World Journal of Urology (2021) 39:4483–4490
https://doi.org/10.1007/s00345-021-03790-7

ORIGINAL ARTICLE

The impact of metabolic syndrome components on urinary parameters and risk of stone formation

Jacob N. Bamberger[1,2] · Daniel C. Rosen[1] · Johnathan A. Khusid[1] · Elie Kaplan-Marans[1] · Blair Gallante[1] · Arjun Kapoor[1] · Ishan Paranjpe[1] · Danie J. Atashsokhan[1] · William M. Atallah[1] · Mantu Gupta[1]

Received: 28 February 2021 / Accepted: 9 July 2021 / Published online: 15 July 2021

Abstract

Purpose To investigate the relationship between metabolic syndrome (MS) and urinary abnormalities in stone-forming patients. Additionally, to delineate whether severity of urinary derangements is impacted by the number of co-occurring MS components.

Methods Stone-forming patients who underwent initial metabolic workup prior to medical intervention at a comprehensive stone clinic were retrospectively reviewed and included in the study. Patients were given a six point (0–5) Metabolic Syndrome Severity Score (MSSS) based on the number of co-occurring MS components and split into six respective groups. Baseline clinical characteristics and metabolic profiles were compared between groups.

Results Four-hundred-ninety-five patients were included in the study. Median age and median BMI was 58 years and 27.26 kg/m^2, respectively. Several significant metabolic differences were noted, most notably a downward trend in median urinary pH ($p < 0.001$) and an upward trend in median urinary supersaturation uric acid ($p < 0.001$) across groups as MSSS increased. Multivariate analysis demonstrated an independent association between higher MSSS and increasing number of urinary abnormalities. A second multivariate analysis revealed that all MS components except hyperlipidemia were independently associated with low urinary pH. Additionally, obesity was independently associated with the greatest number of urinary abnormalities and had the strongest association with hyperuricosuria.

Conclusions Prior research has attributed the strong association of nephrolithiasis and MS to high prevalence of UA nephrolithiasis and low urinary pH. Our findings indicate that all MS components with the exception of hyperlipidemia were independently associated with low urinary pH suggesting a mechanism independent from insulin resistance.

Keywords Nephrolithiasis · Metabolic syndrome · 24-Hour urinalysis · Diabetes mellitus

Abbreviations

MSSS	Metabolic Syndrome Severity Score
MS	Metabolic syndrome
DM	Diabetes mellitus
HLD	Hyperlipidemia
HTN	Hypertension
HTG	Hypertriglyceridemia
IDF	International diabetes federation
AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
BMI	Body mass index
HbA1c	Glycated hemoglobin
SSCaP	Supersaturation calcium phosphate
Ca24	24-Hour urinary calcium
Ox24	24-Hour urinary oxalate
Cit24	24-Hour urinary citrate
SSCaOx	Supersaturation calcium oxalate
SSUA	Supersaturation uric acid
UA24	24-Hour urinary uric acid
Na24	24-Hour urinary sodium
$NH_4$24	24-Hour urinary ammonium
CaOx	Calcium oxalate
UA	Uric acid
OR	Odds ratio
AUA	American Urologic Association

✉ Jacob N. Bamberger
jacob.bamberger@downstate.edu

[1] Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2] SUNY Downstate College of Medicine, Brooklyn, NY, USA

Introduction

Metabolic syndrome (MS) is defined by several coexisting risk factors, which collectively contribute to patient morbidity. More specifically, MS is defined the presence of three or more of the five following coexisting conditions: obesity, diabetes mellitus (DM), hyperlipidemia (HLD), hypertension (HTN), and hypertriglyceridemia (HTG) [1, 2]. Nephrolithiasis is a common urologic pathology and an association between MS and kidney stone disease has been identified [3]. In particular, insulin resistance, which is a principal component of MS, has been implicated as a cause of decreased urinary pH and concurrent increase in uric acid urolithiasis [4–6]. However, the existing literature is limited by a paucity of large cohorts with granular information on both the clinical components of MS as well as 24-h urinary parameters prior to the initialization of treatment.

Kidney stone formers frequently have metabolic abnormalities on 24-h urinalysis and accordingly, 24-h urine analysis is recommended for the work up of recurrent stone formers or patients suspected to be at an elevated risk for recurrent stone formation [7]. Abnormalities on 24-h urine analysis could present predictable, modifiable targets for medical treatment and prevention of future stones. However, prior research has suggested low utilization of 24-h urine studies amongst high-risk stone formers [8]. Furthermore, given the chronic nature of the MS, any added risk of urolithiasis related to 24-h urine abnormalities may persist or worsen throughout the patient's life if left untreated. Prior studies have demonstrated that the presence of a greater number of MS features is associated with adverse outcomes in other disease states. For example, the presence of five MS components confers greater cardiovascular mortality risk than the presence of three MS components [9]. Thus, in the present study we seek to determine which, if any, 24-h urinary abnormalities are associated with MS, and if an association exists between number of MS traits and severity of 24-h urine analysis derangements.

