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Virginia L. Hood
University of Vermont, virginia.hood@uvmhealth.org

Kevan M. Sternberg
University of Vermont, kevan.sternberg@uvmhealth.org

Desiree de Waal
University of Vermont, desiree.dewaal@uvmhealth.org

John R. Asplin
Litholink Coorporation, asplinj@labcorp.com

Carley Mulligan
University of Vermont, cmullig2@uvm.edu

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Authors

Virginia L. Hood, Kevan M. Sternberg, Desiree de Waal, John R. Asplin, Carley Mulligan, and Peter W. Callas

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Virginia L. Hood [ID],[1] Kevan M. Sternberg,[2] Desiree de Waal [ID],[1] John R. Asplin [ID],[3] Carley Mulligan,[4] and Peter W. Callas [ID][5]

Key Points

- Stone-forming patients with metabolic syndrome have metabolic and diet factors contributing to stone risk, including high acid excretion and low urine pH.
- Greater acid excretion is largely the result of higher protein intake, although this does not fully explain the urine pH trends.
- Low urine pH with high supersaturation of uric acid and low supersaturation of calcium phosphate contributed to the distribution of stone composition in those with more metabolic syndrome traits.

Abstract

Background The odds of nephrolithiasis increase with more metabolic syndrome (MetS) traits. We evaluated associations of metabolic and dietary factors from urine studies and stone composition with MetS traits in a large cohort of stone-forming patients.

Methods Patients >18 years old who were evaluated for stones with 24-hour urine collections between July 2009 and December 2018 had their records reviewed retrospectively. Patient factors, laboratory values, and diagnoses were identified within 6 months of urine collection and stone composition within 1 year. Four groups with none, one, two, and three or four MetS traits (hypertension, obesity, dyslipidemia, and diabetes) were evaluated. Trends across groups were tested using linear contrasts in analysis of variance and analysis of covariance.

Results A total of 1473 patients met the inclusion criteria (835 with stone composition). MetS groups were 684 with no traits, 425 with one trait, 211 with two traits, and 153 with three or four traits. There were no differences among groups for urine volume, calcium, or ammonium excretion. There was a significant trend ($P<0.001$) for more MetS traits being associated with decreasing urine pH, increasing age, calculated dietary protein, urine uric acid (UA), oxalate, citrate, titratable acid phosphate, net acid excretion, and UA supersaturation. The ratio of ammonium to net acid excretion did not differ among the groups. After adjustment for protein intake, the fall in urine pH remained strong, while the upward trend in acid excretion was lost. Calcium oxalate stones were most common, but there was a trend for more UA ($P<0.001$) and fewer calcium phosphate ($P=0.09$) and calcium oxalate stones ($P=0.01$) with more MetS traits.

Conclusions Stone-forming patients with MetS have a defined pattern of metabolic and dietary risk factors that contribute to an increased risk of stone formation, including higher acid excretion, largely the result of greater protein intake, and lower urine pH.

Introduction

Metabolic syndrome (MetS), with its components of insulin resistance, obesity, dyslipidemia, and hypertension, is a major health challenge, increasing cardiovascular risk (1,2) and the risk for kidney stones (2–4). The odds of nephrolithiasis increase with the number of MetS traits (5,6).

The US dietary pattern, characterized by excess sugar, refined carbohydrates, red and processed meats, prepackaged foods, high-fat foods, and high-sugar beverages, is prevalent among individuals with MetS (7) and is associated with increased acid production. The kidneys respond to an acidogenic diet by increasing net acid excretion (NAE), excretion of

[1]Department of Nephrology, University of Vermont Medical Center, Burlington, Vermont
[2]Department of Urology, University of Vermont Medical Center, Burlington, Vermont
[3]Litholink Corporation, Laboratory Corporation of America Holdings, Itasca, Illinois
[4]Larner College of Medicine, University of Vermont, Burlington, Vermont
[5]Medical Biostatistics, University of Vermont, Burlington, Vermont

Correspondence: Dr. Virginia L. Hood, Department of Nephrology, University of Vermont Medical Center, 1 South Prospect Street, Burlington, VT 05401. Email: virginia.hood@uvmhealth.org

sulfate (Sul), phosphate, urate, chloride (Cl), calcium (Ca), organic anions forming titratable acid and ammonium (NH_4), plus reduced excretion of bicarbonate and citrate (Cit) (8). The formation of kidney stones is multifactorial and associated with varying concentrations of these urine components that serve as constituents or inhibitors of stone formation along with urine pH. Low urine pH enhances the formation of uric acid (UA) and, to a lesser extent, calcium oxalate (CaOx) stones, both of which are common in those with MetS (9–11). Prior studies in non–stone forming people have shown an inverse relationship between the number of MetS traits and urine pH and acid excretion patterns, with a lower proportion of NH_4 to NAE (9) that may result from insulin resistance with impaired ammonia production (10,11). UA stone formers with similar NAE to non–stone formers have been reported to have less NH_4 and more titratable acid than controls matched according to body mass index (11). We evaluated a large cohort of stone-forming patients to identify patient, urine factors, and stone composition associated with varying numbers of MetS traits, in particular those reflecting acid excretion and diet.

