Kidney Medicine

Protein Intake and High Uric Acid Stone Risk

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Rationale & Objective: We evaluated the metabolic differences between pure and impure uric acid stone formers in this retrospective study of uric acid kidney stone formers diagnosed between 1996 and 2021.

Study Design: Demographics and medical history were compared by χ^2 tests. Twenty-four-hour urine chemistries were compared using logistic regressions while controlling for demographics and comorbid conditions.

Setting & Participants: Patients from Yale Urology and Nephrology Clinics with a documented kidney stone analysis containing uric acid were included. In total, 4,294 kidney stone formers had a stone analysis, and 722 (16.8%) contained uric acid. Patients with all stone analyses ≥ 50% uric acid were allocated to the pure group, while patients with ≥1 stone analysis <50% uric acid were allocated to the impure group.

Results: Among kidney stone formers, the prevalence of uric acid nephrolithiasis was 16.8%. Pure uric acid stone formers were more likely to be older, heavier, and were 1.5 times more likely to have chronic kidney disease. When controlling for age, sex, race, ethnicity, and body mass index, pure uric acid stone formers had lower urinary pH and lower urine citrate normalized for creatinine. Additionally, they had a higher protein catabolic rate, urine urea nitrogen, and urine sulfur normalized for creatinine, all markers of dietary protein intake. These findings persisted after controlling for chronic kidney disease.

Limitations: This is a retrospective study from a single center.

Conclusions: Pure uric acid stone formation is more common with diminished kidney function; however, after controlling for kidney function, pure uric acid stone formation is associated with protein intake, suggesting that modifying protein intake may reduce risk.

Uric acid (UA) stones account for approximately 10% of all kidney stones.[1,2] These stones form in a low urinary pH, which favors UA precipitation.[3] UA stone formation is strongly associated with metabolic syndrome. Insulin resistance, a key hallmark of metabolic syndrome, impairs renal ammoniagenesis and lowers urinary pH by increasing renal proton secretion.[4-6]

Obesity is more common among UA stone formers, and urinary pH is inversely correlated with body mass index (BMI).[7] UA stone formers have a lower estimated glomerular filtration rate (eGFR) than non-stone formers.[8-11] It is known that low urinary pH is linked to higher animal protein intake and UA stone formers report higher dietary protein intake compared to non-stone formers.[12-14] Although dietary guidelines for calcium containing stones are evidence-based, guidelines for UA stones are based on expert opinion in part due to the relative lack of large studies in UA stone formers.[15]

We provide a definition for pure UA stone formers and provide a comprehensive assessment of the metabolic and biochemical profile of these stone formers. We hypothesize that factors associated with protein intake rather than serum or urine UA or kidney function are predominantly driving UA stone formation.

METHODS

Institutional Review Board approval was obtained for this retrospective study of 10,044 patients seen in the Yale Urology and Nephrology Clinics and diagnosed with kidney stones between May 1996 and April 2021. Clinical data were acquired using an automated Joint Data Analytics Team query of our institutional electronic health record and supplemented by manual chart review. Patients were included if they had ≥1 stone chemical analysis with any UA content. We extracted demographic, medical history, 24-hour urine chemistry, blood chemistry, and BMI measurements. All data were stored in a secure, Health Insurance Portability and Accountability Act compliant, REDCap electronic database hosted at Yale School of Medicine. Medical and surgical histories were assigned based on *International Classification of Diseases Ninth* and *Tenth Revision* codes and manual chart review. We calculated age of diagnosis by subtracting the year of the patient's first stone pathology by their year of birth. Stone analyses were performed by Quest Laboratories and ARUP Laboratories by infrared spectroscopy and quantitative polarizing microscopy. We analyzed the earliest serum chemistry, BMI measurement, and 24-hour urine chemistry available per patient. The median interval between 24-hour urine collection and stone analysis was 175 days. Some 24-hour urine parameters were normalized by dividing by 24-hour urine creatinine before statistical analysis.

Among 4,294 patients with a documented stone chemical analysis, 722 (16.8%) had a UA component, and 317 (43.9%) completed a 24-hour urine chemistry; 79.8% were analyzed by Litholink Corporation (a LabCorp Company), 15.8% by Quest Diagnostics, and 4.4% were analyzed by other laboratories. Because each laboratory uses a unique supersaturation calculation algorithm, only

supersaturation data from Litholink were included in this analysis.

In total, 712 (98.6%) UA stone formers had blood chemistries, and all patients had a BMI measurement. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation was used to calculate GFR.

