Advances in Rheumatology

RESEARCH Open Access

Nephrolithiasis in gout: prevalence and characteristics of Brazilian patients

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Abstract

Background: The aims of this article were to assess the prevalence of nephrolithiasis and the factors associated with nephrolithiasis in Brazilian patients with primary gout.

Methods: One hundred twenty-three patients with primary gout were recruited from a tertiary referral hospital in São Paulo, Brazil. All patients underwent ultrasonography and had their clinical and laboratory characteristics assessed.

Results: One hundred fifteen (93.5%) patients were male, with a mean age of 62.9 ± 9.4 years. Twenty-three (18.7%) patients had asymptomatic nephrolithiasis (detected only by ultrasonography), 7 (6.0%) had symptomatic nephrolithiasis (detected by ultrasonography and a positive clinical history), and 13 (10.0%) had a history of kidney stones, but ultrasonography at evaluation did not show nephrolithiasis. Therefore, 35.0% of the patients had nephrolithiasis (detected either by ultrasonography and/or a positive clinical history). Nephrolithiasis was associated with male gender (43 [100%] vs 72 [90%], $p = 0.049$), the use of potassium citrate (13 [30.2%] vs 0, $p < 0.001$) and the use of medications for diabetes (10 [23.3%] vs 8 [10%], $p = 0.047$) and dyslipidemia (15 [34.9%] vs 10 [12.5%], $p = 0.003$); benzbromarone had an inverse association with nephrolithiasis (21 [48.8%] vs 55 [68.8%], $p = 0.030$). In patients with and without nephrolithiasis, no differences were found in the laboratory and ultrasonography characteristics, including serum uric acid levels, urinary uric acid excretion and urine pH.

Conclusions: The prevalence of nephrolithiasis in primary gout was 35.0%, and 18.7% of the patients were asymptomatic. Nephrolithiasis was associated with male gender, diabetes and dyslipidemia. A positive history of nephrolithiasis probably biased the prescription of potassium citrate and benzbromarone.

Keywords: Nephrolithiasis, Urolithiasis, Gout, Metabolic syndrome, Brazil

Introduction

Gout is the most common form of inflammatory arthritis in men, and data from several countries suggest that it is becoming more prevalent [1, 2]. Nephrolithiasis is a renal manifestation of gout that is reported in 14% of patients with gout in primary care [3] compared with only 5.6% of the general population [4]. This prevalence can be as high as 39% when imaging tools are used to actively screen for nephrolithiasis in asymptomatic gout patients [5, 6]. Nephrolithiasis can lead to pain, urinary tract infection or obstruction and chronic kidney disease [3]. The presence of nephrolithiasis has an impact when choosing the appropriate medications for the management of gout.

The main factors associated with nephrolithiasis in patients with gout were described by Yu and Gutman [7]: low urine pH, elevated serum uric acid levels and elevated daily urine urate excretion, leading to mainly uric acid stones. However, recent cross-sectional studies using validated diagnostic criteria for gout and imaging tools for diagnosing nephrolithiasis have revealed other associated factors [5, 6, 8] and an increased prevalence of calcium oxalate stones [6]. To our knowledge, there are no studies from Brazil designed to assess the prevalence of nephrolithiasis and the factors associated with nephrolithiasis in patients with primary gout.

The primary aim of this study was to determine the prevalence of nephrolithiasis among Brazilian patients

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with primary gout admitted to our tertiary center clinic. The secondary aim was to identify the factors associated with nephrolithiasis in our population.

Materials and methods

Subjects

From January 2000 to December 2006, 123 patients diagnosed with primary gout according to the American College of Rheumatology 1977 criteria [9] were consecutively recruited from our gout clinic, which is located in a tertiary referral hospital in São Paulo, Brazil.

Methods

The attending physician filled in a research protocol with the patients' clinical and laboratory characteristics, and the patients underwent ultrasonography; all data were then transcribed into a digital database. Therefore, this is a cross-sectional study. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

The following clinical parameters were assessed: gender, age, self-reported skin color/race, date of gout diagnosis, duration of disease, the presence of tophi, smoking status (past or present), alcohol use disorder (past or present), medications in use and history of nephrolithiasis. A positive history of nephrolithiasis was defined as the patient answering "yes" to the question "Have you ever had kidney stones either associated with pain and/or passage into the urine?"

