Metabolic-mineral study in patients with renal calcium lithiasis, severe lithogenic activity and loss of bone mineral density

Miguel Angel Arrabal-Polo[1], PhD, *Miguel Arrabal-Martin*[1], PhD, *Salvador Arias-Santiago*[2], PhD, *Juan Garrido-Gomez*[3], PhD, *Tomas De Haro-Muñoz*[4], MD, *Armando Zuluaga-Gomez*[1], PhD

INTRODUCTION This study assessed the presence of osteoporosis/osteopenia in patients with severe lithogenic activity and compared their metabolisms with those in patients without lithiasis or with mild lithogenic activity.

METHODS From a sample of 182 patients, those with osteopenia/osteoporosis at the hip and lumbar spine were studied separately in a two-pronged study. 66 patients with bone mineral densities (BMDs) < −1 standard deviation (SD) on a T-score scale at the hip were divided into three groups: group A1 without lithiasis (n = 15); group A2 with lithiasis and mild lithogenic activity (n = 22); and group A3 with lithiasis and severe lithogenic activity (n = 29). Similarly, 86 patients with BMDs < −1 SD on a T-score scale at the lumbar spine were divided into three groups: group B1 without lithiasis (n = 15); group B2 with lithiasis and mild lithogenic activity (n = 29); and group B3 with lithiasis and severe lithogenic activity (n = 42).

RESULTS Patients from group A3 exhibited significantly higher levels of bone remodelling markers as compared to groups A1 and A2. Urinalysis also revealed higher excretion of calcium in 24-hour assessments in this group. Patients from group B3 differed from groups B1 and B2 mainly in bone remodelling markers and 24-hour urinary calcium excretion, which were significantly elevated in patients from group B3.

CONCLUSION Patients with calcium lithiasis and severe lithogenic activity in addition to osteopenia/osteoporosis present with higher levels of hypercalciuria and negative osseous balance, which possibly perpetuate and favour lithiasic activity.

Keywords: bone density, calcium stones, mineral metabolism, osteopenia, osteoporosis
Singapore Med J 2012; 53(12): 808–813

INTRODUCTION

Calcium oxalate and calcium phosphate lithiases have been detected in 70%–75% of patients with renal lithiasis, as their formation is related to alterations in phosphocalcic metabolism and other metabolic pathways, deficits in crystalline precipitation inhibitors, alterations in urine pH, anatomical factors, and low diuresis.[1] Generally, patients with renal lithiasis present with more than one metabolic alteration related to hyperuricosuria, hypercalciuria and urinary oversaturation of calcium, in addition to other features that are a function of the gender and age of the patient.[2,3]

Apart from the abovementioned mineral and metabolic alterations, various studies have reported that patients with renal calcium lithiasis, with or without hypercalciuria, present with bone metabolism alterations that translate into losses in bone mineral density (BMD).[4-6] It has also been demonstrated that patients with recurrent calcium lithiasis present with higher losses of BMD than patients with single episodes of calcium lithiasis or patients without lithiasis.[7] According to Pak et al, metabolic studies that include calculi composition are indicated in patients with recurrent calcium lithiasis.[8] Mineral analysis, and blood and urinary metabolic analyses allow clinicians to establish an adequate diagnosis and understand the pathophysiology of the formation of calcium lithiasis. This enables them to be better able to provide adequate treatment and prophylaxis for patients, with the end goal of preventing recurrences or decreasing the frequency of manifestation of the disorder.[9,10]

An association between BMD and calcium renal lithiasis was observed both clinically[5] and genetically a few years ago. This finding implied that various genes could precondition a patient for the simultaneous occurence of BMD and lithiasis.[11,12] In view of such osseous, lithiasic and hereditary factors, we undertook the present study to assess the presence of metabolic and mineral alterations in patients with renal calcium lithiasis and severe lithogenic activity as well as to determine the loss of BMD (osteopenia or osteoporosis) in these patients.

