

Studies on Urinary Risk Factors in Urolithiasis Patients of Purnia Division of Bihar, India

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Abstract: Urolithiasis disease is a function of a number of risk factors. Present objective is to study the urinary risk factors in urolithiasis patients from Purnia division of Bihar (India). The study would lead to an understanding of the various metabolic abnormalities leading to urinary stone formation in this region. Twenty four hour urinary calcium, magnesium, oxalate, phosphate, uric acid and citrate were estimated in 100 urolithiasis patients (66 males & 34 females) in the age group of 18-55 yrs. Fifty normal healthy persons (30 males & 20 females) in the age group of 20-55 yrs, who served as controls, were also studied for the above urinary parameters. Results revealed that hypercalciuria, hyperoxaluria and hypocitraturia are the main risk factors of urolithiasis in the region. Hyperuricosuria, hypophosphaturia and hypomagnesuria also showed up as marginal risk factors in the urinary stone patients. As such, urolithiasis patient from Purnia division of Bihar should invariably be tested for urinary calcium, oxalate and citrate levels. Urinary uric acid, phosphate and magnesium levels may also be assessed additionally. The treatment / prophylaxis strategy should be to correct these metabolic abnormalities so that the recurrency of the stone episode could be checked.

Keywords: Urolithiasis risk factors, Nephrolithiasis, Hypercalciuria, Hyperoxaluria, Hypocitraturia, Hyperuricosuria, Urinary stones, Urolithology.

INTRODUCTION

Urinary stone disease is related to a number of risk factors [1]. The rates of urinary stone formation have also been found to vary geographically [2]. Certain geographical regions have been identified as endemic stone belts [1]. The regional variation in the prevalence of the disease as well as in the risk factors might be due to variation in the climate, water quality, food habits etc. Review of literature in urolithiasis in the recent past indicates that in India, there is an increased prevalence of the disease in northwestern region [3-6] with some pockets located in Kerala, Maharashtra, Tamil Nadu, Assam, Manipur, Bihar and Jharkhand. Urolithiasis is also a recurrent disease. Once an individual has had a stone, he/she has 35-50% chance of having recurrent stone at some time later in life [7]. As such, it is necessary to study the relevant risk factors in the regional urolithiasis patients for a better treatment as well as prophylactic strategies.

With the above views in mind, we have presently studied the urinary risk factors in urolithiasis patients from Purnia division of Bihar (India). Purnea division is located in the northeastern region of Bihar

province of India. This region has recently been witnessing an increasing number of urolithiasis cases [8].

MATERIALS AND METHODS**Selection of subjects for study**

One hundred patients comprising of 66 male and 34 females, in the age of group of 18-55 years suffering from urinary stone disease were selected for study. The stone patients were selected at random from among those attending the local clinics and were confirmed for suffering from urolithiasis as diagnosed by ultrasonography or X-ray.

Fifty normal healthy persons, comprising of 30 male and 20 females in the age group of 20-55 years, who had no recent report of ill health of any kind and no past history of urolithiasis, were also selected for study as controls. All subjects (stone patients and controls) were in the dietary habit of occasional non-vegetarian food and belonged mostly to the middle income group. The work was carried out in the period, 2014-2016.

Collection and analysis of urine samples

Twenty four hour urine out-put was collected in sterilized plastic containers from each subject. Proper preservatives such as 10N hydrochloric acid for calcium and oxalate estimations, 10N sulphuric acid for citrate estimation and 1% thymol for magnesium, uric acid and phosphate estimations, were used. The samples were preserved in a refrigerator and were used out in minimum possible time after collection. Volume of each specimen was noted and used for analysis of biochemical parameters. For pH determination morning urine samples were used. The pH of urine was detected using dipsticks. The biochemical parameters such as oxalate, phosphate, uric acid, calcium and magnesium were analysed using standard diagnostic assay kits, adopting standard methods [9]. A clinical analyzer was used for all the estimations. Citrate was estimated using a colorimetric method [10]. The value of each of the biochemical parameters were compared between the stone formers and the controls. They were expressed as

mean \pm standard deviation. Statistical analysis of the data was performed by student's t-test.

RESULTS

The urinary calcium, oxalate and urate levels of urinary stone patients were found to be significantly higher ($p < 0.0001$) as compared to controls. The urinary citrate and phosphate levels of stone patients were found to be significantly lower ($p < 0.0001$) than that of controls. Urinary magnesium levels of stone patients was also found to be significantly lower ($p < 0.02$) as compared to that of controls. Twenty four hour urinary volume of stone patients was found to be significantly higher ($p < 0.0001$) than that of controls. The urinary pH of stone patients was found to be significantly lower ($p < 0.0001$) than that of controls.

Twenty four hour urinary constituents of normal healthy persons and urinary stone patients are recorded in Table 1.

Table-1: Twenty four hour urinary constituents in normal healthy persons and urinary stone formers.

