

Prevalence and Risk Factors for Urolithiasis in Primary Gout: Is a Reappraisal Needed?

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ABSTRACT. *Objective.* To assess the prevalence and risk factors for urolithiasis in primary gout.

Methods. One hundred forty patients with primary gout were studied. Urolithiasis was defined as a history of urolithiasis, or nephrolithiasis detected via ultrasonography in patients with no previous record of urolithiasis. Patient age, duration of gout, presence of tophi, obesity, alcoholism, high blood pressure, diabetes, hyperlipidemia, family history of urolithiasis, daily urine output, uricemia, urine pH, FeNa, FeUrate, urine pH/FeUrate index, and daily urine excretion of urate, sodium, calcium and potassium were compared between lithiasic and non-lithiasic subjects.

Results. Fifty-five (39%; 95% CI 31–47) patients had urolithiasis, of which 37 (26%) were diagnosed by clinical history and 18 (13%) by ultrasonography. Patients with a silent kidney stone diagnosed by ultrasound tended to have shorter evolution of gout. Aside from urinary H⁺ ion concentration (lithiasic subjects $5.17 \pm 3.9 \mu\text{M/l}$; non-lithiasic subjects $3.80 \pm 3.01 \mu\text{M/l}$; $p = 0.02$), no difference was found between lithiasic and non-lithiasic subjects for the other variables studied.

Conclusion. Ultrasonography increased the probability of diagnosing urolithiasis by 50%, meaning the prevalence of urolithiasis in gout is likely higher than previously reported. A higher urinary H⁺ ion concentration was the only variable associated with urolithiasis. Due to advances in diagnosis of gout and urolithiasis, as well as biochemical assays, the prevalence and risk factors for urolithiasis in gout require reassessment. (J Rheumatol 2005;32:2189–91)

Key Indexing Terms:

GOUT

UROLITHIASIS

KIDNEY STONES

RISK FACTORS

NEPHROLITHIASIS

PREVALENCE

Gout is a systemic metabolic disease in which several forms of nephropathy can occur¹. The most frequent type of gout-related nephropathy^{2–5} is urolithiasis (10%–20%), and its prevalence is much higher than observed in the general population⁶.

Since Yu and Gutman's 1967 study⁷, the principal accepted risk factors for urolithiasis in gout have been serum uric acid levels, daily urine urate excretion, and urine pH. That study was done using the colorimetric method for uric acid measurement, before validated diagnostic criteria for gout existed, and urolithiasis was diagnosed only from clinical history. Despite all these potential sources of bias, Yu and Gutman's findings have not been reassessed. In response, a

study was done to reassess the influence of a set of clinical, biochemical, and sociodemographic variables on the risk of developing urolithiasis in a group of patients with primary gout, all diagnosed based on the criteria of Wallace, *et al*⁸ and using ultrasonography and clinical history for diagnosis of urolithiasis.

MATERIALS AND METHODS

Subjects. Between March 2000 and September 2001, patients were recruited from the Rheumatology Service of the Ignacio García Tellez Specialties Hospital of the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS), Mérida, México, and from the Gout Clinic at the Rheumatology Service of the Mexico General Hospital of the Secretariat of Health (Secretaría de Salud) in Mexico City. The inclusion criterion was a diagnosis of gouty arthritis based on the Wallace criteria⁸. Presence of primary gout was diagnosed after exclusion of any other pathology or pharmacology-associated cause of hyperuricemia¹. All subjects with a serum creatinine > 1.5 mg/dl or a creatinine clearance < 80 ml/min were eliminated from the analysis of biochemical variables, as were those who did not complete the requested questionnaires. A lithiasic subject was defined as one who acknowledged having had a urine stone delivery or previous surgery for urolithiasis; or in whom a kidney stone was identified by ultrasonography. This procedure was performed on all subjects who denied previous stone delivery or urolithiasis-related surgery.

Methods. A researcher blinded to presence of urolithiasis surveyed all relevant clinical and sociodemographic data for the subjects. Samples were analyzed in a quality-certified laboratory. Serum and urine concentrations of uric acid were measured by the uricase-peroxidase spectrophotometry method, calcium levels by the o-cresol complexone method; a Nova 1 CRT device was used for sodium and potassium measurement. All subjects were

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asked to stop use of all drugs modifying urine and serum uric acid levels 72 h before sampling.

Every subject gave signed informed consent before inclusion, and the protocol was approved by the Research and Ethics Committee of the Ignacio Garcia Téllez Specialties Hospital.

Statistical methods. A chi-square with Yates' correction or Fisher's test was used for comparisons of categorical variables. Numerical variables were compared by unpaired t test. Data were analyzed using SPSS for Windows (v. 7.5) statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred forty subjects [138 men (98%), aged 50.4 ± 11.9 years, disease evolution time 9.8 ± 9.3 years] were included in the study. Ninety-seven patients were from Merida and 43 from Mexico City. No significant difference in gout duration (Merida patients 9.1 ± 9.5 yrs, Mexico City patients 11.7 ± 7.4 yrs; p = 0.16) existed between the 2 patient sources.

