Metabolic Syndrome and Uric Acid Nephrolithiasis

Khashayar Sakhaee, MD, and Naim M. Maalouf, MD

Summary: The metabolic syndrome describes a cluster of metabolic features that increases the risk for type 2 diabetes mellitus and cardiovascular disease. The prevalence of uric acid nephrolithiasis is higher among stone-forming patients with features of the metabolic syndrome such as obesity and/or type 2 diabetes mellitus. The major determinant in the development of idiopathic uric acid stones is an abnormally low urinary pH. The unduly urinary acidity in uric acid stone formers increasingly is recognized to be one of the features observed in the metabolic syndrome. Two major abnormalities have been implicated to explain this overly acidic urine: (1) increased net acid excretion, and (2) impaired buffering caused by defective urinary ammonium excretion, with the combination resulting in abnormally acidic urine. New information is emerging linking these defects to changes in insulin signaling in the kidney. This article reviews the epidemiologic and metabolic studies linking uric acid nephrolithiasis with the metabolic syndrome, and examines the potential mechanisms underlying the unduly acidic urine in these conditions.
Semin Nephrol 28:174-180 © 2008 Elsevier Inc. All rights reserved.
Keywords: Uric acid nephrolithiasis, urine pH, urine ammonium, insulin resistance, metabolic syndrome

The causative mechanisms for uric acid (UA) stone formation are complex. Uric acid nephrolithiasis can develop as a result of congenital or acquired conditions, but the majority of cases are idiopathic. Patients with idiopathic uric acid nephrolithiasis (IUAN) possess many of the phenotypic characteristics of the metabolic syndrome (MS). An abnormally low urinary pH, which is conducive to UA precipitation, has been shown as an invariant feature in this population. This article reviews the epidemiologic and metabolic studies linking IUAN with the MS, and the potential mechanisms underlying the unduly acidic urine in these conditions.

EPIDEMIOLOGY OF URIC ACID NEPHROLITHIASIS AND THE MS

The MS describes a cluster of features that increases the risk for type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease.[1-3] Several definitions have been proposed to identify individuals with the MS based on measurements of obesity, insulin resistance, blood pressure, and serum lipids.[2,4] The MS affects up to 25% of the US population, with a similar prevalence in other industrialized countries.[1] In addition to its association with T2DM and heart disease, the MS also has been linked with several renal manifestations such as chronic kidney disease and uric acid kidney stones.

The prevalence of kidney stones has increased recently in a number of countries,[5-7] in parallel with the growing epidemics of obesity and T2DM.[8,9] In large epidemiologic studies, obesity, weight gain, and T2DM have been associated with an increased risk of nephrolithiasis, although the specific stone composition was not available in these reports (Fig. 1).[10,11]

Address reprint requests to Khashayar Sakhaee, MD, Professor of Medicine, Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8885. E-mail: Khashayar.sakhaee@utsouthwestern.edu
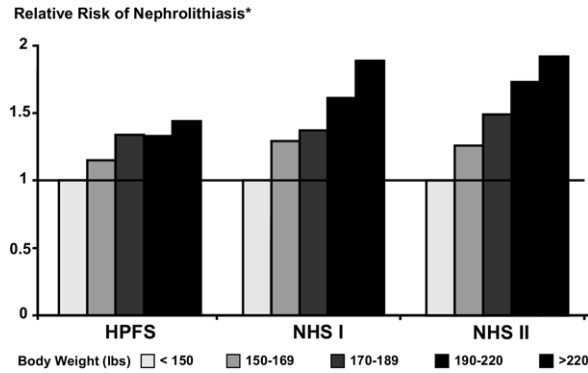
Relative Risk of Nephrolithiasis*

Figure 1. The relationship between body weight and the adjusted relative risk for nephrolithiasis. HPFS, Health Professionals Follow-up Study; NHS I, Nurse's Health Study I; NHS II, Nurse's Health Study II. *Relative risk of nephrolithiasis adjusted for age, use of thiazide diuretics, alcohol use, calcium supplement use, and dietary intake of fluid, animal protein, calcium, magnesium, potassium, sodium, and vitamin C. Body weight: □, less than 150 lb; ▨, 150 to 169 lb; ▦, 170 to 189 lb; ▧, 190 to 220 lb; ■, more than 220 lb. Adapted and reprinted with permission from Taylor et al.[10] *Copyright © 2005, American Medical Association.* All rights reserved.

