

Long-term Recurrence Rates in Uric Acid Stone Formers With or Without Medical Management



Benjamin K. Canales, Nitin Sharma, Stanislav V. Yuzhakov, Shahab Bozorgmehri, Brandon J. Otto, and Vincent G. Bird

OBJECTIVE	To determine if medical therapy affects long-term clinical outcomes in uric acid stone formers (UASF).
METHODS	We identified 53 UASF who had complete stone clearance following stone procedure by computed tomography (CT) and had ≥ 1 postoperative 24-hour urine collection and a clinical follow-up ≥ 6 months with a surveillance CT scan. Patients were divided into “adherent to medical therapy” (compliance with potassium citrate \pm allopurinol verified by computerized pharmacy data) or nonadherent groups. Primary outcomes were CT stone recurrence rate and need for surgical stone intervention.
RESULTS	We found 28 of 53 (53%) adherent and 25 of 53 (47%) nonadherent individuals (14 declined medication, 11 intolerant). With median follow-up of 24 months, no significant differences were noted between groups in regards to stone recurrence (32%; $P = .99$) or in 24-hour urine pH compared to baseline or follow-up (range 5.46-5.62; $P = 0.06$). Adherent patients, however, had smaller CT stone recurrence sizes (6.3 ± 3.8 vs 11.8 ± 6.2 mm, $P = .02$), were 28% less likely to require stone surgery compared to those without therapy ($P < .01$), and trended toward longer time intervals without recurrence (23.1 ± 18.8 vs 10.5 ± 7.5 months, $P = .10$) compared to nonadherents. Study confounders included a variety of medication dosages and adherences, limited nonadherent follow-up, and small study number.
CONCLUSION	UASF adherent to medical therapy had smaller recurrence sizes and fewer surgical interventions vs nonadherent, highlighting the protective role of potassium citrate in UA stone disease. The comparable urine pH and stone recurrence rates between groups, however, underscore areas for improvement in future UA stone prevention strategies. UROLOGY 131: 46–52, 2019. © 2019 Elsevier Inc.

Uric acid (UA) kidney stones are the second most common stone type, occurring in up to 10% of stone formers (SF) worldwide.¹ In these individuals, UA crystallization occurs when urine pH is persistently low (< 5.5), when urinary UA excretion is high (> 750 mg/day), or when elements of both are present.² In conjunction with increased fluid intake and dietary changes, UASF are often prescribed alkalization agents (ie, potassium citrate) and/or xanthine oxidase inhibitors (ie, allopurinol) to increase urinary pH and reduce urinary UA concentration, respectively—thus lowering UA crystal precipitation.³ Despite these preventative strategies, many UASF develop recurrent stones or experience new kidney stone growth.

Over the last 40 years, high-dose alkalization therapy, known as dissolution therapy, has been shown to effectively dissolve 15%-80% of small radiolucent stones in short-term studies of 6-12 weeks.⁴⁻⁹ However, long-term (> 6 month) stone outcomes in UASF have only been reported by 2 groups. Pak ($n = 18$; 1986)¹⁰ and Rodman ($n = 17$; 1991)¹¹ reported a mean rise in urine pH from 5.30 to 6.19 as well as low stone recurrence rates (combined 3/35, 8.6%) in a mixed group of UA stone formers followed for $\sim 2\frac{1}{2}$ years on moderate dose potassium citrate therapy (40-60 meq/day). Despite their reported success, both these studies were limited by small patient number, lack of proper stone analysis/24-hour urines, and by the use of plain radiography instead of computed tomography to evaluate for presence or absence of radiolucent stones.^{10,11}

More recently, a number of authors have evaluated features and risk factors associated with UASF, including male gender, older age, gout, chronic diarrhea, and metabolic syndrome.¹²⁻¹⁵ Despite these insights, no contemporary study has evaluated long-term recurrence rates in this population.

Conflict of Interest: All the authors have no conflict of interest to disclose.