Statistical Analysis and Models

Descriptive statistics were calculated for participants by type of UA stone former. Mean and standard deviation, or median and interquartile range, are presented for continuous variables depending on whether they are normally distributed. Frequency and percentages are used to describe categorical variables. Analysis of variance or Kruskal-Wallis tests were used to compare serum and urine chemistries in the highly pure (HP), moderately high pure (MHP), and moderately pure (MP) groups. t tests or Mann-Whitney U tests were used to compare the moderately impure (MI) and highly impure (HI) groups. Multivariable logistic regression was used to individually test for association of various comorbid conditions, serum chemistries, and urine chemistry variables with stone group. All models compared pure UA stone formers to impure UA stone formers and were adjusted for age of diagnosis, BMI, race, sex, and ethnicity. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and GraphPad Prism version 9 (GraphPad Software). P values < 0.05 were considered statistically significant for all analyses.

Stone Group Classification

The 722 UA stone formers were categorized into groups based on UA purity as done by others.[16] HP UA stone formers were defined as having all stone analyses with 100% UA, MP UA stone formers were defined as having all stone analyses with 50%-99% UA, and HI UA stone formers were defined as having all stone analyses with <50% UA. If a patient had ≥1 pathologies with 100% UA and ≥1 stone pathologies with 50%-99% UA, they were classified as MHP UA stone formers. Finally, if a patient had ≥1 stone analysis 50%-99% UA and ≥1 stone analysis <50% UA, they were categorized as MI UA stone formers. HP, MHP, and MP patients pure comprise the Pure group, while MI and HI patients were in the Impure group, based on previous studies that validated 50% UA as a cutoff.[16,17]

Some stone chemical analyses did not provide a percentage of components. In these cases, stone pathologies reporting only one existing predominant stone component of UA were designated as MP (50%-99%) UA stone formers. A total of 14 patients were excluded from analysis due to insufficient information on the UA component of their stone pathology (10 [1.4%] patients) or an inability to classify into a subgroup due the presence of both a 100% UA stone and a <50% UA stone (4 [0.4%] patients) (Fig 1).

Among 722 UA stone formers, over half (n = 406, 56.2%) were identified as MP (50%-99%) UA stone formers, and nearly 1 in 5 (n = 130, 18.0%) were identified as HI (<50%) UA stone formers. Less than 10% of cases met the criteria for HP (n = 57, 7.9%), MHP (n = 49, 6.8%), or MI UA stone formers (n = 66, 9.1%). Analysis of the urine and serum data (Tables S1 and S2) showed similarities among the HP, MHP, and MP (all stone analyzes >50%) UA stone formers, allowing their reclassification as a cohort of "Pure" UA stone formers (n = 512) and the MI and HI UA stone formers as a cohort of "Impure" (all stone analysis <50%) UA stone formers (n = 196). All patients were included in multivariate analysis. Model 1 controlled for age, sex, ethnicity, and BMI. Model 2 included eGFR, and Model 3 included serum UA, urine calcium, and urine UA.

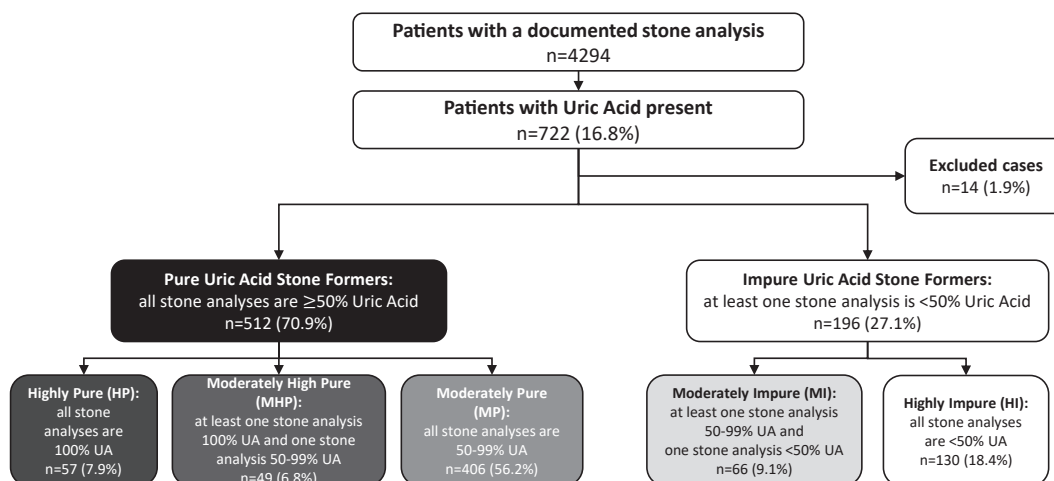**Figure 1.** Flowchart of stone formers for cohort inclusion. Of 4,294 composition confirmed kidney stone patients, 722 (16.8%) had a uric acid stone present. Of these, 512 (70.9%) were defined as Pure uric acid stone formers and 196 (29.1%), were identified as Impure uric acid stone formers. Abbreviations: HI, highly impure; HP, highly pure; MHP, moderately high pure; MI, moderately impure; MP, moderately pure; UA, uric acid.