Methods

Study Design and Participants

Figure 1 provides an overview of the study design and participants. A retrospective review was performed of 24-hour urine studies from patients seen for kidney stone consultation at the University of Vermont Medical Center (UVMMC) from July 2009 to December 2018. Results for patients <18 years of age, those with improper collections, and those with suspected renal tubule acidosis on the basis of urine pH and serum bicarbonate were excluded. Patient
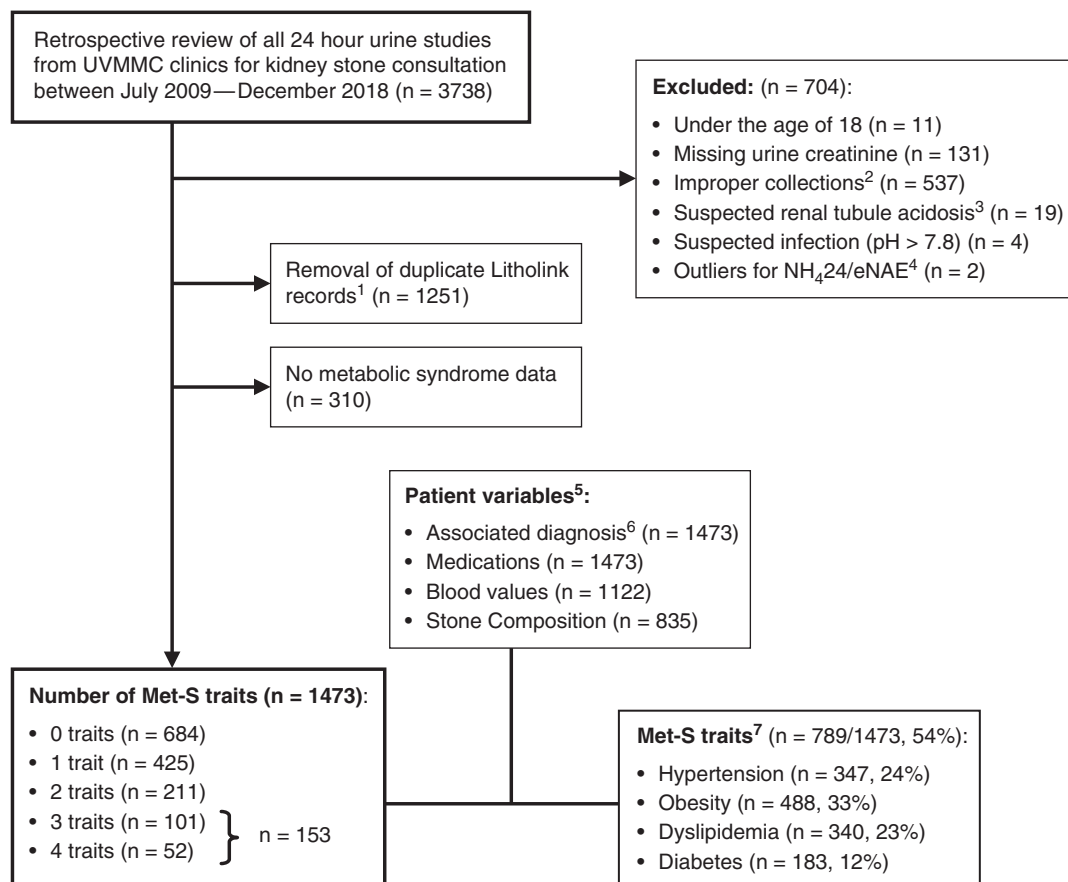
Figure 1. | **Study flow diagram.** 1. If a patient had more than one urine test, the earliest one obtained was used to minimize any treatment effects. 2. Improper collections defined as outside expected range of urine creatinine on the basis of weight (8.7–20.3 mg/kg for women; 11.9–24.4 mg/kg for men) using Litholink range as reference. Urine creatinine values before April 29, 2018, were adjusted to account for a change to an isotope dilution mass spectrometry traceable urine creatinine assay. 3. Renal tubule acidosis defined as blood tCO_2 <22 and urine pH >6.5. 4. Outliers were defined as $NH_4 24/eNAE$ absolute values of 194 and 74 with the next highest 16. 5. Blood values within 6 months of urine collection; stone composition values within 1 year of urine collection. 6. Diagnosis on the basis of ICD-9 and -10 codes listed on "problem list" in medical records. 7. MetS traits defined (1) as needing at least one quality listed: (*1*) Hypertension defined as: diagnosis on problem list, two systolic BP readings >140 mmHg within 6 months of one another, on at least two medications for hypertension. In group 1, 18% had hypertension as the only MetS trait documented. (*2*) Obesity defined as: diagnosis on problem list, body mass index >30 kg/m². (*3*) Dyslipidemia defined as: diagnosis on problem list, triglyceride level >150 mg/dl, high-density lipoprotein <35; on a "statin." (*4*) Diabetes defined as: diagnosis of diabetes or hyperglycemia on problem list, random blood sugar >180 mg/dl, on oral hypoglycemic agent or insulin.

variables, laboratory values, associated diagnoses, and medications were recorded for the time closest to and within 6 months of the first available urine collection after 2009 and for stone composition within 1 year of urine collection. Patients were divided into four groups on the basis of the number of MetS traits (hypertension, obesity, dyslipidemia, and diabetes): none, one, two, and three or four. Each trait was defined by established criteria (1).

Data Collection and Measurement

Blood levels were measured in the UVMMC laboratory using standard autoanalyser methods. Twenty-four-hour urine values were measured through Litholink (Chicago, IL). These included pH, supersaturation of CaOx (SSCaOx), supersaturation of calcium phosphate (SSCaP), supersaturation of UA (SSUA), and 24-hour excretion for volume (L/d), Ca (mg/d), Ox (mg/d), Cit (mg/d), UA (g/d), sodium (Na; mmol/d), potassium (K; mmol/d), magnesium (Mg; mg/d), phosphorus (P; g/d), Cl (mmol/d), NH_4 (mmol/d), Sul (mEq/d), urine urea nitrogen (UUN; g/d), and creatinine (mg/day).

Stone composition was analyzed by Mayo Clinic Laboratories in those who had passed stones or had them removed within 1 year of the urine collection. Many stones had several components. For analysis, stones were categorized as >50% of CaOx, CaP, UA, or other.

