DOI: 10.4081/aiua.2023.10748

ORIGINAL PAPER

Determinants of renal papillary appearance in kidney stone formers: An in-depth examination

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Summary

Objectives: *The aim of this study is to investigate the association between the urinary metabolic milieu and kidney stone recurrence with a validated papillary evaluation score (PPLA).*

Materials and methods: *We prospectively enrolled 30 stone formers who underwent retrograde intrarenal surgery procedures. Visual inspection of the accessible renal papillae was performed to calculate PPLA score, based on the characterization of ductal plugging, surface pitting, loss of papillary contour and Randall's plaque extension. Stone compositions, 24h urine collections and kidney stone events during follow-up were collected. Relative supersaturation ratios (RSS) for calcium oxalate (CaOx), brushite and uric acid were calculated using EQUIL-2. PPLA score > 3 was defined as high.*

Results: *Median follow-up period was 11 months (5, 34). PPLA score was inversely correlated with BMI (OR 0.59, 95% CI 0.38, 0.91, p = 0.018), type 2 diabetes (OR 0.04, 95% CI 0.003, 0.58, p = 0.018) and history of recurrent kidney stones (OR 0.17, 95% CI 0.04, 0.75, p = 0.019). The associations between PPLA score, diabetes and BMI were not confirmed after excluding patients with uric acid stones. Higher PPLA score was associated with lower odds of new kidney stone events during follow-up (OR 0.15, 95% CI 0.02, 1.00, p = 0.05). No other significant correlations were found.*

Conclusions: *Our results confirm the lack of efficacy of PPLA score in phenotyping patients affected by kidney stone disease or in predicting the risk of stone recurrence. Larger, long-term studies need to be performed to clarify the role of PPLA on the risk of stone recurrence.*

KEY WORDS: *Kidney stones; Retrograde intrarenal surgery; Stone recurrence; Management; Stone phenotype.*

Submitted 19 July 2022; Accepted 20 August 2022

INTRODUCTION

Nephrolithiasis is a medical condition characterized by a high prevalence in the general population and high recurrence rates (1), causing an elevated annual expenditure reaching up to $10 billion in the *United States* (2). Kidney stone disease pathogenesis is multifactorial, including genetic predisposition and environmental influence, as for dietary habits (3, 4). Besides, it is known to be associated with a wide spectrum of comorbidities such as obesity (5), arterial hypertension (6), diabetes mellitus (7), metabolic syndrome (8) and increased likelihood of developing chronic kidney disease, especially in secondary forms of systemic diseases (9). It was also shown that patients with urolithiasis have an increased risk of cardiovascular events (10) and vascular calcifications (11), highlighting the systemic involvement of this condition.

Kidney stones develop attached to either Randall's plaques (sub-epithelial interstitial deposits of calcium phosphate on the renal papillae), or stone plugs (crystal deposits in the terminal collecting ducts) (12). Both these can be seen on the papillary surfaces. What promotes plaque formation is not well understood. It has been suggested that idiopathic calcium oxalate stones normally develop on Randall's plaques and that secondary forms of stones are mainly formed from plugs (12).

A better understanding of both etiology and pathogenesis of the different forms of nephrolithiasis is fundamental to prevent recurrences with a more personalized and cause-specific medical treatment. The improved optical ureterorenoscopic inspection techniques may make the evaluation of renal papilla not only possible but hopefully able to produce a large amount of new data and evidence as to the pathogenesis of stones (13). Recently, a renal papillary appearance scoring system was proposed, in order to better characterize and to standardize the visual inspection of renal papillae (PPLA score) (14). Although it could certainly be a useful tool for improving reproducibility in the description of pathological findings in different patients and centers, at this moment the potential implications of this score on kidney stone risk factors are not well understood.

The aim of this study is therefore to investigate the association between the main risk factors for kidney stone recurrence and the endoscopic papillary evaluation score (PPLA) in a cohort of patients with nephrolithiasis. The association between PPLA and subsequent recurrence was also investigated.

