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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

sodium-hydrogen exchanger (Na^+/H^+ exchanger) to increase re-absorption of hydrogen [26,27], making it available for binding with ammonia ions in the renal tubule. The resulting ammonium remains in the renal tubule cells and is not excreted [28], thereby promoting urine alkalinization by buffering the excess hydrogen. Resistance to insulin results in decreased buffering capacity for urinary acidification due to decreased renal ammoniagenesis and amplifies the acidic urine caused by the increased acid excretion. Low urine pH increases the urinary content of un-dissociated uric acid and the frequency of precipitation. Sakhaee and Maalouf proposed that the two major abnormalities implicated in acidic urine are increased net acid excretion and impaired buffering caused by defective urinary ammonium (NH_4^+) excretion [29].

In addition, insulin has been shown to enhance uric acid and sodium re-absorption in the proximal convoluted tubule (PCT), resulting in hyperuricemia and decreased excretion, respectively [30–32]. The resulting hyperglycemia adds to the defective uric acid handling in the PCT by influencing the proximal tubular re-absorption of glucose and sodium. In the studies of Sakhaee *et al.* [14, 33] and Daudon *et al.* [19] fractional excretion of urate was found to be decreased in overweight non-diabetic patients with pure uric acid stones, whereas it did not differ in diabetic patients. This finding emphasizes the importance of obesity and index fat mass versus index lean mass in creating lithogenic urine, as there appeared a heterogeneity within patients with diabetes as to the presence of an acidic urine. Obesity induces insulin resistance and patients with T2DM often are overweight. Fat accumulation results in insulin resistance through the excessive generation of proinflammatory cytokines and the defective production of insulin-sensitizing adiponectin by the inflated mass of adipocytes [34–36]. In addition, the dietary habits of obese diabetics also play a part. High purine consumption and the high acid ash content from animal proteins result in hypocitraturia and lowered urine pH, which favor both calcium and urate stone formation [37].

The influence of estrogens has also been individually studied in renal stone formation and in metabolic syndrome. Published data from the Women's Health Initiative randomized, placebo-controlled hormone substitution trials demonstrate an increased risk of nephrolithiasis in postmenopausal women receiving estrogen therapy [38]. One potential mechanism for the higher incidence could be through enhanced urinary uric acid excretion with estrogen use, aiding to heterogeneous nucleation of calcium oxalate. In healthy postmenopausal women, estrogen therapy enhances intestinal and renal tubular re-absorption of calcium while reducing skeletal turnover. However, there are conflicting reports as to the degree of hypercalciuria and hypocitraturia in stone formers treated with estrogen replacement [39, 40]. Prothrombin-fragment 1 is a molecule found within calcium oxalate stones and more abundantly in the kidneys of stone formers. While estrogens increase the serum concentration of this molecule, no study has demonstrated a similar effect on urinary excretion [41]. Moreover, the impact of estrogen therapy on the urinary biochemical composition of stone components was not evaluated in the WHI study. By contrast, Heller and colleagues did demonstrate lower risk of stone formation in postmenopausal women and explained it as a consequence of decreased 24-h urinary excretion calcium, oxalate, urate and brushite compared to men. They also showed that estrogen- treated women had lower urinary calcium and calcium oxalate saturation [39].

Early experiments in male and female rats by Fan *et al.* studying the influence of sex hormones on calcium oxalate stone formation revealed a negative correlation between urinary oxalate and the plasma estradiol/testosterone ratio and that androgens increase and estrogens decrease urinary oxalate excretion, plasma oxalate concentration, and kidney calcium oxalate crystal deposition [42]. Yaqisawa *et al.* supported the previous hypothesis by similar experiments and concluded that testosterone appears to suppress osteopontin expression in the kidneys and thus increase urinary oxalate excretion, whereas estrogen appeared to have the exact opposite effect, i.e., inhibit stone formation by increasing osteopontin expression and decreasing urinary oxalate [43]. In addition, Oz *et al.* have shown that estrogen deficiency by aromatase inactivation in an animal model leads to renal calcium leak due to changes in expression of many proteins involved in distal tubule calcium re-absorption. Estrogenic signaling also represents a rapidly expanding field of research in metabolic syndrome. Insulin resistance has been shown in estrogen receptor knock-out animal models [44]. Aromatase-knockout mice present a model of the metabolism in postmenopausal women with the metabolic syndrome [45, 46]. Men with decreased levels of aromatase, the principal enzyme of estrogen production, develop abdominal obesity, elevated blood lipids, and impaired bone maturation and insulin resistance [47]. These metabolic changes were reversible with estrogen replacement. Hormone replacement treatment (HRT) has been shown to reduce visceral adipose tissue, fasting serum glucose and insulin levels in both animal and human studies [48–50].

Adipocytes have a variety of receptors including estrogen receptor (ER), PPAR-γ, IGFR, insulin and leptin receptors and they excrete an array of secretory products such as leptin and estrogen [51]. Therefore, metabolic pathway cross-talks are possible. For insulin, IGF, leptin and PPAR-g it is possible to establish links to the estrogenic function although the exact mode of action remains to be elucidated [52].

Recent experimental evidence suggests that metabolic syndrome may be targeted with beneficial results by selective activation of estrogen receptors with the glucagon-like peptide-1 (GLP-1)-estrogen conjugate [53].