From the Department of Urology, University of Florida, Gainesville, FL

Address correspondence to: Benjamin K. Canales, M.D., M.P.H., Department of Urology, University of Florida, 1600 SW Archer Road, P.O. Box 100247, Gainesville, FL 32610-0247. E-mail: Benjamin.Canales@urology.ufl.edu

Submitted: March 21, 2019, accepted (with revisions): May 21, 2019

Therefore, the objective of this study is to assess the metabolic and long-term clinical outcomes of UA stone formation with or without medical management.

MATERIALS AND METHODS

With IRB approval, we identified all UASF (confirmed by mineral analysis) over 18 years of age who underwent kidney stone removal procedure between 2010 and 2016 at our institution and had subsequent follow-up in our institution's metabolic stone clinic. In general, all postoperative UA patients are offered 24-hour urine testing (Litholink, Chicago, IL) and instructed to follow-up in clinic to discuss the results. In subsequent visits, UASF are given general UA stone prevention strategies, such as increasing oral fluid intake to achieve a urine volume >2.5 Liter per day and limiting dietary sodium and purine intake. All patients are offered alkalinization with potassium citrate 30-60 meq/day. Patients with hyperuricemia (serum UA >6.0 mg/dL in females, >7.5 mg/dL in males) or gout history are offered both alkalinization and xanthine oxidase inhibitor (allopurinol 300 mg/day). Patients with renal impairment or with complex metabolic profiles precluding normal medication dosing are referred to nephrology for further medical stone management. Patients are then routinely followed at 6-month intervals with clinic dipstick urine pH, annual computed tomography (CT) scans, and offered follow-up 24 hour urine collections especially if new medications are started.¹⁶

To qualify for inclusion into this specific study, patients from our UA subset were required to be completely stone-free bilaterally postprocedure by CT scan and have (1) stone analysis showing $\geq 30\%$ UA mineral content; (2) at least 1 baseline 24-hour urine collection; (3) ≥ 6 months of clinic follow-up; and (4) at least 1 surveillance CT scan ≥ 6 months following postprocedure scan. We used the methodology of Reichard¹³ to categorize UA stone mineral phenotypes as "mixed" if UA content was between 30% and 89% or "pure" if UA content was 90% and 100%. We classified individuals as "adherent" if they reported adherence to medications during clinic charting and had refill documentation by hospital or pharmacy electronic medical records. Patients

were considered "nonadherent" if they declined medication prescription, if they reported medication discontinuation during study follow-up, or if they failed to fill a pharmacy prescription.

Baseline demographics, relevant comorbidities, metabolic parameters, serum chemistries, and 24-hour urine parameters were recorded from all UA patients who met inclusion criteria. When two 24-hour tests were available at baseline, the results were averaged. For individuals with more than one 24-hour test after the baseline, the last documented collection was recorded as the "follow-up" urine. Stone recurrence was documented if a new stone was found during annual CT surveillance or by patient report of interval stone passage. Time to stone recurrence was defined by the date of reported stone passage or positive CT finding. Recurrence size was determined at the time of last CT follow-up by measuring the largest stone diameter by digital CT calipers. All patients with stone recurrence remained on medical therapy unless they were acutely symptomatic and required surgical intervention. Need for surgical stone procedure was determined by primary urologist based on symptoms and stone size.

Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, NC). Patient demographics, clinical characteristics, 24-hour urine parameters, and clinical outcomes were examined using either one-way analysis of variance (ANOVA)/Wilcoxon-Mann-Whitney tests for normally/non-normally distributed continuous variables, respectively, or chi-square test for categorical variables. All significance tests were 2-sided with P value $<.05$ considered statistically significant.

