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Pathogenesis of Bladder Calculi in the Presence of Urinary Stasis

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Abstract

Purpose—Although minimal evidence exists, bladder calculi in men with benign prostatic hyperplasia are thought to be secondary to bladder outlet obstruction induced urinary stasis. We performed a prospective, multi-institutional clinical trial to determine whether metabolic differences were present in men with and without bladder calculi undergoing surgical intervention for benign prostatic hyperplasia induced bladder outlet obstruction.

Materials and Methods—Men who elected surgery for bladder outlet obstruction secondary to benign prostatic hyperplasia with and without bladder calculi were assessed prospectively and compared. Men without bladder calculi retained more than 150 ml urine post-void residual urine. Medical history, serum electrolytes and 24-hour urinary metabolic studies were compared.

Results—Of the men 27 had bladder calculi and 30 did not. Bladder calculi were associated with previous renal stone disease in 36.7% of patients (11 of 30) vs 4% (2 of 27) and gout was associated in 13.3% (4 of 30) vs 0% (0 of 27) ($p < 0.01$ and 0.05 , respectively). There was no observed difference in the history of other medical conditions or in serum electrolytes. Bladder calculi were associated with lower 24-hour urinary pH (median 5.9 vs 6.4, $p = 0.02$), lower 24-hour urinary magnesium (median 106 vs 167 mmol, $p = 0.01$) and increased 24-hour urinary uric acid supersaturation (median 2.2 vs 0.6, $p < 0.01$).

Conclusions—In this comparative prospective analysis patients with bladder outlet obstruction and benign prostatic hyperplasia with bladder calculi were more likely to have a renal stone disease history, low urinary pH, low urinary magnesium and increased urinary uric acid supersaturation. These findings suggest that, like the pathogenesis of nephrolithiasis, the pathogenesis of bladder calculi is likely complex with multiple contributing lithogenic factors, including metabolic abnormalities and not just urinary stasis.

Keywords

urinary bladder calculi; etiology; hematuria; urinary retention; prostatic hyperplasia

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Study received Mayo Clinic and Methodist Hospital institutional review board approval.

Bladder calculi have historically been associated with incomplete bladder emptying secondary to BPH and BOO, and they are an indication to perform a prostatic debulking surgical intervention.^{1,2} Although urinary retention is fairly common in the community setting, affecting almost 14% of men with moderate to severe lower urinary tract symptoms in a 5-year period,³ bladder calculi develop in only 3% to 8% with BOO due to BPH.⁴⁻⁶ Furthermore, bladder calculi have been observed in men with minimal BPH and urinary stasis.^{1,7} Thus, the association between bladder calculi and urinary stasis is not entirely clear. Unlike studies of upper urinary tract stone disease, factors contributing to the pathogenesis of bladder calculi have not been well explored.

Numerous studies show that metabolic abnormalities contribute to the pathogenesis of nephrolithiasis in the nonobstructed urinary system.⁸⁻¹⁵ However, urinary stasis is also thought to be a contributing factor in certain clinical situations. Select studies of unique patient populations with anatomical abnormalities and elements of urinary stasis suggest that calculus formation is complex and urinary stasis alone does not produce urolithiasis.¹⁶⁻¹⁸ Rather, an additive effect of underlying metabolic abnormalities and decreased urinary flow contributes to the pathogenesis of upper tract calculi. Studies focusing on formation in states of urinary stasis, such as horseshoe kidney, UPJ obstruction or caliceal diverticula, have opened up the idea of enhanced calculogenesis when urinary stasis and underlying metabolic abnormalities are present.

We assessed the role of underlying metabolic abnormalities in the formation of bladder calculi in the presence of BOO secondary to BPH. We prospectively compared patients in urinary retention with and without bladder calculi to identify any underlying metabolic abnormalities associated with bladder calculi.

MATERIALS AND METHODS

We designed a 2-center prospective study to compare men who elected surgery for BOO and BPH with bladder calculi and men who elected surgery for BOO and BPH without bladder calculi. This study was reviewed and approved by the institutional review boards of Mayo Clinic, Rochester, Minnesota, and Methodist Hospital, Indianapolis, Indiana. The primary aims were to identify serum and urinary metabolic difference in the bladder calculus group. Secondary aims were to assess clinical variables associated with bladder calculi.

