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Should metabolic evaluation be performed in patients with struvite stones?

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Abstract Previous studies suggested that patients with pure struvite calculi rarely have underlying metabolic abnormalities. Therefore, most of these patients do not undergo metabolic studies. We report our experience with these patients and their response to directed medical therapy. Between 1/2005 and 9/2012, 75 patients treated with percutaneous nephrolithotomy for struvite stones were identified. Of these, 7 had pure struvite stones (Group 1), 32 had mixed struvite stones (Group 2), both with metabolic evaluation, and 17 had pure struvite stones without metabolic evaluation (Group 3). The frequency of metabolic abnormalities and stone activity (defined as stone growth or stone-related events) was compared between groups. The median age was 55 years and 64 % were female. No significant difference in race, infection history, family history, stone location or volume existed between groups. Metabolic abnormalities were found in 57 % of Group 1 and 81 % of Group 2 patients. A similar proportion of Group 1 and 2 patients received modification to or continuation of metabolic therapy, whereas no Group 3 patients received any directed therapy. In patients with >6 months follow-up, the stone activity rate between Groups 1 and 2 appeared similar whereas Group 3 trended towards higher stone activity rate. Metabolic abnormalities in pure struvite stone formers appear to be more common than previously reported. Directed medical therapy in these patients may reduce stone activity. The role of metabolic evaluation and directed medical therapy needs reconsideration in patients with pure struvite stones.

Keywords Struvite · Nephrolithiasis · Treatment outcome · Recurrence

Abbreviations

UTI	Urinary tract infection
AHA	Acetohydroxamic acid
PNL	Percutaneous nephrolithotomy
IVP	Intravenous pyelogram
NCCT	Non-contrast computed tomography
KUB/TOMO	Plain radiograph of the abdomen with tomogram
BMI	Body mass index
SD	Standard deviation
IQR	Interquartile range

Introduction

Struvite stones have historically been reported to comprise 5–15 % of all renal calculi [1]. Although great strides have been made in management, these oftentimes complex calculi continue to cause significant morbidity [2–4]. Left untreated, struvite stones can grow and involve the entire kidney, leading to recurrent urinary tract infections (UTI), episodes of hematuria, flank pain, pyelonephritis or sepsis. Ultimately struvite calculi may lead to complications such as pyonephrosis, perinephric abscess formation or

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xanthogranulomatous pyelonephritis with eventual renal failure, loss of the kidney, and even death [5, 6]. Effective management of struvite stones should begin with complete stone removal when possible, followed by medical management to prevent stone recurrence [7].

Effective medical preventive therapy after stone removal is imperative for these patients as it has been demonstrated that up to 50 % of patients with struvite stones continue to experience stone growth despite some form of medical therapy [7–10]. Antibiotic prophylaxis and the urease inhibitor acetohydroxamic acid (AHA) have been used with varying reported success and compliance [7, 9–11]. However, the use of metabolic evaluation and therapy in pure struvite stone formers has been controversial [8, 12–14]. There has been a lack of studies evaluating the effect of metabolic-directed therapy in struvite stone formers. Therefore, we performed a retrospective analysis of struvite stone patients treated at our center to determine the rate of metabolic abnormalities in these patients as well as the impact of metabolic-directed therapy on stone activity.

Materials and methods

After institutional review board approval, a retrospective chart review of all patients who had received a percutaneous nephrolithotomy (PNL) between January 2005 and September 2012 was performed. Per institutional standard practice, all retrievable fragments during PNL were submitted for StoneComp™ evaluation (Mandel International Stone and Molecular Analysis Center, Milwaukee, WI). Per StoneComp™ analysis protocol, the entire sample is ground and mixed. Portions are then analyzed with Fourier transform infrared spectroscopy and supplemented as needed with high-resolution X-ray crystallographic methods.

