

Active metabolic lithiasis: A condition that requires proper evaluation and monitoring

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Abstract. Kidney stone evolution is different among patients, with some exhibiting kidney stones once in a lifetime and others experiencing multiple recurrences, with some even presenting with them at short intervals of time. The present study analyzed the risk of recurrence in order to organize a personalized prophylaxis and follow-up for the patients at risk. Prior to the analysis, the patients completed the liquids, antecedents, medication, associated pathologies and aliments questionnaire. A total of 350 patients with kidney stones were consecutively enrolled between April 2019 and April 2022. The spectroscopic analysis of stone samples was performed with the Bruker Alpha II spectrometer, while the stone morphology was assessed using the Olympus SZ61TR stereomicroscope. Intact stones were sectioned and their cores were analyzed separately. Patients with metabolically active lithiasis had stones made of cystine (CYS), uric acid (UA), brushite or calcium oxalate dihydrate. Among patients aged 18-30 years, two morphological factors defining the metabolically active lithiasis were identified: Randall's plaques [odds ratio (OR), 8.8] and poor stone organization (OR, 12.0). In patients aged 31-40 years, one criterion for the diagnosis of metabolically active lithiasis was the identification of pale stone color (OR, 12.0). Among the 149 patients aged >50 years, 24.8% (n=37) had UA lithiasis. Furthermore, the association of the defining elements of the metabolic syndrome significantly

increased the likelihood of the lithiasis recurrence (P=0.03; OR, 4.3). The presence of kidney stones in the family history was significantly associated with the type of stone (P=0.004). Among the 7 patients with CYS stones, 71.4% of them had family history of lithiasis. The study findings suggest that the identification of Randall plaques, a light stone color or a low degree of stone organization is associated with increased odds of lithiasis recurrence.

Introduction

Renal lithiasis is a common condition with an important impact on patients' health and the public health systems. Epidemiological studies show that over the past 50 years, there has been a global increasing trend in the incidence and prevalence of this disease (1,2). The etiology of urolithiasis is complex, and research shows that, especially in young patients, the recurrence rate after 3 years can be as high as 50% (3). The evolution of patients with kidney stones has variations among individuals, with some having kidney stones once in a lifetime and other presenting with multiple recurrences, with some even experiencing them at short time intervals (4).

The metabolic activity of kidney stones is important to define and follow. One of the possible options for classifying urolithiasis is related to the metabolic activity of urinary stones. Wollin *et al* (4) considered metabolically active urinary stones as those that showed dimensional growth on repeated imaging examinations. Daudon *et al* (5) showed that in the presence of Randall's plaques, the color of the stone (an indication of its age), crystal size, degree of the stone's organization (intense lithogenic processes determine the occurrence of stones with a poorly organized structure) and composition, such as the detection of crystalline species like brushite (BRU) and cystine (CYS) involving metabolic processes with intense lithogenic implications, as well as degree of hydration, are the main criteria for the close follow-up of patients with kidney stones. The present study analyzed the probability of the risk of recurrence for the patients monitored at the 'Michel Daudon' Center for Morphological and Spectroscopic Analysis of Reno-Ureteral Lithiasis, located within the Department of Extracorporeal Lithotripsy in 'Dr C. I. Parhon' Hospital (Iasi, Romania).

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Abbreviations: COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carapatite; PACC, amorphous carbonate calcium phosphate; UA, uric acid; CYS, cystine; BRU, brushite; STRU, struvite; OR, odds ratio; RIRS, retrograde intrarenal surgery; PCNL, percutaneous nephrolithotomy; SWL, shock wave lithotripsy; MET, medical expulsive therapy

Key words: kidney stones, metabolically active lithiasis, spectroscopic analysis, stone morphology

Materials and methods

Patients. A total of 350 patients assessed and treated at the 'Dr C. I. Parhon' Hospital were consecutively enrolled in the present study between April 2019 and April 2022. The patients in this research ranged in age from 19 to 76 years (with an average of 49.3 year), and the ratio of men to women was 1.5:1. There were no exclusion criteria in this study.