RESULTS

Pure UA stone formers were older (64 vs 61.5 years; P = 0.008) with a higher BMI (31.6 vs 30.0 kg/m^2; P = 0.021) than impure UA stone formers at baseline. Although UA stone formers were predominately males, there was no difference between pure and impure groups (68% males and 32% females vs 65% males and 35% females, respectively; P = 0.39). There were no significant differences in race or ethnicity.

Pure UA stone formers were 54% more likely to have CKD (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.04-2.27; P = 0.030) than impure UA stone formers, and pure UA stone formers were more likely to have a lower eGFR than impure UA stone formers (75.58 ± 1.12 vs 84.21 ± 2.26 mL/min/1.73 m^2; P = 0.003) when adjusted for age, sex, race, ethnicity, and BMI (Table 1).

There were no additional statistically significant differences in other comorbid conditions between pure and impure UA stone formers despite an increase in gout (OR, 1.53; 95% CI, 0.86-2.71; P = 0.15) and hypertension (OR, 1.17; 95% CI, 0.83-1.65; P = 0.08) in pure UA stone formers. Due to insufficient case numbers, we could not assess for differences in hyperparathyroidism (Table 1).

As the proportional composition of UA decreased, we observed an increase in mean eGFR from 72 mL/min/1.73 m^2 in HP UA stone formers to 87 mL/min/1.73 m^2 in HI UA stone formers (Fig 2). This gradual increase in mean eGFR did not influence urinary supersaturations, as pure and impure UA stone formers did not demonstrate a statistically significant difference in supersaturations for UA (95% CI, 0.89-1.68; P = 0.22) despite observed statistically significant differences in calcium oxalate and calcium phosphate supersaturations (Table 2).

We completed 3 multivariate analyses to evaluate 24-hour urine difference by UA purity while controlling for demographics, BMI, and kidney function. Urine parameters were analyzed in absolute form and normalized to creatinine, where applicable. Model 1 controlled for age, sex, race, ethnicity, and BMI. Model 2 controlled for those parameters and eGFR. Model 3 additionally controlled for urine calcium, serum UA, and urine UA. We present the findings of Models 1 and 2 in Table 2. Figure 3 shows Model 2 and 3.

In Model 1, pure UA stones were associated with lower urinary pH (OR 0.94, 95% CI 0.89-0.98, P = 0.01) and absolute urine calcium; and greater absolute urine urea nitrogen (UUN) and absolute urine sulfate (Table 2). Additionally, pure UA stone formers had lower normalized calcium (OR, 0.94; 95% CI, 0.92-0.96; P < 0.001) and normalized citrate (OR, 0.87; 95% CI, 0.77-0.98; P = 0.02); and greater normalized UUN (OR, 1.21; 95% CI, 1.03-1.42; P = 0.02), normalized urine sulfate (OR, 1.10; 95% CI, 1.00-1.20; P = 0.04), and protein catabolic rate (PCR) (OR 1.22, 95% CI 1.07-1.38, P = 0.003).

In Model 2, when controlling for eGFR, UA stone formers still exhibited lower urine pH (OR, 0.94; 95% CI, 0.89-0.99; P = 0.01), absolute calcium (OR, 0.79; 95% CI, 0.69-0.90; P < 0.001), normalized calcium (OR, 0.94; 95% CI, 0.92-0.96; P < 0.001), and normalized citrate (OR, 0.88; 95% CI, 0.77-0.99; P = 0.04) while exhibiting greater urine PCR (OR, 1.06; 95% CI, 1.02-1.10; P = 0.003), absolute UUN (OR, 1.15; 95% CI, 1.07-1.24; P < 0.001), normalized UUN (OR, 1.20; 95% CI, 1.02-1.42; P = 0.03), and absolute sulfate (OR, 1.02; 95% CI, 1.01-1.04; P = 0.003).

In Model 2, the adjusted odds for pure UA stone formation were higher by 20% for every 1 g/g increase in normalized UUN and 6% higher for every 0.1 g/kg/d increase in PCR. Moreover, the adjusted odds were lower by 6% for every 100 mg/g increase in normalized urine citrate and by 6% for every 0.1 unit increase in urine pH.

Model 3 (Fig 3B) shows that the odds of a pure UA stone related to pH, UUN (absolute and normalized), and PCR persist, even when controlling serum and urine UA and urine calcium.