Materials and methods

Data source and patient population

After obtaining Institutional Review Board approval, we queried our existing endourology database of kidney stone-forming patients who underwent initial metabolic workup at a comprehensive kidney stone clinic in New York City, New York between July 2016 and July 2020. Only patients with a self-reported or specimen proven history of kidney stones, no prior medical treatment of stone disease, and a completed a 24-h urine analysis were included in the study. Patients without any MS components were used as a referent cohort and patients with one or two MS components were included to assess whether metabolic changes occur on a gradient with respect to increasing number of MS components. Patients on any medications aimed at preventing kidney stones at the time of 24-h urine collection were excluded from the study.

Patient characteristics

Patients were scored on a six-point (0–5) MS severity score (MSSS) adapted from the International Diabetes Federation (IDF) and American Heart Association/ National Heart, Lung, and Blood Institute (AHA/NHLBI) guidelines [2]. A patient's MSSS was defined by the sum of the following co-occurring components: (1) obesity—body mass index (BMI) > 30 kg/m^2, (2) DM—current diagnosis or HbA1c ≥ 6.5, (3) diagnosis or treatment of HLD, (4) diagnosis or treatment of HTN, (5) diagnosis or treatment of HTG. The purpose of the zero to five scale used in our analysis was to evaluate whether the effects of MS on metabolic urinary parameters occur in a stepwise fashion. Each component of the MSSS is weighed equally as is consistent with MS components when conferring a clinical diagnosis.

Demographic, clinical, and urinary parameters

Patient demographics, BMI, glycated hemoglobin (HbA1c), prescription medications, and history of DM, HTN, HLD, HTG were obtained from their electronic medical record. Urinary parameters including supersaturation calcium phosphate (SSCaP), calcium (Ca24), oxalate (Ox24), citrate (Cit24), supersaturation calcium oxalate (SSCaOx), pH, supersaturation uric acid (SSUA), uric acid (UA24), sodium (Na24), and ammonium ($NH_4$24) were all collected using the commercially available LithoLink (Litholink, Chicago, IL, USA) 24-h urine analysis. Abnormalities for each metric were identified as deviations from the normal range defined within the LithoLink report.

Stone analysis

Stone samples, either passed and retrieved by the patient or surgically retrieved, were analyzed using infrared spectroscopy (LabCorp, Burlington, NC, USA). Stones were categorized into one of three groups: $> 50\%$ calcium oxalate (CaOx), $> 50\%$ uric acid (UA), or other/mixed based on reported compositions.

Statistical analysis

Baseline patient characteristics were compared between the six MSSS groups using Kruskal–Wallis test for continuous

variables and chi-square test for categorical variables. Univariate comparison of urinary parameters between study cohorts were performed using Kruskal–Wallis tests. Bonferroni post hoc testing was used for any significant metabolic differences across the significant groups to elucidate any significant inter-group differences. Multivariate linear regressions were performed to analyze the association of urinary composition and MSSS adjusting for patient characteristics including age, sex, serum uric acid, and serum creatinine. An additional multivariable linear regression was conducted to analyze the independent effect of each component of MS on each urinary parameter. Binomial regression was used to analyze the relationship between MSSS and stone composition. All analyses were two-tailed and performed using Stata/MP software version 14.1 (StataCorp, College Station, TX).

Results

Baseline characteristics

Baseline characteristics between the six groups are presented in Table 1. Of the 1,056 patients in our database, 495 (46.9%) patients met the inclusion criteria and were included in the study. A statistically significant difference in median age (MSSS 0 = 52 years vs. MSSS 2 = 54 years vs. MSSS 3 = 61 years vs. MSSS 4 = 65.5 years vs. MSSS 5 = 58 years, $p < 0.001$), median BMI (MSSS 0 = 25.1 kg/m^2 vs. MSSS 1 = 28.0 kg/m^2 vs. MSSS 2 = 28.1 kg/m^2 vs. MSSS 3 = 28.7 kg/m^2 vs. MSSS 4 = 29.8 kg/m^2 vs. MSSS 5 = 34.8 kg/m^2, $p < 0.001$), and serum uric acid (MSSS 0 = 4.6 mg/dL vs. MSSS 1 = 5.8 mg/dL vs. MSSS 2 = 6.1 mg/dL vs. MSSS 3 = 5.6 mg/dL vs. MSSS 4 = 5.7 mg/dL vs. MSSS 5 = 7.1 mg/dL, $p = 0.025$) was noted between the groups. Additionally, gender distribution was also found to be significantly different between the study groups (MSSS 0 = 51.7% male vs. MSSS 1 = 46.9% male vs. MSSS 2 = 62.5% male vs. MSSS 3 = 57.9% male vs. MSSS 4 = 72.2% male vs. MSSS 5 = 52.6% male, $p = 0.039$).