The following laboratory data were assessed: serum creatinine, estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation [10]), serum urea, serum uric acid (determined by the uricase method), clearance of uric acid, underexcretion of uric acid, urinary uric acid excretion over 24 h, serum glucose, serum total cholesterol, serum triglycerides and urinalysis. Urine pH was assessed with a dipstick in a fresh urine sample. Underexcretion of uric acid was defined as a clearance of < 6 mL/min. Lithiasis, cysts and indirect signs of chronic kidney disease were evaluated using a grey scale ultrasound imaging. The exam was performed by a random radiologist physician using a curvilinear probe with a transmit frequency of 2.5 to 6.0 MHz; kidneys were evaluated in multiple anatomic planes.

Statistical analysis: Shapiro-Wilk's test was used to test for normality. Continuous variables were compared using Student's t-test or the Mann-Whitney test as appropriate. Categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. A two-tailed P value of ≤0.05 was considered statistically significant. The Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc., Chicago, IL, US) was used for all the statistical analyses.

Results

Out of a total of 123 patients, 115 (93.5%) were male, and 102 (82.9%) were white, with a mean age of 62.9 years (standard deviation – SD ± 9.4). The onset of the disease occurred at 44.9 ± 12,3 years, and the duration of the disease was 18.2 ± 10.5 years. Most of the subjects had a history of alcohol use disorder 73.2%) and smoking tobacco (51.2%). The medications most often prescribed for gout were benzbromarone (61.8%), nonsteroidal anti-inflammatory drugs (NSAIDs, 52.0%), allopurinol (36.6%), colchicine (26.0%) and potassium citrate (10.6%). Medications prescribed for comorbidities included antihypertensive medication (74.8%), lipid-lowering medication (20.3%) and antidiabetic medication (14.6%). One hundred and ten (89.4%) of the patients were classified as having underexcretion of uric acid. Laboratory features included a mean serum creatinine of 1.34 ± 0,55 mg/dL, serum uric acid levels of 7.13 ± 1.95 mg/dL, uric acid clearance of 5.48 ± 3.91 mL/min and a urine pH of 5.79 ± 0.83. The patients' complete and detailed clinical and laboratory characteristics are shown in Table 1.

The prevalence of nephrolithiasis, as assessed either by clinical history or ultrasonography, is depicted in Table 2 and Table 3. Thirty (24.4%) patients had detectable nephrolithiasis on ultrasonography, and 20 (16.3%) reported a positive history of kidney stones, resulting in a total of 43 (35.0%) patients with nephrolithiasis (detected by either ultrasonography and/or positive clinical history). Twenty-three (18.7%) patients had asymptomatic nephrolithiasis (detected only on ultrasonography), 7 (6.0%) had symptomatic nephrolithiasis (detected by ultrasonography and a positive clinical history), and 13 (10.0%) had a positive history of kidney stones, but ultrasonography at evaluation did not show nephrolithiasis.

Comparisons between the patients with nephrolithiasis and those without nephrolithiasis are shown in Table 4 (clinical comparisons) and Table 5 (laboratory and ultrasonography comparisons). Patients with nephrolithiasis were more likely to be male (43 of 43 patients [100%] vs 72 of 80 patients [90%], $p = 0.049$), to be taking potassium citrate (13 [30.2%] vs 0, $p < 0.001$) and to be taking medications for diabetes (10 [23.3%] vs 8 [10%], $p = 0.047$) and dyslipidemia (15 [34.9%] vs 10 [12.5%], $p = 0.003$). Patients with nephrolithiasis were less likely to be taking benzbromarone (21 [48.8%] vs 55 [68.8%], $p = 0.030$). No statistically significant differences were found in the laboratory and ultrasonography characteristics, including serum uric acid levels, urinary uric acid excretion or urine pH.