The prevalence of UA stones is influenced in part by geographic and ethnic diversity. In certain regions of the world, including certain countries in the Middle East, Europe, and Japan, the prevalence of UA stones is higher than in the United States.[12-14] UA stone formers represent 8% to 10% of all nephrolithiasis patients in the United States.[15] Two recent retrospective studies conducted in the United States and Europe have noted a significantly higher prevalence of UA stones among obese patients compared with lean kidney stone formers.[16,17] Additional cross-sectional studies have determined that predominantly UA stones and mixed UA/calcium stones are found in a significantly higher fraction of nephrolithiasis patients with T2DM.[18-20] Overall, T2DM and increasing body mass index, two of the features of the MS, appear to be associated independently with increased propensity for UA stone formation (Fig. 2).[20] Furthermore, a retrospective survey conducted in a large cohort of patients from the Dallas Stone Registry showed a high prevalence of the MS features among UA stone formers, including hypertension, dyslipidemia, glucose intolerance, and hyperuricemia.

PHYSICOCHEMICAL CHARACTERISTICS OF UA

Mammals produce UA as an end product of purine metabolism. UA then is metabolized by the hepatic enzyme uricase to the more soluble allantoin, which then is excreted in the urine. However, human beings and higher primates lack uricase, and because of their inability to metabolize UA, display serum and urine UA concentrations many fold higher than those in other mammals.[21] Because urinary UA excretion in human beings generally exceeds 600 to 800 mg/d, the limited protonated UA solubility of 96 mg/L in urine poses a great risk for UA precipitation.[22] Urine pH is another important determinant of UA solubility in a urinary environment because UA is a weak acid with a dissociation constant (pKa) of 5.35 to 5.5 in urine at 37°C.[23] Thus, unduly acidic urine (urine pH $\leq$ 5.5) leads to precipitation of the sparingly soluble protonated UA, increasing the predisposition to UA nephrolithiasis. In addition, UA crystals in urine increase the propensity toward formation of mixed UA and calcium oxalate stones through the process of heterogeneous nucleation and epitaxial crystal growth (Fig. 3).[24-27] Although urate is more soluble than protonated UA in the urinary environment, its solubility also is affected by urinary cations, with monopotassium urate having a higher solubility compared with monosodium urate.[26,28] This difference in urate solubility is the basis for the use of potassium alkali rather
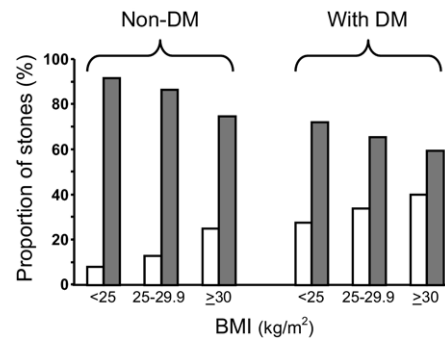

Figure 2. Distribution of calcium and UA stones with respect to body mass index (in kg/m²) and diabetes mellitus status. BMI, body mass index; DM, diabetes mellitus. ■, Calcium stones; □, UA stones. Adapted and reprinted with permission from Daudon et al.[20]
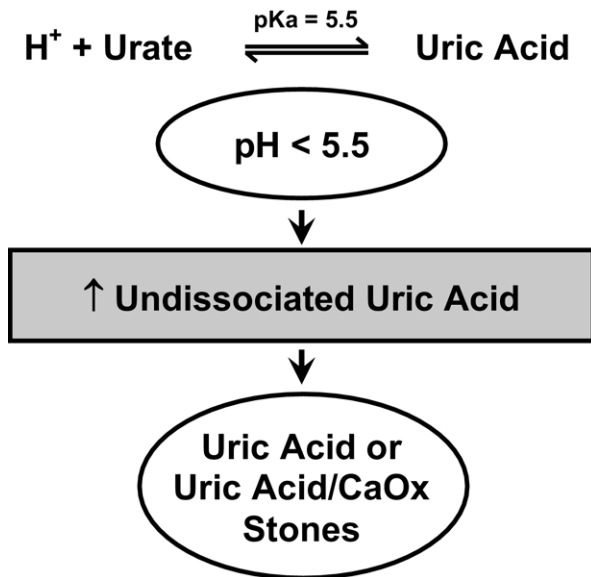
Figure 3. The physicochemical characteristics of UA. UA has a pKa of 5.5. At a urine pH of less than 5.5, the urinary content of sparingly soluble unassociated UA increases, which precipitates directly to form UA stones or indirectly induces mixed UA/calcium oxalate stones.

than sodium alkali in the treatment of UA stones.[29]

PATHOPHYSIOLOGY OF UNDULY ACIDIC URINE IN IUAN

Three significant urinary abnormalities have been described in patients presenting with UA nephrolithiasis[30,31]: hyperuricosuria (caused by increased urinary content of UA), low urinary pH (which reduces the proportion of UA in the form of soluble urate), and low urine volume (which increases the urinary concentration of UA and urate). In certain disease states, UA nephrolithiasis is a result of a combination of 2 or more of these risk factors.[22,30-32]

