100% Uric Acid Stone Formers: What Makes Them Different?

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OBJECTIVE To identify what risk factors on 24-hour urinalysis, if any, predispose patients to have higher percentages of uric acid (UA) stone composition in their stones, with specific emphasis on patients with pure UA stones.

METHODS We retrospectively identified 308 patients from review of a kidney stone analysis database. Patients were grouped according to the percentage UA composition: 10%-20%, 30%-50%, 60%-90%, and 100% UA. Data were extracted from 24-hour urine collections and serum chemistries. Patients taking allopurinol, citrates, or thiazide diuretics were excluded.

RESULTS The percentage UA stone composition increased as patients became older ($P = .05$) or heavier ($P < .001$). Gender did not impact the percentage of UA in stones. Although a higher serum UA level was associated with higher UA stone composition ($P < .0006$), urinary UA levels did not correlate ($P = .1$). In contrast, urinary pH correlated significantly with higher UA stone composition ($P = .03$).

CONCLUSION Older and heavier patients with higher serum UA levels are more likely to have a pure UA stone. This information combined with traditional predictors (urine pH, radiopacity of stone, and Hounsfield units) may help identify those most likely to respond to dissolution therapy. UROLOGY 85: 296–298, 2015. © 2015 Elsevier Inc.

Uric acid (UA) nephrolithiasis is estimated to account for 8%-10% of kidney stones in the United States.[1] Dissolution by urinary alkalinization is the first-line medical management of UA stones.[2-4] The success of dissolution therapy empirically would decrease as percentage UA composition decreases; however, outcomes with dissolution therapy for mixed composition stones with varying proportions of UA are not known. Often, the decision to attempt dissolution therapy, rather than proceed with an endoscopic stone removal, must be based on indirect prediction of stone composition. This is of particular importance given that metabolic syndrome is a shared risk factor for both increased anesthetic risk and UA urolithiasis.[5-7]

It has been well established that urinary metabolic abnormalities are highly prevalent in stone-forming populations. However, the demographic and metabolic characteristics that might distinguish between the varying percentages of UA in stone composition have not been reported. We aim to define the metabolic profiles of 100% UA formers and compare with those of mixed-composition stone formers.

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METHODS

Design

We identified patients from a retrospective review of an institutional review board–approved kidney stone database. Patients who had a UA component to their stone and who had completed a 24-hour urine stone risk profile within 3 months of their stone analysis were selected for the study. Twenty-four-hour urine profiles were performed by the Cleveland Clinic Department of Laboratory Medicine. Specimens were refrigerated before analysis, which was subsequently performed at 37°C with phosphate buffer at pH 7.8. In instances where there was >1 24-hour urine available, the profile closest to the date of the stone analysis was used. Recurrent stone formers without a baseline 24-hour urine before initiation of citrate or other medications to modify UA levels or urinary pH such as allopurinol or thiazides were excluded. Patients were then grouped according to percentage UA composition: 10%-20%, 30%-50%, 60%-90%, and 100% UA. These values are noncontinuous 10%-interval compositions referencing laboratory reports generated by comparing the sample's Fourier transform infrared spectroscopy spectrum with a reference database organized in the same 10% intervals (all analyses performed by The Cleveland Clinic Department of Clinical Biochemistry). Reviewed data included patient demographics, medical therapeutics, 24-hour urine collections (volume, sodium, calcium, oxalate, UA, citrate, and pH), and stone composition.

