Metabolic evaluation of patients with recurrent, multiple or bilateral renal stones in Jaffna

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(Index words: metabolic evaluation, nephrolithiasis, recurrent and multiple or bilateral renal stone formers)

Abstract

Introduction A comprehensive evaluation to identify metabolic abnormalities will help design management strategies for prevention of renal stone recurrences. The objective of this study is to identify the metabolic risk factors in a series of patients with recurrent, multiple or bilateral renal stone disease from the Northern Province, Sri Lanka.

Methods This is a hospital based observational study on patients with recurrent, multiple or bilateral renal stones. Metabolic evaluation workout included, fasting non-tourniquet venous blood sample for serum ionized calcium, creatinine, and uric acid, freshly voided early morning urine sample for pH and laboratory urinalysis, and collection of two sets of 24 hour urine samples on two separate days, for phosphorous, creatinine, oxalate, uric acid, magnesium, calcium and citrate.

Results The mean values of each metabolic parameter measured on the two sets of 24 hour urine samples, were found to be within the normal reference range for the entire 30 patient study group taken as whole, although the mean values for 24 hour urine magnesium (79.79±51.36 mg) and urine calcium (125.02±73.32 mg) were found to be towards the lower limit of normal reference range and the 24 hour urine oxalate (0.38±0.22 mmol) was found to be towards the upper limit of normal reference range. However, 80% of patients individually showed abnormal metabolic results either as single derangement (13 patients, 43.3%) or in multiple combinations of derangements (11 patients, 36.7%). Six patients (20%) did not have any metabolic abnormalities. Hyperoxaluria, hyperuricosuria, hypomagnesuria and hypocitraturia were the metabolic abnormalities identified among the study group.

Conclusion A comprehensive metabolic evaluation of each patient with recurrent, multiple or bilateral renal stone disease can help identify metabolic abnormalities, either as a single abnormality or combinations of abnormalities, specific for them. Such patient profiling will help develop bespoke management strategy based on appropriate dietary advice and specific medical treatment towards prevention of further stone formation.

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Introduction

The European Association of Urology (EAU) guidelines recommend renal stone chemical composition analysis as an important investigation to initiate steps for prevention of recurrent stones [1, 2]. While calcium oxalate is the commonest type of renal stone in Jaffna, incidence of uric acid stone has increased over the past three decades and this has been related to the metabolic syndrome [3].

The recurrence rate of kidney stones increases from 30% at 5 years to 50% at 10 years [4]. A metabolic evaluation of the 'kidney stone former' can detect predisposing risk factors [5]. Metabolic evaluation requires immense patient motivation, compliance and time and additional laboratory funds. It also puts pressure on the health service through multiple patient visits. Hence it is not advocated for non recurrent one time only renal stone formers. Extensive metabolic evaluation has been recommended for recurrent stone formers (defined as having two or more episodes of kidney stones) and those patients with multiple or bilateral stones [6, 7]. Published studies on metabolic evaluation of patients with renal stone disease are sparse in Sri Lanka and none from its Northern Province [8]. A better knowledge of the prevalent metabolic abnormalities among indigenous patients with recurrent, multiple or bilateral renal stone disease is likely to help design bespoke management strategies for prevention of further stone formation.

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Methodology

This is an institutional based observational study carried out on a series of 30 patients who presented to urology and general surgical wards of Teaching Hospital, Jaffna, with recurrent, multiple or bilateral renal stones during a period of two years between July 2016 and June 2018. Approval for this study was obtained from Ethical Review Committee, Faculty of Medicine, University of Jaffna. All the patients on this study gave informed written consent. Only patients with recurrent (defined as having had two or more confirmed episodes of kidney stones), and bilateral or multiple renal stones as confirmed by ultrasonography or intravenous urography were included in this study. Metabolic studies were carried out one month after any procedural intervention for stone disease on this defined group of patients. Exclusions for the study included patients with single renal stone, inadequately removed previous renal stones, recurrent active urinary tract infections, congenital abnormalities of kidneys and chronic renal failure. Samples were collected over a week and the patients were advised to continue drinking the usual amount of water they used to drink without change. Due to practical difficulties, particularly with regard to 24 hour urine collection on 2 different days, a comparable control group could not be recruited with informed consent to be able to compare mean values for each studied metabolic parameter between the study and control groups.