Of a total of 610 patients identified, 75 were found to have struvite on stone analysis. These patients were classified into 3 categories. Group 1: Patients with pure struvite stones who received a metabolic evaluation; Group 2: Patients with mixed struvite stones who received metabolic evaluation; Group 3: Patients with pure struvite stones who did not receive a metabolic evaluation. Patients with mixed struvite stones and no metabolic evaluation were not included in the evaluation (19 patients). Pure struvite was defined as 100 % magnesium ammonium phosphate ± carbonate apatite, while mixed struvite stone was defined as any amount of struvite with other stone compositions. Adequate follow-up was defined as at least 6 months and the presence of post-operative imaging. Patients with adequate follow-up were designated in a subgroup for an analysis of outcomes.

Demographic information from each patient was collected including age, gender, race and body mass index (BMI). Additionally, co-morbidities related to struvite stones, urinary tract abnormalities, family history of stones, prior stone events, baseline and follow-up stone-directed medical therapy, baseline 24 h urinary metabolic profiles, and urinary tract infection history were recorded. Metabolic abnormalities on 24 h urine were defined as: Hypercalciuria $\geq$250 mg/24 h, Hypernatriuria $\geq$150 mmol/24 h, Hyperoxaluria $\geq$50 mg/24 h, Hyperuricosuria $\geq$800 mg/24 h, Gouty diathesis pH $\leq$ 5.5, Hypocitraturia $\leq$320 mg/24 h and Low volume <2 L/24 h. Struvite stone-related co-morbidities were also assessed including spinal cord injury, spinal dysraphism, significant developmental delay, stroke, poor ambulation and diabetes mellitus. Urinary tract abnormalities included neurogenic bladder, stricture, history of exstrophy, and upper tract anatomical abnormalities.

After PNL, patients were treated with AHA and/or prophylactic antibiotics at the discretion of the treating physician. Metabolic assessment consisted of baseline 24 h urine metabolic evaluation at least 2 months after PNL in a standard fashion, with the absence of active infection at the time of collection confirmed by urine culture. Patients with specific metabolic abnormalities were treated with the appropriate medical therapy termed "directed medical therapy". Patients with specific metabolic defects on 24 h urine were also provided dietary instructions if indicated.

Patients were imaged 3 months after surgery to establish stone-free status. Patients were regularly followed at the Stone Center at 3- and 6-month intervals initially and annually thereafter. Initial imaging was either an intravenous pyelogram (IVP), non-contrast computed tomography scan (NCCT), or plain radiograph of the abdomen with tomograms (KUB/TOMO), while follow-up imaging was typically performed annually with a KUB/TOMO. Additional imaging studies were performed as clinically indicated.

Radiologic imaging studies were evaluated to determine stone burden, stone-free status and stone recurrence. Stone events, type and duration of medical therapy were also recorded. Stone Burden was calculated by multiplying maximum length by the maximum width on KUB/TOMO or coronal NCCT image. These values were summed for patients with multiple stones to determine total stone burden. If coronal reformatted NCCT scans were not available, maximum length was calculated by noting the number of slices containing the stone and multiplying these values by slice thickness.

Stone free was defined as zero residual stone fragments observed on 3-month follow-up imaging with either NCCT or IVP, or KUB/TOMO. Stone growth/recurrence was defined as an increase in size of a residual fragment or new stone formation on follow-up imaging. Stone-related events

were defined as: (1) an acute emergency room visit secondary to pain, gross hematuria or a febrile UTI, possibly resulting in stent or percutaneous nephrostomy tube or (2) a definitive endourological procedure such as PNL, ureteroscopy or shock wave lithotripsy on follow-up. Stone activity was defined as stone growth or a stone event at follow-up. Only patients with at least 6 months of follow-up were evaluated for stone growth and activity.

We used a Chi Square or Fisher's Exact and the Kruskal–Wallis or Wilcoxon rank sum tests as appropriate with a Bonferroni correction for multiple comparisons. For Kaplan–Meier analysis, a Log-Rank test was used. Unadjusted $p < 0.05$ was considered significant. JMP (SAS, Cary, NC, USA) was used for statistical analysis software. Data were represented with mean ± standard deviation (SD) or median with Interquartile Range (IQR).