Calculations

The calculations are detailed in Table 1. Estimated NAE (eNAE) was calculated as sum of urine NH_4 and calculated titratable acid from phosphate (TAP) minus calculated bicarbonate (mEq/d). Urine organic acids were not measured. So, titratable acid from organic acids was not assessed. TAP accounts for >75% of titratable acid (12). Protein intake (g/d) was estimated from UUN and nonurea nitrogen (13). Gastrointestinal (GI) alkali intake (mEq/d) was estimated from the difference between excretion of urine cations (Na, K, Ca, and Mg) and anions (Cl and P) (14).

The information analyzed was collected as part of clinical care, housed in the Stone Registry at UVMMC, and extracted in deidentified formats for analysis. This registry is updated yearly and is approved by UVM Institutional Review Board for use in studies that fit acceptable criteria.

Statistical Analyses

Analyses were conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC). For unadjusted comparisons, trends across the four MetS groups were tested using linear contrasts in analysis of variance for continuous variables and Cochran–Armitage trend tests for categorical variables. Adjusted comparisons used linear contrasts in analysis of covariance.

Results

Results are shown in Figure 1 and Tables 2–4. A total of 1473 unique patients met the criteria for inclusion. The number of patients in each MetS category was 684 with no traits, 425 with one trait, 211 with two traits, and 153 with three or four traits. Those with more MetS traits were older and heavier and had higher estimated protein intake. There was no sex difference among the groups.

Blood Values

Blood values are provided in Table 2. A total of 1122 (76%) had at least one value for blood chemistries within 6 months of the Litholink using the measure closest in time to the urine collection. There was a significant trend for increasing glucose and triglycerides and for decreasing high-density lipoprotein, with increasing numbers of MetS traits as expected, given the defining criteria. There were upward, although quantitatively small, trends for serum K and creatinine. One hundred fifty-seven (14%) had an eGFR of <60 ml/min per 1.73 m^2, with a similar average value in each group. Twenty-two had an eGFR of <30 ml/min per 1.73 m^2, with three having an eGFR of <15 mL/min per 1.73 m^2. UA also trended upward as previously described in those with MetS (10,11). There were no differences among the groups for Ca, P, or total CO_2.

Medications

Medications are listed in Table 2. Less than 10% of the group had any commonly used stone prevention medication recorded. This is likely because the database generally reflected blood and urine findings before metabolic evaluation and management at our institution. Of the 1473 patients, 64 (4%) had a thiazide (either alone or combined with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker), and 48 (3%) had a Cit (K, Na, or combination) noted.

Urine Values

Urine values are given in Table 3 and Supplemental Tables 1–3. There were no significant trends for unadjusted values for the groups for 24-hour urine volume, Ca, Sul, Mg, SSCaOx, NH_4, or NH_4/eNAE. There was a significant

Table 1. Equations and calculations	
Calculated Variables	**Equations**
eNAE	eNAE$=NH_424+$TAP$-$Ubicarbonate
TAP	TAP$=$P24$\times 1000/31\langle\{1/[\text{antilog (urine pH}-6.8)+1]\}-0.2\rangle$
Urine bicarbonate, CO_2	Ubicarbonate$=$vol. (L)$\times[1.2\times$antilog (UpH-6.1)]
GI alkali	$\{[\text{Na24}+\text{K24}+(\text{Ca24}/40)\times 2+(\text{Mg24}/24.3)\times 2]-[\text{Cl24}+(\text{P24}\times 1000/31)\times 1.8]\}$
Calculated protein intake, g/d	6.25$\times$(UUN24$+$eNUN) where eNUN$=$weight (kg)$\times 0.031$

eNAE, estimated net acid excretion; TAP, titratable acid from phosphate; GI, gastrointestinal; UpH, urine pH; eNUN, estimated nonurea nitrogen (g/d); UUN, urine urea nitrogen (g/d).

Table 2.   Demographics,[a] medications, and blood values

Subject Characteristics	N Value	Number of Metabolic Syndrome Traits, Mean (SD)				Trend P Value
		0	1	2	3 or 4	
N	1473	684	425	211	153	
Women, n (%)	1473	329 (48%)	200 (47%)	108 (51%)	55 (36%)	0.09
Age[b], yr	1473	49 (15)	54 (14)	58 (12)	62 (10)	<0.001
Weight, kg	1473	78 (18)	91 (21)	93 (20)	100 (20)	<0.001
BMI	1464	26.8 (5.5)	31.4 (6.6)	32.4 (6.5)	34.5 (6.4)	<0.001
Blood values						
Potassium, mEq/L	1076	4.3 (0.4)	4.3 (0.4)	4.3 (0.4)	4.4 (0.4)	<0.001
Phosphorus, mg/dl	342	3.5 (0.6)	3.5 (0.5)	3.5 (0.7)	3.4 (0.6)	0.32
Bicarbonate, mEq/L	1067	27 (3)	27 (3)	27 (3)	27 (3)	0.63
Calcium, mg/dl	996	9.5 (0.5)	9.5 (0.5)	9.4 (0.4)	9.6 (0.5)	0.28
Glucose, mg/d	908	99 (19)	109 (37)	110 (37)	159 (79)	<0.001
HDL, mg/dl	398	59 (15)	51 (17)	53 (14)	44 (16)	<0.001
Triglycerides, mg/dl	399	93 (28)	151 (83)	139 (73)	183 (102)	<0.001
Creatinine, mg/dl	1122	0.90 (0.29)	0.96 (0.37)	1.00 (0.51)	1.04 (0.34)	<0.001
eGFR <60 ml/min per 1.73 m^2	157	47.1 (10.4)	46.4 (13.4)	43.9 (12.9)	45.5 (10.9)	0.67
Uric acid, mg/dl	447	5.2 (1.4)	5.4 (1.3)	5.8 (1.6)	6.0 (1.6)	<0.001
Medications, n (%)						
Thiazide	64 (4%)	5 (1%)	14 (3%)	19 (9%)	26 (17%)	<0.001
Citrate	48 (3%)	12 (2%)	11 (3%)	11 (5%)	14 (9%)	<0.001

BMI, body mass index (kg/m^2); HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.
[a]Race and ethnicity was not documented because the population served is predominantly White.
[b]Age at collection.

trend for the increasing number of MetS traits being associated with decreasing urine pH and SSCaP and increasing urine UA, SSUA, Ox, Cit, Na, K, P, UUN, TAP, and eNAE.