Materials and methods

Study population

We prospectively enrolled all patients undergoing *retrograde intrarenal surgery* (RIRS) procedures for kidney stones at the *U.O.C. Clinica Urologica, Fondazione Policlinico Universitario A. Gemelli IRCCS* from May 2018 to September 2019. All patients were stone-free after RIRS procedure. Additional inclusion criteria were age ≥ 18 years and signed informed consent. At study initiation, all patients were naïve for dietary advice and medical treatment for kidney stone recurrence.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the *Bioethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy* (ID n° 2349). Informed consent was obtained from all individual participants included in the study.

Data collection and measurements

Patients included in this study performed a baseline visit after RIRS procedure at the nephrology stone clinic, *Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*, followed by a 1-year telephonic interview for investigating incident kidney stone events. Either a visible spontaneous passage of stone, evidence of kidney stones at any instrumental exam or new kidney stones removal procedure, were considered as a recurrence and the variable "*overall recurrent kidney stone disease at the end of the study*" was generated accordingly. For each patient, demographic and anthropometric information (sex, age, height, weight), clinical data regarding stone disease (history of symptomatic stone events, family history of kidney stones, solitary kidney), self-reported comorbidities (hypertension, diabetes, cardiovascular diseases, bone fractures), a physical examination and office blood pressure measurements were recorded. Standardized urine analyses (urine pH, daily urinary excretion of calcium, phosphate, magnesium, sodium, potassium, creatinine, urea, citrate, uric acid and oxalate) were conducted. Stones were routinely collected during RIRS procedures, in order to obtain composition analysis, using Fourier-transform infrared spectroscopy. The creatinine-based CKD-EPI equation was used to obtain the *estimated glomerular filtration rate* (eGFR). Among the metabolic evaluation parameters, the main one is represented by supersaturation for calcium oxalate, calcium phosphate and uric acid, representing the propensity of urine to form those crystals. Urine relative *supersaturation ratios* (RSS) for calcium oxalate monohydrate, brushite and undissociated uric acid were calculated by the EQUIL2 program (15). Visual inspection of the accessible renal papillae during RIRS procedures was performed in order to calculate a score of papillary appearance (PPLA score). PPLA score is based on the characterization of 4 ordinal variables (ductal plugging, surface pitting, loss of papillary contour and Randall's plaque extension), representing worsening pictures of renal involvement. PPLA score is an ordinal variable and it ranges from a minimum of 0 to a maximum of 8, produced by the sum of 4 components; each sub-component is an ordinal variable with 3 levels (from 0 to 2). In this study, the modified version of PPLA score was used, considering Randall's plaque extension as an ordinal numeric variable (Table 1) (16). All the images were eval-

Table 1.
PPLA score system for renal papillae (16).

Score	0	1	2
Ductal plugging	0 plaque deposits/ dilated ducts	≤ 5 plaque deposits/ dilated ducts	> 5 plaque deposits/ dilated ducts
Surface pitting	None	≤ 25% papillary surface	> 25% papillary surface
Loss of contour	None	Depressed	Flattened
Randall's plaque extension	Low	Medium	High

Table 2.
Baseline characteristics of the study cohort.

Characteristic	Participants (n = 30)
Males	19 (63)
Age, years	60.2 (12)
SBP, mmHg	130 (10)
DBP, mmHg	83 (5)
Body Mass Index, kg/m^2	25.8 (4)
eGFR creatinine Equation CKD-EPI 2009, mL/min per 1.73 m^2	84.2 (19)
Arterial hypertension	14 (47)
Diabetes	3 (10)
Cardiovascular disease	6 (20)
Bone fractures	2 (7)
Hyperparathyroidism	1 (3)
Positive family history for kidney stones	11 (37)
History of recurrent kidney stones	10 (33)
Solitary kidney	1 (3)
1-year kidney stone recurrence	9 (30)
PPLA score subgroups (0-6)	
0	1 (3)
1	1 (3)
2	7 (23)
3	4 (13)
4	5 (17)
5	9 (30)
6	3 (10)
High PPLA score (> 3)	17 (57)
RSS for calcium oxalate	35.52 (20.20, 64.31)
RSS for calcium phosphate	0.42 (0.23, 1.82)
RSS for uric acid	1.03 (0.77, 1.89)
Urine pH	5.5 (5.0, 6.0)
Urine calcium, mg/day	183 (122, 283)
Urine phosphate, mg/day	770 (600-988)
Urine uric acid, mg/day	450 (326, 552)
Urine citrate, mg/day	427.1 (177.35, 614.7)
Urine oxalate, mg/day	19.5 (15.0, 26.8)
Urine creatinine, g/day	1.2 (1.0, 1.7)
Urine sodium, mEq/day	145.9 (138.3, 191.0)
Urine potassium, mEq/day	59.4 (48.0, 78.0)
Urine magnesium, mg/day	100.0 (80.2, 120.0)
Urine volume, mL/day	2,000 (1,550, 2,400)
Hypercalciuria	6 (20)
Hyperoxaluria	2 (7)
Hypocitraturia	11 (37)
Calcium oxalate stones	17 (57)
Urate stones	3 (9)
Calcium phosphate stones	0
Mixed calcium oxalate and urate stones	5 (17)
Mixed calcium oxalate and calcium phosphate stones	8 (26)

