

Metabolic evaluation in urolithiasis – study of the prevalence of metabolic abnormalities in a tertiary centre

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Introduction Metabolic abnormalities are one of the most important risk factors for urinary stone disease. Our objective was to determine the prevalence of metabolic abnormalities in patients referred to the urolithiasis outpatient clinic of a tertiary centre.

Material and methods We performed a cross-sectional study evaluating 67 patients referred to the urolithiasis outpatient clinic. Metabolic evaluation was performed, including one 24-hour urine sample.

Results Metabolic abnormalities could be identified in 92.5% patients. Almost a quarter of the patients had only one metabolic abnormality and 67.6% had more than one abnormality. The most prevalent metabolic abnormalities were hypercalciuria (54.5%), hyperoxaluria (34.7%) and hyperuricosuria (32.3%). Patients with hypercalciuria were older (54.7 vs. 47.8 years, $p = 0.018$) and family history of stone disease was significantly more frequent among patients with hyperoxaluria (71.4% vs. 28.6%, $p = 0.013$). There was a positive linear relationship between body mass index (BMI) and urinary calcium ($r = 0.247$, $p = 0.048$) and a negative linear relationship between BMI and urinary pH ($r = -0.254$, $p = 0.046$).

Conclusions Given the high prevalence of metabolic abnormalities, metabolic evaluation should be performed in every patient with urolithiasis evaluated in a tertiary setting.

Key Words: urolithiasis ↔ urinary stone disease ↔ metabolic evaluation

INTRODUCTION

Urinary stone disease or urolithiasis is a common, painful and costly condition [1]. The prevalence of urolithiasis is growing worldwide, irrespective of age, sex and race [2–5], with rates ranging from 7 to 13% in North America, 5–9% in Europe, and 1–5% in Asia [4].

This increase may be explained by changes in diet and lifestyle, higher prevalence of obesity and diabetes, global warming, with rising temperature resulting in dehydration and high urinary concentration of calcium and other stone-forming salts [4, 6].

The metabolic environment of the urine influences stone formation, with crystal production depending on the interplay between the saturation of each salt (calcium, oxalate, phosphate, uric acid) and the urinary concentration of inhibitors (citrate, magnesium, sulphate) and promoters (sodium) [7]. Lifestyle and dietary habits (such as an high salt and protein consumption and a low fluid intake) can induce urinary metabolic abnormalities, undoubtedly playing an important role in the risk of stone disease [3, 4, 8, 9, 10]. Hypertension, metabolic syndrome, diabetes and gout are diseases of affluent societies also associated with a higher prevalence

of urolithiasis. Although a genetic component is often considered part of the stone formers' diagnostic work-up, patients with known genetic causes appear to be less frequent [4]. Age, sex, race, climate, seasonal and geographic variation are also recognised predictors [4].

In general, 50% of patients experience recurrent urinary stones within five years without prophylactic intervention and about ten percent of patients even experience three or more recurrences during their lifetime [2, 11, 12], especially if the metabolic causes remain untreated.

In order to apply effective recurrence prevention (metaphylaxis), understanding the metabolic environment of each patient is required, so that a personalized treatment can be addressed.

To our knowledge, there are scarce epidemiological data concerning the prevalence of metabolic abnormalities among patients diagnosed with urolithiasis. For that reason, we conducted a cross-sectional study in order to determine the prevalence of metabolic abnormalities in patients with urolithiasis referred to the urolithiasis outpatient clinic of a tertiary centre. A second objective was to evaluate potential risk factors associated with several metabolic abnormalities.

MATERIAL AND METHODS

We performed a cross-sectional study including 108 patients over 18 years old admitted in the urolithiasis outpatient clinic of a tertiary centre. These patients were referred to the study centre mainly by general practitioners. The recruitment process took place during a period of 6 months, between January 2017 and June 2017.

Forty-one patients were excluded due to their medication chart, concerning allopurinol, citrate or thiazides, which could change the urinary metabolic profile, or due to the unavailability of assessment of the 24-hour urine samples (Figure 1).

