Does bladder stone composition predict kidney stone composition?

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Introduction: *Bladder stones have historically been associated with urinary stasis secondary to bladder outlet obstruction (BOO). Recent studies indicate that the role of BOO in bladder stone formation is minor. We evaluate the role of urinary lithogenic factors in bladder stone formation by comparing the compositions of bladder stones and kidney stones in patients with multi-site urinary calculi.*

Materials and methods: *We identified patients who were treated for concomitant bladder stones and kidney stones between 2008-2019, and had both stone compositions available. Patients with bladder stone size < 10 mm, urinary foreign bodies, encrusted stents or tumors were excluded. Data regarding urinary symptoms, residual volumes, stone composition and 24-hours urine data were collected.*

Results: *We identified 40 males with a median age of 72 years (IQR 6-14), median residual volume of 76 mL (IQR 41-200), and a median prostate volume of 52 mL (IQR 32-102). Bladder outlet procedures were performed concomitantly with cystolitholapaxy in 21 (53%) patients. The most common bladder stone and kidney stone compositions were CaOx (47.5% and 65%), uric acid (32.5% and 22.5%), calcium phosphate (15% and 10%), and struvite (5% and 2.5%), respectively. Bladder stone and kidney stone compositions were identical in 70% of patients. Bladder stone composition was predictive of kidney stone composition, regardless of the PVR, bladder stone size, or whether an outlet procedure was performed.*

Conclusion: *We found a high concordance between bladder stone and kidney stone composition, suggesting that metabolic abnormalities have a significant role in bladder stone formation. Bladder stone composition can be used to guide surgical and medical treatment for kidney stones in metabolically active stone patients.*

Key Words: nephrolithiasis, cystolithiasis, stone composition, bladder outlet obstruction

Introduction

The pathophysiology of bladder stones formation is not entirely understood. Historically, bladder stones have been associated with urine stasis secondary to bladder outlet obstruction (BOO), and were classically considered an indication for a bladder outlet procedure.[1] Contemporary literature has challenged this paradigm. Several large studies have shown that among patients who have undergone transurethral prostatectomy (TURP) or holmium laser enucleation of the prostate (HoLEP), only 3-5 percent had bladder stones.[2,3] Additionally, bladder stones were found in a large portion of patients with minimal residual volumes and normal voiding pressures.[4,5]

The association between kidney and bladder stones is well established, as several studies have shown high prevalence of kidney stones among patients with bladder stones. It was suggested that these stones have formed in the upper urinary tract, migrated to the bladder, and remained trapped because of BOO.[1,5] Whether the same metabolic abnormalities that lead to kidney stone formation also cause bladder stones is largely unknown. One study showed that among patients who have undergone surgery for BOO, those with bladder stones had lower urinary pH, low urinary magnesium, and increased supersaturation of uric acid in comparison to patients without bladder stones. However, most stones were calcium based.[6]

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To assess the role of underlying metabolic abnormalities on bladder stones formation, we performed a retrospective study of patients who have undergone surgery for kidney and bladder stones, with or without bladder outlet surgery. We compared the stone compositions and 24 hour urine collection results, in order to determine the predictive value of bladder stone composition for kidney stones. This information is valuable not just for the understanding of the pathophysiology of bladder stones, but also for physician-patient counseling regarding stone prevention strategies.

Materials and methods

After Internal Review Board approval, we identified all male patients who have undergone surgical treatment (percutaneous nephrolithotomy or ureteroscopy) for bladder and kidney stones, concomitantly or within 1 year, between 2008 and 2019. All patients had stone compositions available from both the bladder and kidney. We included only bladder stones measuring 10 mm or greater in order to exclude recently passed ureteral stones. We excluded patients with recent renal colic, calcified bladder tumors (2 patients), retained stents (2 patients) or urinary foreign objects (1 patient). We collected data regarding demographics, urinary symptoms, post void residual volume (PVR), AUA score, medications for benign prostatic hyperplasia or kidney stones prevention, and whether a BOO surgery was done. We reviewed all images and recorded data regarding stone size, stone number, and Hounsfield unit (HU) measurement. We collected data on 24-hour urine collection (Litholink Laboratory Reporting System; Litholink Corporation, Chicago, IL, USA) when available. Urine samples were considered adequate if 24-hour creatinine was 10 mg/kg or more.