Results

Of the 75 patients who met the initial criteria, 39 had a metabolic evaluation. Seven patients were found to have pure struvite stones and metabolic evaluation (Group 1), 32 patients had mixed struvite stones and metabolic evaluation (Group 2), and 17 patients with pure struvite stones did not have metabolic evaluation (Group 3). The 19 patients with mixed struvite stones but no metabolic evaluation were excluded for analysis. For subgroup analysis of outcomes, 5 of Group 1, 20 of Group 2, and 12 from Group 3 were found to have adequate follow-up.

Median age was 55 years (IQR: 42–63.5) and 64 % were female. No significant difference was found for age, gender, BMI, race, presence of comorbidities, anatomical abnormalities, UTI history, or family history of stones between the groups (Table 1). The distribution of multiple or complex staghorn stones as well as the preoperative stone burden was similar between the groups. Statistical significance was found between groups with regard to prior stone events and definitive procedures, but on intergroup comparison, a difference was only observed between Groups 2 and 3 for procedures. There was also no significant difference in the frequency of previous directed medical therapy between Group 1 and 2 (Table 2). Appropriately, no patients from Group 3 were found to have any pre- or post-operative directed medical therapy.

Overall metabolic abnormalities were identified in 57 % of Group 1 and 81 % of Group 2 patients, yet no significant differences were found between the groups ($p = 0.319$) (Table 2). As such, there was no difference in the occurrence of hypercalciuria, hyperoxaluria, hyperuricosuria, gouty diathesis and hypocitraturia between the groups. Notably, there was a high proportion (87 %) of patients with hypercalciuria with associated hypernatriuria. There was no significant difference in 24 h urine metabolic values between mixed and pure struvite stone formers (Table 1).

Immediately post-operatively, a greater proportion of Group 1 patients received AHA versus Group 2 (86 and 28 %, respectively) ($p = 0.008$). A smaller proportion of Group 2 patients also received antibiotic therapy (34 %) compared to Group 1 (86 %) and Group 3 (76 %), though only the difference between Group 2 and 3 was statistically significant ($p = 0.007$) (Table 2). Regarding directed medical therapy, 86 % Group 1 and 88 % Group 2 patients received continuation of or changes to directed medical therapy, whereas Group 3 patients received no such management ($p > 0.999$) (Table 2).

Of the 5 patients from Group 1 with adequate follow-up, one patient (20 %) had stone activity at 15 months. Of the 20 from Group 2, 30 % of patients had stone activity within a median time of 19 months (IQR: 18–32). While in Group 3, of the 12 patients with adequate follow-up, there was an increased trend in stone activity, with 50 % having stone growth or events within a median time of 17 months (IQR: 9–22). There was no statistical significance in post-treatment urinary infections, stone activity rate or time to activity between groups ($p = 0.90$, 0.45, 0.55, respectively) (Table 3). However, on Kaplan–Meier analysis, a difference was found between Group 2 and Group 3 with respect to stone activity ($p = 0.01$). No difference was identified between Group 1 and Group 2 or 3 ($p = 0.76$ and 0.26, respectively) (Fig. 1).

Discussion

Struvite stones cause significant morbidity and mortality if left untreated. Although surgical clearance is the cornerstone of management, the use of metabolic evaluation to direct preventative therapy has been controversial. In the 1970s and 1980s, metabolic evaluation was recommended by several authors based on findings of high prevalence of metabolic abnormalities [12, 13, 15, 16]. However, these recommendations were opposed later by others on the basis of low recurrence rate [17], pure infectious etiology with urease enzyme production as the key to stone formation [13, 18, 19], or low occurrence of metabolic abnormalities in pure struvite stone formers [8]. Furthermore, the American Urological Association guidelines for management of staghorn calculi from 2005 recommended against metabolic evaluation of pure struvite stones [14].

