

Original Research Article

The various metabolic factors involved in stone recurrence: a prospective study

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ABSTRACT

Background: Nephrolithiasis is the most common chronic kidney condition, is globally increasing in both sexes. Five main types of renal stones viz., calcium oxalate stones, calcium phosphate stones, uric acid stones, struvite stones and cystine stones. Purpose of the study is to evaluate various metabolic factors contributing to recurrent renal stone and determining appropriate medical treatment and diet modification to prevent recurrent renal stone disease.

Methods: This study was carried out in P.G. Department of Surgery, S.R.N. Hospital associated with M.L.N. Medical College, Allahabad. A total of 120 cases of recurrent renal calculi in and outpatient between August 2017 and July 2019 were included in the study. All patients were stone free at the time of metabolic urine evaluation.

Results: Most of the patients in the study were in the age 21 to 50 years. 80% were males and 20% were females. In 24-hour urine analysis most common metabolic abnormality seems to be hyperoxaluria (92.5%) followed by hypercalciuria (82.5%), high pH (67.5%), and least common seems to be hypocitraturia (15%), followed by hyperphosphaturia (20%), hypernatreturia (25%), and low level of potassium (25%).

Conclusions: All patient of recurrent stone formation are advised increase fluid intake. In patient with hypercalciuria and hypocitraturia, dietary restriction of protein, oxalate and sodium, treatment includes thiazides supplemented with potassium citrate. In patient with hyperoxaluria dietary restriction of oxalate rich food and in hyperuricosuria dietary restriction of animal protein is advised.

Keywords: Dietary modifications, Medication, Metabolic, Nephrolithiasis, Recurrent stones

INTRODUCTION

Nephrolithiasis is the most common chronic kidney condition, after hypertension. The incidence and prevalence of nephrolithiasis is globally increasing in both sexes. Nearly 10% of the world's population are expected to develop kidney stones in their lifetime. Higher excretion of calcium, uric acid and oxalate and lower urine pH and citrate excretion have been described in patients with metabolic syndrome and high body mass index (BMI). Insulin resistance and hyperinsulinemia were observed in overweight patients and may contribute to increase calcium and post-prandial oxalate excretion, thus, favouring calcium-oxalate stone formation.¹

Environmental factors like increasing environmental temperature also play role in stone formation.

Although nephrolithiasis has traditionally been considered a renal disorder, there is overwhelming evidence that it is in fact a systemic disorder. Primary hyperparathyroidism, renal tubular acidosis and Crohn's disease are well-described conditions that increase the risk of formation of calcium containing stones. Primary hyperparathyroidism may be found in 5% of stone formers.

A history of gout increases the likelihood of forming kidney stones, both uric acid and calcium oxalate. Individuals with gout were 50% more likely to have a history of stones.² When examined prospectively, a history of gout was

associated with a doubling of the risk of forming a stone, independent of diet, weight and medications.³

More recently, diabetes mellitus was found to raise the risk of stone formation, independent of diet and body size.⁴

Anatomical abnormalities like horseshoe shaped kidney and ureteropelvic junction obstruction also predisposes to nephrolithiasis. The role of inheritance is clearest in monogenic diseases such as Cystinuria, Dent's disease and Primary hyperoxaluria.

The dietary contribution of urinary oxalate may be higher in stone formers. Up to 1/3 of patients with calcium oxalate nephrolithiasis may have increased absorption of dietary oxalate, and in some cases a deficiency of oxalate degradation by the bacterium *Oxalobacter formigenes* in the gut could be the culprit.

High animal protein intake leads to increased calcium and uric acid excretion as well as decreased urinary citrate, all of which increase the risk of stone formation. Recently, phytate was also found to reduce substantially the likelihood of stone formation in younger women.⁵ Magnesium complexes with oxalate, thereby potentially reducing oxalate absorption in the gastrointestinal tract and decreasing calcium oxalate supersaturation in the urine. Vitamin C (ascorbic acid) can be metabolized to oxalate; thus, higher vitamin C intake could increase the risk of calcium oxalate stone formation. A metabolic trial demonstrated that the consumption of 1000 mg of supplemental vitamin C twice daily increased urinary oxalate excretion by 22%.⁶

Vitamin B6 is a cofactor in oxalate metabolism, and vitamin B6 deficiency increases oxalate production and urine oxalate excretion, so high intake of vitamin B6 may reduce the risk of kidney stone formation. When the urine output is less than 1 litre/day, risk of stone formation is markedly higher.