Fifty-five subjects (39%; 95% CI 31–47) were diagnosed as urolithiasic. Lithiasis was clinically diagnosed in 37 (26%) of these patients, and 18 (13%) were diagnosed with lithiasis solely by ultrasonography. Ultrasonography increased the possibility of diagnosing urolithiasis by 50%. Subjects with lithiasis diagnosed by ultrasonography showed a trend toward shorter disease evolution compared to the clinically-diagnosed subjects (8.1 ± 5.3 vs 11.6 ± 8.9 yrs; p = 0.07). No difference in prevalence of lithiasis was found between the 2 patient sources [Mérida 40/94 subjects (42%); Mexico City 15/43 subjects (33%); p = 0.35], although the Mexico City patients (8/15, 53%) tended to have a higher prevalence of ultrasound-diagnosed lithiasis compared to Merida subjects [10/40 (25%); p = 0.04].

Apart from a higher urinary H+ ion concentration in the lithiasic group, no difference was identified between the lithiasic and the non-lithiasic gout patients for any of the other variables analyzed (Tables 1 and 2).

DISCUSSION

The prevalence and risk factors associated with urolithiasis in gout were originally studied by Yu and Gutman⁷. They reported a prevalence of urolithiasis of 24%, and a correlation between urate serum levels, daily urine urate excretion,

and lower urine pH and prevalence of urolithiasis. When published, their findings seemed authoritative and the study became a classic^{5,9-13}. For a number of reasons their findings now need reassessment. In their report, diagnosis of urolithiasis was only done clinically, leading to possible misclassification of subjects with a silent stone. As well, the Wallace criteria⁸ for gouty arthritis had not been published, and at that time uric acid measurement was done by a colorimetric method, now considered inaccurate.

The prevalence of urolithiasis in patients with primary gout in our study was 39%, much higher than in previous reports^{1-5,9-13}. Further, the results suggest that if renal ultrasonography is done for gout patients with no history of stones, the prevalence of urolithiasis may increase significantly.

Of all the results, only a higher urinary H+ ion concentration was associated with the presence of urolithiasis in primary gout. No difference was observed between lithiasic and non-lithiasic gout patients for any of the other variables that have been proposed previously as urolithiasis risk factors^{5,7,9-13}. In addition, the urate excretion anomalies identified by Pak, *et al*¹⁴ in the condition known as “gouty diathesis” were not identified in the urolithiasic gout patients we studied.

A reassessment of prevalence and risk factors for nephrolithiasis in gout is needed because diagnosis methods for gout and lithiasis have improved notably over the last 38 years and more accurate analytical assays have been developed.

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Table 1. Comparison of categorical variables between lithiasic and non-lithiasic gout patients.

Variable	Lithiasic	Non-lithiasic	p
Family history of urolithiasis	20/53	26/78	0.74
Obesity	40/53	50/79	1.0
Alcoholism			
None	6/54	7/80	
Moderate	29/54	35/80	
Severe	19/54	38/80	0.36
Tophi	17/54	27/79	0.89
High blood pressure	23/54	33/78	0.48
Diabetes	5/54	3/81	0.33
Hyperlipidemia	41/52	64/80	1.0

Table 2. Comparison of numerical variables between lithiasic and non-lithiasic gout patients.

Variable	Lithiasic	Non-lithiasic	p
Age, yrs	51 ± 11	50 ± 12	0.53
Body mass index	29 ± 4	30 ± 5	0.86
Gout evolution, yrs	10 ± 8	10 ± 10	0.82
Serum uric acid, mg/dl	7.8 ± 1.9	7.9 ± 1.9	0.95
Urine pH	5.4 ± 0.5	5.6 ± 0.5	0.11
Urinary H ⁺ ion concentration, μ M/l	5.17 ± 3.90	3.80 ± 3.01	0.02
24-hour urine uric acid, mg	572 ± 308	529 ± 303	0.43
24-hour urine volume, ml	1692 ± 672	1849 ± 827	0.23
24-hour urine calcium, mg	172 ± 126	171 ± 115	0.98
24-hour urine sodium, mEq/l	95.7 ± 36.8	96.3 ± 39.1	0.43
24-hour urine potassium, mEq/l	22.2 ± 12.8	29.2 ± 38.2	0.22
Sodium excretion fraction	0.96 ± 0.56	0.83 ± 0.4	0.16
Urate excretion fraction	0.67 ± 0.36	0.57 ± 0.36	0.12
Urine pH/urate excretion fraction index	105 ± 19	102 ± 18	0.39

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