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Temporal Changes in Kidney Stone Composition and in Risk Factors Predisposing to Stone Formation

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Abstract

Purpose—The prevalence of kidney stones has increased globally in recent decades. However, studies investigating the association between temporal changes in risk of stone formation and stone types are scarce. We investigated temporal changes in stone composition, demographic, serum and urinary parameters of kidney stone formers from 1980–2015.

Materials and Methods—Retrospective analysis of 1516 patients diagnosed with either calcium or uric acid stones at initial visits in a university kidney stone clinic from 1980–2015.

Results—From 1980–2015, the proportion of uric acid stones within all stone formers increased from 7% to 14%. While age and BMI of both uric acid and calcium stone formers increased over time, uric acid stone formers were consistently older, had higher BMI, and lower urinary pH than calcium stone formers. While the proportion of females with stones has increased over time, the increase in female gender was more prominent among calcium stone formers. Urinary pH, phosphorus, oxalate, and sodium increased over time within calcium stone formers, but remained unchanged in uric acid stone formers. After accounting for various parameters of stone risk, the strongest clinical discriminant of uric acid vs. calcium stone was urinary pH. Limitations of this study include the retrospective single center design and available number of patients with stone analysis.

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Disclosure Summary

The authors have nothing to disclose.

Conclusions—From 1980 to 2015, the proportion of uric acid stones increased significantly. With time, there were proportionately more female calcium but not uric acid stone formers. Urinary pH is the most prominent factor distinguishing uric acid from calcium stones.

Key Terms

nephrolithiasis; uric acid stones; calcium stones; urinary pH

Introduction

Over the past decades, the prevalence of kidney stones (KS) has increased significantly in both genders in the United States¹. The greater prevalence of the metabolic syndrome (MS) contributed to this increase in KS², and is predicted to impact its economic burden³. Several pathophysiological models are proposed to explain the causal relationship between obesity, MS, and KS formation⁴⁻⁸. However, studies investigating the association between temporal changes in obesity with KS formation and stone type are limited^{9,10}. Two prior studies showed lower urinary pH, and increasing urinary calcium, phosphorus, and uric acid with time as risk factors for KS^{9,10}.

In this study, we comprehensively examined stone risk profile and clinical variables in KS formers over the past 35 years.

Material and Methods

Study participants

We reviewed charts of 2,166 kidney stone formers (KSF) with available stone analysis who underwent initial metabolic evaluation at their initial visit to University of Texas Southwestern Medical Center (UTSWMC) from 1980 to 2015. Patients were mostly recurrent stone formers who were referred to our Center for further evaluation. Excluded were patients < 21 years old, with primary hyperparathyroidism, cystine stones, infection-related stones, chronic kidney disease stage 4 or higher, renal tubular acidosis, or chronic diarrheal states. This study was approved by the Institutional Review Board at UTSWMC.

Data collection and measurements

Stone analysis was assessed at the Urolithiasis Laboratory in Houston TX, by optical crystallography (Zeiss/Olympus petrographic microscope). Patients with stones > 70% in calcium content were classified as calcium stone formers (CaSF), whereas those with > 30% in uric acid content were classified as uric acid stone formers (UASF)¹¹. Patients were instructed to hold all medications known to influence urinary KS profiles such as alkali treatment, allopurinol, and thiazide diuretics, for two weeks prior to stone analysis. Demographic characteristics recorded at the first visit included age, gender, body mass index (BMI), family history of KS, and personal history of urinary tract infections.

Initial stone visits included two 24-hour urine samples obtained while the subjects continued their *ad-lib* diet. Results of the two 24-hour urine results were averaged. At the completion of urine collections, a fasting venous serum was obtained for calcium (sCa, normal lab

values (NL) 2.18–2.58 mmol/L), uric acid (sUA, NL 180–420 $\mu\text{mol/L}$), glucose (sGlu, NL 3.3–5.8 mmol/L), and triglyceride (sTG, NL <1.7 mmol/L), all measured by autoanalyzer (Synchron CX9ALX; Beckman, Brea, CA). The 24-hour urine samples were analyzed for total volume (uTV), creatinine (uCr) by picric acid method (Olympus AU400), upH (NL 5–7) by digital pH electrode, sodium (uNa, NL 100–260 mmol/day) and potassium (uK, NL 25–100 mmol/day) by flame photometry (BWB Technologies, UK), calcium (uCa, NL 2.5–7.5 mmol/day) by atomic absorption spectrophotometry (Varian-Agilent Technologies, Palo Alto, CA), uric acid (uUA, NL 1.48–4.43 mmol/day) by uricase, oxalate (uOx, NL 0.11–0.46 mmol/day) and sulfate (uSO₄, NL 14–84 mEq/day) by ion chromatography (Dionex, Sunnyvale, CA), citrate (uCit) by citrate lyase (Cobas Fara, Roche, NJ), phosphorus (uP), chloride (uCl, NL 80–250 mmol/day), and ammonium (uNH₄⁺) by the glutamate dehydrogenase. Urinary parameters were also normalized to body weight (BW). The following parameters were calculated: 24-hour creatinine clearance (CrCl), net gastrointestinal absorption of alkali (NGIA)¹², urinary bicarbonate (HCO₃⁻) estimated from upH, and titratable acidity (TA)¹³ for calculation of net acid excretion (NAE): (uNH₄⁺ + TA) - (uCit^{2/3-} + HCO₃⁻), expressed in milliequivalents (mEq).

