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Metabolic abnormalities and recurrence in high-risk urinary stone formers: A prospective cohort study

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Introduction High-risk urinary stone formers are advised to undergo comprehensive metabolic assessment and targeted prophylaxis; however, recurrence outcomes under guideline-based prevention programs remain uncertain.

Material and methods We conducted a prospective, single-center observational cohort study including adult high-risk stone formers rendered stone-free after surgical/endourological treatment. All patients underwent standardized blood tests, 24-hour urine evaluation, and stone composition analysis. Patients with at least one metabolic abnormality received risk factor-specific therapy, whereas those without abnormalities received non-specific measures and lifestyle counseling. Recurrence was defined as a newly detected stone ≥3 mm on follow-up imaging.

Results Sixty-four patients were included (mean age 33.47 ±10.32 years; 60.9% male). At least one metabolic abnormality was identified in 42 patients (65.6%); hypocitraturia was the most frequent abnormality (53.1%). Metabolic syndrome was present in 16 patients (25.0%) and was more common among patients with metabolic abnormalities (33.3% vs 9.1%; p = 0.033). Over a mean follow-up of 24.5 months, recurrence occurred in 10 patients (15.6%). Recurrence rates were 16.7% (7/42) in the targeted-therapy group and 13.6% (3/22) in the non-specific group (p = 0.749), corresponding to a relative risk of 1.22 (95% confidence interval 0.35–4.27). Among patients who experienced recurrence (n = 10), the time to recurrence was 11.8 ±5.69 months (median 12.5 months; range 4–19 months).

Conclusions In this high-risk cohort, metabolic abnormalities were common, and metabolic syndrome clustered with metabolic risk factors. Between-group recurrence estimates were imprecise; larger studies with robust adjustment for baseline risk and adherence are needed. The observational, risk-stratified design precludes causal inference regarding the effectiveness of targeted medical metaphylaxis.

Key Words: urolithiasis ‹› metabolic risk factors ‹› secondary prevention ‹› 24-hour urine ‹› hypocitraturia

INTRODUCTION

Among urinary tract pathologies, stone disease represents the third most common clinical condition after infections and prostatic disorders [1]. In patients diagnosed with urolithiasis, a detailed medical history and thorough physical examination constitute the cornerstone of the initial evaluation [1]. In recent decades, a marked increase in the incidence of urinary stone disease has been reported, with prevalence rates ranging between 2% and 20% across different geographic regions [2–4]. This rising trend increases not only the procedural burden on healthcare systems but also the overall cost of treatment [3].

A major challenge in stone disease is the high rate of recurrence, even after stone-free status has been achieved with appropriate interventions [4].

Therefore, systematic assessment of metabolic risk factors and correction of identified abnormalities are clinically important [5-7]. Together with stone type determination, metabolic evaluation is a fundamental component of metaphylaxis [6–9].
European Association of Urology (EAU) guidelines recommend comprehensive metabolic evaluation in stone formers classified as high risk for recurrence, followed by preventive measures guided by stone composition and the urinary risk profile [9]. However, in routine practice, high-risk cohorts are heterogeneous and preventive regimens vary, which can make observed recurrence outcomes difficult to interpret.
In this prospective single-center cohort, high-risk stone formers underwent stone composition analysis and metabolic assessment. Patients with metabolic abnormalities received targeted pharmacologic therapy in addition to general preventive measures, whereas metabolically normal patients were managed with general measures alone. We aimed to report the prevalence and pattern of metabolic abnormalities and to explore recurrence rates and time to recurrence during follow-up, while acknowledging the observational design and limited statistical power for between-group comparisons.
Stone composition and baseline metabolic diagnoses have been associated with patterns of surgical recurrence in previous observational studies, highlighting the potential value of combining stone analysis with a structured metabolic assessment [10–12].

MATERIAL AND METHODS

Study design

This single-center, prospective, observational cohort.