DISCUSSION

In this retrospective study, we present the largest cohort of UA stone formers studied to comprehensively characterize metabolic and biochemical features that define "pure" UA stone formers and elucidate those lithogenic risk factors for UA stone formation. A previous retrospective analysis defined a UA stone by a composition of >50% UA; however, the biochemical characterization of the stone former was limited to 24-hour urine assessment of volume, sodium, calcium, oxalate, UA, citrate, and pH.[17] Those investigators observed UA stone formers to have clinically significant lower urinary pH, UA, and calcium. This same biochemical characterization was applied with serum UA data on a larger retrospective cohort to characterize a pure UA stone former with a 100% UA stone versus a stone former with a 10%-20% UA stone composition, with only urine pH and serum UA levels clinically significant to define a pure UA stone former.[16]

Our cohort of UA stone formers, more than twice the size of prior observational cohorts, allows comprehensive retrospective biochemical characterization of UA stone formers. We confirm that pure UA stone formers are defined by those patients with a UA stone composition >50%, and we stratified those individuals by a classification of HP UA stone formers, MHP UA stone formers, and MP UA stone formers based on percentage of UA stone composition. We demonstrated that 24-hour urine chemistries in absolute or normalized values did not differ significantly between the pure UA stone former subgroups. Moreover, we demonstrated that serum chemistry data, including UA, did not differ significantly among the subgroups. Therefore, we posit that a "pure" UA stone former is biochemically defined, based on serum and urine chemistries, as a stone former producing stones with a UA composition >50%. Likewise, an "impure" UA stone former may be clinically defined as a stone former with a present UA stone component of <50%. Given the clinically

Table 1. Baseline Characteristics of Uric Acid Stone Formers

Demographics	Pure (n = 512)	Impure (n = 196)	*P*-value	Odds ratio (95% CI)	Hazard plot
Median age at diagnosis, y (IQR)	64.0 (55.0-72.0)	61.5 (52.0-70.0)	0.008[a]	-	-
Median BMI, kg/m² (IQR)	31.6 (27.8-36.3)	30.0 (26.2-36.1)	0.021[a]	-	-
Race			0.13		
African American	41 (8%)	8 (4%)		-	-
White	444 (87%)	174 (89%)		-	-
Other	27 (5%)	14 (7%)		-	-
Ethnicity			0.12		
Hispanic	24 (5%)	15 (8%)		-	-
Not Hispanic	488 (95%)	181 (92%)		-	-
Sex			0.39		
Female	163 (32%)	69 (35%)		-	-
Male	349 (68%)	127 (65%)		-	-
Medical History					
Hyperthyroidism	12 (2%)	1 (1%)	0.17	4.12 (0.53-32.79)	-
Sarcoidosis	7 (1%)	2 (2%)	0.68	0.84 (0.21-3.30)	-
Chronic kidney disease	196 (38%)	56 (29%)	0.03[a]	1.51 (1.04-2.27)	
Gout	69 (13%)	17 (9%)	0.15	1.53 (0.86-2.71)	
Recurrent urinary tract Infections	70 (14%)	36 (18%)	0.07	0.65 (0.41-1.47)	
Coronary artery disease	162 (32%)	56 (29%)	0.67	0.92 (0.62-1.34)	
Diabetes mellitus	249 (49%)	90 (46%)	0.65	0.92 (0.65-1.31	
Hypertension	271 (53%)	88 (45%)	0.08	1.17 (0.83-1.65)	
Hyperparathyroidism	24 (5%)	8 (4%)	0.85	1.08 (0.46-2.54)	
Obstructive sleep apnea	147 (29%)	52 (27%)	0.93	0.98 (0.66-1.47)	
Migraines	18 (4%)	12 (6%)	0.35	0.69 (0.32-1.50)	
Bowel disease	33 (6%)	22 (11%)	0.10	0.62 (0.34-1.10)	