uated one by one from 4 expert surgeons (> 50 flexible ureteroscopy for renal stones) and 5 junior surgeons (< 50 procedures performed). All the graders evaluated the videos of the papillae using the same video system and were allowed to review the video more than one time. Moreover, the percentage of agreement for the single item was evaluated in the two subgroups of surgeons and among senior graders, to ensure inter-grader concordance. Hypercalciuria was considered as urine calcium excretion > 250 mg/24h for women and 300 mg/24h for men, hyperuricosuria as urine uric acid excretion > 750 mg/24h for women and 800 mg/24h for men, hyperoxaluria as urine oxalate excretion > 45 mg/24h and hypocitraturia as urine citrate excretion < 320 mg/24h (17).

Statistical analysis

Continuous variables were reported as medians with 25th and 75th percentiles or means with *standard deviation* (SD) and categorical variables were reported as counts with percentages. PPLA score > 3 was defined as high. The inter-observer surgeon concordance among all 10 investigators and between the median values of the two subgroups (junior vs senior) was analysed by the Kendall coefficient of concordance. Ordinal logistic regression was used to analyse the association between stone risk factors (hypertension, diabetes, body mass index, cardiovascular disease, history of recurrent kidney stones, family history of kidney stones, RSS for calcium oxalate, calcium phosphate and uric acid, urine pH, urinary excretions of calcium, oxalate, citrate, uric acid and urine volume) and PPLA and its components (ductal plugging, surface pitting, loss of papillary contour, Randall's plaque extension). The analyses were repeated after modelling PPLA as lower (≤ 3) and higher (> 3) using logistic regression models. The association between PPLA and 1-year kidney stone recurrence was analysed with logistic regression models. Statistical tests were two-sided and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using the software Stata version 16 (*StataCorp, College Station, TX, USA*).

Results

A total of 30 stone formers were enrolled in this study. Mean age was 60.2 (SD 12.4) years and most patients were males (n = 19, 63%). Overall, 47% were hypertensive (n = 14), 10% were diabetic (n = 3), 20% presented cardiovascular comorbidities (n = 6). As regards kidney stone disease, 33% had a positive history of recurrence (n = 10) and 37% had a positive family history of stones (n = 11). Stone composition analysis, available in 23 patients (69%), revealed that calcium oxalate stones were the most frequent (56.5%), followed by mixed calcium oxalate and calcium phosphate stones (26.1%) (Table 2). Overall, 20% of the study sample had hypercalciuria (n = 6), 37% hypocitraturia (n = 11) and 7% hyperoxaluria (n = 2). The most frequent total PPLA score was 5 (n = 9, 30%) and 57% of patients had a PPLA score > 3 (n = 17).

Concordance between surgeon groups in the evaluations of plugging, pitting, loss of papillary contour and Randall's plaque extension were 86%, 73%, 72% and 80%, respectively. Among senior surgeons concordance was even higher with a percentage of 91%, 80%, 76% and 85% agreement. The Kendal coefficient of concordance was 0.93 among senior surgeons and 0.88 comparing the two groups of senior and junior surgeons.

