DISTINCT METABOLIC AND STONE COMPOSITION PATTERNS IN FIRST EPISODE AND RECURRENT UROLITHIASIS PATIENTS

M. Ivănuță[1,2,3], D. Puia[1,2,3*], Ana-Maria Ivănuță[4], C. Pricop[1,2,3]
1. Grigore T. Popa University of Medicine and Pharmacy Iasi
2. Dr. C. I. Parhon Clinical Hospital Iasi, Romania
3. Michel Daudon Center for Morphological and Spectroscopic Analysis of Urinary Stones
4. Sf. Spiridon County Clinical Emergency Hospital Iasi, Romania
[*]Corresponding author. E-mail: dragos-puia@umfiasi.ro

DISTINCT METABOLIC AND STONE COMPOSITION PATTERNS IN FIRST EPISODE AND RECURRENT UROLITHIASIS PATIENTS (Abstract): The objective of this study was to identify clinical, metabolic, and compositional factors associated with stone recurrence, using morpho-spectroscopic stone analysis combined with biochemical and dietary assessment. **Materials and methods:** We retrospectively analyzed 1,380 patients with urinary lithiasis evaluated at the Michel Daudon Morphological and Spectroscopic Analysis Center, Iași, Romania, between 2018 and 2022. Patients were divided into first-episode (n=842) and recurrent (n=538) groups. Demographic data, metabolic profile, dietary habits, and stone composition were assessed. Multivariable logistic regression was used to identify independent predictors of recurrence. **Results:** Recurrent patients accounted for 39.1% of the cohort and were significantly older. Calcium oxalate monohydrate and dihydrate stones predominated in first episodes, whereas uric acid, urate-mixed, and struvite calculi were more frequent in recurrent cases. Obesity, hyperuricemia, hypertension, type 2 diabetes, and chronic kidney disease were significantly more prevalent among recurrent stone formers. Dietary assessment showed that low fruit and vegetable intake and high sodium consumption were strongly associated with recurrence. Logistic regression identified hyperuricemia (OR=2.3), obesity (OR=1.9), hypertension (OR=1.5), and chronic kidney disease (OR=1.6) as independent predictors. **Conclusions**: Stone recurrence is characterized by a distinct clinical and metabolic profile, compositional shifts toward uric acid and struvite calculi, and unfavorable dietary habits. These findings confirm the systemic nature of lithiasis and support the integration of morpho-spectroscopic, metabolic, and nutritional evaluation into standard urological practice. **Keywords:** URINARY STONE DISEASE, RECURRENCE, MORPHO-SPECTROSCOPIC ANALYSIS, METABOLIC SYNDROME, URIC ACID, PREVENTION.

INTRODUCTION

Urinary stone disease represents a major and growing public health challenge worldwide. Its lifetime prevalence is estimated between 10-12% in Europe and North America, with increasing incidence also reported in developing countries (1). The disease is highly recurrent: more than 50% of patients are expected to develop a new episode within 10 years after the first event. Beyond the acute burden of renal colic and the need for surgical or endourological interventions, recurrence is associated with progressive renal impair-

ment, reduced quality of life, and considerable healthcare costs (1, 2).

The etiology of urinary stone disease is multifactorial. Established risk factors include metabolic abnormalities such as obesity, hypertension, diabetes mellitus, dyslipidemia, and hyperuricemia, which are frequently clustered in the metabolic syndrome (3, 4). Dietary habits strongly modulate lithogenic risk: high sodium intake and an elevated sodium-to-potassium ratio significantly increase stone risk, whereas diets rich in potassium, fruits, and vegetables are protective (5). High intake of animal protein and oxalate-rich foods contributes to uric acid and calcium oxalate stones, respectively (6, 7). Lifestyle patterns also play a role: sedentary behavior increases risk, while vigorous physical activity has been shown to mitigate it (1, 8).

Epidemiological data reveal changing demographic trends. Traditionally, stone disease was more common in men; however, recent reports suggest a narrowing gender gap, with increasing incidence among women and even among adolescents. Moreover, disparities have been reported across ethnic and socioeconomic groups, with disproportionate increases among Black and Hispanic populations in the United States and with variable access to metabolic evaluation and surgical care (4). Such observations underline the systemic and societal dimensions of stone disease beyond its local urological manifestations.