Patient selection and definition of high-risk status

Beginning April 1, 2020, consecutive adult patients (≥18 years of age) with urinary stone disease who were classified as high risk for recurrence per EAU guidance were assessed [9]. Sixty-four patients met eligibility criteria and were included. High-risk status was assigned based on the presence of at least one EAU high-risk factor, including the following: early onset urolithiasis; familial stone disease; recurrent stone formation or short interval since the last stone episode; specific stone types (brushite-containing, uric acid/urate-containing, infection stones); solitary kidney and/or chronic kidney disease; diseases associated with stone formation (e.g., hyperparathyroidism, metabolic syndrome, nephrocalcinosis, gastrointestinal malabsorptive conditions); genetically determined stone disorders (e.g., cystinuria, primary hyperoxaluria, distal renal tubular acidosis); anatomical abnormalities of the kidney/urinary tract; and relevant environmental/professional exposures [9].
Inclusion criteria were as follows: age ≥18 years; stones confirmed by non-contrast computed tomography; fulfillment of high-risk criteria [6–9]; and achievement of complete stone-free status after intervention.
Exclusion criteria were as follows: age <18 years; malignancy; pregnancy/lactation; inability to perform stone analysis; residual fragments ≥3 mm on postoperative imaging; non-adherence or loss to follow-up.
Demographics (age, sex, and body mass index) and cardiometabolic comorbidities were recorded using a standardized case report form. Metabolic syndrome was defined using harmonized criteria: presence of at least three of the following: increased waist circumference, elevated fasting glucose or diabetes, elevated blood pressure or antihypertensive treatment, elevated triglycerides, and/or reduced high-density lipoprotein cholesterol, based on available clinical records [13].

Imaging, management, and confirmation of stone-free status

All patients underwent non-contrast computed tomography. Procedure selection (ureterorenoscopy, percutaneous nephrolithotomy, and selected cases of shock wave lithotripsy with endoscopic completion where appropriate) was based on stone size, location, and burden. Stone-free status was assessed at postoperative month 1 using ultrasonography and plain abdominal radiography (kidney-ureter-bladder). Patients with residual fragments ≥3 mm were classified as not completely stone free and were excluded.
Urinalysis and urine culture were obtained before metabolic evaluation. When infection was present, antibiotics were administered and metabolic work-up was deferred until resolution.

Metabolic evaluation and stone analysis

After confirmation of stone-free status and absence of active infection, patients underwent metabolic assessment comprising biochemical blood tests and a single 24-hour urine collection. Serum evaluation included creatinine, urea, uric acid, calcium, electrolytes, and parathyroid hormone as clinically indicated, along with a complete blood count.

The 24-hour urine analysis included volume and routine lithogenic parameters (e.g., calcium, oxalate, citrate, uric acid, magnesium, urea, phosphorus, cystine, and pH where available), supplemented by urinalysis and selected spot urine measurements. Patients were instructed to maintain their usual diet during collection. Metabolic abnormalities were defined using laboratory reference ranges and guideline-referenced thresholds (e.g., hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, hypomagnesuria, low urine volume, low urine pH). Stone composition was determined by X-ray diffraction from retrieved fragments. Definitions of urinary abnormalities were based on established thresholds [14–16].

Patients were categorized into the following groups:

1. **Metabolic risk factor group:** ≥1 metabolic abnormality; received specific medical therapy tailored to stone type/metabolic profile.
2. **No metabolic risk factor group:** no pathological metabolic findings; managed with non-specific measures only.

Therapeutic approach

Non-specific therapy (no metabolic risk factors): no pharmacological treatment. Lifestyle and preventive advice included fluid intake to achieve urine volume ≥2 l/day (distributed throughout the day and before bedtime), a balanced diet rich in fruits/vegetables/fiber, avoidance of excessive animal protein, normal dietary calcium intake, salt restriction, and weight reduction when indicated.

Specific therapy (metabolic risk factors): general recommendations plus targeted pharmacologic treatment selected according to the identified disturbance and stone type. Examples included pyridoxine for hyperoxaluria, potassium citrate for hypocitraturia and/or low urine pH, thiazide therapy when hypercalciuria was present, allopurinol for hyperuricosuria, magnesium supplementation for hypomagnesuria, tiopronin for cystinuria, and antibiotics when infection stones were suspected or documented. Regimens were individualized by the treating physician in line with contemporaneous guideline recommendations. Adherence was assessed at each follow-up visit using patient reports corroborated by prescription records.

