

Metabolic and Renal Profile Differences in Pure vs Mixed Uric Acid Kidney Stones: A Retrospective Study

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Objective: Uric acid stones are commonly classified into pure uric acid stones (PUCS) and mixed uric acid stones with calcium oxalate (MUCS). This study aims to investigate the metabolic differences between PUCS and MUCS patients, in order to inform prevention strategies and guide management and follow-up care for uric acid urolithiasis.

Methods: We conducted a retrospective analysis of 88 patients diagnosed with uric acid stones (PUCS: 37, MUCS: 51). Comprehensive data were collected, including blood tests and stone composition analysis.

Results: Both PUCS and MUCS patients exhibited obesity, but only PUCS patients showed significant lipid metabolism abnormalities, with HDL levels significantly lower than in MUCS patients ($p < 0.05$). Renal dysfunction was observed in both groups, but was more severe in the PUCS group, as indicated by higher serum creatinine levels ($p < 0.05$). Additionally, serum calcium levels were significantly higher in the MUCS group compared to the PUCS group ($p < 0.05$). No significant differences were found in 24-hour urinary excretion of uric acid, sodium, potassium, chloride, or phosphorus between the two groups.

Conclusion: Patients with PUCS exhibit more pronounced disturbances in lipid metabolism and renal function compared to those with MUCS. It is essential to prioritize and enhance the monitoring of metabolic assessments and renal function during the postoperative follow-up of patients with PUCS.

Keywords: pure uric acid stone, mixed uric acid stone, metabolic, urolithiasis, stratification evaluation

Introduction

Kidney stones represent a prevalent urological condition characterized by high recurrence rates and a steadily rising incidence over time. Among them, uric acid stones are closely associated with metabolic disturbances. The Uric acid stones account for 10%-15% of all urinary stones.¹ In epidemiological studies, uric acid stones are more common in men and in the elderly.² Pure uric acid stones (PUCS) account for 3% to 14% of all uric acid stone cases. Alterations in dietary practices or environmental conditions, or a combination thereof, may precipitate an escalation in the incidence of uric acid stones. The pathogenesis of uric acid stones is associated with reduced urine volume, hyperuricosuria, and consistently low urine pH levels.³ Epidemiological evidence from multiple studies indicates a strong association between type II diabetes, mellitus obesity, and metabolic syndrome with low urinary pH.⁴⁻⁷ Notably, when the pH falls below 5, conditions become conducive to the formation of uric acid crystals.⁸

In most instances, uric acid stones are found in combination with calcium oxalate stones, specifically the calcium oxalate monohydrate variety. Surprisingly, no comprehensive investigation has been undertaken to examine the metabolic distinctions between PUCS and mixed uric acid stone(MUCS). The current study was undertaken to bridge this



knowledge gap by establishing essential guidelines for preventing uric acid urolithiasis and providing precise management and follow-up protocols for patients with uric acid stones.

Materials and Methods

Selection of Patients

We retrospectively analyzed 88 patients who underwent surgical treatment at Beijing Tsinghua Changgung Hospital between May 1, 2016, and April 1, 2019, with postoperative stone composition analysis showing uric acid stones. Patient data, including clinical information, laboratory test results, and stone composition, were obtained from hospital records to ensure transparency in the selection and data collection process. All data were fully anonymized prior to analysis, and the authors did not have access to identifiers such as names, medical record numbers, or contact information at any stage of the study. Informed consent was waived under ethical approval for the use of anonymized retrospective data. The datasets used in this study were accessed for research purposes on 15/01/2025. This study was reviewed and approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (Approval No.24009-6-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Declaration of Helsinki.

Inclusion criteria: 1. Patients who were diagnosed with kidney stones, underwent surgical treatment, and the results of postoperative stone composition analysis were uric acid stones (pure or mixed uric acid stones); 2. Patients underwent 24-hour urine tests before surgery and blood tests. The exclusive criteria were as follows: 1) with diseases that are prone to recurrent stones, such as primary hyperparathyroidism, enterogenic hyperoxaluria, hereditary renal tubular acidosis, Cushing's syndrome, and sarcoidosis.; 2) Patients who have been taking vitamin D, acid-suppressing medications, hormones, and diuretics for the last 3 months.;3) lack of clinical information including age, gender, and BMI.

