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ORIGINAL RESEARCH

Can risk factors distinguish pure and combination struvite stone formers in a South African cohort?

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Purpose: This study aims to assess whether clinical variables distinguish pure struvite stone formers from combination/mixed struvite stone formers.

Methods: A retrospective folder review was done on patients in the Western Cape, South Africa between January 2015 and December 2020. All patients with stone analyses reporting struvite were included. Demographic data, stone factors, surgical management, and risk factors for struvite nephrolithiasis were recorded. Risk factors and clinical variables of pure struvite stone (PSS) formers and combination/mixed struvite stone (CSS) formers were compared. This protocol was approved by an institutional review board.

Results: A total of 53 patients were included, 30 (56.6%) with PSS and 23 (43.4%) with CSS. There was a female predominance of 32/53 (66.7%). The mean age (SD) was 46 ± 13 years. There were no differences in age (46 ± 12 vs 45 ± 15, $p = 0.371$) or gender distribution between the PSS and CSS groups.

There were no differences between PSS and CSS patients in the prevalence of urinary tract infections (UTI), staghorn configuration, location of stones, stone management or the prevalence of any individual risk factor (immunosuppression, anatomical abnormalities, recurrent UTIs) examined.

The distribution of the number of risk factors differed significantly between PSS and CSS formers ($p = 0.022$, Mann-Whitney U-test).

Conclusion: Although the distribution of the number of risk factors was different between patients with PSS and CSS formers, overlap in the number of risk factors within groups limits the clinical usefulness of this finding. Individual risk factors do not discriminate PSS formers from CSS formers and should not be used to guide clinical decisions. Routine stone analysis is recommended in struvite nephrolithiasis.

Keywords: struvite, nephrolithiasis, risk factors, renal stones

Background

Struvite nephrolithiasis is associated with infection by urea-splitting organisms and represents approximately 5–15% of renal calculi in published series and 24% of staghorn calculi. In South African series, 4–9% of stones are reported as struvite. These are reported more often in women (2:1 ratio) due to their higher susceptibility to urinary tract infections (UTIs) and also in patients with anatomical abnormalities, urinary stasis, neurogenic bladder dysfunction and immunosuppression.[1-5] Urease-producing organisms hydrolyse water and urea into ammonia and carbon dioxide. Ultimately, urinary pH is increased by the generation of ammonium. *Proteus mirabilis* is the most commonly implicated organism in struvite nephrolithiasis. However, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Pseudomonas species*, *Providencia, Staphylococcus aureus* and *Ureaplasma urealyticum* have also been reported.[2] Although *Escherichia coli* is a common cause of (UTIs), it rarely produces urease and is not usually associated with the pathogenesis of struvite stones. The increase in urinary pH (pH > 7.2) allows the precipitation of naturally occurring ions in urine (magnesium, calcium and phosphate) into struvite, and carbonate apatite when the pH is 6.8–7.2. Struvite calculi are composed primarily of magnesium ammonium phosphate hexahydrate but may also contain carbonate apatite.[4]

Bacterial colonies produce biofilms that shield bacteria from antibiotics; however, both the bacteria and the exopolysaccharides they secrete become integrated into stones as a matrix/scaffold for crystalline components of the struvite calculus.[1] Struvite calculi, therefore, often assume the shape of the renal collecting system and are described as "staghorn" stones as the shape resembles the horns of a stag. Although there is no consensus on the definition, a stone that occupies the renal pelvis and one or more calices is often described as a staghorn stone.[6] Staghorn stones are more challenging to manage surgically due to their size and involvement of multiple calyces.[7]

Chronic infection and obstruction cause deterioration of renal function and may present with severe sequelae such as a non-functioning kidney, pyonephrosis, granulomatous pyelonephritis, perinephric collections, empyema, and fistulae to surrounding organs and skin.[8] The mainstay of treatment is the complete removal of the stone (usually by percutaneous nephrolithotomy) and long-term antibiotic prophylaxis to prevent recurrence.[1,2,7]

