Retrospective Review of Serum and Urinary Lithogenic Risk Factors in Patients With Osteoporosis and Osteopenia

Miguel Angel Arrabal-Polo, María Sierra Girón-Prieto, María del Carmen Cano-García, Antonio Poyatos-Andujar, Miguel Quesada-Charneco, Felix Abad-Menor, Salvador Arias-Santiago, Armando Zuluaga-Gomez, and Miguel Arrabal-Martin

OBJECTIVE To analyze differences in bone remodeling markers, lithogenic factors and bone densitometry among the 3 groups of patients (controls, patients with relapsing calcium renal lithiasis, and patients with loss of bone mineral density without lithiasis).

MATERIAL AND METHODS This is a cross-sectional study including 203 patients who were divided in 3 groups: group 1 (controls), group 2 (patients with relapsing calcium renal lithiasis), and group 3 (patients with osteopenia and/or osteoporosis in the lumbar spine or hip). Bone densitometry, calcium-phosphorous and bone metabolism analysis, and analysis of lithogenic risk factors in fasting urine samples and 24-hour urine samples were performed. Statistical analysis was performed with SPSS 17.0. A $P \leq .05$ was considered statistically significant.

RESULTS Patients in group 2 presented greater calcium excretion and a lower citrate excretion in 24-hour urine samples as compared with the other 2 groups. The proportion of hypercalciuria and hypocitraturia was higher in group 2. In addition, patients in group 2 presented a lower loss of bone mineral density as well as altered bone remodeling markers as compared with those in group 1. Patients in group 3 also presented alterations in urine calcium and citrate excretion with respect to the control group, with elevated fasting calcium and citrate levels and calcium-to-citrateratio.

CONCLUSION Lithogenic risk factors are altered in patients with osteopenia and/or osteoporosis without renal lithiasis although to a lesser extent than patients with calcium renal lithiasis. UROLOGY 85: 782–785, 2015. © 2015 Elsevier Inc.

A high proportion of patients with hypercalciuria and relapsing calcium renal lithiasis lose bone mineral density.[1] The loss of bone mineral density in patients with calcium renal lithiasis is associated with different factors such as elevated cytokine levels, especially IL-1, TNF-alpha,[1,2] which stimulates bone resorption direct or indirectly by the production of prostaglandins.[3] In addition, inflammatory and immunologic processes, as well as genetic factors,[4] may be underlying factors in the association between calcium renal lithiasis and osteoporosis. In fact, these patients may have several common genetic alterations. The hormones controlling calcium-phosphorous metabolism, such as vitamin D and parathyroid hormone, do not seem to play an essential role in patients with calcium renal lithiasis, hypercalciuria, and idiopathic osteopenia.[5] However, some authors have detected an increase in vitamin D receptors' sensitivity influencing bone resorption.[6,7] Another factor to be considered is the effect of diet on lithogenesis and on the loss of bone mineral density. A diet rich in sodium and animal proteins and low in calcium favors the development of calcium lithiasis and the loss of bone mineral density caused by an altered calcium-phosphorous metabolism and the appearance of metabolic acidosis.[3,8]

A range of studies have demonstrated that relapsing calcium renal lithiasis is associated with bone demineralization,[9-11] and calcium renal lithiasis is a risk factor for osteoporotic bone fracture.[12]

The objective of this study was to examine and analyze differences in bone remodeling markers, lithogenic

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From the Servicio de Urología, Hospital La Inmaculada, Huercal-Overa, Spain; the Centro de Salud de Atarfe, Spain; the Programa de Doctorado de Medicina Clínica y Salud Pública, Universidad de Granada, Spain; the Servicio de Analisis Clinicos, Hospital Universitario San Cecilio, Granada, Spain; the Servicio de Endocrinología, Hospital Universitario San Cecilio, Granada, Spain; the Servicio de Urología, Hospital Universitario San Cecilio, IBS Granada, Granada, Spain; and the Departamento de Medicina, Universidad de Granada, Spain

Address correspondence to: Miguel Angel Arrabal-Polo, Servicio de Urología, Hospital La Inmaculada, Virgili Street, 9 bajo C, Huercal-Overa, Almeria 04600, Spain. E-mail: arrabalp@ono.com

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factors, and bone densitometry among the 3 groups of patients (controls, patients with relapsing calcium renal lithiasis, and patients with loss of bone mineral density without lithiasis).

MATERIALS AND METHODS

Study Groups

A cross-sectional study was performed from January 2013 to December 2013, including 203 patients from Eastern Andalusia, Spain, who were divided in 3 groups:

- Group 1: 61 patients aged 18-70 years without renal lithiasis
- Group 2: a total of 75 patients with a diagnosis of relapsing kidney lithiasis (relapsing lithiasis defined as $\geq$2 unrelated episodes of lithiasis) aged 18-70 years
- Group 3: a total of 67 patients with loss of bone mineral density aged 18-70 years.