As apparently existing evidence are conflicting and controversial, no safe conclusion can be drawn regarding estrogen replacement and risk of stone formation in the metabolic syndrome. While estrogens appear to be protective for metabolic syndrome, the evidence from Maalouf *et al.* from the Women's Health Initiative study suggest a lithogenic effect of HRT. A degree of contamination in the latter study has to be acknowledged, as some of the participants were also enrolled in a calcium and vitamin D supplement investigation and received treatment that is associated with increased stone risk [38]. Only a trial specifically designed to investigate healthy versus metabolic

syndrome patients on HRT would answer to the question of nephrolithiasis risk in these groups.

4. Prevention and management

Medical management is directed at correcting the underlying metabolic abnormalities of metabolic syndrome as well as those that lead to stone formation, namely low urine volume, hyperuricosuria and low urine pH. It also encompasses the implementation of a robust preventative strategy. It is important to stress patient compliance as a key factor to any preventive strategy. Adequate patient information regarding drinking and dietary recommendations plays a major role. A considerate approach in a dedicated outpatient setting and establishing good communication and a relationship of trust by setting realistic targets with the patient are essential elements to success. Lifestyle and diet modification is the primary approach independent of risk factors. Patients should be encouraged to mobilize regularly, lose weight to achieve a BMI of less than 25–27 (with respect to age, sex and body habitus) and manage conditions that lead to excessive fluid loss. A fluid intake of 2–3 L of neutral pH, clear fluids per day, in order to produce a diuresis of at least 2 L/day is pivotal to stone prevention for all stone formers. A limitation of salt intake to 4–5 g/day, animal protein intake up to 1 g/kg BW/day, normal calcium intake 1–1.2 g/day (because of the inverse relationship between dietary calcium and stone formation) [54] and a balanced diet low in fats and carbohydrates and rich in fruit and vegetables constitute the general metaphylaxis plan. Lifelong commitment is necessary and should be explained clearly from the beginning. Appropriate lifestyle and dietary modifications should never be abandoned even when a pharmacological approach is started. There is recent evidence that a Mediterranean type diet appears to improve the metabolic profile and possibly reverse the effects of metabolic syndrome five years onwards [55]. The Mediterranean diet emphasizes consumption of olive oil, fruits, vegetables, and seeds, which contain mono- and poly- unsaturated fatty acids, dietary fiber, magnesium, potassium, antioxidant vitamins (i.e. folate, vitamin E), polyphenols, and other phytochemicals that combat oxidative stress, inflammation, and insulin resistance. The beneficial effects of this diet have also been studied relative to lithogenic risk in metabolic syndrome patients and have been found to be substantial [56].

Correction of low urine pH by urine alkalinization is central in preventing recurrent urate stones [57]. Sodium reduction is advised, as well as reduction in animal protein intake and carbohydrates and loss of weight [58]. Along with alkalinization, the addition of allopurinol is indicated in cases of hyperuricemia or hyperuricosuria (excretion >1.2 g/day). Allopurinol is a xantine-oxidase inhibitor that prevents uric acid production from purine. It is administered orally at doses 100–300 mg/day [59]. Care must be taken when administering allopurinol for prolonged periods. Reported side effects include Steven-Johnson or Lyell syndrome, vasculitis, hepatitis, renal failure and formation of xanthine stones. A new potential pharmacologic therapy for recurrent stone disease due to uricosuria is described by Goldfarb *et al.* Febuxostat, a nonpurine inhibitor of xanthine oxidase (also known as xanthine dehydrogenase or xanthine oxidoreductase) has recently been shown to lower urinary uric acid significantly more compared to allopurinol or placebo [60]. Febuxostat, at a daily dose of 80–120 mg, has also been shown to be more effective than allopurinol 300 mg in lowering serum urate [61]. However, a recent Cochrane review concludes that after 3 years of follow-up there were no statistically significant differences regarding clinical effectiveness and side effects between febuxostat 80 mg or 120 mg and allopurinol [62]. Dissolution therapy is generally effective, and most patients achieve durable results with lifelong alkali therapy. Urological intervention should be considered for increased stone burden that does not respond to preventative and medical therapy and leads to complications such as intractable pain, recurrent urinary tract infections and prolonged obstruction with progressive renal insufficiency [63].

5. Conclusions

An increased prevalence of nephrolithiasis is reported in patients with obesity, insulin resistance, type 2 Diabetes and the other characteristics of the metabolic syndrome. Various factors, including low urine pH, hyperuricosuria, hypercalciuria and hypocitraturia are involved in increasing the risk of uric acid nephropathy and uric acid lithiasis in patients with metabolic syndrome. The association is so strong that it is suggested that patients with uric acid stones, especially if overweight, should be screened for the presence of type 2 Diabetes or components of the metabolic syndrome. Sex hormones and estrogen status represent a new direction in understanding and researching stone formation in metabolic syndrome, with conflicting evidence regarding HRT. Lifestyle and dietary modification along with appropriate medical management and diabetic control constitute the hallmark in prevention and treatment of both conditions. Specific measures for uric acid lithiasis and nephropathy should be considered in the form of improving urine pH and controlling hyperuricemia. Modern endourologic surgery may be employed where medical management is not sufficient and complications ensue. Continuous research in the field of lithogenesis and metabolic syndrome will provide additional information required for more effective prevention and treatment of these two prevalent conditions.

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