When adjusted for age (Supplemental Table 1), the only differences from the unadjusted were upward trends for NH$_4$ and S excretion. When stratified for sex, there were significant upward trends for Na, Ox, and P in women but not men and for Cit in men but not women. The trends for decreasing urine pH and increasing TAP and eNAE remained strong in men and women adjusted or unadjusted for age but for NH$_4$ only when adjusted for age. When adjusted for creatinine excretion (Supplemental Table 2), trends for NAE, TAP, and NH$_4$ mirrored unadjusted values. There was a significant downward trend for NH$_4$/eNAE when adjusted for age but only in women. However, the interaction between sex and MetS traits for NH$_4$/eNAE was not significant ($P=0.16$).

When adjusted for calculated protein intake or age and protein intake, the trend for decreasing urine pH remained strong as did the upward trend for Ox. However, the upward trend for TAP was attenuated, and there was no longer a significant trend for eNAE, Na, K, or Cit. There was a significant downward trend for UUN, P, Sul, and NH$_4$ and no trend for GI alkali. GI alkali showed a downward trend after adjusting for age and protein ($P<0.01$) but not for either age or protein alone.

The ratio of NH$_4$/eNAE displayed much variability but did not significantly differ among the groups. The age-adjusted significant downward trend in women was lost when adjusted for protein. (Supplemental Table 3).

Stone Composition

Stone composition is provided in Table 4. A total of 835 (57%) patients had information about stone composition within a year of the Litholink values: 593 (71%) had >50% CaOx, 126 (15%) >50% CaP, 83 (10%) >50% UA, and 33 (4%) mixed/other stones. Although CaOx stones were the most common in all groups, there was a trend for an increasing proportion of UA stones ($P<0.001$) and decreasing proportion of CaP stones ($P=0.09$) and CaOx stones ($P=0.01$) with an increasing number of MetS traits.

Discussion

Our study shows that in a large group of stone-forming people with varying numbers of MetS traits, urine pH and acid excretion patterns were similar to those described by others in non–stone forming people with MetS (9). However, the changes associated with MetS in our study were largely the consequence of higher dietary protein intake. Those with more MetS traits were heavier and ate more protein, which, except for urine pH, accounted for most of the variability in acid excretion findings among those with more MetS traits. Other urinary findings of metabolic and dietary factors contributing to excess stone formation in those with MetS were also influenced by diet as discussed below.

Acid Excretion

The urine metabolic profiles showed similar acid excretion findings to a previously published study of a smaller group of non–stone forming people with and without MetS traits (9). The main findings in both this and our study were that with an increasing number of MetS traits, there was decreasing urine pH and greater eNAE that was contributed to by both a greater NH$_4$ (age adjusted) and titratable acid excretion. These findings were unchanged when stratified for sex or adjusted for creatinine excretion

Table 3. Comparison of urine variables and metabolic syndrome traits[a]

Unadjusted Comparisons	Number of Metabolic Syndrome Traits, Mean (SD)				Trend P Value
	0	1	2	3 or 4	
N	684	425	211	153	
Vol24, L/d	1.9 (0.8)	1.9 (0.8)	2.0 (0.8)	2.0 (0.8)	0.33
Cr24, mg/d	1346 (410)	1465 (463)	1433 (416)	1483 (383)	0.002
pH	6.1 (0.5)	6.0 (0.5)	5.9 (0.5)	5.8 (0.5)	<0.001
Ca24, mg/d	208 (105)	219 (123)	208 (121)	208 (161)	0.73
SSCaP	1.3 (1.0)	1.2 (1.0)	1.0 (1.0)	0.9 (1.1)	<0.001
SSCaOx	6.5 (3.1)	6.9 (3.2)	6.5 (3.3)	6.3 (3.2)	0.24
Ox24, mg/d	35 (14)	39 (21)	41 (27)	43 (18)	<0.001
Cit24, mg/d	574 (294)	607 (365)	631 (374)	672 (556)	0.002
UA24, g/d	0.60 (0.21)	0.64 (0.24)	0.66 (0.23)	0.68 (0.25)	<0.001
SSUA	0.8 (0.9)	1.0 (0.9)	1.1 (0.9)	1.4 (1.0)	<0.001
Na24, mmol/d	154 (68)	179 (90)	173 (71)	177 (75)	0.002
K24, mmol/d	60 (23)	64 (25)	67 (23)	69 (26)	<0.001
Cl24, mmol/d	154 (65)	178 (83)	176 (71)	182 (70)	<0.001
P24, g/d	0.90 (0.32)	0.97 (0.38)	0.96 (0.33)	0.99 (0.39)	0.01
Sul24, mEq/d	37 (15)	40 (17)	38 (17)	40 (18)	0.07
Mg24, mg/d	99 (39)	103 (45)	104 (43)	106 (55)	0.08
UUN24, g/d	10.4 (3.8)	11.3 (4.2)	11.2 (4.0)	12.0 (4.7)	<0.001
Protein, calculated[b]	80 (26)	88 (29)	88 (27)	94 (31)	<0.001
$NH_4$24, mmol/d	34 (14)	35 (17)	35 (18)	36 (17)	0.18
TAP, mEq/d	17 (9)	19 (10)	20 (9)	22 (10)	<0.001
eNAE, mEq/d	45 (26)	50 (29)	51 (28)	55 (26)	<0.001
$NH_4$24/eNAE	0.76 (1.25)	0.71 (0.85)	0.69 (0.71)	0.64 (0.35)	0.17
GI alkali, mEq/d	27 (21)	29 (29)	28 (23)	26 (25)	0.81
Adjusted for protein					
Vol24, L/d	2.0	1.9	2.0	1.9	0.32
Cr24, mg/d	1403	1430	1396	1378	0.18
pH	6.1	6.0	6.0	5.8	<0.001
Ca24, mg/d	217	214	202	190	0.003
SSCaP	1.3	1.2	1.0	0.9	<0.001
SSCaOx	6.5	6.9	6.5	6.3	0.27
Ox24, mg/d	36	38	40	41	<0.001
Cit24, mg/d	590	596	620	642	0.07
UA24, g/d	0.63	0.62	0.64	0.62	0.92
SSUA	0.8	1.0	1.1	1.3	<0.001
Na24, mmol/d	162	174	168	162	0.7
K24, mmol/d	63	62	65	65	0.13
Cl24, mmol/d	161	173	171	168	0.31
P24, g/d	0.95	0.94	0.93	0.89	0.003
Sul24, mEq/d	39	38	37	35	<0.001
Mg24, mg/d	102	101	101	99	0.39
UUN24, g/d	11.1	10.8	10.8	10.6	<0.001
Protein, calculated[b]	–	–	–	–	–
$NH_4$24, mmol/d	35	34	34	33	0.01
TAP[b], mEq/d	18	19	19	19	0.02
eNAE[b], mEq/d	48	48	49	49	0.45
$NH_4$24/eNAE	0.75	0.71	0.7	0.66	0.32
GI alkali[b], mEq/d	28	28	27	25	0.14

