Lithogenic Activity as a Factor to Consider in the Metabolic Evaluation of Patients With Calcium Lithiasis

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Metabolic evaluation is important in high-risk patients with a history of urinary calculi, in order to prevent recurrence. This study aimed to compare patients with calcium calculi and mild lithogenic activity with those with moderate to severe lithogenic activity. Patients with moderate to severe activity had higher levels of urinary calcium level (271.9 mg/24h versus 172.1 mg/24 h, $P < .001$), uric acid (612.3 mg/24 h versus 528.9 mg/24h, $P = .008$), and fasting calcium-creatinine ratio (0.16 versus 0.12, $P = .001$) compared to those with mild lithogenic activity. No association was observed between lithogenic factors in 24-hour urine and mild lithogenic activity in multivariable analysis. We initially thought that in patients who develop recurrent calculi after 5 years or who have mild lithogenic activity, complete metabolic evaluation would not be necessary. However, based on our study findings, it may be important to conduct further studies assessing the lithogenic activity.

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Brief Communication

In a recent article on metabolic assessment and prevention of relapse for patients with urolithiasis, 24-hour urine study was recommended for patients who are at a high risk for stone formation, whereas for low-risk patients, it is sufficient to perform general preventive measures.[1] Although we agree with this recommendation, there is a large group of patients with calcium calculi that may require different assessments. Some authors recommend performing a comprehensive metabolic evaluation in all patients with calculi regardless of whether it is an initial or recurrent episode.[2,3] Others like Chandhoke and colleagues[4] propose that metabolic evaluation may be of greater benefit for patients with calcium calculi with a previous history of calculus, multiple calculi, or calcium calculi that are difficult to treat, or patients with 1 kidney, calcium calculi, and gastrointestinal disease, nephrocalcinosis or known bone diseases.

Ultimately, the decision whether to perform a metabolic evaluation in a patient with calcium calculus disease is based on whether or not it is the first episode and the existence of risk factors (metabolic or kidney diseases, infants or adolescents, hyperparathyroidism, renal tubular acidosis, solitary kidney, digestive diseases, and other rare genetic pathologies).[1,5] However, there is little mention in the clinical guidelines on the lithogenic activity of patients and whether or not lithogenic activity needs to be determined.

In the protocol for integrated management of urolithiasis in Andalusia,[6] lithogenic activity is classified as mild (urinary calculus ≤ 2 cm; a healthy contralateral kidney, diagnosed with ultrasonography or urography; without recurrence or mild recurrence, defined as 2 episodes separate 5 years at least), moderate (mild activity with moderate recurrence, defined as 2 episodes in 2 to 5 years), and severe (urinary calculus > 2 cm; more than 2 calculi or severe recurrence, defined 2

episodes in 1 year or 3 episodes in 3 years). The aim of this study was to divide patients with calcium calculi into 2 groups according lithogenic activity (mild lithogenic activity versus moderate-severe lithogenic activity) and analyze the main metabolic risk factors to determine whether conducting 24-hour urine study in patients with mild lithogenic activity is warranted.

In a multicenter observational study, 163 patients were enrolled from Hospital Granada and Hospital La Inmaculada between January 2013 and December 2014. They were categorized into 2 groups of 78 patients with calcium calculi and mild lithogenic activity (group 1) and 85 patients with calcium calculi and moderate-severe lithogenic activity (group 2). Inclusion criteria were an age greater than 18 years, a diagnosis of calcium lithiasis (analyzed by infrared spectrometry), and metabolic assessment of blood, 24-hour urine, and fasting urine. Patients with bone disease, nephrocalcinosis, renal tubular acidosis, gastrointestinal disease, primary hyperparathyroidism, unique kidney disease, and anatomic abnormalities were excluded, as well as those receiving lithogenic drugs. Blood samples were taken to measure creatinine, sodium, potassium, chloride, uric acid, calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D levels. Fasting urine was used to assess pH and calcium-creatinine ratio, and 24-hour urine collection to assess creatinine clearance and calcium, uric acid, citrate, and oxalate levels.

Statistical analysis was performed with the SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, Ill, USA). Quantitative variables were compared using the Student *t* test and qualitative variables, using the chi-square test. Multivariable binary logistic regression analysis was used to calculate the odds ratios and 95% confidence intervals. The study protocol was approved by the Ethics Committee of the hospitals where the study took place. Patients were informed about the study and gave their consent to participate.