We compared the frequency of bladder and kidney stone compositions and calculated the sensitivity, specificity, positive, and negative predictive values to detect kidney stone composition. Stone composition was determined by the most common component using Fourier transformed infra-red (FTIR) spectrometry. We also compared the results of 24-hour urine parameters between calcium oxalate and uric acid stone formers, based on bladder and kidney stones composition.

Statistical analysis was done using SPSS, version 25. Descriptive analyses (mean with standard deviation) were used for continuous variables, proportions for discrete variables, and comparative tests included chi-square for discrete variables and Kruskal–Wallis for continuous variables.

Results

Forty male patients were treated for both bladder and kidney stones during the study period. Median age was 72 years (IQR 64-76) and median body mass index (BMI) was 28 kg/m^2 (IQR 24.8-32). Diabetes mellitus, high blood pressure, and gout were found in 10 (25%), 17 (41%), and 3 (8%), of the patients, respectively.

Median AUA score was 10 (IQR 6-14). Median PVR and prostate volume were 76 mL (IQR 41-200) and 52 mL (IQR 32-102), respectively. Bladder outlet procedures were performed concomitantly with cystolitholapaxy in 21 (53%), and included TURP in 10 patients, TUIP in 2 patients, and HoLEP in 8 patients. Patients who underwent bladder outlet procedures had larger prostate volume (92.6 mL versus 49.8 ml, p = 0.045) and higher PVR (216.3 mL versus 80.8 mL, p = 0.05) in comparison to patient who did not undergo a bladder outlet procedure. There was no difference in age, IPSS, bladder stone size or number between the groups. Thirteen patients had one bladder stone and 6 patients had 10 stones or more. Median bladder stone burden was 17 mm (IQR 12-30) and median kidney stone size was 12 mm (IQR 9-15).

The most common bladder stone composition was calcium oxalate (CaOx) in 19 (47.5%) patients, followed by uric acid (UA), calcium phosphate (CaPh), and struvite in 13 (32.5%), 6 (15%), and 2 (5%) patients, respectively. Kidney stone compositions were CaOx in 26 (65%) patients, followed by UA, CaPh, and struvite in 9 (22.5%), 4 (10%), and 1 (2.5%) patients, respectively. Primary and secondary compositions of bladder and kidney stones are presented in Table 1. CaOx dihydrate

TABLE 1. **Distribution of bladder and kidney stone composition**

	Primary composition		Secondary composition	
	Bladder	**Kidney**	**Bladder**	**Kidney**
Calcium oxalate	47.5%	65%	17.5%	7.5%
Uric acid	32.5%	22.5%	5%	15%
Calcium phosphate	15%	10%	20%	3%
Struvite	5%	2.5%	0%	2.5%

TABLE 2. **Clinical characteristics of calcium and uric acid bladder stones formers**

	Calcium oxalate (19)	Uric acid (13)	p value
Age (mean, SD)	70.3, 8.6	67, 12.7	0.38
BMI (mean, SD)	28.9, 5.8	29.1, 5.7	0.91
PVR (mean, SD)	147, 200	179, 275	0.7
Prostate volume (mean, SD)	81.9, 68.6	80.1, 73.5	0.94
Number of stones	4.1, 7	9.1, 11.2	0.19
Cumulative stone size	17.7, 10.6	29.7, 13.2	< 0.01
Stone attenuation	1146.7, 202	520.1, 111.4	< 0.01

BMI = body mass index; PVR = post void residual

stone was found in only one patient and comprised a minor part. Therefore, CaOx was reported as a single composition. Overall, in 28 (70%) patients, bladder and kidney stones had analogous compositions, including CaOx in 19, UA in 8 (20%), and struvite in 1 patient. All 6 (15%) patients with CaPh bladder stones had CaOx kidney stones, and 5 (12.5%) patients with UA bladder stones had CaPh (4 patients) and CaOx (1 patient) kidney stones. Bladder and kidney stones had pure composition in 22 (55%) patients each, of which 9 (75%) had identical compositions. In comparison to UA bladder stone, CaOx stones were smaller and had higher stone attenuation on preoperative imaging. There was no difference in preoperative age, AUA score, prostate volume, or PVR, Table 2.