All the samples analyzed in the present study were obtained from patients after extracorporeal shock-wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery (RIRS), medical expulsive therapy (MET) and open surgery. Prior to the analysis, the patients were asked to complete the liquids, antecedents, medication, associated pathologies and aliments questionnaire (6). Patients who previously received treatment for lithiasis or reported spontaneous elimination of urinary stones were considered to have lithiasis recurrence. Each stone was examined morphologically using the Olympus SZ61TR stereomicroscope (Olympus Corporation) to identify structural elements that suggest the stone's metabolic activity (Randall's plaque, organization degree and the color of the stone) (5).

Intact stones were manually sectioned, and their cores were spectroscopically analyzed separately where possible. The spectroscopic analysis was performed with the Bruker Alpha II FT-IR spectrometer, using the technical guidelines supplied by the manufacturer (Bruker Corporation) and the results were evaluated according to the Daudon's database (7). All the patients signed informed consent forms and the study was approved by the Research Ethics Board of the 'Dr C. I. Parhon' Hospital (Iasi, Romania; approval no. 18/08.03.2022).

Statistical analysis. Statistical analysis was performed using SPSS software version 27 (IBM Corp.) and the data were compared using the χ^2 test followed by applying Fisher's exact test when compared groups contained <5 cases. Odds ratio (OR) values were calculated using Pearson's χ^2 test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Categorization. A total of eight categories of kidney stones were identified in the study cohort, with the most frequent crystalline species being calcium oxalate monohydrate ($\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$; COM; 36.0%) and calcium oxalate dihydrate ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$; COD; 35.7%) (Table I). An element was considered as the main component of the kidney stone if its percentage notably exceeded the percentage of the second element, according to the result of the spectroscopic analysis (Table II).

Kidney stone recurrence according to composition. Out of a total of 350 calculi, most of the stones analyzed in the present study were fragments resulting after SWL (46%; $n=160$), followed by stones coming from PCNL (26%; $n=90$), MET (16%; $n=58$), RIRS (10%; $n=36$) and open surgery (2%; $n=6$).

Recurrence was found in patients with CYS (100%), BRU (87.5%), carabapatite (CA; 73.3%), COD (66.4%) and uric acid (UA; 61.7%) stones (Table III).

According to age groups and the stones' major constituting elements, the impact of the criteria of metabolically active lithiasis was analyzed and compared (Table IV). In the current investigation, Randall plaques were discovered in 106 of 350 patients (30.3%), of which 39 (36.8%) were obtained from MET, 34 (32.0%) were stone fragments after PCNL and 17 (16.03%) were obtained from RIRS, while 16 samples were fragments after SWL. Furthermore, Randall's plaques were observed in the majority of patients with COM lithiasis (54.8%), followed by COD lithiasis (40.8%) and CA lithiasis (26.7%). Randall plaques were not observed in the other types of stones.

Lithiasis recurrence according to the criteria of metabolically active lithiasis. Of the 48 patients aged 18-30 years, 54.1% ($n=26$) had COD stones. The objective criteria for the metabolically active lithiasis identified in these patients were the presence of Randall's plaques and the poor morphological organization of the stones, which are associated with an 8.8- and 12-fold increased risk of recurrence, respectively.

In addition, 48 patients between the ages of 31 and 40 were assessed, with 17 (35.4%) having COD stones and 23 (47.9%) exhibiting COM stones. In patients with COD lithiasis, the presence of a poor structural organization was associated with a 12-fold higher recurrence incidence.

In the 41-50 age group, 105 patients were identified, for which 33.3% COM stones ($n=35$) and 40% COD stones ($n=42$) were identified. Among the patients with COD stones in this age group, there was an association between the recurrence risk and the pale color of the stone with an associated OR of 5.6.

A total of 79 patients were included the 51-60 age range, 36.7% COM ($n=29$) and 27.8% COD ($n=22$) were identified. In the case of patients with COD stones, the poor structural organization present in 77.2% of the stones was associated with a risk of lithiasis recurrence.

Regarding the 59 patients aged 61-70 years, 25.4% ($n=15$) had COD and 42.3% ($n=25$) had COM stones. In the particular case of patients with COD stones, the pale color of the stone found in 60% of the patients was associated with an increased risk of lithiasis recurrence. Regardless of age, for patients with COM stones, no metabolically active lithiasis criteria with statistical significance were identified (Table IV).

Thus, the present analysis found that 66.4% of patients with COD stones were patients with recurrent stones compared with 49.2% of those with COM stones (Table V $P=0.006$, which demonstrates the higher degree of COD recurrence).