The current study is the first in almost 20 years to describe metabolic abnormalities separately in pure and mixed struvite stone formers and to evaluate the effect of directed medical therapy on stone activity. Streem previously reported on occurrence of metabolic abnormalities in 53 % (9 of 17) of struvite stone formers with 17 % having

Table 1 Patient demographics of struvite stone patients with or without metabolic evaluation

	Pure struvite + metabolic evaluation Group 1	Mixed struvite + metabolic evaluation Group 2	Pure struvite No metabolic evaluation Group 3	*p* value
Patients (*n*)	7	32	17	
Age ± SD	49 ± 18	52 ± 13	57 ± 15	0.55†
Gender				0.78‡
Male (*n*)	3 (43 %)	12 (38 %)	5 (29 %)	
Female (*n*)	4 (57 %)	20 (62 %)	12 (71 %)	
BMI ± SD	30 ± 8	29 ± 7	26 ± 6	0.24†
Race				0.29‡
White (*n*)	7 (100 %)	24 (75 %)	11 (65 %)	
Black (*n*)	0 (0 %)	5 (16 %)	4 (24 %)	
Other (*n*)	0 (0 %)	3 (9 %)	2 (12 %)	
Prior stone event (*n*)	1 (14 %)	21 (66 %)	5 (29 %)	0.007‡**
Definitive procedure	1 (14 %)	19 (59 %)	3 (18 %)	0.004‡**
Comorbidities (*n*)	3 (43 %)	11 (34 %)	5 (29 %)	0.82‡
History of recurrent UTI's (*n*)	3 (43 %)	14 (44 %)	8 (47 %)	0.97‡
Family history (*n*)	1 (14 %)	3 (9 %)	2 (12 %)	0.92‡
Stone side				0.82‡
R (*n*)	5 (71 %)	19 (59 %)	10 (59 %)	
L (*n*)	2 (29 %)	13 (41 %)	7 (41 %)	
Stone characteristics				0.98‡
Single (*n*)	1 (14 %)	6 (19 %)	2 (12 %)	
Multiple (*n*)	2 (29 %)	9 (28 %)	5 (29 %)	
Staghorn (*n*)	4 (57 %)	17 (53 %)	10 (59 %)	
Stone burden (median)	9.3 cm^2	10.6 cm^2	11.4 cm^2	0.95†
IQR	3.7–30.5 cm^2	7.2–19.4 cm^2	4.2–31.5 cm^2	
24 H urine results ± SD				
Creatinine (mg)	1344 ± 288	1290 ± 597	–	0.73¥
Calcium (mg)	237 ± 107	224 ± 163	–	0.55¥
Sodium (mmol)	217 ± 115	191 ± 92	–	0.76¥
Oxalate (mg)	59 ± 52	35 ± 16	–	0.18¥
Citrate (mg)	444 ± 189	406 ± 270	–	0.70¥
Uric acid (mg)	661 ± 196	635 ± 293	–	0.70¥
pH	6.4 ± 0.4	6.1 ± 0.5	–	0.17¥
Volume (L)	1.8 ± 0.8	1.7 ± 0.9	–	0.94¥

† Kruskal–Wallis, ‡ Chi Square, ¥ Wilcoxon rank sum, * no statistical difference on intergroup comparison, ** statistical difference between Group 2 and 3 on intergroup comparison

hypercalciuria, 12 % renal tubular acidosis, 6 % hyperoxaluria and 6 % hypocitraturia [4]. However, pure and mixed struvite stones were not separated in the analysis. We found a higher than expected prevalence of metabolic abnormalities in pure struvite stone formers at 57 %. It appeared that mixed stone formers had a higher prevalence of these abnormalities. However, this difference was not statistically significant. In one of the few studies on metabolic evaluation of pure struvite stones, Lingeman et al. reported metabolic abnormalities in only 14.2 % of a small cohort of pure struvite stone formers (2 of 14), with hypercalciuria being the only abnormality identified [8]. We identified hypercalciuria in 43 %, hyperoxaluria in 29 %, hyperuricosuria in 29 % and hypocitraturia in 14 % of our pure struvite stone formers (Table 2). Interestingly, the distribution of these metabolic abnormalities was not significantly different between all groups. The lack of difference may be attributed to small sample size. Lingeman et al. further reported that calcium levels were significantly higher in mixed stones (342 vs 136 mg/day). Interestingly, we did not find