In four patients, bladder and kidney stones had uric acid and calcium phosphate compositions, respectively. This finding warrants discussion, as uric acid stones normally dissolve in the alkali pH

TABLE 3. **Performance of bladder stone to predict kidney stones composition**

	Sensitivity	Specificity	PPV	NPV
Overall (40) – composition of bladder stone				
Calcium oxalate	73	100	100	28.6
Uric acid	100	87	69	100
Calcium phosphate	75	91	50	97
Struvite	100	97	50	100
PVR > 100 (15)				
Calcium oxalate	75	100	100	50
Uric acid	100	58	50	100
Calcium phosphate	100	93	50	100
Struvite				
BPH surgery (21)				
Calcium oxalate	71	100	100	63
Uric acid	100	81	62	100
Calcium phosphate	100	95	67	100
Struvite				
Bladder stone > 17 mm				
Calcium oxalate	50	100	100	75
Uric acid	100	75	73	100
Calcium phosphate	100	89	33	100
Struvite				

PPV = positive predictive value; NPV = negative predictive value; PVR = post void residual; BPH = benign prostatic hyperplasia

which promotes calcium phosphate stones formation. Coexistence of calcium phosphate and uric acid stones has been reported in patients with bilateral stones and discordant compositions, and has been attributed to variations in renal micro-environment. In addition, it is possible that one kidney developed tubular damage form obstruction, ischemia, or even after shockwave lithotripsy, resulting in an acidification defect and high urine pH, and increased acid secretion and low urine pH in the contralateral kidney. Lastly, there is variation in reporting mixed stones composition between commercial labs, which could account for this finding.

The sensitivity, specificity, positive and negative predictive value of bladder stone composition to detect kidney stone compositions are presented in Table 3. The specificity and PPV of CaOx stones were 100%, indicating that if a patient has a CaOx bladder stone, the kidney stone will be the same composition. The sensitivity and NPV of UA stones were also 100%, indicating that if a patient has a non-UA bladder stone, his kidney stone will also be a non-UA stone. These results remained consistent regardless of the PVR, bladder stone size, or whether a BOO surgery was performed, suggesting the severity of BOO has minimal added effect over the metabolic abnormality in determining bladder stone composition, Table 3.

A 24-hour urine collection was available in 21 (52.5%) patients. The most common metabolic abnormality was low urine volume. In 17 (81%) patients, followed by low urine pH (52.3%), hypocitraturia (52.4%), hypercalciuria (42.8%), hyperoxaluria (42.8%), and hyperuricosuria (14.3%). There was no difference in 24-hour urinary parameters between patients with CaOx and UA bladder stones. As expected, patients with UA kidney stones had lower urinary pH (5.3 versus 5.8, p = 0.02) and higher supersaturation of uric acid (2.03 versus 1.15, p = 0.04) in comparison to patients with CaOx kidney stones, Table 4.

Discussion

Our report is, to our knowledge, the only study that has compared the compositions of bladder and kidney stones obtained from the same patients. We analyzed the results across different severities of lower urinary tract symptoms in order to evaluate whether metabolic abnormalities play a different role in the setting of BOO.

Our study supports the presence of bladder stones in the absence of urinary obstruction demonstrated in earlier studies. We found high concordance between bladder and kidney stones compositions. This information is valuable for understanding the pathogenesis of bladder stones formation. Additionally, it highlights the clinical utility of bladder stone composition in guiding medical treatment and preventive therapy and counseling in patients with concomitant bladder and kidney stones.

Bladder stones account for 5% of urinary stones in developed countries. Reported risk factors include recurrent infections, urinary foreign bodies, nephrolithiasis, and urinary stasis, either from neurogenic bladder or secondary to BOO.[7] Historically, stasis was considered a main mechanism of bladder stones formation, based on observations of increased risk for kidney stone formation in patients with horseshoe kidneys or UPJ obstruction.[8] However, further studies have shown that metabolic abnormalities, rather than urinary stasis, contribute to kidney stones formation

TABLE 4. **Comparison of 24-hour urine parameters in CaOx and uric acid stone formers based on bladder and kidney location. Means and standard deviations are presented.**

	Bladder			Kidney		
	CaOx (10)	**Uric acid (7)**	**p**	**CaOx (14)**	**Uric acid (5)**	**p**
Vol	2.02, 1.35	1.91, 0.77	0.85	2.06, 1.18	1.68, 0.57	0.5
ca	178.5, 74.5	159.7, 76.2	0.62	204, 78.6	151.8, 80.6	0.1
ox	34.8, 13.9	34.6, 8.8	0.97	35.1, 12.3	34.6, 7.8	0.93
ss CaOx	6.1, 3.76	5.45, 3.914	0.74	6.26, 3.64	5.62, 7.83	0.75
pH	5.63, 0.512	5.52, 0.55	0.69	5.8, 0.57	5.3, 0.15	0.02
cit	523.2, 361	488.6, 341	0.845	554.4, 344.5	450.2, 402	0.58
ua	0.57, 0.18	0.63, 0.21	0.52	0.57, 0.18	0.66, 0.25	0.76
ssUA	1.4, 0.74	1.61, 0.94	0.6	1.15, 0.18	2.03, 0.25	0.04