RESULTS

We identified a total of 113 of 1355 (8.3%) patients from our surgical database with $\geq 30\%$ UA stone composition, including 59 (52%) patients with pure UA and 54 (48%) patients with mixed UA stone composition. Mean age and body mass index for this total cohort was 59.5 years and 35.7 kg/m², respectively, with 70% of the cohort male and 82% Caucasian. Out of these 113 individuals, 53 met all required study inclusion criteria with median follow-up time of 24 months. Demographics, comorbidities, and metabolic evaluation (Table 1) were similar between

Table 1. Demographics, comorbidities, and metabolic evaluation for UA stone population

	Total UA Population (n = 53)	Medical Adherence (n = 28)	Medical Nonadherence (n = 25)	P Value
<i>Demographics</i>				
Age (years)	61.4 ± 11.7	62.2 ± 12.2	60.6 ± 11.6	0.31
BMI (kg/m ²)	35.5 ± 10.3	38.4 ± 9.7	32.3 ± 10.5	0.02
Sex (% male)	35 (66%)	17 (61%)	18 (72%)	0.39
Caucasian	43 (81%)	23 (82%)	20 (80%)	0.84
<i>Comorbidities</i>				
Diabetes	24 (45%)	15 (54%)	9 (36%)	0.20
Hypertension	41 (77%)	23 (82%)	18 (72%)	0.38
Hyperlipidemia	28 (53%)	15 (54%)	13 (52%)	0.91
Gout	4 (8%)	3 (11%)	1 (4%)	0.36
History of cancer	11 (21%)	8 (29%)	3 (12%)	0.14
Bowel disorder	6 (11%)	3 (11%)	3 (12%)	0.88
CKD	7 (13%)	3 (11%)	4 (16%)	0.57
Family history of stones	41 (77%)	24 (86%)	17 (68%)	0.12
≥ 2 stone surgeries	32 (60%)	18 (64%)	14 (56%)	0.54
<i>Metabolic evaluation</i>				
Serum UA (mg/dL)	6.59 ± 1.62	6.51 ± 1.58	6.68 ± 1.70	0.37
HbA1c (%)	7.30 ± 2.06	8.04 ± 2.09	6.32 ± 1.70	0.06

BMI, body mass index; CKD, chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) <59 mL/min/1.73 m²; HbA1c, hemoglobin A1C. Bold = $p < .05$. All means are shown \pm STD.

Table 2. Initial and follow-up 24-hour urines in uric acid stone formers by adherence

24 Hour Urine Variables (Range, Units)	Adherent		P Value	Nonadherent		P Value
	Initial (n = 28)	Follow-Up (n = 24)		Initial (n = 25)	Follow-Up (n = 8)	
pH (5.8-6.2)	5.47 ± 0.4	5.62 ± 0.3	.06	5.46 ± 0.4	5.46 ± 0.3	.48
Volume (0.5-4, L)	1.93 ± 0.9	1.98 ± 0.8	.42	1.85 ± 0.9	2.09 ± 1.2	.28
SS CaOx (<10)	5.89 ± 3.7	7.38 ± 3.6	.08	6.09 ± 3.8	8.73 ± 3.5	.045
Calcium (<250, mg)	184.0 ± 123	225.2 ± 153	.14	195.4 ± 168	237.1 ± 61	.10
Oxalate (<40, mg)	40.5 ± 13	41.7 ± 26	.41	37.1 ± 13	43.7 ± 13	.10
SS UA (0-1)	1.80 ± 0.9	1.05 ± 0.7*	<.001	1.84 ± 0.9	1.97 ± 1.4*	.38
UA (<0.8, gm)	0.70 ± 0.3	0.65 ± 0.3	.30	0.66 ± 0.3	0.65 ± 0.2	.49
Citrate (<550, mg)	571.5 ± 534	778.8 ± 242	.18	622.0 ± 414	599.9 ± 406	.45
Ammonium (15-60, mmol)	35.6 ± 10.8	22.4 ± 10.7*†	<.001	34.8 ± 11.0	30.3 ± 15.3*	.18
Sulfate (<80, meq)	37.3 ± 10.7	38.2 ± 11.0	.39	34.3 ± 15.0	36.8 ± 14.0	.33
Potassium (20-100, mmol)	47.1 ± 20	70.6 ± 17*	<.001	54.5 ± 23	49.7 ± 20*	.30

CaOx, calcium oxalate; SS, supersaturation; UA, uric acid.

Bold = statistically significant differences *within* adherent and nonadherent groups ($P < .05$).

* Statistically significant differences *between* adherent and nonadherent groups ($P < .05$).