Vol24, 24-hour urine volume; Ca24, 24-hour urine calcium; Ox24, 24-hour urine oxalate; Cit24, 24-hour urine citrate; pH, 24-hour urine pH; Na24, 24-hour urine sodium; K24, 24-hour urine potassium; Mg24, 24-hour urine magnesium; P24, 24-hour urine phosphorus; $NH_4$24, 24-hour urine ammonium; Cl24, 24-hour urine chloride; Sul24, 24-hour urine sulfate; UUN24, 24-hour urine urea nitrogen; Cr24, 24-hour urine creatinine; SSCaP, supersaturation of calcium phosphorus; SSUA, supersaturation of uric acid; SSCaOx, supersaturation of calcium oxalate; TAP, titratable acid from phosphate; eNAE, estimated net acid excretion; GI, gastrointestinal.
[a]For the urine measures, none of the variables had more than three missing values.
[b]See Table 1 for equations and calculations.

(a surrogate for lean body mass). However, in contrast to the referenced study, we did not show a significant decrease in the ratio of NH_4/eNAE except in women when adjusted for age and thus cannot ascribe the change in acid excretion to a shift away from NH_4 excretion (9), although there was great variability in all analyses for this ratio.

Table 4.   Predominant stone composition

Stone Composition	0 Criteria	1 Criterion	2 Criteria	3 or 4 Criteria	P Value
$N=802^a$	376	222	112	92	
Uric acid	24 (6%)	18 (8%)	11 (10%)	30 (33%)	<0.001
CaP	67 (18%)	37 (17%)	15 (13%)	7 (8%)	0.09
CaOx	285 (76%)	167 (75%)	86 (77%)	55 (60%)	0.01
Stones with any uric acid composition					
$N=835$	398	229	116	92	
Any uric acid	28 (7%)	20 (9%)	12 (10%)	30 (33%)	<0.001

CaP, calcium phosphate; CaOx, calcium oxalate.
[a]835 patients had stone data, two were removed with predominately infection stones, two with predominately cystine stone, one with predominately other (CaCarb stone); 28 of these patients did not have >50% of any one stone constituent and were removed from the data.

The main influences on the acid excretion variables in the MetS groups were protein intake and age. When adjusted for protein or age and protein, the increases in NH_4 and NAE and downward trend for NH_4/eNAE in women were attenuated. Only 76% had values allowing calculation of eGFR, with 22 having an eGFR of <30 ml/min per 1.73 m^2. Hence, impaired renal function was an unlikely explanation for changes in acid excretion among the groups.

Urine pH was the only variable that was not influenced by age, sex, protein intake, or any other urine factors analyzed and was independently associated with MetS traits in this analysis as has been noted by others (9,10).

Our findings suggest that those with more MetS traits are heavier and consume more protein and that the changes in renal acid excretion are greatly influenced by dietary protein intake. In a previous study (9) of non–stone formers with MetS, where NAE depended relatively less on NH_4 and more on TA excretion than in those without MetS, diet was not controlled and there was no mention of UUN or estimated protein intake, which may have differed among the groups.

Urine pH

In all prior studies of non–stone formers, urine pH trended down as the number of MetS traits increased (9,10). Urine pH has been shown to decrease with age in both men and women (15). Although those with more MetS traits were older, the trend was not changed when adjusted for age, stratified by sex, or adjusted for protein in our study. Low urine pH can result from increased acid excretion or reduced urinary buffering or both. Reduced NH_4/NAE was noted in a diet-controlled study of UA stone formers who tend to have a lower urine pH, indicating the low urine pH in these subjects could be due to lower buffering from less NH_4, but no comment was made about MetS characteristics (11). We did not find the same pattern in our stone-forming patients with a variety of stone compositions. Urine buffers with organic anions were not assessed but would likely be quantitatively too small to explain any urine pH variability among the groups.

Increased acid excretion results from increased acid generation that in steady state is largely due to dietary protein intake. The findings of a downward trend for Sul excretion, a surrogate for animal protein, loss of the upward trend for P excretion, and attenuation of the trend for TAP when adjusted for protein could be a consequence of greater dietary animal protein intake in those with more MetS traits. Interestingly, Na excretion, which also trended upward in those with more MetS traits, was lost when adjusted for protein. Acid excretion values were not affected when adjusted for GI alkali.