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Uric Acid Stone Formers

Demographics			Pure (n = 512)	Impure (n = 196)	*P*-value	Odds ratio (95% CI)	Hazard plot
Blood Chemistries	Units	N					
Parathyroid hormone, median (IQR)	pg/mL	259	52.4 (34.7-71.6)	44.2 (30.0-57.0)	0.56	1.00 (1.00-1.00)	
HgA1C, median (IQR)	%	456	6.3 (5.7-7.6)	6.2 (5.8-7.3)	0.53	1.02 (0.95-1.10)	
Sodium, median (IQR)	mmol/L	697	139.0 (137.0-141.0)	140.0 (138.0-141.0)	0.81	0.99 (0.94-1.05)	
Potassium, median (IQR)	mmol/L	698	4.2 (3.9-4.5)	4.2 (3.9-4.5)	0.31	0.84 (0.59-1.19)	
Bicarbonate, median (IQR)	mmol/L	697	24.3 (22.5-26.0)	24.5 (22.5-26.6)	0.24	0.97 (0.91-1.02)	
BUN, median (IQR)	mg/dL	697	19.0 (16.0-24.0)	17.0 (14.0-22.0)	0.06	1.02 (1.00-1.05)	
Creatinine, median (IQR)	mg/dL	699	1.0 (0.9-1.2)	0.9 (0.7-1.2)	0.73	0.97 (0.81-1.16)	
eGFR, median (IQR)	mL/min/1.73 m^2	699	77.8 (60.5-94.0)	87.4 (72.1-100.8)	0.003[a]	0.91 (0.85-0.97)	
Calcium, mean (SD)	mmol/L	697	9.35 (0.49)	9.31 (0.57)	0.16	1.26 (0.91-1.75)	
Magnesium, median (IQR)	mg/dL	494	1.9 (1.7-2.1)	1.9 (1.7-2.0)	0.59	1.18 (0.65-2.12)	
Phosphorus, median (IQR)	mg/dL	439	3.4 (2.9-3.8)	3.3 (2.9-3.7)	0.17	0.87 (0.71-1.06)	
Uric acid, median (IQR)	mg/dL	374	6.5 (5.2-7.7)	5.9 (4.8-7.0)	0.06	1.12 (0.99-1.26)	

Note: Age of diagnosis and BMI assessed by unpaired *t* test. Race, ethnicity, and sex assessed by χ^2 tests. Medical history and blood chemistries assessed by logistic regression. Odds ratios and *P* values adjusted for age, sex, race, ethnicity, and BMI. Hazard plot is not provided for hyperthyroidism and sarcoidosis due to insufficient case numbers. CKD and hyperparathyroidism patients were diagnosed by ICD-10 codes.
Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; ICD-10, *International Classification of Diseases, Tenth Revision*; IQR, interquartile range.
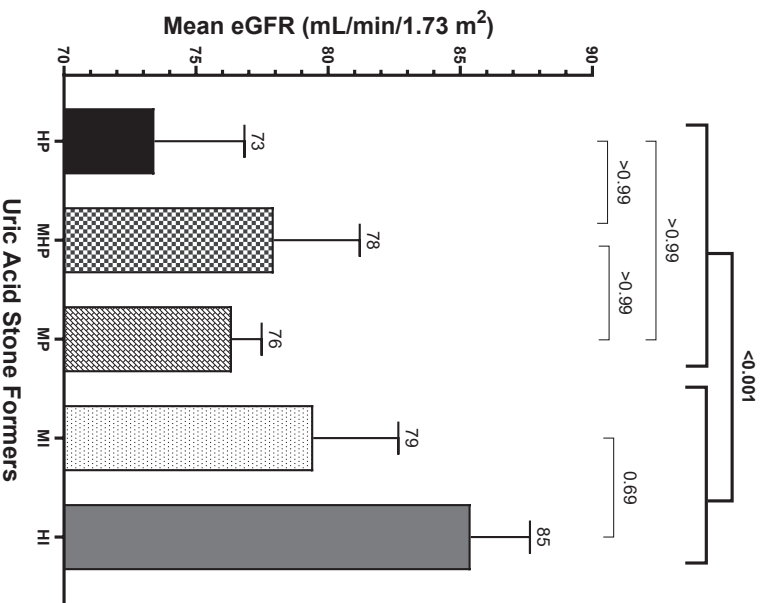[a]Indicates *P* value < 0.05.

Figure 2. Estimated glomerular filtration rate (eGFR) declines with increasing uric acid purity. Uric acid stone formers within the 3 classes had differing mean eGFR, with significant differences between the pure uric acid stone formers (including the highly pure [HP], moderately high pure [MHP], and moderately pure [MP]) and the impure uric acid stone formers (including the moderately impure [MI], and highly impure [HI]). *P* values calculated by Kruskal-Wallis and unpaired *t* tests.

significant differences in this group with respect to urine pH, calcium, and supersaturations of calcium salts, and nearly significant differences in serum UA (0.055) and urine UA saturation (0.08), we adjusted for urine UA, serum UA, and urine calcium in Model 3.

UA stones are first and foremost a consequence of an acidic urine, with metabolic syndrome (obesity, diabetes mellitus), reduced eGFR, and high protein intake the primary drivers for urinary acidification in the absence of gastrointestinal losses. In our cohort, the prevalence of bowel disease (either bowel surgery or inflammatory disease) was 6%-11%, with no difference in serum bicarbonate, urinary oxalate (a marker for secondary hyperoxaluria), or absolute urinary citrate. Normalized urinary citrate was higher in the impure group, with a slightly higher rate of bowel disease, arguing against gastrointestinal loss as a major factor in our findings. We also did not find a higher rate of gout, hypertension, or diabetes mellitus between groups.