Data Collection

The urine test, conducted 24 hours before surgery, measured the concentrations of calcium, urate, phosphorus, potassium, sodium, chloride, and the total urine volume over 24 hours. For blood tests, the following parameters were assessed preoperatively: hematocrit, creatinine, estimated glomerular filtration rate (eGFR), uric acid, phosphorus ions, magnesium ions, calcium ions, vitamin D, parathyroid hormone, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Additionally, the diagnostic criteria for Hyperuricemia (HUA) were defined as blood uric acid levels $>420 \mu\text{mol/L}$ (7 mg/dL) in men and $>357 \mu\text{mol/L}$ (6 mg/dL) in women. Hyperuricosuria (HUU) was defined as urinary excretion of more than 4 mmol/day of uric acid in adults, or $>0.12 \text{ mmol/kg/day}$ in children.

Statistical Analysis

The patients were divided into two groups: the PUCS group (Pure Uric Acid Stones), which included stones composed of 100% uric acid, and the MUCS group (Mixed Uric Acid Stones), which included stones with mixed uric acid components. Measurements will be expressed using the mean (standard error [SE]). To assess differences between groups of data Student's *t*-test was used. Categorical variables were expressed as percentages and the chi-square test was used to assess differences between groups. IBM SPSS Statistics 21 statistical software was used for the analysis, and the difference was considered statistically significant with a *p*-value <0.05 .

Results

A total of 88 cases of uric acid stones were included in the study. Among them, 37 patients had pure uric acid stones (31 males and 6 females), and 51 patients had mixed stones composed of uric acid and calcium oxalate monohydrate (38 males and 13 females). There was no statistically significant difference in gender distribution between the two groups ($\chi^2 = 1.089$, $p = 0.296 > 0.05$).

The mean BMI in both the PUCS and MUCS groups exceeded 24 kg/m^2 , indicating that patients in both groups were generally overweight. No statistically significant difference in serum uric acid (HUA) levels was observed between the groups ($p > 0.05$). However, lipid metabolism abnormalities were present only in the PUCS group, where HDL levels were below 1 mmol/L. In contrast, the MUCS group did not exhibit such abnormalities. The difference in HDL levels

Table 1 Serum Metabolism in Groups PUCS and MUCS

	PUCS (n=37)	MUCS (n=51)	P value
Gender, n(%)			0.30
Male	31(83.8)	38(74.5)	
Female	6(16.2)	13(25.5)	
Age, years	55.7±13.8	55.0±11.9	0.74
BMI	26.7±4.0	26.5±4.2	0.75
Hyperuricemia, n(%)			0.37
+	15(40.5)	16(31.4)	
-	22(59.5)	35(68.6)	
Serum creatinine, μmol/L	153.6±91.0	106.3±55.0	<0.01
Serum uric acid, mmol/L	406.6±121.0	386.1±99.6	0.44
eGFR, mL/min	59.0±36.1	75.8±27.5	0.01
HCT, %	35.0±5.9	37.1±5.0	0.07
Serum phosphorus, mmol/L	1.2±0.3	1.2±0.2	0.43
Serum Magnesium, mmol/L	0.8±0.2	0.8±0.1	0.18
Serum calcium, mmol/L	2.1±0.1	2.2±0.1	0.04
Serum Vitamin D, ng/mL	13.1±5.9	19.7±11.0	0.25
Serum PTH, pg/mL	28.5±13.7	45.0±16.3	0.09
Serum HDL, mmol/L	0.8±0.2	1.0±0.2	<0.001
Serum LDL, mmol/L	2.6±1.0	2.7±1.2	0.68

between the two groups was statistically significant ($p < 0.05$). The serum creatinine level was higher in the PUCS group ($p < 0.05$). In addition, the levels of active vitamin D3 and parathyroid hormone were higher in the MUCS group than in the PUCS group, but the difference was not statistically significant; however, the blood calcium level was higher in the MUCS group than in the PUCS group ($p < 0.05$). (Table 1 and Figure 1).

