4 | 73.8 ± 14.2 | 77.6 ± 14.9 | 0.422 |
| Height (cm) | 165 ± 8.3 | 165.3 ± 8 | 166.9 ± 9.8 | 0.517 |
| BMI (kg/m$^2$) | 28.2 ± 6 | 26.9 ± 4.2 | 27.7 ± 4.4 | 0.408 |
| Serum calcium (mg/dl) | 9.2 ± 0.4 | 9.2 ± 0.4 | 9.3 ± 0.5 | 0.08 |
| Serum phosphorus (mg/dl) | 3.2 ± 0.5 | 3.1 ± 0.5 | 3 ± 0.5 | 0.15 |
| Serum alkaline phosphatase (U/L) | 64.4 ± 21.2 | 62.6 ± 17.7 | 73.7 ± 32.7[a] | 0.03 |
| Serum iPTH (pg/ml) | 44.8 ± 17.2 | 49.3 ± 15.7 | 55.1 ± 25.6[a] | 0.02 |
| Serum osteocalcin (ng/ml) | 13.9 ± 5.1 | 14.9 ± 5.7 | 17.2 ± 5.5[a] | 0.005 |
| Serum $\beta$-crosslaps (ng/ml) | 0.331 ± 0.150 | 0.359 ± 0.156 | 0.528 ± 0.208[a] | 0.0001 |
| Serum 25 OH vitamin D (ng/ml) | 22.5 ± 9.6 | 24.2 ± 7.4 | 23.5 ± 9.1 | 0.94 |
| Serum $\beta$-crosslaps/osteocalcin | 0.024 ± 0.08 | 0.026 ± 0.010 | 0.032 ± 0.012[a] | 0.001 |
| Urine volume (ml) | 1,956 ± 754 | 1,718 ± 746 | 1,879 ± 704 | 0.21 |
| Creatinine clearance (ml/min) | 119.5 ± 38.7 | 121.6 ± 37.1 | 145.7 ± 42.7 | 0.32 |
| Urine calcium (mg/dl) | 11.6 ± 6.6 | 15.6 ± 7.5 | 18.2 ± 9.1[a] | 0.0001 |
| Urine creatinine (mg/dl) | 88.2 ± 46.3 | 98.6 ± 45.5 | 92.6 ± 45.8 | 0.470 |
| Urine phosphate (mg/dl) | 54.6 ± 27.1 | 58.1 ± 29.9 | 54.2 ± 25.1 | 0.68 |
| Urine uric acid (mg/dl) | 37.1 ± 21.9 | 38.2 ± 14.7 | 35.9 ± 15.2 | 0.75 |
| Urine oxalate (mg/dl) | 1.8 ± 0.9 | 1.9 ± 0.9 | 1.8 ± 0.8 | 0.71 |
| Urine citrate (mg/dl) | 51.5 ± 32.5 | 44.9 ± 25.6 | 32.4 ± 26.1[b] | 0.002 |
| Urine fasting calcium/creatinine | 0.09 ± 0.04 | 0.10 ± 0.03 | 0.16 ± 0.05[a] | 0.0001 |
| Urine 24 h calcium/creatinine | 0.14 ± 0.07 | 0.16 ± 0.07 | 0.21 ± 0.08[a] | 0.0001 |
| Urine calcium/citrate | 0.22 ± 0.08 | 0.35 ± 0.10 | 0.56 ± 0.26[a] | 0.002 |
| Urine calcium/oxalate | 8.1 ± 6.7 | 9.8 ± 6.7 | 16.4 ± 31.6[a] | 0.05 |

The values are expressed as mean ± standard deviation

[a] Statistical differences are obtained due to high levels in group B with respect to the other two groups

[b] Statistical differences are obtained due to low levels in group B with respect to the other two groups

