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Metabolic Risk Factors in Calcium Oxalate Stone Formers: A Comparative Analysis with Healthy Control

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ABSTRACT

Objective: To determine the metabolic abnormalities in the urine of calcium oxalate stone former patients and non-stone formers. **Method:** A descriptive study was performed in the Department of Urology, SIUT, Karachi, Pakistan, from June 27, 2022, to December 26, 2022. Patients with suspected renal calculi were evaluated, and those confirmed with them had surgical interventions including percutaneous nephrolithotomy, open surgery, or minimally invasive techniques. Stone specimens were examined with infrared techniques. Urine (24-hour) and blood specimens were obtained from 44 patients with calcium oxalate calculi and 51 healthy controls, with serum metabolic parameters evaluated using standard chemical methods. Data were documented electronically. **Results:** The comparison of metabolic parameters between stone formers and non-stone formers indicated no significant differences in mean urine uric acid levels (415.98 ± 156.51 vs. 366.80 ± 128.52 mg/24 hours, P = 0.096), urine phosphorus (5.84 ± 0.60 vs. 6.19 ± 0.73 mmol/24 hours, P = 0.723), urine oxalate (25.23 ± 15.70 vs. 30.83 ± 28.27 mg/24 hours, P = 0.246), or urine citrate (148.39 ± 113.85 vs. 190.29 ± 151.16 mg/24 hours, P = 0.135). Notable differences were detected in urine magnesium (80.93 ± 33.33 vs. 78.24 ± 39.68 mg/24 hours, P = 0.013) and urine calcium levels (179.02 ± 102.95 vs. 122.02 ± 91.36 mg/24 hours, P = 0.005) between the two cohorts. **Conclusion:** In conclusion, those with calcium oxalate stones exhibited elevated amounts of magnesium and calcium in their urine relative to those without stones.

INTRODUCTION

Urolithiasis is characterised by the existence of calculi in the renal pelvis, ureter, bladder, or urethra.[1] Recent epidemiological statistics reveal a notable rise in the incidence and prevalence of urolithiasis globally.[2,3,4] The incidence of stone formation in the Western and Southern parts of Asia varies between 5% and 19.1%. [5,6] The epidemiology of urolithiasis is complicated, shaped by variables including sex, climate, ethnicity, occupation, and obesity. The prevalence has significantly increased in tropical locations, perhaps due to alterations in lifestyle, dietary practices, dehydration, and diminished water consumption. Various factors, such as age, sex, climate, metabolic disorders, and genetics, influence the formation of urinary calculi. Among these, metabolic disorders represent the most critical modifiable risk factors for the prevention of stone formation.[7] Urinary calculi frequently comprise many chemicals, with 80% predominantly consisting of calcium oxalate combined with calcium phosphate, followed by uric acid, struvite, and cysteine.[8] Calcium oxalate stones generally comprise calcium oxalate monohydrate and calcium oxalate dihydrate, frequently in conjunction. The metabolic irregularities associated with stone disease varied among populations, with environmental and genetic variables potentially elucidating these variations.[9] Metabolic assessment and intervention are crucial for preventing recurrence in patients with urinary calculi. Individuals with calcium stones, especially those with recurring, numerous, or bilateral formations, as well as children with a history of stones, should consistently undergo assessment, as correctable anomalies are frequently detected in these populations.[10,11] Wang et al. conducted a study revealing a 90.13% prevalence of calcium oxalate stones and analysed the metabolic irregularities in the urine of individuals with and without stones. The research identified notable disparities in urine parameters, encompassing uric acid, phosphorus, magnesium, calcium, oxalic acid, and citric acid concentrations among the groups.[12]

This study is to evaluate metabolic irregularities in the urine of individuals with calcium oxalate stones and those without stones. Although extensive study has been performed globally, localised data is still scarce. The absence of such data is especially significant in Eastern and Southern Asia, where geographical, climatic, nutritional, and lifestyle characteristics diverge from those in the Western world. This study seeks to offer significant insights that may guide future healthcare policies and enhance patient outcomes in light of geographical disparities and the lack of pertinent information.