Fasting, non-tourniquet venous blood sample was taken for serum ionized calcium, creatinine, and uric acid. The first morning sample of freshly voided urine was collected for the assessment of pH based on strip urinalysis and for a full laboratory analysis. Patients were given two separate bottles for collection of 24 hour urine sample on two separate days. One bottle with 10ml hydrochloric acid as preservative for measurement of phosphorous, creatinine, oxalate, uric acid, magnesium and calcium and the second bottle with 10gm boric acid as preservative for measurement of citrate. Biochemical studies were performed by the Asiri Laboratory and the analytical methods used were phosphomolybdate method for phosphorus, Arsenazo III method for calcium, Xylidylblue calorimetric method for magnesium, enzymatic UV method for citric acid, uricase calorimetric method for uric acid and enzymatic calorimetric method for oxalate.

A Research Grant from Jaffna University met the laboratory cost of the study. Patients were not given any financial incentives for the study. In line with international reference standard, values measured in a 24 hour urine sample were considered abnormal when calcium exceeded 300mg/day (hypercalciuria), oxalate exceeded 0.49mmol/day in males and 0.32mml/day in females (hyperoxaluria), uric acid exceeded 750 mg/day (hyperuricosuria), citrate less than 288 mg/day (hypocitraturia) and a urine volume less than 1500 ml/day for a definition of low urine output.

The clinical details of patients and their metabolic study results were entered on an Excel spreadsheet. The final analysis of data was carried out using SPSS version 21 for Windows. Descriptive statistics was computed for all biochemical variables and for each of the diagnostic categories. The mean value with standard deviation and the median value for each biochemical variable were calculated. The interquartile range was used to assess the spread of each metabolic abnormality within the study group.

Results

Mean age of patients in this case series with recurrent, multiple or bilateral renal stones, was 47.10 (± 15.75) years. There were 20 males (66.7%) and 10 females (33.3%). Of the 30 patients, 24 (80%) had bilateral or multiple stones and 6 (20%) had recurrent stones. A low 24 hour urine volume of less than 1500 ml was found in 12 patients (40%).

Table 1. Metabolic parameters measured in 24 hour urine samples

Metabolic parameter	*Mean*	*SD*	*Median*	*Interquartile range*
Urine Oxalate	0.38	0.22	0.32	0.33
Male: 0.08-0.49 mmol/24h	0.43	0.24	0.36	0.43
Female: 0.04-0.32mmol/24h	0.29	0.15	0.26	0.25
Urine uric acid (250-750 mg/24h)	515.44	227.89	495.89	276.61
Urine citric acid (288-902 mg/24h)	448.31	207.22	410.0	338.28
Urine phosphorus (500-1500 mg/24h)	457.62	180.40	456.15	210.31
Urine magnesium (60-210 mg/24h)	79.79	51.36	66.9	38.36
Creatinine clearance (70-151 ml/min 1.73 sq.m)	97.23	29.23	93.5	43.25
Urine calcium (100-300 mg/24h)	125.02	73.32	117.55	103.5

All 30 patients of the study group went through the complete metabolic workout. Mean values of the metabolic parameters measured in 24 hour urine were found to be within the normal reference when taking all 30 patients as one single study group. Based on the median value and the inter quartile range of each parameter measured in 24 hour urine for the study group as a whole, urine oxalate was found to be in the upper limit of normal reference range and urine magnesium, urine phosphate and urine calcium were found to be in the lower limit of normal reference range. As Table 2 indicates however, individual patients in the study group showed isolated or combined abnormal metabolic values. This indicates that no one metabolic test stands out as the significant common abnormal metabolic test for the group of patients with recurrent, bilateral or multiple renal stones.