† Results shown after excluding 3 individuals with bowel disease. All means are reported ± STD.

groups except adherent individuals had higher body mass index (38.4 vs 32.3, $P = .02$) and trended to have higher serum % hemoglobin A1c levels (8.04 vs 6.32, $P = .06$). Rates of pure/mixed UA composition were similarly distributed between both adherent (54%, 46%) and nonadherent (52%, 48%) groups. Compared to reported normal reference values (Table 2),¹⁷ the entire UA cohort had lower mean baseline 24-hour urine pH 5.46 ± 0.31 (normal 5.8-6.2) and elevated mean UA supersaturations 1.82 ± 0.9 (normal <1.0). There were no significant differences noted between adherent and nonadherent groups in baseline 24-hour urine parameters (Table 2), nor between pure vs mixed UASF groups (data not shown).

Medication and 24-Hour Urine Follow-Up

In the surveillance period, 25 of 53 (47%) individuals were consider “nonadherent” to medical therapy: 14 chose dietary therapy alone without medication; 9 were intolerant of potassium citrate due to gastrointestinal disturbance; and 2 discontinued potassium citrate due to cost. None of these individuals elected sodium bicarbonate. The remaining 28 of 53 (53%) were adherent to medical therapy, including: 17 on potassium citrate monotherapy; 9 on combination potassium citrate and allopurinol 300 mg (4 with gout history, 5 with hyperuricemia); 1 on sodium bicarbonate (1300 mg BID); and 1 on sodium citrate solution (15 mL BID). Mean potassium citrate dose was 34 ± 5.2 meq/day. Follow-up 24-hour urines were collected in 24 of 28 (86%) adherent and 8 of 25 (32%) nonadherent patients. Individuals adherent to medical therapy decreased UA supersaturation by 42% and increased urinary potassium ~25 meq/day compared to baseline and nonadherents ($P < .001$; Table 2). Mean follow-up 24-hour urine pH was not significantly different ($P = .06$) from baseline or nonadherents (Table 2). However, 58% of adherent individuals (14/24) increased urine pH >5.5 compared to only 2 of 8 (25%) of nonadherents. Clinic

dipstick urine pH did not correlate to 24-hour urine pH values (data not shown).

Stone Recurrence and Size

Of 53 individuals in follow-up, 17 (32%) had stone recurrence (16 by CT imaging; 1 self-reported stone passage) and 7 (13%) required additional stone surgery (mineral type unchanged compared to initial stone). For the entire group, mean stone recurrence size was 9.0 ± 5.5 mm with mean time interval to stone recurrence of 16.8 ± 15.3 months. Relative to nonadherents, patients adherent to medication had 47% smaller stone recurrence size (6.3 ± 2.8 vs 11.8 ± 6.2 , $P = 0.04$) and lower rates of surgical intervention (0% vs 28%, $P < .01$; Table 3). Over the 2 years of follow-up and regardless of therapy, 32% of our population had CT documented stone recurrences regardless of medical management (Table 3). UA stone type was then evaluated as another potential recurrence predictor. Compared to patients with mixed stones, pure UASF trended to have higher stone recurrence rates (39% vs 26%, $P = .32$) and sooner recurrence times (12.4 ± 8.2 vs 24.2 ± 21.8 , $P = .14$), but no significant metabolic or clinical differences were noted between these 2 groups (Table 3). Recurrence probabilities using Kaplan-Meier failure curves were calculated for medication adherence (Fig. 1A, log-rank $P = .318$) and % UA stone composition (Fig. 1B, log-rank $P = 0.326$). Recurrence events were similar for each variable, but a number, particularly nonadherents, were censored due to loss of follow-up.

