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Review

The influence of metabolic syndrome and its components on the development of nephrolithiasis

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Abstract The prevalence of kidney stone disease is increasing, afflicting 7%–11% of the United States population. Multiple systemic conditions, including obesity and diabetes, are also on the rise. Further, the literature has demonstrated a strong association between metabolic syndrome, its components, and kidney stone disease. In this article, we aim to review the associations of metabolic syndrome and nephrolithiasis, discussing the pathophysiology, urinary parameters, and clinical presentations. With this knowledge, urologists will have a more comprehensive understanding of this complex population of metabolic stone formers enabling improved patient management and treatment of stone disease.

1. Introduction

Metabolic syndrome (MetS) is a constellation of systemic conditions that place an individual at risk for cardiovascular disease. In this paper, we will review the associations between MetS, its components, and the development of kidney stones. We will also discuss the metabolic factors that drive this risk. We performed a review of the literature using the PubMed Search database. The key terms which we queried were metabolic syndrome, kidney stones, obesity, hypertension, diabetes, hyperlipidemia/dyslipidemia, vascular disease, peripheral arterial disease, and coronary artery disease. We incorporated information from articles which examined the associations between MetS and kidney stone disease as well as the individual components of MetS and their associations.

Various parameters have been used to define MetS. While these definitions vary, the cornerstones include obesity, dyslipidemia, hypertension, and hyperglycemia [1]. Of the numerous guidelines in circulation, the United States National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is used most frequently due to its

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flexibility and reliance on basic metabolic laboratories that are widely available in clinics. The ATP III guidelines for diagnosis of MetS require the presence of three or more of the following five criteria depicted in Table 1. We recognize that some of the guidelines criteria used for defining MetS have limitations and, in these instances, alternative instruments may be utilized. For example, a disadvantage of the ATP III guidelines is the inability to apply them across different ethnic groups, especially in defining obesity and insulin resistance. To address this issue, the International Diabetes Federation (IDF) proposed new guidelines in 2005 with ethnic and racial specific cutoffs. Guidelines from the American Association of Clinical Endocrinologists (AACE), World Health Organization (WHO), and the European Group for the Study of Insulin Resistance (EGIR) are largely focused on insulin resistance determined by euglycemic hyperinsulinemic clamp studies, which are not routinely performed in clinical practice. Other methods of defining Mets are outlined in Table 2. It is important to note that based on these classification systems individuals who are under pharmacologic treatment for diseases such as hypertension, insulin resistance and hyperlipidemia are still considered to have these entities even if they are controlled.

A separate discussion of each component of the Mets with respect to kidney stone risk follows. These include obesity, insulin resistance/diabetes, hypertension, and hyperlipidemia/dyslipidemia. The interplay between these four factors defines MetS. Similarly, while MetS has overarching systemic effects, it also induces specific changes in body organs, some of which contribute to the development of kidney stones. Vascular complications which can develop as a consequence of MetS such as peripheral arterial disease and coronary artery disease, and the association with stone risk are also reviewed. We then review the influence of MetS as a whole entity on kidney stone formation.

2. Obesity and urolithiasis

Waist circumference is a quick metric of visceral obesity. The accumulation of adipose tissue increases release of adipocyte derived inflammatory cytokines which potentiate other factors contributing to MetS [2]. Taylor and associates [3] utilized three large epidemiological prospective cohort studies to examine 4 827 kidney stone incidents. They showed that body mass index (BMI) and waist circumference, two distinct measures of obesity, were associated with an increased risk of kidney stone formation. Inci and associates [4] found BMI to be significantly higher in stone forming patients. In a study of 84 225 women with no history of kidney stones, Sorensen and colleagues [5] identified a BMI dependent increased risk of incident kidney stones, 25—29.9 kg/m^2 (1.3 fold), 30—34.9 kg/m^2 (1.62 fold), and $\geq$35 kg/m^2 (1.81 fold) as compared to BMI $<$ 25 kg/m^2. Body fat may impact kidney stone formation. Increasing visceral adipose tissue, as measured by computed tomography (CT), was reported to be associated with the risk of developing uric acid and calcium oxalate stones [6]. Kidney stone risk has also been shown to be positively correlated with the ratio of visceral to subcutaneous fat tissue and nonalcoholic fatty liver disease [7—10].