IUAN

The etiologic mechanisms for UA stone formation are complex. UA nephrolithiasis can develop as a result of congenital or acquired conditions, but the majority of cases are idiopathic.[31] IUAN is heterogeneous, and initially was coined as *gouty diathesis*[33] to describe its clinical–biochemical presentation. It initially was defined as UA nephrolithiasis that cannot be explained by an inborn error of metabo-

lism[31,34,35] or secondary causes such as chronic diarrhea,[36] strenuous physical exercise,[37] or excessive intake of animal protein.[38]

IUAN patients comprise the vast majority of UA stone formers, and the most important and invariant feature in these patients is a low urine pH.[39] Therefore, an unduly acidic urinary pH in the IUAN population is not related to the environmental and disease states associated with a disturbance in the acid–base status. The lower urine pH is, in part, related to higher body weight in these patients (Fig. 4).[40]

Two significant abnormalities have been implicated to explain the overly acidic urine in IUAN: (1) increased net acid excretion (NAE) that cannot be explained by dietary factors, and (2) impaired buffering caused by defective urinary ammonium excretion, with the combination resulting in abnormally acidic urine.

INCREASED NAE

Increased NAE has been described in patients with IUAN.[39] High NAE may occur as a result of increased endogenous organic acid production or as a result of dietary influences (such as low intake of dietary alkali, or increased consumption of dietary acid). However, dietary factors alone cannot explain the unduly acidic urine because IUAN patients showed higher NAE versus non–stone-forming controls when both
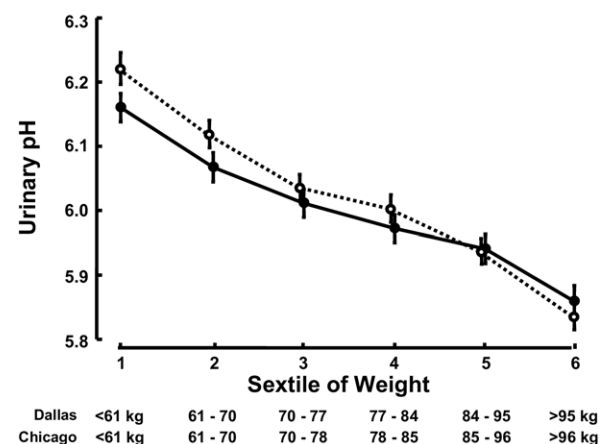

Figure 4. The association between body weight and urine pH in nephrolithiasis. Urinary pH by sextile of body weight is shown. Vertical bars indicate mean ± SE. ——, Dallas; ----, Chicago. Reprinted by permission from Macmillan Publishers Ltd: Kidney International, copyright 2004.[40]

groups were evaluated while consuming the same fixed metabolic diet.[39] The pathophysiologic mechanism(s) accounting for the increased NAE have not been elucidated fully, although they may be related to the MS and insulin resistance because T2DM patients without stones as well as IUAN patients appear to have greater NAE than nondiabetic, insulin-sensitive controls.[41]

DIMINISHED RENAL AMMONIUM EXCRETION

Increased NAE cannot alone explain the more acidic urine because buffers in urine can buffer the excess acid. Ammonium is an important urinary buffer,[42] and renal ammonium production and excretion are regulated by the ambient acid–base environment. Patients with IUAN show reduced ammonium excretion under a standard metabolic diet, a defect that is amplified after an acute acid load.[39] The ratio of urinary ammonium excretion to NAE (NH_4^+/NAE ratio) also has been used to describe urinary ammoniagenesis in the face of acid intake, and this ratio is lower in IUAN patients than in control subjects.[39] These findings are consistent with a defect in renal ammoniagenesis that leads to impaired buffering, and that further amplifies the acidic urine caused by the increased NAE. Defective renal ammoniagenesis and low urine pH may be a feature of the MS in general rather than isolated to IUAN patients; non–stone-forming individuals with increasing number of features of the MS have progressively lower urine pH and NH_4^+/NAE ratio (Fig. 5).[43]

CELLULAR MECHANISMS

Obesity is associated with insulin resistance as well as a low urine pH.[40,44] A previous study reported a high prevalence of obesity, T2DM, and glucose intolerance in IUAN subjects.[39] Evidence supporting a mechanistic connection between peripheral insulin resistance and the low urinary pH and ammonium was shown in metabolic studies using the hyperinsulinemic euglycemic clamp technique.[45] Furthermore, in a study conducted in lean normal subjects under a standard metabolic diet, urinary ammonium excretion increased significantly during
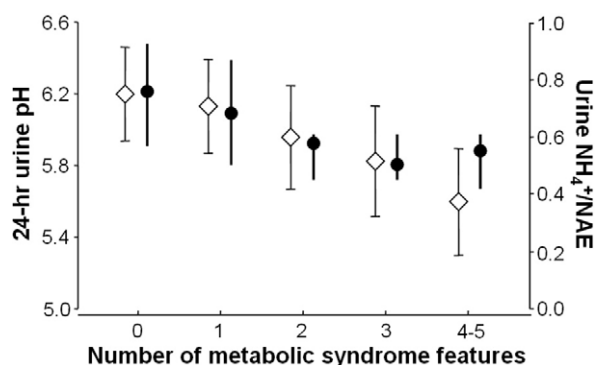