Table 2. Distribution of abnormal metabolic values in patients with recurrent, multiple or bilateral renal stones

Metabolic abnormality		**Single abnormality**				**Two abnormalities**	
	No abnormalities	Hyperoxaluria	Hypomagnesuria	Hyperuricosuria	Hypocitraturia and Hyperoxaluria	**Multiple abnormalities**	**Total**
Male	3	6	3	1	1	6	20
Female	3	1	1			5	10

Among the 30 patients in this case series, 6 patients (20%) did not have any abnormal metabolic measurements, 13 patients (43.3%) had single metabolic derangement only and 11 patients (36.7%) had multiple abnormal metabolic values. Hyperoxaluria and hypomagnesuria were found in 7 and 4 patients respectively.

Table 3. Metabolic parameters measured in fasting blood samples

Metabolic parameter	*Mean*	*SD*	*Median*	*Interquartile range*
Serum calcium (1.12-1.32 mmol / l)	1.17	0.54	1.18	0.05
Serum uric acid (3.5-7.2 mg / dl)	5.0	1.39	4.9	1.95

The mean values of the metabolic parameters measured in fasting blood samples of 30 patients in this study group were found to be within the normal reference range. Considering the individual patients in the study group, 2 patients had hyperuricemia and none had hypercalcaemia.

Table 4. Urine pH among patients with recurrent, multiple or bilateral renal stones

Urine pH	6.0	6.5	7.5
Number of patients	24 (80%)	5 (6.7%)	1 (3.3%)

24 patients (80%) had a urinary pH of 6.0 or less based on strip urinalysis.

Discussion

Male to female ratio was 2:1 in our study group of 30 patients and the most affected age group was 40-59 years. This is comparable to the peak age and sex ratio among South Asian renal stone formers, as reported from Pakistan and in South India [7,9].

Challenges were experienced in motivating patients and asking them to strictly collect 24 hour urine samples not once but on two separate days. Unsurprisingly, other researchers studying same subject matter have described similar difficulties [9, 10].

Supersaturation, nidus formation and urinary stasis are the identified aetiopathological factors for urolithiasis [11]. The promoters for stone formation are calcium, oxalate, urate, cystine, low urine pH, low urine flow and bacterial products [12]. Inorganic inhibitors discouraging the crystallization process are magnesium, citrate and pyrophosphate [13]. Hyperoxaluria increases the saturation of calcium oxalate resulting in crystal formation [14]. Reported prevalence of this condition varies from 3.6% to 64.5% around the globe [15, 7, 16, 17]. Hyperoxaluria was found in 9 (30%) patients in our study group. This was found as a single metabolic abnormality in 7 patients and in combination with other abnormalities such as hyperuricosuruia (1 patient), hypocitraturia and hyperuricemia (1 patient). Diets containing oxalate in high amounts are nuts, brewed tea, chocolates, broccoli and spinach and patients can be advised to avoid them in their diet. Low calcium intake enhances oxalate absorption as a result of less binding of oxalates with calcium in the intestine. As such, patients with hyperoxaluria can also be advised to increase calcium intake. Of the 9 patients with hyperoxaluria, 6 patients had associated hypocalciuria; indicating a possibility of their low calcium intake. Vitamin B6 (pyridoxine) enhances the conversion of glyoxalate to glycine, hence offered to patients with primary hyperoxaluria [14, 18].

Magnesium inhibits calcium oxalate crystallisation in urine and also inhibits dietary absorption of oxalate. Hypomagnesuria reduces this inhibitory effect on nucleation and growth of calcium oxalate crystals [12]. Prevalence of this condition varies from 0% to 30% [15, 7, 16, 17]. 9 patients in our study group had hypomagnesuria (30%), with 4 showing it as a single metabolic abnormality and the rest in combination with hyperuricosuria (1 patient), hypocitraturia (3 patients), hypocalciuria (5 patients) and hypophosphaturia (4 patients). These patients can be advised to include in their diet those food rich with magnesium such as green leafy vegetables, avocado, black beans and sea food.

Citrate combines with calcium and forms soluble complex reducing the formation of calcium oxalate and calcium phosphate crystals. Hypocitraturia reduces this inhibitory effect and increases the levels of ionized calcium leading to calcium crystallization [11]. Hypocitraturia was found in 7 patients (23.3%). All 7 had it combined with at least one other metabolic abnormality namely hypocitraturia were hyperoxaluria, hyperuricosuria, hypophosphaturia and hypomagnesuria. These patients with hypocitraturia need to be advised to increase citrate rich foods in their diet (such as grape, orange and lemon). Potassium citrate 30-60 mEq /d in divided doses is shown to increase pH of urine and to increase urinary citrate levels, hence can be offered to these patients [6].