Both lower and higher Cit excretion have been previously described in those with MetS (16,17). We showed an upward trend for Cit excretion in those with more MetS traits that was lost when adjusted for protein intake. Low urine pH and higher acid excretion in those with more MetS traits would reduce not increase Cit excretion.

Effects of Medications

There was an upward trend for both thiazide and Cit intake in those with more MetS traits; however, it is unlikely that these significantly influenced the urine findings because only 4% were taking thiazides and 3% a citrate. Also, for urine Cit, thiazides would not enhance Cit excretion because thiazides cause hypocitraturia. Although Cit intake could increase excretion, the quantitative effect is hard to calculate, and the effect was lost when adjusted for protein. Urine acid excretion values (pH, NH_4, NAE, and Cit) were not changed by excluding those with the Cit supplements listed. The higher NH_4, TAP, eNAE, and lower urine pH should not result from the intake of either of these classes or drugs because they both can cause systemic alkalosis. So, this would not explain the increase in acid excretion.

Effects of Diet

In steady state, urine excretion of Na, K, Ca, P, Mg, and UUN (protein) and volume reflects intake and absorption. There were trends to higher Na and P excretion that were lost and Sul excretion (a surrogate for acidogenic components of animal protein) that decreased when corrected for protein intake, perhaps indicating effects of animal or processed food protein. Ca excretion, while not differing in the unadjusted or age-adjusted analyses, did decrease when adjusted for protein. Urine K excretion was higher in those with more MetS traits in the unadjusted analysis, but this trend was lost when adjusted for protein. This was also expected because protein foods are a source of K. GI alkali, a surrogate for base intake, did not differ among MetS groups with or without adjustment for protein. Dietary

factors in the MetS groups can influence many of the metabolic risk factors found in the urine of stone formers with MetS. Protein intake seems to be the dominant force for the changes noted in urine Ca, P, UA, K, Sul, Cit, and Na. As Na and these other factors are highly correlated with protein (Supplemental Table 4), the findings after adjustment for protein suggest that those with more MetS traits eat protein associated with more processed food with more Na and P.

Stone Formation

Stone formation is usually not caused by a single chemical anomaly but rather a combination of factors influencing urine super-saturation or loss of inhibitors. Standard US dietary patterns are low in plant-based foods and high in animal protein and additives such as P and Na. Those with more MetS traits appeared to consume more animal protein, which tends to increase the risk of stone formation due to an interplay of factors, including increased acid production.

Stone composition was available for only 57% of our patients. So, these findings may not represent stones for the entire group. The majority of stones were CaOx, with fewer being CaP or UA, which is similar to the general population of stone formers. However, the pattern of stone composition was similar to that suggested in other studies of MetS, with a significant trend to more UA stones in those with more MetS traits (10,18). This likely results from the trend to lower urine pH predisposing to the formation of insoluble UA not more soluble Na urate as pH decreases. In addition, both blood and urine UA values were higher in those with more MetS traits—a phenomenon also noted in other studies. CaOx stones were less frequent in those with the most MetS traits, and there was a nonsignificant trend to fewer CaP stones, which could also result from lower urine pH. Urine SSUA and SSCaP mirrored these observations, remaining as significant trends, while SSCaOx showed no relationship to MetS traits.

Limitations

Using registry information has many limitations that can affect both accuracy and interpretation. In this study, these include diagnoses listed on problem lists that are provider dependent, variation in definition, and lack of measurement of some criteria for the metabolic syndrome traits such as waist/hip ratio or fasting blood sugar levels. In addition, we lacked direct measurement of bicarbonate and organic acid excretion. So, we were unable to calculate titratable acid completely. Not all had blood chemistries within 6 months of urine collection, and the number for each value varied. However, we could not detect that these issues were more problematic for any groups in particular. Conclusions about dietary influence on these findings are open to interpretation because even in steady state, excretion reflects not just intake but absorption and perhaps metabolism. This was an observational study of a population that allows for hypothesis generation rather than testing, and none of the findings can prove causality.

Summary

Our study found that stone-forming patients with MetS have a defined pattern of metabolic and dietary risk factors that can contribute to increased risk of stone formation,

including high animal protein, and associated high Na intake and lower urine pH. Greater acid excretion is largely the result of dietary factors, including higher protein intake, although this does not fully explain the urine pH trends. The lower urine pH and associated higher SSUA and lower SSCaP contributed to the distribution of stone composition in those with more MetS traits. Studies are needed to determine if changing specific dietary factors can reduce risk for those with MetS and kidney stones.

Author Contributions

J. Asplin and K. Sternberg were responsible for resources; J. Asplin, P. Callas, and K. Sternberg were responsible for validation; P. Callas, V. Hood, and D. de Waal curated the data; P. Callas was responsible for the formal analysis and the software; P. Callas, V. Hood, C. Mulligan, K. Sternberg, and D. de Waal were responsible for the methodology; V. Hood, C. Mulligan, K. Sternberg, and D. de Waal were responsible for the conceptualization of the study; V. Hood and K. Sternberg were responsible for the investigation; V. Hood wrote the original draft of the manuscript; D. de Waal was responsible for project administration; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0002292021/-/DCSupplemental.

Supplemental Table 1. Urine variables and MetS traits stratified by sex.

Supplemental Table 2. Acid excretion variables adjusted for protein, creatinine, and MetS traits.

Supplemental Table 3. Comparison of NH424/eNAE and MetS traits.

Supplemental Table 4. Correlation coefficients for urine variables.