Uric acid lithiasis and associated pathology. Regarding the effect of associated comorbidities on the risk of recurrence, high blood pressure and type II diabetes were not particularly associated with the likelihood of lithiasis recurrence in patients with UA stones. However, for patients with obesity, hypertension and diabetes, the risk of lithiasis recurrence was 4.3-fold higher compared with patients without these comorbidities (Table VI).

The present analysis considered the relationship between body mass index and the composition of kidney stones, revealing that 93.6% of patients with uric acid stones were obese, compared with 52.8% of patients with COD stones and 63.5% of patients with COM stones (Table VII).

Table I. Categories of stones related to the percentage of their main component and the patients' age.

Main component	Age group, years						Total, n
	18-30	31-40	41-50	51-60	61-70	>70	
UA, n (%)	1 (2.1)	1 (2.1)	8 (17.0)	17 (36.2)	16 (34.0)	4 (8.5)	47 (13.4)
BRU, n (%)	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	0 (0.0)	0 (0.0)	8 (2.3)
CA, n (%)	3 (20.0)	2 (13.3)	4 (26.7)	3 (20.0)	2 (13.3)	1 (6.7)	15 (4.3)
COD, n (%)	26 (20.8)	17 (13.6)	42 (33.6)	22 (17.6)	15 (12.0)	3 (2.4)	125 (35.7)
COM, n (%)	11 (8.7)	23 (18.3)	35 (27.8)	29 (23.0)	25 (19.8)	3 (2.4)	126 (36.0)
CYS, n (%)	1 (14.3)	1 (14.3)	4 (57.1)	1 (14.3)	0 (0.0)	0 (0.0)	7 (2.0)
PACC, n (%)	0 (0.0)	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	5 (1.4)
STRU, n (%)	4 (23.5)	3 (17.6)	6 (35.3)	3 (17.6)	1 (5.9)	0 (0.0)	17 (4.9)
Total, n (%)	48 (13.7)	48 (13.7)	105 (30.0)	79 (22.6)	59 (16.9)	11 (3.1)	350 (100.0)

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carbapatite; UA, uric acid; PACC, amorphous carbonate calcium phosphate; CYS, cystine; BRU, brushite; STRU, struvite.

Stone recurrence and family history of kidney stones. The presence of lithiasis in the family history was statistically associated with the type of stone ($P=0.004$). A total of 71.4% of patients with CYS stones had a family background of lithiasis, while for the other categories of kidney stones, the percentage was <30% (COD, 28.8%; CA, 26.7%; COM, 19%) (Table VIII).

In the future, further studies will be performed to analyze the parathyroid hormone levels in all patients with COD and CA (>20%) in the composition of stones, as all patients examined to date have shown elevated levels of this hormone (5).

Discussion

Epidemiological studies show that in Western countries there has been an increasing prevalence of kidney stones over the past few decades. Two literature reviews conducted on data collected from seven countries show that the incidence of kidney stones is 114-720 per 100,000 inhabitants and the prevalence is 1.7-14.8% (8,9).

The increasing incidence of kidney stones might be attributed to current unhealthy dietary habits (such as fast food), obesity and poor hydration. Previous studies have also found a genetic predisposition to lithogenesis (9,10).

Most patients diagnosed with kidney stones are socially active individuals belonging to the age group of 20-60 years. The economic impact on the public health systems is high and it is estimated that, in the 2000s in the United States, the costs for the treatment of patients with kidney stones were ~2.1 billion US dollars. There is a major concern about the costs of treating lithiasis, with several urological centers reporting their increase (11-13).

There are several types of stones with different etiopathogenic substrates, which therefore require personalized treatment. The determination of the chemical composition of the stones is essential for the application of specific prophylactic measures (5).

The recurrence of lithiasis is one of the main factors behind the morbidity caused by this condition (3,5,9). Until

