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Revisiting The Risk Factors Of Renal Stone Disease

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Abstract

Background: Renal stone disease is a multifactorial disease with a global prevalence of 2-20%. Identifying these risk factors is of great importance in contributing to the prevention or reduction in the recurrence risk of kidney stone disease.

Objective: To observe the demographic and biochemical risk factors among renal stone patients and to demonstrate any difference in the above parameters among stone formers and non-stone formers.

Methods: A hospital-based observational study was conducted from January 2015–February 2016 among 30 renal stone disease patients diagnosed by X-ray or ultrasonography attending surgery OPD at Tertiary care hospital, Delhi. Thirty healthy spouses of the patients or a close relative in case of unmarried patients who were staying with the patient in the same home and 15 healthy unrelated volunteers, both without history suggestive of renal stone and on screening ultrasonography revealed no renal stone disease were recruited as controls. A pretested semi-structured questionnaire for demographic profile was used for data collection along with 24-hour urine and fasting blood samples for biochemical analysis.

Results: The mean age of stone formers was 34.4 years and the male-to-female ratio was 3.4:1. Twenty percent of the patients belonged to the overweight category. Common metabolic abnormality detected in urine among patients was hyperoxaluria(47.1%), followed by hypercalciuria(23.5%) and hyperuricosuria(17.6%). The urine analysis values for oxalate, uric acid, phosphate, potassium, and specific gravity of urine were significantly higher in renal stone patients as compared to the spouses/relatives and healthy volunteers($p<0.05$). On multivariate analysis, hyperoxaluria and hyperuricosuria were found to be independent risk factors of renal stone disease.

Conclusion: Among renal stone patients most common metabolic abnormality detected was hyperoxaluria, hypercalciuria, and hyperuricosuria. Hyperoxaluria and Hyperuricosuria were found to be independent risk factors for stone formation.

Keywords: Renal stone, Renal calculi, Risk factors, hyperoxaluria, hypercalcemia, hyperuricosuria

Introduction

The renal stone disease has a global prevalence of 2-20%[1,2,3]. The epidemiology of renal stone disease is changing along with the change in the world population and there is a significant difference between the countries and within the country. [3] Its found that the prevalence of renal stone is more common among men than in women with lifetime

risk in men 10-20% compared to women ie, 3-5%.[4] There is also a direct correlation between BMI and renal stone formation[5] and in patients who work in a hotter climate, athletes, and regular strenuous physical workouts.[6,7] It is stated that a decrease in urine volume is a real risk factor for stone formation,[7] hypercalciuria, hyperuricosuria, hyperoxaluria, Hypocitraturia[8] along with hypomagnesuria and hypophosphaturia are the most common parameters found in stone formers.[9,10] The present study was designed to reanalyze the risk factors including demographic characteristics and biochemical parameters in the Indian population. Which would help to further highlight the changing epidemiology of the disease as well as to provide a framework for appropriate clinical evaluation and use of diagnostic tools when approaching a patient with a suspected renal stone.

Material And Methods

A hospital-based observational study was conducted in the department of Surgery o a tertiary care hospital in Delhi. The study participants were patients with renal stone disease attending surgery Out Patient Department, who were diagnosed to have renal stone by X-ray or ultrasonography (USG). We recruited 30 renal stone patients for the study. The healthy spouse of the patients or the close family member in case of unmarried patients who were staying with the patient in the same home environment and consuming the same diet was one control group and 15 healthy unrelated volunteers, were the second control group. Both the control groups had no history suggestive of renal stone disease and screening ultrasonography revealed no renal stone disease.