Statistical analyses

Continuous variables were reported as mean±standard deviation or median [25th, 75th percentile]. Categorical variables were reported as counts or percentages. Baseline characteristics were compared between UASF and CaSF groups by Cochran-Armitage tests and unpaired t-test/non-parametric test for categorical and continuous variables respectively. Two-way analysis of variance (ANOVA) with polynomial trend analysis was implemented for comparing changes in UASF and CaSF over three time periods and assessing the interaction between stone types and among time periods. Results analyzing study year as a continuous variable were similar (not shown). For ANOVA results, the main effect p-values from the F statistics for stone group and time trend within each group are reported separately. As a secondary analysis, stone risk factors were evaluated for single variable and multivariable logistic regression and receiver operating characteristic (ROC) analysis to evaluate their association with stone type (dependent variable UASF with CaSF as the reference group). Internal validation of the logistic model and area under the ROC curve was performed using 5,000 bootstrap replications. P<0.05 was considered statistically significant. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Demographic and biochemical characteristics of KSF

Table 1 presents the demographic, serum and urine biochemical characteristics of the cohort grouped according to stone type. 1516 subjects were included, of whom 1365 (90%) were CaSF and 151 (10%) were UASF. UASF were significantly older, had higher BMI, and included fewer females (UASF vs. CaSF: 25% vs. 34%, p=0.03) compared with CaSF. UASF had significantly higher sUA, sGlu, and sTG compared with CaSF (Table 1).

24-hour urine biochemical variables of UASF showed higher uNa, uK, and uP compared with CaSF (Table 1). 24-hour urine acid-base profiles of UASF showed lower upH but

higher uSO_4 and NAE compared with CaSF, while uCit was not statistically different between the two groups. NGIA was lower in UASF compared with CaSF. UASF had higher uNH_4^+ , but lower uNH_4^+/NAE (UASF vs. CaSF, expressed as median [25th, 75th percentile]: 0.65 [0.59, 0.77] vs. 0.77 [0.66, 0.92] mEq/mEq, $p<0.0001$) and uNH_4^+/uSO_4 (UASF vs. CaSF: 0.79 [0.61, 1.11] vs. 0.91 [0.69, 1.21] mEq/mEq, $p=0.01$) compared with CaSF (Table 1).

Since the subjects differed in body weight, we normalized the 24-hour urinary parameters to BW. When corrected to BW, uNa, uK, and uP were similar between the two groups. UASF had lower uCa, uOx, and uUA compared with CaSF (Table 1). 24-hour urine acid-base profiles corrected to BW demonstrated similar uSO_4 and uNH_4^+ between UASF and CaSF. UASF had higher NAE, but lower NGIA and uCit excretion compared with CaSF (Table 1).

Time trends in demographics and biochemical characteristics in UASF versus CaSF

Patients were stratified based on year of initial visit: 661 (44%) were evaluated from 1980–1990, 445 (29%) from 1990–2000, and 410 (27%) from 2000–2015.

Over the time periods, the proportion of UASF increased significantly (from 7% to 14%, $p=0.007$) (Figure 1A). The proportion of female patients did not change among UASF ($p=0.52$), but increased among CaSF over the three time periods from 24% to 42% ($p<0.001$) (Figure 1B). With time, and in both groups, there was a significant increase in age ($p=0.005$ in UASF, and $p<0.0001$ in CaSF, Figure 2A) and BMI ($p<0.0001$ in both groups, Figure 2B). Within each time period, both age and BMI were significantly higher in UASF than CaSF ($p<0.0001$ for both, Figures 2A and 2B). UASF had consistently higher sUA ($p<0.0001$), sGlu ($p<0.0001$), and sTG ($p=0.0007$) compared with CaSF in all time periods (Supplemental Figures 1A, 1B and 1C).

Temporal changes in urinary profiles with time as a continuous variable are shown in Figures 3 and 4. UASF had lower upH ($p<0.0001$) and uUA ($p=0.02$) than CaSF (Figures 3A and 3B). UpH and UA remained constant within UASF (P for Trend=0.30 for upH and 0.81 for uUA), but increased within CaSF (P for Trend=0.0002 for upH and 0.0001 for uUA). Both groups had similar uOx ($p=0.23$) and Ca ($p=0.07$) (Figures 4A and 4B). UOx increased within CaSF (P for Trend<0.0001) but remained constant within UASF (P for Trend=0.18). UASF and CaSF had distinct uNa (UASF vs. CaSF, $p=0.04$) and uP (UASF vs. CaSF, $p=0.001$) (Figures 4C and 4D), with uNa and uP increasing significantly within CaSF (P for Trend<0.0001 for both) while remaining constant within UASF (P for Trend=0.21 and 0.37, respectively).

Urinary parameters shown in Supplemental Figure 2 demonstrated similar changes over time in uCit, NAE, and NGIA, but a significant difference in uSO_4 ($p<0.0001$) and uK ($p=0.01$) between the two groups.

For each stone group, we examined the interaction between gender and time. While there were sex differences for some urinary variables (e.g., pH, urinary calcium, etc.) the patterns over time were similar for these urinary variables as well as age and BMI (i.e., non-significant time-gender interactions).

