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# Association of Urine Findings with Metabolic Syndrome Traits in a Population of Patients with Nephrolithiasis

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Kidney360

# Association of Urine Findings with Metabolic Syndrome Traits in a Population of Patients with Nephrolithiasis

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## 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.

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## 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

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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

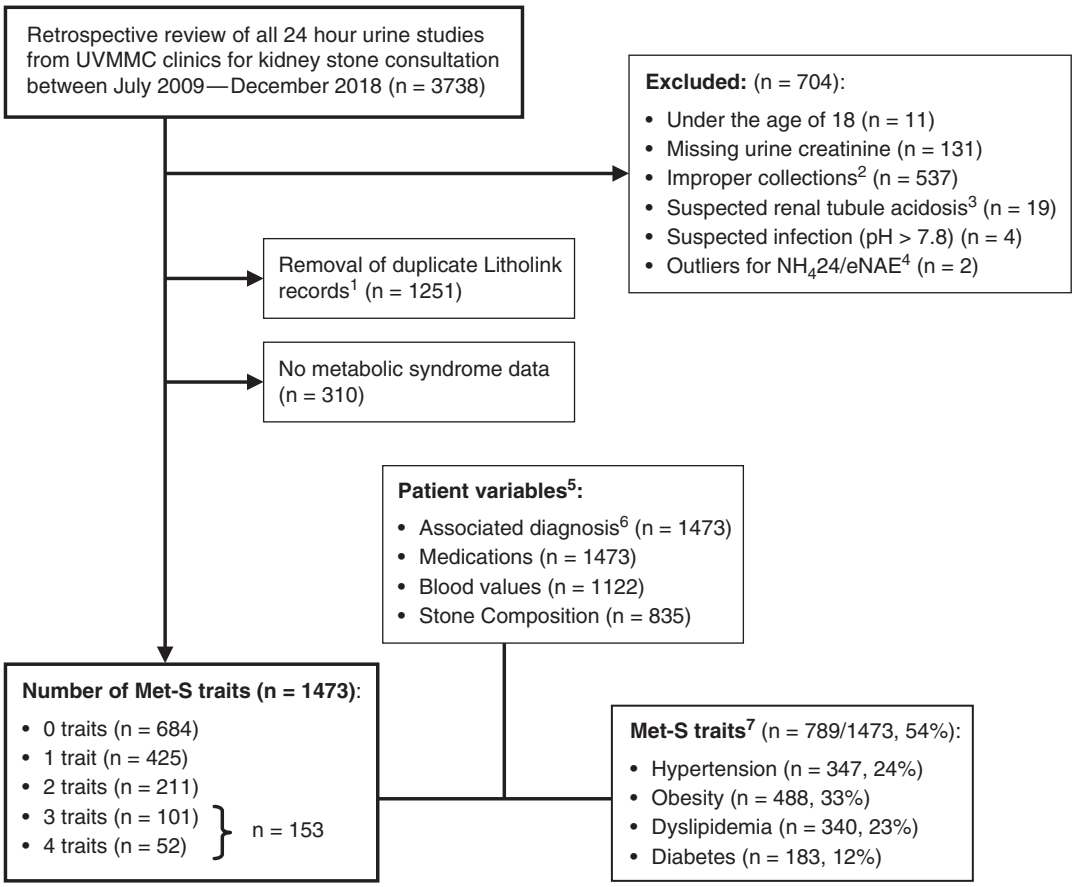


**Figure 1.** | **Study flow diagram.** 1. If a patient had more than one urine test, the earliest one obtained was used to minimize any treatment effects. 2. Improper collections defined as outside expected range of urine creatinine on the basis of weight (8.7–20.3 mg/kg for women; 11.9–24.4 mg/kg for 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$24/eNAE absolute values of 194 and 74 with the next highest 16. 5. Blood values within 6 months of urine collection; stone composition values within 1 year of urine collection. 6. Diagnosis on the basis of ICD-9 and -10 codes listed on "problem list" in medical records. 7. MetS traits defined (1) as needing at least one quality listed: (*1*) Hypertension defined as: diagnosis on problem list, two systolic BP readings >140 mmHg within 6 months of one another, on at least two medications for hypertension. In group 1, 18% had hypertension as the only MetS trait documented. (*2*) Obesity defined as: diagnosis on problem list, body mass index >30 kg/$m^2$. (*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_4$24+TAP–Ubicarbonate |
| TAP | TAP=P24 × 1000/31⟨{1/[antilog (urine pH–6.8)+1]}–0.2⟩ |
| Urine bicarbonate, $CO_2$ | Ubicarbonate=vol. (L)×[1.2×antilog (UpH–6.1)] |
| GI alkali | {[Na24+K24+(Ca24/40)×2+(Mg24/24.3)×2]–[Cl24+(P24 × 1000/31)×1.8]} |
| Calculated protein intake, g/d | 6.25×(UUN24+eNUN)<br>where eNUN=weight (kg)×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.

### Disclosures

J. Asplin is currently employed by Litholink Corporation, has ownership interest in LabCorp, and other interests in/relationships with Oxalosis and Hyperoxaluria Foundation Scientific Advisory Committee. All remaining authors have nothing to disclose.

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### 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.

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**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 | | | | |
|---|---|---|---|---|---|
| | Number of Metabolic Syndrome Traits | | | | Trend |
| **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 | | | | |
|---|---|---|---|---|---|
| | Number of Metabolic Syndrome Traits | | | | Trend |
| | 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 | |

**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 | | | | |
|---|---|---|---|---|---|
| | Number of Metabolic Syndrome Traits | | | | Trend |
| **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 | | | | |
|---|---|---|---|---|---|
| | Number of Metabolic Syndrome Traits | | | | Trend |
| | 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 | |