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Association of Serum Uric Acid and Calcium Levels with Recurrence of Renal Calculi

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Abstract

Background: Renal calculi are a common urological problem with a high recurrence rate. Metabolic abnormalities, particularly disturbances in uric acid and calcium metabolism, play a significant role in stone formation and recurrence. Identifying simple biochemical predictors may aid in early risk stratification and targeted prevention.Aim of the study was to evaluate the association of serum uric acid and serum calcium levels with recurrence of renal calculi. ***Material and Methods***: This hospital-based observational study was conducted in the Department of Urology, Mamata Medical College, Khammam and included 50 patients diagnosed with renal calculi. Patients were divided into recurrent (n=25) and non-recurrent (n=25) groups. Demographic, clinical, imaging, and laboratory parameters including serum uric acid, serum calcium, serum creatinine, and urine pH were analyzed. Pearson correlation and comparative statistical tests were applied. ***Results***: Recurrent stone formers had significantly higher mean serum uric acid (7.6 ± 1.2 mg/dL vs 5.8 ± 1.1 mg/dL, $p < 0.001$) and serum calcium levels (9.8 ± 0.6 mg/dL vs 9.2 ± 0.5 mg/dL, $p < 0.01$). Urine pH was significantly lower in the recurrent group (5.4 ± 0.6, $p < 0.001$). Serum uric acid showed a positive correlation with stone size ($r = 0.58$) and a negative correlation with urine pH ($r = -0.61$). ***Conclusion***: Elevated serum uric acid and higher serum calcium levels are significantly associated with recurrence of renal calculi and may serve as useful biochemical markers for recurrence risk assessment.

Keywords: Renal calculi; Nephrolithiasis; Recurrence; Serum uric acid; Serum calcium; Urine pH; Hyperuricemia; Hypercalciuria; Metabolic risk factors.

INTRODUCTION

Renal calculi (urolithiasis/nephrolithiasis) remain a significant global health concern with rising incidence, increased healthcare utilization, and long-term morbidity related to obstruction, infection, and chronic kidney disease. Epidemiological studies indicate a growing lifetime prevalence, influenced by dietary changes, obesity, diabetes, and climate-related dehydration.[1] A major clinical challenge in stone disease is recurrence. Even after complete stone clearance, recurrence rates remain substantial, with approximately 20% recurrence at 5 years and over 30% at 10 years in several cohorts.[2] The European Association of Urology (EAU) guidelines report recurrence rates approaching 50% within 5 years in high-risk patients, underscoring the need for effective risk stratification and preventive strategies.[3]

Most renal stones are calcium-based (calcium oxalate ± calcium phosphate), while uric acid stones represent a smaller but clinically important subset, particularly in patients with metabolic syndrome, gout, obesity, and type 2 diabetes.[4] Stone formation results from urinary supersaturation of lithogenic salts under conditions such as low urine volume, acidic pH, and reduced inhibitors like citrate. Current guidelines recommend structured metabolic evaluation in recurrent stone formers, including stone analysis, urine studies (often 24-hour collections), and serum biochemical assessment.[5,6] The American Urological Association (AUA) advocates individualized preventive management based on metabolic risk factors and stone composition.[7]

Serum uric acid (SUA) and serum calcium are readily available biomarkers that may reflect systemic metabolic disturbances contributing to lithogenesis. Hyperuricemia increases urinary urate load and, particularly in acidic urine, promotes uric acid crystallization. Moreover, urate crystals may facilitate calcium oxalate nucleation, linking elevated SUA to both uric acid and calcium-based stones.[4,8] Uric acid nephrolithiasis is strongly associated with low urinary pH, and alkalinization therapy can dissolve many such stones, highlighting the clinical importance of the urate–pH axis.[9] Hyperuricemia has also been observed in calcium oxalate stone formers, suggesting that SUA may serve as a broader

metabolic risk marker rather than being limited to uric acid stones alone.[10] Emerging population-based data further support an independent association between hyperuricemia and kidney stone disease.[8]