References

1. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 365: 1415–1428, 2005 https://doi.org/10.1016/S0140-6736(05)66378-7
2. Wong Y, Cook P, Roderick P, Somani BK: Metabolic syndrome and kidney stone disease: A systematic review of literature. *J Endourol* 30: 246–253, 2016 https://doi.org/10.1089/end.2015.0567

3. Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR, Chu DI, Copelovitch L, Saigal CS, Furth SL: Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. *Clin J Am Soc Nephrol* 11: 488–496, 2016 https://doi.org/10.2215/CJN.07610715

4. Taylor EN, Stampfer MJ, Curhan GC: Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 68: 1230–1235, 2005 https://doi.org/10.1111/j.1523-1755.2005.00516.x

5. Ferraro PM, Taylor EN, Eisner BH, Gambaro G, Rimm EB, Mukamal KJ, Curhan GC: History of kidney stones and the risk of coronary heart disease. *JAMA* 310: 408–415, 2013 https://doi.org/10.1001/jama.2013.8780

6. Liu Y-T, Yang P-Y, Yang Y-W, Sun H-Y, Lin I-C: The association of nephrolithiasis with metabolic syndrome and its components: A cross-sectional analysis. *Ther Clin Risk Manag* 13: 41–48, 2017 https://doi.org/10.2147/TCRM.S125480

7. Lutsey PL, Steffen LM, Stevens J: Dietary intake and the development of the metabolic syndrome: The Atherosclerosis Risk in Communities study. *Circulation* 117: 754–761, 2008 https://doi.org/10.1161/CIRCULATIONAHA.107.716159

8. Adeva MM, Souto G: Diet-induced metabolic acidosis. *Clin Nutr* 30: 416–421, 2011 https://doi.org/10.1016/j.clnu.2011.03.008

9. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K: Low urine pH: A novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol* 2: 883–888, 2007 https://doi.org/10.2215/CJN.00670207

10. Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K: The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance. *Kidney Int* 65: 386–392, 2004 https://doi.org/10.1111/j.1523-1755.2004.00386.x

11. Bobulescu IA, Park SK, Xu LHR, Blanco F, Poindexter J, Adams-Huet B, Davidson TL, Sakhaee K, Maalouf NM, Moe OW: Net acid excretion and urinary organic anions in idiopathic uric acid nephrolithiasis. *Clin J Am Soc Nephrol* 14: 411–420, 2019 https://doi.org/10.2215/CJN.10420818

12. Kok DJ, Poindexter J, Pak CY: Calculation of titratable acidity from urinary stone risk factors. *Kidney Int* 44: 120–126, 1993 https://doi.org/10.1038/ki.1993.221

13. Maroni BJ, Steinman TI, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 27: 58–65, 1985 https://doi.org/10.1038/ki.1985.10

14. Oh MS: A new method for estimating G-I absorption of alkali. *Kidney Int* 36: 915–917, 1989 https://doi.org/10.1038/ki.1989.280

15. Menezes CJ, Worcester EM, Coe FL, Asplin J, Bergsland KJ, Ko B: Mechanisms for falling urine pH with age in stone formers. *Am J Physiol Renal Physiol* 317: F65–F72, 2019 https://doi.org/10.1152/ajprenal.00066.2019

16. Cupisti A, Meola M, D'Alessandro C, Bernabini G, Pasquali E, Carpi A, Barsotti G: Insulin resistance and low urinary citrate excretion in calcium stone formers. *Biomed Pharmacother* 61: 86–90, 2007 https://doi.org/10.1016/j.biopha.2006.09.012

17. Kamel KS, Cheema-Dhadli S, Halperin ML: Studies on the pathophysiology of the low urine pH in patients with uric acid stones. *Kidney Int* 61: 988–994, 2002 https://doi.org/10.1046/j.1523-1755.2002.00197.x

18. Maalouf NM: Metabolic syndrome and the genesis of uric acid stones. *J Ren Nutr* 21: 128–131, 2011 https://doi.org/10.1053/j.jrn.2010.10.015

Association of Urine Findings with Met-S Traits in a Population of Patients with Nephrolithiasis

Supplementary Tables

Table 1S. Urine Variables and Met-s Traits stratified by gender

		Mean				Trend
		Number of Metabolic Syndrome Traits				
Age adjusted comparisons		0	1	2	3,4	P Value
N		684	425	211	153	
	N Female (F)	329	200	108	55	
	N Male (M)	355	225	103	98	
Vol 24 (L/d)		2.0	1.9	2.0	2.0	0.77
	F	1.8	1.8	2.0	1.8	0.83
	M	2.0	2.0	2.0	2.0	0.94
Cr24 (mg/d)		1330	1469	1453	1518	<0.001
	F	1020	1148	1200	1227	<0.001
	M	1596	1758	1751	1716	0.006
pH		6.1	6.0	6.0	5.8	<0.001
	F	6.2	6.1	6.0	5.8	<0.001
	M	6.1	6.0	5.9	5.8	<0.001
Ca24 (mg/d)		204	220	213	215	0.44
	F	197	200	207	183	0.49
	M	209	238	221	236	0.17
SSCaP		1.2	1.2	1.1	1.0	0.01
	F	1.3	1.2	1.1	1.1	0.09
	M	1.2	1.2	1.1	1.0	0.06
SSCaOx		6.4	6.9	6.6	6.5	0.98
	F	6.3	6.6	6.6	6.2	0.85
	M	6.5	7.2	6.7	6.7	0.94
Ox24 (mg/d)		35	39	41	42	<0.001