the mid-1950s, the formation and elimination of a stone was considered a singular event, but as studies on this subject became more rigorous, the data suggested that patients with lithiasis may develop recurrences in high proportions. Williams (10) reported a 75% recurrence rate over a follow-up period of >10 years, while Ljunghall and Hedstrand (14) reported a recurrence rate of lithiasis of 46 and 43% in men and women, respectively. In contrast to these statistics from the United States (10) and Sweden (14), different results were reported in France, where the recurrence rate was found to be 52% for women and 54% for men (15). Due to these various lithiasis recurrence rates, the European Urology Guidelines has suggested several criteria to identify and quantify the number of patients at high risk of recurrence, including: i) General factors, such as the early onset of the disease and the family history of kidney stones; ii) factors related to the composition of the stones, such as stones composed of BRU, UA, urates and CYS; iii) the presence of other medical conditions associated with lithogenesis, including hyperparathyroidism, metabolic syndrome and polycystic kidney disease; iv) genetic disorders such as cystinuria, primary hyperoxaluria, type I tubular acidosis and cystic fibrosis; v) dietary factors; and vi) occupational exposure to high temperatures (16). In addition to these elements of metabolically active lithiasis specified by international guidelines, a previous study conducted on large groups of patients showed that, according to the composition of the stones and their morphological features, the recurrence rate can be as high as 82.7% (17).

There are different data on the incidence of Randall's plaques. The first statistic on these structures, provided by Alexander Randall, indicated an incidence of 19.6% (18). Subsequently, another study performed on large groups of patients identified the presence of Randall's plaques in 73% of patients with renal calculi and demonstrated that Randall's plaques were mostly associated with stones composed of calcium oxalate (77%), UA (63%), amorphous carbonate calcium phosphates (PACC; 58%), CYS (50%) and struvite (STRU; 29%) (19). In a large study, after the morphological and spectroscopic analysis of 45,774 stones, Daudon *et al* (20)

Table II. Kidney stone classification based on the patient's age and the percentage of the main chemical component.

Main component	Total range, %	Age group, years									
		18-30		31-40		41-50		51-60		61-70	
		n	%	n	%	n	%	n	%	n	%
COD	80-99	23	88.5	14	82.3	20	47.6	14	63.7	10	66.7
	60-79	3	11.5	2	11.8	10	23.8	6	27.2	3	20
	51-59	0	0.0	1	5.8	12	28.6	2	9.1	2	13.3
COM	80-99	8	72.7	15	65.2	27	77.1	16	55.2	14	56
	60-79	3	27.3	6	26.1	6	17.2	6	20.7	4	16
	51-59	0	0.0	2	8.8	2	5.7	7	24.1	7	28
UA	80-99	0	0.0	0	0.0	2	25.0	3	17.7	5	31.2
	60-79	1	100.0	1	100.0	6	75.0	12	70.6	8	50
	51-59	0	0.0	0	0.0	0	0.0	2	11.7	3	18.7
BRU	80-99	2	100.0	1	100.0	2	50.0	0	0.0	0	0.0
	60-79	0	0.0	0	0.0	2	50.0	1	100.0	0	0.0
	51-59	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
CYS	80-99	1	100.0	1	100.0	2	50.0	0	0.0	0	0.0
	60-79	0	0.0	0	0.0	2	50.0	1	100.0	0	0.0
	51-59	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
CA	80-99	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	60-79	2	66.7	1	50.0	2	50.0	2	66.7	1	100.0
	51-59	1	33.3	1	50.0	2	50.0	1	33.3	0	0.0
STRU	80-99	0	0.0	0	0.0	1	16.7	1	33.3	0	0.0
	60-79	2	50.0	2	66.7	2	33.3	2	66.7	1	100.0
	51-59	2	50.0	1	33.3	3	50.0	0	0.0	0	0.0
PACC	80-99	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	60-79	0	0.0	0	0.0	1	50.0	2	66.7	0	0.0
	51-59	0	0.0	0	0.0	1	50.0	1	33.3	0	0.0

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carbapatite; UA, uric acid; PACC, amorphous carbonate calcium phosphate; CYS, cystine; BRU, brushite; STRU, struvite.

Table III. Lithiasis recurrence according to stone composition.

Mineral component	Group		Total, n
	Recurrence, n (%)	First episode, n (%)	
UA	29 (61.7)	18 (38.3)	47
BRU	7 (87.5)	1 (12.5)	8
CA	11 (73.3)	4 (26.7)	15
COD	83 (66.4)	42 (33.6)	125
COM	62 (49.2)	64 (50.8)	126
CYS	7 (100.0)	0 (0.0)	7
PACC	0 (0.0)	5 (100.0)	5
STRU	8 (47.1)	9 (52.9)	17
Total	207 (59.1)	143 (40.9)	350

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carbapatite; UA, uric acid; PACC, amorphous carbonate calcium phosphate; CYS, cystine; BRU, brushite; STRU, struvite.

demonstrated that 19.5% of the examined stones had Randall's plaques and 92.5% of them were COM or COD stones. Matlaga

and Lingeman found that attached stones seem to be more common among calcium oxalate stone formers (48%) than in

Table IV. Comparative analysis of criteria for metabolically active lithiasis relative to age groups and stone composition.