Metabolic syndrome and urine parameters

Based on univariate analysis, patients with a higher MSSS score were more likely to demonstrate urinary derangements in a 24-h urine test. As shown in Table 1, several significant differences were noted including SSCaP (MSSS 0 = 0.8 vs. MSSS 1 = 0.6 vs. MSSS 2 = 0.6 vs. MSSS 3 = 0.4 vs. MSSS 4 = 0.3 vs. MSSS 5 = 0.2, $p < 0.001$), urinary pH (MSSS 0 = 6.2 vs. MSSS 1 = 5.9 vs. MSSS 2 = 5.8 vs. MSSS 3 = 5.7 vs. MSSS 4 = 5.6 vs. MSSS 5 = 5.7, $p < 0.001$) (Fig. 1A), SSUA (MSSS 0 = 0.5 vs. MSSS 1 = 0.9 vs. MSSS 2 = 0.9 vs. MSSS 3 = 1.0 vs. MSSS 4 = 1.3 vs. MSSS 5 = 1.1, $p < 0.001$), and sodium excretion (MSSS 0 = 132.9 vs. MSSS 1 = 150.7 vs. MSSS 2 = 168.2 vs. MSSS 3 = 164.2 vs. MSSS 4 = 163.6 vs. MSSS 5 = 193.1, $p = 0.004$). In the Bonferroni post hoc test, groups of patients with 3, 4, and 5 MSSS risk factors exhibited significantly lower pH compared to the 0 MSSS risk factor group (MSSS 3 = 5.7 vs. MSSS 0 = 6.2, $p = 0.021$; MSSS 4 = 5.6 vs. MSSS 0 = 6.2, $p < 0.001$; and MSSS 5 = 5.7 vs. MSSS 0 = 6.2, $p = 0.037$). Additionally, the cohort with four risk factors had significantly greater SSUA compared to the group with 0, MSSS 4 = 1.3 vs. MSSS 0 = 0.5, $p = 0.003$.

Multivariate linear regression analyses adjusted for age, sex, serum creatinine, and serum UA revealed that patients demonstrated significant urinary changes with a higher MSSS (Table 2). Notably, when compared to patients with MSSS equal to zero and held as a referent, patients with one or more risk factors were significantly more likely to have low urinary pH (MSSS 1 odds ratio [OR] 1.97, $p = 0.001$; MSSS 2 OR 2.48, $p = 0.002$; MSSS 3 OR 3.15, $p < 0.001$; MSSS 4 OR 5.71, $p < 0.001$; MSSS 5 OR 2.92, $p = 0.029$).

Individual components of metabolic syndrome and urine parameters

On multivariate testing, each MS component, aside from HLD, was found to be independently associated with changes in urinary parameters. Obesity was independently associated with hyperuricosuria (OR 3.3; CI 2.1–5.1, $p < 0.001$), increased SSUA (OR 1.63; CI 1.1–2.5, $p = 0.020$), hypercalciuria (OR 1.65; CI 1.1–2.6, $p = 0.024$), and hyperoxaluria (OR 1.93; CI 1.3–2.9; $p = 0.002$). Diabetes mellitus was independently associated with increased SSUA (OR 1.68; CI 1.1–2.6, $p = 0.021$), low urinary pH (OR 2.63; CI 1.7–4.1, $p < 0.001$). Hypertension was associated with lower urinary pH (OR 1.56; CI 1.0–2.4; $p = 0.040$) as was HTG (OR 1.8; CI 1.0–3.1, $p = 0.038$). No MS components were found to independently predict hypocitraturia or elevated SSCaOx (Table 2).

Stone analysis

Three-hundred-twenty-two patients had a known stone composition and were included in an additional sub-analysis pertaining to stone composition (Supplementary Table 1 and Fig. 1B). Patients in the MSSS 0 group had the highest rates of predominately CaOx stones (79.2%), whereas only 60% of those in the MSSS 3 group had predominately CaOx stones (OR 0.39; 95% CI 0.19, 0.81, $p = 0.011$). The decreased percentage of CaOx stones was due to an increased rate of UA stones. Patients with MSSS equal to or greater than 2 were found to have significantly higher rates of predominately UA stones compared to patients with no MS risk factors (OR

Table 1 Baseline patient characteristics and 24-h urine parameters stratified by metabolic syndrome severity score