METHODS

A cross-sectional study was conducted with a control group, in which 182 patients from Eastern Andalusia, Spain, were included. The study group comprised 56 patients without renal lithiasis selected from a general urology unit, 67 patients with renal calcium lithiasis and mild lithogenic activity, and 59 patients with renal calcium lithiasis and serious lithogenic activity selected from an endourology and lithotripsy unit. Only patients with calcium stones were included in the study. This study was approved

[1]Urology Department, San Cecilio University Hospital, [2]Medicine Department, Faculty of Medicine, Granada University, [3]Traumatology, [4]Biochemical Department, San Cecilio University Hospital, Granada, Spain
Correspondence: Dr Miguel Angel Arrabal-Polo, Resident, Urology Department, San Cecilio University Hospital, 143 Camino de Ronda Street, 4F, Granada 18003, Spain. arrabalp@ono.com

by the ethics committee at the San Cecilio University Hospital, Granada, Spain. All patients were provided information regarding the study.

Mild lithogenic activity was considered to be renal lithiasis < 2 cm (1–2 calculi) with a healthy contralateral kidney and with either no recurrence or only mild recurrence. Severe lithogenic activity was considered to be lithiasis > 2 cm or > 2 calculi, bilateral lithiasis, or serious recurrence (two episodes in one year or three episodes in three years).[13] The control group consisted of patients without any lithiasis pathology. The present study included men and women between 25–60 years of age without renal lithiasis or with mild or severe lithogenic activity. The exclusion criteria were as follows: (a) patients above 60 years of age or under 25 years of age; (b) patients with congenital bone pathologies, congenital renal pathologies, hyperparathyroidism, intestinal inflammatory disease or renal tubular acidosis; and (c) patients who had received treatments with biphosphate, hormone replacement therapy, or thiazide, potassium citrate, corticosteroid, calcium or vitamin D treatments.

The World Health Organization (WHO) criteria was followed and BMD loss was classified according to standard deviation (SD; T-score) as follows: normal (BMD > –1 SD on the T-score scale), osteopenia (BMD –1 to –2.5 on the T-score scale) or osteoporosis (BMD < –2.5 SD on the T-score scale).[14] BMD was determined by dual-energy X-ray absorptiometry (Hologic QDR 4500; Hologic, Leuvensestenweg, Belgium). Once the BMDs of the hip and lumbar spine were obtained for all patients and the WHO criteria for assessing the loss of BMD applied, all patients with normal hip and lumbar spine BMDs were excluded. In this manner, two groups of patients were created – group A had altered BMDs of the hip and group B had altered BMDs of the lumbar spine. A distinction was made between these two groups of patients because of the difference in the nature of bone loss seen in them – the loss of trabecular bone is predominant in the lumbar spine, while the loss of cortical bone is predominant in the hip. Traditional classifications of idiopathic or primary osteoporosis delineate osteoporosis into types 1 and 2. In type 1, there is a loss of trabecular bone, while in the type 2, the loss of cortical bone is seen. Therefore, the authors set out to study the metabolic and mineral characteristics of patients with calcium renal stones and altered BMDs of the hip and lumbar spine, respectively.

From a total of 182 patients, 66 patients presented with osteopenia/osteoporosis of the hip and 86 patients presented with osteopenia/osteoporosis of the lumbar spine. These patients were studied separately in a two-pronged study to analyse the characteristics of lithiasic patients with BMD loss in the hip and lumbar spine. In part one of the study, 66 patients with BMDs < –1 SD on a T-score scale at the hip were divided into three groups: group A1 without lithiasis (n = 15); group A2 with lithiasis and mild lithogenic activity (n = 22); and group A3 with lithiasis and severe lithogenic activity (n = 29). In part two of the study, 86 patients with BMDs < –1 SD on a T-score scale at the lumbar spine were divided into three groups: group B1 without lithiasis (n = 15); group B2 with lithiasis and mild lithogenic activity (n = 29); and group B3 with lithiasis and severe lithogenic activity (n = 42).

The following analyses were carried out: (a) serum analysis of calcium (mg/dL), phosphorus (mg/dL), alkaline phosphatase (U/L), parathyroid hormone (iPTH; pg/mL), osteocalcin (ng/mL), β-CrossLaps (ng/mL), β-CrossLaps/osteocalcin ratio, vitamin 1,25-dihydroxyvitamin D3 (ng/mL) and chloride/phosphorus ratio (osteocalcin was determined by chemiluminescence [LIAISON-Osteocalcin automatic analyzer; DiaSorin, Vercelli, Italy] and β-CrossLaps using the ECLIA electrochemiluminescence immunoassay [Elecsys Modular ANALYTICS E170 automatic analyzer; Roche Diagnostics, Barcelona, Spain]); and (b) 24-hour urinalysis, including diuresis (mL), creatinine clearance (mL/min), sodium (mEq/L), calcium (mg/dL), phosphorus (mg/dL), uric acid (mg/dL), chloride (mEq/L), oxalate (mg/dL), citrate (mg/dL), 21-hour calciuria, 24-hour phosphaturia, 24-hour uricosuria, 24-hour oxalateuria, 24-hour citraturia, tubular resorption of phosphate, and fasting calcium/creatinine, 24-hour calcium/creatinine, 24-hour calcium/citrate, oxalate/creatinine, oxalate/citrate, and calcium/oxalate ratios.