A, 18-30 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COD	Total, n	16	10	26			
	Randall plaque, n (%)	11 (68.8)	2 (20.0)	13 (50.0)	0.04 ^a	8.8	1.35-57.43
	Pale color, n (%)	11 (68.8)	6 (60.0)	17 (65.4)	0.69	-	-
	Poor organization, n (%)	12 (75.0)	2 (20.0)	14 (53.8)	0.013 ^a	12.0	1.76-81.74
COM	Total, n	3	8	11			
	Randall plaque, n (%)	3 (100.0)	6 (75.0)	9 (81.8)	0.50	-	-
	Pale color, n (%)	-	-	-	-	-	-
	Poor organization, n (%)	1 (33.3)	1 (33.3)	2 (18.1)	0.49	-	-
B, 31-40 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COD	Total, n	13	4	17			
	Randall plaque, n (%)	7 (53.8)	-	7 (41.2)	0.10	-	-
	Pale color, n (%)	11 (84.6)	2 (50.00)	13 (50.0)	0.21	-	-
	Poor organization, n (%)	12 (92.3)	1 (25.00)	13 (76.4)	0.02 ^a	12.0	1.71-757.79
COM	Total, n	12	11	23			
	Randall plaque, n (%)	7 (58.3)	5 (45.5)	12 (52.2)	0.68	-	-
	Pale color, n (%)	1 (8.3)	1 (9.09)	2 (8.6)	0.73	-	-
	Poor organization, n (%)	1 (8.3)	1 (9.09)	2 (8.6)	0.73	-	-
C, 41-50 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COD	Total, n	31	11	42			
	Randall plaque, n (%)	15 (48.8)	1 (9.1)	16 (38.1)	0.03 ^a	9.3	1.07-82.35
	Pale color, n (%)	27 (87.0)	6 (54.5)	33 (78.6)	0.03 ^a	5.6	1.15-27.44
	Poor organization, n (%)	4 (12.9)	0 (0.0)	4 (9.5)	0.55	-	-
COM	Total, n	18	17	35			
	Randall plaque, n (%)	10 (55.6)	7 (41.2)	17 (48.6)	0.39	-	-
	Pale color, n (%)	3 (16.6)	4 (23.5)	7 (20.0)	0.69	-	-
	Poor organization, n (%)	3 (16.6)	5 (29.4)	8 (22.8)	0.44	-	-
D, 51-60 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COD	Total, n	10	12	22			
	Randall plaque, n (%)	5 (50.0)	5 (41.7)	10 (45.5)	0.51	-	-
	Pale color, n (%)	8 (80.0)	5 (41.6)	13 (59.0)	0.09	-	-
	Poor organization, n (%)	10 (100.0)	7 (58.3)	17 (77.2)	0.03 ^a	-	-
COM	Total, n	11	18	29			
	Randall plaque, n (%)	7 (63.6)	10 (55.6)	17 (58.6)	0.71	-	-
	Pale color, n (%)	1 (9.1)	3 (16.6)	4 (13.7)	0.50	-	-
	Poor organization, n (%)	3 (27.2)	4 (22.2)	7 (24.1)	0.54	-	-
E, 61-70 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COD	Total, n	11	4	15			

Table IV. Continued.

E, 61-70 years							
Components	Characteristics	Recurrence	First episode	Total	P-value	Odds ratio	95% CI
COM	Randall plaque, n (%)	5 (45.5)	0 (0.0)	5 (33.3)	0.23	-	-
	Pale color, n (%)	9 (81.8)	0 (0.0)	9 (60.0)	0.01 ^a	-	-
	Poor organization, n (%)	6 (54.5)	0 (0.0)	6 (40.0)	0.1	-	-
	Total, n	14	11	25			
	Randall plaque, n (%)	6 (42.9)	8 (72.7)	14 (56.0)	0.22	-	-
	Pale color, n (%)	2 (14.3)	3 (27.3)	5 (20.0)	0.62	-	-
	Poor organization, n (%)	1 (7.1)	3 (27.3)	4 (16.0)	0.27	-	-

^aP<0.05. COM, calcium oxalate monohydrate; COD, calcium oxalate dehydrate; -, not applicable.