Metabolic Syndrome Severity Score							*p*
MSSS	0	1	2	3	4	5	
n (%)	176 (35.6)	98 (19.8)	72 (14.5)	76 (15.4)	54 (10.9)	19 (3.8)	
Baseline patient characteristics							
Median (IQR)[a]							
Age, years	52.0 (38.0, 62.5)	54.0 (45.0, 65.0)	61.0 (54.0, 66.0)	65.5 (51.0, 71.0)	65.0 (57.0, 70.0)	58.0 (51.0, 65.0)	**< 0.001**
BMI, kg/m^2	25.1 (21.9, 26.8)	28.0 (24.8, 32.1)	28.1 (25.4, 34.6)	28.7 (25.7, 32.6)	29.8 (27.4, 34.4)	34.8 (31.8, 35.9)	**< 0.001**
Serum UA, mg/dL	4.6 (3.8, 5.9)	5.8 (4.8, 6.7)	6.1 (5.6, 6.8)	5.6 (4.4, 6.8)	5.7 (4.5, 7.2)	7.1 (5.7, 7.4)	**0.025**
N (%)[b]							
Sex							
Male	91 (51.7)	46 (46.9)	45 (62.5)	44 (57.9)	39 (72.2)	10 (52.6)	**0.039**
Female	85 (48.3)	52 (53.1)	27 (37.5)	32 (42.1)	15 (27.8)	9 (47.4)	
Diabetes Mellitus	0 (0.0)	16 (16.3)	29 (40.3)	36 (47.4)	44 (81.5)	19 (100.0)	**< 0.001**
Hypertension	0 (0.0)	31 (31.6)	41 (56.9)	49 (64.5)	48 (88.9)	19 (100.0)	**< 0.001**
Hyperlipidemia	0 (0.0)	6 (6.1)	20 (27.8)	52 (68.4)	46 (85.2)	19 (100.0)	**< 0.001**
Hypertriglyceridemia	0 (0.0)	12 (12.2)	27 (37.5)	58 (76.3)	52 (96.3)	19 (100.0)	**< 0.001**
24-h urine parameters							
Median (IQR)[a]							
Volume[c]	1.7 (1.2, 2.3)	1.8 (1.2, 2.5)	1.8 (1.4, 2.4)	2.0 (1.5, 2.7)	2.0 (1.4, 2.5)	1.7 (1.3, 2.4)	0.2
SS CaOx	6.1 (3.7, 9.1)	5.9 (3.9, 9.0)	6.0 (3.6, 8.6)	5.6 (3.4, 8.3)	6.2 (4.4, 8.2)	5.1 (2.3, 9.4)	0.8
Calcium[d]	158.2 (106.5, 224.5)	175.2 (108.2, 258.8)	160.2 (102.4, 221.7)	169.7 (96.1, 275.7)	155.7 (117.1, 248.0)	147.0 (79.0, 260.0)	0.8
Oxalate[d]	35.8 (29.2, 43.6)	38.0 (27.4, 44.9)	36.1 (27.7, 50.4)	36.9 (30.0, 48.0)	43.8 (31.8, 51.6)	34.1 (27.0, 53.0)	0.082
Citrate[d]	507.3 (373.4, 739.0)	576.0 (357.1, 752.6)	526.7 (329.9, 855.9)	579.9 (385.0, 850.7)	527.0 (358.0, 879.0)	672.7 (266.0, 1037.6)	0.7
SSCaP	0.8 (0.4, 1.6)	0.6 (0.3, 1.5)	0.6 (0.2, 1.3)	0.4 (0.1, 1.0)	0.3 (0.1, 0.8)	0.2 (0.1, 1.3)	**< 0.001**
pH	6.2 (5.7, 6.5)	5.9 (5.6, 6.4)	5.8 (5.5, 6.5)	5.7 (5.4, 6.3)	5.6 (5.4, 5.9)	5.7 (5.3, 6.2)	**< 0.001**
SSUA	0.5 (0.2, 1.3)	0.9 (0.3, 1.5)	0.9 (0.3, 2.1)	1.0 (0.4, 1.8)	1.3 (0.7, 2.0)	1.1 (0.5, 1.8)	**< 0.001**
Uric Acid[e]	0.6 (0.5, 0.7)	0.7 (0.4, 0.8)	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)	0.7 (0.5, 0.8)	0.6 (0.4, 1.0)	0.3
Sodium[f]	132.9 (107.6, 171.5)	150.7 (101.0, 222.6)	168.2 (115.3, 205.6)	164.2 (124.7, 201.2)	163.6 (117.6,209.0)	193.1 (130.3, 224.9)	**0.004**
Ammonium[e]	34.0 (25.5, 43.8)	38.8 (24.5, 48.2)	31.9 (21.1, 39.6)	31.5 (22.0, 46.5)	34.0 (24.4, 44.4)	36.0 (22.5, 49.2)	0.3

