DOI: 10.4081/aiua.2021.2.195

ORIGINAL PAPER

The new patterns of nephrolithiasis: What has been changing in the last millennium?

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Summary ***Nephrolithiasis has been increasing over the last millennium. Although early epidemiologic studies have shown that kidney stones were two to three times more frequent in males than in females, recent reports have suggested that this rate is decreasing. In parallel a dramatic increase of nephrolithiasis has also been observed among children and adolescents. Furthermore, epidemiologic studies have shown a strong association between metabolic syndrome (Mets) traits and kidney stone disease. Patients with hypertension have a higher risk of stone formation and stone formers are predisposed to develop hypertension compared to the general population. An incidence of nephrolithiasis greater than 75% has been shown in overweight and obese patients compared to those of normal weight. It has also been reported that a previous diagnosis of diabetes mellitus increases the risk of future nephrolithiasis. Additionally, an association between metabolic syndrome and uric acid stone formation has been clearly recognized. Furthermore, 24-h urinary metabolic abnormalities have been decreasing among patients with nephrolithiasis over the last decades. Finally, nephrolithiasis could cause chronic kidney disease (CKD) and end stage renal disease (ESRD), especially in women and overweight patients. According to these observations, a better understanding of these new features among stone former patients may be required. Hence, the recognition and the correction of metabolic disorders could help not only to reduce the primary disease, but also stone recurrence.***

KEY WORDS: *Nephrolithiasis; Metabolic syndrome (Mets); Gender; Children; Adolescents.*

Submitted 13 April 2021; Accepted 17 May 2021

INTRODUCTION

Several studies in the last decades have showed an overall increased incidence of kidney stones (1, 2). However, nephrolithiasis is increasing in women at a greater rate than in men and the common ratio 3:1 male to female is reducing (3, 4). An increased incidence of nephrolithiasis among children during the last 25 years has also been observed (5).

Moreover, other studies have shown Mets is increasing in parallel to the incidence and prevalence of nephrolithiasis (6). Various definitions have been included for defining Mets criteria. The *United States National Cholesterol Education Program* (NCEP) *Adult Treatment Panel III* (ATP III) is the most simple since it can be used by basic metabolic laboratories commonly present in clinics. Among five established criteria, three or more are needed to diagnose Mets. These are: waist circumference > 102 and 80 cm in men and women respectively, serum triglycerides > 150 mg/dL, high density lipoprotein < 40 mg/dL and < 50 mg/dL in men and woman respectively, blood pressure (BP) > 130/85 mmHg and fasting blood sugar < 100 mg/dL (7) (Table 1). A study based on self-reported histories has shown an increasing association of nephrolithiasis and Mets traits (3.7% with no traits, 7.5% for three traits and 9.8% for five traits) (8). Furthermore, the patients with more than 4 Mets traits also showed a significant increase in the chances of recurrent or multiple stones with respect to patients with 0 traits (9). Mets may also cause cardiovascular disease, a condition frequent in patients with nephrolithiasis (10).

These new insights confirm a new pattern of patients with nephrolithiasis that should be regarded as a systemic disease representing the result of the interaction of multiple risk factors.

This article will review the possible explanations for these new features of stone disease, with the aim to better assess them and their association with nephrolithiasis and to suggest measures for prevention not only for primary systemic disease, but also for stone recurrence.

Mets and nephrolithiasis

Obesity, the most frequent tract of Mets, is also a condition of risk for nephrolithiasis. A positive correlation between obesity and the first-time stone, recurrent stone formation and shorter interval of recurrence have been demonstrated. *Taylor et al.* have reported that waist circumference, *body mass* (BMI), weight gain, weight gain during adulthood are linked to an increase of incidental stones (11). Other studies have shown that BMI is higher in stone formers (12, 13). In a large cohort of women without history of stones the risk for incidental stones increases with BMI 1.3 fold for 25-29 kg/m^2 higher, 1.62 for 30-34.9 kg/m^2 and 1.81 fold for ≥ 35 kg/m^2) with respect to BMI < 25 kg/m^2 (14). Next, body fat can influence the risk for stone formation. *Kim et al.* have shown a link between uric acid and calcium oxalate stones and visceral adipose tissue measured on *computed tomography* (CT) (15). A link has also been reported between non-alcoholic fat liver disease and the risk of stone formation and visceral to subcutaneous fat tissue ratio (16).