Table 1 NCEP ATP III classification.

Factors	Values
Waist circumference (cm)	>102 (males), >88 (females)
Fasting glucose (mg/dL)	≥100 or Rx
Triglycerides (mg/dL)	≥150 or Rx
High-density lipoprotein (ng/mL)	<40 (males), <50 (females), or Rx
Blood pressure (mmHg)	>130 (systolic), >85 (diastolic), or Rx

NCEP ATP III: United States National Cholesterol Education Program Adult Treatment Panel III; Rx, pharmacologic intervention for that element.

3. Insulin resistance and urolithiasis

In three large cohorts, type 2 diabetes mellitus was a risk factor for developing kidney stones; on multivariate analysis, the relative risk of stone disease in those with diabetes was 1.38 in older women, 1.67 in younger women, and 1.31 in men [11]. Uric acid kidney stone formation has been linked to diabetes. For example, it has been reported that uric acid stone formers have a higher prevalence of diabetes as well as glucose intolerance [12]. Furthermore, those with type 2 diabetes mellitus are at an increased risk of uric acid stone formation [13].

Fasting glucose levels assist in detecting insulin resistant diabetes mellitus, a disease with progressive negative systemic effects. Hyperglycemia secondary to insulin resistance leads to accumulation of advanced glycation end products (AGEs) inducing a pro-inflammatory state and vascular endothelial dysfunction [14]. Insulin resistance is also associated with decreased ammonium production in the proximal tubule resulting in decreased urine pH, the major driver of uric acid stone formation [15].

4. Hypertension and urolithiasis

Hypertension, a component of MetS, has a bidirectional association with kidney stone risk. Patients with hypertension have been shown to possess a higher risk for stone development and stone formers are predisposed to develop hypertension compared to the general population [16,17]. The risk of hypertension was higher after a first symptomatic kidney stone event when evaluating Olmstead County data from 2000 to 2011 [18].

5. Dyslipidemia and urolithiasis

Elevated serum triglycerides and low high-density lipoprotein (HDL) levels, components of MetS, negatively influence cardiovascular health. Dyslipidemia has been suggested as an independent risk factor for nephrolithiasis as it is associated with lower urine pH [19]. The specific derangements contributing to this increased risk have not been defined. Masterson and colleagues [20] in a retrospective study of 52 184 patients demonstrated an association between dyslipidemia and nephrolithiasis, hazard ratio of 2.2. While low-density lipoprotein (LDL) and triglycerides were not individually associated with stone formation, low HDL

Table 2 Metabolic syndrome classifications.

Classification	Required elements	Criteria	Obesity	Hyperglycemia	Dyslipidemia (mg/dL)	Hypertension (mmHg)	Other criteria
WHO	IR	Required element and ≥2/5	BMI > 30 kg/m^2 M: WHR > 0.9 F: WHR > 0.85	Present	TG ≥ 150 or M: HDL-C < 35 F: HDL-C < 39	>140/90	Microalbuminuria
EGIR	Hyperinsulinemia in non-T2DM patients	Required element and ≥2/4	M: WC ≥ 94 cm F: WC ≥ 80 cm	Present	TG ≥ 150 or HDL-C < 39	>140/90 or Rx	
AACE	IR	Required element + any other element + clinical judgment	BMI ≥ 25 kg/m^2	Present	TG ≥ 150 and M: HDL-C < 40 F: HDL-C < 50	>130/85	Other features of IR
IDF	CO (WC or BMI > 30 kg/m^2)	Required element and ≥2/4	Not part of criteria	Fasting glucose ≥ 100 mg/mL	TG ≥ 150 or Rx M: HDL < 40 or Rx F: HDL < 50 or Rx	S ≥ 130 D ≥ 85 or Rx	

ACCE, American Association of Clinical Endocrinologists; BMI, body mass index; CO, central obesity; D, diastolic, EGIR, European Group for the Study of Insulin Resistance; F, female; HDL, high-density lipoprotein; IDF, International Diabetes Foundation; IR, insulin resistance; M, male; Rx, pharmacologic intervention for that element; S, systolic; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio.

values (<45 g/L for men; <60 g/L for women) had a hazard ratio of 1.4. Inci and associates [4] have reported significantly higher levels of total serum cholesterol and triglycerides in kidney stone formers. For total cholesterol, this relationship was accentuated in patients with uric acid and calcium oxalate monohydrate-dihydrate stones (COM-COD). Additionally, LDL levels were found to be significantly higher in COM-COD stone formers than the COM cohort.