Vol = volume; ca = calcium; ss CaOx = super saturated calcium oxylate; cit = citrate; ua = uric acid; ssUA = super saturated UA

in these populations.[9] There are several other reasons to question the role of urine stasis in bladder stone formation; first, only 3% to 8% of patients with urinary stasis secondary to BOO develop bladder stones.[2,3] Second, only half of patients with bladder stones had urodynamic evidence of BOO.[5] Jong et. al showed that among patients who underwent TURP, intravesical protrusion of the prostate was significantly higher in patients with bladder stones, however, these finding have not been validated in other studies.[10]

While the present study was not designed to evaluate the role of BOO in bladder stones formation, the results are in line with previous studies showing that bladder stones are often not associated with BOO. Only half of the patients underwent bladder outlet procedures, some of them with low AUA score and residual volumes.

The evolving understanding of bladder stones formation has led several authors to study the role of metabolic abnormalities. However, current data is limited. Childs et al prospectively compared lithogenic risk factors of patients with and without bladder stones who underwent bladder outlet procedure. Patients with bladder stones were more likely to have a history of kidney stones and gout, low urine pH, hypomagnesuria, and increased supersaturation of uric acid. Interestingly, UA stones comprised only 19% of stones, while CaPh and CaOx comprised 39% and 42%, respectively. This was not explained by the urinary parameters.[6] Due to variability in daily urine parameters and unmeasured lithogenic factors (Tamm-Horsfall, osteopontin, etc.), normally tested urinary parameters do not always reflect urinary risk factors. Therefore, the best indicator of lithogenic abnormalities is stone composition. In the present study, kidney stone composition was used as a measure of all known and unknown urinary parameters over time. Concordance between kidney and bladder stones compositions was suggestive of the effect of urinary parameters of bladder stones formation. We found bladder and kidney stones compositions highly concordant, with 70% being identical. In the remaining 30%, kidney stone composition was highly predictable. All 6 patients with CaPh bladder stones had CaOx kidney stones, possibly sharing the same urinary risk factors other than higher bladder pH. Among 13 patients with UA bladder stones, 8 had UA kidney stones and 5 had CaOx kidney stones, which were easily identified from preoperative imaging.

The distribution of bladder stone compositions is noteworthy. Uric acid stones comprised 22 and 32.5 percent of kidney and bladder stones, respectively, suggesting there is at least another additional mechanism at play in bladder stone formation. Douenias et al found that 59% and 19% of patients had UA and CaOx stones, respectively. However, among 17 patients with history of kidney stones, 10 (59%) patients had calcium based bladder stones, similar to our results.[1] One possible explanation is that in patients with kidney stones, significant urinary abnormalities contribute to CaOx bladder stones formation, however, in patients with normal, or moderate urinary abnormalities, uric acid form more frequently. This may be because UA stones don't require the anchoring mechanisms associated with calcium stones pathophysiology.[11] Our results are in agreement with recent literature which disputes the role of heterogeneous enucleation in bladder stone formation. The same proportion of mixed stones was found in kidney and bladder stones, and mixed uric acid and CaOx stones were found in one kidney stone and one bladder stone.

Four patients had UA bladder stones and CaPH kidney stones. This finding deserves discussion as normally UA stones dissolve under the alkali pH needed to form CaPH stones. Coexistence of these compositions has been reported in patients with bilateral stones and discordant compositions, and has been attributed to variations in renal micro-environment.[12] Possible explanations to this finding include: 1) unilateral tubular damage form obstruction, ischemia, or shockwave lithotripsy, resulting in an acidification defect and high urine pH, and increased acid secretion and low urine pH in the contralateral kidney,[13] 2) Bladder stones were made of ammonium urate. This type of stone forms in alkali urine, but is extremely rare in developed countries. 3) Variation in reporting mixed stones composition between commercial labs.[14]