No conflict of interest declared.

Table 1.
NCEP ATP III: United States National Cholesterol Education Program.

Adult treatment panel III, Rx, Pharmacologic intervention for that component	
	Criteria
Waist circumference (cm)	> 102 (males), > 88 (females)
Fasting glucose (mg/dL)	≧ 100 or Rx
Triglycerides (mg/dL)	≧ 150 or Rx
High-density lipoprotein (mg/dL)	< 40 (males), < 50 (females) or Rx
Blood pressure (mmHg)	> 130 (systolic), > 85 (diastolic) or Rx

Additionally, obesity has been associated with impaired carbohydrate tolerance and inappropriate calcium response to glucose ingestion. Obese patients show an increased excretion of calcium, sodium, uric acid and a lower urinary pH in relation to the non-obese (17). Defects in renal ammoniagenesis and excessive *net acid excretion* (NAE), which are common in patients with Mets, could cause a decreased urinary pH (18). Next, renal acidification defects lead to hypocitraturia, another important risk for stone formation (13). Furthermore, an increased excretion of oxalate correlated with BMI has been reported among diabetic and overweight patients promoting calcium oxalate stone formation. Hence, both the percentage of uric acid and calcium oxalate stones was found higher in obese than non-obese patients (34.9 *vs* 23.1 and 7.7 *vs* 2.8 respectively) (19).
Diabetes mellitus has been clearly linked to nephrolithiasis. A previous diagnosis of diabetes increases the risk for stone formation and a previous diagnosis of stone disease leads to the onset of diabetes mellitus. In a cross-sectional study of 3 large cohorts on multivariate analysis, the relative risk of prevalent stone disease in patients with type 2 diabetes was 1.38 in older women, 1.67 in younger women and 1.31 in men. Additionally, the risk of incident type 2 diabetes in patients with history of stone disease was 1.33, 1.48 and 1.49 respectively (20). Patients with type 2 diabetes have a decreased ammonium production resulting in lower urinary pH and increased risk of uric acid stone formation and an increased excretion of oxalate which promotes calcium oxalate stone formation (21). However, uric acid stones are more frequent in patients with diabetes and glucose intolerance (22). An association between the gravity of diabetes evaluated with fasting plasma insulin and glucose and hemoglobin A1c and the risk for stone formation has also been observed (23).
It is well known that elevated serum triglycerides and low *high-density lipoprotein* (HDL) levels increase the cardiovascular risk. Next, dyslipidemia is associated with lower urinary pH and could be considered as an independent risk factor for kidney stones (24). An association between dyslipidemia and kidney stone disease has been reported by Masterson and colleagues. This retrospective study shows an association between dyslipidemia and kidney stones with a hazard ratio of 2.2. Then, examining individually dyslipidemia factors, it was shown that *low-density lipoprotein* (LDL) and triglycerides are not associated with stone formation, while low HDL values (< 45 mg/dL for men; < 60 mg/dL for women) had a hazard ratio of 1.4 (25). Furthermore, nephrolithiasic patients show higher levels of total serum cholesterol and triglycerides (12). The association of total cholesterol with stone formation was higher in uric acid and calcium oxalate monohydrate/dihydrate. Besides, LDL levels were higher in calcium oxalate monohydrate/dihydrate stone formers than in calcium oxalate monohydrate group.
Several studies have shown an association between hypertension and nephrolithiasis: patients with hypertension are more at risk for nephrolithiasis (26) and patients with a history of nephrolithiasis have an increased risk for development of hypertension (27). Furthermore, hypertensive patients had a significantly increased calcium, oxalate and uric acid excretion with respect to normotensive controls (26, 28). Another study has shown stone formers with hypertension have reduced urinary excretion of citrate and urine pH and increased titrable acid excretion when compared with normotensive stone formers (29). The link between hypertension and stone disease could be high sodium dietary intake, common in hypertensive patients, promoting increased urinary excretion of calcium.
The association between cardiovascular disease and nephrolithiasis has also been recognized. A longitudinal study of patients affected by cardiovascular disease with follow-up more than 20-years has showed a correlation between cardiovascular features and stone disease (30). Next, a link between carotid atherosclerosis and kidney stone disease has also been observed. Another study by the *Rochester Epidemiology Project* spanning 10 years has found that calcium oxalate stone formers show a high risk of mortality from cardiovascular disease and higher total cholesterol, lower HDL, higher systolic blood pressure and elevated highly sensitive C reactive protein (hsCRP) (31). Calciuria and oxaluria have also been positively correlated with 10- year cardiovascular disease risk including mortality (32). Furthermore, a positive association between risk factors for coronary artery disease (smoking) was reported (33).
Finally, abdominal aortic calcification found on CT have been associated with uric acid stone formation, low urine pH and hypocitraturia (34).

