

Original Research Article

24-hour urinary constituents in stone formers: a study from Kashmir

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ABSTRACT

Background: Urolithiasis is a common disorder. Studies have shown that metabolic causes of urolithiasis include hypercalciuria, hypocitraturia, high or low pH of urine, hyperuricosuria, hyperoxaluria and hypomagnesuria. We intended to conduct this study with the aim to provide historical data regarding the 24-hour urinary analysis in this part of India with a distinct and different geographical and cultural background.

Methods: A total of 186 patients having urinary stone disease attending the departments of Nephrology and Urology in Sher-I- Kashmir institute of medical sciences were included. 26 healthy members of hospital staff were taken as controls. Demographic and clinico-pathological characteristics of each patient were recorded in a questionnaire. Urine was collected for 24-hours from 186 patients and 26 controls. 10ml sample of this urine collection was stored at 20c0 before processing for urinary parameters.

Results: The mean concentration of calcium salts, Magnesium, Oxalate and Uric acid in the 24-hour urinary analysis of urolithiasis patients is higher than that of the normal healthy controls and the relation was statistically significant. On comparing the 24-hour urinary constituents among urolithiasis patients and health controls, the concentration of phosphate was almost equal in both cases and controls while the concentration of oxalate was much higher in cases than controls.

Conclusions: In present study hypercalciuria is main cause of renal calculi along with hypocitraturia, hypomagnesuria and hyperphosphaturia in our valley. Measurement of 24-hour urine constituents is still gold standard for evaluation of stone formers.

Keywords: 24-hour urinary constituents, Hypercalciuria, Kashmir renal diseases, Urolithiasis

INTRODUCTION

Urolithiasis is a common disorder. Studies have shown that metabolic causes of urolithiasis include hypercalciuria, hypocitraturia, high or low pH of urine, hyperuricosuria, hyperoxaluria and hypomagnesuria. Citrate is a natural substance that inhibits urinary calcium stone formation. Deficient urinary excretion of citrate has often been associated with urinary stone disease.

Moreover, successful correction of hypocitraturia, which has been documented largely in adults, positively correlates with a decreased stone recurrence rate.¹ In urolithiasis assessment of plasma concentration of metabolites and electrolytes along with the concentrations of urinary excretory products, urine pH and hormonal assay is of prime importance.² Concentrations of serum electrolytes, calcium, phosphate, creatinine and uric acid have to be measured as the first biochemical investigation

of patients with urolithiasis. In addition, 24-hour urine volume, creatinine, calcium, phosphate, uric acid, oxalate, citrate, urine pH and serum level of parathyroid hormone (PTH) may be assessed.³ The purpose of this study was to do complete metabolic evaluation of stone formers and also find out the quantitative relations between urine and serum parameters in local population, as the incidence of urolithiasis in this region is very high as well as portable ground water is extremely hard.

Inhibitors are the molecules which increase the super saturation required to initiate nucleation, decrease the crystal growth and aggregation and inhibit secondary nucleation (deposition of new crystals on pre-existing crystal surfaces of similar type) whereas promoters cause reduction of the formation product of the supersaturated solution. The loss of balance between the urinary promoters and inhibitors has been suggested to increase the risk of stone formation more than disturbance in any single substance. Inhibitors of stone formation include citrate, magnesium, pyrophosphate, tamm-horsfall protein, urinary prothrombin fragment 1, renal lithostathine, Glycosaminoglycans, Osteopontin (uropontin), Nephrocalcin and high urine volume. Promoters of stone formation include calcium, sodium, oxalate, urate, low urine ph, tamm-horsfall protein and low urine volume.⁴ As the incidence of stone formation has increased over the last few decades in Kashmir Valley and no such data is available regarding the urinary profile of urolithiasis patients. We intended to conduct this study with the aim to provide historical data regarding the 24-hour urinary analysis in this part of India with a distinct and different geographical and cultural background.

METHODS

The aim of this study was to evaluate the 24-hour urinary constituents in stone formers. This was a hospital based case control study.

Inclusion criteria

Patient who is a first time or recurrent stone former, Single or multiple stones, Stone greater than 5mm diagnosed by plain x-ray of KUB region, IVP or KUB ultrasound.

Exclusion criteria

Children under 13 years old, pregnant women, Urine output less than 1000ml/24 hours, chronic kidney disease with creatinine clearance less than 30ml/min/1.37m²sq using the Cockcroft and Gault formula. Patients enrolled for study were asked for 24-hour urine collection and proper collection was further tested by 24-hour urinary creatinine. Patients with proteinuria >150mg/dl were not enrolled for study.