Significant ($p < 0.05$) values bolded

IQR interquartile range, *BMI* body mass index, *SS CaOx* supersaturation calcium oxalate, *SSCaP* supersaturation calcium phosphate, *SSUA* supersaturation uric acid

[a]Kruskal-Wallis test

[b]Chi-square test

[c]L/day

[d]mg/day

[e]g/day

[f]mmol/day

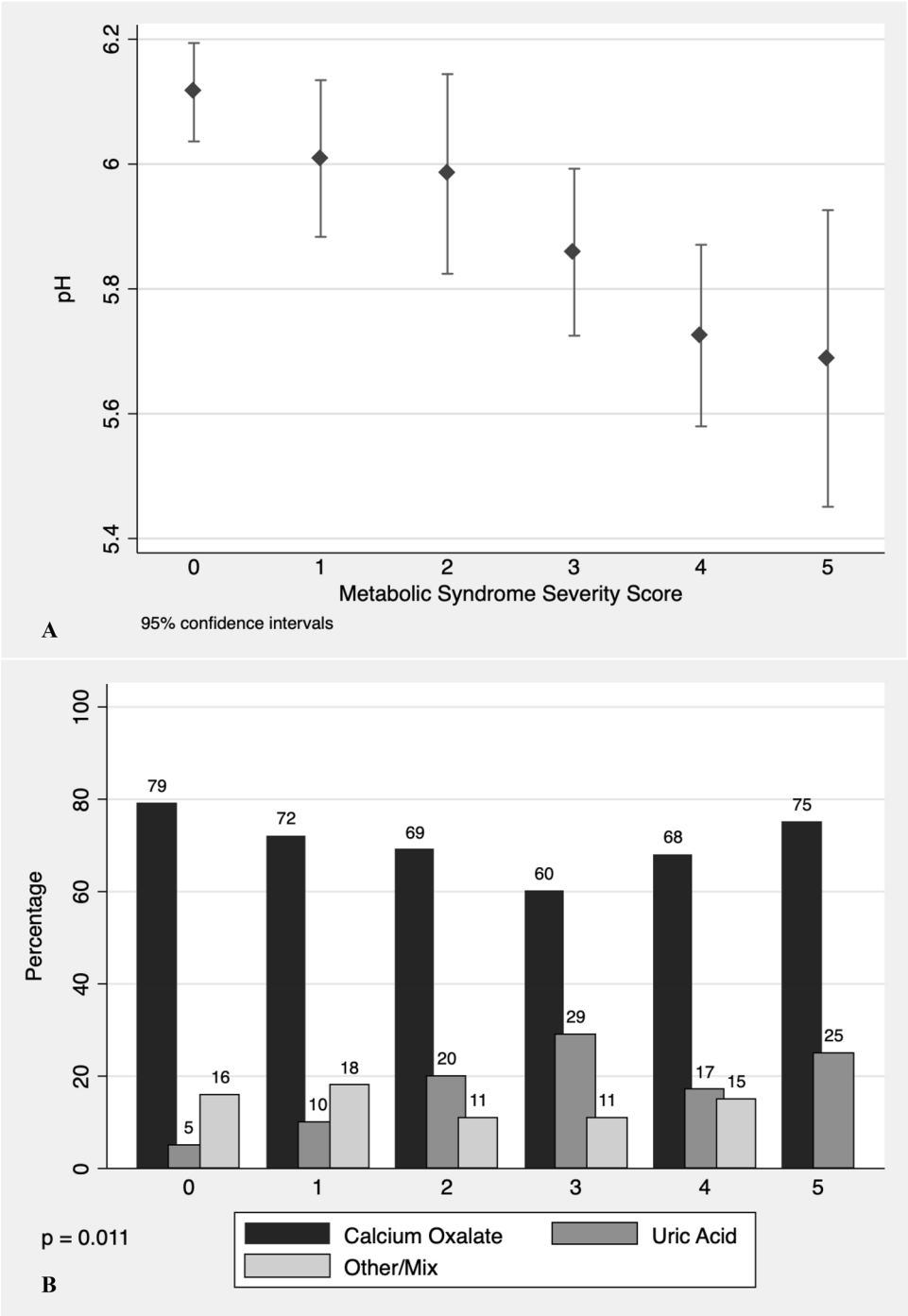

Fig. 1 Mean urinary pH (**A**) and percent stone compositions (**B**) stratified by Metabolic Syndrome Severity Score

2.06–7.88, $p < 0.05$). No significant differences were noted in rates of mixed/other stones between groups.