	F	30	34	37	41	<0.001
	M	40	43	45	44	0.12
Cit24 (mg/d)		578	606	626	664	0.01
	F	545	565	616	576	0.39
	M	608	642	637	715	0.02
UA24 (g/d)		0.59	0.64	0.67	0.70	<0.001
	F	0.51	0.56	0.62	0.61	<0.001
	M	0.66	0.72	0.73	0.76	<0.001
SSUA		0.8	1.0	1.1	1.3	<0.001
	F	0.7	0.8	1.0	1.3	<0.001
	M	0.9	1.2	1.2	1.4	<0.001
Na24 (mmol/d)		151	180	177	183	<0.001
	F	128	149	168	158	<0.001
	M	171	208	188	200	0.03
K24 (mmol/d)		61	64	66	67	0.003
	F	51	53	60	57	0.02
	M	70	73	73	74	0.12
Cl24 (mmol/d)		151	178	178	187	<0.001
	F	129	149	171	162	<0.001
	M	170	205	189	203	0.003
P24 (g/d)		0.89	0.97	0.97	1.00	0.001
	F	0.75	0.78	0.86	0.88	<0.001
	M	1.02	1.14	1.11	1.09	0.14
Sul24 (mEq/d)		37	40	39	41	0.02
	F	30	32	32	32	0.23
	M	42	47	46	46	0.07
Mg24 (mg/d)		99	103	104	106	0.06

	F	88	90	91	101	0.03
	M	107	115	118	111	0.42
UUN24 (g/d)		10.4	11.3	11.3	12.0	<0.001
	F	8.6	9.2	9.7	9.9	0.004
	M	11.9	13.1	13.1	13.4	0.003
Protein (calculated)		80	88	88	95	<0.001
	F	67	74	78	81	<0.001
	M	91	101	101	104	<0.001
$NH_4$24 (mmol/d)		33	36	36	38	<0.001
	F	28	32	33	33	0.02
	M	36	39	41	41	0.02
TAP		17	19	20	22	<0.001
	F	14	15	17	19	<0.001
	M	20	23	23	23	0.002
eNAE		44	50	52	56	<0.001
	F	36	40	46	49	<0.001
	M	51	58	60	61	0.001
$NH_4$24/eNAE		0.77	0.70	0.67	0.61	0.08
	F	0.91	0.70	0.69	0.52	0.02
	M	0.65	0.71	0.66	0.66	0.99
GI alkali		27	29	27	25	0.23
	F	24	25	26	20	0.29
	M	31	32	28	29	0.31

Table 2S: Acid Excretion Variables Adjusted for Protein, Creatinine and Met-S Traits

	Mean				Trend
	Number of Metabolic Syndrome Traits				
	0	1	2	3,4	P Value
All Patients					
N	684	425	211	153	
NH4					
Unadjusted	34	35	35	36	0.18
Adjusted for protein	35	34	34	33	0.01
Adjusted for creatinine	35	34	35	34	0.76
TAP					
Unadjusted	17	19	20	22	<0.001
Adjusted for protein	18	19	19	19	0.02
Adjusted for creatinine	18	19	19	21	<0.001
eNAE					
Unadjusted	45	50	51	55	<0.001
Adjusted for protein	48	48	49	49	0.45
Adjusted for creatinine	47	48	50	52	0.007

Table 3S. Comparison of NH$_4$24/eNAE and Met-S Traits

	Mean (SD)				
	Number of Metabolic Syndrome Traits				Trend
	0	1	2	3,4	P Value
Unadjusted					
NH$_4$24/eNAE	0.76 (1.25)	0.71(0.85)	0.69 (0.71)	0.64 (0.35)	0.17
Female (F)	0.88 (1.32)	0.70 (0.99)	0.72 (0.93)	0.60 (0.24)	0.10
Male (M)	0.65 (1.16)	0.71 (0.74)	0.65 (0.39)	0.66 (0.40)	0.94
Gender by metabolic traits interaction					0.16
Age adjusted					
NH$_4$24/eNAE	0.77	0.70	0.67	0.61	0.08
F	0.91	0.70	0.69	0.52	0.02
M	0.65	0.71	0.66	0.66	0.99
Gender by metabolic traits interaction					0.16
Protein adjusted					
NH$_4$24/eNAE	0.75	0.71	0.70	0.66	0.32
F	0.87	0.71	0.75	0.63	0.19
M	0.65	0.71	0.65	0.66	0.99
Gender by metabolic traits interaction					0.16
Age and protein adjusted					
NH$_4$24/eNAE	0.76	0.71	0.68	0.63	0.17
F	0.89	0.71	0.71	0.55	0.05
M	0.64	0.71	0.66	0.67	0.94
Gender by metabolic traits interaction					0.16

Table 4S: Correlation Coefficients for Urine Variables

	Protein	Age	Cit24	Na24	K24	$NH_4$24	GI alkali
Protein	1						
Age	0.03	1					
P value	0.19						
Cit24	0.26	0.06	1				
P value	<0.001	0.02					
Na24	0.61	-0.07	0.24	1			
P value	<0.001	0.01	<0.001				
K24	0.60	0.16	0.38	0.43	1		
P value	<0.001	<0.001	<0.001	<0.001			
$NH_4$24	0.60	-0.17	0.08	0.32	0.15	1	
P value	<0.001	<0.001	0.004	<0.001	<0.001		
GI alkali	0.22	0.09	0.39	0.39	0.54	-0.32	1
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

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Supplementary Tables

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Vol 24 (L/d)		2.0	1.9	2.0	2.0	0.77
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Ca24 (mg/d)		204	220	213	215	0.44
	F	197	200	207	183	0.49
	M	209	238	221	236	0.17
SSCaP		1.2	1.2	1.1	1.0	0.01
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Age and protein adjusted					
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M	0.64	0.71	0.66	0.67	0.94
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P value	0.19						
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P value	<0.001	0.02					
Na24	0.61	-0.07	0.24	1			
P value	<0.001	0.01	<0.001				
K24	0.60	0.16	0.38	0.43	1		
P value	<0.001	<0.001	<0.001	<0.001			
NH$_4$24	0.60	-0.17	0.08	0.32	0.15	1	
P value	<0.001	<0.001	0.004	<0.001	<0.001		
GI alkali	0.22	0.09	0.39	0.39	0.54	-0.32	1
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	