ROC analysis, clinical predictors of uric acid KS formation

A receiver operating characteristic (ROC) model was used to evaluate the effects of upH, and other variables in estimating the risk of uric acid stone formation (Figure 5). UpH had the strongest association with uric acid stone formation [Area under curve (AUC) for pH=0.74, BMI=0.68, Age=0.65, Time periods=0.57, Gender=0.55, and CrCl=0.54, Figure 5). The AUC for the full multivariable model was marginally higher than upH alone at 0.77 (95% CI: 0.73–0.82). The bootstrap-corrected AUC from internal validation was 0.76 (optimism correction=0.0096).

Discussion

To our knowledge, this is the longest longitudinal retrospective study of a large number of KSF evaluated over 35 years. The three principal findings of this study are: 1) The rising trend in proportion of uric acid stones associated with increased BMI and low upH with time; 2) The substantial growth in the proportion of female CaSF during the study period; and 3) UpH alone is a powerful clinical discriminant of whether a stone former has uric acid or calcium stones. Several minor findings are: 1) The increasing trends of uOx, uP, and uNa only in CaSF; 2) Similar uCa in both groups; and 3) 24-hour CrCl is not a significant predictor of stone types.

MS and obesity are major health burdens in the U.S., affecting 30% of general population^{14, 15}. Excessively acidic urine, the principal abnormality and promoter of uric acid crystallization and uric acid stone¹⁶, was reported in aging patients^{17, 18}, obesity, and type 2 diabetes mellitus¹⁹. Consistent with these findings, we observed an association between uric acid stones and increased BMI, older age, and low upH (Figures 2A, 2B and 3A). A proposed mechanism is increased acid load to the kidney coupled with a sustained increased delivery of fat to the kidneys that occurs with high-fat Western diet, which could lead to renal proximal tubular injury (lipotoxicity) and consequently defective renal ammoniogenesis^{20, 21} and lower urine pH due impaired buffering by ammonium. This is supported by studies in non-stone forming human subjects who exhibited an inverse relationship between visceral fat, upH and uNH_4^+ ^{6, 22}, and higher renal fat content with greater BMI^{22, 23}, as well as in animal and cell culture models^{20, 21}. The lower uNH_4^+ /NAE and uNH_4^+ / uSO_4 ratios (uSO_4 : a surrogate marker of dietary acid) in UASF compared with CaSF ($p=0.01$, Table 1) are compatible with the blunted ammoniogenic response to acid load in UASF. The defective NH_4^+ excretion is not the sole factor in causing abnormally acidic urine; acid load is also increased since UASF have higher NAE and lower NGIA per body weight compared to CaSF ($p<0.0001$, Table 1).

The National Health and Nutrition Examination Survey (NHANES) demonstrate a narrowing in the gender gap reported in KS prevalence in the United States¹. A recent study by Moses et al also confirmed the narrowing gender gap by showing significant increase of female stone formers with >50% UA content²⁴. Our results confirm the NHANES findings, with an increase in female CaSF proportion from 24% to 42% over time (Figure 1B), but differ from Moses et al's findings, possibly due to the use of different stone analysis cutoff (70% vs. 50%²⁴). Another study by Yang et al from China indicated that the occurrence of uric acid stone decreased from 2002 to 2014²⁵, while we observed the opposite. The

difference may be related due to ethnic group and/or BMI differences. However, our results resemble what is reported in the U.S population¹⁸. While gender influences excretion of key urinary factors related to stone formation²⁶, the underlying cause(s) for the rising female KSF proportion over time has not yet been fully elucidated. Nevertheless, the magnitude of the impact of obesity on increasing the risk of KS formation has been reported to be greater in women than in men⁸. Other hypothesized mechanism for the narrowing gender gap in the incidence of nephrolithiasis including an aging female population with estrogen lack with potential skeletal calcium and alkali loss, calcium/vitamin D supplement use, and post-menopausal hormone replacement. In terms of stone type, our logistic model did not find gender to be a significant predictive risk factor of stone type (Figure 5).

A third major finding is the ability of upH to serve as strong discriminant (AUC for pH=0.74) of UA stone in our results, followed by BMI (AUC=0.68) and Age (AUC=0.65), and the lowest three factors were time, gender, and CrCl (Figure 5). This finding may be clinically tool to predict patient's stone type and appropriate treatment plan during initial visit, when imaging and/or stone analysis is not available readily. Chronic kidney disease (CKD) may alter urine pH, by reducing ammonium excretion and impacting other urinary parameters. CKD has also been hypothesized as a risk factor for stone formation in previous studies, thus we chose to evaluate creatinine clearance. Still, 24-hour CrCl was not a strong predictor in our model (Figure 5), contrasting previous studies that demonstrated renal function (eGFR) may affect stone type²⁶⁻²⁹.

Some minor findings are also noteworthy. The lack of temporal change in uCa in CaSF despite increasing sodium intake (Figure 4C)³⁰ may be due to increased intestinal binding of calcium by higher dietary phosphate blunting intestinal calcium absorption and reducing uCa excretion (Figure 4B). The increasing trend in uP in CaSF (Figure 4D) confirmed the possibility of increased dietary phosphate intake over time. Besides changes in dietary intake of oxalate precursors, the increasing trend in uOx excretion in CaSF (Figure 4A) may be explained by increased dietary phosphate intake mainly due to increasing addition of inorganic phosphate in processed foods over time (Figure 4D), complexing intestinal luminal Ca, resulting in enhanced intestinal Ox absorption^{7, 9, 10}.

