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MINIREVIEWS

Role of insulin resistance in uric acid nephrolithiasis

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Abstract

Metabolic syndrome has been implicated in the pathogenesis of uric acid stones. Although not completely understood, its role is supported by many studies demonstrating increased prevalence of uric acid stones in patients with metabolic syndrome and in particular insulin resistance, a major component of metabolic syndrome. This review presents epidemiologic studies demonstrating the association between metabolic syndrome and nephrolithiasis in general as well as the relationship between insulin resistance and uric acid stone formation, in particular. We also review studies that explore the pathophysiologic relationship between insulin resistance and uric acid nephrolithiasis.

Key words: Nephrolithiasis; Kidney calculi; Uric acid; Insulin resistance; Metabolic syndrome

Core tip: Increasing awareness of the association between prevalence of metabolic syndrome and uric acid nephrolithiasis has caused a closer examination into modifiable risk factors for stone recurrence. The mechanism behind this association is thought to be due to decreased ammoniagenesis as caused by insulin resistance in the proximal tubule of the kidney. The presence or recurrence of uric acid stones should prompt the physician to look for traits of metabolic syndrome. Further studies into this causal relationship may provide additional medical interventions to decrease incident stones.

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INTRODUCTION

In the United States, the prevalence of kidney stones has risen since 1976 and was estimated to be 8.8% in 2010[1,2]. The magnitude of this problem is exacerbated by a recurrence rate as high as 50% within 5 years[3]. The prevalence of kidney stones is largely dependent on many un-modifiable patient factors including gender, ethnicity, and geography[1]. However, a growing interest in the relationship between modifiable risk factors such as obesity, diabetes mellitus (DM) and metabolic syndrome (MetS) has developed in light of the increasing prevalence of these conditions[4].

The majority of kidney stones are calcium-based with uric acid (UA) nephrolithiasis comprising only 10% of calculi in the overall stone-forming population[5]. However, UA stones disproportionally affect certain cohorts. Among obese patients, UA nephrolithiasis accounts for up to 63% of the stone burden[6].

The central role insulin resistance appears to play in UA stone formation has been the subject of much research and debate. The exploration of this important relationship is the purpose of the current review. We first present epidemiologic studies that demonstrate the link between MetS and nephrolithiasis in general. We then

Table 1 Insulin resistance and kidney stone formation

Ref.	Type	Year	*n*	Study population	Relevant variables	Conclusion
Taylor *et al*[8]	Prospective	2005	241623	Health professionals from 3 different study cohorts starting as early as 1980	Patient reported BMI, waist circumference, and incidence of nephrolithiasis	Obesity, weight gain, and waist circumference are positively associated with renal stone disease
Taylor *et al*[7]	Cross-sectional	2005	220478	Health professionals	Patient reported incidence of diabetes and kidney stones	Patients with DM have higher relative risk of having stones. Patients with kidney stones were more likely to develop DM
Rendina *et al*[27]	Cross-Sectional, single institution	2009	2132	Consecutive Caucasian inpatients in a single Italian hospital	AHA/NHLBI criteria for MetS diagnosis, kidney stones diagnosed on US	MetS, specifically HTN and obesity (in females) is significantly associated with US evidence of kidney stones
Chang *et al*[28]	Prospective, single institution	2011	3872	South Korean workers participating in comprehensive health exam from 2002-2009	National Cholesterol Education Program's Third Adult Treatment Panel criteria for MetS diagnosis, kidney stone diagnosed on US	MetS is significantly associated with acidified urine and increased risk of kidney stones MetS over time as well as each additional MetS trait predicted development of kidney stones
Kabeya *et al*[9]	Cross-Sectional, single institution	2012	2717	Japanese patients undergoing MetS screening	Fasting serum insulin, FPG, HbA1c, US for diagnosis of kidney stone	Glycemic control may be an independent risk factor for kidney stones. The number of MetS traits is positively associated with kidney stone risk; specifically, patients with all 5 traits are at a 2.7 x increased risk of kidney stones compared to those with 2 traits
Kohjimoto *et al*[29]	Cross-Sectional	2013	11555	Japanese survey	MetS traits, incident kidney stones – multiple and recurrent	Increasing number of MetS traits increased stone burden

IR: Insulin resistance; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; FPG: Fasting plasma glucose; MetS: Metabolic syndrome; DM: Diabetes mellitus; UA: Uric acid.

highlight studies examining the increased prevalence of UA stones in patients with insulin resistance. Finally, we review currently accepted pathophysiologic mechanisms that support the role of insulin resistance in UA stone formation.