Patient demographic data were obtained from medical records and during the medical appointment, including age, sex, tobacco (non-smoker, former or present smoker; pack-years) and alcohol (yes/no) consumption, physical exercise (no exercise, 1–3 days/week, 4–5 days/week, 6–7 days/week), weight and height to calculate the body mass index (BMI), comorbidities such as hypertension, diabetes mellitus type 2 and dyslipidaemia, medical or surgical history (including past history of urologic interventions such as extracorporeal shock wave lithotripsy, ureteroscopy laser stone fragmentation or nephro-

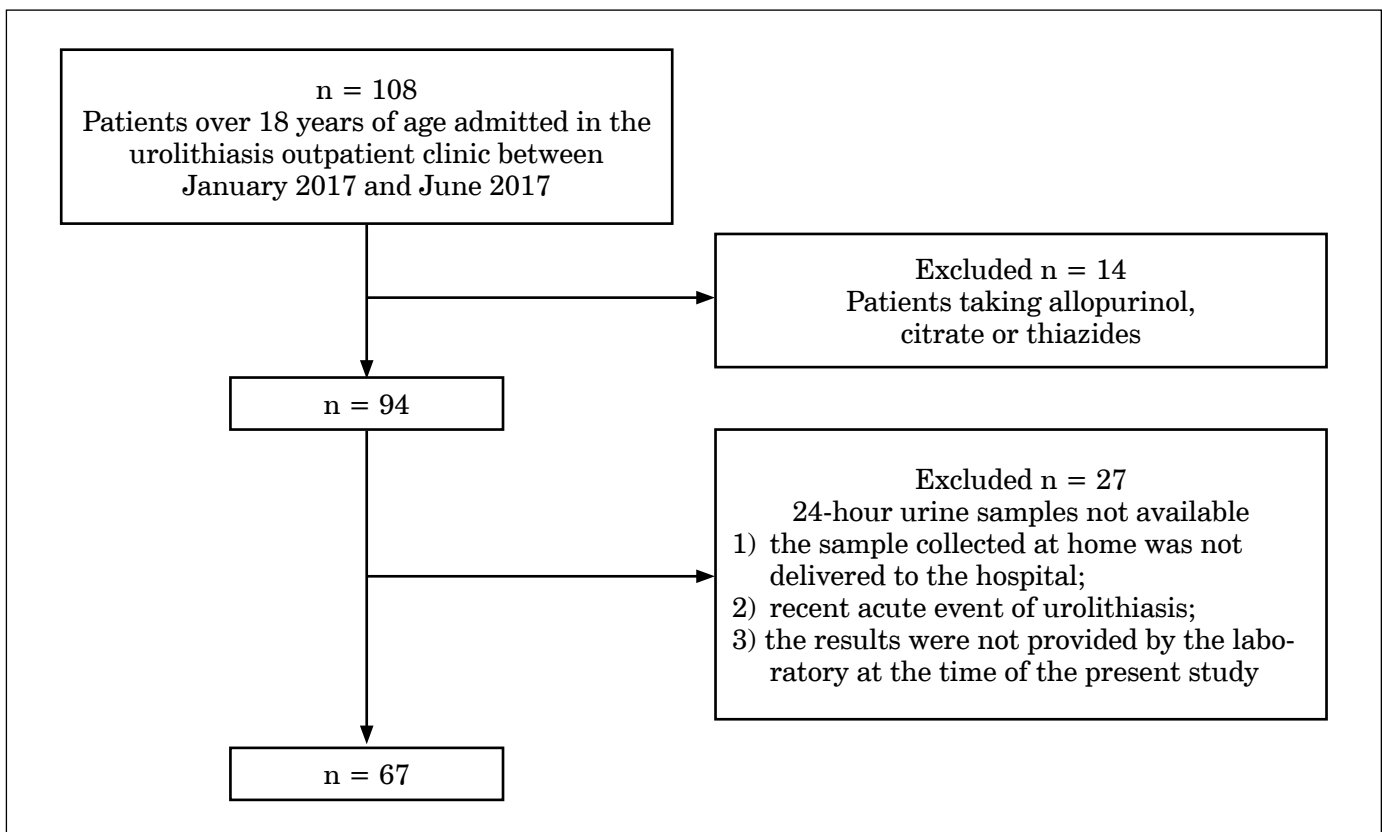


Figure 1. Patient selection process.

lithotomy), medication chart, personal history and family stone history.

Initial evaluation of every patient also included: urinalysis, 24-hour urine sample (with analysis of urinary calcium, oxalate, phosphate, uric acid, sodium and magnesium), bacteriologic examination of urine, serum analysis of creatinine, urea, ionised calcium and parathyroid hormone (PTH) and non-contrast computerized tomography (CT). Hydrochloric acid (HCl) was added into the container for oxalate measurement in the 24-hour urine sample. For the other measurements, patients received an empty container and were instructed to keep it in a cool place during the collection.