Men who elected laser PVP, transurethral prostate resection or HoLEP for BOO and BPH were screened for enrollment at each site. Inclusion criteria for the bladder calculus group included elective surgical management for BOO and BPH with at least 1 bladder calculus. Inclusion criteria for the control group included elective surgical management for BOO and BPH without bladder calculi or a history of bladder calculi and a history of increased PVR (greater than 150 cc) or urinary retention requiring catheter drainage. Patients were not considered for analysis if they could not provide informed consent or had an untreated urinary tract infection.

After enrollment, demographic and clinical information was collected prospectively, including medical history, medication use, American Urological Association symptom score, prostate specific antigen, prostate volume, urinary flow studies (voided volume, PVR, and maximum and average urine flow) and screening preoperative urine culture. Medical histories were reviewed and medication intake was assessed. Serum electrolytes and metabolites, 24-hour urine supersaturation, urinary electrolytes, pH and volume were prospectively collected. Serum SPEC analysis and bladder calculus assessment were done at the clinical laboratory at each site and urinary SPEC analysis was performed at Mayo Clinic. Only urine SPECs with a creatinine per kg body weight per 24 hours of greater than 10 mg/

kg per day were considered adequate and used for comparison. In the bladder calculus group we collected data on stone size and components.

Study data were collected and managed using REDCap Electronic Data Capture tools (Vanderbilt University, Nashville, Tennessee) and hosted at Mayo Clinic.¹⁹ Statistical analysis was done using SAS®, version 9.1.3. Patient demographics and clinical information were summarized by calculus or control group using descriptive statistics. Continuous laboratory variables were compared across study groups using the Mann-Whitney U test and categorical demographic or clinical variables were compared across study groups using the Pearson chi-square tests. Tests were 2 sided and considered significant at $p < 0.05$.

RESULTS

A total of 57 patients were enrolled in the study, including 27 controls and 30 with bladder calculi. In the control group 23 patients elected HoLEP and 4 elected PVP. In the stone group 18 patients elected HoLEP, 11 elected PVP and 1 elected transurethral prostate resection. There was not enough power to detect a difference in patient age but the calculus group tended to be younger (mean age 73.3 vs 67.7 years, $p = 0.10$). When medical history was assessed, there was not enough power to detect difference in the rates of hypertension, diabetes, renal tubular acidosis, chronic renal insufficiency or prostate cancer. A diagnosis of gout was reported in 13.3% of patients (4 of 30) with bladder calculi compared to 0% of controls (0 of 27) ($p = 0.05$). A significant difference in renal stone disease history was noted in patients with bladder calculi, of whom 36.7% (11 of 30) reported renal stone disease compared to 7.4% of controls (2 of 27) ($p < 0.01$). No patient was identified with hyperparathyroidism, small bowel resection or short gut disease, gastric bypass or ileostomy. There was no observed difference in medication use between the groups, including anticholinergics, α -blockers, 5 α -reductase inhibitors, thiazides, calcium supplementation, potassium citrate, gout medications or topiramate.

Table 1 lists detailed data on symptomatic BPH evaluation. Controls had a greater median PVR than the stone group and were more likely to require intermittent catheterization or an indwelling Foley catheter for urinary retention at presentation (78% or 21 of 27 vs 35% or 10 of 30, $p < 0.01$). There was no difference in indwelling Foley catheter use between the groups. No difference in history of urinary tract infection or bacteriuria at presentation was noted. There was no significant difference in gross hematuria history at presentation, although there was a trend toward hematuria in those with calculi.

Table 2 lists 24-hour urinary metabolic evaluation data after excluding 9 patients due to insufficient 24-hour urine collections, leaving 27 with stones and 21 controls available for analysis. Patients with calculi had significantly lower 24-hour urinary pH and magnesium. Although no difference was seen in urinary uric acid (median 578 vs 610 mg/SPEC, $p = 0.48$), patients with calculi had increased uric acid supersaturation compared to controls (mean 2.2, range 0.1 to 6.4 vs 0.6, range 0.1 to 2.6, $p < 0.01$). No difference was observed in serum electrolytes between the 2 groups.

Cystolitholapaxy was performed in patients with bladder stones. Table 3 shows calculus composition and mean percent composition by stone component. The most frequent stone components were calcium oxalate and calcium phosphate, followed by uric acid. Mean calculus weight was 34.60 gm (range 0.3 to 407.70).