METABOLIC SYNDROME AND NEPHROLITHIASIS

MetS comprises traits of insulin resistance (IR), obesity, hypertension (HTN), and hyperlipidemia. Multiple studies demonstrate that MetS and its constituent components are associated with increased risk of kidney stones (Table 1).

One of the largest studies to examine the link between components of MetS and nephrolithiasis was by Taylor *et al*[7] who reported a cross-sectional analysis of three large national patient surveys: Nurses Health Study I, Nurses Health Study Ⅱ, and Health Professionals Follow-Up Study. This investigation included over 200000 health professional males and female nurses responding to surveys administered every 2 years with an age range of 25 to 75 years of age. The study concluded that DM type Ⅱ was significantly associated with kidney stone formation with a relative risk of 1.38 in older women, 1.67 in younger women, and 1.31 in men as compared to non-diabetic patients after controlling for age, body-mass index (BMI), thiazide use, and diet. Additionally, they reported that among patients with kidney stones, the relative risk of developing diabetes was 1.33 in older women, 1.48 in younger women, and 1.49 in men as compared to patients without nephrolithiasis. In a separate analysis of these data, Taylor *et al*[8] reported that obesity, weight gain, and waist circumference were risk factors for incident kidney stones. Together, these studies support the underlying connection between the main components of MetS and kidney stones. While the conclusions of these studies are strengthened by the very large size of the study cohort, the analysis is likely biased by the use of self-reported outcomes in these datasets.

In another large study, Kabeya *et al*[9] showed a significant association between certain traits of MetS and kidney stone formation in 2717 healthy Japanese individuals. Traits significantly associated with increased risk of kidney stone formation included glucose intolerance (fasting plasma glucose ⩾ 100 mg/dL, OR 1.53) and HTN (Systolic ⩾ 130 mmHg, Diastolic ⩾ 85 mmHg, OR 1.42). In addition, they demonstrated a dose-dependent relationship between metabolic syndrome traits and kidney stone formation. The odds of patients with three or more traits of MetS (abdominal obesity, glucose intolerance, HTN, hypertriglyceridemia, and/or low high density lipoprotein) developing kidney stones was 1.48 times higher than those without these traits. This association was not shown for patients with two or fewer traits of MetS. This finding is especially important, as a dose dependent response suggests a causal link between MetS and kidney stones. Although this study provides robust evidence for this association, it was limited by inclusion of a single Japanese population, reducing generalizability to other at risk populations. In addition, the cross-sectional study design confounds the temporal relationship between kidney stone formation and MetS.