Figure 5. The inverse association between 24-hour urinary pH ($\diamond$) and the ratio of urinary ammonium to NAE ($\bullet$) with the number of features of the MS in 148 non–stone-forming individuals. (Significant linear trend for both parameters, $P < .005$.) Urine pH is shown as mean $\pm$ SE. Urine NH_4^+/NAE is shown as median and interquartile range. Reprinted with permission from Maalouf et al.[43]

the hyperinsulinemic phase of the clamp study.[45] These studies support the premise that insulin resistance potentially plays a principle role in urinary acidification.

Insulin receptors are expressed widely in various segments of the kidney, including vasculature, glomerulus, and renal tubular epithelium cells.[46,47] Experimental studies in vitro have shown the stimulatory role of insulin in ammoniagenesis.[48,49] Moreover, insulin stimulates the renal tubular sodium–hydrogen exchanger, sodium hydrogen exchange isoform 3 (NHE3),[50] in part via the conventional PI3K–SGK1 pathway.[51] Because NHE3 plays a significant role in the direct transport or trapping of ammonium in the renal tubular lumen,[52] resistance to insulin (as in the MS) may lead to reduced renal ammonium excretion. Alternatively, increased circulating free fatty acid, which often is found in the MS, may serve as a substitute substrate for glutamine, thereby reducing the proximal renal tubular cell utilization of glutamine and renal ammoniagenesis.[53]

RENAL LIPOTOXICITY

Under normal circumstances, when caloric intake matches caloric utilization, most triglycerides are deposited into adipocytes.[54,55] With the disturbance of this tightly regulated homeostatic mechanism, triglycerides are redistrib-

uted to and accumulated within parenchymal cells of the liver, cardiomyocytes, skeletal myocytes, and pancreatic β cells.[56-60] The process of fat accumulation in tissues other than adipocytes is termed *lipotoxicity*.[55] In human subjects, fat redistribution to nonadipocyte tissue is associated with impaired insulin sensitivity,[57] cardiac dysfunction,[59] and steatohepatitis.[56,61] Whether renal lipotoxicity in patients with the MS contributes to an alteration in insulin signaling pathways and consequently influences endogenous acid production and reduces renal ammoniagenesis has not yet been studied.

THE ROLE OF INHIBITORS AND PROMOTERS IN UA STONE FORMATION

As described previously, the physicochemical factor that is most invoked as the culprit for UA stone formation is unduly acidic urine. However, a urine pH of less than 5.5, an invariant feature in subjects with IUAN, also is present in a subset of patients with the MS who do not form kidney stones.[43] One possibility is that some of the MS patients have asymptomatic UA stones. Alternatively, it is plausible that the lack of an inhibitor or the presence of a promoter for UA crystal growth in urine may, in part, account for the difference in the propensity for stone formation between these 2 populations. Other than pH-dependent solubility, the existing literature is scanty on factors that might be involved in UA stone formation. In vitro experiments have identified macromolecules that inhibit the adhesion of UA crystals to renal epithelial cells, indirectly suggesting an inhibitory role of these compounds against UA precipitation.[62] In one case-control study, patients with IUAN had reduced urinary glycosaminoglycan excretion compared with non–stone-forming controls.[63] Additional studies are needed to identify which factors, in addition to low urine pH, are necessary for the formation of UA stones.

CONCLUSIONS

The prevalence of kidney stone disease is escalating in the United States, in parallel with the increase in obesity.[5-7] UA stones in particular are associated with the MS and T2DM.[19,20] Re-

cent studies have shown that unduly acidic urine found in IUAN subjects is one of the characteristics associated with the MS. Potential mechanisms implicated in the development of this excessive urine acidity include increased NAE and defective ammonium excretion. Emerging data suggest that these disturbances are a result of defective insulin signaling and/or possibly renal lipotoxicity. Finally, it appears that low urinary pH is necessary but not sufficient for UA stone formation because only a fraction of individuals with the MS and low urine pH develop UA nephrolithiasis. This suggests that, in addition to low urine pH, additional factors, possibly the presence of urinary promoters or the absence of inhibitors of UA crystallization, are needed for the formation of UA stones.

Acknowledgment

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