Discussion

The prevalence of nephrolithiasis in patients with primary gout in our population was 35.0%, which is higher

Table 1 Clinical and laboratory features of 123 Brazilian patients with primary gout

	Value
Male gender	115 (93.5%)
Skin color/race	
White	102 (82.9%)
Brown or Black	14 (11.4%)
Asian	7 (5.7%)
Age (years)	62.9 ± 09.4
Age at the onset of disease (years)	44.9 ± 12.3
Duration of disease (years)	18.2 ± 10.5
Tophi	69 (56.1%)
Underexcretion of uric acid	110 (89.4%)
Alcohol use disorder	90 (73.2%)
Current	23 (18.7%)
Past	67 (54.5%)
Smoking history	63 (51.2%)
Current	10 (8.1%)
Past	53 (43.1%)
Medication	
Allopurinol	45 (36.6%)
Benzbromarone	76 (61.8%)
Potassium citrate	13 (10.6%)
Colchicine	32 (26.0%)
Glucocorticoids	7 (5.7%)
NSAIDs	64 (52.0%)
Antidiabetic medication	18 (14.6%)
Antihypertensives	92 (74.8%)
Lipid-lowering medication	25 (20.3%)
Serum creatinine (mg/dL)	1.34 ± 0.55
Serum urea (mg/dL)	44.1 ± 25.3
eGFR – CKD EPI (mL/min/1.73 m^2)	63.9 ± 21.7
Serum uric acid levels (mg/dL)	7.13 ± 1.95
Uric acid clearance (mL/min)	5.48 ± 3.91
Uric acid clearance < 6 mL/min	85 (69.1%)
Urinary uric acid excretion (g/24 h)	0.53 ± 0.30
Serum glucose (mg/dL)	105.7 ± 26.8
Serum total cholesterol (mg/dL)	205.4 ± 49.4
Serum triglyceride (mg/dL)	231.4 ± 399.6
Urinalysis	
pH	5.79 ± 0.83
Pyuria (> 10 leukocytes/HPF)	6 (4.9%)
Hematuria (> 3 erythrocytes/HPF)	12 (9.8%)
Significant proteinuria	5 (4.1%)

Data are expressed as the total (%) or the mean ± SD
CKD – EPI Chronic Kidney Disease Epidemiology Collaboration equation
eGFR estimated glomerular filtration rate
HPF high-power field
NSAIDs nonsteroidal anti-inflammatory drugs

than the prevalence observed in patients with gout in population-based studies (14.0%) [3] or in the general population (5.6%) [4]. The main reason for this high prevalence in our population is that the patients were actively screened for nephrolithiasis with an imaging tool: only 20 (16.3%) patients reported a positive history of nephrolithiasis; however, ultrasonography identified 23 (19%) asymptomatic patients. Wan et al. [8] and Alvarez-Nemegyei et al. [5] also described a high prevalence of nephrolithiasis (31.6 and 39.3%, respectively) among patients with primary gout who underwent ultrasonography at tertiary centers. Shimizu et al. [6] found a prevalence of 33.9% in patients with primary gout assessed with computerized tomography (CT). A meta-analysis of epidemiological studies by Roughley et al. [3] and a study by Yu and Gutman [7] described that the prevalence of nephrolithiasis is much lower if it is self-reported (14 and 22.3%, respectively). Another factor that may have contributed to this high prevalence is that these patients were assessed in a tertiary referral center, where patients with more severe gout were referred. A high prevalence of metabolic syndrome, which can be inferred by the proportion of subjects taking medications for hypertension, diabetes and dyslipidemia, may also have played a role because metabolic syndrome is an independent risk factor for the formation of kidney stones [11, 12].

To our knowledge, there are no studies from Brazil designed to assess the prevalence of nephrolithiasis and the factors associated with nephrolithiasis in patients with primary gout. Azevedo et al. [13] described a small cohort of 48 patients with gout who were taking allopurinol, benzbromarone or both, and the self-reported prevalence of nephrolithiasis was 25%. Hasegawa et al. [14] studied the prevalence of renal cysts detected by ultrasonography in patients with gout; the prevalence of nephrolithiasis was 21%, and the presence of cysts was inversely related to nephrolithiasis. Souza et al. [15] compared the clinical and laboratory features of gout in men and women, and the self-reported prevalence of nephrolithiasis was 22.6 and 18.5%, respectively. None of these studies analyzed the factors associated with nephrolithiasis in Brazilian subjects.