It is recommended that recurrent renal stone formers and "high-risk" stone formers are investigated to identify serum or urinary factors which may predispose patients to recurrent nephrolithiasis.[9] Serum biochemistry and 24-hour urine collection are done after stones have been completely removed. Although metabolic evaluation for patients with infection-related/struvite stones was previously controversial, recent publications have reported a higher prevalence of metabolic anomalies than previously reported.[1,2,5-8] Despite the increasing evidence of underlying metabolic abnormalities in patients with struvite nephrolithiasis, it is still uncommon for patients with presumed infection stones to have a metabolic evaluation in our service. This is relevant in the resource-limited setting where patients who present with non-functioning kidneys due to obstructing calculi are rarely investigated after nephrectomy. Budgetary constraints in a resource-limited healthcare service and transport costs for patients to return to healthcare facilities for tests hamper the access to full metabolic evaluation for stone formers. An undiagnosed underlying predisposition to recurrent calculi in a patient with a single kidney is potentially catastrophic. There is a well-documented correlation between nephrolithiasis and renal dysfunction.[7,10]

Although the risk factors for struvite nephrolithiasis are well-defined, few studies interrogate the predictive value of risk factors to identify struvite stone formers. Stone analysis is standard in well-resourced healthcare systems but is often not done in resource-constrained services.[11] Until recently, this was often the case in our service, and struvite nephrolithiasis was a presumptive diagnosis based on risk factors and clinical variables.

Scant published data are available about the epidemiology of struvite nephrolithiasis and nephrolithiasis in general in South Africa. It is unclear whether local stone formers are similar in risk factor profile to other populations. There is one report which showed that local stone formers form different types of stones compared to Ghanaian stone formers; however, this study reported on all stone compositions and did not examine clinical risk factors.[11]

This study aims to assess whether risk factors and clinical variables are useful to differentiate between pure and combination/mixed struvite stone formers and to report the basic demography and risk factor prevalence in this population of stone formers.

Methods

A retrospective folder review of patients who were entered onto a prospective database at a specialist nephrolithiasis clinic, was performed. All patients who had struvite-containing calculi collected during surgery between January 2015 and December 2020 were included. Stones were analysed at Pathcare laboratories (outsourced by National Health Laboratory Services) using Fourier transform infrared (FTIR) spectroscopy (Agilent Technologies, Cary 630 FT-IR spectrometer). Demographic data, medical history (diabetes, HIV, immunosuppressive disorders/treatment), anatomical abnormalities (ileal conduit, neuropathic bladder), and use of indwelling or intermittent self-catheterisation were recorded. Stone factors such as location (renal or ureteric), stone shape (staghorn or non-staghorn) and surgical procedure performed (percutaneous nephrolithotomy [PCNL] or endoscopic removal) were recorded. Positive urine cultures during the six months prior to surgery were also recorded. The protocol was approved by an institutional ethics review board (University of Cape Town Human Research Ethics Committee).

Continuous variables were reported as means, and categorical variables were reported as percentages. Pearson's chi-square was used to compare categorical variables. In addition, a two-tailed, independent T-test was used for continuous variables. IBM® SPSS version 26 was used for statistical analyses.

Results

A total of 53 patients with struvite-containing nephrolithiasis were included in this study. Of these, 30/53 (56.6%) of calculi contained only struvite (and other components associated with infection), 16/53 (30.2%) contained struvite and calcium oxalate, and 7/47 (13.2%) contained a combination of struvite and uric acid. There was a female predominance of 32/53 (60.4%). The mean age (SD) of the population was 46 ± 13 years. There were no differences in age (46 ± 12 vs 45 ± 15, $p = 0.371$) and gender (Pearson chi-square $p = 0.285$) distribution between the PSS and CSS groups (Table I).

Of the total number of patients, 35/53 (66%) of the stones were renal and the rest (18/53, 34%) were ureteric calculi. Also, 24/35 (68.5%) of renal stones were staghorn configuration stones.

The distribution of stone location was similar between PSS formers (9, 30% ureteric vs 21, 70% renal) and CSS formers (9, 39.1% ureteric vs 12, 60.9% renal). There were no significant differences in location based on stone composition ($p = 0.487$, Pearson's chi-square).

More PSSs (16/21, 76.1%) were staghorn-shaped than CSSs (8/12, 57.1%). This difference was not statistically significant ($p = 0.179$, Pearson's chi-square).

Eighteen (60%) patients with PSS were managed with PCNL versus 12 (52.5%) patients in the CSS group. The rest of the stones were managed endoscopically with ureteroscopy and laser lithotripsy, except for one ureteric stone removed laparoscopically.

In total, 30/35 (85.7%) of renal stones were managed by PCNL. There was no difference in the surgical management (PCNL vs endoscopic) between PSS and CSS ($p = 0.569$, Pearson's chi-square).