We considered the following metabolic abnormalities: hyperoxaluria, hypercalciuria, raised PTH, hypercalcemia, hyperuricosuria, hypomagnesuria and hyperphosphaturia.

Reference laboratory values for urine and serum biochemical parameters in adults were made according to the European Association of Urology (EAU) Guidelines for Urolithiasis [13]. Since the reference values for serum PTH and urinary sodium are not given in these guidelines, we used those from our hospital laboratory (high levels for serum PTH was 65 pg/ml and 220 mmol/day for urinary sodium).

Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS), version 24.0. Descriptive statistics were calculated for the sociodemographic, clinical and metabolic abnormalities. We used t-test for independent samples and nonparametric Mann-Whitney U test for comparisons between categorical and continuous variables, Chi-square for categorical variables and linear correlation for assessment between continuous variables. We considered statistically significant results for a p value <0.05.

Ethical approval was granted by the local Ethical Committee. Participants were informed about the study and methods and confidentiality was ensured. All participants signed a written informed consent according to the Declaration of Helsinki for human research ethics.

RESULTS

Participant characterization – demographic and clinical characterization

The majority of the population were women, making a female/male ratio of 1.39:1. The median age at the time of the consultation was 52 years old, with most patients between 43 and 60 years of age. Frequencies of smoking and alcohol consumption and physical activity are shown in Table 1.

Table 1. Sociodemographic and clinical characterization. Absolute and relative frequency of sociodemographic and clinical variables

Variables	
Age (years)*	52 (43–60) [†]
Sex*	
Male	28 (41.8) [‡]
Female	39 (58.2) [‡]
Smoker (including former-smoker)*	30 (44.8) [‡]
Smoking load [§]	
1–10 pack-years	14 (46.7) [‡]
11–20 pack-years	5 (16.7) [‡]
>20 pack-years	11 (37.7) [‡]
Alcohol consumer (Yes)*	23 (34.3) [‡]
Physical exercise	
No	30 (45.5) [‡]
1–3 days per week	20 (30.3) [‡]
4–5 days per week	4 (6.3) [‡]
6–7 days per week	12 (17.9) [‡]
BMI (kg/m ²) [¶]	
Underweight**	1 (1.5) [‡]
Normal ^{††}	25 (37.9) [‡]
Overweight ^{†††}	26 (39.4) [‡]
Obesity ^{§§}	14 (21.2) [‡]
Hypertension (yes)*	14 (20.9) [‡]
Diabetes mellitus (yes)*	8 (11.9) [‡]
Hyperlipidemia (yes)*	18 (26.9) [‡]
Personal history of lithiasis (yes) ^{¶¶}	45 (72.6) [‡]
Age of first episode (median; P25-P75) (years)	45 (36–52) [†]
Past lithiasic intervention ^{¶¶¶}	
None	53 (79.1) [‡]
SWL	6 (8.9) [‡]
URS	5 (7.5) [‡]
SWL + URS	1 (1.5) [‡]
SWL + PNL	1 (1.5) [‡]
URS + PNL	1 (1.5) [‡]
Family history of urolithiasis (yes) ^{¶¶¶¶}	22 (42.3) [‡]

BMI – body mass index; SWL – shock wave lithotripsy; URS – ureteroscopy; PNL – percutaneous nephrolithotomy

* 67 patients were evaluated in this variable; [†] The results represent the median and P25-P75, respectively; [‡] The results represent the frequency, n (%);

[§] 30 patients were evaluated in this variable; ^{||} 66 patients were evaluated in this variable; [¶] 62 patients were evaluated in this variable; ^{||||} 48 patients were evaluated in this variable; ^{¶¶} 52 patients were evaluated in this variable;

** Underweight – BMI <18 kg/m²; ^{††} Normal – BMI between 18 and 24.9 kg/m²;

^{†††} Overweight – BMI between 25 and 29.9 kg/m²; ^{§§} Obesity – BMI >30 kg/m²

As depicted in Table 1 for clinical characterization, 1.5% of patients were underweight, 37.9% presented normal BMI and 60.6% were overweight or obese. Taking other comorbidities into account, 20.9% had hypertension, 11.9% had diabetes mellitus and 26.9% presented with dyslipidaemia. Almost 73% of patients admitted had personal history of lithiasis, with a median age of 45 years at first episode. Regarding past lithiasic intervention, 20.9% of patients presented with positive history. According to family history of urolithiasis, 32.7% of patients only

referred one first degree relative while 9.6% mentioned two or more first degree relatives.