METHOD

A descriptive study was performed at the Department of Urology at SIUT, Karachi, spanning six months, from June 27, 2022, to December 26, 2022, subsequent to the acceptance of the synopsis. The study intended to examine the prevalence of calcium oxalate stones, previously estimated at 90.13%.[12] The sample size, accounting for a 6% margin of error and a 95% confidence level, was determined to be 95 patients, comprising 44 patients with stones and 51 controls. The sampling technique used was non-probability consecutive sampling.

The study's inclusion criteria encompassed: patients aged 18 to 60 years, diagnosed with renal stones for the first time, established calcium oxalate stone formers, healthy participants, both sexes, and patients who gave informed consent. The exclusion criteria included patients with urinary disorders (such as proteinuria, recurrent urinary tract infections, congenital urinary tract obstruction, or bladder outflow obstruction), individuals with chronic diseases (including chronic renal failure and chronic liver disease), those with a history of chronic drug use, and patients with known metabolic abnormalities or thyroid disorders (either hypo- or hyperthyroidism).

The research started after receiving approval from the ethical review board, eligible patients identified by ultrasonography, were incorporated into the study after providing written informed consent. Information concerning participants' age, gender, height, weight, BMI, educational attainment, residential status, income level, employment status, smoking and alcohol consumption, medical comorbidities, presenting symptoms, diagnosis, and family history of urolithiasis was gathered and documented on an authorised proforma. Individuals suspected of possessing renal calculi underwent screening for stone detection. Individuals having verified radiological diagnoses of calculi necessitating intervention had stone extraction treatments conducted by a urologist. Following stone extraction, the specimens were dispatched to a laboratory for compositional analysis by infrared techniques to ascertain the prevalence of calcium oxalate stones.

Urine specimens were obtained from 44 patients diagnosed with calcium oxalate calculi and preserved in non-reactive plastic containers at 2-8°C. Furthermore, blood samples were collected to assess serum concentrations of urea, creatinine, uric acid, phosphate, and calcium, which were evaluated using conventional chemical methodologies. The information obtained were input into SPSS version 21 for analysis. The Shapiro-Wilk test was used to evaluate the normality of continuous variables including age, height, weight, BMI, and metabolic markers. A p-value exceeding 0.05 signifies a normal distribution. Descriptive statistics, including mean and standard deviation or median and interquartile range, were employed based on the data distribution. Frequency and percentage were computed for categorical variables such as gender, educational attainment, residential status, income, occupational status, smoking habits, alcohol consumption, medical comorbidities (e.g., diabetes, hypertension), presenting complaints, diagnoses, family history of urolithiasis, and stone composition. Independent t-tests or Mann-Whitney U tests were conducted to examine metabolic anomalies between calcium oxalate stone formers and non-stone formers. Stratification was conducted based on characteristics like age, BMI, gender, educational attainment, residential status, income, occupational status, medical comorbidities, and familial history of urolithiasis. Post-stratification, independent t-tests or Mann-Whitney U tests were utilised, with a p-value of less than 0.05 being statistically significant.

RESULTS

This table displays the descriptive statistics and p-values for the various variables examined in the study. The average age of the participants was 33.88±9.79 years, with a p-value of 0.060, signifying no statistically significant difference. Likewise, height (1.68±0.08 m, p=0.153), weight (77.64±11.55 kg, p=0.059), and BMI (27.57±4.51 kg/m², p=0.116) exhibited no significant differences.

Urine biochemical parameters were evaluated as follows: uric acid (389.58±143.52 mg/dL, p=0.246), magnesium (79.48±36.71 mg/dL, p=0.325), phosphorus (6.03±0.69 mg/dL, p=0.211), calcium (148.42±100.52 mg/dL, p=0.063), oxalate (28.24±23.36 mg/dL, p=0.998), and citrate (170.88±136.10 mg/dL, p=0.086). All parameters exhibited no statistically significant differences (p>0.05), indicating homogeneity within the research sample for these measurements. These findings establish a fundamental comprehension of the physiological and biochemical characteristics of the individuals being studied.