Statistical Analysis

Basic descriptive statistics were used to classify the study sample, as appropriate based on distribution of the data. Specifically, continuous variables with a parametric distribution were reported as means and standard deviations. Likewise, categorical

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Table 1. Demographic characteristics and 24-hour urine parameters according to percentage uric acid composition

Variable	10%-20% (N = 150)	30%-50% (N = 12)	60%-90% (N = 55)	100% (N = 91)	*P* Value (100% vs 10%-20%)
Percentage uric acid composition on stone analysis					
Age (y)	55 ± 1.0	53 ± 3.6	57 ± 1.7	60 ± 1.3	.05
BMI (kg/m^2)	29 ± 0.6	32.8 ± 2.2	33.2 ± 1.0	34.3 ± 0.8	<.0001
Sex (% male)	66	66	62	64	.4
Serum uric acid (mg/dL)	5.89 ± 0.11	6.08 ± 0.39	6.61 ± 0.18	6.53 ± 0.14	<.0006
24-h urine analysis					
Volume (mL/d)	1845 ± 90	2053 ± 325	1690 ± 139	1676 ± 120	.5
Sodium (mmol/d)	174 ± 7	181 ± 26	179 ± 11	174 ± 10	.9
Calcium (mg/d)	195 ± 10	241 ± 36	185 ± 16	171 ± 13	.22
Oxalate (mg/d)	54.1 ± 1.9	54.0 ± 6.8	48.0 ± 3.1	51.3 ± 2.5	.38
Uric acid (mg/d)	560 ± 19	607 ± 68	499 ± 31	498 ± 24	.1
Citrate (mg/d)	501 ± 39	731 ± 139	565 ± 63	652 ± 51	.07
pH	5.89 ± 0.79	5.83 ± 0.49	5.63 ± 0.72	5.62 ± 0.62	.03

BMI, body mass index.

variables were reported as frequencies and percentiles. A 1-way analysis of variance was used to assess for differences in variables across multiple groups with subsequent pairwise comparison of means performed with the Tukey-Kramer honestly significant difference test. Standard chi-square analyses were used for categorical measures. A *P* value <.05 was considered significant for all tests. All calculations were performed using JMP, version 10 (SAS Institute, Inc), statistical software.

RESULTS

A total of 308 patients were identified (65% male) with a mean age of 57 ± 12 years and mean body mass index (BMI) of 31 ± 7.8 kg/m^2. Overall, 91 patients had 100% UA stones, 55 had 60%-90% UA stones, 12 had 30%-50% UA stones, and 150 had 10%-20% UA stones (Table 1). The most common secondary component of non-100% UA stones was calcium oxalate. Patients with 100% UA stones were older than those with 10%-20% UA stones (60 vs 55 years; $P = .05$). Patients had a higher BMI if their stone was 100% UA (34.3 kg/m^2; $P < .0001$) or 60%-90% UA (33.3 kg/m^2; $P = .012$) compared with patients with 10%-20% UA (29.5 kg/m^2).

Mean urine pH of patients was lower for those with 100% UA (5.62 ± 0.62; $P = .02$) and patients with 60%-90% UA (5.63 ± 0.72; $P = .03$) compared with 10%-20% UA (5.89 ± 0.79). Mean serum UA was higher for patients with 100% UA (6.5 ± 1.18; $P = .003$) and patients with 60%-90% UA (6.61 ± 1.49; $P = .005$) compared with patients with 10%-20% UA (5.89 ± 1.4) No significant difference (all $P > .1$) was seen in mean urinary UA levels: 560 ± 19 (10%-20% UA), 607 ± 68 (30%-50% UA), 499 ± 31 (60%-90% UA), 498 ± 24 (100% UA). Similarly, there were no significant differences in gender distribution or urinary volume, sodium, calcium, oxalate, or citrate (Table 1).

COMMENT

Previous studies have used a combination of radiographic and urinary parameters in an attempt to define stone composition in the absence of a direct analysis of stone composition from a stone that has been surgically removed or spontaneously passed.[8-10] However, it has also been demonstrated that these measures, such as computed tomography attenuation values, vary widely depending on the scanner model used.[11] These studies have used varying percentages of UA stone composition; none focused on pure 100% UA stones.