Only half of the patients in this study had a 24-hour urine collection. We found a correlation between urinary parameters and kidney stone composition. Uric acid kidney stone formers had lower urinary pH than CaOx stone formers, while the latter group had a trend toward higher urinary calcium. The lack of correlation between bladder stone composition and urinary parameters was a result of the patient in whom bladder and kidney stone compositions were discordant. In these patients, factors such as infection with urase producing or non-urease producing bacteria could promote low or high bladder urine pH, leading to calcium phosphate or uric acid stones formation, respectively.[15]

Our study has several limitations. First, this cohort of patients with both bladder and kidney stones appears to be different than the general stone-forming

population, both in stone type distribution, and in the prevalence of metabolic abnormalities. Indeed, 81% of patients in this had low urine pH, which is much higher than in the general population, suggesting that kidney stone patients with low urine pH may be more susceptible to bladder stone formation than those with normal pH. Whether these patients form uric acid or calcium oxalate stones may depend on other factors, but low urine pH is a risk factor for both types of stones. In addition, all patients in the present study were males. This limitation is inherent to the studied scenario, since both kidney and bladder stones are more common in men.

Nevertheless, this study is novel in providing information about the correlation between bladder and kidney stones across different severities of BOO, which is useful for planning of surgical and medical intervention for kidney stones or BOO in the setting of concomitant bladder stones.

Conclusions

There is high concordance between bladder and kidney stone composition suggesting that urinary parameters play an important role in bladder stone formation. This is valuable clinical information for guiding treatment for kidney stones. □

References

1. Douenias R, Rich M, Badlani G, Mazor D, Smith A. Predisposing factors in bladder calculi. Review of 100 cases. *Urology* 1991;37(3):240-243.
2. Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. *J Urol* 2010;183(3):1105-1109.
3. Mebust WK, Holtgrewe HL, Cockett ATK, Peters PC. Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol* 1989;141(2):243-247.
4. Shah HN, Hegde SS, Shah JN, Mahajan AP, Bansal MB. Simultaneous transurethral cystolithotripsy with holmium laser enucleation of the prostate: a prospective feasibility study and review of literature. *BJU Int* 2007;99(3):595-600.
5. Millan-Rodriguez F, Errando-Smet C, Rousaud-Baron F, Izquierdo-Latorre F, Rousaud-Baron A, Villavicencio-Mavrich H. Urodynamic findings before and after noninvasive management of bladder calculi. *BJU Int* 2004;93(9):1267-1270.
6. Childs MA, Mynderse LA, Rangel LJ, Wilson TM, Lingeman JE, Krambeck AE. Pathogenesis of bladder calculi in the presence of urinary stasis. *J Urol* 2013;189(4):1347-1351.
7. Philippou P, Moraitis K, Masood J, Junaid I, Buchholz N. The management of bladder lithiasis in the modern era of endourology. *Urology* 2012;79(5):980-986.
8. Husmann DA, Milliner DS, Segura JW. Ureteropelvic junction obstruction with concurrent renal pelvic calculi in the pediatric patient: a long-term followup. *J Urol* 1996;156(2 Pt 2):741-743.
9. Raj G V, Auge BK, Assimos D, Preminger GM. Metabolic abnormalities associated with renal calculi in patients with horseshoe kidneys. *J Endourol* 2004;18(2):157-161. 2004.
10. Kim JW, Oh MM, Park HS et al. Intravesical prostatic protrusion is a risk factor for bladder stone in patients with benign prostatic hyperplasia. *Urology* 2014;84(5):1026-1029.
11. Evan AP, Lingeman JE, Coe FL et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003;111(5):607-616.
12. Kadlec AO, Fridirici ZC, Acosta-Miranda AM, Will TH, Sakamoto K, Turk TM. Bilateral urinary calculi with discordant stone composition. *World J Urol* 2014;32(1):281-285.
13. Evan AP, Coe FL, Connors BA, Handa RK, Lingeman JE, Worcester EM. Mechanism by which shock wave lithotripsy can promote formation of human calcium phosphate stones. *Am J Physiol Renal Physiol* 2015;308(8):F938-F949.
14. Krambeck AE, Khan NF, Jackson ME, Lingeman JE, McAteer JA, Williams JC Jr. Inaccurate reporting of mineral composition by commercial stone analysis laboratories: implications for infection and metabolic stones. *J Urol* 2010;184(4):1543-1549.
15. Hedelin H, Bratt C-G, Eckerdal G, Lincoln K. Relationship between urease-producing bacteria, urinary pH and encrustation on indwelling urinary catheters. *Br J Urol* 1991;67(5):527-531.