Pathophysiological mechanisms of stone formation are closely linked to morphological and compositional features. Randall's plaques, intratubular crystallization, and papillary erosions represent distinct initiating pathways, each associated with specific stone types. Comprehensive morpho-constitutional analysis, as proposed by Daudon and colleagues, combines macroscopic morphology with infrared spectroscopy to provide insights into the mechanisms of stone genesis and recurrence. Stone composition also predicts clinical behavior: calcium oxalate monohydrate and dihydrate stones are usually small and more likely to pass spontaneously, whereas struvite, brushite, and cystine stones tend to be larger and associated with higher recurrence rates. Furthermore, metabolic conditions influence stone type: uric acid stones are strongly associated with obesity, diabetes, and insulin resistance, while calcium phosphate and brushite stones are linked to hypercalciuria and hyperparathyroidism (1, 3, 9–11).

In Romania, recent studies have highlighted the interplay between stone composition, metabolic comorbidities, and dietary risk factors, with hypertension associated with calcium oxalate monohydrate, diabetes with uric acid stones, obesity with calcium oxalate dihydrate, and specific dietary habits predisposing to urate and oxalate lithiasis. Such findings support the need for an integrated clinical, metabolic, and morpho-spectroscopic approach in the evaluation of stone formers(11-14).

Despite these advances, few studies have directly compared the metabolic and morpho-spectroscopic profiles of patients at their first stone episode versus those with documented recurrence. Given the clinical and economic impact of recurrent stones, identifying compositional shifts and associated metabolic abnormalities is crucial for guiding preventive strategies.

The aim of our study was to compare the clinic-biological metabolic profile and morpho-spectroscopic characteristics of urinary stones between patients presenting with a first episode and those with recurrence. By integrating morphological classification, infrared spectroscopic analysis,

and metabolic assessment, we sought to elucidate the factors driving recurrence and to highlight potential targets for prevention.

MATERIALS AND METHODS

Study design and setting. We conducted a retrospective, observational study at the Urology Clinic of "Dr. C. I. Parhon" Clinical Hospital, Iași, Romania, in collaboration with the Michel Daudon Morphological and Spectroscopic Analysis Center. The study covered the period from January 2018 to June 2025. All patients underwent standard evaluation and treatment for urinary stone disease according to current urological guidelines.

Study population. During the study period, 1,520 patients diagnosed with urinary lithiasis were evaluated. For each patient, only a single stone specimen was analyzed, either collected spontaneously or retrieved during surgical/endourological procedures. After exclusion of incomplete or fragmented samples, a total of 1,380 stones were available for analysis. Patients were categorized into two groups.

Clinical and anthropometric evaluation. All patients underwent standardized clinical examination including measurement of body mass index (BMI), waist circumference, and blood pressure. Relevant comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, and chronic kidney disease (CKD) were recorded based on clinical history and laboratory data.

Stone analysis. Macroscopic morphological assessment of calculi was performed according to the Daudon classification, documenting external surface, section, and crystalline organization. Infrared spectroscopy (FTIR) was used for compositional analysis, enabling precise identification of crystalline phases (e.g., calcium oxalate monohydrate, calcium oxalate dihydrate, uric acid, urates, carbapatite, struvite, cystine, protein matrix). Each stone was assigned a morpho-constitutional type based on combined macroscopic and spectroscopic findings.

Dietary evaluation. Patients completed a standardized dietary questionnaire developed in our department, focusing on the frequency and quantity of consumption of salt, animal proteins, oxalate-rich foods, dairy products, alcohol, fruits, and vegetables. Reported intake patterns were categorized as favorable or unfavorable based on established nutritional recommendations for stone prevention.

Statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as absolute numbers and percentages. Comparisons between groups (first episode *vs.* recurrence) were performed using Student's t-test or Mann–Whitney U test for continuous variables and χ^2 or Fisher's exact test for categorical variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using *SPSS v. 26* (IBM Corp., Armonk, NY, USA).

All patients signed informed consent forms prior to participation. The study protocol was reviewed and approved by the Research Ethics Board of the "Dr. C. I. Parhon" Clinical Hospital, Iași, Romania (approval no. 18/08.03.2022).

RESULTS

A total of 1,380 patients were included in the analysis. Of these, 842 (60.9%) presented with a first episode of urolithiasis, while 538 (39.1%) had a history of recurrence.

The overall mean age was 52.8 ± 13.4 years (range 18-79), with a male-to-female ratio of 1.4: 1. Patients with recurrence were older on average than first-episode patients (55.1 ± 12.9 *vs.* 51.2 ± 13.7 years, p=0.01).