One advantage of our analysis over prior studies is that we relied on urinary biochemical profiles as part of a structured protocol. This study explored a large number of KSF through cross sectional sampling over time, taking into account of gender, age, and BMI. The statistical analysis also attempted to identify clinical predictors of stone type that may be available to clinicians who may not readily have access to stone composition analysis/imaging or, in some instances, even to 24-hour urinary analysis.

Limitations include: 1. the observational single center design with possible selection bias; 2. lack of follow-up data; and 3. absence of information on dietary intake at the time of urine collection. We utilized a 70% cut-off for classifying stone composition¹¹. Use of different definitions/cut-offs by various investigators impacts comparison across centers and study populations.

Conclusion

Three principal findings of this study include trending rise in proportion of UASF associated with increased BMI and low upH, growth in proportion of female CaSF during the study period, and low upH being a strong clinical discriminant of uric acid stone occurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviation (in order of appearance)

KS	Kidney Stones
MS	Metabolic Syndrome
upH	Urinary pH
KSF	Kidney Stone Formers
UASF	Uric Acid Stone Formers
CaSF	Calcium stone Formers
BMI	Body Mass Index
NL	Normal Lab values
sCa	Serum Calcium

sUA	Serum Uric Acid
sGlu	Serum Glucose
sTG	Serum Triglyceride
uTV	Urinary Total Volume
uCr	Urinary Creatinine
uNa	Urinary Sodium
uK	Urinary Potassium
uCa	Urinary Calcium
uUA	Urinary Uric Acid
uOx	Urinary Oxalate
uSO₄	Urinary Sulfate
uCit	Urinary Citrate
uP	Urinary Phosphorus
uCl	Urinary Chloride
uNH₄⁺	Urinary Ammonium
BW	Body Weight
CrCl	Creatinine Clearance
NGIA	net gastrointestinal absorption of alkali
HCO₃⁻	Bicarbonate
NAE	Net Acid Excretion
mEq	Milliequivalents
ROC	Receiver Operating Characteristic
AUC	Area Under the Curve

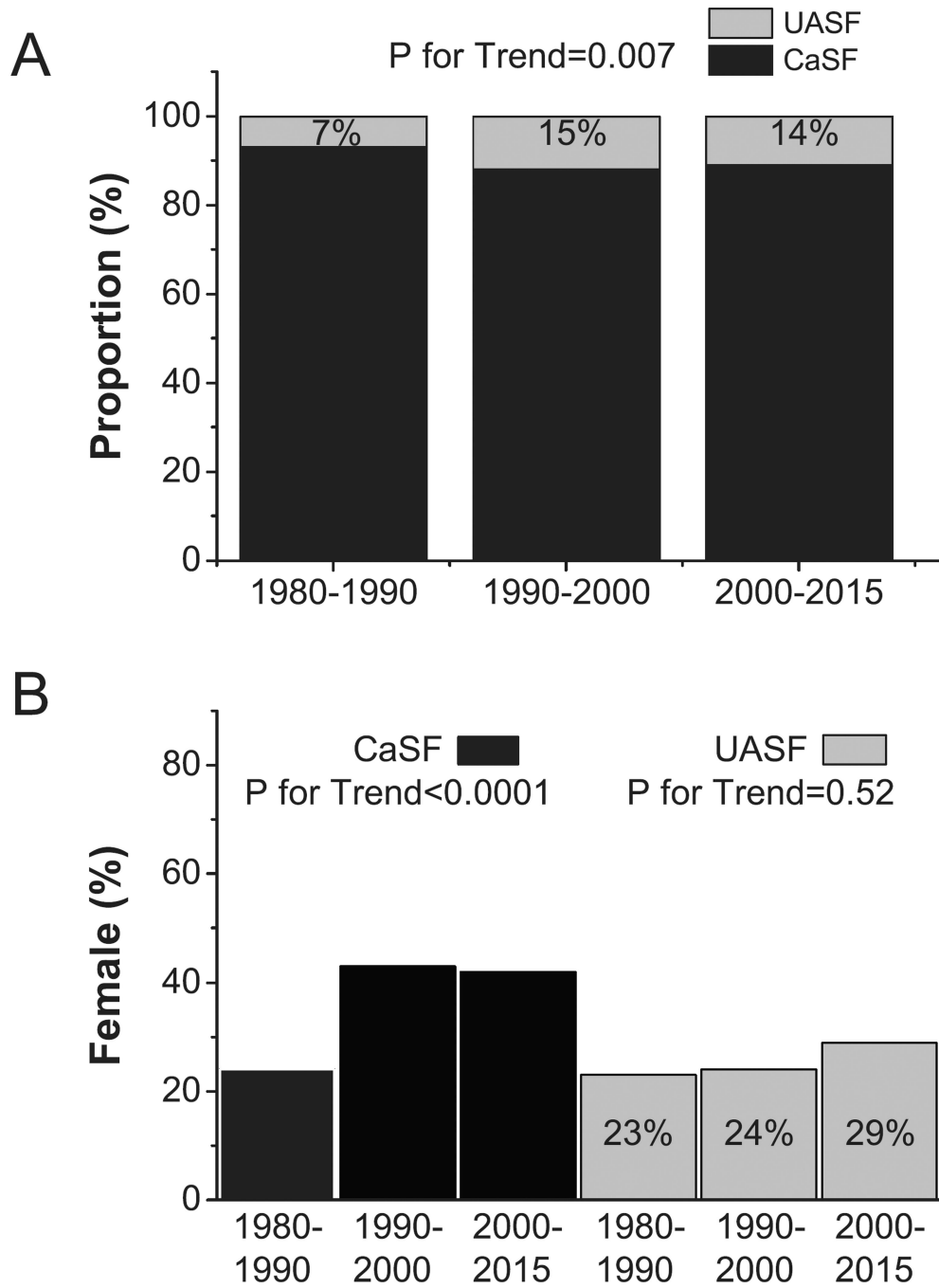


Figure 1.
 A) Proportion of UASF/CaSF at different time periods; B) Female percentage among UASF/CaSF at different time periods.