Table 2 Insulin resistance and uric acid stone formation

Ref.	Type	Year	*n*	Study population	Relevant variables	Conclusion
Lieske *et al*[30]	Retrospective, Case Control, single county in Minnesota	2006	7122	Known stone former *vs* Control	Stone analysis, metabolic evaluation	DM, obesity, and HTN are associated with the development of kidney stones. DM is significantly associated with UA stone formation
Daudon *et al*[10]	Cross-sectional	2006	2464	DM *vs* Non-DM stone formers	Stone analysis, BMI, clinical and lab data in a subset of stone formers	DM is associated with a higher overall frequency of kidney stones, specifically, UA. UA stone formation can reflect IR and patients should be evaluated for MetS and/or DM if UA stones are diagnosed.
Akman *et al*[11]	Retrospective, single institution	2012	146	MetS *vs* Non-MetS undergoing PCNL	Kidney stone analysis, imaging for initial/recurrent kidney stone diagnosis, baseline blood chemistry and urinalysis	Patients with MetS have a higher frequency of UA stones (21.9% *vs* 4.1%) and a higher rate of all stone recurrence following PCNL
Cho *et al*[12]	Retrospective, three institutions	2012	712	MetS *vs* Non-MetS undergoing endourologic intervention for stones	Stone analysis, metabolic data, International Diabetes Federation definition for MetS	MetS, specifically the traits of impaired fasting glucose and hypertriglyceridemia, is significantly associated with UA stone formation, but calcium based stones remain most common in this group
Kadlec *et al*[31]	Retrospective, single institution	2012	590	All stone formers undergoing endourologic intervention	Stone analysis, MetS factors (presence of obesity, DM, HTN, and HL)	DM and HTN, components of MetS, are significantly associated with UA containing stones
Stansbridge *et al*[32]	Retrospective, single institution	2013	1504	UA stone formers *vs* Non-UA	24H urine, stone analysis, relevant underlying diagnoses, including DM	UA containing stones are increased in DM, but calcium containing stones are still the most common in DM
Inci *et al*[33]	Case-control, single institution	2012	99	Control *vs* Stone formers (substratified by stone type)	Stone analysis, metabolic evaluation	BMI and Hyperlipidemia, two major traits of IR/MetS, are significantly associated with calcium and UA stone formation
Zhou *et al*[34]	Retrospective, single institution	2013	269	UA stone formers *vs* Non-UA stone formers undergoing PCNL	CT for visceral fat area measurement, stone analysis, metabolic evaluation	HTN and visceral fat area, two traits highly associated with IR/MetS, are independent risk factors associated with UA stone formation

IR: Insulin resistance; MetS: Metabolic syndrome; DM: Diabetes Mellitus; UA: Uric acid; HTN: Hypertension; PCNL: Percutaneous nephrolithotomy.

INSULIN RESISTANCE INCREASES RISK OF URIC ACID NEPHROLITHIASIS

Because different types of kidney stones have a tendency to form in different urine milieus, there has been substantial interest in studying the link between insulin resistance and UA stone formation. Low urine pH is a factor of both insulin resistance and UA stone formation; it has therefore been hypothesized that MetS should favor the formation of UA stones[10]. Multiple studies performed stone analyses in order to query the relationship between insulin resistance and specific kidney stone type (Table 2). In a study of 2464 kidney stone formers, Daudon *et al*[10] found that in patients with DM, UA stones accounted for 35.7% of all stones while only 11% in non-diabetic patients, $P < 0.0001$. The authors recommended that patients with UA stones should be evaluated for insulin resistance or MetS as the prevalence of DM in the UA stone population (27.8%) was significantly higher than the prevalence of DM in the population forming other stone types (6.9%).

Other studies have also demonstrated increased odds of UA stones in patients with MetS. In particular, Akman *et al*[11] found UA stones to be significantly more common in patients with MetS compared to patients without MetS (21.9% *vs* 4.1%, $P < 0.001$) in a group of 146 stone formers. Furthermore, the authors suggested that patients with MetS may be more susceptible to UA stone recurrence. In their study, a trend toward higher recurrence of UA stone formation was demonstrated in patients with MetS as compared to patients without MetS (42.9% *vs* 0%, $P = 0.51$). Although a statistically significant association was not found, the study may have been underpowered to detect a difference. Therefore, a relationship between MetS and UA stone recurrence may exist, and further study is required.

In a separate study of UA stone formation in MetS, Cho *et al*[12] showed that MetS was an independent risk factor for UA stone. In an analysis of individual MetS traits, a direct relationship between UA stone and MetS traits was uncovered: as the number of MetS traits increased, the risk for UA stones increased (10.2% in patients with one MetS trait and as high as 30.4% with four components). These studies are limited by their use of cross-sectional or retrospective designs. Nevertheless, the relationship between UA stones and MetS established by these studies should prompt physicians to evaluate patients presenting with UA stones for underlying insulin resistance and related comorbidities.