TABLE I.

Demographic characteristics of the study population

Variable	First episode (n=842)	Recurrence (n=538)	Total (n=1,380)
Age, years (mean ± SD)	51.2 ± 13.7	55.1 ± 12.9	52.8 ± 13.4
Age range (years)	18–77	20–79	18–79
Male sex, n (%)	498 (59.1%)	333 (61.9%)	831 (60.2%)
Female sex, n (%)	344 (40.9%)	205 (38.1%)	549 (39.8%)
Urban residence	505 (60.0%)	334 (62.1%)	839 (60.8%)
Rural residence	337 (40.0%)	204 (37.9%)	541 (39.2%)
County of residence			
Iași	547 (65.0%)	350 (65.1%)	897 (65.0%)
Suceava	84 (10.0%)	55 (10.2%)	139 (10.1%)
Botoșani	76 (9.0%)	46 (8.6%)	122 (8.8%)
Neamț	63 (7.5%)	39 (7.2%)	102 (7.4%)
Vaslui	46 (5.5%)	33 (6.1%)	79 (5.7%)
Other counties	26 (3.0%)	15 (2.8%)	41 (3.0%)

Table II summarizes the clinical and metabolic characteristics of the study population. Patients with recurrent stones were significantly older and had higher BMI compared to those with a first episode. The prevalence of abdominal obesity, hyper-uricemia, hypertriglyceridemia, hypertension, type 2 diabetes mellitus, and chronic kidney disease was markedly higher among recurrent stone formers, highlighting their more unfavorable metabolic profile.

TABLE II.

Clinical and metabolic characteristics of first-episode *vs.* recurrent patients

Parameter	First episode (n=842)	Recurrence (n=538)	p-value
Age, years (mean ± SD)	51.2 ± 13.7	55.1 ± 12.9	0.01
Male sex, n (%)	498 (59.1%)	333 (61.9%)	0.37
Female sex, n (%)	344 (40.9%)	205 (38.1%)	—
BMI, kg/m² (mean ± SD)	27.1 ± 3.9	29.3 ± 4.4	<0.001
Abdominal obesity, n (%)	176 (20.9%)	168 (31.2%)	0.003
Hyperuricemia, n (%)	159 (18.9%)	187 (34.8%)	<0.001
Hypertriglyceridemia, n (%)	126 (15.0%)	141 (26.2%)	0.002
Hypertension, n (%)	178 (21.1%)	174 (32.4%)	0.004
Type 2 diabetes, n (%)	83 (9.8%)	93 (17.3%)	0.01
CKD (eGFR <60), n (%)	27 (3.2%)	37 (6.9%)	0.03

Clinical and metabolic characteristics. Patients with recurrence displayed a more adverse metabolic profile. They had higher mean BMI and significantly higher prevalence of abdominal obesity, hyperuricemia, hypertriglyceridemia, hypertension, diabetes, and CKD compared to first-episode patients. Recurrent stone formers were older, more frequently obese, and exhibited a significantly higher burden of metabolic comorbidities than first-episode patients.

Stone composition

Calcium oxalate was the predominant stone type (59.8%), with whewellite (calcium oxalate monohydrate, COM) at 37.1% and weddellite (calcium oxalate dihydrate, COD) at 22.7%. Uric acid stones accounted for 13.9%, urate-predominant mixed forms for 13.5%, carbapatite for 8.4%, struvite for 4.1%, and rare forms (cystine/protein) for 0.3%.

Marked compositional differences were observed between groups. First-episode patients predominantly formed calcium oxalate stones (COM 43.0%, COD 24.7%), while recurrent patients more frequently had uric acid (20.4% *vs.* 9.7%, p<0.001) and urate-containing mixed calculi (17.7% *vs.* 10.8%, p=0.002). Struvite stones were also more common in recurrent cases (6.6% *vs.* 2.4%, p=0.01). Recurrent stone formers showed a significant compositional shift toward uric acid–containing, mixed, and infection-related stones compared to first-episode patients.

TABLE III.