According to the criteria set by Park and Pearle,[10] patients were classified as having hypercalciuria if 24-hour calcium excretion was > 200 mg, hyperoxaluria if oxalate excretion was > 40 mg, hyperuricosuria if uric acid excretion was > 600 mg and hypocitraturia if citrate excretion was < 320 mg. Statistical analyses of the data were performed using nonparametric Mann-Whitney U test for qualitative-quantitative variables and the chi-squared test for qualitative variables. The Pearson's correlation test, or Spearman's rho test, was applied for the analysis of linear correlations between quantitative variables. The normality of the variables was verified by applying the Kolmogorov-Smirnov test, and the analysis of variance was conducted using Levene's test. A p-value ≤ 0.05 was considered to be statistically significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences for Windows version 17.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

With respect to composition, analysis of the calculi from patients with mild and severe lithogenic activity did not reveal differences between the two groups (Table I). The mean ages of the patients in groups A1, A2 and A3 were 51.5 ± 6.4 years, 46.7 ± 5.6 years and 48.9 ± 5.4 years, respectively. There was no statistically significant difference in the age of the patients in these three groups. There was also no significant difference found in the percentage of patients with osteopenia and osteoporosis among the three groups.

A comparison of the various variables evaluated among the three patient groups revealed that only osteocalcin levels were significantly elevated in the blood of the patients from group A2 when compared to the patients in group A1 (p = 0.04). Meanwhile, the urine of the patients from group A2 had significantly higher levels of sodium (p = 0.03), calcium (p = 0.03), chloride (p = 0.01)

Table I. Stone composition in patients with mild and serious calcium lithiasis.

Composition	Patients with mild lithiasis (%)	Patients with serious lithiasis (%)
Calcium oxalate monohydrate	6.5	7.3
Calcium oxalate dehydrate	31.5	30.7
Mixed calcium oxalate	18.6	19.9
Calcium phosphate	12.6	14.8
Calcium oxalate phosphate	30.8	27.3
Total	100	100

Table II. Comparison of variables among patients with osteopenia/osteoporosis of the hip (group A).