DISCUSSION

Although UA represents the second most common stone type, very little clinical data is available to guide long-term practice.¹⁸ This manuscript represents the first

Table 3. Outcomes for uric acid stone formers stratified by medical therapy adherence or by mineral content

Total (n = 53)	Adherent (n = 28)	Nonadherent (n = 25)	P value	Pure UA (n = 28)	Mixed UA (n = 25)	P value	Serum Creatinine (mg/dL)	Δ SS UA	Δ SS CaOx	Δ in Urine pH	Median Follow-Up (Months)	Stone Recurrence Number	Stone Recurrence Size (mm)	Stone Recurrence Time (Months)	Surgical Intervention Number
	1.14 ± 0.4	1.20 ± 0.4		1.19 ± 0.4	1.14 ± 0.4		1.14 ± 0.4	-0.73 ± 1.1	1.86 ± 5.6	0.15 ± 0.4	25.0 (15.8-47.5)	9 (32%)	6.3 ± 2.8	23.1 ± 18.8	0 (0%)
								-0.13 ± 1.6	1.95 ± 3.6	0.01 ± 0.3	21.0 (7.0-37.0)	8 (32%)	11.8 ± 6.2	10.5 ± 7.5	7 (28%)
		.58						.12	.48	.14	.13	.99	.04	.10	.003
								-0.46 ± 1.2	3.04 ± 4.8	0.07 ± 0.3	30.5 (12.8-45.0)	11 (39%)	8.9 ± 6.0	12.4 ± 8.2	5 (18%)
								-0.70 ± 1.3	0.72 ± 5.4	0.20 ± 0.4	19.0 (13.0-29.0)	6 (26%)	9.2 ± 5.1	24.2 ± 21.8	2 (8%)
		.28						.29	.10	.18	.18	.32	.93	.14	.29

CaOx, calcium oxalate; SS, supersaturation; UA, uric acid; Pure = 90%-100% UA content; Mixed = 30%-89% UA content. Bold = p<0.05.

contemporary series to use serial CT scans and 24-hour urine collections to assess how UASF fare longitudinally with or without medical management. Similar to other reports, our UASF population is predominated by obese, middle-aged Caucasian males with conditions linked to insulin resistance as a component of obesity and metabolic syndrome, including hypertension (77%), hyperlipidemia (53%), and diabetes mellitus (45%).^{12,14,19} The metabolic abnormalities of overly acidic urine and hyperoxaluria lead to elevations in UA and CaOx supersaturation and a propensity to form pure and mixed UA stones.^{20,21}

Despite their high preponderance of risk factors, UASF compliant with medical therapy had reduced stone recurrence sizes and need for additional stone procedures compared to nonadherents. Nonetheless, the most concerning finding from our study was that, regardless of therapy or stone subtype, 32% of our UA population had a new stone recurrence at 2 years. Our routine practice is to prescribe 20 meq BID to all UASF for long-term prevention, titrating urine pH to >6 only when patients have a CT recurrence. It is possible that this standard preventive alkaline dose (~40 meq/day) was inadequate for a urine pH response. Although UA urinary supersaturation decreased almost 50%, adherents did not have statistically significant increases ($P = .06$) in 24-hour urine pH compared to nonadherents. We did not ask patients to use pH paper to achieve steady state urine pH targets like we do for those undergoing acute UA dissolution therapy. This was due to a perceived bias that urine pH strips are too labor-intensive for more than a 2-3 month period and are inadequate to represent 24-hour urine pH. Our data suggest a need to development either alternative strategies that overcome this alkalization issue or higher dosing regimens that promote patient compliance. According to the EAU guidelines for medical management of UA stones, long-term replacement should consist of “alkaline citrate 9-12 grams/day” (~80-110 meq/day) for a “prevention urine pH of 6.2-6.8.” Although this would certainly be ideal, UASF are notoriously resistant to urinary alkalization,²² and very few patients can tolerate 10-14 potassium citrate pills daily for more than a few weeks. AUA prevention guidelines are much less prescriptive, calling for replacement “. . .tailored to each individual in order to raise urine pH to an optimal level (Expert Opinion).”¹⁶ We plan to use our data to more aggressively titrate alkaline therapy to a higher urine pH in order to improve medical prevention benefits.²³ We will also offer pH paper to interested patients who wish to self-monitor urinary pH until a steady state is achieved. Ultimately, it is up to the treating physician and patient to strike a balance between pill number, compliance, and desired clinical outcome.