Consistent with prior observations, we found that pure UA stone formers were significantly likely to be older and more obese. In each group of stone formers, we found more men than women affected, consistent with prior

Table 2. Urinary Lithogenic Risk Factors for Uric Acid Stone Formation

Urine Parameter	Units	Pure	Impure	Model 1 Odds Ratio (95% CI)	*P*	Model 2 Odds Ratio (95% CI)	*P*
Volume, median (IQR)	L	1.9 (1.4-2.4)	1.6 (1.3-2.1)	1.06 (1.02-1.10)	0.004[a]	1.21 (1.07-1.38)	0.005[a]
pH, median (IQR)	n/a	5.4 (5.2-5.7)	5.7 (5.4-6.1)	0.94 (0.89-0.984)	0.01[a]	0.94 (0.89-0.99)	0.01[a]
Creatinine, mean (SD)	Mg	1,790.70 (616.20)	1,655.93 (590.09)	1.10 (1.03-1.17)	0.003[a]	1.10 (1.03-1.17)	0.003[a]
SS calcium oxalate, median (IQR)	n/a	3.8 (2.2-5.8)	6.4 (3.5-9.0)	0.81 (0.73-0.89)	<0.001[a]	0.81 (0.74-0.90)	<0.001[a]
SS calcium phosphate, median (IQR)	n/a	0.2 (0.1-0.4)	0.6 (0.2-1.0)	0.22 (0.13-0.42)	<0.001[a]	0.25 (0.14-0.45)	<0.001[a]
SS uric acid, median (IQR)	n/a	1.5 (1.0-2.2)	1.4 (0.5-2.3)	1.23 (0.89-1.69)	0.21	1.21 (0.88-1.66)	0.25
Protein catabolic rate, median (IQR)	g/kg	1.0 (0.9-1.2)	0.9 (0.8-1.0)	1.22 (1.07-1.38)	0.003[a]	1.06 (1.02-1.10)	0.003[a]
Osmolality, mean (SD)	n/a	512.26 (180.45)	477.95 (185.21)	1.00 (1.00-1.00)	0.11	1.00 (1.00-1.00)	0.11
Calcium, median (IQR)	mg	125.0 (61.8-189.0)	187.5 (97.1-279.5)	0.78 (0.69-0.89)	<0.001[a]	0.79 (0.69-0.90)	<0.001[a]
Calcium, normalized median (IQR)	mg/g	69.0 (39.0-101.6)	114.7 (63.0-164.1)	0.94 (0.92-0.96)	<0.001[a]	0.94 (0.92-0.91)	<0.001[a]
Uric acid, mean (SD)	g	0.63 (0.28)	0.62 (0.26)	1.56 (0.57-4.35)	0.40	1.67 (0.60-4.68)	0.33
Uric acid, normalized mean (SD)	g/g	365.23 (136.56)	392.01 (147.05)	1.00 (1.00-1.00)	0.95	1.00 (1.00-1.00)	0.13
Citrate, median (IQR)	mg	506.0 (263.0-722.0)	567.6 (272.0-942.7)	1.00 (1.00-1.00)	0.11	1.00 (1.00 - 1.00)	0.17
Citrate, normalized median (IQR)	mg/g	287.7 (153.9-425.8)	335.3 (175.4-512.3)	0.87 (0.77-0.98)	0.02[a]	0.88 (0.77-0.99)	0.04[a]
Ammonium, median (IQR)	mmol	34.6 (24.9-47.5)	31.5 (23.0-44.0)	1.02 (1.00-1.04)	0.06	1.02 (1.00-1.04)	0.05[a]
Ammonium, normalized median (IQR)	mmol/g	19.4 (15.3-23.8)	20.7 (26.3-49.1)	0.99 (0.97-1.02)	0.46	0.99 (0.97-1.02)	0.52
Sulfur, median (IQR)	mEq	44.2 (28.4-59.5)	34.0 (26.3-49.1)	1.02 (1.01-1.04)	0.002[a]	1.02 (1.01-1.04)	0.003[a]
Sulfur, normalized mean (SD)	mEq/g	24.87 (9.44)	22.43 (80.4)	1.10 (1.00-1.20)	0.04[a]	1.09 (1.00-1.20)	0.06
UUN, median (IQR)	mg	13.2 (10.3-15.7)	10.9 (8.0-13.0)	1.15 (1.07-1.24)	<0.001[a]	1.15 (1.07-1.24)	<0.001[a]
UUN, normalized median (IQR)	mg/g	6.9 (6.1-8.3)	6.5 (5.3-8.0)	1.21 (1.03-1.42)	0.02[a]	1.20 (1.02-1.42)	0.03[a]
Sodium, mean (SD)	mmol	179.33 (77.13)	170.03 (75.82)	1.00 (1.00-1.01)	0.25	1.00 (1.00-1.01)	0.25
Sodium, normalized median (IQR)	mmol/g	97.8 (74.1-125.7)	100.4 (77.9-132.3)	1.00 (0.99-1.00)	0.43	1.00 (0.99-1.00)	0.45
Oxalate, median (IQR)	mg	36.0 (28.8-46.0)	37.6 (26.0-42.4)	1.01 (0.99-1.03)	0.31	1.01 (0.99-1.03)	0.29
Oxalate, normalized median (IQR)	mg/g	20.2 (16.2-26.5)	20.9 (18.2-26.7)	0.99 (0.97-1.02)	0.50	0.99 (0.97-1.02)	0.54
Potassium, median (IQR)	mmol	65.7 (49.5-83.6)	58.0 (45.4-75.0)	1.88 (3.42-1.04)	0.04[a]	2.00 (1.10-3.67)	0.02[a]
Potassium, normalized median (IQR)	mmol/g	37.0 (29.1-46.6)	36.0 (27.3-47.8)	1.00 (0.98-1.02)	0.90	1.00 (0.99-1.02)	0.74
Phosphorus, median (IQR)	g	1.0 (0.7-1.2)	0.9 (0.7-1.1)	2.30 (0.99-5.33)	0.05	2.44 (1.04-5.69)	0.04[a]
Phosphorus, normalized median (IQR)	g/g	543.4 (472.9-651.0)	570.6 (451.9-680.6)	1.00 (1.00-1.00)	0.42	1.00 (1.00-1.00)	0.52
Magnesium, median (IQR)	mmol	88.2 (63.0-120.9)	100.8 (65.8-122.4)	1.00 (0.99-1.01)	0.81	1.00 (0.99-1.01)	0.89
Magnesium, normalized median (IQR)	mmol/g	52.5 (37.2-66.5)	57.0 (47.8-70.7)	0.99 (0.98-1.00)	0.04[a]	0.99 (0.98-1.00)	0.06

