Archives of Clinical & Experimental Surgery

Original Article

Arch Clin Exp Surg 2017;6:81-85

doi:10.5455/aces.20160402122723

# Metabolic abnormalities and genitourinary tract anatomical alternations in patients with recurrent urolithiasis

John Neil, Jose Binu

**ABSTRACT**

**Background:** Preventing the recurrence of episodes of stone formation is the focus of interest for patients. This retrospective study aimed to determine the prevalence of metabolic abnormalities and anatomical alterations of the genitourinary tract in patients with recurrent urolithiasis.

**Methods:** Patients who had recurrent renal calculi were included. Laboratory assessment was performed on two 24-hour samples of urine. The first 24-hour urine was a random specimen and the second was obtained after the patient had been on a sodium-, oxalate- and calcium-restricted diet for at least one week. The patients with hypercalciuria further underwent fasting and calcium load testing and were assessed in terms of parathyroid hormone levels. Urine culturing was conducted to rule out urinary tract infection. All patients were evaluated with ultrasound and intravenous pyelography for any anatomical abnormalities.

**Results:** A total of 30 patients (20 male and 10 females) were included in the study. The most frequently found metabolic alterations were hypercalciuria, low urinary volume, urinary tract infection and hyperoxaluria. Anatomic alterations were found in 26.5% of patients, mainly in the form of renal cysts, pelvi-ureteric junction obstructions, horse shoe kidneys and atrophic kidney.

**Conclusions:** 80% of patients with recurrent stone disease had some measure of metabolic abnormality to account for the disease. The use of two 24-hour urine samples significantly improved the detection rate of metabolic abnormalities compared to a single sample. The major limitation of this study was the small number of patients as well as the short study duration.

***Key words:*** *Renal calculi, genitourinary tract, urinary tract infection, hyperoxaluria, hypercalcemia, hypercalciuria*

## Introduction

The estimated occurrence of urolithiasis is at maximum up to 5% of the population, while the risk of passing a kidney stone over the course of a lifetime is 8-10% [1]. Stone formation takes place twice as often in men as in women. The peak age in men is at 30 years, whereas women have a bimodal age distribution, peaking at 35 and 55. The probability of secondary stone formation varies between 5-7 years and was found to take place in approximately 50% of those patients who had a first stone. Significant patient discomfort was found in cases of symptomatic urinary calculi. The surgical treat-

***Author affiliations*** : *Department of General Surgery, Amala Institute of Medical Sciences, Amala Nagar, Kerala, India*
***Correspondence*** : *Jose Binu, MS, Department of General Surgery, Amala Institute of Medical Sciences, Amala Nagar, Kerala, India*
*e-mail: drbinujose@yahoo.com*
***Received / Accepted*** : *January 13, 2016 / March 05, 2016*

ments for calculi are associated with risk of morbidity. Furthermore, the patients may suffer financial problems moreso than the physical torment.

Preventing the recurrence of an episode of stone formation is the focus of interest for most patients. The aim of medical management of stone disease is to decrease the super saturation of crystal components in the urine. In terms of specific medical therapy, it is inevitable to need to perform a metabolic evaluation in order to correct the diagnosis as well as to administer either a fluid, dietary or drug therapy to achieve optimal management of the patient. A population-based evaluation that should be able to identify associated metabolic disorders responsible for recurrent stone disease is necessary. Common metabolic problems include distal renal tubular acidosis, primary hyperparathyroidism, a history of gout, chronic metabolic acidosis and enteric hyperoxaluria, cystinuria and gouty diathesis [2]. The urinary-associated risk factors for stone formation are comprised of hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and low urinary volume [3]. Therefore, without metabolic evaluation, it is impossible to know which patients will benefit from dietary restrictions centered on calcium, oxalate and uric acid. Though many of the conditions that cause renal stones are relatively uncommon, a selective medical therapy is indicated either to prevent recurrent stone formation or to correct the underlying non-renal complications. Incidence of stones was higher in patients with an anatomical abnormality that may result in urinary stasis [4]. The anatomical abnormalities that increase the risk of stone diseases are obstruction of the pelviuretral junction (PUJ), hydronephrotic renal pelvis, or calices, calyceal diverticulum, horseshoe kidney, ureterocele, vesicoureteral reflux, urethral stricture and tubular ectasia (medullary sponge kidney) [5]. Urologists today seem to have the primary responsibility in not only the surgical but also in the medical management of urolithiasis. With knowledge of patients' stone analysis and therapy preferences, an appropriate metabolic evaluation and treatment plan can be implemented. This study's goal was to evaluate the metabolic abnormalities and anatomical alterations of the genitourinary tract in patients with recurrent urolithiasis.