Follow-up and definition of recurrence

Patients attended follow-up every 6 months. At each visit, urinalysis, relevant blood tests, plain abdominal radiography, and urinary ultrasonography were performed. Non-contrast computed tomography was used if symptoms or imaging suggested recurrence. Recurrence was defined as detection of a new stone ≥3 mm in diameter. Patients with marked non-adherence or missed follow-up were excluded. This ≥3 mm operational threshold was applied consistently (including exclusion of residual fragments ≥3 mm at postoperative month 1) and was chosen to reduce misclassification related to the sensitivity and measurement variability of US/KUB surveillance; sub-3 mm events may therefore be under-ascertained.

Statistical analysis

Normality was tested using the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation or median (minimum-maximum), as appropriate. Group comparisons used Student's t-test or the Mann-Whitney U test. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate. For recurrence comparisons, effect sizes are reported as relative risk (RR) with 95% confidence intervals. No *a priori* power analysis was performed; the sample size reflected eligible consecutive patients. Analyses were performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA). Two-sided $p < 0.05$ was considered statistically significant.

Bioethical standards

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Gaziantep University Clinical Research Ethics Committee (approval No. 2020/87; approval date: 26 February 2020). Written informed consent was obtained from all participants.

RESULTS

Sixty-four high-risk stone formers were included. Their mean age was 33.47 ±10.32 years and mean body mass index was 27.69 ±5.21 kg/m². Overall, 60.9% (n = 39) were male and 39.1% (n = 25) were female. Metabolic syndrome was present in 16 patients (25.0%). Mean follow-up was 24.5±8.6 months (Table 1).

Stone analysis showed calcium oxalate as the most common composition (n = 44; 68.8%). Metabolic evaluation identified ≥1 metabolic risk factor in 42 patients (65.6%); 22 patients (34.4%) had no abnormality. The most frequent abnormality was hypocitraturia (n = 34; 53.1%), followed by hyperoxaluria (n = 29; 45.3%), hypercalciuria (n = 25; 39.1%), low urine pH (n = 18; 28.2%), cystinuria

(n = 9; 14.1%), low urine volume (n = 9; 14.1%), hypomagnesuria (n = 7; 10.9%), hyperuricosuria (n = 2; 3.1%), and hyperphosphaturia (n = 2; 3.1%) (Table 2).

Metabolic syndrome was more common among patients with metabolic risk factors (14/42; 33.3%) than among those without (2/22; 9.1%) (p = 0.033; Table 2A). Overall, 87.5% (14/16) of patients with metabolic syndrome had at least one metabolic risk factor.

During follow-up, recurrence occurred in 10 patients (15.6%). Among patients who experienced recurrence (n = 10), the time to recurrence was 11.8 ±5.69 months (median 12.5 months; range 4–19 months). Recurrence rates were 16.7% (7/42) in the targeted-therapy group and 13.6% (3/22) in the general-measures group, without a statistically significant difference (p = 0.749; RR 1.22, 95% CI 0.35–4.27; Table 3). Mean time to recurrence was 11.71 ±5.59 months vs 12.0 ±7.21 months, respectively (p = 0.947). Recurrences clustered within the first 1–2 years; given the small number of events, between-group comparisons should be interpreted as exploratory.

DISCUSSION

In this prospective single-center cohort of high-risk stone formers, metabolic abnormalities were frequent (65.6%), with hypocitraturia being the most common (53.1%). During a mean follow-up of 24.5 months, overall recurrence was 15.6%. Recurrence outcomes were similar between groups defined by metabolic evaluation (those receiving targeted therapy for detected abnormalities vs those managed with general preventive measures only), although the study was underpowered for definitive comparisons.

A rising prevalence of stone disease has been described in various regions, with estimates between 2% and 20% [1–4]. In high-risk cohorts, recurrence has been reported in 15%–44%, often within the first 2 years [8, 17, 18]. Our recurrence rate and timing are consistent with this pattern and remain clinically relevant during early follow-up [6, 8, 17, 18].

Calcium oxalate predominated (68.8%), aligning with Li et al. (69.3%) [10] and with established epidemiologic data emphasizing calcium-containing stones [11].

In our cohort, metabolic syndrome was present in 25% of patients and was significantly associated with the presence of at least one metabolic risk factor. This supports careful assessment of cardiometabolic comorbidities when planning recurrence prevention in high-risk stone formers, alongside a structured metabolic work-up [12–16].