Frequency and type of metabolic abnormality in patients with urolithiasis

Metabolic abnormalities (considering any of these – hyperoxaluria, hypercalciuria, raised PTH, hypercalcemia, hyperuricosuria, hypomagnesuria or hyperphosphaturia) were found in 92.5% patients (Confidence Interval 95%: 86.2–98.8%). Almost a quarter (24.9% [CI95%: 15.0–35.8%]) only had one metabolic abnormality, and 67.6% patients (CI95%: 55.9–78.4%) had multiple metabolic abnormalities. Hypercalciuria was the most commonly observed metabolic abnormality and was found in 54.5% (CI95%: 42.5–66.6%) of patients. Other significant metabolic abnormalities were hyperoxaluria (34.7% [CI95%: 21.4–48.8%]), hyperuricosuria (32.3% [CI95%: 20.9–43.7%]) and hypomagnesuria (31.7% [CI95%: 20.3–43.2%]), as shown in Table 2.

As for other urinary parameters, the median of the 24-hour urinary volume was 1650 ml, with 62.7% of patients presenting a 24-hour urinary volume below 2000 ml. The majority of urinary samples had a pH between 5.5 and 6.5 – almost a third (29%) of patients with a urinary pH less than 5.5 and 16.1% higher than 6.5. Approximately one-sixth (15.3%) of patients presented a positive urinary bacteriologic exam, with *Escherichia coli* as the most frequent isolated agent (5 in 9).

Comparison between clinical and metabolic abnormalities

Table 3 compares several sociodemographic and clinical variables with the most frequent metabolic abnormalities found in our study (hypercalciuria, hyperoxaluria, hyperuricosuria and hypomagnesuria). Patients with hypercalciuria were older (54.8 ± 13.9 years vs. 47.8 ± 7.8 years, $p = 0.018$), family history of stone disease was significantly more frequent among patients with hyperoxaluria (71.4% vs. 28.6%, $p = 0.013$) and there was a higher prevalence of present and former smokers among patients with hyperoxaluria ($p = 0.016$). Urinary volume was higher in patients with hypercalciuria (1899.4 ± 627.9 ml vs. 1467.3 ± 736.1 ml, $p = 0.012$) and hyperuricosuria (1946.2 ± 675.2 ml vs. 1551.8 ± 709.7 , $p = 0.037$). Body mass index was associated with urinary calcium and urinary pH. There was a positive linear relationship between BMI and urinary calcium ($r = 0.247$, $p = 0.048$) and a negative linear relationship between BMI and urinary pH ($r = -0.254$, $p = 0.046$). There was also a positive linear relation-

Table 2. Blood and urine parameters. Absolute and relative frequency of blood and urine parameters for metabolic abnormalities

Metabolic abnormality	Frequency (%)	CI 95% (%)
Hypercalciuria (>5 mmol/day)*	36 (54.5)	42.5–66.6
Hyperoxaluria (oxalate >0.5 mmol/day) [†]	17 (34.7)	21.4–48.8
Hyperuricosuria (>4 mmol/day in women and >5 mmol/day in men) [‡]	21 (32.3)	20.9–43.7
Hypomagnesuria (<3 mmol/day) [§]	20 (31.7)	20.3–43.2
Hyperphosphaturia (phosphate level >1.3 g/dl)	10 (17.5)	7.7–27.4
Elevated PTH (>65 pg/ml) [¶]	9 (14.5)	5.7–23.3
Hypercalcemia (ionised calcium >1.32 mmol/L)**	5 (8.3)	1.3–15.3

CI – confidence interval; PTH – parathyroid hormone

* 66 patients were evaluated in this variable; [†] 49 patients were evaluated in this variable; [‡] 65 patients were evaluated in this variable; [§] 63 patients were evaluated in this variable; ^{||} 57 patients were evaluated in this variable; [¶] 62 patients were evaluated in this variable; ** 60 patients were evaluated in this variable

ship between urinary calcium compared with urinary sodium ($r = 0.509$, $p < 0.0001$), uricosuria ($r = 0.514$, $p < 0.0001$), magnesuria ($r = 0.532$, $p < 0.0001$) and phosphaturia ($r = 0.649$, $p < 0.0001$).