Serum calcium plays an equally important role in recurrent stone formation. Although many patients with calcium stones have idiopathic hypercalciuria and normal serum calcium, a subset exhibit hypercalcemia due to primary hyperparathyroidism or other systemic causes. Elevated serum calcium increases urinary calcium excretion and enhances supersaturation of calcium salts, thereby increasing recurrence risk.[6] Clinical guidelines emphasize evaluating calcium metabolism, particularly to exclude hyperparathyroidism in stone formers.[11] Hypercalciuria remains the most common metabolic abnormality in calcium nephrolithiasis and is associated with recurrent disease.[12] Studies in patients with hyperparathyroidism demonstrate significantly higher recurrence rates when the underlying endocrine disorder is not corrected.[13]

Despite established pathophysiological links, the specific predictive role of serum uric acid and serum calcium for recurrence—independent of comprehensive 24-hour urine analysis—remains insufficiently standardized. Most recurrence-prevention literature focuses primarily on urinary parameters.[5–7] However, in routine clinical practice, complete metabolic evaluation is often underutilized due to logistical and economic constraints. Furthermore, recurrence definitions vary across studies, limiting comparability.[2,3] Recent research suggests that systemic metabolic abnormalities, including hyperuricemia and disturbances in calcium metabolism, correlate with recurrent stone composition, but further validation is needed.[14]

Therefore, evaluating the association between serum uric acid and serum calcium levels and recurrence of renal calculi may provide a practical and cost-effective approach for identifying high-risk patients who require closer follow-up and targeted metabolic intervention.

The aim of the present study is to evaluate the association of serum uric acid and serum calcium levels with recurrence of renal calculi, and to determine whether elevated levels of these readily measurable biochemical markers are significantly more frequent among recurrent stone formers compared with non-recurrent patients, thereby supporting their use in recurrence risk stratification and targeted preventive management.[3,6,7]

MATERIALS AND METHODS

Study Design and Setting

This was a hospital-based observational analytical study conducted in the Department of Urology at Mamata General Hospital, Khammam. The study enrolled 50 patients with a prior documented diagnosis of renal calculi who presented to the urology outpatient department (OPD) and/or were admitted for evaluation or management during the study period.

Sample Size

A convenience sample of 50 eligible participants was included based on feasibility, patient flow in the department during the study period, and the resource/time constraints of the study, while ensuring adequate representation of both recurrent and non-recurrent stone formers for comparative analysis.

Study Population and Grouping

All eligible participants underwent clinical assessment and review of prior records. Based on history and available imaging/records, participants were categorized into:

- **Recurrent renal calculi group**: patients with current stone episode plus a documented past history of renal/upper urinary tract calculus (with prior passage or intervention), or radiological evidence of new/recurrent stones after a stone-free period.
- **Non-recurrent (first episode / no recurrence) group**: patients with renal calculi without past history of stones or without evidence suggestive of recurrence.

Inclusion Criteria

- Age ≥ 18 years.
- Patients diagnosed with **renal calculi** on imaging (USG KUB / NCCT KUB / X-ray KUB as applicable).
- Willingness to participate and provide informed consent.
- Availability of **serum uric acid** and **serum calcium** testing as part of study protocol.
- Patients with prior documentation of stone disease (for classification into recurrence group where applicable).

Exclusion Criteria

- Known **chronic kidney disease** (e.g., eGFR < 60 mL/min/1.73 m² or documented CKD), since it can alter uric acid and calcium metabolism.

- Current use (or recent use) of drugs significantly affecting uric acid/calcium levels, such as:
  - Uric acid altering: allopurinol/febuxostat, uricosurics (unless washout feasible/documented)
  - Calcium altering: high-dose vitamin D/calcium supplements, thiazides (if not part of stable regimen with documentation)
- Known **primary hyperparathyroidism,** malignancy with hypercalcemia, sarcoidosis/granulomatous disorders (if already diagnosed), as these are strong confounders.
- Pregnant women.
- Active UTI/sepsis at presentation (to avoid acute-phase biochemical variability), unless treated and reassessed.
- Patients with bladder stones only (non-renal origin) or non-urological calcifications mimicking stones.