When defined as 24 hour urine volume less than one liter per day, 12-25% of first time stone formers will have this abnormality. High urinary pH leads to increased saturation of calcium phosphate predisposing to nephrolithiasis and can lead to struvite stones. Low urinary pH predisposes to uric acid nephrolithiasis.

The natural history of renal calculus disease is characterized by recurrence. Recurrence rates of 26-53% after 10 years have been reported. Five main types of renal stones may be distinguished as,

- Calcium oxalate stones composed of calcium oxalate or calcium oxalate mixed with calcium phosphate,
- Pure calcium phosphate stones,
- Uric acid stones
- Struvite stones which are the result of chronic urinary tract infections caused by specific strains of bacteria
- Cystine stones are associated with cystinuria.

Aims and objective of the study is to evaluate various metabolic factors contributing to recurrent renal stone & determining appropriate medical treatment and diet modification to prevent recurrent renal stone disease.

METHODS

This study was carried out in P.G. Department of Surgery, S.R.N. Hospital associated with M.L.N. Medical College, Allahabad from August 2017 to July 2019 after approval from the ethical committee and obtaining written and informed consent from the patient.

Method of collection of data

This is a prospective study. A total of 120 cases of recurrent renal calculi in & outpatient between August 2017 and July 2019 were included in the study. All patients were stone free at the time of metabolic urine evaluation.

A recurrent stone former was defined as a patient who presented to the clinic with symptomatic urinary tract stone plus the evidence of a previous stone formation, including history of passing a stone, presence of a stone on a previous KUB X-ray or ultrasound and history of operation for urinary tract stone.

In every patient who fulfilled the above criteria, a detailed history was obtained, clinical examination was carried out and relevant investigations done.

Diagnosis

All cases of symptomatic recurrent renal calculi were diagnosed by ultrasound KUB and plain X-ray KUB and non-contrast spiral CT if needed.

Inclusion criteria

Patients free of their stones before evaluation, acceptable lab values, patients at risk of or suspected to have renal stones, with prior diagnosis of renal stone; with or without symptoms and complications of renal stones or prior treatment for renal stones, Family history of urolithiasis, presence of bilateral stone disease, presence of inflammatory bowel disease, chronic diarrhoea, or malabsorption, concurrent medical conditions associated with urolithiasis (primary hyperparathyroidism, gout, renal tubular acidosis), presence of nephrocalcinosis and presence of osteoporosis or pathological skeletal fractures were included in the study

Exclusion criteria

Patients with serious life threatening medical illness, conditions which in the view of the investigator might interfere with assessment, safety, results, outcomes of the study, inability to understand and give consent, participants who might not be able to comply with the study procedures till the end of the study.

History of illness

In patients with history of flank pain radiating to the testicle or labia associated with nausea, vomiting and hematuria (may be a sign of stone, infection, tumor, trauma, sloughed papilla, or bleeding), complete history of any systemic illness, any family history of kidney stones were elicited. A dietary history focused on fluid intake and dietary indiscretion will assist in later dietary counseling.

Laboratory investigations

- A complete blood count along with BT/CT and GBP should be obtained to determine infection, inflammation, anemia of chronic disease, and/ or bleeding disorder.
- Evaluation of serum calcium, phosphorous, sodium, potassium, chloride, albumin. RBS, (FBS/PPBS), LFT.
- Renal function tests-blood urea, serum creatinine, serum uric acid.
- Evaluation of 24-hour urine samples(from UROLAB, Ahmedabad) for volume, creatinine, calcium, citrate, oxalate, pH, sodium, phosphorus, magnesium, potassium, uric acid.
- Urine routine, microscopic, culture and sensitivity.

Radiological investigations

- Ultrasound abdomen (KUB) and pelvis
- Plain x-ray KUB
- IVP
- Non-contrast spiral CT abdomen (KUB)