Only 28/53 (52.8%) of patients had a documented UTI during the six months preceding their stone procedure. Five patients (8.5%) had more than one organism identified, while nine patients (17%) had more than one episode (recurrent UTI) during the six months preceding stone surgery. There was no difference between the prevalence of UTI in patients with PSSs and CSSs (16/30, 53.3% vs 12/23, 52.1%, $p = 0.933$). The five patients who cultured more than one organism were all PSS formers. *E. coli* was the most common organism cultured (12/28, 42.8%).

Only 29/53 (54.7%) patients had an identifiable risk factor for struvite nephrolithiasis (immunosuppression, anatomical abnormality, neuropathic bladder, ileal conduit, catheter or recurrent UTIs). Less CSS formers had identifiable risk factors for nephrolithiasis recorded (10/23, 43.5%) than PSS formers (19/30, 63.3%). This difference was not statistically significant ($p = 0.150$, Pearson's chi-square). Diabetes mellitus, neurological bladder dysfunction and recurrent UTIs were the most common risk factors identified, and all occurred in 9/53 patients (17%). Only 3/53 (5.7%) patients were HIV positive. Neurogenic bladder dysfunction seemed higher in patients with PSSs (7/30, 23.3%) than in patients with CSSs (2/22,

Table I: Demographics and risk factors of struvite-only and struvite-combination stones

	All	Struvite-only	Struvite-combination	*p*-value
Demographics				
Patients (*n*)	53	30	23	
Age ± SD (years)	46 ± 13	46 ± 12	45 ± 15	.371*
Male (*n*)	21 (39.6%)	10 (33.3%)	11 (47.8%)	.285†
Female (*n*)	32 (60.4%)	20 (66.7%)	12 (52.2%)	
Stone factors				
Renal	35 (66%)	21 (70%)	14 (60.9%)	.487†
Ureter	18 (34%)	9 (30%)	9 (39.1%)	
Staghorn (of renal total)	24 (68.5%)	16 (76.1%)	8 (57.1%)	
PCNL	30 (56.6%)	18 (60%)	12 (52.5%)	.569†
Endoscopic	23 (43.4%)	12 (40%)	11 (47.8%)	
Risk factors				
Any risk factor present	29 (54.7%)	19 (63.3%)	10 (43.5%)	.150†
Diabetes mellitus	9 (17%)	4 (13.3%)	5 (21.7%)	
HIV	3 (6.4%)	2 (8%)	1 (4.5%)	
Immunosuppression	5 (9.6%)	4 (13.3%)	1 (4.5%)	
Ileal conduit	4 (7.5%)	3 (10%)	1 (4.3%)	
Neurology	9 (17%)	7 (23.3%)	2 (8.7%)	
Indwelling catheter	4 (7.5%)	4 (13.3%)	0	
Self-catheterisation	3 (5.7%)	2 (6.7%)	1 (4.3%)	
Recurrent UTI	9 (17%)	7 (13.2%)	2 (3.8%)	
Urinary tract infection				
UTI‡	28 (52.8%)	16 (53.3%)	12 (52.1%)	.933†
Escherichia coli	12	7	5	
Morganella morgani	1	0	1	
Pseudomonas aeruginosa	2	1	1	
Klebsiella pneumoniae	3	3	0	
Citrobacter	1	0	1	
Enterococcus	3	1	2	
Streptococcus Group B	4	3	1	
Proteus mirabilis	3	3	0	
Candida albicans	1	1	0	
Providencia rettgeri	2	2	0	
Enterobacter aerogenes	1	1	0	
Lactobacillus species	1	1	0	

*Two-tailed T-test, †Pearson chi-square, ‡number of patients with a documented UTI episode(s)
Percentages represent percentage within the stone composition group affected.

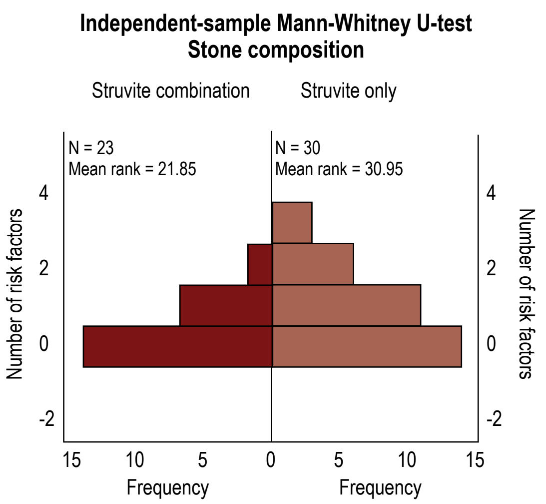

Figure 1: Distribution of risk factors in struvite stone formers

8.7%). The two patients with neurology and combination stones had stones that contained urates in addition to struvite.