A semi-structured questionnaire including the age, sex, place of stay, occupation, and other demographic parameters was recorded. The Renal stone patients as well as controls were asked to collect 24-hour urine in a plastic container and bring it along with them during their next visit. They were also asked to come fasting for a minimum of 8 hours to draw blood samples for analysis. The 24-hour urine brought by the patient was measured for its volume in milliliters and specific gravity was measured by dip-strips. Samples of urine were preserved in a refrigerator with 10N Hydrochloric acid for oxalate measurements and were analyzed by using the biochemical reagent of QAYEE-BIO®. Uric acid, Calcium, Phosphate, urea, and creatinine were analyzed by AU 400 OLUMPUS analyzer. Sodium and potassium levels were estimated by AVL electrolyte analyzer. A fasting urine sample was used for measuring the pH using dip-strips**.** A fasting blood sample was collected and was tested for blood urea, creatinine, sodium, potassium, uric acid, calcium, and phosphate by using an already standardized method in our laboratory. The information obtained from the study subjects were kept confidential. Ethical clearance was obtained from the Institutional committee of ethics and human research.

The data was analyzed using IBM SPSS Statistics for Windows, Version 24.0. (Armonk, NY: IBM Corp). Descriptive tables were generated to find the frequencies of demographic and biochemical parameters among renal stone patients and also among control groups. Comparison of cases and control groups were done using chi square (χ^2) test for categorical variables and analysis of variance (ANOVA) for continuous variables after doing log transformation of factors that were right-skewed. A p-value of <0.05 was taken as significant. All those factors found significant in ANOVA were further analyzed using Dunnett's post hoc test. Multivariate analysis was done by using binary logistic regression.

Observations & Results

Demographic Factors: The mean age of stone formers in our study was 34.4 years. Seventy-one percent of renal stone patients were males. Seventy-six percent patients were employed while the rest 23.5% were homemakers. Almost 60% of the patients were working in occupations requiring moderate levels of physical work while 17.6% were working in heavy physical activities, and 23.5% of patients belonged to the sedentary group. Twenty percent of patients were overweight and obese.

Biochemical Profile: The mean urine volume was 1.71 L/day (SD=0.65) (0.51-3.20L/day). The mean value of urine calcium among stone formers was 143.23mg/day (SD=62.67) and ranged from 35-310mg/day. Around 23.5% of renal stone patients had urine calcium levels of more than 200 mg/day. The mean value of urine oxalate among renal stone patients was 37.74mg/day (SD=8.79) (14.7-55mg/day). There were 47.1% renal stone patients in our study had urine oxalate levels of more than

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40mg/day. The mean value of serum calcium level was 8.91mg/dl (SD=1.32) and ranged from 4.5-11.6mg/dl and there were 8.9% of patients with hypercalcemia. It was observed that there was no difference in demographic factors like gender, BMI, and level of activity among patients and the other groups.

The 24 hours Urine oxalate, phosphate, uric acid, and potassium values were found to decrease across the three groups i.e.patients, spouse / close relative, and healthy volunteers with the highest value among renal stone patients, and this difference was found to be statistically significant with p value 0.002, 0.013, 0.018 and 0.002 respectively (Table No. 1, 2).

The inter-group analysis also showed a statistically significant difference($p<0.05$) among both groups for urine oxalate. Urine phosphate was found to be statistically significant between patients and spouse/close relatives (p=0.008) whereas the difference in urine uric acid(p=0.017) and urine potassium(p=0.001) was found to be statistically significant between patients and healthy volunteers.

Statistically, a significant difference was found in the blood phosphate level among the three groups (p=0.043), and the difference was statistically significant (p=0.028) between stone formers and healthy volunteers.

There were 15 variables that we considered for univariate analysis(Table 3). Among these 15 variables, those which had p-value < 0.25 i.e. 5 variables were included in the binary logistic regression using enter method(Table 4). Urine uric acid and urine oxalate was noted to be significant independent risk factor for stone formation and high urine sodium was a protective factor in stone formation.

