

Risk factors for bladder calculi in patients with benign prostatic hyperplasia

Wei Huang, MD, Jun-Jie Cao, MD, Min Cao, MD, Hong-Shen Wu, MD, Yong-Yi Yang, MD, Zi-Meng Xu, MD, Xiao-Dong Jin, MD, PhD*

Abstract

We aim to find the risk factors that influence the formation of bladder calculi in patients with benign prostate hyperplasia (BPH) and to reduce the surgical intervention related to bladder calculi.

Between January 2015 and October 2016, 332 patients with BPH underwent surgical therapy were retrospectively evaluated. Patients with BPH were categorized into 2 groups: 94 patients with bladder calculi in group 1 and 238 patients without bladder calculi in group 2. Medical history, age, body mass index (BMI), total prostate specific antigen, total prostate volume (TPV), International Prostate Symptom Score (IPSS), intravesical prostatic protrusion (IPP), urodynamic parameters, and urine culture were compared between groups.

There was no significant difference in the age, BMI, peak flow rate, and total IPSS between groups. TPV, total prostate specific antigen, and duration of BPH were significantly lower in group 1 than those in group 2. In addition, IPP was significantly higher in group 1 than group 2 ($P < .001$). Besides, after exclusion of patients with urinary retention and indwelling catheter, group 1 associated with a significantly higher preoperative positive rate of urine culture than that of group 2 ($P = .046$). Multivariate analysis indicated that IPP was a significant independent risk factor for the presence of bladder calculi.

The incidence of bladder calculi in patients with BPH was proved to be closely associated with preoperative positive urine culture and longer IPP in our study. Furthermore, the IPP was presented to be an independent risk factor for the formation of bladder calculi. And early antibacterial therapy of urinary tract infection (UTI) may help to prevent the presence of bladder calculi in patients with BPH.

Abbreviations: AUR = acute urinary retention, BMI = body mass index, BOO = bladder outlet obstruction, BPH = benign prostate hyperplasia, IPP = intravesical prostatic protrusion, IPSS = International Prostate Symptom Score, PVR = postvoid residual, TPV = total prostate volume, UTI = urinary tract infection.

Keywords: benign prostatic hyperplasia, bladder calculi, intravesical prostatic protrusion, urinary retention, urine culture

1. Introduction

Bladder calculi is one of the common complications of benign prostatic hyperplasia (BPH) and the incidence is about 10%.^[1] The presence of bladder calculi in patients with BPH is an absolute indication for surgery.^[2,3] The bladder calculi not only increases patients' sufferings and medical expenses, but also may

be associated with the bladder cancer.^[4] It is generally accepted that urinary retention secondary to bladder outlet obstruction (BOO) is an important cause for the formation of bladder calculi in patients with BPH. But, the incidence of bladder calculi related to urinary retention only accounts for 3% to 8% of patients with BOO due to BPH.^[5-7] Some studies reported that the formation of calculi is complex, and the urinary retention alone may not lead to the urolithiasis.^[8-10] The etiology of bladder calculi in men with BPH is still not clear. The aim of this study is to assess the risk factors that influence the formation of bladder calculi in patients with BPH and to reduce the rate of surgical intervention related to the bladder calculi.

2. Materials and methods

2.1. Study population

We designed a retrospective study to compare patients underwent selected surgical intervention for BPH with and without bladder calculi. Between January 2015 and October 2016, a total of 332 patients with BPH underwent surgical therapy in our hospital were included. They were categorized into 2 groups: group 1 had bladder calculi and group 2 did not. All participants were given written informed consent, and all procedures performed in study in accordance with the ethical standards of the First Affiliated Hospital, Zhejiang University, School of Medicine and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Editor: Shan Wang.

W-H and J-JC contributed equally to this work.

Funding/support: This study was funded by the National Natural Science Foundation of China (grant number 81370799) and Chinese Medicine Research Program of Zhejiang Province (grant number N20100606).

The authors have no conflicts of interest.

Department of Urology, The First Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, Zhejiang, PR China.