An additional *post hoc* test was performed to assess differences in UA stone rates between patients with obesity and HLD compared to patients with no obesity and no HLD. In patients with obesity and HLD ($n = 162$), 32 (68.09%) formed UA stones compared to 15 patients (31.91%) in the no obesity and no HLD cohort ($n = 160$), $p = 0.008$ (Supplementary Table 2).

Discussion

Metabolic syndrome is a common and chronic health condition that has been associated with an increased risk of nephrolithiasis [1]. The American Urologic Association (AUA) recommends that recurrent stone formers undergo a 24-h urine analysis to identify modifiable urinary abnormalities that may increase the risk of subsequent stone episodes [7, 10]. Yet 24-h urine studies are notably underutilized [8].

Table 2 Multivariate analysis of metabolic syndrome severity score and individual components of metabolic syndrome on urinary parameters

Metabolic syndrome severity score on urinary parameters[a]										
	1		2		3		4		5	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Hyperuricosuria	1.96 (1.10,3.48)	**0.022**	1.83 (0.97,3.45)	0.064	1.77 (0.95,3.32)	0.072	2.04 (1.02,4.07)	**0.043**	2.05 (0.72,5.80)	0.177
Increased SSUA	1.89 (1.13,3.14)	0.000	1.99 (1.13,3.49)	0.000	2.17 (1.25,3.75)	**0.006**	3.49 (1.85,6.59)	**< 0.001**	2.47 (0.95,6.42)	0.064
Low pH	1.97 (1.17,3.31)	**0.011**	2.48 (1.41,4.39)	**0.002**	3.15 (1.80,5.51)	**< 0.001**	5.71 (2.94,11.09)	**< 0.001**	2.92 (1.12,7.62)	**0.029**
Hypercalciuria	1.37 (0.80,2.35)	0.248	0.77 (0.40,1.48)	0.434	1.54 (0.87,2.74)	0.137	0.77 (0.37,1.59)	0.483	1.97 (0.74,5.19)	0.172
Hyperoxaluria	1.26 (0.75,2.09)	0.382	1.28 (0.73,2.26)	0.390	1.21 (0.70,2.11)	0.495	2.56 (1.37,4.78)	0.003	1.71 (0.66,4.44)	0.270
Hypocitraturia	0.76 (0.46,1.26)	0.290	1.42 (0.82,2.47)	0.211	0.61 (0.35,1.07)	0.086	1.2 (0.65,2.22)	0.554	0.7 (0.26,1.87)	0.478
Increased SS CaOx	0.61 (0.30,1.21)	0.158	0.79 (0.39,1.64)	0.532	0.53 (0.24,1.16)	0.110	0.79 (0.35,1.78)	*0.575*	0.74 (0.21,2.70)	0.654
Increased SS CaP	1.28 (0.68,2.41)	0.441	0.81 (0.37,1.76)	0.588	0.66 (0.30,1.47)	0.313	0.09 (0.01,0.71)	**0.022**	0.28 (0.04,2.16)	0.221
Metabolic syndrome components on urinary parameters[b]										
	Diabetes Mellitus		Obesity		Hypertension		Hyperlipidemia		Hypertriglyceridemia	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Hyperuricosuria	1.04 (0.63,1.72)	0.87	3.3 (2.11,5.14)	**< 0.001**	0.96 (0.60,1.54)	0.864	1.03 (0.55, 1.93)	0.918	0.83 (0.45, 1.53)	0.542
Increased SS Uric Acid	1.68 (1.08,2.59)	**0.021**	1.63 (1.08,2.46)	**0.02**	1.12 (0.74,1.70)	0.587	0.82 (0.47,1.43)	0.481	1.5 (0.87,2.56)	0.142
Low pH	2.63 (1.68,4.10)	**< 0.001**	1.27 (0.83,1.94)	0.274	1.56 (1.02,2.38)	**0.04**	0.62 (0.35,1.11)	0.11	1.8 (1.03,3.13)	**0.038**
Hypercalciuria	0.83 (0.51,1.34)	0.449	1.65 (1.07,2.55)	**0.024**	0.89 (0.56,1.39)	0.599	1.45 (0.80,2.64)	0.223	0.78 (0.43,1.40)	0.403
Hyperoxaluria	1.36 (0.88,2.12)	0.169	1.93 (1.28,2.90)	**0.002**	1 (0.66,1.53)	0.983	1.02 (0.59,1.78)	0.938	0.95 (0.56,1.64)	0.865
Hypocitraturia	0.85 (0.55,1.31)	0.454	0.83 (0.55,1.26)	0.383	1.51 (1.00,2.29)	0.052	0.68 (0.39,1.18)	0.174	1.15 (0.67,1.95)	0.618
Increased SS CaOx	0.94 (0.52,1.70)	0.833	1.16 (0.68,2.01)	0.583	0.96 (0.55,1.68)	0.894	0.56 (0.26,1.20)	0.138	1.13 (0.56,2.31)	0.727
Increased SS CaP	0.27 (0.11,0.63)	**0.003**	1.42 (0.78,2.57)	0.247	0.58 (0.30,1.11)	0.101	1.88 (0.79,4.48)	0.152	0.52 (0.22,1.25)	0.142