Stone composition in first episode *vs.* recurrence

Stone type	Overall (n, %)	First episode (n=842)	Recurrence (n=538)	p-value
COM	512 (37.1%)	362 (43.0%)	150 (28.4%)	<0.001
COD	314 (22.7%)	208 (24.7%)	104 (19.3%)	0.04
Uric acid	192 (13.9%)	82 (9.7%)	110 (20.4%)	<0.001
Urates (mixed)	186 (13.5%)	91 (10.8%)	95 (17.7%)	0.002
Carbapatite	116 (8.4%)	76 (9.0%)	41 (7.6%)	0.47
Struvite	57 (4.1%)	20 (2.4%)	36 (6.6%)	0.01
Rare (Cys / protein)	4 (0.3%)	3 (0.4%)	1 (0.2%)	0.68
Total	**1,380 (100%)**	**842 (100%)**	**538 (100%)**	—

Multivariable logistic regression analysis (tab. IV) identified several independent predictors of stone recurrence. Increasing age was significantly associated with higher odds of recurrence, with an adjusted OR of 1.18 per decade (95% CI 1.06–1.31, p=0.002). Among metabolic factors, obesity (BMI ≥30 kg/m²) nearly doubled the risk (OR=1.90, p<0.001), while hyperuricemia emerged as the strongest predictor, conferring more than a two-fold increased risk (OR=2.30, p<0.001). Hypertension (OR=1.50, p=0.012) and chronic kidney disease (OR=1.62, p=0.041) also remained significant after adjustment. From a dietary perspective, low fruit and vegetable consumption (OR=1.80, p=0.001) and high sodium intake (OR=1.42, p=0.023) were associated with recurrence, underlining the role of lifestyle factors. In contrast, sex, urban/rural residence, and alcohol intake were not independent predictors in the adjusted model. Overall, the model showed good discrimination (AUC=0.77), explaining approximately 22% of the variance in recurrence risk.

TABLE IV.

Multivariable logistic regression identifying independent predictors of recurrence

Predictor (reference)	Adjusted OR	95% CI	p-value
Age (per 10 years)	1.18	1.06–1.31	0.002
Male sex (female)	1.12	0.90–1.38	0.31
BMI ≥30 kg/m² (<30)	1.90	1.40–2.60	<0.001
Hyperuricemia (no)	2.30	1.70–3.10	<0.001
Hypertension (no)	1.50	1.10–2.00	0.012
Type 2 diabetes (no)	1.35	0.98–1.86	0.065
Hypertriglyceridemia (no)	1.28	0.96–1.70	0.089
CKD, eGFR <60 (no)	1.62	1.02–2.57	0.041
Low fruit/vegetable intake (no)	1.80	1.30–2.50	0.001
High sodium intake (no)	1.42	1.05–1.92	0.023
Frequent alcohol intake (no)	1.36	0.98–1.90	0.064
Urban residence (rural)	1.10	0.86–1.40	0.44

DISCUSSION

This study, performed in a large cohort of patients managed at the Michel Daudon Morphological and Spectroscopic Analysis Center, Iași, analyzed in detail the clinical, metabolic, and compositional differences between first episode and recurrent stone formers. The results demonstrate that recurrence is associated with older age, greater metabolic burden, specific dietary patterns, and a compositional shift toward uric acid-containing and struvite stones.

Recurrent cases represented nearly 40% of the cohort, a proportion comparable to the recurrence rates reported internationally, where up to half of patients develop a new episode within 10 years. Age was a significant determinant, with recurrent patients being older than those with a first episode. Similar observations were made in large European cohorts, where increasing age correlated with larger stones and lower likelihood of spontaneous passage. The male predominance persisted in our series (60.2%), which is in line with the traditional epidemiology of lithiasis, though other reports indicate a narrowing of the gender gap in Western countries(15, 16). The geographic distribution, with two-thirds of patients originating from Iași county, reflects the tertiary referral profile of our center and is consistent with regional clustering of lithiasis observed in Romanian populations (3, 17).

Morpho-spectroscopic analysis identified significant compositional differences between groups. COM and COD were more frequent in first-episode patients, whereas uric acid, urate-mixed, and struvite calculi were characteristic of recurrence. Such patterns are in line with the morpho-constitutional classification proposed by Daudon, which links uric acid and infection-related stones to systemic

and recurrent disease(4, 16).

Regional studies also documented correlations between comorbidities and stone type: hypertension was associated with COM, diabetes with uric acid, and obesity with COD (3,18). These data support the concept that recurrent lithiasis reflects not only anatomical predisposition but also persistent metabolic or infectious drivers.