* Correspondence: Xiao-Dong Jin, Department of Urology, The First Affiliated Hospital, Zhejiang University, School of Medicine, Qingchun Road 79, Hangzhou 310003, Zhejiang, PR China (e-mail: xiaodong-jin@zju.edu.cn).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Medicine (2017) 96:32(e7728)

Received: 6 June 2017 / Received in final form: 12 July 2017 / Accepted: 14 July 2017

<http://dx.doi.org/10.1097/MD.0000000000007728>

Table 1**Comparison of baseline characteristics between group 1 and group 2.**

	Group 1 N=94	Group 2 N=238	P
Age, y	68.5±7.6	69.1±7.8	.509
Duration of BPH, m	28.3±35.0	49.3±52.9	<.001
BMI, kg/m ²	23.2±2.9	23.0±2.9	.824
PSA, ng/mL	3.5±2.8	6.8±7.8	<.001
IPSS	21.4±9.1	20.5±8.0	.674
TPV, g	46.5±25.4	53.4±28.9	.044
IPP, cm	1.1±1.0	0.4±0.5	<.001
AUR, %	10.6	37.4	<.001
Urine culture, %*	10.7 (9/84)	4.0 (6/149)	.046

AUR=acute urinary retention, BMI=body mass index, BPH=benign prostatic hyperplasia, IPP=intravesical prostatic protrusion, IPSS=International Prostate Symptom Score, PSA=prostate specific antigen, TPV=total prostate volume.

* Exclusion of patients with indwelling urinary catheter.

2.2. Inclusion criteria

Patients were enrolled if they underwent transurethral prostate resection for BPH and had a pathologic verification. Exclusion criteria: patients were excluded if they had been confirmed prostate malignancy, neurogenic bladder, bladder foreign body, hydro-nephrosis, previous history of urolithiasis, or urethral stricture.

2.3. Clinical data

Preoperative data collection included age, body mass index (BMI), medical history of BPH, serum prostate specific antigen (PSA), the International Prostate Symptom Score (IPSS), urodynamic examination, urine culture, and transabdominal ultrasonography. The total prostate volume (TPV), intravesical prostatic protrusion (IPP), and the maximum diameter and number of bladder calculi were measured on the supine patients by the same physician using the transabdominal ultrasonography in the condition of proper filling (150–200 mL) of the bladder. The diameter, anteroposterior diameter, and superoinferior diameter were measured firstly, then, the vertical distance from the highest point of the protruding prostate to the bladder neck was measured as the IPP length by the median longitudinal sagittal plane.^[11] Under the recommendations of the International Continence Society, urodynamic examination was performed to record the peak flow rate and postvoid residual (PVR) urine volume.^[12] All the patients underwent transurethral resection of prostate with or without endoscopic lithotripsy.

2.4. Statistical analysis

Statistical analysis was done using SPSS 16.0. Values are presented as the mean±standard deviation. Continuous variables were compared by the Student *t* test or the Mann–Whitney *U* test. Categorical variables were analyzed by the Pearson chi-square tests. Logistic regression analyses were used to determine whether age, BMI, PSA, IPSS, TPV, IPP, or the peak flow rate was an independent risk factor of the presence of bladder calculi in patients with BPH. A *P* value<.05 was considered to be statistically significant.

3. Results

Of the 332 patients with BPH enrolled in the study, patients with bladder calculi were classified as group 1 (n=94) and

Table 2**Univariate and multivariate analysis of data between group 1 and group 2.**

	B	SE	P	Exp (B)	95%CI
Univariate					
Age, y	−0.011	0.016	.486	0.989	0.959, 1.020
BMI, kg/m ²	0.015	0.042	.725	1.015	0.934, 1.102
PSA, ng/mL	−0.142	0.035	<.001	0.868	0.810, 0.929
IPSS	0.014	0.024	.566	1.014	0.968, 1.062
TPV, g	−0.010	0.005	.044	0.990	0.981, 1.000
IPP, cm	1.176	0.187	<.001	3.243	2.264, 4.645
Peak flow rate, m/s	−0.099	0.108	.357	0.906	0.734, 1.118
PVR, mL	−0.005	0.006	.404	0.995	0.984, 1.007
Multivariate					
IPP, cm	1.254	0.198	<.001	3.506	2.380, 5.164