Significant ($p < 0.05$) values bolded

SS CaOx supersaturation calcium oxalate, *SSCaP* supersaturation calcium phosphate, *SSUA* supersaturation uric acid

[a]Metabolic Syndrome Severity Score of 0 held as referent

[b]Non-comorbid group held as referent

Accordingly, understanding the 24-h urine findings of stone formers with MS may help guide therapy in patients who do not complete a 24-h urine analysis. To this end, in the present study, we have analyzed associations between 24-h urine studies and MSSS in a cohort of stone forming patients treated at our tertiary stone clinic. We have identified several important associations.

We found a significant inverse relationship between MSSS and urinary pH. That is, as MSSS increased, urinary pH decreased. Interestingly, this trend did not include patients with MSSS = 5. Given that this group had the smallest number of patients ($n = 19$), underpowering may have prohibited the detection of a statistically significant result. Additionally, we noted that there was a greater proportion of UA stones amongst those with higher MSSS scores. These findings are intuitive as uric acid crystallization is more stochiochemically favorable under more acidic conditions. Furthermore, urinary pH has been previously shown to be inversely related to BMI and insulin resistance [4, 6, 11].

One proposed mechanism for lower urinary pH in MS patients is the failure of insulin to promote proximal tubular excretion of ammonia, which serves as a buffer for hydrogen ions [4]. However, lower urinary pH in those with MS is likely multifactorial as Abate et al. demonstrated some uric acid stone-forming MS patients have low urinary pH without underlying insulin resistance [5]. Indeed, we found that obesity, HTN, and HTG were independently associated low urinary pH suggesting at least a second mechanism unrelated to insulin resistance in MS patients. A possible explanation to this finding may be due to the lithogenic contribution of Western-diets high in animal protein, sodium, and low in fiber that are common in patients with obesity, HTN, and HTG. Herein, an excess of organic acids from purine metabolism account for a portion of the titratable acid in urine, increasing urinary acidity [12, 13]. Prior work by Kadlec et al. similarly found that DM and HTN were associated uric acid nephrolithiasis [14]. Furthermore, a separate study found that patients with elevated BMI had several metabolic abnormalities that predisposed them to stone formation including gouty diathesis, hypocitraturia, and hyperuricosuria [11].

Consistent with previous findings in the literature, no association was found between MS components and hypercalciuria, hyperoxaluria, or hypocitraturia—known risk factors for CaOx stone formation (the most common type of kidney stone overall). Accordingly, it appears that the increased risk for kidney stone disease amongst MS patients noted in prior epidemiologic studies is being driven by greater risk of uric acid stones [4]. Our study revealed similar findings, as the OR of uric acid stones was significantly higher in patients with MSSS > 1 compared to patients with no MS components (Supplementary Table 1). Notably, while patients with higher MSSS had increasing OR of uric acid stones, the majority of patients across all MSSS groups still formed CaOx stones. Such is expected as CaOx stones are by far the most common kidney stone type and low urinary pH promotes CaOx stone formation, albeit not to same extent as uric acid stone formation.

Our study has several notable limitations. This cross-sectional study was conducted retrospectively which may have introduced selection bias. Furthermore, patients were recruited from a single tertiary care center which may limit the generalizability of our findings. Additionally, the obesity component of MS is defined by waist circumference rather than BMI (we did not have data on waist circumference, and accordingly we used BMI as a surrogate for obesity). Despite these limitations, we believe our study provides an important addition to the existing literature. Our study found that the greater risk of nephrolithiasis amongst those with MS appears driven by uric acid nephrolithiasis, a trend that in our data is not explained solely by insulin resistance. Accordingly, though individualized therapy based on 24-h urine studies and stone composition is preferred for stone formers, when empiric therapy is required special attention must be given to those with MS.