Hyperuricosuria by forming sodium urate enhances calcium oxalate crystallization. Hyperuricosuria and low urine pH increase the uric acid ions and predispose to formation of uric acid stones [14]. Through forming sodium urate, it also enhances calcium oxalate crystallization. Apart from this, urinary urate reduces the solubility of calcium and oxalate (the process of “salting out”) [11]. Hyperuricosuria was found in 3 patients (10%), as a single metabolic abnormality in one patient and in combination with other abnormalities such as hyperoxaluria and hypocitraturia in other two patients. Hyperuricemia was found in 2 patients (6.7%). In both it was associated with hypocitraturia, hyperoxaluria, hyperuricosuria and hypomagnesuria. Patients with hyperuricosuria have to restrict both the animal protein and purine intake (such as alcoholic beverages and seafood) to prevent recurrences [6]. Furthermore, uric acid stones were associated with low urine pH and low volume urine rather than hyperuricosuria alone [19]. A low urinary pH increases the free ion activity of uric acid ions. These patients need to be advised to increase fluid intake and thus increase the urine volume (2-3 l/day) and also to take citrate or bicarbonate salts to alkalinize the urine [5]. Allopurinol prevents recurrence of uric acid stones.

Hypercalciuria increases the ionic activity and saturation of calcium oxalate and calcium phosphates crystals [12]. A few studies have demonstrated hypercalciuria as a major metabolic abnormality in recurrent, multiple or bilateral renal stone formers [7, 20]. Patients with hypercalciuria will be advised to reduce the salt intake if it is associated with hypernatriuria. They should also be treated with thiazide diuretics to prevent recurrent stone formation [6]. In our study group, none of the patients had hypercalciuria.

Low volume of urine not only increases the concentration but also augments stasis [11]. Low urine volume was noticed in 12 (30%) patients. Among them, 4 patients had no metabolic abnormalities. In the remaining 8 patients one patient had single metabolic abnormality and 7 patients had combinations of metabolic abnormalities. Increasing water intake reduces the risk of renal stone formation by 60-80% [21]. Fluid intake of 2.5-3 l/d could establish a urine output of 2.5 l/d and help prevent recurrent renal stone formation [1, 2, 6, 22].

Studies carried out in South Asian and other countries revealed many metabolic abnormalities in patients with recurrent, multiple or bilateral renal stones [7,13,15]. In comparison, publications that originated from European

countries demonstrate fewer metabolic abnormalities in their recurrent, multiple or bilateral renal stone formers [16]. Hence outcome of metabolic evaluation in this defined group of patients is likely to be beneficial in South Asian countries.

A limitation in this study includes the smaller number of patients within the study group. The other limitation is that the study was carried out on the out-patient setting where collection of urine samples, in particular 24 hour urine collection on two different days, was entirely dependent on the total compliance and motivation of the patients. Despite these limitations in our study, 80% of patients with recurrent, bilateral or multiple renal stones had either single or multiple metabolic abnormalities, each individual showing a different set of abnormal metabolic profile. It is encouraging to note that larger studies from other South Asian countries namely Pakistan and South India have reported similar outcomes. Hence the full gamut of biochemical workout needs to be carried in each and every patient for offering relevant dietary and therapeutic advice based on their individual metabolic abnormal profile. The cost of a comprehensive metabolic evaluation for a patient was about Sri Lankan rupees 12,000.00. While this relative initial high cost is less affordable within the country's free health service or even among the majority of fee paying patients, it is worth considering the long term cost effectiveness of offering these tests to prevent further stone formation and thus prevent recurrent admissions to the hospital for repeated procedural interventions.

Conclusion

In conclusion, the metabolic evaluation can identify the risk factors in patients with recurrent, bilateral or multiple renal stones. Dietary advice and medical treatments to prevent further stone formation could be tailored to individual patients based on their own specific metabolic profile.