Note: Odds ratios and *P* values are adjusted for age, sex, race, ethnicity, and BMI (Model 1) or age, sex, race, ethnicity, BMI, and eGFR (Model 2). Twenty-four hour urine findings are presented in absolute form and normalized to urine creatinine. Risk factors are independent of eGFR.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate, IQR, interquartile range; n/a, not applicable; SD, standard deviation; SS, supersaturated; UUN, urine urea nitrogen.
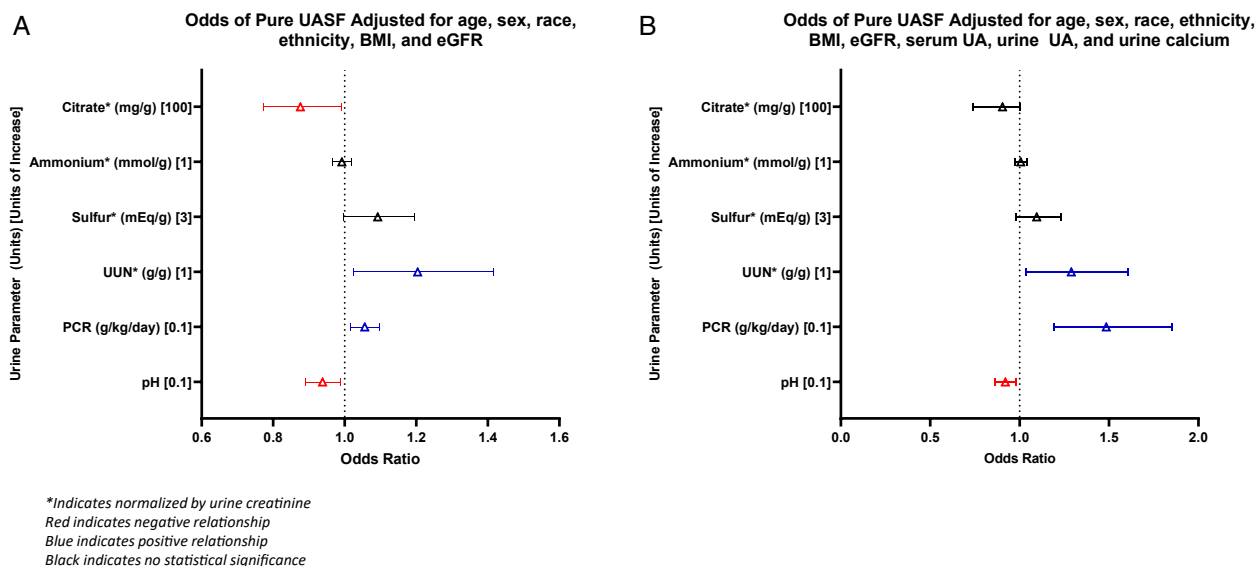[a]Indicates *P* < 0.05.