PPLA score was inversely correlated with BMI (*Odds Ratio* [OR] 0.59, 95% *confidence interval* [CI] 0.38, 0.91, p = 0.018), type 2 diabetes mellitus (OR 0.04, 95% CI 0.003, 0.58, p = 0.018) and history of recurrent kidney stones (OR 0.17, 95% CI 0.04, 0.75, p = 0.019) (Table 3). The associations between type 2 diabetes and BMI with PPLA score were not confirmed after excluding patients with uric acid stones. Among the PPLA components, Randall's plaque

Table 3.
Association between PPLA score and risk factors for kidney stones or stone recurrence.

	PPLA score				High PPLA score (> 3)			
Variable	**No**	**Odds Ratio**	**95% CI**	**p-value**	**No**	**Odds Ratio**	**95% CI**	**p-value**
Hypertension	30	0.42	0.11, 1.57	0.197	30	0.34	0.08, 1.52	0.159
Diabetes	30	0.04	0.003, 0.58	0.018*	30	0.33	0.99, 1.09	0.069
Body Mass Index, kg/m^2	30	0.59	0.38, 0.91	0.018*	30	0.78	0.61, 0.99	0.039
Cardiovascular disease	30	0.98	0.21, 4.68	0.979	30	0.71	0.12, 4.30	0.713
History of recurrent kidney stones	30	0.17	0.04, 0.75	0.019*	30	0.08	0.01, 0.53	0.009
Positive family history for kidney stones	30	1.83	0.48, 6.98	0.379	30	1.58	0.34, 7.22	0.559
1-year kidney stone recurrence	27	0.81	0.48, 1.37	0.426	27	0.15	0.02, 1.00	0.050*
Overall recurrent kidney stone disease	30	0.10	0.02, 0.48	0.004*	30	0.03	0.01, 0.28	0.001*
RSS for CaOx	30	1.01	0.99, 1.03	0.529	30	1.00	0.95, 1.06	0.948
RSS for Brushite	20	0.94	0.64, 1.37	0.726	20	0.54	0.23, 1.26	0.153
RSS for Uric acid	7	0.97	0.65, 1.45	0.887	7	Not estimatable		
Urinary excretion of calcium, mg/day	29	1.001	1.00, 1.01	0.657	29	1.00	1.00, 1.01	0.294
Urinary excretion of oxalate, mg/day	30	0.95	0.90, 1.01	0.098	30	0.97	0.91, 1.03	0.330
Urinary excretion of citrate, mg/day	30	1.00	1.00, 1.01	0.493	30	1.00	1.00, 1.00	0.934
Urinary excretion of uric acid, mg/day	7	1.00	0.99, 1.01	0.488	7	1.00	0.99, 1.01	0.815
Urinary excretion of sodium, mEq/day	28	0.98	0.96, 1.00	0.050*	28	0.97	0.93, 1.01	0.150
Urinary volume, mL/day	30	0.81	0.19, 3.43	0.774	30	0.48	0.09, 2.53	0.385
Urine pH	30	1.10	0.41, 2.93	0.853	30	1.84	0.53, 6.38	0.337

Table 4.
Association between each PPLA sub-score (ductal plugging, surface pitting, loss of papillary contour, Randall's plaque extension) and risk factors for kidney stones or stone recurrence.