Hypocitraturia was the leading abnormality, consistent with reports in recurrent stone formers [14–16]. Given citrate's inhibitory role in crystallization

Table 1. *Baseline demographic characteristics of the patients*

Variable	n	Mean ±SD	%
Age [years]	64	33.47 ±10.32	–
BMI [kg/m²]	64	27.69 ±5.21	–
Sex: Male	39	–	60.9
Sex: Female	25	–	39.1
Presence of metabolic syndrome	16	–	25.0

BMI – body mass index; n – number of patients; SD – standard deviation

Table 2. *Relationship between metabolic risk factors and metabolic syndrome*

A. Association between the presence of metabolic risk factors and metabolic syndrome

	Metabolic risk factors present (n = 42)	Metabolic risk factors absent (n = 22)	p-value
Metabolic syndrome present	14 (33.3)	2 (9.1)	0.033*
Metabolic syndrome absent	28 (66.7)	20 (90.9)	–

B. Distribution of metabolic risk factor types

Metabolic risk factor	n (%)
Hypocitraturia	34 (53.1)
Hyperoxaluria	29 (45.3)
Hypercalciuria	25 (39.1)
Low urine pH	18 (28.2)
Cystinuria	9 (14.1)
Low urine volume	9 (14.1)
Hypomagnesuria	7 (10.9)
Hyperuricosuria	2 (3.1)
Hyperphosphaturia	2 (3.1)

*Statistically significant at p <0.05. χ^2 test was used.

Table 3. *Comparison of recurrence according to metabolic evaluation groups*

	All patients (n = 64)	Patients with metabolic risk factors receiving specific therapy (n = 42)	Patients without metabolic risk factors receiving non-specific therapy (n = 22)
Recurrence present	10 (15.6)	7 (16.7)	3 (13.6)
Recurrence absent	54 (84.4)	35 (83.3)	19 (86.4)

RR 1.22 (95% confidence interval 0.35–4.27). Statistical significance was set at p<0.05 (two-sided; χ^2 test).
CI – confidence interval; RR – relative risk

and aggregation, this high prevalence has practical implications for risk stratification and treatment planning. Furthermore, real-world data highlight heterogeneity in preventive counseling and treatment patterns [23].

Key limitations include the modest sample size and small number of recurrence events (n = 10), limiting statistical power and precluding robust time-to-event modeling. Given the small number of recurrence events (n = 10), formal time-to-event analyses (Kaplan–Meier/Cox) would have limited interpretability and potentially unstable estimates; therefore, we report recurrence timing descriptively and emphasize that all between-group comparisons are exploratory. The non-randomized design and group definition by metabolic status (rather than randomized treatment assignment) allow residual confounding and confounding by indication (e.g., differences in intrinsic recurrence risk, stone burden, procedure type, or comorbidities). Follow-up imaging relied on ultrasonography and radiography, with computed tomography used selectively, which may underestimate small or asymptomatic recurrences. The targeted-therapy group was heterogeneous across disturbances and medications, preventing assessment of individual agents. Adherence was assessed primarily by self-report and prescription records. Metabolic assessment relied on a single 24-hour urine collection despite known day-to-day variability and guideline recommendations for two collections in high-risk patients [9]. Larger multicenter studies, ideally randomized and incorporating time-to-event methods and standardized imaging, are needed to quantify the impact of individualized prophylaxis on recurrence. In addition, our operational recurrence definition required a newly detected stone ≥3 mm, which may further underestimate very small recurrences.

CONCLUSIONS

In high-risk stone formers followed for approximately 2 years, metabolic abnormalities were common – particularly hypocitraturia – supporting the clinical value of comprehensive metabolic evaluation. Metabolic syndrome was frequent and significantly associated with metabolic abnormalities, underscoring the importance of integrating systemic cardiometabolic assessment into prevention strategies. Recurrence occurred in 15.6% of patients and tended to arise within the first 1–2 years. Within the constraints of this underpowered, non-randomized cohort, recurrence rates were similar between groups defined by metabolic evaluation; these findings should be interpreted as exploratory and may inform the design of adequately powered studies evaluating targeted metaphylaxis.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The study was approved by the Gaziantep University Clinical Research Ethics Committee (approval No. 2020/87; approval date: 26 February 2020).

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