Figure 3. Protein intake increases risk of pure uric acid stones. The urine variables citrate, ammonium, sulfur, UUN, PCR, and pH all reflect protein intake. An asterisk indicates that the urine variable is normalized to urine creatinine; red indicates negative relationship, and blue indicates positive relationship. Black indicates no statistical significance. (A) In Model 2, citrate, UUN, PCR and pH are significant. (B) In the final model (adjusted in addition for serum UA, urine UA, and urine calcium), UUN, PCR, and pH remain significant. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PCR, protein catabolic rate; UA, uric acid; UASF, uric acid stone former; UUN, urine urea nitrogen.

observations[18] and perhaps due to increased urine pH and citrate in women.[19] We observed pure UA stone formers to have statistically significant lower eGFR than impure UA stone formers and were 1.5 times more likely to have CKD (eGFR <60 mL/min/1.73 m^2) than the impure UA stone formers. These findings are consistent with a prior study demonstrating increased predominant UA stones with stratified declines in eGFR[20] and with our prior findings of the impact of chronic kidney disease on stone risk and stone type.[8] Although gout and hypertension were more likely to be associated with pure UA stone formers,[21,22] these comorbid conditions were not found to be significantly associated with pure UA stone formers in our study. Because of size of our cohort, we were able to evaluate unique variables in metabolic syndrome, such as weight, hypertension, and diabetes mellitus and found an association with protein intake independent of these other contributors to UA stones.

There is expert opinion but no evidence-based dietary guideline for the management of UA nephrolithiasis.[15,23] It has been postulated that UA nephrolithiasis may be managed by lowering intake of animal-based protein to reduce urinary UA excretion.[24] A small study demonstrated that an alkaline diet with a low purine component will increase urinary pH and increase urinary UA excretion.[25] It has also been shown that increased animal-based protein contributes to an increase in dietary acid load, and specifically an increase in sulfur amino acids, which in turn lowers urinary pH and limits urinary UA excretion.[26] We found that pure versus impure UA stone formers have a statistically significant higher protein catabolic rate and

lower pH along with other urinary markers of dietary protein intake—UUN and sulfate—in the presence of a highly acidic urinary environment, even when controlling for other factors such as CKD and obesity. Moreover, we observed that normalized urinary citrate excretion was lower in pure UA stone formers. These clinically significant differences in urinary chemistry profiles persist despite the presence of CKD and suggest that a diet in high animal protein and low in fruits and vegetables may be associated with pure UA stone formation.

In our cohort of stone patients from 1996 to 2021, we observed an increased prevalence of UA stone formation of 16.8%, up from a previously observed 10.2%-10.8% for the prevalent period from January 1996 to June 2016 in the United States.[1] Given the well-established association of UA stone formation with metabolic syndrome,[4] and the increased prevalence of metabolic syndrome among the US population aged greater than or equal to 60 years from 46.6% to 48.6% for the prevalent periods of 2003-2012 and 2011-2016, respectively,[27] one might expect a clinical increase in UA nephrolithiasis.

The retrospective design of our study is a limitation to our findings. The nature of this study design is subject to incomplete data for analysis. A second limitation is the lack of uniformity in laboratory reporting of 24-hour urine chemistries. Urinary supersaturations are calculated and reported in a manner that limits standardization across various laboratories due to the proprietary software chosen for those calculations, and as a result we analyzed data concerning supersaturations from only one laboratory. This lack of uniformity also contributed to

incomplete urinary data concerning protein intake for 50 patients. A third limitation would be the presentation of data as normalized to creatinine. Because we only had single 24-hour collections, we felt that correcting for creatinine would minimize patient errors in sample collection and would also allow better comparison against a range of body types and ages. Importantly, the key findings of a significance of urine UUN was seen with analysis of both the absolute value, and value normalized to creatinine.

In conclusion, our study provides the comprehensive metabolic characterization of UA stone formers to clinically identify pure UA stone formers. In doing so, we observed an increased prevalence of UA stone formers and presented the first body of clinical evidence that UA nephrolithiasis is influenced by dietary protein intake independent of kidney function. These findings provide clinical evidence to support an alkali diet, low in animal-based protein, restricted in sulfur-containing amino acids, and rich in fruits and vegetables as evidence-based dietary guidelines in the management of UA nephrolithiasis. Furthermore, our study provides evidence for the clnical practice of treating pure UA stone formers with citrate-based alkalizing agents.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Blood Chemistries and 24-Hour Urine Parameters by Pure Uric Acid Stone Formers.

Table S2: Blood Chemistries and 24-Hour Urine Parameters by Impure Uric Acid Stone Formers.

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