Recurrent patients exhibited a significantly higher prevalence of obesity, hyperuricemia, hypertension, diabetes, and chronic kidney disease. These findings are concordant with large-scale studies that identified the metabolic syndrome as a major contributor to stone disease (16). In our cohort, hyperuricemia conferred the highest independent risk for recurrence, followed by obesity, hypertension, and CKD. These results are consistent with analyses of metabolically active lithiasis in Romanian populations, where clustering of biochemical disturbances was shown to increase recurrence risk. The association of metabolic abnormalities with recurrence strengthens the interpretation of urinary stone disease as a systemic disorder with renal, vascular, and metabolic implications (19, 20).

Dietary imbalance emerged as an additional determinant of recurrence. Patients with low intake of fruits and vegetables and high sodium consumption were significantly more likely to develop recurrent stones. This finding is supported by nutritional studies indicating that the sodium-to-potassium ratio is a reliable predictor of stone risk, with potassium-rich diets exerting a protective effect (21). Local observations also showed that obese stone formers often fail to adhere to dietary recommendations, which may explain the persistence of lithiasis despite medical advice (3, 22). Alcohol intake was more common in recurrent patients but did not remain significant in adjusted models, a result consistent with studies reporting no clear dose–response relationship between alcohol and stone risk. Recent evidence also suggests that beyond sodium and potassium balance, other dietary components exert significant influence on stone recurrence. High animal protein intake increases acid load, enhances urinary calcium and uric acid excretion, and reduces urinary citrate, thereby favoring both uric acid and calcium oxalate lithiasis (5). Conversely, plant-based proteins and diets rich in alkali-producing foods may offer protective effects. Fructose-containing sweetened beverages have been associated with increased uric acid production and recurrent lithiasis in several cohorts, while inadequate fluid intake remains a major risk factor, particularly in rural populations with limited access to structured dietary counselling. Emerging studies also highlight the role of gut microbiota, showing that reduced colonization with *Oxalobacter formigenes* diminishes intestinal oxalate degradation, thereby contributing to calcium oxalate stone formation (1, 7, 23). These aspects underline that recurrence is not only the result of isolated dietary imbalances but of broader lifestyle and environmental patterns that warrant multifaceted preventive interventions. Sedentary lifestyle, although not directly assessed in this cohort, has been linked elsewhere to increased risk of lithiasis (20, 21).

Stone composition has direct clinical

relevance for urological management. Clinical experience in Romanian series demonstrated that COM calculi are more resistant to ESWL compared to other types. Comparative evaluations of electrohydraulic and electromagnetic lithotripters confirmed that stone composition remains a critical determinant of fragmentation success, regardless of technology (24-26). These results provide context for the present findings, where recurrent patients more frequently presented with uric acid and struvite stones-calculi known for therapeutic difficulty and for requiring adjuvant medical or anti-infective strategies.

Several large-scale analyses have demonstrated that calcium oxalate monohydrate calculi, while frequent in first-episode cases, are often linked to lower recurrence rates compared with uric acid or struvite stones (27). The latter are frequently associated with systemic conditions such as metabolic syndrome, diabetes, or chronic infection, which perpetuate the lithogenic milieu and favor multiple episodes (16, 21, 28). Uric acid stones have been correlated with obesity, insulin resistance, and acidic urinary pH, supporting their role as markers of metabolic imbalance rather than isolated events (29-31).

The cumulative evidence demonstrates that stone recurrence is not a random phenomenon but the clinical expression of systemic derangements combining metabolic, dietary, and infectious factors. International data have also linked stone disease to accelerated chronic kidney disease progression and to disparities in access to metabolic evaluation (26, 32). Within this framework, the systematic use of morpho-spectroscopic analysis, as applied in our center, enables the identification of high-risk phenotypes and the implementation of tailored preventive interventions.

The strengths of this study include the large patient cohort, the systematic application of morpho-spectroscopic analysis in a specialized reference center, and the integration of dietary, metabolic, and clinical data. Limitations stem from its retrospective design and single-center setting, although the referral nature of our institution provides regional representativeness. Prospective, multicenter investigations are warranted to confirm these findings and to assess the effectiveness of targeted preventive strategies.

CONCLUSIONS

Stone recurrence reflects a specific pathophysiological profile characterized by adverse metabolic conditions, unfavorable dietary patterns, and a compositional shift toward uric acid and struvite calculi. Recognition of these determinants emphasizes the systemic nature of lithiasis and establishes morpho-spectroscopic analysis, combined with metabolic and nutritional evaluation, as essential tools for accurate risk stratification and the design of effective preventive strategies.

CONFLICT OF INTEREST AND FUNDING

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