In the current study, patients with nephrolithiasis were more likely to be male and to be undergoing medical treatment for diabetes and dyslipidemia. The highest prevalence of nephrolithiasis in males and in patients with metabolic syndrome has already been described in the general population [12]. A positive history of nephrolithiasis probably biased the prescription of potassium citrate and benzbromarone. The classical main factors associated with nephrolithiasis in patients with gout described by Yu and Gutman [7] (low urine pH, elevated serum uric acid levels and elevated daily urine urate excretion) were not statistically significant in our

Table 2 Ultrasonography findings plus the prevalence of nephrolithiasis

	N = 123
Ultrasonography findings	
Nephrolithiasis	30 (24.4%)
Cysts	46 (37.4%)
Chronic kidney disease appearance	10 (8.1%)
Positive history of nephrolithiasis	20 (16.3%)
Total prevalence of nephrolithiasis (ultrasound and/or history)	43 (35.0%)

Data are expressed as the total (%)

population, probably because these laboratory data were assessed in patients who were already taking medications that modify these laboratory parameters. Interestingly, Alvarez-Nemegyei et al. [5] found that a higher urinary pH was associated with nephrolithiasis, which can be explained by the fact that alkalinizing agents are prescribed more often for patients with nephrolithiasis. Other factors that have been associated with nephrolithiasis in patients with gout, including serum uric acid levels ≥10 mg/dL [8] and elevated serum creatinine and urea [6], were not observed in our population.

A complete urinary excretion profile and the composition of the calculi was not assessed in our sample; a recent study from Shimizu et al. [6] showed that only one third of the calculi from patients with gout were of pure uric acid, compared to more than two thirds observed in the classic study from Yu and Gutman [7]. This may be partially explained by the increasing prevalence of metabolic syndrome, a known risk factor for calcium oxalate stones [11, 12]. However, further studies are necessary to confirm this shift in the composition of nephrolithiasis from patients with gout.

This study has several limitations. It was a cross-sectional study including patients who were recruited from a tertiary referral center; therefore, they may have had more severe disease than patients from primary care facilities. All the data were collected and stored in a digital database in 2006; however, only in 2019 were these data analyzed and prepared for publication. Despite the potential shifts in diet, lifestyle and disease prevalence that may have occurred in Brazil from 2006 to 2019, these results may still be representative of our population. Our patients were assessed with ultrasonography, which is less sensitive than CT for the diagnosis of nephrolithiasis [16], and ultrasonography cannot be used to infer the composition of kidney stones. However, ultrasonography is less expensive than CT, does not involve exposure to ionizing radiation [17] and is considered by the European Association of Urology to be a primary diagnostic imaging tool [18]. Urine pH was

Table 3 Positive history of nephrolithiasis vs ultrasonography

	Positive history of nephrolithiasis		
	Yes	No	Total
	20	103	
US with nephrolithiasis	7	23	30
US without nephrolithiasis	13	80	93

US ultrasonography

Table 4 Comparison between patients with and without nephrolithiasis (clinical characteristics)

	Nephrolithiasis (*N* = 43)	Without Nephrolithiasis (*N* = 80)	*P* Value
Male gender	43 (100%)	72 (90.0%)	0.049
Skin color/race: white	37 (86.0%)	65 (81.2%)	0.500
Age (years)	61.3 ± 9.7	63.8 ± 9.3	0.161
Age of onset of disease (years)	42.3 ± 11.4	46.4 ± 12.7	0.080
Duration of disease (years)	19.0 ± 10.8	17.8 ± 10.4	0.502
< 5 years	1 (9.1%)*	10 (90.9%)*	0.168†
5–15 years	19 (38.0%)*	31 (62.0%)*	–
> 15 years	23 (37.1%)*	39 (62.9%)*	–
Tophi	24 (55.8%)	45 (56.2%)	0.963
Underexcretion of uric acid	38 (88.4%)	72 (91.4%)	0.624
Alcohol use disorder	36 (83.7%)	54 (67.5%)	0.053
Current	9 (20.9%)	14 (17.5%)	0.642
Past	27 (62.8%)	40 (50.0%)	0.174
Smoking history	25 (58.1%)	38 (47.5%)	0.260
Current	2 (4.7%)	8 (10.0%)	0.491
Past	23 (53.5%)	30 (37.5%)	0.088
Medication			
Allopurinol	19 (44.2%)	26 (32.5%)	0.199
Benzbromarone	21 (48.8%)	55 (68.8%)	0.030
Potassium citrate	13 (30.2%)	Zero	< 0.001
Colchicine	15 (34.9%)	17 (21.2%)	0.100
Glucocorticoids	2 (4.7%)	5 (6.2%)	1.000
NSAIDs	23 (53.5%)	41 (51.2%)	0.813
Antidiabetic medication	10 (23.3%)	8 (10.0%)	0.047
Antihypertensives	34 (79.1%)	58 (72.5%)	0.424
Lipid-lowering medication	15 (34.9%)	10 (12.5%)	0.003