The proportion of patients with immunosuppression, diabetes mellitus, HIV, ileal conduits, and indwelling/intermittent catheterisation was similar between both PSS and CSS formers (Table I).

The distribution of the number of risk factors differed significantly between PSS and CSS formers ($p = 0.022$, Mann-Whitney U-test) (Figure 1).

Discussion

The proportion of pure struvite stones in this series (56%) is higher than in other series reported by Flannigan et al. (13.2%) and Iqbal et al. (47%).[2,8] This discrepancy may be partially accounted for by the slightly higher prevalence of neuropathic bladder dysfunction

(11.6% vs 17%) and ileal conduit urinary diversions (7.5% vs 2.5%) than reported in the Flannigan series.[2] However, other studies reporting on risk factors in struvite stone formers only report metabolic risk factors identified on 24-hour urine studies, as in the Igbal et al. study;[8] therefore, comparisons cannot be made to assess whether this cohort was similar to other populations in risk factor profile.[2,8]

It is not unexpected that there was little difference in the management of stones between the PSS and CSS groups. The distribution of stone location was similar between these groups and surgical management is dictated by stone location and size, not composition.[9]

Infection with urease-producing organisms seemed low in this cohort, but was similar to the 30% reported by Flannigan et al.[2] Although *E. coli* was the most common isolate reported, very few isolates produce urease and, therefore, this organism is not usually associated with the pathogenesis of struvite lithiasis. *E. coli* is the most common cause of UTI in the general population; thus, although not implicated in struvite pathogenesis, the high prevalence of *E. coli* UTI is expected. The low proportion of patients with UTI (58%) makes it a poor indicator of struvite nephrolithiasis. The similarity in the number of UTI episodes and type of organisms cultured between the groups makes UTI a poor discriminator between pure and combination struvite stones.

In patients who require nephrectomy for non-functioning, infected, obstructed kidneys due to staghorn calculi, struvite composition is assumed based on the presence of infection and staghorn shape, and stone analysis is usually not done. Although relatively more renal PSSs than CSSs assumed a staghorn conformation in this cohort, more than half of renal CSSs were also staghorn stones. The stone shape is therefore not helpful to exclude other components in stones. Based on the number of patients in this study who had CSS stones in a staghorn conformation, it cannot be assumed that staghorn stones with infection imply a pure struvite stone.

The recommended management for struvite stones is complete removal and prolonged antibiotic prophylaxis to prevent recurrence.[6,9] Calcium oxalate and uric acid calculi may be associated with metabolic risk factors which predispose affected patients to stone recurrence. Metabolic evaluation can identify modifiable risk factors which, if appropriately managed, may reduce the risk of recurrent renal calculi.[3,4,8] Knowledge of stone composition is therefore imperative to guide both surgical management and postoperative measures to reduce recurrence.

Risk factors for struvite nephrolithiasis were not as common as expected in this cohort; however, the lack of studies on the prevalence of clinical risk factors precludes comparison. When compared to the series by Flannigan et al.,[2] one of the only studies that identified clinical risk factors in struvite nephrolithiasis, the prevalence of diabetes mellitus, neurogenic bladder, ileal conduits and self-catheterisation seemed similar.[2] Recurrent UTIs were more common in their cohort (34.7% vs 12.8%). They did not report any differences in the prevalence of risk factors between pure and combined struvite calculi which is in keeping with our findings.

Although the distribution of the number of risk factors was different between patients with PSS and CSS, overlap in the number of risk factors within groups limits the clinical usefulness of this finding.

Conclusion

Larger studies could establish multiple variable risk nomograms to more reliably discriminate pure from combination struvite stones. Individual risk factors do not discriminate pure struvite stones from combination struvite stones and should therefore not be used to guide clinical decisions. Routine stone analysis is recommended in struvite nephrolithiasis.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required. Investigations were part of usual care plan and not influenced by the study protocol.

Ethical approval

This study was approved by the University of Cape Town Human Research Ethics Committee (HREC REF 383/2018).

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