Gender and nephrolithiasis

A new tract of this new epidemiology is the shifting in gender of nephrolithiasis. Although nephrolithiasis is still more frequent in men than in women, the ratio male to female is reducing and the most recent NHANES data showed an overall prevalence of 10.6% in men and 7.1% in women (35). The changing role of women in the workplace has been considered. Modification of lifestyle and dietary habits in relation to working activity could contribute to the shifting in gender difference of stone formation. Dietary factors promoting stone formation such as high animal protein, high salt and low calcium diets are more usual in men than in women, although the expansion of the high protein diet or higher fructose intake and low fluid intake to females could be a further cause of changing in gender of nephrolithiasis (36, 37). Obesity has also been associated with increased stone

risk among women. *Taylor et al.* show that overweight among females increases the risk for stone disease with respect to men with the same characteristics. In this study, body mass, weight gain during adulthood as well as waist circumferences increased the risk of stone formation among females (11). It has also been reported that uric acid stones are present in more than 50% of obese females (38). Additionally, hyperinsulinemia, that is usually found in obese patients, may be associated to urinary acidosis with the consequent risk for uric acid stone formation (39). This could be the link between gender, obesity, insulin level and kidney stones. Another risk factor for stone formation among reproductive aged women is pregnancy. *Reinstaller et al.* have observed women with a history of pregnancy have more than twice the chance of stone formation than those who were never pregnant. Lithogenic factors such as hypercalciuria, hyperuricosuria and increased urinary pH have been observed during pregnancy. These data suggest that an increased lifetime lithogenicity could occur among females since many of them are pregnant in working age (40). Finally, it has been reported struvite and hydroxyapatite stones are more common in women aged less than 55 years (41). As urinary infections are increasing among females, they could be a factor for stone formation as well a further cause for the shifting in the gender of nephrolithiasis.

Children and nephrolithiasis

Another feature of the new pattern of nephrolithiasis is a dramatic increase of nephrolithiasis among children and adolescents over the past 25 years (42). A 25-year population based study performed in *Olmsted County* (*Minnesota*) has reported that 41% of children under the age of 18 showed incidence of stones on CT with an increase of 4% of stones per year. Next, among 12-17 year olds the incidence rate was 6% (43).

Database from the Healthcare Cost and utilization Project Kids' inpatient admission for pediatric nephrolithiasis in 2003 shows a higher frequency among girls. This difference in gender slightly changes in favour of boys within the first decade only (44). Another study in South Carolina has reported an increase to emergency department admissions for nephrolithiasis of children aged 0 to 18 years between 1996 to 2007 (5). The annual incidence of kidney stones was higher among school aged children and adolescents. In fact, the annual incidence rate among 14 to 18 years olds dramatically increased by about 50% from 1996 to 2007 (25 per 100.000 *vs* 54 per 100.000 respectively), while the incidence of stones for children younger than 9 years remained stable (less than 5 per 100.000). Moreover, among children and adolescents, girls had a higher incidence of kidneys stones than boys, as also reported by other studies (45). The reason for these features is not clear, probably because of the few cohort studies performed which have not allowed the analysis of the link between gender and risk factors.