Torricelli et al[12] developed a nomogram that was able to increase the reliability of distinguishing between calcium oxalate and UA stones based on the 24-hour urine collections, the patient's BMI, and age. However, in this study, classification as calcium oxalate or UA stone group was based on a predominant component defined as >50%. This could allow for a number of mixed stone-forming patients being classified as having UA stones and potentially counseled for dissolution therapy, when they in fact may have a lower chance of complete dissolution.

The study by Torricelli et al reported that UA stone formers had a significantly lower urinary UA than patients with calcium oxalate stones. We found no difference in urinary UA levels when looking at patients with varying percentage composition of UA stones. Urinary pH, however, was significantly lower in the 100% UA group compared with patients with 10%-20% UA composition. Although the study by Torricelli et al suggested that urine pH was not helpful in distinguishing between a UA and a calcium oxalate stone, our study suggests that pH may be more important when trying to distinguish 100% UA stones from mixed-composition stones. Additionally, patients with 100% UA stones had a higher serum UA than patients with 10%-20% UA stones. Although prior studies have established an association between hyperuricemia and UA urolithiasis, our study suggests that even high-normal ranges of serum UA may be a marker for pure UA stone formation.[13,14]

When dissolution therapy was directed by radiolucent stones on plain films, a complete dissolution rate of only 10% was reported.[15] One might predict failure of dissolution in patients with mixed-stone composition, if the

stone is coated in a calcium shell, precluding the alkaline urine from contacting the UA crystals.[16] Identifying demographic and metabolic differences between 100% UA stone formers and those forming mixed UA stones would theoretically help in selecting the appropriate patient for a trial of dissolution when considering the recurrent asymptomatic stone former or an asymptomatic initial stone. However, given the asymmetric number of patients in the 30%-50% UA stone group, the study was likely underpowered to show statistically significant differences among all groups. Additionally, a comparison of interest between pure UA and 60%-90% UA stones, as those are both likely to be radiolucent and would benefit from additional information to determine appropriateness for dissolution therapy, failed to reach statistical significance. Although the variations in clinical parameters such as urinary pH and serum UA levels plausibly account for corresponding variations in stone composition, the available data are unlikely to contribute in a meaningful way to deciding what therapy should be considered appropriate (dissolution vs interventional). It appears that analysis of 24-hour urine values may not increase the clinician's confidence in success of dissolution therapy much beyond the previously described combination of low Hounsfield units (<500 HU) and initial urinary pH $\leq$5.5, successfully increased by alkalinization therapy.[10]

This study is retrospective in nature and is subject to the inherent limitations and potential selection biases. The date of stone analysis, as it was readily available, was used as a proxy for timing of stone passage or surgical retrieval in determining which 24-hour urine values to use for analysis. There are also limitations associated with the available 24-hour urine values. Urinary sulfate reporting was incomplete, and thus, we were unable to evaluate whether the lower urine pH associated with increased BMI is related to higher animal protein intake. Urinary ammonium was likewise unavailable, and thus, we were unable to evaluate whether lower urinary ammonium (adjusted for urinary creatinine) is associated with lower urinary pH in obesity. The accuracy of classification and reporting of various parts of mixed stones and whether or not a stone fragment vs a whole stone was used for analysis is unknown. Although the 24-hour urine collections were reported within 3 months of stone composition analysis, we do not know if the analysis was performed on a recently passed or removed stone, and we do not know how long the stone was in place. In addition, all patients were evaluated at a single tertiary-care center, and thus, our results may not be generalizable to other populations.

CONCLUSION

Patients with 100% UA stones are older, heavier, and have a higher serum UA level and lower urinary pH than patients with mixed-stone composition. Urinary UA is not significantly different among groups. Defining associations such as these will enable development of clinical algorithms, in combination with radiographic appearance that facilitate prediction of the probability a patient has a 100%-UA stone. This will then enable the clinician to counsel them more accurately on their treatment options. Given the present data, it is unclear whether metabolic and demographic characteristics alone will provide enough sensitivity to predict percentage composition of a UA stone.

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