The average 24-hour urine volume of patients in both the PUCS and MUCS groups was less than 2000 mL. The difference in 24-hour urinary calcium, phosphorus, potassium, sodium, chloride, and uric acid concentrations and 24-hour excretion between the two groups was not statistically significant ($p > 0.05$), refer to Table 2.

We found that only 40.5% of the patients in the PUCS group had HUA, which was higher than the 31.4% in the MUCS group, indicating that blood uric acid was not always elevated in patients with stones of uric acid. However, the difference between the two groups was not statistically significant by the chi-square test (Table 1). In the PUCS group, 16.2% of the patients with HUA were found to have elevated blood uric acid levels, compared to 11.8% of the patients with HUA in the MUCS group. Again, it can be seen that the proportion of HUU in the PUCS group was higher than that in the MUCS group, but the difference was still not statistically significant. These findings suggest that only a subset of uric acid stone patients exhibit hyperuricemia or hyperuricosuria (HUA: 35.2%; HUU: 13.6%), with hyperuricemia being more commonly observed than hyperuricosuria.

Discussion

With changes in people's lifestyles and dietary patterns, the prevalence of hyperuricemia has been steadily increasing, now ranking as the fourth most common condition after hypertension, diabetes, and hyperlipidemia, affecting approximately 10% of the total population. Notably, there is a trend of this condition affecting younger individuals.⁹ This study revealed that 35.2% of patients with uric acid stones had concurrent hyperuricemia (HUA).

Pure uric acid stones account for less than half of all uric acid stone cases (42% in the PUCS group), with the remainder consisting of mixed stones. Among these, the calcium oxalate stones are predominantly in the form of monohydrate calcium oxalate stones. Interestingly, our study found that all cases involved a combination of uric acid stones with monohydrate calcium oxalate stones (58% in the MUCS group). Uric acid crystals and calcium oxalate monohydrate (COM) crystals often serve as heterogeneous nucleation sites for one another, facilitating mutual