Table 1

Clinical and Metabolic Profiles: Mean Values and Statistical Significance n=95

Variable	Mean ± SD	P-value
Age Group	33.88±9.79	0.060
Height	1.68±0.08	0.153
Weight	77.64±11.55	0.059
BMI	27.57±4.51	0.116
Urine Uric Acid	389.58±143.52	0.246
Urine Magnesium	79.48±36.71	0.325
Urine Phosphorous	6.03±0.69	0.211
Urine Calcium	148.42±100.52	0.063
Urine Oxalate	28.24±23.36	0.998
Urine Citrate	170.88±136.10	0.086

The table illustrates the clinical and diagnostic distribution among individuals. Renal stones constituted the predominant diagnosis (41%), succeeded by renal and ureteric stones (27.2%), ureteric stones (18.2%), and bladder stones (13.6%). Among the total, 46.3% were diagnosed with renal calculi. The predominant symptoms were lumbar pain (45.5%), haematuria (36.3%), and dysuria (18.1%). Calcium oxalate stones were prevalent, identified in 86.2% of cases, whereas only 13.8% exhibited a negative result for this composition.

Table 2

Clinical Profiles and Stone Characteristics: Diagnosis, Symptoms, and Composition n=95

Diagnosis	Frequency	Percentage
Renal Stone	18	41%
Ureteric Stone	8	18.2%
Renal + Uretic Stone	12	27.2%
Urinary Bladder Stone	6	13.6%
Renal stone	**Frequency**	**Percentage**
YES	44	(46.3%)
NO	51	(53.7%)
Presenting complains	**Frequency**	**Percentage**
Lumber Pain	20	45.5%
Hematuria	16	36.3%
Burning Micturition	8	18.1%
Calcium oxalate	**Frequency**	**Percentage**
Yes	50	86.2%
No	8	13.8%

The table compares different demographic and clinical characteristics between individuals with kidney stones and those without. Among individuals with diabetes mellitus, 18.2% were stone formers, whereas the prevalence in non-stone formers was 23.5%. Urban inhabitants constituted 29.5% of stone formers and 31.3% of non-stone formers. Family history of urolithiasis was observed in 16% of individuals with stones and 19.6% of those without stones. Hypertension was more prevalent among stone formers (56.8%) than in non-stone formers (64.7%). Additional characteristics encompass tobacco usage, alcohol intake, and obesity prevalence, with elevated obesity rates noted in both cohorts.

Table 3

Comparison of Demographic and Clinical Characteristics Between Stone Formers and Non-Stone Formers n=95

Group	Diabetes Mellitus	
	Diabetic	**Non-Diabetic**
Stone Formers (n = 44)	8 (18.2%)	36 (81.8%)
Non Stone Formers (n = 51)	12 (23.5%)	39 (76.5%)
Group	**Residential Status**	
	Urban	**Rural**
Stone Formers (n = 44)	13 (29.5%)	31 (70.5%)
Non Stone Formers (n = 51)	16 (31.3%)	35 (68.6%)
Group	**Family History of Urolithiasis**	
	Yes	**No**
Stone Formers (n = 44)	7 (16%)	37 (84%)
Non Stone Formers (n = 51)	10 (19.6%)	41 (80.4%)
Group	**Hypertension**	
	Hypertensive	**Non-hypertensive**
Stone Formers (n = 44)	25 (56.8%)	19 (43.2%)
Non Stone Formers (n = 51)	33 (64.7%)	18 (35.3%)
Group	**Tobacco Use**	
	Yes	**No**
Stone Formers (n = 44)	14 (31.9%)	30 (68.1%)
Non Stone Formers (n = 51)	22 (43.1%)	29 (56.8%)
Group	**Alcohol Consumption**	
	Yes	**No**
Stone Formers (n = 44)	3 (6.8%)	41 (93.2%)
Non Stone Formers (n = 51)	5 (9.8%)	46 (90.2%)
Group	**Obesity Status**	
	Obese	**Non-obese**
Stone Formers (n = 44)	28 (63.6%)	16 (36.4)
Non Stone Formers (n = 51)	36 (70.6%)	15 (29.4)

The table shows the socioeconomic and educational status of those with kidney stones and those without. The majority of stone formers (56.8%) had a monthly family income between 20,000 and 100,000, comparable to non-stone formers (70.6%). Regarding education, the majority of participants from both categories possessed secondary education (41%) or intermediate education (34.1% among stone formers, 31.3% among non-stone formers). The occupational status indicates a greater percentage of employed individuals in both groups, with stone formers at 61.3% and non-stone formers at 62.7%, reflecting comparable trends.