**Table 5** Binary logistic regression analysis model adjusted for age, alkaline phosphatase, iPTH, osteocalcin, and 24-h urine calcium/creatinine ratio

| | OR | 95 % CI | *p* |
|---|---|---|---|
| *Binary logistic regression group O and B (variables with significant relationship)* | | | |
| Urine calcium (mg/dl) | 1.09 | 1.01–1.21 | 0.05 |
| Urine citrate (mg/dl) | 0.997 | 0.995–0.999 | 0.01 |
| Urine fasting calcium/creatinine | 1.51 | 1.19–1.91 | 0.001 |
| *Binary logistic regression group O and A (variables with significant relationship)* | | | |
| Urine calcium (mg/dl) | 1.094 | 1.031–1.162 | 0.003 |
| *Binary logistic regression group A and B (variables with significant relationship)* | | | |
| Serum $\beta$-crosslaps (ng/ml) | 21.78 | 1.61–295.05 | 0.02 |
| Urine citrate (mg/dl) | 0.998 | 0.997–0.999 | 0.05 |
| Urine fasting calcium/creatinine | 1.19 | 1.07–1.33 | 0.001 |

In the linear correlation analysis among the principal quantitative variables implicated in bone and calcium phosphate metabolism of the patients in the study, we observed a statistically significant positive linear correlation between the marker beta-crosslaps and osteocalcin ($r = 0.514$; $p = 0.001$), calciuria ($r = 0.212$; $p = 0.005$), the calcium/creatinine ratio in post-fasting urine ($r = 0.534$; $p = 0.0001$) and calcium/citrate ($r = 0.154$; $p = 0.04$); a statistically significant negative linear correlation was observed among hip densitometry T-score values ($r = -0.226$; $p = 0.003$), neck of the femur T-scores ($r = -0.187$; $p = 0.02$), and lumbar spine T-scores ($r = -0.352$; $p = 0.0001$). There was a statistically significant positive linear correlation between osteocalcin and the calcium/creatinine ratio in post-fasting urine ($r = 0.341$; $p = 0.0001$) and a statistically significant negative linear correlation between the T-score values from hip densitometry ($r = -0.158$; $p = 0.04$) and the lumbar spine T-scores ($r = -0.221$; $p = 0.004$). Calciuria was positively linearly correlated with citraturia ($r = -0.209$; $p = 0.06$) and with the ratios of calcium/creatinine in post-fasting urine ($4 = 0.470$; $p = 0.0001$) and calcium/creatinine in 24-h urine ($r = 0.509$; $p = 0.001$). There was no correlation with the T-score values from hip or spine densitometry, but it is notable that citraturia was positively linearly correlated with the T-scores from hip densitometry ($r = 0.217$; $p = 0.006$) and the lumbar spine T-scores ($r = 0.205$; $p = 0.009$). The calcium/creatinine ratio in post-fasting urine was negatively linearly correlated with the T-scores from hip densitometry ($r = -0.237$; $p = 0.002$), the T-scores of the neck of the femur ($r = -0.217$; $p = 0.009$), and the T-scores of the lumbar spine ($r = -0.292$; $p = 0.0001$).

We conducted a binary logistic regression analysis using the backward method. Between group O and group B, we observed that calciuria, citraturia, and the calcium/creatinine ratio in post-fasting urine were correlated with severe lithogenic activity. Between groups O and A, we observed that only calciuria was correlated with lithogenic activity. Between groups A and B, we observed that a correlation existed among the values for beta-crosslaps, citraturia, and the calcium/creatinine ratio in post-fasting urine between mild and severe lithogenic activity (Table 5).

## Discussion

The pathogenesis of bone mineral density loss in patients with hypercalciuria is unclear. Defective tubular reabsorption of calcium with secondary hyperparathyroidism or defective tubular reabsorption of phosphate with hypophosphatemia and increased synthesis of vitamin D could explain the osteopenia that is observed in some patients with calcium lithiasis, but a reduced bone mineral content is also found in patients with calcium renal calculi without hyperparathyroidism or hormonal alterations secondary to hypophosphatemia [12]. These cases could be related to other hormonal alterations of calcium metabolism [4], nutritional factors, cytokines [13], or prostaglandins. In recent years, some authors have defended the clinical relationship, considering the genetics of calcium lithiasis with bone demineralization phenomena due to alterations in CLDN14 and other genes and that genetic factors are the primary cause of hypercalciuria and the progression toward urinary lithiasis [14, 15]. The study of bone remodeling could be useful for the early detection of increased bone resorption in these patients [2].