Variable	Mean ± SD			Comparative p-value		
	Group A1	Group A2	Group A3	A1–A2	A1–A3	A2–A3
Serum analysis						
Calcium (mg/dL)	9.1 ± 0.4	9.2 ± 0.4	9.3 ± 0.5	0.40	0.33	0.84
Phosphorus (mg/L)	3.2 ± 0.5	3.1 ± 0.5	3.1 ± 0.6	0.67	0.45	0.60
Alkaline phosphatase (U/L)	68.3 ± 15.9	61.3 ± 22.1	78.3 ± 41.7	0.10	0.48	0.02
iPTH (pg/mL)	48.4 ± 17.6	49.1 ± 17.5	56.6 ± 22.4	0.72	0.38	0.19
Osteocalcin (ng/mL)	14.4 ± 7.9	15.8 ± 3.9	17.4 ± 6.5	0.04	0.07	0.40
β-CrossLaps (ng/mL)	0.366 ± 0.260	0.352 ± 0.122	0.546 ± 0.225	0.43	0.01	0.002
β-CrossLaps/osteocalcin	0.024 ± 0.008	0.023 ± 0.009	0.033 ± 0.013	0.71	0.02	0.009
Vitamin 1,25-dihydroxyvitamin D_3 (ng/mL)	23.2 ± 4.3	26.2 ± 3.4	27.6 ± 4.5	0.15	0.13	0.52
Chloride/phosphorus	31.1 ± 4.3	33.3 ± 5.8	36.4 ± 11.3	0.45	0.11	0.38
Urine analysis						
Diuresis (mL)	1,865 ± 792	1,502 ± 620	1,844 ± 692	0.18	0.96	0.06
Creatinine clearance (mL/min)	102.2 ± 28.9	110.1 ± 42.6	116.5 ± 49.1	0.91	0.45	0.62
Sodium (mEq/L)	81.3 ± 36.5	117.7 ± 46.1	115.8 ± 45.4	0.03	0.03	0.86
Calcium (mg/dL)	9.6 ± 5.1	14.9 ± 7.1	16.7 ± 8.6	0.03	0.004	0.60
Phosphorus (mg/dL)	50.1 ± 28.9	56.6 ± 23.3	50.2 ± 26.1	0.30	0.77	0.24
Uric acid (mg/dL)	35.6 ± 32.8	37.9 ± 13.5	34.9 ± 15.1	0.08	0.33	0.45
Chloride (mg/dL)	71.2 ± 31.8	113.3 ± 50.7	114.1 ± 46.4	0.01	0.01	0.71
Oxalate (mg/dL)	1.72 ± 0.56	2.01 ± 1.04	1.64 ± 0.88	0.52	0.42	0.18
Citrate (mg/dL)	52.56 ± 37.85	40.18 ± 25.11	28.15 ± 21.73	0.62	0.03	0.10
Fasting calcium/creatinine	0.09 ± 0.04	0.10 ± 0.04	0.16 ± 0.05	0.36	0.001	0.001
24-hour calcium/creatinine	0.15 ± 0.08	0.16 ± 0.08	0.20 ± 0.07	0.46	0.03	0.06
Tubular resorption of phosphate (%)	82.1 ± 5.7	83.2 ± 4.2	81.4 ± 7.9	0.79	0.96	0.63
Calcium/oxalate	8 ± 4.4	7.4 ± 4.6	10.4 ± 5.4	0.11	0.008	0.40
Oxalate/creatinine	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.17	0.24	0.86
Oxalate/citrate	0.04 ± 0.02	0.05 ± 0.03	0.06 ± 0.04	0.56	0.20	0.25
Calcium/citrate	0.18 ± 0.1	0.37 ± 0.16	0.59 ± 0.25	0.01	0.0001	0.08
24-hour calciuria	169.8 ± 107.7	214.1 ± 114.1	290.1 ± 143.9	0.172	0.004	0.04
24-hour phosphaturia	781.9 ± 254.9	795.1 ± 380.3	856.4 ± 369.5	0.63	0.77	0.47
24-hour uricosuria	600.1 ± 587.3	528.1 ± 214.3	596.8 ± 221.1	0.56	0.08	0.13
24-hour oxaluria	27.7 ± 10.6	29.8 ± 19.1	28.6 ± 13.6	0.97	0.71	0.79
24-hour citraturia	885.3 ± 819.5	524.9 ± 321.9	469.6 ± 363.8	0.19	0.05	0.42

iPTH: parathyroid hormone; SD: standard deviation

and calcium/citrate (p = 0.01) when compared to the patients from group A1 (Table II).

The blood of the patients from group A3 had significantly higher levels of β-CrossLaps (p = 0.01) and β-CrossLaps/osteocalcin ratio (p = 0.02) when compared to the patients in group A1. The urine of the patients from group A3 had significantly higher levels of sodium (p = 0.03), calcium (p = 0.004), chloride (p = 0.01), citrate (p = 0.03), 24-hour calcium excretion (p = 0.004), 24-hour citrate excretion (p = 0.05), 24-hour calcium/creatinine (p = 0.03), fasting calcium/creatinine (p = 0.001), calcium/oxalate (p = 0.008) and calcium/citrate (0.0001) when compared to the patients from group A1 (Table II). The blood of the patients from group A3 had elevated levels of alkaline phosphatase (p = 0.02), β-CrossLaps (p = 0.002) and β-CrossLaps/osteocalcin ratio (p = 0.009) when compared to the patients from group A2. The urine of the patients from group A3 had significantly higher levels of fasting calcium/creatinine (p = 0.001) and 24-hour calcium excretion (p = 0.04) than that found in the patients from group A2 (Table II).

A comparison of the various patients in group A showed that differences were only seen in hypercalciuria among the three groups, with 40% of patients from group A1, 54.5% of patients from group A2 and 79.3% of patients from group A3 having urinary calcium excretion levels > 200 mg/day. Differences in hypercalciuria were found between patients from group A3 and the other two groups (p = 0.02) with the standardised residues being more elevated among the patients in group A3.