Method

After thorough history was taken for evidence of previous stone episode, all symptomatic patients were subjected to USG Abdomen and Pelvis. Patients whose USG did not pick up calculi were subjected to X-ray KUB. If calculi were not visualized by USG abdomen and Pelvis or X-ray KUB those patients were subjected to non-contrast CT KUB. At the time of presentation blood was drawn and sent for renal function tests, serum calcium, phosphorous, serum electrolytes. The acute renal colic episode was treated appropriately, stone were treated with appropriate procedures like ESWL, URSL, PCNL. Stone free patients were asked to collect 24 hour urine. Before 24 hours patient was advised not to take items like lemon, citrus fruits, cold drinks, cakes, alcoholic beverages, ice creams etc. and medicines like aspirin, Vitamin C, diuretics etc. The first morning void was discarded, since this represented urine from the previous night, from that point on, all urine was collected in the appropriate laboratory-provided container. Urine should be collected carefully as the container contains strong acid as preservatives (6 mL concentrated Hydrochloric acid in 6mL distilled water). Keep the collected urine at cool place, do not refrigerate it. When the patient awakened the next morning, the first morning void was collected with the rest of the specimen, thereby completing a full

twenty four hours. Before sending the sample to laboratory for twenty four hour urine analysis, fresh urine sample was collected for pH analysis. Only around 20 ml sample of twenty four hour urine was sent to the laboratory along with pH, total volume and body weight of the patient (if patient is less than 13 years of age) report for analysis of urine creatinine, calcium, phosphorous, sodium, uric acid, citrate, oxalate, magnesium and potassium. No refrigeration was needed during transport.

RESULTS

A total 120 patients (96 males and 24 females) were included in this study and conducted in the P.G. Department of Surgery, S. R. N. Hospital, M. L. N. Medical Collage, Allahabad.

Most of the patients were in the age 21 to 50 years and 30% were in 21-30 years group (Table 1). In this study 80% of patients were males and 20% were females (Table 2).

Table 1: Age of patient.

Age of patient (in years)	No. of patients	%
0-10	12	10
11-20	15	12.5
21-30	36	30
31-40	18	15
41-50	24	20
51-60	9	7.5
>60	6	5
Total	120	100

Table 2: Gender of patient.

Gender	No. of patients	%
Males	96	80
Females	24	20
Total	120	100

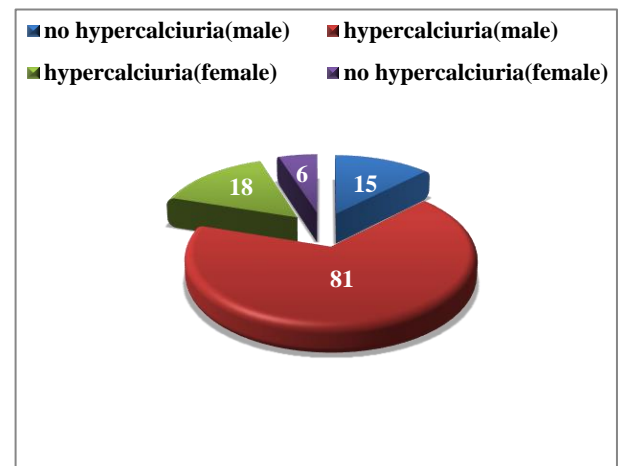


Figure 1: 24 hour calcium of patient.

In this study 82.5% patients had hypercalciuria (Figure1), 92.5% patients had hyperoxaluria (Table 3), 15% patients had hypocitraturia (Table 4), 32.5% patients had hyperuricosuria (Table 5), 25% patients had hypernatreturia (Figure 2), 20% patients had hyperphosphaturia (Figure 3), 67.5% patient had high urine pH (Table 6) and 55% patients had hypomagnesuria (Table 7).

Table 3: 24 hour urinary oxalate of patient.

24 hour urinary oxalate	No. of patients	% of patients
<40 mg/day no hyperoxaluria	9	7.5
>40 mg/day hyperoxaluria	111	92.5
Total	120	100

Table 4: 24 hour urinary citrate of patient.

24 hour of urinary citrate	No. of patients	% of patients
<320 mg/day hypocitraturia	18	15
>320 mg/day no hypocitraturia, 1.2 mg/kg/day for children	102	85
Total	120	100

Table 5: 24 hour urinary uric acid of patient.

24 hour urinary uric acid	No. of patients	% of patients
<600 mg/day no hyperuricosuria	81	67.5
>600 mg/day hyperuricosuria	39	32.5
Total	120	100

Table 6: 24 hour urine pH of patient.

24 hour urine pH	No. of patient	% of patient
5.5-6.2 normal urine pH	39	32.5
>6.2 high level of urine pH	81	67.5
Total	120	100

Table 7: 24 hour urinary magnesium of patient.

