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Metabolic evaluation of high-risk stone formers: a retrospective study

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Abstract

Background The purpose of this study was to assess the metabolic abnormalities in high-risk stone formers.

Methods This was a retrospective observational study done at Tribhuvan University Teaching Hospital, Nepal, over 1-year period. High-risk stone formers were identified and were evaluated with serum chemistries and 24-h urinary chemical evaluation. Stone analysis was also included whenever available. Common metabolic abnormalities and stone analysis results were reported and compared with different studies. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as percentage and proportions.

Results During 1 year of period, sixty-five patients had undergone extensive metabolic evaluation, but complete data were available for only forty-six patients. Of the total patients ($n = 46$), 63% were male ($n = 29$) and rest (36.9%) were female. Mean age of patients was 34.4 ± 15.1 years. Common reasons for metabolic evaluation were multiple stones (40%), bilateral stones (27%), recurrent stones (17%) and others (16%). Most common stone type was mixed stone with predominant composition being calcium oxalate mono- and dihydrate (62.9%). Twenty-four-hour urinary metabolic evaluation showed hyperoxaluria (32.6%) as most common abnormalities followed by hypocitraturia (21.7%) and hypocalciuria (21.7%).

Conclusion Hyperoxaluria and hypocitraturia are common metabolic abnormalities in our patients. These findings help in counselling dietary measures to patients.

Keywords Renal stone, High-risk stone formers, Metabolic abnormalities, Metabolic evaluation

1 Background

Urinary tract stones are known to recur over years and may be manifestation of underlying systemic disease [1–5]. Identification of responsible factors of stone formation and timely initiation of preventive measures is necessary duty of a practicing urologist. Several studies have shown variable rate of stone recurrence ranging from 30 to 75% over 5–10 year's duration [1, 2].

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Metabolic evaluation of stone formers helps to identify the physiological basis of stone formation. Ideally it should be cheap, simple and applicable for clinical practice [6]. Common metabolic problems include but are not limited to distal renal tubular acidosis (RTA), primary hyperparathyroidism, enteric hyperoxaluria and gouty diathesis. These conditions need to be identified and treated to prevent recurrent stones and to correct physiological disturbances leading to non-renal complications [7, 8].

Current American Urological Associations (AUA) guidelines suggest that physician can perform metabolic evaluation in high-risk stone formers or interested first stone formers [9]. This evaluation is a shared decision between physician and patient. High-risk

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individuals are those with obesity, metabolic syndrome, family history of stone disease and with medical conditions such as hyperparathyroidism, gout, renal tubular acidosis, type 2 diabetes mellitus, urinary tract infection, sarcoidosis, gastrointestinal diseases and intestinal resection surgery [9–11]. Similarly, children are the another important group of patients requiring full metabolic evaluation as abnormalities are common [12, 13]. Cost is one of the factor which need to be considered while planning metabolic evaluation. Some studies have reported that metabolic evaluation is only cost effective in high-risk and recurrent stone formers compared to first time stone formers [14, 15]. Commonly detected metabolic abnormalities are hypercalciuria, hypocitraturia, hyperoxaluria with different proportions in different studies [16–20].

South-Asian countries have different geographic location, dietary habits and genetic differences compared to western countries. Recurrent stone formers are commonly encountered in clinical practice; however, studies are not published from our country. We aim to study our patients regarding their metabolic abnormalities.

2 Methods

This was an observational study done in Institute of Medicine, Tribhuvan University Teaching Hospital, Department of Urology and Kidney Transplant Surgery. It was a retrospective study done on patients who visited Urology Department over 1 year from June 2020 to May 2021. Patients diagnosed as urinary stone disease who had high risk factors for stone recurrence were recruited for study. Detail medical and surgical history was retrieved from case sheet. Management modality applied to each individual patients was noted. Metabolic evaluation if done for those patients was recorded. This included basic metabolic evaluation including serum calcium, sodium, potassium, uric acid, phosphorus, Vitamin D, intact Parathyroid hormone (PTH), urine routine and microscopic examination and urine culture and sensitivity. Urinary evaluation was done when patient was rendered stone free or was free of any obstructing stone preferably after 20 days of operation. Serum and urinary evaluation was done with normal dietary pattern and fluid intake. Single 24-h urinary evaluation including urinary volume, citrate, calcium, phosphorus, sodium, potassium, uric acid, creatinine was also recorded.

24-h urine collection: This was done in specific plastic bottle provided by laboratory. On the first day of collection, first morning void was discarded and subsequent voiding was collected till first morning voiding of second day. Internal check of complete 24-h urine collection was done from total urinary creatinine level.