Table 1: Twenty-four hours urinary parameters: Renal stone patients, spouse/relative and healthy volunteers

24-hour urine analysis	Renal stone patient	Spouse/Close Relative	Healthy volunteer	p value	Dunnet's post hoc test
	Mean±SD	Mean±SD	Mean±SD		
Volume	3.22±0.16	3.19±0.22	3.30±0.11	0.173	C vs Sp (p=0.862)
					C vs Hv (p=0.248)
Specific gravity	**0.0066±0.003**	**0.0054±0.002**	**0.0039±0.003**	**0.005**	C vs Sp (p=0.128)
					C vs Hv (p=0.002)
Calcium	2.13±0.20	1.99±0.35	1.95±0.18	0.056	C vs Sp (p=0.100)
					C vs Hv (p=0.066)
Oxalate	**1.56±0.12**	**1.44±0.19**	**1.40±0.16**	**0.002**	**C vs Sp (p=0.010)**
					C vs Hv (p=0.005)
Creatinine	1.09±0.29	0.95±0.46	0.95±0.29	0.288	C vs Sp (p=0.266)
					C vs Hv (p=0.395)
Phosphate	**2.64±0.17**	**2.44±0.34**	**2.5±0.22**	**0.013**	**C vs Sp (p=0.008)**
					C vs Hv (p=0.180)
Urea	0.70±0.19	0.79±0.37	0.82±0.38	0.409	C vs Sp (p=0.458)
					C vs Hv (p=0.414)
Uric acid	2.52±0.22	2.37±0.28	2.29±0.36	**0.018**	C vs Sp (p=0.068)

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					C vs Hv (p=0.017)
Sodium	2.19±0.23	2.25±0.32	2.32±0.15	0.255	C vs Sp (p=0.547)
					C vs Hv (p=0.189)
Potassium	**1.56±0.33**	**1.42±0.27**	**1.20±0.35**	**0.002**	C vs Sp (p=0.149)
					C vs Hv (p=0.001)

Table 2: Blood parameters: Renal stone patients, spouse/relative, healthy volunteers

Blood parameter	**Stone Former**	**Spouse/Close Relative**	**Healthy volunteer**	**p value**	**Dunnet's post hoc test**
	Mean±SD	**Mean±SD**	**Mean±SD**		
Sodium	2.14±0.02	2.14±002	2.15±0.01	0.244	C vs Sp (p=0.813)
					C vs Hv (p=0.370)
Potassium	0.63±0.06	0.63±0.04	0.65±0.05	0.424	C vs Sp (p=0.947)
					C vs Hv (p=0.344)
Calcium	0.94±0.05	0.95±0.04	0.96±0.04	0.421	C vs Sp (p=0.675)
					C vs Hv (p=0.339)
Phosphate	**0.53±0.08**	**0.54±0.10**	**0.61±0.17**	**0.043**	C vs Sp (p=0.832)
					C vs Hv (p=0.028)
Uric acid	0.70±0.10	0.64±0.13	0.66±0.14	0.124	C vs Sp (p=0.079)
					C vs Hv (p=0.521)
Urea	1.32±0.13	1.35±0.14	1.38±0.11	0.394	C vs Sp (p=0.713)
					C vs Hv (p=0.306)
Creatinine	-0.09±0.12	-0.10±0.10	-0.05±0.09	0.334	C vs Sp (p=0.855)
					C vs Hv (p=0.456)

All values are the log of observed values

***C: Renal stone patients; Sp: Spouse/ Close relative; Hv: Healthy volunteer**

Table 3: Univariate analysis: risk factors in cases and controls

Risk Factors		**Kidney Stone Disease**		**p value**
		Cases (+)	**Controls (-)**	
Gender	Male (+)	21 (38.9%)	33 (61.1%)	0.753
	Female (-)	9 (42.9%)	12 (57.1%)	
BMI	Overweight (+)	7 (35%)	13 (65%)	0.594