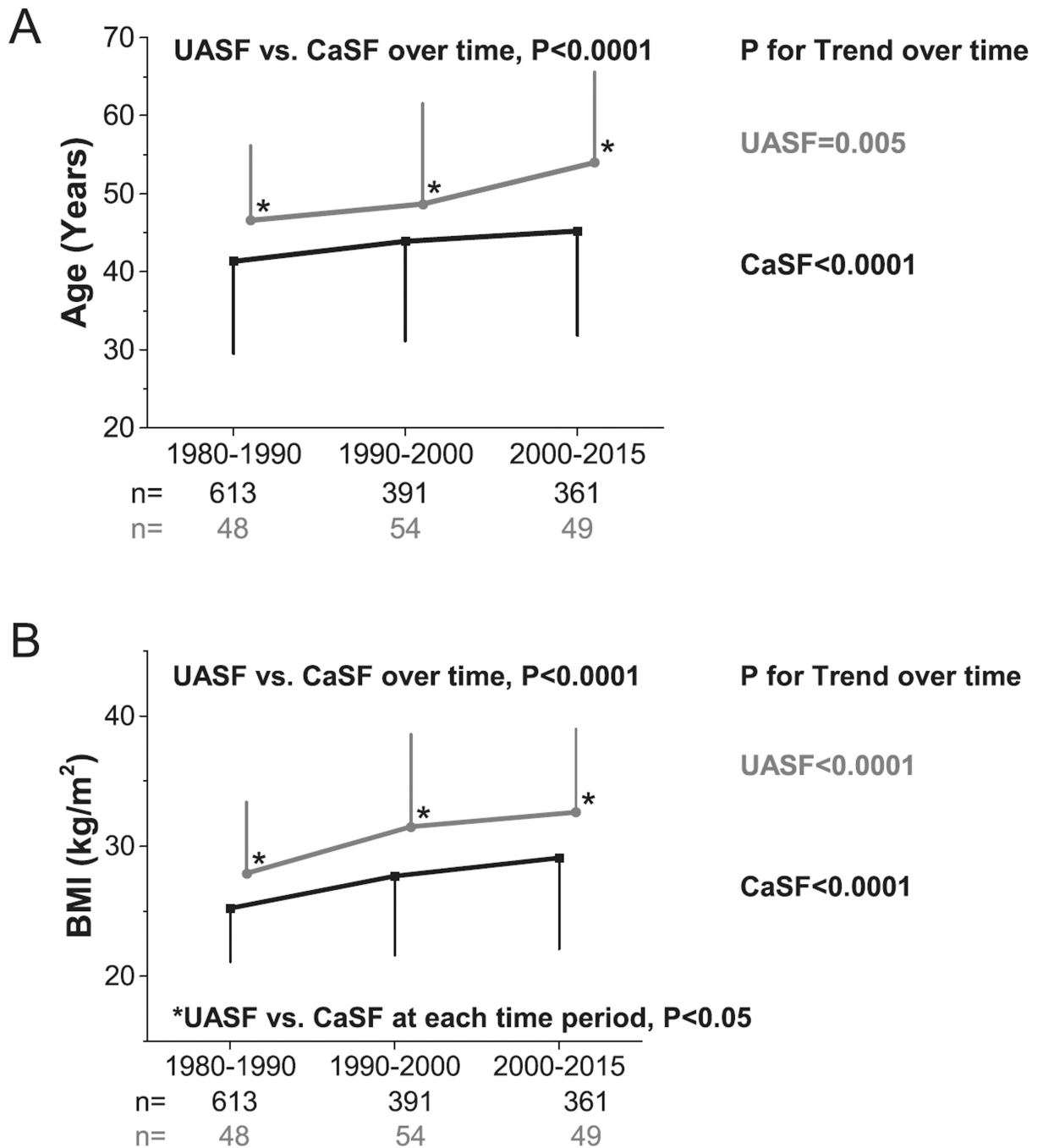
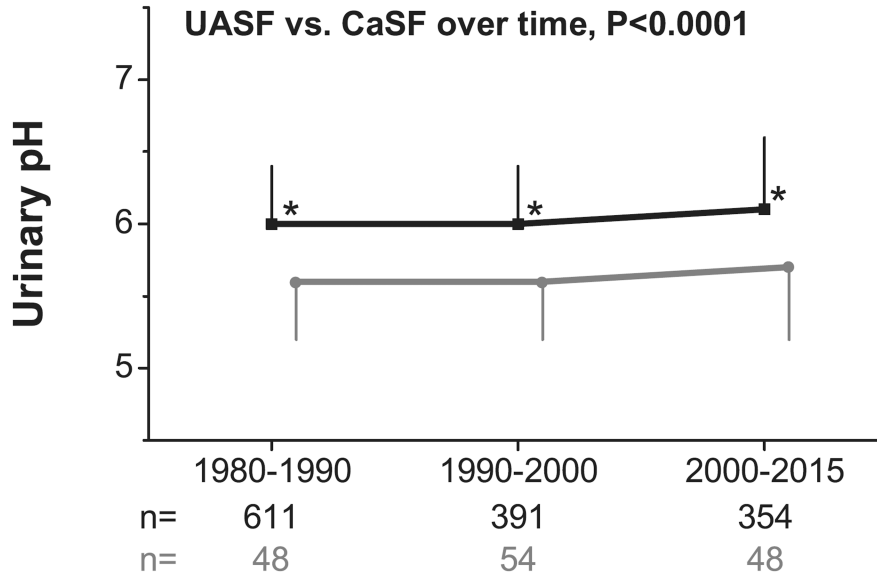