The mean ages of the patients in groups B1, B2 and B3 were 49.4 ± 6.5 years, 47.1 ± 8.3 years and 46.1 ± 11.5 years, respectively. There was no statistically significant difference

Table III. Comparison of variables among patients with osteopenia/osteoporosis of the lumbar spine (group B).

Variable	Mean ± SD			Comparative p-value		
	Group B1	Group B2	Group B3	B1–B2	B1–B3	B2–B3
Serum analysis						
Calcium (mg/dL)	9.2 ± 0.4	9.3 ± 0.4	9.3 ± 0.5	0.37	0.52	0.86
Phosphorus (mg/L)	3.3 ± 0.5	3.1 ± 0.5	3.1 ± 0.6	0.34	0.11	0.42
Alkaline phosphatase (U/L)	67.7 ± 13.9	65.3 ± 22.5	76.6 ± 37.5	0.34	0.57	0.13
iPTH (pg/mL)	49.9 ± 17.7	49.9 ± 15.5	55.5 ± 27.6	0.71	0.88	0.64
Osteocalcin (ng/mL)	15.1 ± 7.8	14.5 ± 5.2	17.5 ± 5.6	0.46	0.07	0.01
β-CrossLaps (ng/mL)	0.377 ± 0.261	0.407 ± 0.186	0.537 ± 0.216	0.29	0.008	0.007
β-CrossLaps/osteocalcin	0.025 ± 0.011	0.029 ± 0.011	0.031 ± 0.012	0.16	0.04	0.57
Vitamin 1,25-dihydroxyvitamin D_3 (ng/mL)	24.3 ± 6.8	22.7 ± 7.5	23.5 ± 9.1	0.45	0.42	0.76
Chloride/phosphorus	31.8 ± 5.2	33.7 ± 6.6	36.6 ± 10.2	0.44	0.08	0.29
Urine analysis						
Diuresis (mL)	1,782 ± 777	1,638 ± 677	1,855 ± 740	0.71	0.77	0.21
Creatinine clearance (mL/minute)	116.2 ± 53.8	117.1 ± 40.6	155.8 ± 65.5	0.83	0.20	0.14
Sodium (mEq/L)	99.1 ± 56.2	120.3 ± 45.5	122.8 ± 44.1	0.11	0.12	0.74
Calcium (mg/dL)	11.1 ± 6.9	14.7 ± 6.1	19.5 ± 9.6	0.05	0.002	0.06
Phosphorus (mg/dL)	55.3 ± 30.3	55.8 ± 29.8	54.4 ± 23.4	0.88	0.85	0.82
Uric acid (mg/dL)	40.6 ± 33.1	36.7 ± 14.5	38.4 ± 15.6	0.56	0.41	0.59
Chloride (mg/dL)	94.6 ± 65.3	115.5 ± 50.9	121.3 ± 43.9	0.08	0.03	0.40
Oxalate (mg/dL)	1.75 ± 0.68	1.98 ± 1.01	1.64 ± 0.79	0.82	0.30	0.15
Citrate (mg/dL)	54.44 ± 35.44	41.81 ± 21.64	29.69 ± 25.31	0.54	0.008	0.02
Fasting calcium/creatinine	0.09 ± 0.04	0.11 ± 0.03	0.16 ± 0.05	0.02	0.0001	0.0001
24-hour calcium/creatinine	0.12 ± 0.05	0.16 ± 0.08	0.22 ± 0.08	0.11	0.0001	0.009
Tubular resorption of phosphate (%)	82.1 ± 5.8	83.2 ± 3.9	81.2 ± 7.4	0.98	0.54	0.45
Calcium/oxalate	6.5 ± 3.3	7.7 ± 4.3	12.2 ± 6.5	0.24	0.006	0.07
Oxalate/creatinine	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.86	0.43	0.42
Oxalate/citrate	0.03 ± 0.01	0.04 ± 0.03	0.06 ± 0.02	0.60	0.01	0.04
Calcium/citrate	0.20 ± 0.10	0.35 ± 0.19	0.65 ± 0.37	0.02	0.0001	0.001
24-hour calciuria	176.3 ± 105.4	230.3 ± 119.9	327.1 ± 139.6	0.12	0.0001	0.002
24-hour phosphaturia	824.7 ± 287.8	829.9 ± 382.6	912.8 ± 309.1	0.79	0.40	0.18
24-hour uricosuria	645.7 ± 569.7	552.4 ± 213.5	631.7 ± 184.2	0.53	0.10	0.07
24-hour oxaluria	27.5 ± 13.6	31.7 ± 18.5	30.4 ± 20.7	0.43	0.77	0.79
24-hour citraturia	892.8 ± 786.3	657.4 ± 457.6	503.8 ± 398.2	0.26	0.03	0.10