Methodology

- **Structured Case Record Form (CRF)/Proforma** including:
  - Demographics: age, sex, BMI
  - Clinical details: symptoms, duration, comorbidities (DM, HTN, gout), fluid intake
  - Stone history: first episode vs recurrence, prior interventions (ESWL/URS/PCNL/open), stone-free interval (if available)
  - Imaging findings: stone size, site, number, laterality, hydronephrosis
  - Laboratory parameters: serum uric acid, serum calcium (total), serum creatinine (for baseline renal function), urine pH.

Outcome Measure

- **Primary outcome:** Recurrence status (recurrent vs non-recurrent renal calculi).
- **Primary predictors:** Serum uric acid and serum calcium levels.
- **Secondary descriptors:** Stone burden (size/number/site), comorbidities, urine pH (if recorded), and prior intervention history.

Statistical Analysis

Data were analyzed using standard statistical software SPSS version 23.0. Continuous variables (serum uric acid, serum calcium) were summarized as mean ± SD (or median with IQR if non-normal). Group comparisons between recurrent and non-recurrent stone formers were done using independent t-test (or Mann–Whitney U test if non-parametric). Categorical variables were expressed as frequency/percent and compared using Chi-square/Fisher's exact test. Correlation between biochemical levels and stone burden (size/number) was assessed using Pearson or Spearman correlation as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

TABLE 1: Demographic Characteristics of Study Participants

Variable	Recurrent Group (n=25)	Non-Recurrent Group (n=25)	Total (n=50)	p-value
Age (years)	46.8 ± 9.4	38.6 ± 8.7	42.7 ± 9.8	0.004*
Male	18 (72%)	15 (60%)	33 (66%)	0.37
Female	7 (28%)	10 (40%)	17 (34%)	—
BMI (kg/m²)	27.9 ± 3.6	25.4 ± 3.2	26.6 ± 3.6	0.01*

*Statistically significant (p < 0.05)

Table 1 presents the demographic profile of the study population. The mean age of patients in the recurrent group was significantly higher than that of the non-recurrent group (46.8 ± 9.4 vs 38.6 ± 8.7 years, p = 0.004), indicating an association between increasing age and recurrence of renal calculi.

Male predominance was observed in both groups, accounting for 72% of recurrent cases and 60% of non-recurrent cases; however, this difference was not statistically significant (p = 0.37).

The mean BMI was significantly higher among recurrent stone formers (27.9 ± 3.6 kg/m²) compared to non-recurrent patients (25.4 ± 3.2 kg/m²), with a statistically significant difference (p = 0.01). This suggests that higher BMI may be associated with an increased risk of recurrence.

TABLE 2: Clinical Characteristics of Study Participants

Variable	Recurrent (n=25)	Non-Recurrent (n=25)	Total (n=50)	p-value
Flank pain	22 (88%)	23 (92%)	45 (90%)	0.64
Hematuria	11 (44%)	8 (32%)	19 (38%)	0.37
Burning micturition	9 (36%)	6 (24%)	15 (30%)	0.35
Nausea/Vomiting	14 (56%)	12 (48%)	26 (52%)	0.57
Duration of symptoms (days)	7.8 ± 3.6	5.1 ± 2.9	6.4 ± 3.5	0.01*
Diabetes Mellitus (DM)	10 (40%)	5 (20%)	15 (30%)	0.12
Hypertension (HTN)	9 (36%)	6 (24%)	15 (30%)	0.35
Gout	5 (20%)	1 (4%)	6 (12%)	0.08
Low fluid intake (<2 L/day)	18 (72%)	11 (44%)	29 (58%)	0.04*

*Statistically significant ($p < 0.05$)

Table 2 summarizes the clinical presentation and associated comorbidities of the study population. Flank pain was the most common presenting symptom in both groups (90% overall), with no significant difference between recurrent and non-recurrent patients ($p = 0.64$). Other symptoms such as hematuria, burning micturition, and nausea/vomiting were comparable between the two groups and did not show statistical significance.

The mean duration of symptoms was significantly longer in the recurrent group (7.8 ± 3.6 days) compared to the non-recurrent group (5.1 ± 2.9 days), indicating delayed presentation or greater stone burden among recurrent patients ($p = 0.01$).