Studies on larger number of patients with recurrent, bilateral or multiple renal stones in different parts of Sri Lanka would further help to define the existing prevalence of metabolic abnormalities in similarly affected patients and to understand if any regional variations exist within the country. A debate among specialists dealing with this defined group of patients needs to be initiated with a view to drawing a clinical management guideline including consideration of the long term cost effectiveness and benefit of full metabolic workout on them.

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References

1. Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petrik A, Turk C. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *European Urology* 2015; **67**(4):750-63.
2. Tiselius HG, Daudon M, Thomas K, Seitz C. Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. *European Urology Focus.* 2017; **3**(1): 62-71.
3. Rajendra S. Is there unique difference in the type of renal stones in Northern Sri Lanka? Analysis of chemical composition of renal stones in Jaffna by infrared spectroscopy. *Sri Lanka Journal of Surgery* 2020; **38**(1).
4. Asplin J, Chandhoke P. The stone forming patient. Kidney stones: medical and surgical management. Philadelphia: *Lippincot Raven* 1996: 335-7.
5. Johri N, Cooper B, Robertson W, Choong S, Rickards D, Unwin R. An update and practical guide to renal stone management. *Nephron Clinical Practice* 2010; **116**(3): c159-71.
6. Dion M, Ankawi G, Chew B, Paterson R, Sultan N, Hoddinott P, Razvi H. CUA guideline on the evaluation and medical management of the kidney stone patient-2016 update. *Canadian Urological Association Journal* 2016; **10**(11-12): E347.
7. Ahmad I, Pansota MS, Tariq M, Tabassum SA. Frequency of metabolic abnormalities in urinary stones patients. *Pakistan Journal of Medical Sciences* 2013; **29**(6): 1363.
8. Abeygunasekera AM. Urinary stone disease in Sri Lanka. *The Ceylon Medical Jjournal* 2004; **49**(2): 41-3.
9. Dhandapani C, Shibulal JS, Nrayanasamy K. Metabolic evaluation of patients with recurrent and multiple renal stones: A prospective study. *Asian J Pharm Clin Res.* 2016; **9**(3): 212-8.
10. Krepinsky J, Ingram AJ, Churchill DN. Metabolic investigation of recurrent nephrolithiasis: compliance with recommendations. *Urology* 2000; **56**(6): 915-20.
11. Bose A, Monk RD, Bushinsky DA. Kidney stones. In Williams Textbook of Endocrinology 2016: 1365-84.
12. Singh VK, Rai PK. Kidney stone analysis techniques and the role of major and trace elements on their pathogenesis: a review. *Biophysical Reviews* 2014; **6**(3-4): 291-310.
13. Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. *The American Journal of Medicine* 1995; **98**(1): 50-9.
14. Moe OW. Kidney stones: pathophysiology and medical management. *The Lancet* 2006; **367**(9507): 333-44.

15. Bhangu GS, Bansal D, Shah AS, Lubana PS. Recurrent stone formers – metabolic evaluation: a must investigation. *International Surgery Journal* 2016; **4**(1):86-90.

16. Wikstrom B, Backman U, Danielson BG, Fellstrom B, Johansson G, Ljunghall S. Ambulatory diagnostic evaluation of 389 recurrent renal stone formers. *Klinische Wochenschrift* 19831; **61**(2): 85-90.

17. Tiselius HG, Daudon M, Thomas K, Seitz C. Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. *European Urology Focus* 2017; **3**(1): 62-71.

18. Park S, Pearle MS. Urolithiasis: update on metabolic evaluation of stone formers. *The Scientific World Journal* 2005; **5**: 902-14.

19. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. *KidneyIinternational* 2008; **73**(4): 489-96.

20. Amaro CR, Goldberg J, Amaro JL, Padovani CR. Metabolic assessment in patients with urinary lithiasis. *International Braz J Urol.* 2005; **31**(1): 29-33.

21. Cheungpasitporn W, Rossetti S, Friend K, Erickson SB, Lieske JC. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. *Journal of Nephrology* 2016; **29**(2): 211-9.

22. Borghi L, Meschi T, Maggiore U, Prati B. Dietary therapy in idiopathic nephrolithiasis. *Nutrition Reviews* 2006; **64**(7): 301-12.