Table 1 Normal reference values of 24-h urinary parameters

Parameters	Measuring principles	Values
Citrate	Enzymatic	0.6–4.81 (mmol/day)
Oxalate	Spectrophotometry	0.07–0.48 (mmol/day)
Calcium	Arsenazo 3	2.5–7.5 (mmol/day)
Phosphorus	Molybdate UV	12.9–41.9 (mmol/day)
Uric acid	Uricase	1.4–4.4 (mmol/day)
Potassium	Indirect ISE	11–80 (mEq/l)
Sodium	Indirect ISE	25–301 (mEq/l)

Table 2 Clinical parameters

Parameters	Mean (range)
Average age (years)	34.4 ± 15.1 (4–70)
Mean BMI (kg/m^2)	24.3
Male/female ratio	1: 1.7
Family history of stone disease	21%

Urinary parameters were analyzed using different principles from a single laboratory. Normal reference values and method of analysis are shown in Table 1.

Stone analysis was performed in selected cases by Fourier transform Infrared Spectroscopy (FTIR) method.

Data were collected and entered in Microsoft Windows Excel. All statistical analyses were conducted in SPSS version 25. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as percentage and proportions.

3 Results

During 1 year of study period, sixty-five patients had undergone extensive metabolic evaluation, but complete data were available for only forty-six patients. Of the total patients ($N = 46$), 63% were male ($n = 29$) and rest (37%) were female ($n = 17$). Mean age of patients was 34.4 ± 15.1 years. Average BMI was 24.3 kg/m^2. The average 24-h urine volume was 2400 ml. Clinical parameters of patient are shown in Table 2.

High-risk stone formers are those with multiple, bilateral, recurrent stones, children with stones, Hyperparathyroidism, patient with bowel resection or malabsorption syndrome, etc. In our study, common reasons for metabolic evaluation were multiple stones (40%), bilateral stones (27%), recurrent stones (17%) as shown in Table 3.

Co-morbidity associated with stone disease patients was as follows: Hypertension (54%), Diabetes mellitus (31%) and hypothyroidism (15%). Symptomatic stones were managed with different modalities. More than half

Table 3 Reason for metabolic evaluation

Reason for evaluation	Percentage (%)
Multiple Stones	40
Bilateral Stones	27
Recurrent stones	17
Young age	8
Miscellaneous	8

of patients (53%) were managed with Retrograde intrarenal surgery (RIRS) followed by Percutaneous Nephrolithotomy (PCNL) (33%). Rest of the patient (13%) were managed with uretero-renoscopic lithotripsy (URSL) and very few (1%) with observation. Stone analysis data were available for twenty-five patients. Most common stone type was mixed stone with predominant composition being calcium oxalate (62.9%) as shown in Table 4.

Single 24-h urinary analysis was done for all patients at least 20 days after being stone free or rendered non-obstructing stone. Patients were advised for normal diet intake during evaluation. 24-h urinary metabolic evaluation showed hyper-oxaluria (32.6%) as most common abnormalities followed by hypocitraturia (21.7%) and hypocalciuria (21.7%) as shown in Table 5. One patient of each hypocitraturia and hypercalciuria was diagnosed as Distal RTA (Renal Tubular Acidosis) and hyperparathyroidism. About 23.91% of patients had more than one metabolic abnormalities.

4 Discussion

Urinary stone disease is prevalent all around the world with increasing incidences with modernization [21, 22]. Treatment and management has changed from open operative procedures to minimal invasive and endoscopic procedures. There is growing concern and medical research in the field of prevention of urinary stone disease.

Dietary habits, obesity, increasing metabolic syndrome, Diabetes mellitus, different metabolic disorders have their part to share for the cause of increased stone

Table 4 Stone types

Stone type	Number ($N=27$)	Percentage (%)
Mixed stone with predominant calcium oxalate	17	62.9
Mixed stone with predominant matrix protein	4	14.8
Phosphate stone	4	14.8
Pure oxalate stone	2	7.4

Table 5 24-h urinary metabolic evaluation

Urinary parameters	Number ($N=46$)	Percentage (%)
Hyperoxaluria	15	32.6
Hypocitraturia	10	21.7
Hypocalciuria	10	21.7
Hyperuricosuria	7	15.2
Hypercalciuria	7	15.2
Hyperphosphaturia	5	10.8
More than one abnormalities	11	23.9
No any abnormalities	16	34.7

disease [23–25]. Urinary stone disease can cause pain, infection, renal impairment and requires some form of treatment. In addition to it, stones may recur after some interval, adding misery and cost of treatment. It is prime duty of urologist to prevent such recurrences by investigating and identifying the cause of recurrences.

This study is first of its kind from our country to the best of our knowledge. In our study, we had younger group of patients (mean age 34.4 ± 15.1 vs. 52.1 ± 13.2) as compared to other studies [16, 17]. Our patients had higher 24-h urinary volume compared to another study (2400 ± 650 ml vs. 1719 ± 712 ml) [17]. This could be because with diagnosis of stone disease, patient start drinking plenty of water.

Our study shows higher incidence of hyperoxaluria as compare to other studies [18–20] but lower incidence compared to study by Joshi et al. from India [16]. This could be high consumption of diet rich in oxalates such as potato, green leafy vegetables like spinach, coffees, and oranges. This theory is further supported by report of highest per capita consumption of potato in our country (84 kg) compared to other neighboring countries like India (26 kg) and China (43.8 kg) [26]. As compared to western studies, hypercalciuria (15.2%) was not so common in our study [18–20]. This could be because of dietary differences between developing countries versus developed countries with more amount of meat and calcium supplementation in food in latter countries.