DISCUSSION

In our series, the most striking finding was the very high prevalence of metabolic abnormalities (92.5%), resembling the findings of several other studies, which considered metabolic abnormalities as one of the most important factors for stone formation [10, 14, 15].

Hypercalciuria (detected in 54.5% of patients) was the most frequent metabolic abnormality, followed by hyperoxaluria (34.7%) and hyperuricosuria (32.3%), a finding also observed in larger studies, most of them with patients with recurrent stone formation history [10, 14, 16, 17]. We included 17 patients with first self-reported episode of stone disease and, interestingly, all of them presented at least one metabolic abnormality.

Nevertheless, in some studies, a predominance of other abnormalities such as hyperoxaluria [10] or hypomagnesuria [18] was found. These disparate results may be explained by climate, seasonal, dietary or lifestyle variations, which highlights the importance of studying the prevalence of different metabolic changes in each population. This matter assumes a preponderant role, given the ability to modify these metabolic abnormalities with preventive (metaphylactic) measures, including diet and lifestyle changes along

Table 3. Comparison between clinical variables and metabolic abnormalities

	Hypercalciuria			Hyperoxaluria			Hyperuricosuria			Hypomagnesuria		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Age (years)*	54.7 (±13.7)	47.8 (±7.8)	0.018[†]	52.2 (±10.0)	51.6 (±12.4)	0.875 [†]	52.2 (±9.2)	51.1 (±12.2)	0.716 [†]	52.7 (±12.2)	51.5 (±11.2)	0.698 [†]
Sex (Male)	17 (47.2%)	10 (33.3%)	0.253 [†]	8 (47.1%)	9 (28.1%)	0.185 [†]	8 (38.1%)	19 (43.2%)	0.697 [†]	7 (35.0%)	19 (44.2%)	0.491 [†]
Smoker (Yes)	15 (41.7%)	14 (46.7%)	0.684 [†]	12 (70.6%)	11 (34.4%)	0.016[†]	10 (47.6%)	19 (43.2%)	0.736 [†]	8 (40.0%)	20 (46.5%)	0.628 [†]
BMI (Kg/m ²)*	27.2 (±3.9)	25.6 (±3.7)	0.116 [†]	27.1 (±2.8)	25.8 (±4.2)	0.257 [†]	26.8 (±3.7)	26.1 (±3.8)	0.488 [†]	27.5 (±4.1)	25.8 (±3.7)	0.113 [†]
Hypertension (Yes)	8 (22.2%)	6 (20.0%)	0.826 [†]	5 (29.9%)	6 (18.8%)	0.480 [†]	6 (28.6%)	8 (18.2%)	0.353 [†]	5 (25.0%)	8 (18.6%)	0.739 [†]
Diabetes mellitus (Yes)	5 (13.9%)	3 (10.0%)	0.719 [†]	3 (17.6%)	2 (6.3%)	0.326 [†]	2 (9.5%)	5 (11.4%)	1.000 [†]	4 (20.0%)	3 (7.0%)	0.195 [†]
Hyperlipidemia (Yes)	13 (36.1%)	5 (16.7%)	0.077 [†]	5 (29.4%)	7 (21.9%)	0.729 [†]	6 (28.6%)	11 (25.0%)	0.759 [†]	5 (25.0%)	12 (27.9%)	0.809 [†]
Family history of urolithiasis (Yes)	12 (44.4%)	9 (39.1%)	0.704 [†]	10 (71.4%)	6 (28.6%)	0.013[†]	8 (50.0%)	13 (38.2%)	0.432 [†]	7 (41.2%)	15 (45.5%)	0.773 [†]
Water intake (litres)	1.5 (±0.9)	1.5 (±0.7)	0.868 [§]	1.6 (±0.8)	1.3 (±0.7)	0.196 [§]	1.5 (±0.7)	1.4 (±0.8)	0.233 [§]	1.4 (±0.6)	1.5 (±0.8)	0.988 [§]
Urinary volume (ml)*	1899.4 (±627.9)	1467.3 (±736.1)	0.012[†]	1902.9 (±603.2)	1560.9 (±729.6)	0.105 [†]	1946.2 (±675.2)	1551.8 (±709.7)	0.037 [†]	1488.5 (±690.6)	1807.7 (±708.4)	0.099 [†]

BMI – body mass index

Level of significance <0.05 . p-values denoting statistical significance are highlighted in bold

* Results represent mean and the respective standard deviation; † t-test for independent samples; ‡ Chi-square; § Non-parametric test used: Mann-Whitney U test

with the introduction of some pharmacological options (i.e. allopurinol, citrate or thiazides) that might prevent urinary stone formation [10].