In addition to dose, there may be other explanations for the similar rate of stone recurrence in our adherent and nonadherent patients. First, our nonadherent group had almost 1 year less follow-up than our adherents, and thus, we may have underestimated recurrences in our

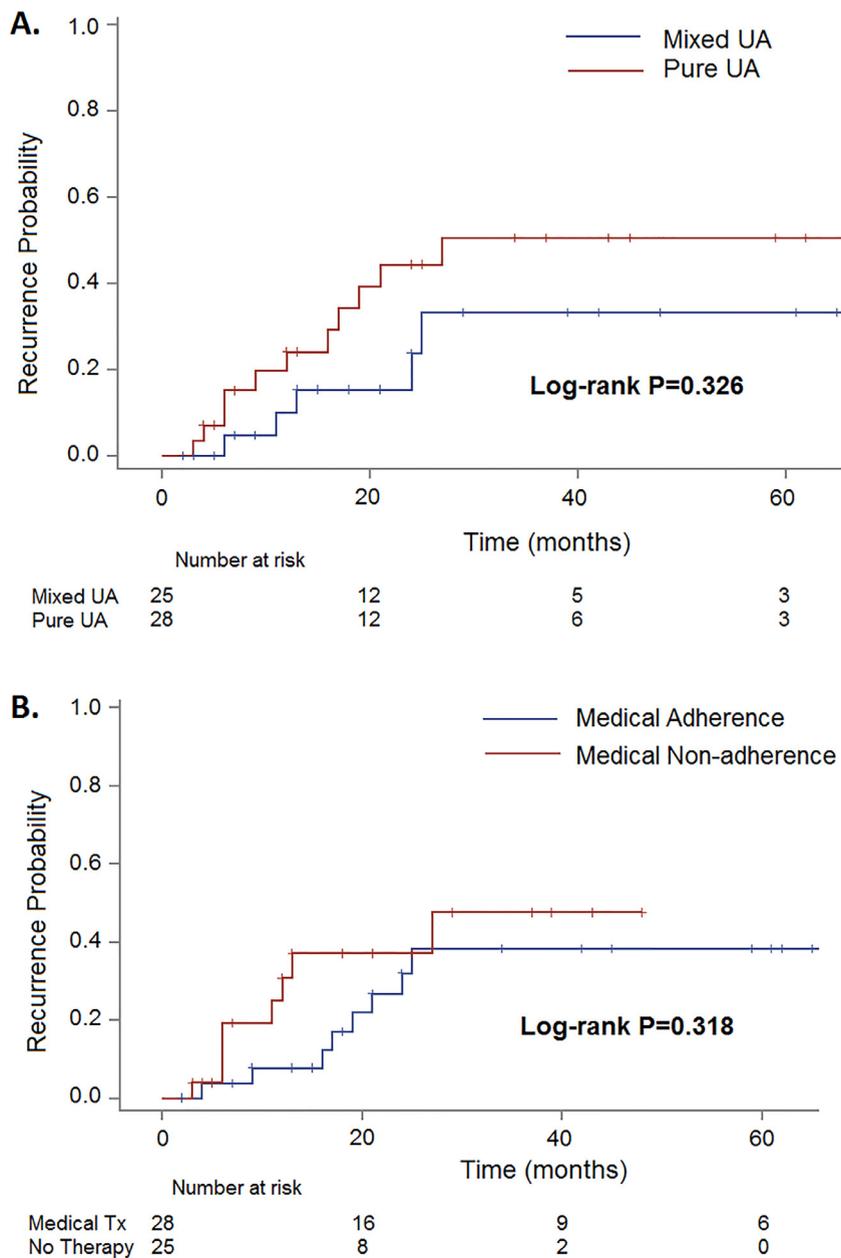


Figure 1. (A) Kaplan-Meier failure curve for patients with uric acid stones stratified by mixed (blue) or pure (red) UA stone type. Although a trend difference was visible by plot, recurrence rates were not significantly different by log-rank test ($P = .326$). (B) Kaplan-Meier failure curve for patients with uric acid stones stratified by medical therapy adherent (blue) or nonadherent (red) with similar recurrence rates noted between both groups ($P = .318$). (Color version available online.)