Figure 2. A) Age trends of UASF/CaSF at different time periods; B) BMI trends of UASF/CaSF at different time periods. P-value at the top of each figure compares UASF vs. CaSF group effect, while p-values to the right of each line corresponds to test for linear trend across time periods within each group. Asterisk (*) indicates p<0.05 between for CaSF vs. UASF at corresponding time period.

A

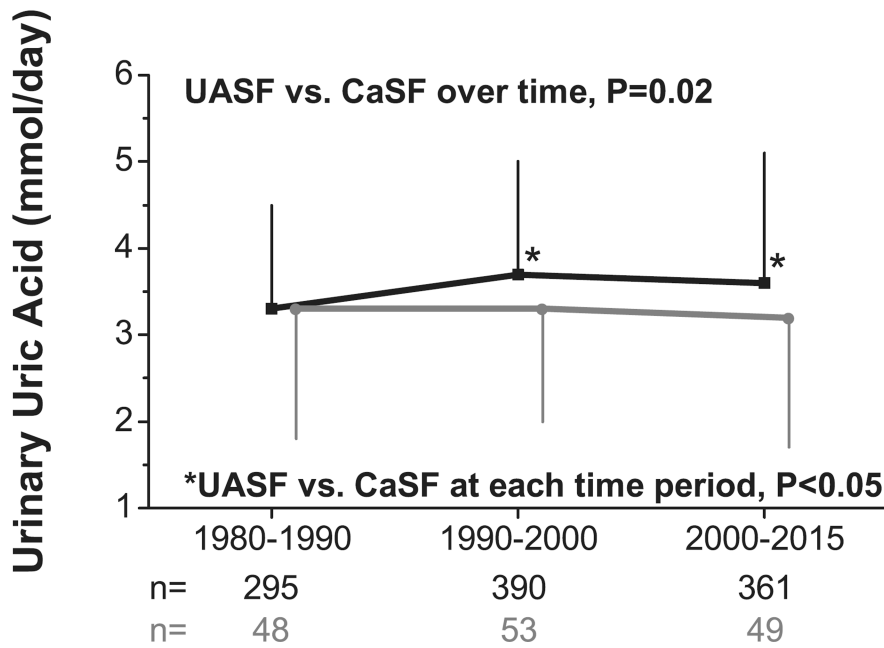


P for Trend over time

CaSF=0.0002

UASF=0.30

B



P for Trend over time

CaSF=0.0001

UASF=0.81

Figure 3.

A) Urinary pH trends of UASF/CaSF at different time periods; B) Urinary uric acid trends of UASF/CaSF at different time periods; P-value at the top of each figure compares UASF vs. CaSF group effect, while p-values to the right of each line corresponds to test for linear trend across time periods within each group. Asterisk (*) indicates p<0.05 between for UASF vs. CaSF at corresponding time period.