## Methods

### *Patient selection*

A retrospective study was conducted on patients who were diagnosed for recurrent (more than one episode) renal calculi in the outpatient clinic of the General Surgery Department, Amala Institute of Medical sciences, Thrissur, Kerala, India, during a period of 12 months. A detailed history was taken and thorough physical examination performed. Past medical history emphasized previous urinary tract infections, diet and fluid intake, medications, including vitamin intake, bowel disease, gout, renal disease, bone or parathyroid disease and bowel surgery. Laboratory assessment consisted of two samples of 24-hour urine with dosing calcium, uric acid, creatinine, sodium, pH, oxalate, citrate, qualitative cystine, magnesium and total volume. The first 24-hour urine sample was a random specimen and the second 24-hour urine sample was obtained after the patient had been on a sodium-, oxalate- and calcium-restricted diet for at least one week. A urine culture was performed to rule out urinary tract infections (UTI). Complete blood count and a basic metabolic panel, including serum electrolytes and non-protein nitrogenous substances, were analyzed. Parathyroid hormone levels were assessed in patients with hypercalcemia. All patients were evaluated with an ultrasound scan and intravenous pyelography (IVP) to determine any anatomical abnormalities. Written consent was obtained from the patients or their relatives and the study design was approved by the Institutional Ethics Committee for Research, Amala Institute of Medical Sciences, Amala Nagar, Thrissur, India. Patients with renal calculi who were admitted for emergency care were excluded from the study.

## Results

A total of 30 patients (20 males and 10 females) of age groups ranging from 20-70 years (mean age: 38.6) with recurrent renal calculi were included in the study (Figure 1). The greatest prevalence was found in the 30-39 years group with equal predominance in both genders whereas male predominance was found in the 40-49 years age group. Among the renal calculi, calcium oxalate stones were observed in 22 (73.33%) cases, whereas uric acid was the least noted (only 1 case). Magnesium ammonium phosphate was found in 4 cas-

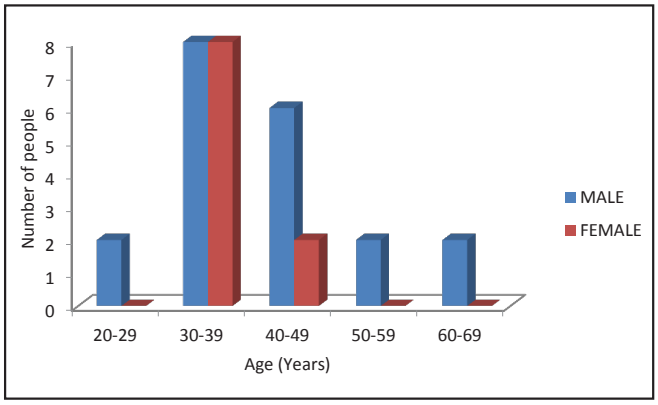


**Figure 1.** Distribution of age and gender.

**Table 1.** Chemical composition of stones.

| Stone composition | Occurrence |
|---|---|
| Calcium oxalate | 22 (73.3%) |
| Magnesium ammonium phosphate | 4 (13.3%) |
| Mixed calcium oxalate and phosphate | 2 (10%) |
| Uric acid | 1 (3.3%) |

**Table 2.** Metabolic alterations associated with renal calculi.

| Metabolic alteration | Occurrence |
|---|---|
| Absorptive hypercalciuria | |
| Type 1 | 2 (6.6%) |
| Type 2 | 5(16.6%) |
| Renal phosphate leak | 0 |
| Renal hypercalciuria | 1(3.3%) |
| Resorptive hypercalciuria | 0 |
| Hyperoxaluria | 3(10%) |
| Hyperuricosuria | 1(3.3%) |
| Hypocitraturia | 0 |
| Hypomagnesemia | 0 |
| Urinary tract infection | 8(26.6%) |
| Low urinary volume | 9(30%) |
| No alteration detected | 6(20%) |

es (13.3%) (Table 1). Absorptive hypercalciuria was discovered as the major metabolic alteration in 16.6% of cases and no cases were found with resorptive hypercalciuria, hypocitraturia or hypomagnesemia. Renal hypercalciuria and hyperuricosuria were established in 3.3% of the total patient sample population (Table 2). The metabolic abnormality in single verses two 24-hour urine sample was highest for hypercalciuria (20% in the single versus 26.6% in the two 24-hour urine samples) (Table 3). The major anatomical alteration was renal cyst (16.6%) followed by a 3.3% incidence for PUJ obstruction, horse shoe kidney and atrophic kidney (Table 4).The anatomic alterations associated with specific types of renal calculi are described in Table 5. The incidence of calcium oxalate was associated with renal cyst.