iPTH: parathyroid hormone; SD: standard deviation

in the ages of the patients in these three groups nor was there a significant difference in the percentage of patients with osteopenia and osteoporosis among these groups. A comparison of the variables evaluated among the three patient groups revealed that there was no difference in blood parameters between patients in groups B1 and B2. However, the urine levels of calciuria (p = 0.05), fasting calcium/creatinine (p = 0.02) and calcium/citrate (p = 0.02) were significantly higher in the patients from group B2 as compared to the patients from group B1 (Table III).

Comparison of the variables between groups B1 and B3 showed that the blood of the patients in group B3 had a significantly higher level of β-CrossLaps (p = 0.008) and a significantly higher β-CrossLaps/osteocalcin ratio (p = 0.004). The urine of the patients from group B3 had significantly higher levels of calciuria (p = 0.002), chloride (p = 0.03), citraturia (p = 0.008), 24-hour calcium excretion (p = 0.0001), 24-hour calcium/creatinine (p = 0.0001), 24-hour citraturia (p = 0.03), fasting calcium/creatinine (p = 0.0001), calcium/oxalate (p = 0.006), calcium/citrate (p = 0.0001) and oxalate/citrate (p = 0.01) as compared to patients from group B1 (Table III).

On comparing the variables between groups B2 and B3, we found that the blood of the patients from group B3 had higher levels of osteocalcin (p = 0.01) and β-CrossLaps (p = 0.007) as compared to that in the patients from group B2. The urine of the patients from group B3 had significantly higher levels of citraturia (p = 0.02), fasting calcium/creatinine (p = 0.0001), 24-hour calcium/creatinine (p = 0.009), oxalate/citrate (p = 0.04), calcium/citrate (p = 0.001) and 24-hour calcium excretion (p = 0.002) than that found in the patients from group B2 (Table III).

As with the patients in group A, patients in group B were also assessed for the prevalence of hypercalciuria, hyperuricosuria, hyperoxaluria and hypocitraturia. Similar to our findings for patients in group A, we found that the only difference among the three groups of patients in group B was in hypercalciuria. 40% of patients from group B1, 62.1% of patients from group B2 and 88.1% of patients from group B3 had urinary calcium excretion > 200 mg/day. The percentage of hypercalciuria in patients from group B3 was much higher than that found in the other two groups, as was seen from the standardised residues following statistical analysis.

DISCUSSION

Metabolic evaluations of patients with recurrent lithiasis and significant lithogenic activity have been performed in the past few years, reflecting efforts to address the need to decrease the number of episodes of lithiasis formation. Such initiatives not only serve to reduce related healthcare costs but are also in line with the needs and desires of patients. Blood and urinary metabolic

studies are generally indicated for patients with calcium lithiasis who have medical histories of lithiasis formation, patients with calcium lithiasis and multiple lithiasis, patients with calcium lithiasis that is difficult to treat, children with calcium calculi, and patients in whom calcium calculi formation is associated with bone diseases.[15]

In various studies conducted on patients in whom lithiasis forms habitually, it has been observed that there is some type of metabolic alteration in nearly 90%–95% of such patients that could be diagnosed through metabolic-mineral studies.[16,17] The most frequently observed metabolic alteration is hypercalciuria which, according to various series, can range from 31.2%–74%.[17-19] The second most common metabolic alteration in patients with this type of lithiasis is hypocitraturia.[8,16,20] Various authors have observed an important relationship between hypercalciuria and the loss of BMD, with an elevated percentage of patients with hypercalciuria presenting with osteopenia and elevated urinary calcium excretion.[21,22] Jaeger et al have also demonstrated the presence of BMD loss in patients with lithiasis without hypercalciuria.[23] These findings emphasise the importance of completing adequate metabolic-mineral studies for patients with calcium lithiasis, and performing bone metabolism and BMD studies, as elevations in bone resorption markers in patients with recurrent calcium lithiasis have been highlighted and reported by Arrabal-Polo et al.[7]