nonadherents. Conversely, we may have selected out an extremely high-risk group in our adherents, since almost a third of them required both alkalinization and allopurinol therapy. Perhaps this group was more adherent to medical therapy because they had experienced so many previous stone events, and the comparison to a nonadherent group was biased. It could also be that our prescribed citrate dose was adequate but our adherent patients were nonresponders. In a series of 125 mixed stone formers who were prescribed citrate salts and reported adherence with medication, less than half of these compliant individuals were

able to raise his/her urine pH or citrate levels to a normal range, even when taking the prescribed dose.²⁴

Another possibility is that our “adherent” patients were not as compliant with their medication as reported and, consequently, never received the full benefit of medical therapy. We doubt this occurred in our population since adherents had significantly higher 24-hour urinary concentrations of potassium (an acceptable surrogate for potassium citrate use) vs nonadherents. However, medical adherence, particularly for stone prevention, can be challenging for many patients who lack the motivation,

finances, and/or discipline.²⁵ Indeed, 21% (11/53) of our cohort discontinued prescribed therapy due to either side effects or cost and could not be convinced to start second-line medication. Although retrospective, our data reflects the “real-world” problems that arise when patients with complex medical conditions are started on lifelong alkaline therapy. In a review of all randomized controlled trials using citrate for calcium oxalate stone prevention, about 20% of patients over 27 months' time developed upper GI disturbance and/or rash leading to a four-fold increase in drop-out compared to placebo.²⁶ Even more disturbing, Dauw et al searched claims data and found that nearly 50% of patients prescribed pharmacological prevention therapies for kidney stones were nonadherent, particularly those on potassium citrate.²⁷ These numbers correspond well to our 25% rate of patient medication disinterest and 21% rate of citrate discontinuation over our study course. Overall, it is possible that limitations in follow-up and combinations of medication dose, adherence, and/or treatment response confounded our study results.

These limitations and complexities notwithstanding, there are positives to our study. Our adherent patients had smaller stone recurrence size ($P = .02$) and less rates of intervention over time ($P < .01$) than our nonadherent patients. Although speculative, these clinical differences may have been due to the non-pH dependent, protective effects of citrate. In vitro, potassium citrate forms soluble mineral complexes and inhibits crystal growth/binding. It also has the clinical ability to reduce stone recurrence and urinary mineral supersaturation.²⁸⁻³⁰

In obese UASF, clinicians must customize potassium citrate therapy for each individual in order to strike the right balance of urine pH, stone prevention, cost, and side effect tolerability. Because the underpinnings of UA stone formation are complex and linked to obesity and diabetes, perhaps a multipronged treatment strategy that comprehensively targets weight loss, insulin resistance, and urine pH while providing more patient-friendly medications may be the key to more effective and personalized UA disease therapies in the future.

CONCLUSION

Despite similar urine pH and stone recurrence rates, UASF adherent to medical therapy had smaller stone recurrence size and reduced rates of surgical intervention relative to UASF not on active treatment. In order to improve delivery of care to this challenging population, better prevention strategies that take into account dietary factors, barriers to medication adherence, and dose titration are sorely needed.

References

1. Abou-Elela A. Epidemiology, pathophysiology, and management of uric acid urolithiasis: a narrative review. *J Adv Res.* 2017;8:513–527.
2. Trinchieri A, Montanari E. Prevalence of renal uric acid stones in the adult. *Urolithiasis.* 2017;45:553–562.