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	Non overweight (-)	23 (41.8%)	32 (58.2%)	
Level of activity	Sedentary (+)	8 (42.1%)	11 (57.9%)	0.828
	Others (-)	22 (59.3%)	34 (60.7%)	
Ph	<5.5 (+)	16 (50%)	16 (50%)	0.127
	Others (-)	14 (32.6%)	29 (67.4%)	
Specific gravity	>1.03 (+)	1 (100%)	0	0.400
	Others (-)	29 (39.2%)	45 (60.8%)	
Urine volume	<1.5L (+)	14 (46.7%)	16 (53.3%)	0.336
	Other (-)	16 (35.6%)	29 (64.4%)	
Urine calcium	>200 (+)	7 (63.6%)	4 (36.4%)	0.104
	Others (-)	23 (35.9%)	41 (64.1%)	
Urine oxalate	**>40 (+)**	**13 (61.9%)**	**8 (38.1%)**	**0.016**
	Others (-)	**17 (31.5%)**	**37 (68.5%)**	
Urine uric acid	>600 (+)	5 (71.4%)	2 (28.6%)	0.108
	Others (-)	25 (36.8%)	43 (63.2%)	
Urine phosphate	>800 (+)	1 (25%)	3 (75%)	0.646
	Others (-)	29 (40.8%)	42 (58.2%)	
Urine urea	>24 (+)	0	1 (100%)	1.000
	Others	30 (40.5%)	44 (59.5%)	
Urine sodium	>220 (+)	10 (30.3%)	23 (69.7%)	0.129
	Others (-)	20 (47.6%)	22 (52.4%)	
Blood calcium	>11 (+)	1 (100%)	0	0.400
	Others (-)	29 (39.2%)	45 (60.8%)	
Blood uric acid	>7 (+)	2 (66.7%)	1 (33.3%)	0.560
	Others (-)	28 (38.9%)	44 (61.1%)	
Blood potassium	<3.5 (+)	3 (60%)	2 (40%)	0.383
	Others (-)	27 (38.6%)	43 (61.4%)	

Table 4: Multivariate analysis risk factors of renal stone disease among cases and controls

Variable	Reference Category	B	S.E.	P	OR	95% CI
Urine sodium	<220	-1.609	.662	.015	.200	(.055-.731)
Urine uric acid	<600	2.288	1.067	.032	9.856	(1.219-79.713)

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Urine calcium	<200	1.239	.817	.129	3.452	(.696-17.109)
Urine oxalate	<40	2.069	.678	.002	7.920	(2.095-29.936)
Urine pH	>5.5	.682	.551	.216	1.977	(.671-5.825)

***SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.**

Reference code=0; Nagelkerke R-square = 0.337, p=0.001

Discussion

Demographic Risk Factors: The mean age of patients with renal stones was 34.4±14.33 years. The male-to-female ratio was 3.4:1, which was similar to other Indian studies[11,12]. However, many western studies[13,14,15,16] have observed a narrowing gap between the genders. The reasons cited for the above findings were the increasing prevalence of overweight amongst women. A significant inverse association was observed between the level of physical activity and the risk of developing renal stones[17]. In our study, a large majority of stone formers (77.6%) were moderate to heavy workers**.** A similar finding was noted by Apurba et al[18] in which 89.1% of stone formers belonged to moderate to heavy levels of activity. This can be due to more fluid loss and reduced urine output associated with moderate to heavy levels of physical activity. In our study, 20.6% of the patients with renal stones were found to be overweight. Compared to the prevalence of overweight people in the general population of India ie. 11%[19] and the world, 13%[20], this figure appears to be high. A study by Qazi Naheeb et al[21], noted that 38% of their patients with the renal stone disease were overweight and 34% were obese. Another research from London reported 39% with normal BMI, 40.5% were overweight and 20.5% were obese suggesting obesity has a positive correlation with renal stone formation[22.]

Biochemical Risk Factors

The mean urine volume among renal stone patients was 1.71 L/day (SD=0.65). There were 20.6% of the patients with less than 1-liter Urine volume. There was no significant difference between the urine output of cases and controls. Leonetti et al 23 noted a urine volume of 1.85 L/day among renal stone patients and it was significantly lower among stone formers when compared with healthy individuals. Conversely, an Indian study showed no significant difference between the urine volume in patients with renal stones and controls[24].

The mean urine pH of the patients was 5.75 (SD=0.59) and it ranged from 5-8. There was no difference in the urinary pH of the controls. Similar results were observed in other studies conducted in Canada[25] and India[26].