A total of 186 patients having urinary stone disease attending the departments of Nephrology and Urology in Sher-I- Kashmir institute of medical sciences were included.²⁶ healthy members of hospital staff were taken as controls. Demographic and clinico-pathological characteristics of each patient were recorded in a questionnaire. Urine was collected for 24 hours from 186 patients and 26 controls. 10ml sample of this urine collection was stored at 20°C before processing for urinary parameters.

Five metabolic parameters were looked for; hypercalciuria in males > 7.5 mmol (300 mg)/24hr, females: > 6.25 mmol (250mg)/ 24hr, hyperoxaluria >0.46mmol (40mg)/24hr, hyperuricosuria > 4.46mmol (750 mg)/24hr, hypomagnesuria < 3 mmol/24hr and hypocitraturia: < 1.56 mmol (300mg)/24hr.

The frequency of each metabolic abnormality and value of each constituent was compared between controls and stone formers. Various enzymatic assays and spectrophotometric technique were used to measure the concentration of calcium, magnesium, oxalate, citrate uric acid and phosphate in 24 hours urine. They were done on Beckman coulter automated analyzer AU 680.

A written informed consent was obtained from each patient. This study was approved by ethical committee of SKIMS.

Statistical Methods: Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Data was analyzed by means of descriptive statistics viz, Mean, standard deviation, percentages and presented by Bar diagrams. For parametric data, Student's independent t-test was employed. A P-value of less than 0.05 was considered statistically significant.

RESULTS

The comparison between the patients of urolithiasis and the healthy controls have been elaborated in (Table 1). The mean concentration of calcium salts, Magnesium, Oxalate and Uric acid in the 24-hour urinary analysis of urolithiasis patients is higher than that of the normal healthy controls and the relation was statistically significant (p<0.001). Furthermore the 24 urinary volume was significantly increased in the urolithiasis patients than the control group. It has been seen that the salts promoting stone formation are considerable present in higher quantities in patients with urolithiasis than in healthy controls. The 24 hour urine was analysed for the presence of various constituents, it was seen 60.8% patients had hypercalciuria as the predominant salt in the urine followed by deficiency of citrate (i:e) Hypocitraturia which in turn increases the formation of urinary stones. Hypomagnesuria was also seen among 50% of patients followed by hyperphosphaturia (47.3%) (Figure 1).

Table 1: 24-hour urinary characteristics in cases and control.

Parameters	Stone forming Patients (n = 186)	Controls(n = 26)	P-value
	Mean±SD	Mean±SD	
Calcium	9.41±2.07	5.04±0.44	<0.001*
Magnesium	2.66±0.54	3.74±0.30	<0.001*
Oxalate	41.58±5.45	33.78±2.85	<0.001*
Uric Acid	4.37±0.21	2.42±0.49	<0.001*
Citrate	1.32±0.18	1.93±0.32	<0.001*
Phosphate	42.32±1.87	41.08±0.67	<0.001*
Urine Volume	2.60±0.59	1.59±0.15	<0.001*

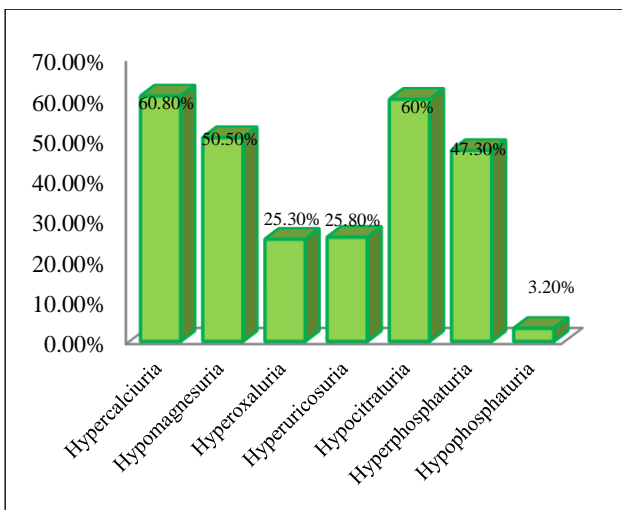


Figure 1: Percentage of urinary abnormalities in patients.

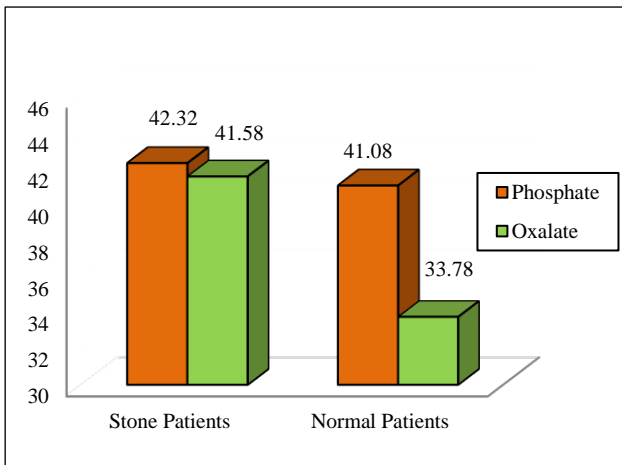


Figure 2: Comparison between stone patients and normal patients based on 24-hour urine constituents

On comparing the 24-hour urinary constituents among urolithiasis patients and health controls, the concentration of phosphate was almost equal in both cases and controls 42.32% and 41.08% respectively. The concentration of oxalate salts in patients with urolithiasis was much higher (41.58%) than in healthy controls (33.78%) (Figure 2).