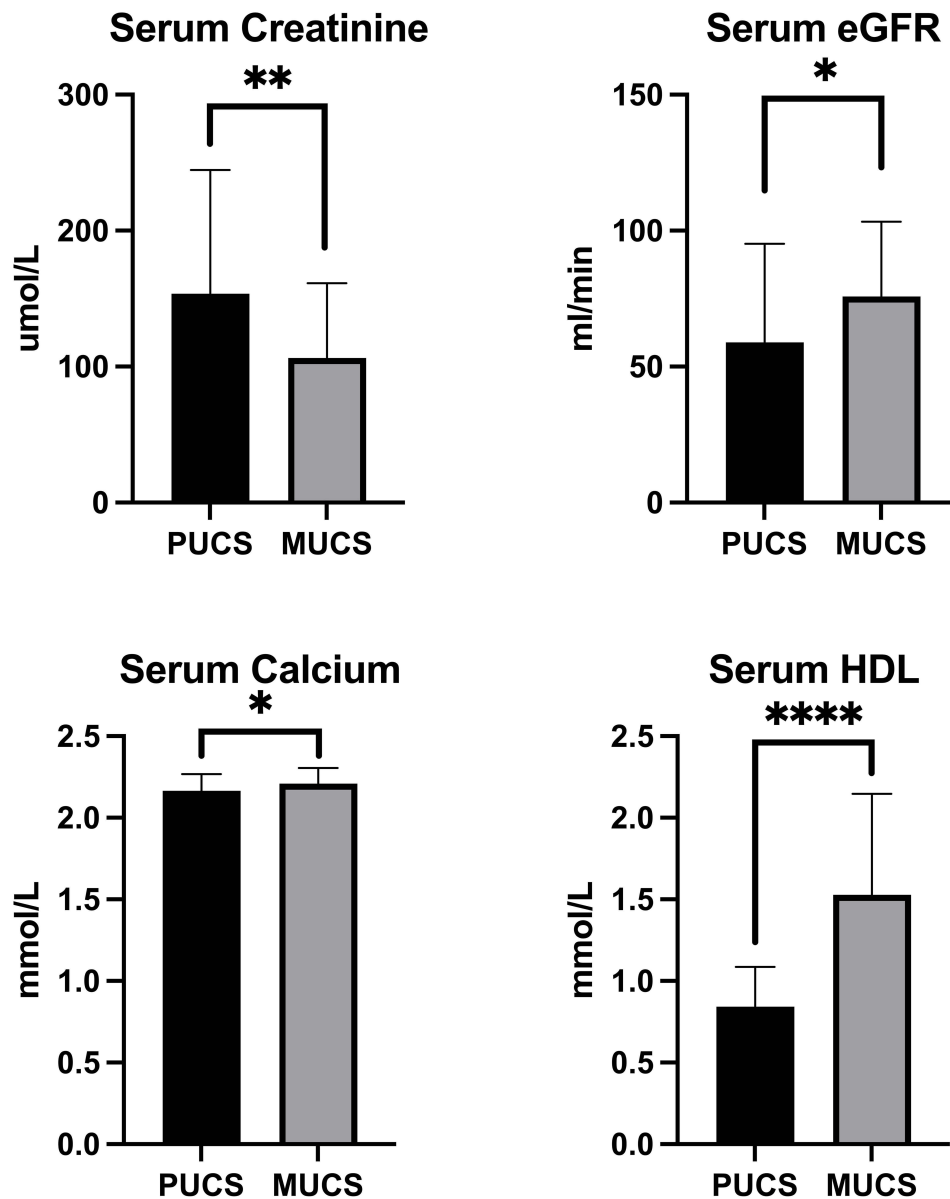


Figure 1 Serum metabolism in groups PUCS and MUCS.

Notes: * $P < 0.05$; ** $P < 0.01$, **** $P < 0.001$.

crystallization during kidney stone formation.^{3,10} In hyperuricosuric patients, uric acid crystals tend to become the core for the deposition of monohydrate calcium oxalate crystals.

Previous research indicates that HUA contributes to the formation of calcium oxalate kidney stones through three mechanisms: heterogeneous nucleation and epitaxy mechanisms, as well as the later discovered mechanism of HUA leading to a decrease in the activity of acid mucopolysaccharides (AMPS), which are substances that inhibit stone formation.¹¹⁻¹³ The concept of heterogenous nucleation contrasts with homogenous nucleation, where amorphous polymers form crystal nuclei due to temperature changes. Heterogeneous nucleation, on the other hand, involves amorphous polymers being adsorbed onto the surface of solid impurities or solvents to form crystal nuclei.¹⁴ In 1960s, research found that adding a small amount of sodium urate crystals to a relatively unsaturated calcium oxalate solution could induce the formation of monohydrate calcium oxalate crystals.^{15,16} Subsequent studies revealed that the lattice structure of monohydrate calcium oxalate crystals is very similar to that of uric acid crystals, allowing these two structurally similar crystals to undergo epitaxy, where one crystal deposits on the surface of the other.¹⁵⁻¹⁸