Hypocitraturia is second most common abnormality detected on urinary analysis. Many other regional studies from south and east Asian countries have reported hypocitraturia as most common abnormality [20]. Citrate is one of the important inhibiting factor for calcium crystallization. Hypocalciuria (21.7%) is another abnormality detected in our patients which is not reported in other studies. Hypocalciuria may be another reason resulting hyperoxaluria. Low calcium in diet increases oxalate absorption from intestines.

Table 6 Comparative study of various urinary parameters in different population across world

Studies	Percentage of patients with urinary metabolic abnormalities				
	Hyperoxaluria	Hypocitraturia	Hyperuricosuria	Hypercalciuria	Hyperphosphaturia
Joshi et al. [16] (India)	56%	82%	NA	41%	NA
Hong et al. [17] (Malaysia)	NA	73%	NA	NA	NA
Curhan et al. [18] (USA)	23.6%	8%	17%	32%	NA
Stitchantrakul [19] et al. (Thialand)	13%	69.6%	7.2%	15.2%	NA
Siener et al. [20] (Germany)	14%	51%	41.3%	25.2%	NA
Current study (Nepal)	32.6%	21.7%	15.2%	15.2%	10.8%

NA not available

Table 7 Comparative study of mean value of urinary parameters across world

Studies	24 h urinary parameters (mmol/day)				
	Oxalate mean (SD)	Citrate mean (SD)	Uric acid mean (SD)	Calcium mean (SD)	Phosphate mean (SD)
Hong et al. [17] (Malaysia)	0.39 (0.11)	1.28 (1.08)	3.08 (1.04)	4.09 (2.37)	19.33 (5.32)
Curhan et al. [18] (USA)	0.38 (0.12)	3.56 (1.76)	3.11 (1.13)	5.65 (2.9)	8.89 (2.7)
Stitchantrakul et al. [19] (Thailand)	0.16 (0.01)	1.62 (0.12)	3.24 (0.10)	3.7 (1.5)	18.82(0.67)
Siener et al. [20] (Germany)	0.39 (0.17)	2.62 (1.55)	4.00 (1.99)	6.64 (2.91)	31.0 (11.9)
Current study (Nepal)	0.44 (0.24)	1.29 (1.03)	3.16 (1.44)	3.71 (1.85)	22.39(12.97)

Mean 24 h urinary oxalate value of our study is higher than means of different studies. This could be because of different dietary habits, geographic, ethnic, genetic makeup and low dietary calcium consumption. Mean 24 h urinary calcium value from our study is comparable to studies from Asia, however, lower than studies from developed world. This could be due to lesser consumption of diet containing calcium like meat, cheese, dairy products, calcium and vitamin D supplements from our part of world. This may be one of reason for high oxalate value too because calcium chelates excess oxalate from bowel (Table 6).

Mean citrate value in our patient is lower than the values from western people but comparable to mean from Asian studies. We could not find any secondary causes of hypocitraturia in our patients. However, United Nations Food and Agricultural Organization (FAO) in 2017 published that south Asian countries had lower per capita citrus fruit consumption compared to developed countries (65.4 kg vs. 90 kg) [26]. This may the reason for lower values for our patients (Table 7).

Important limitation of our study is its retrospective nature with possibilities of biases and relatively smaller number of patients. Based on our patients' urinary profile, we recommend following for stone recurrence prevention.

1. Drinking plenty of water > 3 l/day as a part of general recommendation.
2. Consuming calcium rich diet and decreasing diet in oxalate.
3. As, this is a retrospective study, confirmation of the findings of this study need to be done by larger prospective study or randomized control trial to compare different dietary intervention to reduce stone recurrence in future.

5 Conclusion

Hyperoxaluria and hypocitraturia are the two most common metabolic urinary abnormalities in our patients. These findings help in counselling dietary measures to patients.

Abbreviations

RTA	Renal tubular acidosis
AUA	American Urological Associations
PTH	Parathyroid hormone
FTIR	Fourier transform infrared spectroscopy
RIRS	Retrograde intrarenal surgery
PCNL	Percutaneous nephrolithotomy
URSL	Ureterorenoscopic lithotripsy

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Author contributions
PP, BL, PRC, PRG, UKS designed the study protocol. PP, SP, MMP and SC collected data. PP and BL analyzed data and prepared the manuscript. All authors read the final manuscript and approved it.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted with approval of institutional review committee of Institute of Medicine, Tribhuvan University with approval number of 509 (6-11) E2 077/078. Informed written consent to participate in the study was provided by all participants or their parent or legal guardian in the case of children under age of 16.

Consent for publication
Written informed consent for the publication of details and images relatingto individual participants was taken from all participants or their parent or legal guardian in the caseof children under age of 16 as and when necessary.

Competing interests
Authors declare that they have no competing interests.

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