Pathogenesis of Bladder Calculi in the Presence of Urinary Stasis

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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.

Key Words: urinary bladder calculi, etiology, hematuria, urinary retention, prostatic hyperplasia

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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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

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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, 5α-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 hema-