Table 2 Urine Metabolism in Groups PUCS and MUCS

	PUCS (n=37)	MUCS (n=51)	P value
Hyperuricosuria, n(%)			0.55
+	6(16.2)	6(11.8)	
-	31(83.8)	45(88.2)	
24 hour urine volume, mL	1898.3±667.4	1926.3±743.9	0.87
Urine uric acid, umol/L	3.0±1.2	3.0±0.8	0.88
24 hour urine uric acid, mmol/d	1694.1±736.2	1774.5±853.4	0.68
Urine calcium, mmol/L	1.5±1.5	1.8±1.1	0.30
24 hour urine calcium, mmol/d	2.3±1.9	3.1±1.0	0.09
Urine Sodium, mmol/L	89.1±36.3	96.4±41.8	0.45
24 hour urine Sodium, mmol/d	158.7±64.4	175.9±92.4	0.39
Urine Potassium, mmol/L	18.8±6.9	18.5±8.7	0.90
24 hour urine Potassium, mmol/d	33.4±12.5	31.3±11.8	0.48
Urine phosphorus, mmol/L	10.5±5.7	10.6±5.2	0.97
24 hour urine phosphorus, g/d	18.4±8.2	18.2±7.8	0.94
Urine Chlorine, mmol/L	70.8±26.9	75.0±34.8	0.60
24 hour urine Chlorine, mmol/d	124.7±49.9	132.9±63.8	0.57

However, there are significant differences between hyperuricosuric calcium oxalate stones and uric acid stones, mainly reflected in variations in urinary pH. Uric acid stones are more likely to form when the urinary pH is less than 5.5, whereas the formation of hyperuricosuric calcium oxalate stones requires a pH value higher than 5.5. Additionally, uric acid stones do not necessarily involve hyperuricosuria.^{19,20} Our study found that based on the EAU criteria for hyperuricosuria, only 13.6% of Chinese patients with uric acid stone had concurrent HUU. Although the observed proportions of HUA and HUU were slightly higher in the PUCS group compared to the MUCS group, these differences did not reach statistical significance. This may in part be attributed to the limited sample size and variability within the population. Given that HUA and HUU are important metabolic risk factors associated with uric acid stone formation, more detailed stratified analyses—such as subgrouping patients by severity or combining metabolic parameters—may help to uncover more subtle associations. Future studies employing larger cohorts and refined metabolic classification are warranted to better elucidate the complex relationships between serum and urinary uric acid parameters and stone composition.

For patients with uric acid stones, it is imperative to correct the underlying pathophysiological defects through pharmacotherapy and diet adjustments to prevent the recurrence of urinary tract stones.³ This warrants particular attention in patients with PUCS, where metabolic abnormalities are more pronounced. In managing the high recurrence rate of uric acid stones, the primary preventive strategies include general measures such as increasing water intake and adopting a low-purine diet. For patients with uric acid stones and hyperuricosuria, a low purine diet is particularly crucial. However, in specific clinical scenarios, patients may need interventions with medications such as allopurinol or febuxostat.^{3,8,9,19–22}

In the realm of uric acid stone research, prior studies have illuminated certain disparities in urine metabolic profiles before and after stone removal, particularly concerning variations in urine calcium and phosphate levels. However, these observations have predominantly centered on the post-removal state.²³ Our study has specifically focused on the 24-hour urine metabolic status prior to stone removal, recognizing the importance of future research endeavors that increase sample sizes or adopt prospective designs to encompass post-removal evaluations. This approach will enable a more comprehensive validation of our findings, providing a holistic understanding of the metabolic changes associated with uric acid stones.

Furthermore, previous research on various types of uric acid stones has been relatively limited in its scope of blood metabolic analysis, primarily focusing on serum uric acid and serum creatinine levels.^{24,25} Building upon this foundation, our study incorporated a broader blood metabolic profile, including serum lipid levels, eGFR, calcium, and phosphorus.

We identified significant differences in serum uric acid, eGFR, calcium, and HDL levels between PUCS and MUCS patients. In contrast, the 24-hour urine metabolic results were largely comparable between the two groups, with no statistically significant differences in urinary excretion of uric acid, calcium, sodium, potassium, chloride, or phosphorus. These findings are generally consistent with those of previous studies. Although these urinary parameters are commonly implicated in stone pathogenesis, these findings suggest that such parameters may not sufficiently account for the compositional divergence between pure and mixed uric acid stones. However, this does not preclude their role in overall stone pathophysiology. Additionally, our results differ from prior studies that reported lower urine volume and urinary calcium in PUCS patients, which may reflect differences in sample size or study design.^{24,25} Notably, the consistently low 24-hour urine volume (less than 2000 mL) observed in both groups underscores insufficient fluid intake as a shared and modifiable risk factor. These findings highlight the clinical importance of maintaining adequate hydration, while also supporting the need for individualized metabolic evaluation and management. Further studies with larger sample sizes and refined metabolic stratification are warranted to clarify the relative contributions of systemic and urinary factors to uric acid stone composition and recurrence.