		Ductal plugging		Surface pitting		Loss of papillary contour		Randall's plaque extension	
Variable	**No**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Hypertension	30	0.27 (0.06, 1.17)	0.080	0.77 (0.18, 3.34)	0.728	0.53 (0.10, 2.74)	0.448	1.02 (0.23, 4.48)	0.980
Diabetes	30	0.32 (0.32, 0.35)	0.294	0.17 (0.01, 2.15)	0.171	0.09 (0.01, 1.17)	0.065	0.00 (0.31, 3.43)	0.995
BMI	30	0.91 (0.76, 1.10)	0.328	0.83 (0.68, 1.02)	0.079	0.91 (0.74, 1.13)	0.393	0.86 (0.69, 1.07)	0.174
Cardiovascular disease	30	1.12 (0.19, 6.59)	0.904	0.68 (0.12, 3.99)	0.670	0.88 (0.13, 6.12)	0.894	2.12 (0.30, 14.82)	0.447
History of recurrent kidney stones	30	0.32 (0.07, 1.41)	0.131	0.64 (0.13, 3.06)	0.575	0.33 (0.06, 1.88)	0.213	0.03 (0.00, 0.23)	0.001*
Familiarity for kidney stones	30	1.88 (0.44, 8.10)	0.395	2.40 (0.48, 11.93)	0.285	0.68 (0.13, 3.60)	0.648	1.27 (0.28, 5.87)	0.757
1-year kidney stone recurrence	27	0.37 (0.09, 1.41)	0.145	0.50 (0.11, 2.27)	0.369	2.25 (0.41, 12.38)	0.351	0.67 (0.14, 3.21)	0.619
Overall recurrent kidney stone disease	30	0.13 (0.03, 0.65)	0.013*	0.21 (0.04, 1.07)	0.061	0.48 (0.92, 2.51)	0.385	0.10 (0.17, 0.62)	0.013*
RSS for CaOx	30	1.01 (0.98, 1.03)	0.618	1.00 (0.98, 1.03)	0.802	1.00 (0.97, 1.03)	0.870	1.03 (0.99, 1.06)	0.122
RSS for Brushite	20	0.97 (0.66, 1.43)	0.870	0.97 (0.71, 1.32)	0.829	0.81 (0.57, 1.15)	0.229	1.00 (0.71, 1.41)	0.990
RSS for Uric acid	5	2.95 (0.03, 317.29)	0.650	0.01 (0.00, 22.90)	0.235	1.30 (0.58, 2.90)	0.526	1.95 (0.31, 27.19)	0.675
Urinary excretion of calcium, mg/day	29	1.01 (1.00, 1.01)	0.138	1.00 (1.00, 1.01)	0.683	1.00 (0.99, 1.00)	0.209	1.00 (1.00, 1.01)	0.641
Urinary excretion of oxalate, mg/day	30	0.98 (0.93, 1.04)	0.559	0.95 (0.89, 1.02)	0.134	0.95 (0.89, 1.02)	0.157	0.99 (0.93, 1.06)	0.826
Urinary excretion of citrate, mg/day	30	1.00 (1.00, 1.00)	0.797	1.00 (0.99, 1.00)	0.147	1.00 (0.99, 1.00)	0.187	1.00 (1.00, 1.01)	0.173
Urinary excretion of uric acid, mg/day	7	1.00 (0.99, 1.01)	0.993	0.99 (0.98, 1.00)	0.138	1.00 (0.99, 1.01)	0.455	1.04 (0.97, 1.12)	0.284
Urinary excretion of sodium, mEq/day	28	0.98 (0.96, 1.01)	0.180	0.98 (0.96, 1.00)	0.102	0.98 (0.96, 1.00)	0.101	0.99 (0.97, 1.02)	0.530
Urinary volume, mL/day	30	0.78 (0.179, 3.45)	0.748	1.49 (0.30, 7.53)	0.629	0.59 (0.10, 3.40)	0.551	0.56 (0.10, 2.99)	0.496
Urine pH	30	1.62 (0.53, 4.93)	0.400	1.18 (0.37, 3.82)	0.777	0.26 (0.06, 1.06)	0.060	1.47 (0.46, 4.68)	0.512

extension was inversely associated with history of recurrent kidney stones (OR 0.03, 95% CI 0.003, 0.23, p = 0.001) (Table 4). No other significant correlations were found between PPLA components and kidney stone risk factors.
After a median follow-up period of 11 months (5, 34), 30% of patients reported a new symptomatic kidney stone event (n = 9). Higher PPLA score was directly associated with lower odds of new kidney stone events during follow-up (OR 0.15, 95% CI 0.02, 1.00, p = 0.050) and reduced likelihood of overall recurrent kidney stone disease at the end of the study (OR 0.03, 95% CI 0.01, 0.28, p = 0.001).

