Metabolic Syndrome and Uric Acid Nephrolithiasis

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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.

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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.

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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]

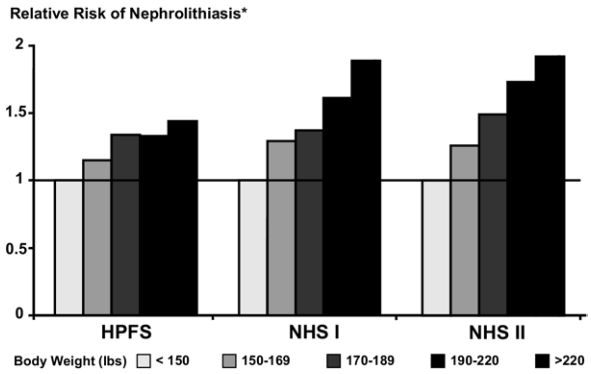

Figure 1. The relationship between body weight and the adjusted relative risk for nephrolithiasis. HPFS, Health Professionals Follow-up Study; NHS I, Nurse's Health Study I; NHS II, Nurse's Health Study II. *Relative risk of nephrolithiasis adjusted for age, use of thiazide diuretics, alcohol use, calcium 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

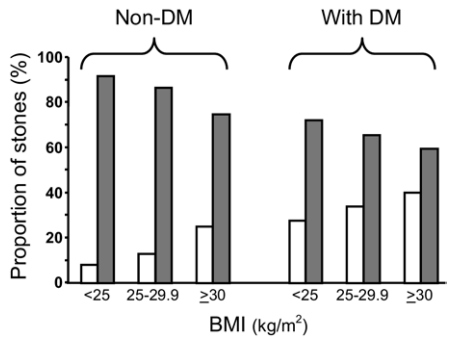

Figure 2. Distribution of calcium and UA stones with respect to body mass index (in kg/m^2) and diabetes mellitus status. BMI, body mass index; DM, diabetes mellitus. ■, Calcium stones; □, UA stones. Adapted and reprinted with permission from Daudon et al.[20]