Parameters	Normal healthy person(n=50)	Urinary stone formers(n=100)	p Significance
Volume(ml/24hr)	1689 \pm 307 ^a	2414 \pm 308 ^a	Significant
Calcium(mg/24 hr)	159 \pm 32.3 ^a	240 \pm 19.0 ^a	Significant
Oxalate(mg/24 hr)	45.3 \pm 7.21 ^a	75.8 \pm 12.8 ^a	Significant
Uric acid(mg/24 hr)	272 \pm 22.8 ^a	415 \pm 51.7 ^a	Significant
citrate(mg/24 hr)	407 \pm 34.4 ^a	147 \pm 54.7 ^a	Significant
Magnesium(mg/24 hr)	122 \pm 17.1 ^b	102 \pm 15.4 ^b	Significant
phosphate(mg/24 hr)	429 \pm 34.3 ^a	231 \pm 21.3 ^a	Significant

Statistical analysis was performed by student's t-test. The data are expressed as mean \pm SD, a = $p < 0.0001$; b = $p < 0.02$

DISCUSSION

The etiology of urinary stone disease is a consequence of a number of risk factors, which over the years lead to a slow process of stone manufacture. The risk factors may be an increased urinary output of stone promoters and a decreased urinary output of stone inhibitors. A balanced state between the promoter and inhibitors is essential to prevent the urolithiasis disease.

The stone promoting risk factors are mainly, hypercalciuria, hyperoxaluria, hyperuricosuria. From inhibitors point of view, the main risk factors are hypocitraturia, hypomagnesuria, hypophosphaturia. Urinary pyrophosphate, some urinary proteins like uropontine, and glycosaminoglycans have also been found to inhibit stone formation. Since most of the stones, particularly the stubborn stones are mainly of calcium oxalate, the urinary calcium and oxalate form the most pertinent risk factors.

Urinary calcium excretion depends on dietary calcium level as well as its absorption from the intestine. Calcium absorption depends on reaction of intestinal contents. Increased alkalinity of intestinal contents causes its precipitation as phosphate which is lost in the faeces. Calcium absorption increases with increased acidity of intestinal contents. Urinary calcium

excretion is hormonally control by parathromone and calcitonine. On an average calcium diet (800mg/day), the urinary excretion of calcium lies between 100-300mg/day [11]. On an average to low calcium diet, it might, however, fall between 50-150mg/day [11]. Presently, a study of Table-1 suggests that hypercalciuria is a risk factor causing urolithiasis in the study area (Purnia division of Bihar). The mean urinary calcium level (240 \pm 19.0mg /24hr) of stone patient has been found to be significantly($p < 0.0001$) higher than the normal healthy persons(159 \pm 32.3mg/24hr) This hypercalciuria might be of any origin such as primary idiopathic hypercalciuria, renal leak hypercalciuria or resorptive hypercalciuria.

Hyperoxaluria is the most pertinent risk factor in urolithiasis. Most of the stubborn stones consist of calcium oxalate. Urinary oxalate arises from endogenous synthesis as well as dietary source. A majority of the oxalate (85%), is in fact, from endogenous synthesis only. Increased oxalate synthesis is related to metabolic disorders. A small increase in oxalate absorption and subsequent urinary excretion highly increases the formation product of calcium-oxalate. This increases the potential for heterogeneous nucleation and crystal growth in this metastable environment. In most of the studies, hyperoxaluria has

been found to be an important risk factor in urinary stone formation [12-14]. In our present study (Table-1) also hyperoxaluria has been found to be a risk factor in the urinary stone disease. The mean oxalate of stone formers ($75.8 \pm 12.8 \text{mg}/24\text{hr}$) has been found to be quite significantly higher ($p < 0.0001$) than that of the normal individuals ($45.3 \pm 7.21 \text{mg}/24\text{hr}$).

Urinary uric acid level is another risk factor of urinary stone disease. Hyperuricosuria has been found to be a risk factor in urolithiasis patient of many regions [12-14]. Hyperuricosuria may be the result of high purine intake or uricosuric drugs or from the tubular defect such as an isolated defect in renal tubular urate reabsorption or from generalised tubular dysfunction [15]. Hyperuricosuria, at low urinary pH ($\text{pH} < 6$) may result in the formation of uric acid stones. Monosodium urate may also be precipitated. Monosodium urate absorbs urinary stone inhibitors and facilitates heterogeneous nucleation. It was proposed that uric acid crystals absorb and inactivate the natural urinary inhibitor such as glycosaminoglycans [16]. Presently, we found hyperuricosuria also as a risk factor of urolithiasis in our region. Mean urinary uric acid level of stone patients ($415 \pm 51.7 \text{mg}/24\text{hr}$) has been found to be significantly ($p < 0.0001$) higher than that of normal individuals. However, this risk factor seems to be only a marginal one in our region, because the urinary uric acid levels of stone patients of our region are still lower than that of patients reported from other regions [13, 14].