3. Siener R, Hesse A. The effect of a vegetarian and different omnivorous diets on urinary risk factors for uric acid stone formation. *Eur J Nutr.* 2003;42:332–337.
4. Trinchieri A, Esposito N, Castelnuovo C. Dissolution of radiolucent renal stones by oral alkalization with potassium citrate/potassium bicarbonate. *Arch Ital Urol Androl.* 2009;81:188–191.
5. Petritsch PH. Uric acid calculi: results of conservative treatment. *Urology.* 1977;10:536–538.
6. Honda M, Yamamoto K, Momohara C, Komori K, Takada T, Fujioka H. [Oral chemolysis of uric acid stones]. *Hinyokika Kyo.* 2003;49:307–310.
7. Sinha M, Prabhu K, Venkatesh P, Krishnamoorthy V. Results of urinary dissolution therapy for radiolucent calculi. *Int Braz J Urol.* 2013;39:103–107.
8. Elsayy AA, Elshal AM, El-Nahas AR, Elbaset MA, Farag H, Sho-keir AA. Can we predict the outcome of oral dissolution therapy for radiolucent renal calculi? A prospective study. *J Urol.* 2019;201:350–357.
9. Moran ME, Abrahams HM, Burday DE, Greene TD. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. *Urology.* 2002;59:206–210.
10. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int.* 1986;30:422–428.
11. Rodman JS. Prophylaxis of uric acid stones with alternate day doses of alkaline potassium salts. *J Urol.* 1991;145:97–99.
12. Trinchieri A, Montanari E. Biochemical and dietary factors of uric acid stone formation. *Urolithiasis.* 2018;46:167–172.
13. Reichard C, Gill BC, Sarkissian C, De S, Monga M. 100% uric acid stone formers: what makes them different? *Urology.* 2015;85:296–298.
14. Friedlander JI, Moreira DM, Hartman C, Elsamra SE, Smith AD, Okeke Z. Comparison of the metabolic profile of mixed calcium oxalate/uric acid stone formers to that of pure calcium oxalate and pure uric acid stone formers. *Urology.* 2014;84:289–294.
15. Abate N, Chandalia M, Cabo-Chan Jr. AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int.* 2004;65:386–392.
16. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192:316–324.
17. Ennis JL, Asplin JR. The role of the 24-h urine collection in the management of nephrolithiasis. *Int J Surg.* 2016;36:633–637.
18. Shekarriz B, Stoller ML. Uric acid nephrolithiasis: current concepts and controversies. *J Urol.* 2002;168:1307–1314.
19. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. *JRSM Cardiovasc Dis.* 2016;5:2048004016633371.
20. Eisner BH, Porten SP, Bechis SK, Stoller ML. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. *J Urol.* 2010;183:2244–2248.
21. Torricelli FC, De SK, Gebreselassie S, Li I, Sarkissian C, Monga M. Dyslipidemia and kidney stone risk. *J Urol.* 2014;191:667–672.
22. Bobulescu IA, Park SK, Xu LHR, et al. Net acid excretion and urinary organic anions in idiopathic uric acid nephrolithiasis. *Clin J Am Soc Nephrol.* 2019;14:411–420.
23. Raffin EP, Penniston KL, Antonelli JA, et al. The effect of thiazide and potassium citrate use on the health related quality of life of patients with urolithiasis. *J Urol.* 2018;200:1290–1294.
24. Astroza GM, Neisius A, Tsivian M, Preminger GM, Lipkin ME. Treatment response in patients with stones, and low urinary pH and hypocitraturia stratified by body mass index. *J Urol.* 2016;195:653–657.
25. Rodman JS. Intermittent versus continuous alkaline therapy for uric acid stones and ureteral stones of uncertain composition. *Urology.* 2002;60:378–382.
26. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev.* 2015: CD010057.

27. Dauw CA, Yi Y, Bierlein MJ, et al. Medication nonadherence and effectiveness of preventive pharmacological therapy for kidney stones. *J Urol*. 2016;195:648–652.
28. Lieske JC, Leonard R, Toback FG. Adhesion of calcium oxalate monohydrate crystals to renal epithelial cells is inhibited by specific anions. *Am J Physiol*. 1995;268:F604–F612.
29. Shang YF, Xu M, Zhang GN, Ouyang JM. Concave urinary crystallines: direct evidence of calcium oxalate crystals dissolution by citrate in vivo. *Bioinorg Chem Appl*. 2013;2013:637617.
30. Pak CY, Fuller C, Sakhaee K, Preminger GM, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol*. 1985;134:11–19.