Comorbidities such as diabetes mellitus, hypertension, and gout were more frequent in recurrent stone formers, although these differences were not statistically significant. Importantly, low fluid intake (<2 L/day) was significantly associated with recurrence (72% vs 44%, $p = 0.04$), highlighting the role of inadequate hydration in stone recurrence.

TABLE 3: Stone History and Prior Interventions Among Study Participants

Variable	Recurrent Group (n=25)	Non-Recurrent Group (n=25)	Total (n=50)	p-value
First Episode	—	25 (100%)	25 (50%)	—
Recurrent Episode	25 (100%)	—	25 (50%)	—
History of ESWL	11 (44%)	0 (0%)	11 (22%)	<0.001*
History of URS	8 (32%)	0 (0%)	8 (16%)	<0.001*
History of PCNL	5 (20%)	0 (0%)	5 (10%)	0.02*
History of Open Surgery	1 (4%)	0 (0%)	1 (2%)	0.31
Mean Stone-Free Interval (months)	18.4 ± 7.6	—	—	—
<12 months recurrence	6 (24%)	—	—	—
12–24 months recurrence	13 (52%)	—	—	—
>24 months recurrence	6 (24%)	—	—	—

*Statistically significant ($p < 0.05$)

Table 3 outlines the stone history and prior treatment details of the study population. Half of the patients (50%) presented with a first episode of renal calculi, while the remaining 50% had recurrent disease. As expected, all patients in the recurrent group had a prior history of stone episodes.

Among recurrent patients, previous interventions were common. A history of ESWL was noted in 44%, URS in 32%, and PCNL in 20% of cases, all of which showed statistically significant associations with recurrence. Only one patient (4%) had undergone prior open surgery, which was not statistically significant.

The mean stone-free interval before recurrence was 18.4 ± 7.6 months. Most recurrences (52%) occurred within 12–24 months, while 24% occurred within the first year and 24% after two years. These findings indicate that recurrence commonly occurs within two years of prior stone clearance, particularly in patients requiring previous endourological interventions.

TABLE 4: Imaging Characteristics of Study Participants

Variable	Recurrent (n=25)	Non-Recurrent (n=25)	Total (n=50)	p-value
Mean Stone Size (mm)	12.8 ± 4.6	8.4 ± 3.2	10.6 ± 4.6	<0.001*
Stone Size Category				
<10 mm	6 (24%)	17 (68%)	23 (46%)	0.002*
10–20 mm	15 (60%)	7 (28%)	22 (44%)	—
>20 mm	4 (16%)	1 (4%)	5 (10%)	—
Stone Number				
Single	9 (36%)	18 (72%)	27 (54%)	0.01*
Multiple	16 (64%)	7 (28%)	23 (46%)	—
Stone Site				
Kidney (renal pelvis/calyx)	18 (72%)	14 (56%)	32 (64%)	0.23
Upper ureter	4 (16%)	6 (24%)	10 (20%)	—
Lower ureter	3 (12%)	5 (20%)	8 (16%)	—
Laterality				
Right	11 (44%)	10 (40%)	21 (42%)	0.78
Left	9 (36%)	11 (44%)	20 (40%)	—
Bilateral	5 (20%)	4 (16%)	9 (18%)	—
Hydronephrosis				
Present	17 (68%)	9 (36%)	26 (52%)	0.02*
Absent	8 (32%)	16 (64%)	24 (48%)	—

Table 4 presents the radiological profile of the study population. The mean stone size was significantly larger in the recurrent group compared to the non-recurrent group (12.8 ± 4.6 mm vs 8.4 ± 3.2 mm, $p < 0.001$). Stones measuring ≥10 mm were more common among recurrent patients, and this difference was statistically significant ($p = 0.002$), indicating greater stone burden in recurrence.

Multiple stones were significantly more frequent in the recurrent group (64%) compared to non-recurrent patients (28%) ($p = 0.01$), whereas single stones were more common in first-episode cases.

Renal (pelvicalyceal) location was the most common site in both groups, with no statistically significant difference in stone site distribution ($p = 0.23$). Laterality was comparable between groups, with similar proportions of right, left, and bilateral stones ($p = 0.78$).