24 hour urinary magnesium	No. of patient	% of patient
<80 mg/day hypomagnesuria	66	55
80-123 mg/day normal level of magnesium	30	25
>123 mg/day hypermagnesuria	24	20
Total	120	100

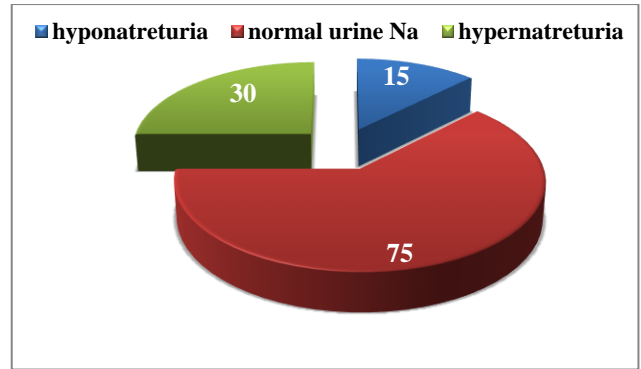


Figure 2: 24 hour urinary sodium of patient.

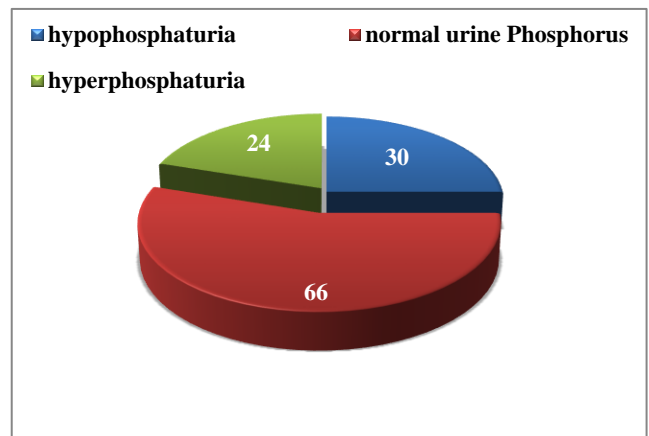


Figure 3: 24 hour urinary phosphorus of patient.

DISCUSSION

Most of the patients in study group were in age 21-50 years among which 30% were in 21-30 years age group. Bullock et al found that men between the ages of 20-50 years appear particularly at risk of kidney stone diseases.⁷ lifshitz et al conducted a study on metabolic evaluation of stone disease patients and reported that the peak age of onset of kidney stone formation is during the 3rd and 4th decade of life. In this study, 80% of patients were males and 20% were females.⁸

In this study, 82.5% patient had hypercalciuria. Goldfarb et al studied the factors associated with prevention of recurrent nephrolithiasis and concluded that the major urinary risk factor was hypercalciuria.⁹ Amaro et al studied 182 patients older than 12 years, 158 patients fulfilled the inclusion criteria and they detected that 74% was hypercalciuric.¹⁰ Kirac et al studied in patients with recurrent calcium oxalate stones formers and evaluate that 32.8% had hypercalciuria.¹¹

In this study 92.5% patients had hyperoxaluria. Amaro et al. study also detected that 24.1% was hyperoxaluric.¹⁰ Kirac et al study hyperoxaluria (64.4%) was the major metabolic abnormality.¹¹

In this study 15% patients had hypocitraturia. de Andrade et al founded that 65.6% patients presented with

hypocitraturia.¹² Amaro et al study, 37.3% patients had hypocitraturia.¹⁰ Stitchenrakus et al studied that 69.6% had hypocitraturia.¹³ Anjum et al study showed 78% patients had hypocitraturia.¹⁴

In this study 32.5% patients had hyperuricosuria. Hosking et al founded that 46.7% had hyperuricosuria. Goldfarb et al studied the risk factor of recurrent nephrolithiasis and founded that hyperuricosuria was also a major risk factor.⁹ deAndrade et al founded that 62.5% had hyperuricosuria.¹²

In this study 55% patient had hypomagnesuria. Amaro et al study showed that 21% had hypomagnesuria.¹⁰ Ansari et al founded that 28% had hypomagnesuria.¹⁵

In this study 20% patients had hyperphosphaturia. Ha et al studied that phosphaturia as a promising predictor of recurrent stone formation in patients with urolithiasis and detected, 19.9% had increased urinary phosphate excretion.¹⁶