Discussion

Novel methods capable of predicting the risk of stone recurrence and to better understand stone phenotype aetiology based on intra-renal crystals deposition are missing. In addition, three different hypotheses regarding the pathophysiology of stone formation have been proposed. The first hypothesis is Randall's plaque formation, with deposition of calcium phosphate crystals in form of apatite inside interstitial parenchyma. The second regards free solute crystallization for urine stasis and the third implies renal tubules crystal deposition as the nucleation factor for stone formation (18). Recently, endoscopic visualization of the accessible portion of renal papillae and collecting duct system were applied for differentiating these pathways, creating a promising additional tool for future evaluation of recurrent stone formers (14). Afterwards, a score of papillary appearance was created to study the association between stone phenotypes, urinary solute excretions and the description and quantification of either Randall's plaque, Bellini duct plugging, focal erosion of papillary surface (pitting) and loss of papillary contour extensions (16).
It can be then hypothesized that PPLA score and its sub-scores might be of help in differentiating patients with the same stone composition, urinary lithogenic risk profile or recurrence risk but with diverse papillary aspects, perhaps reflecting multiple concomitant pathogenesis of nephrolithiasis. For these reasons, the use of PPLA score was recently recommended in all patients who undergo ureteroscopy (19). However, evidence on the association between PPLA score, stone composition and urinary solute excretions is conflicting. In a previous study, *Kuo et al.* analyzed 14 stone formers, firstly showing the association between higher urinary calcium excretion, urine pH and urine volume on Randall's plaque extension (20), whereas analyzing larger cohorts of stone formers, *Linnes et al.* (21) and *Pless et al.* (22) did not confirm this association. In addition, *Sabaté Arroyo et al.* showed both increased frequency of intratubular calcification and papillary crater in patients with calcium oxalate dihydrate and calcium phosphate stones and a correlation between higher urinary calcium excretion and low urinary citrate excretion with papillary crater and Randall's plaque extension, respectively (23).
In the present study, hypercalciuria and hypocitraturia were the most frequent 24-h urine abnormalities, reflecting data of the most common urinary lithogenic risk profile in the general population (24, 25). Although we did not report any significant association between PPLA score or sub-scores and stone composition, RSS for calcium oxalate, brushite and uric acid or urinary lithogenic risk profile, both diabetes and BMI were found to be inversely correlated to PPLA score. However, after excluding patients with uric acid stones, the former correlations were not confirmed. The association between increased risk for incident kidney stones and obesity, BMI and diabetes has been known for a long time (26). Both type 2 diabetes mellitus and obesity share similar pathogenesis

(27), being part of the metabolic syndrome, which is tightly associated to insulin resistance (28). Insulin resistance results in acidic urine pH and defective renal production of ammonia, increasing the likelihood of developing uric acid kidney stones (8). Notably, with a correct urinary alkalization, it is possible to reduce or even dissolve previously formed uric acid stones, provided the absence of combined uric acid and calcium stone composition (29). Thus, the association between higher BMI, type 2 diabetes and lower PPLA score, may be driven by uric acid nephrolithiasis, since it was no longer significant after restriction to calcium stone formers. However, there were too few uric acid stone formers in our cohort to confirm these observations.

In this study on a prospective cohort of 30 stone formers, the association between PPLA score and the risk of 1-year kidney stone recurrence was investigated for the first time. We demonstrated an inverse association between high PPLA score and the odds of stone recurrence after a median follow-up time of 11 months. Patients enrolled in this study were naïve for dietary advice and medical treatment for kidney stone disease. After RIRS procedure, they underwent a work-up and dietary/medical management based on the results of 24h urine collections as well as their medical history; hence this data might reflect a more intensive medical management in the subgroup of patients with more severe pathological findings at papillary visualization.

Limitations of this study are the small sample size and low number of uric acid stone formers.

Overall, this evidence confirms the validity of advanced instrumental exams as a supplementary tool in medical and surgical management of kidney stones (30). Future, larger studies with a systematic assessment of stone recurrence are needed to confirm our findings.

Conclusions

In conclusion, our results confirm the lack of efficacy of PPLA score in phenotyping patients affected by kidney stone disease or in predicting the risk of stone recurrence. Larger, long-term studies need to be performed to clarify the role of PPLA on the risk of stone recurrence, especially in patients characterized by different stone compositions.

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Conflict of interest: The authors declare no potential conflict of interest.