From a urologist's standpoint, advising a stone forming patient to reduce animal protein is common practice. However, both kidney stone disease and metabolic syndrome are managed with diet and these diets may conflict if patients are not appropriately counseled. That is because patients with MS are often advised to consume a low carbohydrate and *high protein* diet. Oftentimes lean animal-based sources, such as chicken and fish, are utilized for this high protein intake [15]. Thus, for stone formers with MS, special consideration should be given to advise patients on consuming acid-neutral proteins such as plant-based proteins and low-fat dairy-based proteins. Indeed, diet is important for the treatment of both MS and nephrolithiasis and so it is important to reconcile these dietary strategies to increase the holistic health of the patient. Our findings highlight the important of coordination of care between the urologist and patient's primary care physician in making dietary recommendations and optimizing care for patients with MS and nephrolithiasis. Further research in a prospective longitudinal fashion is recommended to further validate these findings and determine the mechanistic forces driving lithogenesis in stone formers with metabolic syndrome.

Conclusion

The rising prevalence of nephrolithiasis amongst patients with MS appears to be driven by an increasing prevalence of uric acid nephrolithiasis—a condition primarily driven by low urinary pH. Low urinary pH was independently associated with all MS components aside from hyperlipidemia

suggesting an underlying mechanism independent from insulin resistance. Accordingly, in stone forming patients with MS for whom 24-h urine studies and/or stone analysis is unavailable, consideration should be given to the use of potassium citrate as first line empiric pharmacotherapy and reduction of animal protein as a first line dietary therapy. Given that patients with MS are often on low carbohydrate and high protein diets, stone formers with MS should be advised to obtain protein from acid-neutral sources such as diary and plant products. Further research in a prospective longitudinal fashion is recommended to validate these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-021-03790-7.

Author contributions BJN protocol/project development; data collection or management; data analysis; manuscript writing/editing, RDC protocol/project development; data collection or management; manuscript writing/editing, KJA protocol/project development; manuscript writing/editing, K-ME protocol/project development; data collection or management; data analysis; manuscript writing/editing, GB protocol/project development; data collection or management; manuscript writing/editing, KA protocol/project development; data collection or management; manuscript writing/editing, PI protocol/project development; data collection or management; data analysis; manuscript writing/editing, ADJ data collection or management; manuscript writing/editing, AWM manuscript writing/editing, GM manuscript writing/editing.

Funding All authors report no funding, financial or non-financial interests to disclose.

Declarations

Conflict of interest None.

Ethical approval The study was approved by the Institutional Review Board and necessary informed consent was collected from all participants.

References

1. Liu Y-T, Yang P-Y, Yang Y-W, Sun H-Y, Lin IC (2017) The association of nephrolithiasis with metabolic syndrome and its components: a cross-sectional analysis. Ther Clin Risk Manag 13:41–48
2. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ (2010) The metabolic syndrome. Lancet (London, England) 375(9710):181–183
3. Wong Y, Cook P, Roderick P, Somani BK (2016) Metabolic syndrome and kidney stone disease: a systematic review of literature. J Endourol 30(3):246–253
4. Sakhaee K (2014) Epidemiology and clinical pathophysiology of uric acid kidney stones. J Nephrol 27(3):241–245
5. Abate N, Chandalia M, Cabo-Chan AV, Moe OW, Sakhaee K (2004) The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int 65(2):386–392
6. Taylor EN, Curhan GC (2006) Body size and 24-hour urine composition. Am J Kidney Dis 48(6):905–915
7. Hsi RS, Sanford T, Goldfarb DS, Stoller ML (2017) The role of the 24-hour urine collection in the prevention of kidney stone recurrence. J Urol 197(4):1084–1089
8. Milose JC, Kaufman SR, Hollenbeck BK, Wolf JS Jr, Hollingsworth JM (2014) Prevalence of 24-hour urine collection in high risk stone formers. J Urol 191(2):376–380
9. Samson SL, Garber AJ (2014) Metabolic syndrome. Endocrinol Metab Clin North Am 43(1):1–23
10. Pearle MS, Goldfarb DS, Assimos DG et al (2014) Medical management of kidney stones: AUA guideline. J Urol 192(2):316–324
11. Ekeruo WO, Tan YH, Young MD et al (2004) Metabolic risk factors and the impact of medical therapy on the management of nephrolithiasis in obese patients. J Urol 172(1):159–163
12. Ferraro PM, Bargagli M, Trinchieri A, Gambaro G (2020) Risk of kidney stones: influence of dietary factors, dietary patterns, and vegetarian-vegan diets. Nutrients 12(3):779
13. Bobulescu IA, Park SK, Xu LHR et al (2019) Net acid excretion and urinary organic anions in idiopathic uric acid nephrolithiasis. Clin J Am Soc Nephrol 14(3):411–420
14. Kadlec AO, Greco K, Fridirici ZC, Hart ST, Vellos T, Turk TM (2012) Metabolic syndrome and urinary stone composition: what factors matter most? Urology 80(4):805–810
15. Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R (2020) Dietary strategies for metabolic syndrome: a comprehensive review. Nutrients. https://doi.org/10.3390/nu12102983