DISCUSSION

The pathogenesis of bladder calculi has not been well studied. Historical reports of bladder calculi suggest an etiology of urinary stasis from BOO secondary to BPH. However, stasis

was suggested as a causative mechanism for stone formation based more on observational associations.^{1,2} Despite the association of urinary stasis and bladder calculi, these stones develop in only 3% to 8% of men with urinary stasis and BOO due to BPH.^{4,5} Extensive studies have assessed the importance of metabolic abnormalities in the pathogenesis of upper tract urolithiasis.^{8–15} Furthermore, studies of unique patient populations with elements of upper tract urinary stasis, including horseshoe kidney, UPJ obstruction and caliceal diverticula, suggest that metabolic abnormalities contribute to stone formation rather than or in addition to stasis.^{16–18} Therefore, we hypothesized that there is also an element of underlying metabolic abnormalities in the minority of patients with BOO in whom bladder calculi develop.

We prospectively assessed patients in urinary retention with and without bladder calculi treated with surgical intervention for BPH. Patients with bladder stones were significantly more likely to have a history of renal stone disease and gout than those in urinary retention alone. Furthermore, metabolic abnormalities on 24-hour urine supersaturation studies were more common in calculus cases. In patients with bladder calculi we found significantly higher urinary uric acid and supersaturation as well as lower urinary pH and urinary magnesium. Gout, increased urinary uric acid supersaturation, and low urinary pH and urinary magnesium are associated with urinary stone disease in the assessment of upper urinary tract calculi.^{10,20,21} Therefore, these findings in patients with bladder stones suggest that metabolic abnormalities may contribute to the pathogenesis of bladder calculi. Due to the number of stone types, our study was not powered enough to determine an association between urinary pH and stone composition. However, all patients with uric acid stones had a 24-hour urine pH of less than 5.8, further suggesting a metabolic contribution to stone formation.

Although underlying metabolic abnormalities are suggested by our data, possibly other, unmeasured lithogenic factors contribute to stone formation. Clearly, hypomagnesuria can provide an environment for crystal formation. However, the findings of lower urinary pH and high uric acid supersaturation in patients with bladder calculi more appropriately support the role of metabolic abnormalities in the formation of uric acid stones but do not fully explain the formation of calcium oxalate or calcium phosphate stones in some patients. When considering calcium phosphate stone formation, urinary tract infection may have contributed to pH changes. Although all patients were required to be without urinary tract infection at surgery, previous urinary infections before presentation could have resulted in increased urinary pH and contributed to phosphate stone formation.

Why calcium oxalate stones formed is less clear. Although uric acid was theorized to act as a nidus for calcium oxalate stones, data supporting the hypothesis are conflicting. In vitro studies and analysis of human stone former papillae refuted the theories of heterogeneous nucleation, decreased calcium oxalate crystallization inhibitors and nephron blockage by uric acid crystals to increase calcium oxalate crystallization.^{22,23} However, studies of the ability of uric acid to decrease calcium oxalate solubility showed that adding sodium urate to calcium oxalate in solution leads to crystallization, although this mechanism relies on the presence of underlying conditions supporting calcium oxalate formation.²⁴ For calcium based bladder stone formation urinary stasis most likely significantly contributes to crystal formation.

A limitation of this study is that we did not assess other lithogenic factors, such as Tamm-Horsfall protein, osteopontin, bikunin or other inter- α -trypsin inhibitors, or urinary prothrombin fragment 1. Similar to urinary metabolic abnormalities, these urinary protein factors were identified as lithogenic factors in studies of upper urinary tract calculi and they may also contribute to the pathogenesis of bladder calculi.^{25–30}

Unmeasured lithogenic factors may contribute to the strong association of previous stone episodes and bladder calculus formation or the explanation may be more of a mechanical issue. Small renal calculi that pass into the bladder in men prone to urinary stone formation may be retained in the bladder in the presence of urinary stasis secondary to BPH. The upper tract stone that passes into the bladder may serve as the nidus for larger bladder calculi that will become symptomatic, especially in men with a lithogenic urinary environment. Comparable to nephrolithiasis pathogenesis in the caliceal diverticula or in patients with UPJ obstruction, bladder stone pathogenesis is likely multifactorial with multiple lithogenic factors, including metabolic abnormalities and urinary stasis due to BOO. Thus, despite findings of differences in 24-hour urine metabolic studies between men with BOO secondary to BPH with and without bladder calculi, further prospective analyses are needed to establish an exact causal mechanism for stone formation.

