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Metabolic syndrome and urolithiasis

La lithiase urinaire dans le Syndrome Metabolique

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ABSTRACT

Lithiasis of the urinary tract is nowadays recognized as a significant health care issue, affecting millions of people worldwide and resulting in hospital admissions, medication prescription, elaborate surgical treatment and loss of working hours. It is a multifactorial disease influenced by lifestyle, environmental and genetic factors, amongst others. The recently discovered association between the metabolic syndrome and nephrolithiasis represents another breakthrough in understanding stone disease and risk factors. A comprehensive analysis of the pathophysiology and the latest developments in research will be presented, as well as preventative and treatment options that can be employed in this special group of patients.

1. Introduction

Lithiasis of the urinary tract is nowadays recognized as a significant health care issue, affecting millions of people worldwide and resulting in hospital admissions, medication prescription, elaborate surgical treatment and loss of working hours. It is a multifactorial disease influenced by lifestyle, environmental and genetic factors, amongst others. The recently discovered association between the metabolic syndrome and nephrolithiasis represents another breakthrough in understanding the stone disease and its risk factors. A comprehensive analysis of the pathophysiology and the latest developments in research will be presented, as well as preventative and treatment options that can be employed in a special group of patients.

2. Epidemiology

Worldwide, urinary tract stone disease is becoming a growing issue, with a prevalence of between 2 and 20% [1,2]. Prevalence of nephrolithiasis in the United States has doubled over the past three decades. This increase has also been noted in most European countries and Southeast Asia [3]. Racial and ethnic differences are seen in kidney stone disease, primarily occurring in Caucasian males and least prevalent in young African-American females [4]. In men, the incidence of kidney stones appears to rise after the age of 20 and peaks between 40 and 60 yr of age [5]. In women, the respective incidence rate is higher in the late 20s and decreases by age 50 [4, 5].

Nephrolithiasis has become increasingly recognized as a systemic disorder that is associated with chronic kidney disease, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus (T2DM), and the metabolic syndrome [6,7]. It is a chronic illness with a recurrence rate greater than 50% over 10 yr [8, 9]. Although

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largely asymptomatic at first, it carries a 48.5% five-year probability of symptomatic manifestations [10]. A significant increase in the incidence of kidney stones in the pediatric population has been identified between 1996 and 2007 and it is believed to be linked to the concomitant rise in respective obesity figures [11]. The earliest research is by Curhan *et al.*, who investigated the epidemiologic background of nephrolithiasis with respect to age, gender, dietary and environmental factors, as well as obesity and body size. Their initial results suggested that the body size is associated with the risk of stone formation and that the magnitude of risk varies by gender [12].

Subsequent research addressed the matter of obesity and particular mineral constitution of the urine, providing evidence that urine biochemistry is affected by obesity and T2DM promoting lithogenesis, especially of uric acid and calcium oxalate stones [13–18]. Professor Daudon and his research team were amongst the first to investigate and establish a strong statistical correlation between the two conditions and specific stone composition. By performing Fourier infrared spectroscopy to characterize the stone composition, they discovered Calcium Oxalate (CaOx) as the most prevalent component of stones in both genders, but to a lesser extent in women than in men and in non-diabetic than in diabetic stone formers. No significant difference was observed for calcium phosphates (CaP) or magnesium ammonium phosphates (MAP) between the two groups. In contrast, uric acid was found as the main component of stones in a significantly higher proportion of diabetic than non-diabetic patients (28.5 vs 13.0%; $P < 0.0001$), the difference being more marked in females (36.8 vs 9.7%) than in males (24.9 vs 14.7%) [19]. In a further study of 2464 patients (1760 men, 704 women, including 272 patients with and 2192 patients without T2DM), they identified the proportion of uric acid stones rising gradually with the body mass index (BMI), from 27.8% in the normal-BMI group (<25 kg/m^2) to 40.3% in the obese group (>30 kg/m^2). They concluded that that T2DM constitutes a strong independent factor for uric acid nephrolithiasis, with overweight/obesity acting as an additional risk factor [20]. Another supporting finding was an increased prevalence in women, which contradicts with previous reports supporting lower prevalence of urolithiasis in general and uric acid lithiasis in particular in women [21].

More recent studies from Korea and Japan substantiate previous findings and the association of metabolic syndrome traits with kidney stones. In particular, Kabeya *et al.* demonstrated an increased odds ratio for nephrolithiasis in patients with three or more traits [22]. Chang and coworkers demonstrated a relationship between metabolic syndrome traits and urine acidity in a study population of South Korean men as well as increased risk of kidney stones [23], while Kohjimoto *et al.* found that clustering of traits were associated with hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia [24]. In a recent retrospective analysis of hospital records over a period of 5 years, Kadlec *et al.* identified hypertension and diabetes as independent predictors of differences in composition, specifically uric acid stones (higher proportion), and calcium phosphate stones (lower proportion) in patients with metabolic syndrome [25].

Overall, there has been an abundance of epidemiologic studies substantiating a link between metabolic syndrome and urinary tract lithogenesis. Further studies investigated the pathophysiology of the predisposition in metabolic syndrome in an attempt to provide more information regarding the disorder that could probably lead to effective prevention and/or treatment strategies.

3. Mechanisms of stone formation in metabolic syndrome

According to guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions:

- Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
- Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)
- Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
- HDL-C <40 mg/dL in men or <50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
- Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.

Conditions associated with insulin resistance, such as obesity, the metabolic syndrome and T2DM are associated with increased stone risk (Table 1). Insulin resistance leads to reduced renal ammonia production, resulting in a more acidic urine pH, thus favoring uric acid and mixed calcium oxalate stone formation. The specific mechanism for urinary acidification has been suggested by recent *in vitro* studies. Insulin receptors are expressed in the renal tubular epithelium, and insulin stimulates the renal tubular

Table 1
Lithogenic influences in metabolic syndrome.

Normal physiology	Impaired in metabolic syndrome	Net lithogenic product
Insulin promotes hydrogen ion re-absorption and ammonium production	Insulin resistance promotes hydrogen ion loss and decreased renal ammoniagenesis	Acidic urine and uric acid precipitation
Regulated protein and fat metabolism	Obesity (decreased adiponectin) and associated dietary habits(increased animal protein and purine metabolism) promote insulin resistance	Hypocitraturia, acidic urine pH, increased lithogenesis by calcium and urate
Estrogens promote hyperuricosuria	Controversial (see text)	Heterogeneous nucleation of calcium oxalate
Aromatase aids in estrogen production	Aromatase deficiency	Renal calcium leak