There is great variability in the literature regarding the prevalence of urolithiasis according to gender. Our sample revealed a predominance of women (1.39:1), the same ratio pointed by Amaro et al. [14], but different from other studies, with a gender ratio male/female of 1.5–2.5 across the world. The gender ratio discussion of this study is precluded by the methods of patients' referral which influences our outpatient clinic representativeness of the general population.

It is known that obesity and weight gain increase the risk of stone formation [8]. In our study, the majority (60.6%) of patients were overweight or obese and the increase of BMI was associated with a higher urinary calcium excretion. These patients may benefit from nutritional counseling for weight loss, aiming for the reduction of stone recurrence and decreasing cardiovascular risk. We also observed that BMI was inversely related to urinary pH, explained by the hypothesis that obesity may induce excessive production of acidic urine secondary to insulin resistance [19]. Almost a third (29%) of patients presented a urinary pH less than 5.5, a documented risk for uric acid nephrolithiasis. Patients with persistently low urinary pH benefit from urine alkalinization [7, 19].

Patients with hypercalciuria were older than those without this metabolic abnormality, with a median age around 55 years. Otto et al. also observed that middle age patients are more likely to be hypercalciuric [20].

The higher prevalence of present and former smokers among patients with hyperoxaluria sustains the studies of Hamano et al. The authors suggested an interplay between cigarette smoking and arginine vasopressin, resulting in a further decrease of urinary output and enhancing stone formation. Therefore, smoking cessation can be effective in reducing calcium stone recurrence [21].

According to the European Association of Urology Guidelines for Urolithiasis [13], one preventative risk for stone formation relies on a higher fluid intake, 2.5–3.0 l/day, in order to maintain a urinary volume between 2 and 2.5 l/day. We observed that 62.7% of patients presented a lower 24-hour urine output (<2 l in 24 h) and recommending an increased fluid intake should be considered the first option as a general treatment of these patients.

Despite our findings, in clinical practice the implementation of an extensive metabolic evaluation is still controversial. In our opinion, given the high prevalence of metabolic abnormalities in our population, it seems to be worth performing an extended metabolic evaluation in all patients admitted to

the urolithiasis clinics in a tertiary hospital. In fact, this work-up has prompted the prescription of preventive measures and drugs in a significant number of patients. We believe that this work-up is also cost effective, with a reduction of new stone-related events, such as admission to the Emergency Department (ER) and possible need for urgent surgical intervention, follow-up consultations and future non-invasive or minimally invasive procedures. Whether or not this proactive attitude should be extended to primary health care level remains to be elucidated. Despite being an important ionic molecular inhibitor, our laboratory was unable to measure urinary citrate which is an important limitation of this study. Also, some urine samples did not present oxalate measurement due to unexpected laboratory technical problems. We decided to perform just one 24-hour urine collection for the sake of the patient's convenience and adherence, and in fact the need for one versus two 24-hour urine collections during the initial metabolic evaluation is still an unsolved issue [22].

Although this is a cross-sectional descriptive study, the present patient database represents a cohort of patients that will allow further investigation. Ongoing studies intend to evaluate initial metabolic

profiles as predictors of therapeutic success and recurrence outcomes. The identification of metabolic abnormalities and the implementation of specific diet changes and pharmacological treatment, when clinically indicated, should be complemented with a close follow-up of all patients in order to estimate future recurrence rates, clinical outcomes for ER admission and the need for surgical procedures.

CONCLUSIONS

Given the significant burden of urinary stone disease in our clinical practice along with the significantly high prevalence of metabolic abnormalities, we support the metabolic evaluation, irrespective of the presence or absence of recurrence, as an invaluable step in the clinical work-up of these patients. This immediate metabolic evaluation is the key for a better and individualized management, guiding the selection of proper pharmacological and dietary measures to prevent recurrent stone formation and to relieve all clinical and economic burden behind this condition.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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