Table 3 Pathophysiologic relationship between insulin resistance and uric acid stone formation

Ref.	Study Type	Year	*N*	Study population	Outcomes	Conclusion
Facchini *et al*[13]	Cross-sectional, single institution	1991	36	Healthy volunteers with varying degrees of IR	24H urine (pH, UA), UA clearance, steady-state plasma glucose, metabolic evaluation	As IR increases serum UA increases and urinary UA clearance decreases. Thus, increased serum UA concentration may be considered an additional trait of MetS
Cappuccio *et al*[14]	Cross-sectional, single institution	1993	568	Factory volunteers	Fasting spot urine (UA), fractional excretion of Na+, fasting blood analysis	The higher the serum UA level, the greater the amount of renal Na+ reabsorption. This phenomenon is consistent with hyperinsulinemia, and possibly IR, as insulin is known to increase renal sodium reabsorption
Pak *et al*[15]	Retrospective, single institution	2001	56	UA stone formers *vs* matched control with diet control	24H urine	UA stone formers have increased serum UA, decreased fractional excretion of urinary UA, and decreased urinary pH
Sakhaee *et al*[16]	Prospective, single institution	2002	70	Healthy *vs* stone formers (UA *vs* Calcium *vs* Mixed) with diet control	24H urine (pH, NH4+), fasting glucose	UA stone formers are more likely to have IR/DM. UA stone formation occurs due to impaired NH4+ excretion and urine acidification. Acid loading further decreases urinary pH in these patients as compared to non-UA stone formers/Controls
Abate *et al*[17]	Prospective, single institution	2004	68	Stone free patients *vs* UA stone formers with diet control	24H urine (pH, NH4+), glucose disposal rate	Acute hyperinsulinemia leads to elevated urinary pH and NH4+ excretion in normal insulin-sensitive subjects. Alternatively, IR is associated with low urinary pH and impaired NH4+ excretion and could be renal manifestations of IR causing UA stone formation
Maalouf *et al*[23]	Cross-sectional, single institution	2007	148	MetS *vs* No MetS (all stone free)	24H urine (pH, NH4+), Homeostasis model for IR, metabolic evaluation	Acidic urine is a feature of MetS and is associated with the degree of IR. As MetS traits increase, urine pH decreases
Bobulescu *et al*[24]	Prospective, single institution	2013	35	Matched patients with and without UA stones, matched non-stone forming diabetic controls	24H urine, urinary ammonium excretion	Both uric acid non-diabetic patients as well as DM non-stone forming patients had lower urinary pH as compared to matched non-stone forming non-diabetic controls
Cameron *et al*[25]	Prospective, single institution	2011	19	UA stone formers *vs* normal controls with diet control	24H urine, diurnal urinary pH	UA stone formers had decreased urinary pH with increased undissociated UA secretion compared to normal controls

IR: Insulin resistance; DM: Diabetes mellitus; UA: Uric acid; MetS: Metabolic syndrome.

PATHOPHYSIOLOGY OF URIC ACID STONE FORMATION IN PATIENTS WITH INSULIN RESISTANCE

The pathophysiologic basis for UA stone formation in patients with insulin resistance has been widely studied and a summary of important articles on this subject can be found in Table 3. Surprisingly, UA stone formation in insulin resistance does not depend on the presence of more UA in the urine. In fact, several studies revealed that insulin resistance decreases UA clearance[13,14]. This finding suggests that another causal mechanism may be responsible for UA nephrolithiasis in patients with insulin resistance. Clinically, UA stone formers have low urinary pH. Pak *et al*[15] studied 56 pure and mixed UA stone formers and 68 control subjects. Patients were instructed to consume a calorie restricted diet and maintain high fluid intake. They showed that UA stone formers had higher serum UA levels but lower urinary UA levels. Urinary pH was 5.34 in UA stone formers compared to 6.17 in control subjects. This study suggests that it may be low urine pH rather than elevated urine UA levels that plays a critical role in UA stone formation.

In 2002, Sakhaee *et al*[16] published a key study revealing a defect in urinary ammoniagenesis among UA stone formers. After equilibrating to a control diet, UA stone formers demonstrated lower urinary pH and decreased urinary ammonium excretion as compared to normal controls and calcium stone formers. Furthermore, after patients were given an acidic load, pure and mixed UA stone formers experienced a greater degree of urine acidification when compared to both normal controls and calcium stone formers. These findings suggest that although diet has a strong impact on stone formation, patients forming UA stones may be at a particular disadvantage relative to their calcium stone forming peers at any level of diet acidity.