6. Cardiovascular disease and urolithiasis

The associations between cardiovascular disease and kidney stones have been well chronicled [21]. Aydin and colleagues [22] reported that cardiovascular disease and mortality were significantly higher in calcium oxalate kidney stone formers than non-stone formers. Those with calcium oxalate stones also had significantly higher total cholesterol, lower HDL, higher systolic blood pressure, and elevated highly sensitive C-reactive protein (hsCRP). They also found that urinary calcium and oxalate were positively correlated with 10-year cardiovascular disease risk and 10-year cardiovascular mortality. Hamano and associates [23] also reported a positive association between several coronary artery disease risk factors and the development of calcium oxalate stones. These factors included smoking, hypertension, hypercholesterolemia, and obesity. Rule and colleagues [24] found kidney stone formers are at increased risk of myocardial infarction independent of some of these risk factors. Kidney stone risk is also associated with peripheral arterial vascular disease. In a longitudinal epidemiologic study (CARDIA) Reiner and associates [25] found that the kidney stone formers had greater carotid artery wall thickness. Patel and colleagues [26] demonstrated that the presence of abdominal aortic calcification found on CT was associated with uric acid stone formation, low urine pH, and hypocitraturia.

7. MetS and urolithiasis

Studies of large patient cohorts have demonstrated the correlation with MetS and the development of kidney stones. West and associates [27] analyzed the United States National Health and Nutrition Examination Survey (NHANES III) and found that patients with MetS had 2 times the risk of developing a kidney stone based on self-reporting [27]. In a longitudinal study of 2132 patients in Southern Italy, Rendina and colleagues [28] reported that 50.9% of patients with echographic evidence of nephrolithiasis qualified for a diagnosis of MetS. Furthermore, after adjusting for age, the occurrence of MetS was associated with echographic evidence of nephrolithiasis (odds ratio 2.0). West and associates [29] reported that the kidney stone prevalence was 3.7% with no traits, 7.5% for three traits, and 9.8% for five traits [27]. Similar correlations have been reported in Japan and South Korea [29]. This relationship has also been demonstrated in radiographic screening studies. Jeong and colleagues [30] reported that among almost 35 000 residents of South Korea who were screened with ultrasonography or CT, 2.4% had stones, 13.7% had MetS, and the odds ratio based on imaging for MetS and kidney stones was 1.25. Table 3 outlines these studies including the classification utilized.

Table 3 Association between MetS and nephrolithiasis.

Reference	Country	Study population	Mean age (years)	Female (%)	MetS criteria	MetS population	NL definition	NL population	Prevalence	Adjusted OR
West et al. (2008) [27]	USA	14 870	50.1	52.4	AHA/NHLBI	4949	Self-reported history	699	History of NL in 8.8% of MetS patients *vs.* 4.3% in non-MetS patients Component number 0: 3% 3: 7.5% 5: 9.8%	E: 1.52 Component number 0: 1.0 1: 1.40 2: 2.09 3: 2.56 4: 3.85 5: 3.42
Rendina et al. (2009) [28]	Italy	2 132	63.8	51.3	AHA/NHLBI	725	US and self-reported history	298	50.9% of patients with evidence of NL met criteria for MetS	E: 2.0 M: 1.89 F: 2.19
Jeong et al. (2011) [30]	Korea	34 895	50.0	40.4	NCEP ATP III	4 779	CT and/or US	839	In MetS, 71% increased OR of kidney stone prevalence *vs.* non-MetS Component number 0: 1.75% 1: 2.45% 2: 2.76% 3: 3.87% 4: 3.12% 5: 4.37%	E: 1.25
Kohjimoto et al. (2013) [52]	Japan	11 555	52.5	26.1	Obesity, BMI $\geq$ 25 kg/m^2; hypertension, BP $\geq$ 140/90 mmHg; dyslipidemia, LDL $\geq$ 140 mg/dL, HDL $<$ 40 mg/dL, or TG $\geq$ 150 mg/dL; diabetes, fasting $\geq$ 126 mg/dL, 2-h 75-g glucose test $\geq$ 200 mg/dL or HbA1c $\geq$ 6.5%	6 306	Previous radiologic diagnosis	11 555	Component number 0: 57.7% 1: 61.7% 2: 65.2% 3: 69.3% 4: 73.3%	E: 1.78