## Discussion

Nephrolithiasis is one of the most common diseases of the urinary tract and has high prevalence and recurrence. Urolithiasis affects primarily young males [6]. In our study, there was a predominance of the male gender (66.6% vs 33.3%) in the 40-49 age group and the patients' mean age was 38.6 years, which is in accordance to the literature. We discerned a causal alteration in 80% of patients. Metabolic alterations most frequently found were hypercalciuria, low urinary volume, urinary tract infection and hyperoxaluria.

Hypercalciuria is defined as urinary calcium excretion greater than 300 mg/day in men and greater than 200 mg/day in women [7]. This is the most common type of metabolic abnormality found in patients. Absorptive hypercalciuria is secondary to increased calcium absorption from the intestine, which leads to elevated urinary excretion of calcium. In absorptive hypercalciuria, the fasting urinary calcium excretion is normal. In type I absorptive hypercalciuria, patients have an increased urinary calcium excretion even on a calcium-restricted diet. Type II absorptive hypercalciu-

**Table 3.** Metabolic abnormalities in single versus two 24-hour urine samples.

| Metabolic abnormality | % in single 24-hour urine | % in two 24-hour urine |
|---|---|---|
| Hypercalciuria | 6(20%) | 8(26.6%) |
| Hyperoxaluria | 2(6.6%) | 3(10%) |
| Hyperuricosuria | 1(3.3%) | 1(3.3%) |
| Urinary tract infection | 5(16.6%) | 8(26.6%) |
| Low urinary volume | 6(20%) | 9(30%) |

**Table 4.** Anatomic alteration associated with renal calculi.

| Anatomic alterations | Occurrence |
|---|---|
| Renal cyst | 5(16.6%) |
| PUJ obstruction | 1(3.3%) |
| Horse shoe kidney | 1(3.3%) |
| Atrophic kidney | 1(3.3%) |

**Table 5.** Anatomic alterations associated with specific types of renal calculi.

| Stone composition | Renal cyst | PUJ obstruction | Horse shoe kidney | Atrophic kidney |
|---|---|---|---|---|
| Calcium oxalate | 3 | 0 | 0 | 1 |
| Magnesium ammonium phosphate | 0 | 1 | 0 | 0 |
| Mixed calcium oxalate and phosphate | 2 | 0 | 1 | 0 |
| Uric acid | 0 | 0 | 0 | 0 |

ria is the most common type of absorptive hypercalciuria and is dependent on dietary calcium. Type III absorptive hypercalciuria is secondary to renal phosphate leak. Low serum phosphate increases vitamin D level 1.25-fold, resulting in the increased absorption of phosphate as well as calcium from the intestine. In our study, 8 (26.6%) patients had hypercalciuria, the majority of which was absorptive hypercalciuria type II. Resorptive hypercalciuria accounts for less than 5% of calcium stones. These patients had hypercalciuria based on increased calcium bone loss, as in hyperparathyroidism. Parathyroid hormones were elevated along with urinary phosphate. Renal leak hypercalciuria is an intrinsic defect of the renal tubule to reabsorb calcium. In our study, we had one case of renal hypercalciuria, but no cases of resorptive hypercalciuria.

Hyperoxaluria is defined in adults as oxaluria exceeding 40 mg/day [8]. Inherited primary hyperoxaluria is a rare metabolic disorder that causes renal oxalosis in childhood, when it is usually fatal. In adults, hyperoxaluria is usually secondary to increased oxalate absorption from the gastrointestinal tract. This condition is frequently observed in patients with inflammatory bowel disease (IBD) and in patients that underwent small bowel bypass surgery for the treatment of morbid obesity. Foods with high oxalate content include spinach, soy, rhubarb, beets, nuts, chocolate, tea, wheat bran and strawberries. We had 3 cases of hyperoxaluria, but none of these patients had any previous history of bowel resection or IBD.

Hyperuricosuria is defined as uric acid excretion exceeding 750 mg/day and is associated with calcium oxalate stones in 20% of patients [9]. In hyperuricosuric calcium nephrolithiasis, uric acid may bind to stone inhibitors or promote calcium oxalate stone formation on a uric acidmidus [10]. We had one patient with hyperuricosuria whose stone was composed of calcium oxalate.