The bone remodeling cycle consists of three sequential phases: the resorption period, transition period, and formation period; the identification of the markers of bone formation and resorption provides data regarding the

pathophysiology of osteopenia/osteoporosis [12]. During bone resorption, calcium and bone collagen are liberated, and the derivatives of collagen type I, amino- and carboxy-terminal telopeptides (beta-crosslaps) are considered to be specific markers of bone resorption [16, 17]. Beta-crosslaps is an osteopeptide alpha-1 carboxy-terminal of collagen type I; its measured levels in the serum have been shown to indicate less biological variability than its measured levels in the urine [18].

In the present study, we observed that patients with recurrent calcium nephrolithiasis with severe lithogenic activity have an accelerated bone metabolism, which manifests in the elevation of bone remodeling markers, such as beta-crosslaps, osteocalcin, the beta-crosslaps/osteocalcin ratio, and alkaline phosphatase, compared to the control group and the group with calcium nephrolithiasis with mild lithogenic activity. Vitamin D levels were higher in this group of patients, but the differences were not significant, and 15 % had low vitamin D levels compared to 0 % in the control group. The fact that there are no differences in the levels of vitamin D among the three groups of patients indicates that the calcium stones in our study were independent of the levels of vitamin D. However, bone mineral density loss is explained by increased bone resorption (elevated levels of Beta-crosslaps in group B), together with increased fasting urinary calcium (high calcium/creatinine in the group fasted B) that facilitates calcium lithogenesis. This increased bone resorption in patients with increased lithogenic activity can be influenced genetically as explained by other authors [14, 15]. However, other authors consider vitamin D to be an important hormone in the pathogenesis of recurrent calcium nephrolithiasis because its elevation increases the urinary excretion of calcium and phosphorus [19], and its deficit elevates iPTH levels. Increased levels of vitamin D can produce absorptive hypercalciuria and decreased levels of vitamin D can produce resorptive hypercalciuria, so both conditions can produce calcium nephrolithiasis. A recently published study of more than 15,000 participants has shown that high levels of vitamin D do not appear to be related to the presence of calcium stones, although prospective studies are needed to confirm this [20]. However, low levels of vitamin D produce a secondary increase in iPTH that produces an increase in bone resorption with resorptive hypercalciuria. It was observed in a study that after administration of vitamin D in patients with low levels of vitamin D, iPTH decreases and therefore also it controls the lithogenic activity [21]. We think that the most important role of vitamin D in relation to calcium stones is low levels of this hormone, which contributes to increased bone resorption and fasting hypercalciuria. Higher levels of iPTH were observed in group B compared to the other two groups; however, in the multivariate analysis, no correlation with osteopenia/osteoporosis was observed, which demonstrated that bone activity in patients with calcium lithiasis and severe lithogenic activity was independent of iPTH. We also observed that patients in group B had higher levels of calciuria and calcium/creatinine ratios in post-fasting urine and 24-h urine and lower levels of urine citrate. These differences were statistically significant compared to groups O and A. These results corroborate the hypothesis tested in other studies that patients with calcium lithiasis who have high levels of calciuria and low levels of citraturia have a greater loss of bone mineral density [22], as observed in the patients in our study. Other authors contend that there is an overall loss of bone mineral density in patients with fasting hypercalciuria [23] and a certain grade of metabolic acidosis [24].