Table 2 Metabolic abnormalities by type of struvite stone and the presence of metabolic evaluation

	Pure + eval Group 1	Mixed + eval Group 2	Pure no eval Group 3	*p* value
Patients (*n*)	7	32	17	
Mixed stone composition				
Brushite (*n*)	–	7 (22 %)	–	–
Ammonium (*n*)	–	6 (19 %)	–	–
Phosphate (*n*)	–	16 (50 %)	–	–
Calcium (*n*)	–	8 (25 %)	–	–
Matrix (*n*)	–	2 (6 %)	–	–
Metabolic abnormalities				
Any (*n*)	4 (57 %)	26 (81 %)	–	0.32§
Hyper calciuria (n)	3 (43 %)	12 (38 %)	–	>0.99§
With hyper natriuria (*n*)	2 (67 %)	11 (92 %)	–	0.37§
Hyper Oxaluria (*n*)	2 (29 %)	5 (16 %)	–	0.59§
Hyper Uricosuria (*n*)	2 (29 %)	12 (38 %)	–	>0.99§
Gouty Diathesis (*n*)	0 (0 %)	4 (13 %)	–	>0.99§
Hypo Citraturia (*n*)	1 (14 %)	13 (41 %)	–	0.39§
Medical therapy				
Lithostat post-op (*n*)	6 (86 %)	9 (28 %)	9 (53 %)	0.008§*
Antibiotic post-op (*n*)	6 (86 %)	11 (34 %)	13 (76 %)	0.007§**
Metabolic therapy				
Pre-op (*n*)	3 (43 %)	10 (31 %)	0	0.67§*
Post-op (*n*)	5 (71 %)	28 (88 %)	0	0.29§*
Change or continuation (*n*)	6 (86 %)	28 (88 %)	0	>0.99§*

§ Fisher's Exact, * Intergroup comparison between Group 1 and 2, ** Intergroup comparison between Group 2 and 3

any difference in 24 h urine metabolic values between pure and mixed struvite stone formers (Table 1).

There is a paucity of studies in the literature evaluating the impact of metabolic evaluation on treatment alterations or the ultimate effect of metabolic treatment in impacting struvite stone outcomes. In Lingeman et al.'s study, 50 % of pure struvite and 43 % of mixed struvite stone formers had stone growth [8]. All of their patients received antibiotic prophylaxis, 14 % received AHA, 38 % thiazide diuretics and 23 % urinary acidification. However, the authors did not classify treatments according to stone type or delineate the impact of metabolic evaluation on treatment during the study. Other investigations have either failed to separate pure from mixed struvite stones or have not performed metabolic evaluation or directed medical treatment, whereby the impact of metabolic abnormalities and treatment on recurrence could not be ascertained [3, 4, 17].

Similar to Lingeman et al., we found 42 % stone growth and 50 % stone activity in patients with pure struvite stones who did not receive metabolic evaluation. These patients did not receive directed medical therapy. However, metabolic evaluation resulted in a change or continuation of metabolic therapy in 86 % of pure and 88 % of mixed struvite stone formers. Stone activity was found to be 20 and 30 % in these two groups, respectively. Moreover, Kaplan–Meier analysis revealed a significant difference in stone activity between the mixed struvite stone formers who underwent metabolic assessment and the pure struvite stone patients who did not undergo evaluation (Fig. 1). The difference between the pure struvite stone patients who did and did not undergo metabolic evaluation was not statistically significant, but the curves were widely separated. This finding may be due to the small number of patients and relatively short follow-up.