Citrate is an important inhibitor of calcium oxalate stone formation [11]. Hypocitraturia is defined as less than 320 mg/day of urinary citrate excretion [12]. Citrate can decrease the amount of ionic calcium available for stone formation by its complex formation with calcium property. In addition, it has direct inhibitory activity on calcium oxalate nucleation [13]. Surprisingly, none of our patients had hypocitraturia.

A urinary volume of less than 2 litres per day is a regular finding in recurrent calcium stone formers [14]. As the goal of medical management is to decrease the super saturation of crystal components, increasing urinary volume achieves this goal in stone formers of all types. A clinical trial involving idiopathic calcium stone formers has also shown a significant benefit of increased water intake alone in the prevention of stones [15]. In our study, 30% of patients had urine output of less than 2 litres per day.

For struvite stones, patients should be followed closely for recurrent infections. Underlying anatomical abnormalities that predispose patients to recurrent infections should be corrected. It has been reported by Olavi et al. that nanobacteria can induce tubular damage and renal cyst formation, while also favoring the growth of crystals [16]. Metabolic evaluation should be performed in most patients, especially if calcium stones coexists with struvite stones. Three out of four patients in our study with struvite stone had urinary infection with proteus, and the other patient had pseudomonas infection. A proper multidisciplinary approach can reduce the incidence and rate of recurrence of urolithiasis.

**Conclusion**

Our study, though limited by the small number of patients as well as the short study duration, showed that 80% of patients with recurrent stone disease had some form of metabolic abnormality to account for the disease. Two 24-hour urine samples significantly im-

proved the detection rate of metabolic abnormalities compared to a single sample.

**Acknowledgment**

The authors gratefully acknowledge the valuable help of Dr. Ajith, TA, Professor, Department of Biochemistry, Amala Institute of Medical Sciences, Thrissur, Kerala, India, during the preparation of the manuscript.

**Funding**: No funding sources

**Ethical Approval**

The study was approved by the Institutional Ethics Committee.

**Conflict of interest statement**

The authors have no conflicts of interest to declare.

**References**

1. Malvinder S. Kidney Stones. BMJ 2004;328:1420-4.
2. Pak CY, Oata M, Lawrence EC, Snyder W. The hypercalciurias. Causes, parathyroid functions, and diagnostic criteria. J Clin Invest. 1974;54:387-400.
3. Goldfarb DS, Coe RL. Prevention of Recurrent Nephrolithiasis. Am Fam Physician 1999;60:2269-76.
4. Raj G, Auge B, Assimos D, Preminger G. Metabolic abnormalities associated with renal calculi in patients with horseshoe kidneys. J Endourol 2004;18:157-61.
5. Miller NL, Lingeman JE. Management of kidney stones. BMJ 2007;334:468-72.
6. Hughes P. Kidney stones epidemology. Nephrology 2007;12:S26-30.
7. Coe FL, Kavalach AG. Hypercalciuria and Hyperuricosuria in Patients with Calcium Nephrolithiasis. N Engl J Med 1974;291:1344-50.
8. Baggio B, Gambaro G, Favaro S, Borsatti A. Prevalence of Hyperoxaluria in Idiopathic Calcium Oxalate Kidney Stone Disease. Nephron 1983;35:11-4.
9. Curhan GC. Epidemiology of Stone Disease. Urol Clin North Am 2007;34:287-93.
10. Chandhoke PS. Evaluation of the Recurrent Stone Former. Urol Clin North Am 2007;34:315-22.
11. Kok DJ, Papapoulos SE, Bi OL. Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int 1990;37:51-6.
12. Kristina L, Stephen YN, Ross P. Quantitative Assessment of Citric Acid in Lemon Juice, Lime Juice, and Commercially-Available Fruit Juice Products J Endourol 2008;22:567-70.
13. Polo MAA, Santiago SA, Prieto MSG, Menor FA, Pintado FLC, Gomez AZ, et al. Hypercalciuria, hyperoxaluria, and hypocitraturia screening from random urine samples in patients with calcium lithiasis. Urol Res 2012;40:511-5.
14. Stitchantrakul W, Kochakarn W, Ruangraksa C, Domrongkitchaiporn S. Urinary Risk Factors for Recurrent Calcium Stone. J Med Assoc Thai 2007;90:688-98.
15. Park S, Pearle. MS. Pathophysiology and Management of Calcium Stones Urol Clin North Am 2007;34:323-34.
16. Kajander EO, Ciftcioglu N, Miller-Hjelle MA, Hjelle JT. Nanobacteria: controversial pathogens in nephrolithiasis and polycystic kidney disease. Curr Opin Nephrol Hypertens 2001;10:445-52.