This study provides a comprehensive analysis of blood metabolic differences between the two types of uric acid stones, while also integrating urinary metabolic assessments, thereby contributing to a better understanding of the metabolic underpinnings of uric acid urolithiasis. Patients with uric acid stones often exhibit metabolic abnormalities such as obesity and lipid metabolism disorders, confirming that these stones are associated with systemic metabolic disturbances. Moreover, patients with PUCS demonstrated more pronounced renal impairment compared to those with MUCS. Both hyperuricemia and hyperuricosuria were associated with reduced renal function, suggesting that kidney dysfunction may, in some cases, precede the clinical detection of hyperuricemia or hyperuricosuria. Although serum calcium levels were higher in the MUCS group, which may have contributed to the pathogenesis of uric acid mixed with calcium oxalate stones, the differences in active vitamin D3 and parathyroid hormone levels between the two groups were not statistically significant. These observed differences in renal function, serum calcium, and lipid metabolism may carry implications for stratifying metabolic risk in patients with uric acid stones. While such associations do not imply direct causality, they suggest that distinct metabolic profiles may underlie different stone compositions. For example, the presence of lipid metabolism abnormalities and relatively impaired renal function in the PUCS group may reflect a higher metabolic burden, warranting more intensive clinical monitoring and potential pharmacological interventions to manage lipid profiles and prevent further renal damage. Specifically, lifestyle interventions such as adopting a low-purine diet and using urate-lowering medications may be beneficial for these patients. In contrast, elevated serum calcium levels in the MUCS group may indicate a different underlying metabolic disturbance, and calcium-related metabolic factors might need to be taken into account in their clinical evaluation. Recognizing these differential patterns could help guide individualized risk stratification, dietary recommendations, and follow-up strategies, although further prospective studies are needed to validate these findings.

This study has several limitations that should be considered in future research. First, the exact composition percentages of mixed uric acid stones were not detailed, and variations in these ratios could influence metabolic findings differently. Future research could attempt to precisely quantify the proportions of different components to obtain more accurate results. Additionally, while the potential impact of stone obstruction on renal function was acknowledged, the chosen preoperative blood tests were used to assess renal function due to the possible influence of stone removal surgery, particularly for more complex stones. This study did not assess familial relationships or environmental factors, which could potentially influence metabolic findings and stone formation. Future studies should incorporate these factors to gain a more comprehensive understanding of their impact on uric acid stone formation. Furthermore, variability in the findings, particularly in serum creatinine and uric acid levels, may reflect several factors, such as comorbid conditions (eg, hypertension, diabetes, and hyperlipidemia) that are prevalent in patients with both PUCS and MUCS. These conditions could contribute to metabolic variability between the two groups. Additionally, measurement errors related to sample collection, timing, and assay variability may have influenced some of the observed variability. A comparison of urine pH values between pure and mixed stones, which was not included in this study, could provide valuable insights into stone formation. Finally, The small sample size and retrospective design limit both the statistical power and generalizability of the findings, underscoring the need for future studies with larger, prospective cohorts to clarify the

relative contributions of various factors to uric acid stone formation and recurrence. These studies will help validate the results and further explore the underlying mechanisms.

Conclusions

In conclusion, patients with Pure Uric Acid Stone (PUCS) exhibit markedly more pronounced disturbances in lipid metabolism and heightened renal impairment compared to those with Mixed Uric Acid Stone (MUCS). Enhanced and prioritized monitoring of metabolic profiles and renal function is essential during postoperative follow-up in the PUCS cohort. These findings provide useful contributions to clinical guidelines on stone prevention. However, the sample size of this study is limited. Future validation of the results and conclusions presented herein requires larger cohort studies.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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