Hydronephrosis was significantly more common in recurrent patients (68% vs 36%, $p = 0.02$), suggesting greater obstruction and disease severity in those with recurrence.

TABLE 5: Laboratory Parameters of Study Participants

Parameter	Recurrent (n=25)	Non-Recurrent (n=25)	Total (n=50)	p-value
Serum Uric Acid (mg/dL)	7.6 ± 1.2	5.8 ± 1.1	6.7 ± 1.5	<0.001*
Hyperuricemia (>7 mg/dL males, >6 mg/dL females)	16 (64%)	7 (28%)	23 (46%)	0.01*
Serum Calcium – Total (mg/dL)	9.8 ± 0.6	9.2 ± 0.5	9.5 ± 0.6	0.002*
High-Normal / Elevated Calcium (>10.2 mg/dL)	5 (20%)	1 (4%)	6 (12%)	0.08
Serum Creatinine (mg/dL)	1.18 ± 0.22	1.02 ± 0.19	1.10 ± 0.22	0.01*
Urine pH	5.4 ± 0.6	6.1 ± 0.5	5.8 ± 0.6	<0.001*
Urine pH <5.5	14 (56%)	5 (20%)	19 (38%)	0.007*

Table 5 compares the laboratory parameters between recurrent and non-recurrent stone formers. The mean serum uric acid level was significantly higher in the recurrent group (7.6 ± 1.2 mg/dL) compared to the non-recurrent group (5.8 ± 1.1 mg/dL), with a highly significant difference ($p < 0.001$). Hyperuricemia was also significantly more prevalent among recurrent patients (64% vs 28%, $p = 0.01$), indicating a strong association between elevated uric acid levels and recurrence. Mean serum calcium levels were significantly higher in recurrent stone formers (9.8 ± 0.6 mg/dL vs 9.2 ± 0.5 mg/dL, $p = 0.002$). Although high-normal or elevated calcium levels (>10.2 mg/dL) were more common in the recurrent group, this difference did not reach statistical significance ($p = 0.08$).

Serum creatinine was modestly but significantly higher in recurrent patients (1.18 ± 0.22 mg/dL vs 1.02 ± 0.19 mg/dL, p = 0.01), possibly reflecting repeated obstruction or renal stress.

Urine pH was significantly lower in the recurrent group (5.4 ± 0.6 vs 6.1 ± 0.5, p < 0.001). Acidic urine (pH <5.5) was significantly more common among recurrent patients (56% vs 20%, p = 0.007), underscoring the role of urinary acidity in stone recurrence.

TABLE 6: Pearson Correlation Matrix Among Biochemical and Imaging Variables (n = 50)

Variable	Serum Uric Acid	Serum Calcium	Stone Size	Urine pH
Serum Uric Acid	1	0.32*	0.58**	-0.61**
Serum Calcium	0.32*	1	0.41**	-0.28*
Stone Size (mm)	0.58**	0.41**	1	-0.46**
Urine pH	-0.61**	-0.28*	-0.46**	1

*Correlation significant at p < 0.05
**Correlation significant at p < 0.01

Table 6 shows the Pearson correlation analysis between serum uric acid, serum calcium, stone size, and urine pH. Serum uric acid demonstrated a moderate positive correlation with stone size (r = 0.58, p < 0.01), indicating that higher uric acid levels were associated with increased stone burden. It also showed a significant negative correlation with urine pH (r = -0.61, p < 0.01), suggesting that elevated uric acid levels are linked to more acidic urinary environments.

Serum calcium showed a mild positive correlation with serum uric acid (r = 0.32, p < 0.05) and a moderate positive correlation with stone size (r = 0.41, p < 0.01), indicating that higher calcium levels may contribute to larger stones. A weak but significant negative correlation was observed between serum calcium and urine pH (r = -0.28, p < 0.05).

Stone size was moderately negatively correlated with urine pH (r = -0.46, p < 0.01), suggesting that lower urinary pH is associated with increased stone size. Overall, these findings reinforce the metabolic relationship between elevated serum uric acid, higher serum calcium, acidic urine, and greater stone burden.