In view of the above, we chose to conduct a metabolic-mineral study on patients with calcium lithiasis and severe lithogenic activity who also presented with abnormal hip and lumbar spine BMDs (osteopenia or osteoporosis). We found a higher percentage of patients with hypercalciuria (> 200 mg/day) in the groups of patients who had calcium lithiasis and severe lithogenic activity (group A3, 79.3%; group B3, 88.1%) when compared to patients from the control group, and patients with calcium lithiasis and mild lithogenic activity. The differences in percentage values between groups A3 and B3 and the other groups (groups A1 and A2, and groups B1 and B2, respectively) were statistically significant, indicating that hypercalciuria is common and frequent in these types of patients. However, we did not find any difference with respect to percentage values between the various patient groups in relation to hyperoxaluria (excretion > 40 mg/day), hyperuricosuria (excretion > 600 mg/day) or hypocitraturia (excretion < 320 mg/day).

We observed that patients with calcium lithiasis and severe lithogenic activity with loss of BMD at the hip (group A3) presented with a higher urinary excretion of calcium (higher 24-hour calciuria and elevated calcium/creatinine and calcium/citrate ratios) but lower urinary excretion of citrate than the patient groups without lithiasis. In addition, patients in group A3 presented with higher levels of the bone resorption marker (β-CrossLaps) and higher β-CrossLaps/osteocalcin ratios, indicating a negative bone turnover in these patients or that bone resorption was greater than bone formation for these patients when compared to the control group. Similar to other studies,[7] when compared to the group of patients with calcium lithiasis and mild lithogenic activity, patients in our study with severe lithogenic activity and BMDs < –1 SD on the T-score scale presented with higher amounts of urinary excretion of calcium (hypercalciuria) and bone resorption activity, which was reflected in their fasting calcium/creatinine ratios and 24-hour calciuria levels as well as the elevated levels of bone resorption markers seen in these patients.

In the same way, patients with calcium lithiasis and severe lithogenic activity with loss of BMD at the lumbar spine (group B3) presented with higher levels of bone resorption markers than the control group and the groups with mild lithogenic activity. Patients in group B3 also had a higher level of urinary excretion of calcium than the other patient groups. Notably, in patients from group B3, hypocitraturia levels and calcium/citrate ratio were higher than that in patients from group B1, both of which were statistically significant. This finding of ours was in agreement with other studies which reported that calcium/citrate ratios tended to be elevated in patients with lithiasis and hypercalciuria[24] and that hypocitraturia manifested more often in patients with recurring lithiasis than in patients experiencing an isolated episode.[25] According to Pak et al[26] and Caudarella et al,[27] treatment with potassium citrate not only decreases the recurrence of lithiasis but also improves the BMD in such patients.

This present study has some limitations. First, only one metabolic investigation was carried out, as the authors found this to be acceptable. Although two metabolic studies may have provided more metabolic alterations, in our experience, we have not found any substantial advantage associated with conducting two metabolic evaluations instead of one. Second, the number of patients included in our study was small, although the results obtained on applying nonparametric tests on the selected group provided fairly accurate conclusions. Nonetheless, the results might have been more conclusive if a larger number of patients was included for parametric tests in each group.

In conclusion, we found that patients with recurrent calcium lithiasis and severe lithogenic activity with loss of BMD (osteopenia/osteoporosis) presented with higher levels of calcium urine excretion, greater elevations of bone resorption markers and lower levels of citrate excretion than patients without lithiasis. For this reason, exhaustive metabolic-mineral and bone studies were conducted in these patients with the goal of establishing appropriate medical treatment. We propose that metabolic studies, including calciuria, fasting calcium/creatinine, 24-hour calcium/ creatinine, citraturia, calcium/citrate and bone remodelling markers (β-CrossLaps, osteocalcin and β-CrossLaps/osteocalcin) as variables, be performed in patients with calcium renal stones and BMD loss.

REFERENCES

1. Arrabal Martín M, Fernández Rodríguez A, Arrabal Polo MA, Ruíz García MJ, Zuluaga Gómez A. [Study of the physical-chemical factors in patients with renal lithiasis]. Arch Esp Urol 2006; 59:583-94. Spanish.