AHA, American Heart Association; BMI, body mass index; CT, computed tomography; E, entire study population; F, female; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; M, male; MetS, metabolic syndrome; NCEP ATP III, United States National Cholesterol Education Program Adult Treatment Panel III; TG, triglycerides; NHLBI, National Heart Lungs and Blood Institute; NL, nephrolithiasis; OR, odds ratio; US, ultrasonography.

8. Stone composition

Patients with MetS typically harbor calcium oxalate and uric acid stones. Kadlec and associates [31] analyzed nearly 600 patients for the involvement of MetS on kidney stone composition. They found that calcium oxalate stones were the most prevalent and uric acid was the next most common composition. Calcium phosphate stones were less prevalent. Relative to the generic stone forming population, the percentage of uric acid stones was significantly higher, and the percentage of calcium phosphate stones was significantly lower in patients with MetS. Cho and colleagues [32] found that the major discordance in composition between those with and without MetS was with uric acid stones, a higher prevalence of such stones in the MetS cohort.

Components of the MetS may also independently influence stone composition. Kadlec and associates [31] found that both hypertension and diabetes mellitus are independently associated with increased uric acid stone frequency and a lower prevalence of calcium phosphate stones. Li and colleagues [33] found that uric acid stone formers have a higher prevalence of obesity compared to other stone formers; 53.1% of uric acid stone formers, 34.3% for calcium phosphate, 42.7% for calcium oxalate, and 38.7% for mixed composition. Ekeruo and associates [34] reported that, in obese stone formers, uric acid stones were more prevalent, apatite stones were less common, and calcium oxalate stones seemed to be equally distributed between both cohorts. Nerli and colleagues [35] demonstrated that type 2 diabetic stone formers had a 30% prevalence of uric acid calculi compared to 11% in non-diabetic stone formers. Similarly, the prevalence of uric acid stones has been reported to be significantly higher in those with dyslipidemia, 12% *vs.* 5.1% [19]. It has been observed that stone composition tends to change with aging and that uric acid stones are more common in older age when compared to calcium oxalate stones [36,37]. This may explain why there is a high prevalence of uric acid stones in patients with MetS, as these patients are generally older.

9. Metabolic factors

The propensity for patients with MetS to form uric acid and calcium oxalate stones is influenced by certain changes in the urinary environment. We subsequently review these urinary stone risk factors and the potential mechanisms leading to stone development.

Uric acid stone formation is a disease of low urine pH which reduces the solubility of uric acid resulting in the generation of such stones. This is attributed to ineffective generation of ammonium in the proximal renal tubule, which is thought to be linked to insulin resistance. A reduction in ammonium generation results in decreased buffering capacity. Thus, there is an increase in titratable acidity and net acid excretion resulting in low urine pH. The lower urine pH provides a favorable urinary milieu for uric acid stone formation [38]. Experiments with the Zucker rat, a model for MetS, show that these animals have lower urine pH, lower urinary ammonium excretion and a higher net acid excretion as compared to lean rats. These differences may be related to an increase in renal fat depositions, fat content being significantly higher in the Zucker rat kidneys. Using an established cell line, this group demonstrated that fat exposure negatively impacts the generation of ammonium in proximal tubular cells [39]. These responses have been correlated to the number of components of the MetS. Maalouf and associates [15] reported that there was a negative correlation between component number and urine pH whereas this positively correlated with urinary ammonium.