The mean age of the participants was 50.3 ± 13.6 years in group 1 and 50.9 ± 12.8 years in group 2 with no significant difference. Men constituted

Table 1. Demographic Characteristics and Metabolic Evaluation Results in Patients With Mild Lithogenic Activity (Group 1) and Moderate-Severe Lithogenic Activity (Group 2)

Parameter	Group 1 (n = 78)	Group 2 (n = 85)	*P*
Demographic data			
Age, y	50.3 ± 13.6	50.9 ± 12.8	.80
Sex			
Male	45 (57.7)	47 (55.3)	
Female	34 (43.3)	38 (44.7)	.70
Serum parameters			
Glucose, mg/dL	98.8 ± 22.1	92.6 ± 15.7	.08
Creatinine, mg/dL	0.98 ± 0.30	0.86 ± 0.20	.003
Sodium, mmol/L	141.8 ± 2.2	141.4 ± 2.6	.20
Potasium, mmol/L	4.6 ± 0.4	4.4 ± 0.4	.06
Chloride, mmol/L	101.8 ± 2.9	104.1 ± 2.7	< .001
Uric acid, mg/dL	5.6 ± 1.1	4.8 ± 1.3	< .001
Calcium, mg/dL	9.6 ± 0.5	9.5 ± 0.4	.30
Phosphorus, mg/dL	3.1 ± 0.5	2.9 ± 0.4	.06
iPTH, pg/mL	48.5 ± 31.8	47.6 ± 19.7	.80
25-OH Vitamin D, ng/mL	26.9 ± 11.6	27.6 ± 8.8	.70
24 h urine parameters			
Creatinine clearance, mL/min	102.6 ± 29.4	118.7 ± 46.7	.01
Calciuria, mg/24 h	172.1 ± 102.9	271.9 ± 117.3	< .001
Uricosuria, mg/24 h	528.9 ± 156.2	612.3 ± 228.1	.008
Citraturia, mg/24 h	521.6 ± 222.4	550.5 ± 309.4	.50
Oxaluria, mg/24 h	24.7 ± 11.5	30.6 ± 23.7	.07
Fasting urine parameters			
pH	6.1 ± 0.8	5.8 ± 0.6	.005
Calcium-creatinine ratio	0.12 ± 0.08	0.16 ± 0.07	.001

Table 2. Principal Lithogenic Factors in Patients With Mild Lithogenic Activity (Group 1) and Moderate-Severe Lithogenic Activity (Group 2)

Metabolic Abnormality	Group 1 (n = 78)	Group 2 (n = 85)	*P*
Hypercalciuria (> 260 mg/24 h)	12 (15.4)	44 (51.8)	< .001
Hyperoxaluria (> 40 mg/24 h)	24 (30.8)	21 (24.7)	.38
Hyperuricosuria (> 750 mg/24 h)	12 (15.4)	21 (24.7)	.14
Hypocitraturia (< 320 mg/24 h)	12 (15.4)	23 (27.1)	.07
Fasting calcium-creatinine ratio			
< 0.11 absorptive hypercalciuria	42 (53.8)	17 (20.0)	
> 0.11 fasting hypercalciuria	36 (46.2)	68 (80.0)	< .001

57.7% of the patients in group 1 men and 55.3% in group 2, with no significant difference. Significant differences between the two groups were observed in the serum levels of creatinine, chloride, and uric acid; 24-hour urine creatinine clearance, calciuria, and uricosuria; and fasting urine pH and calcium-creatinine ratio (Table 1). Hypercalciuria was significantly more frequent in group 2 than in group 1, while with no differences were found in the percentage of patients with hyperoxaluria, hypocitraturia, and hyperuricosuria (Table 2). Logistic regression model for metabolic risk factors of stone formation in 24-hour urine (calciuria, oxaluria, citraturia, and uricosuria) demonstrated no relationship with mild lithogenic activity.

The current urolithiasis guidelines of the European Association of Urology recommend metabolic evaluation of patients with high-risk of developing calculi based on the presence of risk factors,[7] but this does not include evaluation for lithogenic activity. The metabolic evaluation includes analysis of the calculus, blood, and 24-hour urine collection to assess major metabolic risks.[7,8] In this study, we have shown that patients with mild lithogenic activity have less metabolic alterations as compared to patients with moderate to severe activity, and the results of the study of 24-hour urine showed no relationship with mild activity. Based on the current guidelines, this evaluation would not be performed in this group of patients with mild activity despite presenting recurrent lithiasis, albeit after 5 years. Lithogenic activity should be considered in designing future long-term studies comparing the outcomes of patients according to their lithogenic activity and for inclusion in clinical practice guidelines.

This study lacked a follow-up of the patients for determinations of metabolic evaluation, and also we reduced the results into the two groups (mild activity versus moderate-severe activity). It would be preferable to confirm the results obtained with a cohort study.

CONFLICT OF INTEREST

None declared.

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