2. Lancina Martín JA, Rodríguez-Rivera García J, Novás Castro S, et al. [Metabolic risk factors in calcium urolithiasis according to gender and age of patients]. Actas Urol Esp 2002; 26:111-20. Spanish.
3. Yagisawa T, Hayashi T, Yoshida A, et al. Comparison of metabolic risk factors in patients with recurrent urolithiasis stratified according to age and gender. Eur Urol 2000; 38:297-301.
4. Giannini S, Nobile M, Sartori L, et al. Bone density and skeletal metabolism are altered in idiopathic hypercalciuria. Clin Nephrol 1998; 50:94-100.
5. Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int 2011; 79:393-403.
6. Sutton RA. Stones and bones: bone resorption and metabolism in stone formers. Curr Opin Urol 1998; 8:309-13.
7. Arrabal-Polo MA, Arrabal-Martin M, de Haro-Munoz T, et al. Mineral density and bone remodelling markers in patients with calcium lithiasis. BJU Int 2011; 108:1903-8.
8. Pak CYC, Poindexter JR, Adams-Huet B, Pearle MS. Predictive value of kidney stone composition in the detection of metabolic abnormalities. Am J Med 2003; 115:26-32.
9. Krepinsky J, Ingram AJ, Churchill DN. Metabolic investigation of recurrent nephrolithiasis: compliance with recommendations. Urology 2000; 56:915-20.
10. Park S, Pearle MS. Pathophysiology and management of calcium stones. Urol Clin North Am 2007; 34:323-34.
11. Thorleifsson G, Holm H, Edvardsson V, et al. Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. Nat Genet 2009; 41:926-30.
12. Milliner DS. Stones, bones and heredity. Acta Paediatr Suppl 2006; 95:27-30.
13. Arrabal-Polo MA, Arrabal-Martin M, de Haro-Muñoz T, et al. Biochemical determinants of severe lithogenic activity in patients with idiopatic calcium nephrolithiasis. Urology 2012; 79:48-54.
14. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series 843, Genevea, Switzerland, 1994.
15. Chandhoke PS. Evaluation of the recurrent stone former. Urol Clin North Am 2007; 34:315-22.
16. Spivacow FR, Negri AL, del Valle EE, Calviño I, Zanchetta JR. Clinical and metabolic risk factor evaluation in young adults with kidney stones. Int Urol Nephrol 2010; 42:471-5.
17. Amaro CR, Goldberg J, Amaro JL, Padovani CR. Metabolic assessment in patients with urinary lithiasis. Int Braz J Urol 2005; 31:29-33.
18. del Valle E, Spivacow R, Zanchetta JR. [Metabolic changes in 2612 patients with nephrolithiasis]. Medicina (B Aires) 1999; 59:417-22. Spanish.
19. Spivacow FR, Negri AL, del Valle EE, et al. Metabolic risk factors in children with kidney stone disease. Pediatr Nephrol 2008; 23:1129-33.
20. Peres LA, Molina AS, Galles MH. Metabolic investigation of patients with urolithiasis in a specific region. Int Braz J Urol 2003; 29:217-20.
21. Audran M, Bataille P, Sebert JL, et al. [Bone density in idiopathic hypercalciuria in men. Study by dual photon absorptiometry, X-ray computed tomography and histomorphometry]. Rev Rhum Mal Osteoartic 1991; 58:747-50.
22. Zanchetta JR, Rodriguez G, Negri AL, del Valle E, Spivacow FR. Bone mineral density in patients with hypercalciuric nephrolithiasis. Nephron 1996; 73:557-60.
23. Jaeger P, Lippuner K, Casez JP, et al. Low bone mass in idiopathic renal stone formers: magnitude and significance. J Bone Miner Res 1994; 9:1525-32.
24. Srivastava T, Winston MJ, Auron A, Alon US. Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res 2009; 66:85-90.
25. DeFoor WR, Jackson E, Minevich E, et al. The risk of recurrent urolithiasis in children is dependent on urinary calcium and citrate. Urology 2010; 76:242-5.
26. Pak CY, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. J Urol 2002; 168:31-4.
27. Caudarella R, Vescini F, Buffa A, Stefoni S. Citrate and mineral metabolism: kidney stones and bone disease. Front Biosci 2003; 8:s1084-106.