Hypocitraturia is a known risk factor for nephrolithiasis, occurring in as many as 20–60 % of stone formers [20–22]. Citrate complexes with both calcium and magnesium decreasing the availability of these ions for crystallization. Although magnesium plays an inhibitory role in calcium stone formation [23], experimental studies have shown that reduction in urinary magnesium may inhibit struvite stone formation [24]. In vitro work has demonstrated that citrate reduces struvite crystal formation rate by complexing magnesium and interfering with the crystal structure [25]. Hypocitraturia resulting from metabolic deficiency or bacterial metabolism may lead to loss of this protective effect [26]. As such, we found hypocitraturia in 14 % of pure and

Table 3 Outcomes in patients with adequate follow-up by struvite type and the presence of metabolic evaluation

	Pure + eval Group 1	Mixed + eval Group 2	Pure no eval Group 3	*p* value
Patients (*n*)	5	20	12	
Post-operative therapy				
Lithostat (*n*)	4 (80 %)	6 (30 %)	6 (50 %)	0.10[§]
Antibiotics (*n*)	4 (80 %)	8 (40 %)	9 (75 %)	0.075[§]
Metabolic therapy (*n*)	4 (80 %)	19 (95 %)	0	0.37[§]*
Post-operative outcomes				
Stone free (*n*)	2 (40 %)	9 (45 %)	4 (33 %)	0.89[§]
Median follow-up (mo)	22 (IQR: 11–28)	39 (IQR: 17–60)	20 (IQR: 10–29)	0.041[†]**
Urinary infection (*n*)	2 (40 %)	10 (50 %)	5 (42 %)	0.90[§]
Stone activity (*n*)	1 (20 %)	6 (30 %)	6 (50 %)	0.45[§]
Stone growth (*n*)	1 (20 %)	4 (20 %)	5 (42 %)	0.45[§]
Stone event (*n*)	1 (20 %)	5 (25 %)	3 (25 %)	>0.99[§]
Time to activity (mo)	15	19 (IQR: 18–32)	17 (IQR: 9–22)	0.55[†]

[†] Kruskal–Wallis, [§] Fisher's Exact, * statistical difference between Group 1 and 2 on intergroup comparison, ** statistical difference between Group 2 and 3 on intergroup comparison

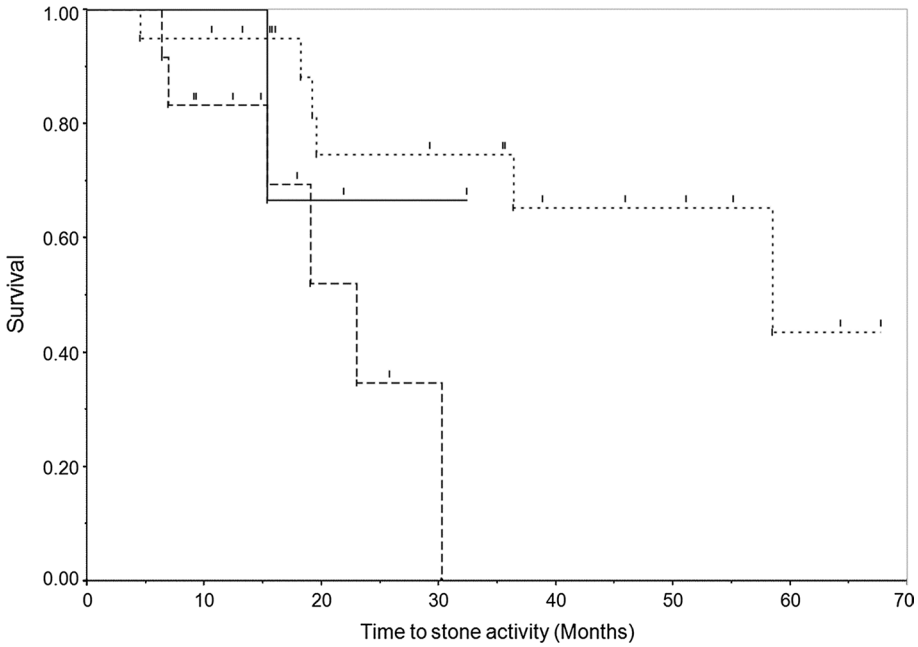

Fig. 1 Survival analysis with Kaplan–Meier Curve (Months) in patients with adequate follow-up. (*Solid line*) Group 1, (*dot line*) Group 2, (*dash line*) Group 3. Group 2 vs 3, $p = 0.01$ (Log-Rank)