Table V. Comparative analysis of the recurrence of the main calcium oxalate species.

Component	Group		Total, n	P-value
	Recurrence, n (%)	First episode, n (%)		
COD	83 (66.4)	42 (33.6)	125	0.006 ^a
COM	62 (49.2)	64 (50.8)	126	

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; ^aP<0.05.

Table VI. Association of metabolic syndrome with uric acid stones.

Metabolic syndrome	Patients with uric acid stones (n=47)				P-value	Odds ratio
	Recurrence (n=29)		First episode (n=18)			
	n	%	n	%		
Diabetes	17	58.6	8	44.4	0.34	
Hypertension	17	58.6	7	58.9	0.18	
Diabetes + hypertension	17	58.6	6	33.3	0.09	
Diabetes + hypertension + obesity	16	55.2	4	22.2	0.03 ^a	4.3

^aP<0.05.

the general population, and that the majority of papillae (91%) carried plaques (21). Patients with Randall's plaques identified via morphological examination had a higher degree of lithiasis recurrence in comparison to patients for which these structures were not identified (17).

In the present study, Randall's plaques were identified in 30.3% of all the analyzed stones, but in contrast to the study by Low *et al* (19), in which the presence of these structures was reported in most types of stones (19), the presence of Randall's plaques was observed in only three large categories of stones: COM (54.8%), COD (40.8%) and CA (26.7%). Bouslama *et al* (22) analyzed 359 lithiasis fragments, of which

311 were extracted invasively, 21 from extracorporeal lithotripsy and 27 from the ureteral passage of stones, and found that 26.2% of fragments presented papillary umbilications, while 20.3% featured Randall's plaques.

There is geographic variability in the identification of Randall's plaques. In Italy, Ruggera *et al* (23) found that the incidence of Randall's plaques was 44.7%, while in France Letavernier *et al* (24) found an incidence of 34.1%.

In the present study, apart from the groups of patients with calcium oxalate stones, the other groups contained relatively small numbers. Despite this limitation, the present study confirmed the central role of Randall's plaques in the

Table VII. Patient grouping according to BMI categories and stone composition.

Component	BMI groups			Total, n
	Normal, n (%)	Overweight, n (%)	Obesity, n (%)	
UA	3 (6.4)	18 (38.3)	26 (55.3)	47
BRU	3 (37.5)	4 (50.0)	1 (12.5)	8
CA	5 (33.3)	5 (33.3)	5 (33.3)	15
COD	59 (47.2)	41 (32.8)	25 (20.0)	125
COM	46 (36.5)	53 (42.1)	27 (21.4)	126
CYS	6 (85.7)	1 (14.3)	0 (0.0)	7
PACC	0 (0.0)	4 (80.0)	1 (20.0)	5
STRU	7 (41.2)	8 (47.1)	2 (11.8)	17
Total	129 (36.9)	134 (38.3)	87 (24.9)	350

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carbapatite; UA, uric acid; PACC, amorphous carbonate calcium phosphate; CYS, cystine; BRU, brushite; STRU, struvite; BMI, body mass index.

Table VIII. Family history of lithiasis related to stone composition.

Component	Positive family history of lithiasis	
	Yes	No
UA	5 (10.6)	42 (89.4)
BRU	0 (0.0)	8 (100.0)
CA	4 (26.7)	11 (73.3)
COD	36 (28.8)	89 (71.2)
COM	24 (19.0)	102 (81.0)
CYS	5 (71.4)	2 (28.6)
PACC	1 (20.0)	4 (80.0)
STRU	2 (11.8)	15 (88.2)
Total	77 (22.0)	273 (78.0)

COM, calcium oxalate monohydrate; COD, calcium oxalate dihydrate; CA, carbapatite; UA, uric acid; PACC, amorphous carbonate calcium phosphate; CYS, cystine; BRU, brushite; STRU, struvite.

recurrence of lithiasis. At the level of the whole study cohort, the presence of Randall's plaques was associated with an increase in the likelihood of recurrence. In the particular case of patients aged 18-30 years with COD stones, the presence of Randall's plaques increased the risk by 8.8-fold.