Hypercalciuria was observed in 23.5% of stone formers and the mean value of urine calcium was 143.23 mg/day (SD=62.67). The present study failed to detect any significant difference in urine calcium between cases and controls. Studies conducted in Rajasthan showed mean urinary excretion of calcium of 190 mg/day, with a significant difference between cases and controls[14,15]. Similarly, Curhan et al[18] observed the urinary excretion of calcium was significantly high among patients in comparison with controls. A Pakistan study noticed no difference in urinary excretion of calcium between stone formers and controls which supported the findings of our study. Much less incidence (7- 10 %) of hypercalciuria was observed in studies from Thailand, north-west India, and Iran[20]

Hyperoxaluria was found to be an independent and significant risk factor for kidney stone disease in our study. Almost 47% of the patients had hyperoxaluria with urinary excretion of oxalate of more than 40mg/day. Hyperoxaluria appeared as a major metabolic factor affecting 50-60% of renal stone patients at Sindh institute of urology and transplant[11]. In studies conducted in North India, around 55% of renal stone patients had hyperoxaluria.[12,13]

The mean urinary oxalate excretion was found to be significantly higher among patients with renal stones compared to controls in the present study. A similar significant difference was noticed between patients and controls[,14,15,16]. Heavy consumption of oxalate-rich foods may be an important cause of hyperoxaluria.

Another independent risk factor for kidney stone disease found in our study was hyperuricosuria. The mean urine uric acid level among stone formers was

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365.55 mg/day (SD=193.48), with a range of 72-832 mg/day. Rajkiran et al[14] observed the urinary uric acid in rural and urban renal stones patients of Rajasthan as 323 and 423mg/day respectively. Another study[15] observed the daily urinary excretion of uric acid to be 205 mg/day. Western studies[17,18] have shown higher excretion of urinary uric acid compared to Indian studies. In the present study, hyperuricosuria was present in 17.6% of the patients. Similarly, A north Indian study[13] found 18% of patients with hyperuricosuria. Kirac et al[21] demonstrated 19.4 % of hyperuricosuria among stone formers in Turkey. In the present study urine uric acid was found to be an independent risk factor for stone formation. A similar finding was observed by Rendina et al[19]. Rizvi et al[11] and Leonetti et al[16].

The mean value of urine phosphate level in patients with renal stones was 464.56 mg/day (SD=185.2). An almost similar result of mean excretion of phosphate in urine was observed in a study comparing non-operated and operated stone formers[27]. However, another Indian study showed higher mean excretion of phosphate among rural tribal, rural nontribal, and urban stone formers with values of 616, 537, and 762, respectively[26]. Much higher urinary phosphate values were observed in the Boston study[28]. The present study also observed a significant difference in urinary phosphate between renal stone patients and controls. A similar significant difference was found in other Indian and western studies[26,27,28].

The mean value of urine sodium among patients with renal stones in our study was 105.2mEq/day. A study found urine sodium values of 129mEq/day and 135mEq/day among operated and non-operated stone formers[29]. Hypernatriuria is observed in 12% of stone formers[30], however, it was seen in only one patient in the present study. The current study found an inverse association between urinary sodium and the risk of renal stone formation with no significant difference. Similarly, no significant difference was found in both Indian and Western literature[23,26,27,28].

The mean value of urine potassium among stone formers in our study was 34.03 mEq/day (SD=51.56) and ranged between 8.1-271 mEq/day. In the present study urinary excretion of potassium was significantly high among stone formers. However no significant difference was found in other Indian studies,[24,26] conversely western study has found significantly low urinary potassium in stone formers compared to non-stone formers[28].

Conclusion

The presentation of renal stone patients in our study was in middle age, more among males and among moderate to heavy workers. The most common metabolic abnormality detected was hyperoxaluria, hypercalciuria, and hyperuricosuria. The high specific gravity of urine was found to be a risk factor for renal stone disease. Hyperoxaluria and Hyperuricosuria were found to be independent risk factors for stone formation.

Author contribution: First and second author has conceptualized and were involved in data acquisition, literature search & drafting of the manuscript. The third and fourth authors were involved in editing and reviewing of the manuscript.

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