Table 2: Clinical characteristics of the stones in patients.

Characteristic	Patients n=186, % (N)
Etiology of stones	
Idiopathic	58%
Hyperparathyroidism	15%
Recurrent UTIs	18%
Nephrocalcinosis	9%
Number of stones	
Solitary	58%
Multiple	42%
Location of stones	
Renal	65.6%
Ureteral	25.6%
Vesical	5.9%
Urethral	2.7%
Stone recurrence	
First Time formers	83%
Recurrent formers	17%
Hydronephrosis	
Hydronephrosis present	31%
Hydronephrosis patients having UTI	38%

(Table 2) shows the clinical characteristics of the urolithiasis patients. The most common cause of urolithiasis was found to be idiopathic in 58% patients followed by Hyperparathyroidism (15%). 18% of patients reported to have recurrent urinary tract infections and only 9% had nephrocalcinosis. 58% of the study participants were having history of solitary urinary system stones. Most of the patients had renal stones (66%), followed by Ureteral stones (25%). 83% of the cases were first time stone formers and 31% were having hydronephrosis and 38% reported to have urinary tract infections along with hydronephrosis.

DISCUSSION

24-hr urine collection to date is still the gold standard for metabolic evaluation in urinary stone disease.⁵ Many published series noted that urinary stone disease is more common in males than females. The male to female ratio in our study was 2.8:1 which is in agreement with studies

of Shokouhi et al, Rayhan et al, Nazir et al all showing a ratio of 2.7:1.⁶⁻⁸ Increased incidence in males has been attributed to increase dietary protein intake and muscle mass which increases the excretion of phosphates and reduces urinary citrate concentration. The lower risk of stone formation in women is being attributed to estrogens which may also help to prevent formation of calcium stones by keeping urine alkaline and raising protective citrate levels. Kidney stone incidence varies in different parts of the world, however, in Asia stone forming belt has been reported to stretch across Sudan, Saudi Arabia, UAE, Iran, Sindh province of Pakistan, Northern India, Myanmar, Thailand and Indonesia.⁹ The effect of stone geography on the incidence of stone formation may be direct through its effect on temperature whereby high temperatures increase perspiration which may result in concentrated urine or in our population it could be attributed to high intake of animal protein and sodium in the form of salt tea, which in some studies have shown increases urinary calcium and uric acid concentrations and lowers urinary citrate concentration. It can also be due to mineral composition of the drinking water we use.

It is generally agreed that over saturation of urine with calcium is one of the most important risk factors for calcium nephrolithiasis. In this study, we did not look for the cause of hypercalciuria and therefore we could not specify whether it was absorptive, restorative or renal hypercalciuria. Surprisingly, the frequency of hypercalciuria in our study was (61.2%) in males and (60.5%) in females and mean urinary calcium concentration was high in stone formers as compared to healthy controls. This was in accordance with, Yagisawa et al, Mittal et al, who have reported the incidence of hypercalciuria to (45.9%) and (28%) respectively for first stone former and (58.1%) and (46%) respectively for recurrent stone formers.^{10,11} Kumar et al, Orazaki et al, Tafekli et al, BabicIvanic et al have all reported the incidence of hypercalciuria to be very high in stone formers.¹²⁻¹⁴ However Hussein et al, Sriboonlue et al, Esen et al, have reported low incidence of hypercalciuria.^{5,16,17} Hypercalciuria is a multifactorial disorder however in our subjects high frequency of it may be due to consumption of diet rich in animal protein which contributes to hypercalciuria (higher bone resorption:lower tubular calcium reabsorption to buffer the acid load provided by meat: elevated calcium filtered load. The effect of increase in dietary sodium intake on increasing calcium excretion is well established. Every 100mmol increase in dietary sodium results in approximately in a 25mg rise in urinary calcium. The adverse effects of a high salt intake also contribute to bone loss.¹⁷ Henceforth increase urinary calcium concentrations might be an important factor in pathogenesis of urinary stone.