Nephrolithiasis in children is idiopathic in origin in most cases, although rare genetic anomalies or a secondary cause of lithiasis such as neurological or congenital urinary anomalies of the urinary tract have also been identified. Besides, the risk of infected stones has decreased probably in relation to improved diagnosis and management of anatomical and neurological conditions promoting urinary infections. Conversely, environmental factors have been suggested in the pathogenesis of idiopathic nephrolithiasis. In fact, it has been reported that obesity and nephrolitihiasis among children are increasing in parallel (46). Dietary habits such as high intake of fructose (47) or salt (48) and low intake of fluid (49), which are the same risk factors for stone formation in adults, could be involved.

Chronic kidney disease (CKD) and nephrolithiasis

Nephrolithiasis has also been associated with CKD. Several studies have showed that, although kidney stones can cause CKD with acute or chronic damage of the urinary tract, the risk for *end stage kidney disease* (ESKD) or mortality from CDK are not increased (50). Data from the *Alberta Kidney* Disease network confirm similar results (51). Further cross-section analysis of NAHNES 2007 to 2010 has also reported a greater prevalence of CKD and ESRD in nephrolithiasis patients with odds ratios of 1.50 and 2.37 respectively (52). Specific conditions associated with the risk of CKD in stone formers have been analysed by *Gambaro et al.* (53). The results of this study have showed that nephrolithiasic patients have twice the risk of CKD or ESRD and the risk is higher in women and overweight stone formers.

Comment

There are changing patterns of nephrolithiasis. Shifting in gender prevalence and the increase of kidney stone disease among children and adolescents have been well observed. Moreover, a strong association between Mets traits and nephrolithiasis has been reported. Hence, it has been hypothesized that different metabolic alterations may modify urinary "*milieu*" through a common mechanism resulting in overly acidic urine with consequent salt precipitation and stone formation.

We have previously reported about metabolic disorders among 109 nephrolithiasic patients evaluated between 2017 and 2018 (54).

In this study metabolic urinary anomalies (hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia) in 24h urine samples were observed only in 11 patients, while in a cohort of stone formers evaluated between 2007-2008 these figures were present in 28 of them. Conversely, metabolic disorders (hypertension, diabetes, dislypidemia, overweight) were present in 72% and more than 2 in 38% of the cases.

The decrease of urinary metabolic abnormalities observed in the group in the last decade could suggest that a complete metabolic evaluation is not necessary in all patients with associated comorbidities, while it may be performed in cases of relapses of stone events (55, 56).

The increase of metabolic disorders in the last decade confirm among nephrolithiasic the association between Mets and nephrolithiasis and supports the hypothesis that nowadays stone disease could be considered as a systemic disorder (Table 2).

Changes in lifestyle and dietary habits could have coincided with an increase of metabolic syndrome and in parallel of stone formation (57). Patients with Mets obvious-

Table 2.
Summary of new patterns of nephrolithiasis.

- The latest epidemiological studies have showed a change in gender distribution and an increasing prevalence among children and adolescents of nephrolithiasis.
- The incidence and prevalence of kidney stones have been increasing in parallel with Mets, whereas rates of metabolic abnormalities diagnosed in 24-h urine is decreasing.
- Nowadays, stone disease could be recognized not as a modification of urine composition or an ordinary flank pain, but as a systemic condition including Mets, cardiovascular diseases and CKD.

ly consume more food which could influence the urinary excretion of risk factors for stone formation. Preventative measures and careful patient education should be included to promote a healthy lifestyle. An increase of physical activity has been reported to prevent metabolic syndrome. Further, an increase of fluid intake to achieve a daily urinary volume of 2 litres and a diet rich in fruit and vegetable have reduced metabolic syndrome, stone formation and urinary infections (58, 59). Specific medical treatment (antidiabetics, antihypertensive, antilipemic and anticoagulant drugs) could be required to correct each component of metabolic syndrome (60).

Conclusions

The patterns of nephrolithiasis are changing.
Nephrolithiasis is still common among men, but the gender gap is narrowing as is the increase in occurrence among children and adolescents. With the parallel increase in incidence of both nephrolithiasis and systemic disorders, lifestyle changes with dietary and specific medicaments could be the most effective way to prevent primary disease and recurrent stone disease. Nephrolithiasis from ordinary flank pain could be recognized as a systemic condition and the correction of systemic disorders could not only reduce morbidity and mortality for diabetes, cardiovascular disease and development of CKD, but also minimize the risk of stone formation.

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