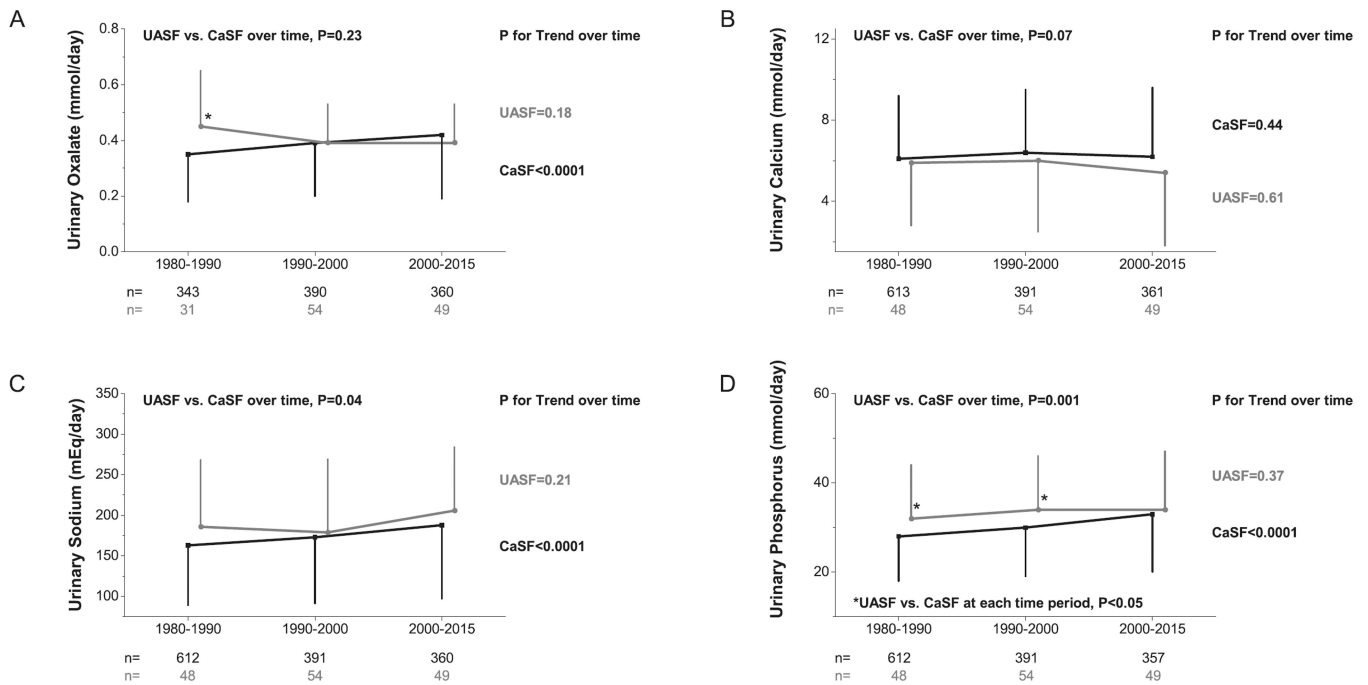
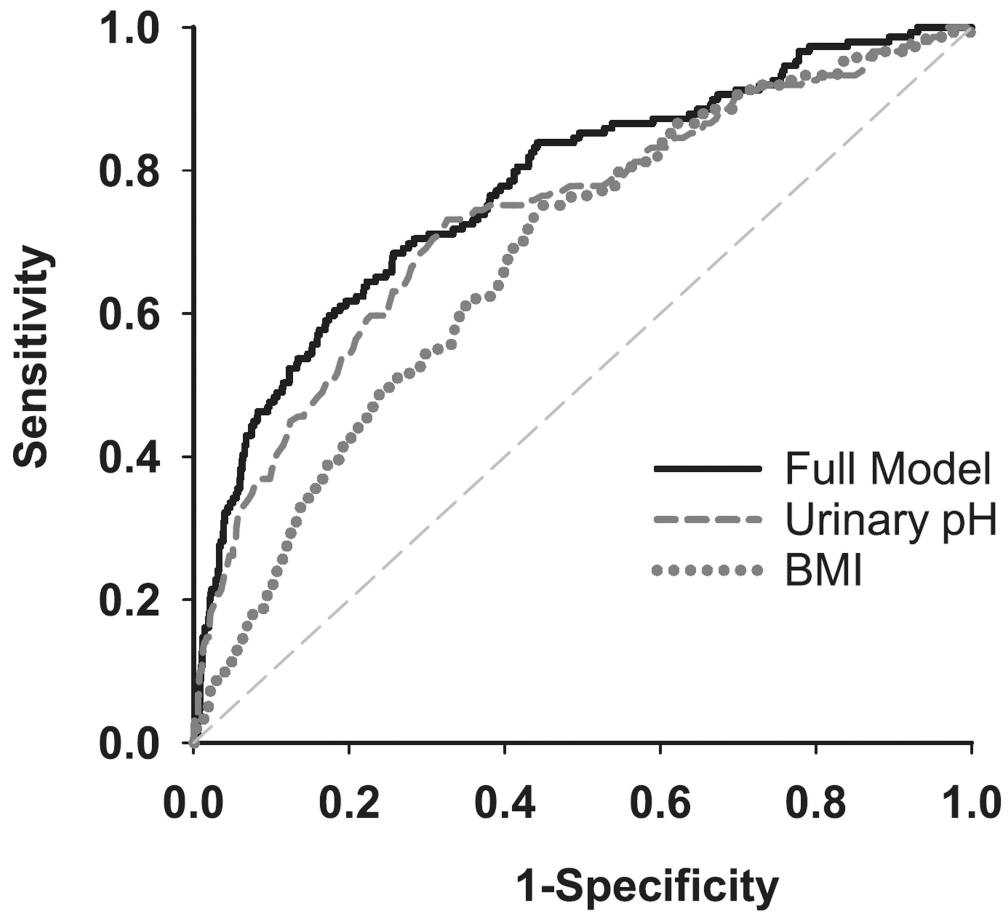


Figure 4.

A) Urinary oxalate trends of UASF/CaSF at different time periods; B) Urinary calcium trends of UASF/CaSF at different time periods. C) Urinary sodium trends of UASF/CaSF at different time periods. D) Urinary phosphorus trends of UASF/CaSF at different time periods. P-value at the top of each figure compares UASF vs. CaSF group effect, while p-values to the right of each line corresponds to test for linear trend across time periods within each group. Asterisk (*) indicates p<0.05 between for UASF vs. CaSF at corresponding time period.



<u>Model</u>	<u>AUC</u>	<u>95% Confidence Interval</u>
Full Model	0.77	0.73-0.82
Urinary pH	0.74	0.68-0.78
BMI	0.68	0.64-0.72
Age*	0.65	0.61-0.70
Time Periods*	0.57	0.52-0.61
Gender*	0.55	0.51-0.58
Creatinine Clearance*	0.54	0.49-0.59

Figure 5. Receiver Operating Characteristic (ROC) analysis and areas under the curves (AUC) for clinical predictors of uric acid stone formation. Multivariable full model includes: urinary pH, BMI, time period, gender, and creatinine clearance. Urinary pH and BMI from univariable analysis are shown. Asterisks (*) indicate **variables** that are not shown on the figure.