The lower urine pH has been linked to some of the components of the MetS. A negative correlation between BMI/body weight with urinary pH has been reported by several investigators. In a large group of stone formers, Maalouf and associates [40] reported a significantly negative correlation between urine pH and body weight [4]. Ekeruo and colleagues [34] demonstrated a similar negative correlation between BMI and urine pH in a similar cohort. Patients with increased BMI are known to have higher levels of visceral obesity and hepatic steatosis, both of which are associated with lower urine pH [41]. Wrobel and associates [42] reported a similar negative correlation between BMI and urine pH in a group of calcium oxalate stone formers. Insulin resistance has been found to be significantly correlated with low 24-h urine pH. Strengthening this association, severe insulin resistance was associated with recurrent uric acid stone formers [43]. Eisner and colleagues [44] demonstrated that patients with type 2 diabetes mellitus had more acidic urine. In addition, higher hemoglobin A1c (HbA1c) levels have been demonstrated to be inversely related to urinary pH [45]. Dyslipidemia is also reported to be associated with low urine pH [19].

Increased oxalate excretion appears to be a potential driving force for calcium oxalate kidney stone in those with MetS. Urinary oxalate excretion is influenced by various components of the MetS. For example, Lemann and associates [46] reported a positive correlation between urinary oxalate excretion and lean body mass. Taylor and Curhan [47] established a positive association between BMI and urinary oxalate in a large epidemiologic cohort study. Ekeruo and associates [34] found that obese kidney stone formers had higher urinary oxalate excretion than non-obese stone formers. In addition, a greater proportion of obese kidney stone formers had hyperoxaluria. Others have demonstrated this relationship between obesity and urinary oxalate excretion [48,49]. Urinary oxalate excretion has also been reported to be higher in diabetic kidney stone formers than those who do not form calculi [44,50,51]. A positive correlation between components of the MetS and prevalence of hyperoxaluria has been reported [52]. A number of yet undefined factors may be promoting increased urinary oxalate excretion including diet, renal and gastrointestinal oxalate transport, the fecal microbiome, and augmented endogenous oxalate synthesis.

Other urinary stone risk parameters have been associated with the MetS and its components. Ticinesi and colleagues [53] investigated the association of urinary calcium and urinary oxalate excretions in calcium stone formers with MetS traits. The only trait associated with increased urinary calcium was hypertension. No MetS traits were associated with oxalate excretion. Siener and associates [54] found a positive association between BMI and excretion of uric acid and ammonium in male and female calcium oxalate stone formers. However, there was only a positive correlation for calcium excretion in

males and oxalate excretion in females. Taylor and Curham [47] reported a positive correlation between BMI and uric acid and phosphate excretion in a multivariate analysis. While they found a positive correlation with urinary calcium excretion and BMI in a univariate analysis, this was not present when adjustments were made for urinary sodium and phosphate excretion. Cupisti and associates [55] reported that insulin resistance was associated with lower urinary citrate excretion. Kohjimoto also demonstrated [52] a positive correlation between the number of MetS components and prevalence of hypercalciuria, hypocitraturia and hyperuricosuria.

Diet can certainly influence kidney stone risk, and this has been strongly demonstrated in large epidemiologic cohort studies as well as carefully performed metabolic studies. The impact of calcium, sodium, oxalate, animal protein and fluid intake are well chronicled [56—67]. It is highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are contributory. Patients with MetS are more likely to consume excess food which could impact the excretion of urinary analytes known to influence stone risk. However, the collective associations between diet, MetS and the development of kidney stones have not been investigated.

10. Conclusion

There is compelling evidence that MetS and its components are associated with the risk of developing kidney stones, typically calcium oxalate and uric acid. Changes in urinary risk factors appear to be contributory. However, other processes such as systemic inflammation and oxidative stress, which are prevalent in this cohort, may also play a role. Reversing these conditions may also eradicate stone risk factors and should be considered a management strategy; an approach that has been demonstrated in animal models [68].

Author contributions

Study design: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.
Data acquisition: Carter Boyd, Dustin Whitaker, Kyle Wood.
Data analysis: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.
Drafting of manuscript: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.
Critical revision of the manuscript: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.
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Conflicts of interest

The authors declare no conflict of interest.

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