Findings in this study may be limited by the small study and control group sizes since random variability of any assessed outcome in a small cohort is more likely to affect observed trends. Our study was also limited in that we did not evaluate for other, less commonly measured lithogenic factors. The BOO and BPH characteristics of the study and control groups were comparable but significantly more patients in urinary retention required catheterization in the control group. Also, chronic infection can alter urinary citrate and pH, which may have confounded our metabolic findings. However, we assessed the urinary milieu in which stones formed and urine retention is common, which is also a risk factor for urinary infection. When assessing patients with urinary stasis, urinary infection is always a confounding factor.

Despite the potential limitations, this study provides further insight into the pathogenesis of bladder calculi and suggests that metabolic factors most likely have a significant role in stone formation, in addition to urinary stasis due to BOO and BPH.

CONCLUSIONS

In this prospective, comparative analysis of patients with BOO and BPH, and patients with bladder calculi with BOO and BPH, those with calculi were more likely to have a history of renal stone disease and gout. Metabolically, patients with calculi were more likely to have lower urinary pH and magnesium, and higher uric acid supersaturation on 24-hour urine studies. These findings suggest that, like the pathogenesis of upper tract urolithiasis, bladder stone pathogenesis is likely complex with multiple contributing lithogenic factors and not just urinary stasis.

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Abbreviations and Acronyms

BOO	bladder outlet obstruction
BPH	benign prostatic hyperplasia
HoLEP	holmium laser enucleation of prostate
PVP	photovaporization of prostate
PVR	post-void residual urine
SPEC	specimen

UPJ ureteropelvic junction

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Table 1

Urological evaluation for BOO secondary to BPH

	Bladder Calculi		Control	p Value
No. pts	30		27	
No. urinary tract infection history (%)	1	(3.3)	2	(7.4) 0.49
No. pos preop urine culture (%)	6	(20.0)	9	(33.3) 0.29
No. gross hematuria (%)	11	(36.7)	4	(14.8) 0.06
No. indwelling catheter at evaluation (%)	6	(20.0)	5	(18.5) 0.24
No. catheter at evaluation (%)	10	(34.5)	21	(77.8) <0.01
Median ng/ml PSA (range)	5.5	(0.3–14.1)	3.2	(0.3–17.2) 0.10
Median cc prostate vol (range)	88	(34–250)	102	(25–200) 0.96
Median ml voided vol (range)	115	(9–404)	143	(0–336) 0.84
Median ml/sec max urine flow (range)	6.3	(1.0–17.0)	5.0	(0–15.0) 0.76
Median ml PVR (range)	300	(6–1,000)	446	(170–1,000) 0.02

Table 2

Serum electrolytes, and 24-hour urinary electrolytes and supersaturation values from metabolic evaluation

	Median Bladder Calculi	Median Control	p Value
No. pts	27	21	
Serum electrolytes:			
Sodium (mmol/l)	140	141	0.59
Creatinine (mg/dl)	1.1	1.0	0.83
Bicarbonate (mmol/l)	28	26	0.46
Calcium (mg/dl)	5.0	5.0	0.54
Uric acid (mg/dl)	6.0	5.6	0.27
Phosphorus (mg/dl)	3.3	3.3	0.99
24-Hr urinary supersaturation:			
Calcium oxalate	3.3	4.3	0.52
Sodium urate	3.9	2.9	0.37
Uric acid	2.2	0.6	<0.01
Hydroxyapatite	3.1×10^7	1.2×10^7	0.32
Brushite	1.2	1.3	0.95
24-Hr urinary electrolytes:			
Sodium (mmol/24 hrs)	164	130	0.65
Potassium (mmol/24 hrs)	66	73	0.39
Phosphorus (mg/SPEC)	936	764	0.36
Calcium (mg/SPEC)	213	212	0.85
Magnesium (mmol/24 hrs)	106	167	0.01
Chloride (mmol/24 hrs)	144	119	0.48
Citrate (mg/SPEC)	677	570	0.60
Oxalate (mg/SPEC)	26	31	0.17
Uric acid (mg/SPEC)	578	610	0.48
Creatinine (mg/SPEC)	1,587	1,157	0.07
24-Hr urine pH	5.9	6.4	0.02

Table 3

Bladder calculus composition

Composition	No. Pts	Mean % Composition (range)
Calcium oxalate monohydrate	11	90 (10–100)
Calcium phosphate (apatite)	9	20 (10–100)
Uric acid	8	100 (10–100)
Calcium phosphate (brushite)	8	90 (20–100)
Calcium oxalate dihydrate	7	37 (10–100)