41 % of mixed struvite stone formers (Table 2). We suggest that treatment with potassium citrate may reduce this citrate deficit and help prevent struvite crystallization, although this is not ascertainable through our study. It is generally believed that struvite stones cannot form in urinary pH < 7.19 [27]. In the current study, the mean urinary pH in our struvite stone formers was 6.2 ± 0.5, which allowed us to supplement citrate with potassium citrate without concern for over alkalization (Table 1). Although we do not have values of the urinary pH prior to surgical stone removal, it is possible that the finding of low urine pH in our struvite stone formers was reflective of clearance of stone and infection.

Hypercalciuria is also an important risk factor for stone disease and is known to occur in 35–65 % of metabolic stone formers [28]. We identified hypercalciuria in 43 % pure and 38 % mixed struvite stone formers (Table 2). High calcium excretion at alkaline pH levels complexes with carbonate and phosphate ions to form carbonate apatite, a component of struvite [18]. Lowering urinary calcium may prevent apatite crystal growth resulting in a positive impact on struvite stone disease. The majority (87 %) of patients with hypercalciuria were found to have hypernatriuria. Therefore, dietary modifications may be beneficial for struvite stone formers.

Overall stone-free rates of 40.5 % achieved in our study were relatively modest. This finding can be explained by the fact that a high percentage of our patients had staghorn calculi, with a high mean stone burden (1765 mm^2) Secondly, post-operative imaging consisted of either NCCT, KUB/TOMO, or IVP. Finally, we adhered to a strict definition of "stone free" as absolutely no fragments on high-quality imaging. Others have reported high stone-free rates utilizing only plain radiograph, with the CROES PNL global study reporting a stone-free rates of 82 % in 2806 patients with a mean stone burden of only 463 mm and a residual fragment <4 mm being stone free [29]. The BAUS PNL data registry of 1009 patients reported stone-free rates of 47 and 77 % for staghorn and non-staghorn calculi, respectively, using less stringent criteria [30].

Our study had several limitations. It is a retrospective review with an inherent bias in treatment selection and follow-up. There was an absence of any uniform metabolic evaluation and treatment protocol. Due to the small number of patients, the study was under powered, and we were therefore unable to analyze the effects of any specific preventive medication on stone activity or confounders.

Nevertheless, our findings suggest a potential need to evaluate and treat pure struvite stone formers for metabolic abnormalities. Because of small sample size and inability to standardize for potential confounders, it is difficult to make a definitive recommendation. Ours is perhaps the only study that suggests an effect of metabolic evaluation on stone activity. The idea of metabolic evaluations for these patients should be reconsidered. A larger prospective study could help to better understand this issue.

Conclusions

Metabolic abnormalities in struvite stone formers including patients with pure struvite stones appear to be more common than previously reported. Although likely underpowered, our findings suggest further inquiry into role of metabolic evaluation in pure struvite stone formers.

Compliance with ethical standards

Conflict of interest Muhammad Waqas Iqbal, Richard H. Shin, Ramy F. Youssef, Adam G. Kaplan, Fernando J. Cabrera, Jonathan Hanna, and Charles D. Scales declare that they have no conflict of interest. Michael N. Ferrandino is a Proctor for Intuitive Surgical. Glenn M. Preminger is a consultant for Boston Scientific, Mission Pharmacal and has received a speaker honorarium from Olympus. Michael E. Lipkin is a consultant for Boston Scientific and has received a speaker honorarium from Lumenis.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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