Table 1

Demographic, serum, and urinary parameters of all subjects, and comparison between calcium stone formers and uric acid stone formers. Continuous variables are summarized as mean ± standard deviation or median [25th, 75th percentile].

	Total Sample	Calcium Stone Formers (CaSF)	Uric Acid Stone Formers (UASF)	P-value (UASF vs. CaSF)
<i>Demographics</i>				
Sample Size (n)	1516	1365	151	
Proportion in Total Population (%)		90%	10%	
Age (years)	43.7±12.6	43.1±12.6	49.6±11.7	<0.0001
Race/Ethnicity				0.69
White	1414	1271	143	
Black	45	41	4	
Hispanic	16	15	1	
Asian	29	28	1	
American Indians	5	5	0	
Weight (kg)	81.5±20.0	80.3±19.5	92.8±20.8	<0.0001
BMI (kg/m ²)	27.4±6.0	27.0±5.8	30.7±6.7	<0.0001
% Female	33%	34%	25%	0.03
<i>Serum</i>				
Calcium (mmol/L)	2.37±0.11	2.37±0.11	2.37±0.11	0.46
Uric Acid(μmol/L)	352±96	348±93	394±110	<0.0001
Glucose (mmol/L)	5.2±1.2	5.1±1.1	5.9±1.8	<0.0001
Triglyceride (mmol/L)	1.7±1.4	1.7±1.4	2.1±1.7	0.01
<i>Urine</i>				
Volume (mL/day)	1808±927	1809±936	1801±849	0.94
pH	5.99±0.45	6.03±0.44	5.65±0.44	<0.0001
Cr-Clearance (mL/min/1.73m ²)	97.5±27.9	97.6±27.4	95.8±31.6	0.57
Creatinine (mmol/day)	14.0±4.5	13.8±4.4	15.6±4.4	<0.0001
Sodium (mEq/day)	175±82	173±82	189±84	0.02
Potassium (mEq/day)	52±22	51±22	56±23	0.01
Calcium (mmol/day)	6.1±3.1	6.2±3.1	5.7±3.4	0.13
Oxalate (mmol/day)	0.4±0.2	0.4±0.2	0.4±0.2	0.29
Uric Acid (mmol/day)	3.5±1.3	3.5±1.3	3.3±1.4	0.08
Citrate (mmol/day)	2.68±1.62	2.66±1.57	2.82±2.03	0.40
Phosphorus (mmol/day)	31±12	30±11	34±12	0.001
Sulfate (mEq/day)	39.8±19.3	38.7±17.7	46.9±22.4	<0.0001
Ammonium (mEq/day)	36.8±17.2	36.2±17.2	39.9±17.0	0.05
NAE (mEq/day)	48.2±29.3	46.2±29.4	59.3±25.7	<0.0001

	Total Sample	Calcium Stone Formers (CaSF)	Uric Acid Stone Formers (UASF)	P-value (UASF vs. CaSF)
NAE/Sulfate (mEq/mEq)	1.19 [0.88, 1.61]	1.18 [0.87, 1.61]	1.26 [0.96, 1.59]	0.30
Ammonium/NAE (mEq/mEq)	0.75 [0.64, 0.91]	0.77 [0.66, 0.92]	0.65 [0.59, 0.77]	<0.0001
Ammonium/Sulfate (mEq/mEq)	0.90 [0.68, 1.21]	0.91 [0.69, 1.21]	0.79 [0.61, 1.11]	0.01
NGIA (mEq/day)	28.5±42.6	30.0±42.0	18.0±45.1	0.01
NGIA/Potassium (mEq/mEq)	0.54 [0.28, 0.81]	0.56 [0.29, 0.83]	0.40 [0.11, 0.64]	0.0004
<i>Urine per Kg Bodyweight</i>				
Creatinine (µmol/day/kg)	173.2±45.5	173.4±45.5	171.3±45.3	0.59
Sodium (mEq/day/kg)	2.17±0.94	2.18±0.95	2.07±0.88	0.14
Potassium (mEq/day/kg)	0.65±0.27	0.65±0.28	0.62±0.25	0.14
Calcium (mmol/day/kg)	0.08±0.04	0.08±0.04	0.06±0.04	<0.0001
Oxalate (µmol/day/kg)	4.8±2.4	4.9±2.4	4.4±1.7	0.004
Uric Acid (µmol/day/kg)	43.6±15.6	44.4±15.3	36.5±16.1	<0.0001
Citrate (µmol/day/kg)	33.2±20.2	33.6±20.1	29.9±21.2	0.01
Phosphorus (mmol/day/kg)	0.38±0.13	0.38±0.13	0.37±0.12	0.24
Sulfate (mEq/day/kg)	0.48±0.21	0.48±0.20	0.50±0.22	0.34
Ammonium (mEq/day/kg)	0.44±0.22	0.44±0.22	0.43±0.21	0.70
NAE (mEq/day/kg)	0.56±0.36	0.55±0.37	0.63±0.30	0.02
NGIA (mEq/day/kg)	0.35±0.48	0.38±0.48	0.19±0.49	<0.0001

Cr: Creatinine; NAE: Net Acid Excretion; NGIA: Net Gastrointestinal Absorption of Alkali; BW: Body Weight.

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