Data are expressed as the total (%) or the mean ± SD, unless otherwise stated
NSAIDs nonsteroidal anti-inflammatory drugs
* Percentage for each subgroup
† *p* value for the comparison among the three disease duration subgroups

Table 5 Comparison between patients with and without nephrolithiasis (laboratory and ultrasonography characteristics)

	Nephrolithiasis (*N* = 43)	Without Nephrolithiasis (*N* = 80)	*P* Value
Serum creatinine (mg/dL)	1.26 ± 0.42	1.38 ± 0.61	0.507
Serum urea (mg/dL)	41.7 ± 22.2	45.4 ± 26.8	0.387
eGFR – CKD EPI (mL/min/1.73 m^2)	68.0 ± 22.3	61.6 ± 21.1	0.116
Serum uric acid levels (mg/dL)	7.20 ± 2.11	7.09 ± 1.87	0.785
Uric acid clearance (mL/min)	5.25 ± 3.38	5.61 ± 4.18	0.518
Uric acid clearance < 6 mL/min	32 (74.4%)	53 (67.1%)	0.400
Urinary uric acid excretion (g/24 h)	0.55 ± 0.33	0.52 ± 0.28	0.879
Serum glucose (mg/dL)	111.3 ± 36.1	102.6 ± 19.8	0.256
Serum total cholesterol (mg/dL)	207.1 ± 57.7	204.5 ± 44.8	0.924
Serum triglycerides (mg/dL)	307.8 ± 639.3	190.4 ± 156.3	0.627
Urinalysis			
pH	5.87 ± 0.80	5.75 ± 0.85	0.383
Pyuria (> 10 leukocytes/HPF)	2 (4.7%)	4 (5.0%)	1.000
Hematuria (> 3 erythrocytes/HPF)	7 (16.3%)	5 (6.2%)	0.074
Significant proteinuria	1 (2.3%)	4 (5.0%)	0.657
Ultrasonography			
Cysts	20 (46.5%)	26 (32.5%)	0.126
CKD appearance	3 (7.0%)	7 (8.8%)	1.000

Data are expressed as the total (%) or the mean ± SD
CKD Chronic kidney disease
CKD – EPI Chronic Kidney Disease Epidemiology Collaboration equation
eGFR estimated glomerular filtration rate
HPF high-power field

assessed with a dipstick, which has a good statistical correlation with the gold standard method – a pH meter [19]. Nevertheless, dipstick is more inaccurate than a pH meter, especially in higher pH values [19]; for that reason, our findings of the pH in this population sample should be interpreted with caution.

Conclusion

The prevalence of nephrolithiasis in primary gout is high, and many patients are asymptomatic. Therefore, patients should be screened for this condition either with ultrasonography or CT. Identifying patients with lithiasis is important for preventing complications associated with this pathologic process and to determine the most appropriate therapy for gout. In the current study of Brazilian subjects, nephrolithiasis was associated with male gender and treatments for diabetes and dyslipidemia.

Acknowledgments
The authors thank all the patients who participated in this study.

Author's contributions
LSH contributed with the conception, design of the work, analysis and interpretation of data and have drafted the manuscript. CGS contributed with the conception, design of the work, and substantively revised the manuscript. RF contributed with the conception, design of the work, acquisition, analysis and interpretation of data and have drafted the manuscript. All authors read and approved the final manuscript.

Funding
This study received no funding.

Availability of data and materials
The primary data referent to the present study is available upon request to the corresponding author.

Ethics approval and consent to participate
This study was approved by the hospital ethics committee (protocol 3.377.422).

Consent for publication
All authors are aware of the full content of the manuscript and provided consent for the submission to Advances in Rheumatology.

Competing interests
The authors have declared no conflicts of interest.

Received: 15 August 2019 Accepted: 23 December 2019
Published online: 31 December 2019

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