In this study, 67.5% patient had high urine pH. Deshmukh et al were evaluated in 100 renal stone patients with first episode of renal stone having age 22 to 45 years from both sex and compared to 100 normal healthy control group, pH of urine in stone formers was lower than the controls.¹⁷ Sakhaee et al studied the urinary pH as a risk factor for stone formations and supported that low urinary pH. Strohmaier et al studied in urinary stone formers with hypocitraturia and concluded that normal urinary pH is at higher risk of recurrence than low urine pH.¹⁸

In this study 25% patients had hypernatreturia. Freitas Junior et al studied in elderly men with urolithiasis and hypernatruria was detected in 64% patients.¹⁹

This study and various studies conducted by different authors revealed same metabolic factors responsible for formation of renal stone which are increased level of calcium, oxalate, sodium, phosphate, uric acid and decreased level of citrate, magnesium in urine.

In all patient of recurrent stone formation increase fluid intake to yield an output of at least 2 litres of urine per day was advised. Patient should reduce the intake of colas and other soft drinks acidified with phosphoric acid, fruit flavored soft drinks are preferable as they are often acidified with citric acid. In patient with hypercalciuria dietary restriction of protein, oxalate (in chocolate, beets, nuts, rhubarb, spinach, strawberries, beans (including soyabean and wheat bran) and sodium. No restriction of dietary calcium is required.

Medical treatment includes thiazides (hydrochlorothiazide and chlorthalidone) with usual starting dose of 25-50 mg once daily, with the dosage increased up to 50 mg twice daily. The major side effect of thiazide is hypokalemia, which leads to reductions in urinary citrate

excretion, therefore thiazide therapy is usually accompanied with potassium citrate supplementation to replace potassium and replenish urinary citrate.

Potassium citrate comes in oral tablets and liquid forms (with various flavours to improve palatability). The usual dose is 20-30 mEq taken twice daily as needed. Amiloride a potassium sparing diuretic can also be used to prevent hypokalemia that may also have a minor effect in reducing urinary calcium excretion. Triamterene should not be used because it is poorly soluble and is associated with stone formation through precipitation of drug.

In patient with hypocitraturia dietary restriction of protein and sodium is advised. Potassium citrate supplementation (sodium citrate if potassium citrate is not tolerated). Potassium is preferred citrate preparation as sodium salt can increase urinary citrate excretion. Potassium citrate may be limited by gastrointestinal intolerance, particularly in older patients and patients with dyspepsia.

In patient with hyperoxaluria dietary restriction of oxalate rich food is advised. In patient with hyperuricosuria dietary restriction of purine (i.e. animal protein) is advised. Medical treatment with allopurinol can be effective in reducing the ability of uric acid to facilitate the crystallization of calcium oxalate if other risk factors are not identified.

In a patient with low urinary pH supplementation with potassium citrate is advised as it causes urine alkalinization.

CONCLUSION

Most of the patients in the study were in the age 21 to 50 years and 30% were in 21-30 years group. 80% of patients were males and 20% were females. In this study 82.5% patients had hypercalciuria, 92.5% patients had hyperoxaluria, 15% patients had hypocitraturia, 32.5% patients had hyperuricosuria, 25% patients had hypernatreturia, 20% patients had hyper phosphaturia, 55% patients had hypomagnesuria, and 67.5% patient had high urine ph.

In 24-hour urine analysis most common metabolic abnormality seems to be hyperoxaluria (92.5%) followed by hypercalciuria (82.5%), high pH (67.5%), and least common metabolic abnormality seems to be hypocitraturia (15%), followed by hyperphosphaturia (20%), hypernatreturia (25%), and low level of potassium (25%).

So, on the basis of our study we can plan different medical management and dietary modification to prevent recurrent stone formation.

All patient of recurrent stone formation is advised increase fluid intake, reduce the intake of colas and other soft drinks. In patient with hypercalciuria dietary restriction of protein, oxalate and sodium. No restriction

of dietary calcium is required. Medical treatment includes thiazides (hydrochlorothiazide and chlorthalidone) accompanied by potassium citrate supplementation, Amiloride can also be used. In patient with hypocitraturia dietary restriction of protein and sodium with potassium citrate supplementation is advised. In patient with hyperoxaluria dietary restriction of oxalate rich food is advised. In patient with hyperuricosuria dietary restriction of purine (i.e. animal protein) is advised. Medical treatment with allopurinol can be done. In a patient with low urinary pH supplementation with potassium citrate is advised. With this prevention and treatment modalities we can prevent and treat various patients with recurrent renal stones and morbidities associated with it.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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