After conducting a multivariate study and adjusting for several bone and calcium phosphate metabolism variables, we observed a correlation between lithogenic activity and the levels of alkaline phosphatase, iPTH, osteocalcin, beta-crosslaps, and the calcium/creatinine ratio in post-fasting urine and calcium, citrate, and calcium/creatinine, calcium/citrate, and calcium/oxalate ratios in 24-h urine. Among those patients without lithiasis and with mild lithogenic activity, calciuria is the largest determining factor, while among those patients without lithiasis and with severe lithogenic activity, the determining factors are calciuria, citraturia, and calcium/creatinine in post-fasting urine. Moreover, these three variables are determinants of osteopenia/osteoporosis.

The correlation between osteopenia/osteoporosis and calcium nephrolithiasis has been recognized in a number of studies. Audran et al. [25]. and Zancheta et al. [26]. detected osteopenia in up to 55 % of patients with hypercalciuria [5–12]. Various studies have indicated that up to 60 % of patients with calcium lithiasis have hypercalciuria, and many authors have observed a loss of bone mineral density in stone formers with hypercalciuria. However, osteopenia has also been found in patients with normal urine calcium levels [27, 28]; therefore, it is evident that a reciprocal relationship exists between lithiasis and the loss of bone mass, which should be established for each patient. Caudarella et al., in a group of 196 cases of calcium lithiasis, observed osteopenia in 54 %, osteoporosis in 14 %, and hypercalciuria in only 21.7 % of cases [5]. Tugcu et al., in a group of patients with calcium lithiasis and normal urine calcium, observed osteoporosis in 11.3 % and osteopenia in 65.4 % of cases, compared to a rate of osteopenia of 20 % in the control group. Overall, 26 % of patients with lithiasis had hyperoxaluria, 15.3 % had hypocitraturia, 6 % had hyperuricosuria, 8.6 % had hypocitraturia and hyperoxaluria, and 44 % had a normal urine composition. With these results, Tugcu demonstrated a severe loss of bone mass in patients with normal urine calcium and with calcium nephrolithiasis [7]. In Peris's study, it was observed

that idiopathic osteoporosis is the most frequent cause of male osteoporosis; in those cases and in their family histories, an association between osteoporosis and hypercalciuria was frequent. The most frequent causes of secondary osteoporosis in men included corticosteroid therapy, hypogonadism, and alcoholism [29].

In a group of patients under 15 years of age with hypercalciuria and/or lithiasis, Schwaderer observed a correlation between an increase in BMI and a loss of bone mineral density, finding osteopenia in 42.6 % of children with hypercalciuria and 54.1 % of children with nephrolithiasis [3]. Penido observed higher levels of iPTH and calciuria and lower levels of citraturia in children with idiopathic hypercalciuria compared to a control group; these results are similar to those obtained in our study [2]. Recently, Letavernier et al. showed that patients with osteopenia presented higher fasting calciuria compared with normal bone density patients. Also, we found that the levels of fasting calcium/creatinine were associated with high risk of bone mineral density loss independently of other factors [30]. In this way, we observed in our patients that fasting calcium/creatinine was increased in patients with calcium stones and severe lithogenic activity, who present more bone mineral density loss than patients without stones. Also, in our study, we observed that 49.2 % of patients with calcium lithiasis and severe lithogenic activity had bone mineral density loss in the hip (45.8 % osteopenia and 3.4 % osteoporosis), and 71.2 % had bone mineral density loss in the lumbar spine (55.9 % osteopenia and 15.3 % osteoporosis). Other authors not only defended this relationship, but also observed a higher incidence of fractures in patients with nephrolithiasis [31].

## Conclusions

Patients with calcium lithiasis and severe lithogenic activity have a greater loss of bone mineral density and osteopenia/osteoporosis, compared to patients without lithiasis or with calcium lithiasis and mild lithogenic activity. The elevation of beta-crosslaps in the plasma and the calcium/creatinine ratio in post-fasting urine and low levels of urine citrate are determinants of osteopenia/osteoporosis and discriminators between mild and severe lithogenic activity.

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