The frequency of lithiasis recurrence depends on the biochemical type of the stone. In a group of 12,000 patients examined in France, Daudon *et al* (17) showed that in terms of recurrence related to the composition of the stone, the most frequent were CYS stones (89.0%), followed by BRU (74.6%), UA (51.0%), COD (42.0%), STRU (42.0%), COM (38.0%) and PACC (30.9%) stones, respectively. In the present study, it was demonstrated that the hierarchy in terms of the recurrence rate was similar to the study by Daudon *et al* (17) despite the different geographic locations of France and Romania. The stones composed of UA, CYS, BRU and COD result from complex

active metabolic processes, which explains the higher recurrence rates of these morphotypes (16,17). A family history of kidney stones is an important criterion for the risk of recurrence. In an observational study published in 1997, Curhan *et al* (25) reported that the presence of a family history of kidney stones was associated with a 2.5-fold increase in the risk of recurrence and that 17.2% of patients with a personal risk of lithiasis have also a family history, compared with the 6.4% of patients without lithiasis that did not have a family history.

Relatively similar data have been reported in smaller groups of patients. Ahmadi *et al* (26) found that 28.6% of the patients with lithiasis have first-degree relatives with kidney stones regardless of their sex (26). In the present study, among all patients, 77 out of 350 (22.0%) had at least one first-degree relative with kidney stones and cystine lithiasis patients were more likely to have relatives with lithiasis.

In patients with lithiasis, the incidence of obesity has been reported in various studies as 10-35% (27-29). Daudon *et al* (30) showed that there is a strong association with obesity, especially in patients with UA stones. The study also stated that these patients should be monitored particularly for metabolic syndrome, which is frequently associated with the condition. The present study found that this relationship was observed in particular in patients with UA stones, and 55.3% of these patients were obese, while 38.3% were overweight, according to World Health Organization criteria (31).

A cross-sectional epidemiological study has demonstrated an independent association between hypertension and the history of kidney stones in the context of calcium metabolism abnormalities in hypertensive patients, although the relationship with the composition of the stones remains unclear (32). The current study found a notable percentage of hypertensive patients, especially in the group of patients with UA stones, but without any statistically significant association.

The present study has the following limitations: i) It is estimated that 21.2% of patients will present with different stone compositions upon successive stone episodes (33); however, in the present study, the initial composition of the stones that occurred before the spectroscopy analysis was

unknown in patients with recurrent lithiasis; ii) the number of parathyroid hormone determinations in patients for whom the spectroscopic analysis suggested the endocrine etiology of lithiasis (>20% of the stones were COD associated with CA) was limited; and iii) the present study did not perform any genetic determinations, whereas Halbritter *et al* (34) demonstrated that up to 15% of patients with recurrent lithiasis who are <25 years old have a monogenic condition involved in the etiopathogenesis of lithiasis, and other previous studies have shown that urinary lithiasis is a condition with important genetic penetrability (34,35). Therefore, further studies are necessary to investigate other possible associations.

The morphological and spectroscopic analysis of the stones or even their fragments is the essential step to recognize metabolically active lithiasis (5). Research is ongoing, however, the present study revealed that that patients with metabolically active lithiasis had stones made of CYS, UA, BRU or COD. Moreover, among patients in the 18-30 age group, two morphological factors defining the metabolically active lithiasis were identified: Randall's plaques and poor stone organization. For patients aged 31-40 years, only one criterion for metabolically active lithiasis was identified (the pale stone color, with a 12.0-fold higher risk of recurrence). Regarding the patients in the 51-60 and 61-70 years age groups, either poor organization or the pale color criteria were respectively identified. Among patients aged >50 years, there was a notable proportion of UA lithiasis and the association with the defining elements of the metabolic syndrome increased the risk of recurrent lithiasis. Overall, the findings suggest that the presence of Randall plaques, a light stone color and a low degree of stone organization are associated with a higher risk of lithiasis recurrence.

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Availability of data and material

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

Authors' contributions

CP, MI and DP conceived and designed the study, were involved in performing the surgery and other procedures (morphological and spectroscopic analysis of the calculi), and analyzed and interpreted the data. MI and DP drafted the manuscript, and CP revised the manuscript. CP and DP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Board of the 'Dr C. I. Parhon' Hospital (Iasi, Romania;

approval no. 18/08.03.2022). All the patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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