Table 4

Socioeconomic and Educational Profiles of Stone Formers vs. Non-Stone Formers n=95

Monthly Family Income	Stone Formers (n = 44) Frequency	Stone Formers (n = 44) Percentage	Non-stone Formers (n = 51) Frequency	Non-stone Formers (n = 51) Percentage
<20,000	10	(22.7%)	8	(15.7%)
20,000-100,000	25	(56.8%)	36	(70.6%)
>100,000	9	(20.4%)	7	(13.7%)
Educational Status	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Illiterate	3	(6.7%)	4	(7.8%)
Primary	4	(9.1%)	5	(9.8%)
Secondary	18	(41%)	21	(41.2%)
Intermediate	15	(34.1%)	16	(31.3%)
Graduate	4	(9.1%)	5	(9.8%)
Occupational Status	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Unemployed	12	(27.3%)	13	(25.5%)
Employed	27	(61.3%)	32	(62.7%)
Personal business	2	(4.5%)	4	(7.8%)
Student	3	(6.8%)	2	(4%)

The table compares different metabolic anomalies between individuals with renal stones (n=44) and those without (n=51). Levels of urine uric acid, phosphorus, oxalate, and citrate exhibited no significant changes between the two groups, with P-values of 0.096, 0.723, 0.246, and 0.135, respectively. Notable disparities were detected in urine magnesium (P=0.013) and calcium (P=0.005), with elevated concentrations in individuals with kidney stones. The data indicate that urinary magnesium and calcium may contribute to renal stone development.

Table 5

Comparison of Metabolic Abnormalities Between Renal Stone Formers and Non-Stone Formers n=95

Metabolic Abnormalities	Renal Stone	Mean	SD	P-Value
Urine Uric Acid	Former n = 44	415.98	156.51	0.096
	Non-Former n = 51	366.80	128.52	
Urine Phosphorous	Former n = 44	5.84	0.60	0.723
	Non-Former n = 51	6.19	0.73	
Urine Magnesium	Former n = 44	80.93	33.33	0.013
	Non-Former n = 51	78.24	39.68	
Urine Calcium	Former n = 44	179.02	102.95	0.005
	Non-Former n = 51	122.02	91.36	
Urine Oxalate	Former n = 44	25.23	15.70	0.246
	Non-Former n = 51	30.83	28.27	
Urine Citrate	Former n = 44	148.39	113.85	0.135
	Non-Former n = 51	190.29	151.16	

The table compares key demographic characteristics between stone formers (n=44) and non-stone formers (n=51). Regarding age group, 72.7% of stone formers and 70.6% of non-stone formers were aged 18-40 years, with no statistically significant difference (P = 0.612). Regarding BMI, 61.4% of stone formers and 76.5% of non-stone formers exhibited a BMI ranging from 19 to 24 kg/m², with no statistically significant difference seen (P = 0.644). In terms of gender, 56.8% of stone formers were male, whereas 70.6% of non-stone formers were male, with no statistically significant difference (SP = 0.574). A greater percentage of both groups originated from rural areas, with no statistically significant difference (P = 0.624). In conclusion, among individuals with diabetes mellitus, 18.2% were stone formers, whereas 23.5% of non-stone formers were diabetic, with no statistically significant difference (P = 0.574). The data indicate that although several demographic characteristics vary among groups, none of the variances attained statistical significance.

Applied Independent test

Table: 6

Stratification of Age Group with Metabolic Abnormalities in the Urine of Calcium Oxalate Stone Former & Non-Stone Former: N=95

Age group [in years]	Stone Formers n=44		Non-stone Formers N=51		P-value
	Frequency	%	Frequency	%	