Given the above findings, it is reasonable to ask what is unique about UA stone formers that could cause this defect in urinary acid handling. Abate *et al*[17] revealed that insulin resistance is a driver of low urinary ammonium and pH. UA stone formers and healthy volunteers underwent a study in which they were maintained at a steady state diet and were given controlled doses of insulin (hyperinsulinemic-euglycemic procedure). Baseline 24-h urine collection revealed evidence of lower urinary pH, lower citrate excretion, higher net acid excretion and lower ammonium excretion in the UA stone formers. This suggests that the acid that is secreted is not being buffered adequately by ammonium. They also noted (though not statistically significant) that UA stone form-

ers with progressively lower urine pH tended to have lower glucose disposal rates (insulin resistance).

The specific mechanism for urinary acidification has been suggested by several novel *in vitro* studies. Insulin receptors are expressed in the renal tubular epithelium, and insulin stimulates the renal tubular sodium-hydrogen exchanger (Na^+/H^+ exchanger) to increase reabsorption of hydrogen[18,19]. The activation and up-regulation of the Na^+/H^+ exchanger by insulin promotes ionic trapping of ammonia in the renal tubule; hydrogen ions become bound to ammonia, which is converted to ammonium and is unable to exit the lumen of the renal tubule[20-22]. Resistance to insulin thereby results in decreased buffering capacity for urinary acidification due to decreased ammonia secretion.

The critical relationship between MetS and urine acidification has been supported by Maalouf *et al*[23] who showed that non-stone formers with MetS had decreasing urinary pH with increasing number of MetS traits. Their work supports the theory that insulin resistance plays a role in renal acid handling causing decreased ammoniagenesis and thereby increasing risk of UA stone formation.

Though insulin resistance appears to be playing a significant role in UA stone formation, not all DM patients go on to develop UA stones. This principle was explored by Bobulescu *et al*[24], who prospectively studied BMI-matched non-diabetic pure UA stones formers, diabetic non-stone formers and non-stone forming non-diabetic control patients. Their results demonstrated that both non-diabetic UA stone formers as well as diabetic non-stone forming patients have decreased urinary pH as compared to matched non-diabetic non-stone forming controls. However, non-diabetic patients with UA stones have impaired ability to secrete ammonium after acid loading as compared to diabetic and non-diabetic control patients without nephrolithiasis[24]. This suggests that while insulin resistance plays a role in UA stone formation, additional derangements may occur in these UA stone formers as compared to non-stone formers with DM.

Another salient and surprising feature of studies examining 24-h urine chemistries in UA stone formers *vs* non-stone formers is a frequent absence of difference in urine chemistries. Cameron *et al*[25] discovered a significant diurnal variation in urine acidification occurring in UA stone formers. This intermittent elevation in urinary acid levels leads to transiently lower urine pH, allowing for the precipitation of UA, despite a relatively normal 24-h urine chemistry.

MANAGEMENT RECOMMENDATIONS

Currently, the American Urologic Association guidelines recommend metabolic testing for recurrent stone formers and high-risk stone patients[26]. This work-up includes an initial 24-h urine chemistry followed by repeat testing if stones recur or after initiation of therapy. For patients with UA stones, fluid intake should be sufficient for 2.5 liters of urine output and dietary changes aimed at limiting animal protein, a key driver of urinary acid levels. Additionally, potassium citrate should be recommended to alkalinize the urine (increase urine pH) in an effort to decrease recurrence of UA stones. Nevertheless, these management guidelines do not address the underlying mechanism responsible for UA stone formation in insulin resistance. Further research targeting the defects in ammoniagenesis in insulin resistance may yield novel therapies for this challenging clinical problem.

CONCLUSION

This review explores the relationship between UA nephrolithiasis and insulin resistance. Several epidemiologic studies identify the association between insulin resistance and kidney stones, specifically UA stones. The mechanism underlying this association relates to the importance of renal insulin receptors in acid handling. Insulin resistance results in impaired excretion of urinary ammonia leading to lower urinary pH. Ultimately, these conditions induce UA precipitation out of the urine, leading to the formation of UA stones. As one of the key components of metabolic syndrome, insulin resistance should be suspected in patients with recurrent UA nephrolithiasis, and attention should be directed to the other components of metabolic syndrome, including hypertension, dyslipidemia, and obesity.

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