In this study, hypocitraturia was the second most common abnormality. Numerous studies have shown that low urinary citrate is a potential cause for calcium urolithiasis. Mean urinary citrate concentration was less

in patients as compared to normal individuals and it was statistically significant. In our patients, high percentage of hypocitraturia (60%) is in accordance with findings of Kumar et al, and Esen et al, where hypocitraturia respectively was noted in (55%) and (44.9%) of stone formers.^{12,18} A South African study also shows hypocitraturia to be most important and commonest risk factor.¹⁹ The relatively high occurrence of citrate depletion in our patients remains unclear, perhaps its multi factorial. In some patients, the exact cause of hypocitraturia is unknown which is known as idiopathic hypocitraturia. It has been found that increased dietary protein intake increases the excretion of phosphates and reduces the excretion of urinary citrate (higher citrate tubular reabsorption) which being an inhibitor of growth leads to stone formation.²⁰

The levels of urinary magnesium in stone formers described in literature are also variable with reported prevalence of hypomagnesuria varying between (8.8%) and (24.4%) however in our study population it was found to be (55.5%) which is in agreement with Hussein et al, and Kumar et al.^{12,23} Oral intake of magnesium decreases the oxalate absorption and urinary excretion in a manner similar to calcium by binding to oxalate in the gut.²¹

Hyperoxaluria occurred in (25.3%) of patients and the difference in the frequency of hyperoxaluria as well as in the mean urinary oxalate excretion was statistically significant between stone formers and healthy controls. This in conformity with Iqbal et al, who had reported it in (11.7%) of patients however Yagisawa et al, Hess et al, Kumar et al, have reported hyperoxaluria to be the major risk factor attributable to oxalate rich diet.^{10,12,22,23} 79.8% was the highest incidence of hyperuricosuria reported by El-Reshaid et al.²⁴ On the contrary Mittal et al and Kumar et al found it to be 7% and 8% respectively in adult stone formers. Our study group had mean urinary uric acid level which was statistically high in stone formers as compared to normal individuals and 25.8% were found to have hyperuricosuria which is in accordance with Hussein et al, Hess et al, Levy et al, and again being attributed to high intake of dietary protein especially red meat (purine overload) and dietary habits of the study population.^{5,23,25} Hyperphosphaturia is closely associated with urinary metabolic abnormalities the reported incidence in stone formers was 19.9%, where as in our study it was 47.3%. This high rate may be due to dietary habits and lifestyle variations.

Low urine volume is perhaps one of the most easily preventable risk factors for calcium stone disease. Low fluid intake with increased loss due to heavy manual work in rural areas results in significantly reduced urine volume. The difference in frequency of urine volume as well as mean urinary volume was statistically significant between stone formers and healthy controls. In our study group low, urinary volume was reported in 38.2%, which is in accordance with Iqbal et al, and Kumar et al.^{12,22}

In present study, different serum parameters were assessed in patients with urolithiasis. It is well known that raised excretion of oxalate, uric acid, calcium and phosphorus in urine increase the formation of urolithiasis while raised excretion of citrate, magnesium and alkali in urine decrease this process. The levels of serum parameters like calcium, PTH were higher than normal in 12.4% and 10.2% patients respectively and higher level of PTH was found to be associated with stone formation. In our study group 17.2% patients had presented with recurrent stones (two or more than two episodes) of which 15% patients had primary hyperparathyroidism and for the rest cause could not be ascertained.

Stones associated with infections are not only infection stones but also other kinds of stones such as calcium oxalate. So, any type of stone may become infected but the term 'infection stones' means that stone formation exclusively depends on urease producing bacteria. In this study 18% of patients were reported to have urinary tract infection which is in accordance with Jan H et al, Huchereiter W et al, who have shown a frequency of 10-15% of urinary tract infection in stone formers.^{26,27}

CONCLUSION

In stone formation multiple, etiological factors are responsible. In present study hypercalciuria is main cause of renal calculi along with hypocitraturia, hypomagnesuria and hyperphosphaturia in our valley. Measurement of 24-hour urine constituents is still gold standard for evaluation of stone formers. The high frequency of hypocitraturia and hypomagnesuria reflect important role of citrate and magnesium in stone formation and prophylactic therapy, with citrate and magnesium having a role in the treatment of urinary stone disease in our population. Persistent urinary tract infection with urea splitting or non-splitting bacteria may be the initial factors in synthesis of infection renal stones. By controlling urinary tract infection, metabolic causes and other risk factors can lead to considerable decrease in incidence of nephrolithiasis in our valley. Patients with renal stone disease in our population should increase fluid intake (at least >2lts/day) despite weather being cold for most of the year. Since we found hypercalciuria to be predominant abnormality and as per studies it is increasingly common in people who take diet rich in animal protein and increase in salt intake. So, we recommend that stone formers should reduce animal protein intake and salt intake. We do recommend increased use of fruits (citrus) and vegetables in the diet of stone formers as hypocitraturia has been a prevalent problem. We also recommend early institution of citrate supplementation in stone formers and aggressive treatment of patients with UTI as per sensitivity testing.

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