Inclusion Criteria. Men and women aged 18-70 years without lithiasis, relapsing calcium lithiasis or osteopenia or osteoporosis.

Exclusion Criteria. Patients aged >70 or <18 years, congenital bone disease, congenital kidney disease, hyperparathyroidism, inflammatory bowel disease, renal tubular acidosis, biphosphonate treatment, hormone replacement therapy, thiazide therapy, potassium citrate therapy, corticosteroid therapy, or calcium and vitamin D therapy.

Methods

All patients were submitted to medical history, physical examination, and measurement of weight, height, body mass index, and blood pressure. Bone mineral density was assessed by simple abdominal x-ray and/or intravenous urogram and ultrasonography for patient classification purposes.

Subsequently, serum and urinary biochemical analyses were performed along with bone densitometry of the hip and lumbar spine.

Blood Tests. Creatinine, urea, uric acid, sodium, potassium, chlorine, calcium, phosphorus, intact parathyroid hormone (PTHi), alkaline phosphatase, osteocalcin (determined by schimioiluminescence using the automatic analyzer LIAISON-Osteocalcin [DiaSorin]) and β-crosslaps (determined by the schimioiluminescence immunoassay "ECLIA" using the automatic analyzer Elecsys MODULAR ANALYTICS E170 [Roche Diagnostics]).

Fasting Urine Tests. Density, pH, calcium, creatinine, oxalate, citrate, uric acid, and calcium/creatinine.

Twenty-four-hour Urine Tests. Volume, creatinine, urea, uric acid, sodium, potassium, chlorine, calcium, phosphorus, citrate, oxalate, calcium/creatinine, and calcium/citrate.

Bone Densitometry. Bone densitometry was performed by dual-energy x-ray absorptiometry using Hologic QDR 4500 equipment.

Statistical Analysis

The analysis of variance test (between the 3 groups) and the Student *t* test were performed for analysis of qualitative-quantitative variable, whereas the chi-square test and binary logistic regression were performed for qualitative variable analysis. Results were obtained by odds ratio, with a 95% confidence interval. The Pearson correlation or, if necessary, the Spearman rho coefficient was calculated to examine the lineal relationship between quantitative variables. The Kolmogorov-Smirnov test was performed to attest the normality of the variables, and variance analysis was performed by the Levene test. A $P \leq .05$ was considered statistically significant. Statistical analysis was carried out using SPSS 17.0 for Windows.

Ethical Considerations

Informed consent was obtained from all patients. This study was approved by the Ethics Committee of the San Cecilio University Hospital and was performed with the financial support of the Fundación Progreso y Salud (Andalusian Regional Government, Spain).

RESULTS

The mean age was 51.81 $\pm$ 10.32 years in group 1, 43.08 $\pm$ 11.59 years in group 2, and 51.88 $\pm$ 11.27 years in group 3 ($P = .0001$). Men and women were similarly distributed (31 men and 30 women in group 1, 39 men and 36 women in group 2, and 35 men and 32 women in group 3).

Densitometry (Table 1) revealed a greater loss of bone mineral density both in the hip and in the lumbar spine in group 3 as compared with groups 1 and 2. Similarly, group 2 presented greater bone demineralization than group 1. As to the variables related with calcium-phosphorous metabolism measured in blood, we observed statistically significant differences among the 3 groups concerning serum calcium and phosphorous. Although PTHi levels were higher in group 3 than in the other groups, vitamin D levels were similar in the 3 groups. Regarding bone remodeling markers, groups 2 and 3 presented higher osteocalcin levels as compared with group 1. Levels of β-crosslaps were more elevated in group 3 as compared with groups 1 and 2 and in group 2 as compared with group 1. Alkaline phosphatase and the β-crosslaps-to-osteocalcin ratio were higher in group 3 as compared with the other groups (Table 1).

Biochemical analysis of 24-hour urine samples revealed higher urine calcium excretion in group 2 as compared with the other groups (Table 2). Citric acid levels in 24-hour urine samples were lower in groups 2 and 3 as compared with group 1, whereas calcium-to-creatinine and calcium-to-citrate ratios were higher in groups 2 and 3 than in group 1. Biochemical analysis of fasting urine samples revealed higher urine calcium excretion and calcium-to-creatinine ratio in groups 2 and 3 as compared with group 1, whereas differences were observed among the 3 groups regarding urine citrate excretion (Table 2).

As to biochemical alterations in urine, according to Table 3, a higher proportion of patients in group 2 presented hypercalciuria and hypocitraturia.

Multivariate binary logistic regression analysis revealed that after adjustment for age, osteocalcin, β-crosslaps, 24-hour calciuria, and fasting calcium/creatinine, elevated fasting calcium/creatinine levels were independently correlated with calcium lithiasis in patients with lithiasis as compared with patients without calcium