Citric acid is one of most pertinent and important inhibitors of urolithiasis. Level of citric acid in urine can alone indicate the level of immunity of a person from urinary stone formation [17]. Hypocitraturia is thus an important risk factor of urolithiasis, particularly calcium urolithiasis. A number of factors might cause hypocitraturia. Increased metabolic demands on the mitochondria of renal cells decreases the excretion of citrate. Such conditions include intracellular metabolic acidosis, hypokalemia, fasting, hypomagnesemia, androgens, gluconeogenesis and an acid-ash diet. Citrate may also be consumed in the urine by bacteria during a urinary tract infection. The cause of hypocitraturia may be unknown in some cases. In contrast, alkalosis, alkaline-ash diet, estrogens, growth hormone, parathyroid hormone and vitamin-D increase urinary citrate levels [18]. Urinary citrate normally inhibits calcium oxalate and calcium phosphate precipitation by complexation of calcium in a soluble form. Citrate also acts by decreasing agglomeration, spontaneous nucleation and crystal growth of calcium oxalate. Citrate may also decrease calcium oxalate calculi by decreasing monosodium urate that can absorb inhibitors and facilitate heterogeneous nucleation. In our present study, hypocitraturia has been found to be a major risk factor of urolithiasis in the region (Purnia division). Mean 24hr urinary citrate level of urinary stone patients has

been found to be $147 \pm 54.7 \text{mg}/24\text{hr}$, which is significantly lower ($p < 0.0001$) than that ($407 \pm 34.4 \text{mg}/24\text{hr}$) of the normal healthy persons. Normal urinary citrate is at least 200mg per day but average to more than 500mg per day in most individuals [19]. Thus, it seems the normal healthy persons that we have studied are more or less normocitraturic, but the stone patients of our study area are definitely hypocitraturic.

Urinary phosphate level has been studied as a risk factor in calcium urolithiasis [12-14]. Low urinary phosphate levels have generally been observed in stone patients [12-14]. The mechanism of inhibitory activity of phosphate is not yet clear. At higher urinary pH (around $\text{pH} = 7$), phosphate may itself precipitate out as hydroxyapatite, brushite or struvite stones. However, at lower pH, urinary phosphate might complex with calcium and thus screen the later from oxalate. Phosphate might also correct absorptive calciuria by reducing the synthesis of calcitriol and to bind calcium in the intestine, thereby reducing intestinal absorption of calcium [20]. In our present study, the urinary phosphate ($231 \pm 21.3 \text{mg}/24\text{hr}$) of stone formers was found to be significantly lower ($p < 0.0001$) than that of the controls ($429 \pm 34.3 \text{mg}/24\text{hr}$). Thus, hypophosphaturia is also seemingly a risk factor of urolithiasis in our study area.

Magnesium inhibits oxalate absorption and excretion and thus prevents its super saturation. Magnesium forms soluble complex with oxalate and thus screen the later from calcium ions. Thus, magnesium is a complexing inhibitor of calcium urolithiasis [21]. Urinary magnesium excretion in children is higher than adults which might be the cause of a lower incidence of urolithiasis in children compared to that of adults [22-24]. In our study, we found the urinary magnesium level of stone patients at $102 \pm 15.4 \text{mg}/24\text{hr}$ which is slightly lower as compared to $122 \pm 17.1 \text{mg}/24\text{hr}$ in controls. Though the mean values do not differ much, however, the levels are significantly different ($p < 0.02$). Thus hypomagnesuria also seems to be a minor risk factor in the urinary stone formers of our area.

Urinary volume is also a risk factor in urinary stone disease. In fact, a high fluid intake and raised urine volume reduces urinary super saturation, thereby reducing the driving force for crystallization and stone formation [25]. In our study, we found the mean urinary volume of stone patients to be at $2414 \pm 308 \text{ml}/24\text{hr}$ which was significantly higher ($p < 0.0001$) than that of normal healthy persons. This observation might have been due to a high water intake by the patients, as advised by the physicians / surgeons treating them. The urinary pH value is also of significance in urolithiasis. Stone formation is induced by abnormally low or high urine pH values. Metabolic acidosis may lead to low urinary pH and lead to

hypocitraturia, thus causing stone formation, particularly the oxalate or uric acid stones. On the other hand at pH around 7, phosphate stones such as hydroxyapatite, brushite or struvite might be formed. Presently, we found the pH of stone patients to be at 5.43 ± 0.27 which is significantly lower ($p < 0.0001$) than 6.24 ± 0.23 of controls. Thus, it seems that acidosis is also a risk factor of urinary stone disease in this Purnia region.

CONCLUSION

Our present studies indicate that some major risk factors like hypercalciuria, hyperoxaluria and hypocitraturia are present in the urinary stone formers in Purnia division. Hyperuricosuria, hypophosphaturia and hypomagnesiuria also showed up as marginal risk factors. Based on our findings, the local urolithiasis patients may be counseled to avoid oxalate rich foods like tomatoes, spinach, groundnut etc. and also restrict the diet rich in animal proteins and salt. The patients may also be advised to consume citrus fruits, particularly potassium rich ones like orange, grapes etc., and also to increase the fluid intake. Our findings will be helpful to the local physicians/surgeons in planning the medical management of the disease. The studies would also go a long way in effective planning of prophylactic/preventive measures to control the occurrence/ recurrence of urinary stone disease in this region.

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