DISCUSSION

The present study evaluated the association between serum uric acid, serum calcium, and recurrence of renal calculi, demonstrating significant metabolic and radiological differences between recurrent and non-recurrent stone formers. Recurrent patients were older, had higher BMI, larger and multiple stones, lower urine pH, and significantly elevated serum uric acid and serum calcium levels. Correlation analysis revealed a moderate positive association between serum uric acid and stone size (r = 0.58) and a significant inverse relationship between urine pH and both uric acid and stone size, supporting the metabolic basis of recurrence.

Recurrent patients were significantly older than non-recurrent individuals (46.8 ± 9.4 vs 38.6 ± 8.7 years, p < 0.01). Age-related recurrence has been widely reported, likely due to cumulative metabolic exposure and progressive renal changes [15]. Scales et al. and Yasui et al. similarly observed increasing recurrence after the fourth decade of life [16]. Male predominance (66%) in our study aligns with established epidemiological data [17]. Higher BMI among recurrent patients (27.9 ± 3.6 kg/m²) further supports the association between obesity and nephrolithiasis, as demonstrated by Taylor et al., who showed increased recurrence risk with rising BMI [18].

Low fluid intake was significantly associated with recurrence, consistent with Borghi et al., who demonstrated that increased hydration reduces recurrence risk [19]. Diabetes and gout were more frequent in recurrent patients, and insulin resistance–associated acidic urine likely contributes to uric acid crystallization [20].

A major finding of this study was significantly elevated serum uric acid in recurrent stone formers (7.6 ± 1.2 mg/dL vs 5.8 ± 1.1 mg/dL, p < 0.001). Hyperuricemia has been shown to promote calcium oxalate nucleation and increase recurrence risk [21]. Population-based studies further confirm the independent association between hyperuricemia and stone disease [22]. The observed positive correlation between serum uric acid and stone size strengthens its potential role as a recurrence predictor. The strong inverse correlation between uric acid and urine pH highlights the importance of urinary acidity in lithogenesis [21,22].

Serum calcium levels were also significantly higher among recurrent patients (9.8 ± 0.6 mg/dL vs 9.2 ± 0.5 mg/dL, p < 0.01). Hypercalciuria remains the most common metabolic abnormality in recurrent calcium stones [23], and untreated primary hyperparathyroidism significantly increases recurrence risk [24]. Even high-normal serum calcium may reflect

subclinical metabolic disturbances contributing to recurrence. The positive correlation between serum calcium and stone size further supports this relationship.

Lower urine pH in recurrent patients (5.4 ± 0.6 vs 6.1 ± 0.5, $p < 0.001$) is consistent with prior reports identifying acidic urine as a major determinant of uric acid and mixed stone formation [25]. Larger and multiple stones in recurrent patients suggest persistent metabolic abnormalities, as noted by Parks et al., who reported higher recurrence when underlying risk factors are not corrected [26].

Strengths and Limitations

The present study has several strengths. It provides a combined evaluation of biochemical and imaging parameters, allowing a comprehensive assessment of the relationship between systemic metabolic abnormalities and stone burden. The use of correlation analysis to demonstrate metabolic–radiologic associations strengthens the biological plausibility of the findings. Additionally, the study specifically focuses on recurrence rather than first-episode nephrolithiasis, thereby addressing a clinically important and relatively underexplored area.

However, certain limitations must be acknowledged. The sample size was relatively small (n = 50), which may limit generalizability. A 24-hour urine metabolic evaluation was not performed, restricting detailed assessment of urinary risk factors. The cross-sectional design precludes establishing causality. Furthermore, parathyroid hormone levels were not assessed, and therefore occult hyperparathyroidism could not be definitively excluded.

CONCLUSION

The present study demonstrates that recurrence of renal calculi is significantly associated with elevated serum uric acid, higher serum calcium levels, larger stone size, and lower urine pH. Serum uric acid showed a positive correlation with stone size and an inverse association with urine pH, suggesting its potential utility as a practical marker for recurrence risk assessment. Elevated or high-normal serum calcium may also contribute to recurrence risk. Routine evaluation of these biochemical parameters may help identify high-risk patients requiring closer follow-up and targeted preventive strategies. Larger longitudinal studies with comprehensive metabolic evaluation are needed to further validate these findings.

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