18 – 40	32	(72.7%)	36	(70.6%)	0.612
>40	12	(27.3%)	15	(29.4%)	
BMI [In kg/m²]	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
19 – 24	27	(61.4%)	39	(76.5%)	0.644
>24	17	(38.6%)	12	(23.5%)	
Gender	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Male	25	(56.8%)	36	(70.6%)	0.574
Female	19	(43.2%)	15	(29.4%)	
Residential Status	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Urban	16	(36.4%)	19	(37.3%)	0.624
Rural	28	(63.6%)	32	(62.7%)	
Diabetes Mellitus	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Diabetic	8	(18.2%)	12	(23.5%)	0.574
Non-Diabetic	36	(81.8%)	39	(76.5%)	
Hypertension	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Hypertensive	25	(56.8%)	33	(64.7%)	0.574
Non-Hypertensive	19	(43.2%)	18	(35.3%)	
Family History Of Urolithiasis	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Yes	7	(16%)	10	(19.6%)	0.585
No	37	(84%)	41	(80.3%)	
Tobacco Use	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Yes	14	(31.8%)	22	(43.1%)	0.248
No	30	(68.2%)	29	(56.9%)	
Alcohol Consumption	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Yes	3	(6.9%)	5	(9.8%)	0.538
No	41	(93.1%)	46	(90.2%)	
Obesity	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Obese	28	(63.6%)	36	(70.6%)	0.583
Non-Obese	16	(36.4%)	15	(29.4%)	
Monthly Income	**Stone Formers n=44**		**Non-Stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
<20,000	10	(22.7%)	8	(15.7%)	
20,000 – 100,000	25	(56.8%)	36	(70.6%)	0.100
>100,000	9	(20.4%)	7	(13.7%)	
Occupational Status	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Unemployed	12	(27.3%)	13	(25.5%)	
Employed	27	(61.3%)	32	(62.7%)	0.435
Personal Business	2	(4.5%)	4	(7.8%)	
Student	3	(6.8%)	2	(4%)	
Educational Status	**Stone Formers n=44**		**Non-stone Formers n=51**		**P-VALUE**
	Frequency	**%**	**Frequency**	**%**	
Illiterate	3	(6.7%)	4	(7.8%)	
Primary	4	(9.1%)	5	(9.8%)	
Secondary	18	(41%)	21	(41.2%)	0.011
Intermediate	15	(34.1%)	16	(31.3%)	
Graduate	4	(9.1%)	5	(9.8%)	

DISCUSSION

Urolithiasis has a raised incidence among females, obese individuals, and older patients, as corroborated by population-based studies. We see an increasing prevalence of hypocitraturia and hyperoxaluria in the current cohort, especially among obese individuals and males.[13] Diabetes mellitus is an increasingly prevalent health concern and a substantial risk factor for the formation and recurrence of urinary calculi. Our data indicate that individuals with type 2 diabetes exhibit a greater occurrence of mixed uric acid stones.[14] Our study revealed that 18.2% of patients with diabetes mellitus were stone formers, compared to a frequency of 23.5% in non-stone formers. In contrast to these investigations, we did not see any increase in stone formation among diabetes patients.

Adolescents demonstrate a lower incidence of urinary system calculi due to increased amounts of endogenous alpha-insulin three-molecule condensation inhibitor. This chemical inhibits calculus formation and is 2 to 7 times more common in adolescents than in other age groups. Furthermore, its concentration decreases with age, increasing the probability of calculus development as individuals grow older.[15] In contrast to this study, our research indicates that the majority of patients are aged between 18 and 40 years.

Yagisawa *et al.*[16] found that the most common metabolic abnormalities were hypercalciuria and low urinary volume. In another study, hypocitraturia and hypomagnesuria appear to significantly contribute to stone formation, with metabolic abnormalities identifiable in a substantial proportion of both primary and recurrent paediatric stone formers.[17] In our investigation, urinary uric acid, phosphorus, oxalate, and citrate levels were comparable in both groups; however, magnesium and calcium levels were elevated in individuals with kidney stones.

This study's findings underscore the significance of urine magnesium and calcium concentrations in the formation of calcium oxalate stones. Although no notable changes were seen in other urine parameters, the increased levels of calcium and magnesium in individuals with stones indicate that they may be essential factors in stone formation. This highlights the necessity for specific management measures to oversee and control these urine constituents in vulnerable persons. Future study should examine the mechanisms behind these defects and investigate targeted preventive strategies.

A limitation of this study is the relatively small sample size, which may limit the generalizability of the findings. Additionally, it focuses on a specific population, potentially restricting broader applicability. The study also did not evaluate dietary habits or genetic factors, which could influence urinary metabolic abnormalities and stone formation.

CONCLUSION

In conclusion, those with calcium oxalate stones exhibited elevated amounts of magnesium and calcium in their urine relative to those without stones. Nonetheless, there were no significant differences in uric acid, phosphorus, oxalate, or citrate concentrations. Further research is required to validate these findings.

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