B=regression coefficient, BMI=body mass index, CI=confidence interval, Exp(B)=odds ratio, IPP=intravesical prostatic protrusion, IPSS=International Prostate Symptom Score, PSA=prostate specific antigen, PVR=postvoid residual, SE=standard error, TPV=total prostate volume.

patients without bladder calculi were classified as group 2 (n=238). The mean age of patients was 68.5±7.6 years (range 53–88 years) versus 69.1±7.8 years (range 50–89 years) in group 1 and 2 (*P*=.51), respectively (Table 1). According to the outcomes of transabdominal ultrasonography, the maximum diameter of the bladder calculi was 2.1±1 cm, and 66% of the patients had at least 2 stones in group 1. No significant differences were found in BMI, total IPSS, peak flow rate, and PVR between 2 groups.

However, group 1 presented a significantly shorter duration of diagnosis of BPH until the time of transurethral resection of prostate than that of group 2 (28.3±35 vs 49.3±52.9 months, *P*<.001). Incidence of acute urinary retention (AUR) in group 1 (10.6%) was also lower than that of group 2 (37.4%). After exclusion of patients with indwelling catheter, a significant difference in the positive rate of urine culture was noted between group 1 and 2 (10.7% vs 4%, *P*=.046). The most common bacteria detected in group 1 were *Enterococcus faecalis* and *Staphylococcus epidermidis*, while *E faecalis*, *Pseudomonas aeruginosa*, and *Escherichia coli* were in group 2.

The TPV and total prostate specific antigen were significantly lower in group 1 than those of group 2. Meanwhile, the IPP was significantly longer in group 1 than that of group 2 (*P*<.001). Univariate and multivariate analysis showed that IPP (HR=3.506, *P*<.001) was an independent risk factor of the presence of bladder calculi in patients with BPH (Table 2).

4. Discussion

Bladder calculi is one of the most common urolithiasis in men over 50 years old, and it could be classified as primary, secondary, and migratory stones. And some authors have proposed that the incidence of bladder calculi is mainly associated with BOO, bladder augmentation, bladder diverticula, urinary tract infection (UTI), neurogenic bladder, or the bladder foreign body.^[13] Generally, BOO associated with prostatic hyperplasia may induce UTI, which could act as initial factor of lithogenesis, especially when the PVR urine volume increased because of poor bladder emptying.^[14] These would lead to the deposition of small crystalline in urine, which could serve as a core for the formation of bladder calculi. Apart from obstruction and infection, metabolic and nutritional disorders were also reported to be related to the formation of bladder calculi.^[14,15]

IPP is an anatomical structure of the prostate caused by the enlargement of the medial and/or lateral lobes of prostate, referring to the vertical distance from the top of the protruding prostate to the bladder base. Chia et al^[16] reported that IPP could act as a clinical indicator to determine the degree of BOO. Lim et al^[17] reported that long IPP would cause BOO by exerting “ball valve” effect on the process of urination, and the funnel effect of the bladder neck would be destroyed. And furthermore, the correlation between IPP and the degree of BOO was proposed to be more reliable than that between other factors (such as IPSS, TPV, peak flow rate, and total prostate specific antigen) and BOO.^[18]

Our study revealed that IPP was significantly longer in group 1 than group 2, which is consistent with the finding of previous study.^[18] Moreover, the results of univariate and multivariate analysis in our study showed that IPP was an independent risk factor of the presence of bladder calculi in patients with BPH, which further indicated that IPP was closely associated with the formation of bladder calculi.

Interestingly, we found the incidence of AUR in group 1 was lower than that of group 2, which could mean that the mechanism of stone formation is multifactorial. AUR with indwelling catheter could increase the positive rate of urine culture. To avoid the bias, patients with indwelling catheters were excluded when we evaluated the positive rate of urine culture. We found the preoperative positive rate of urine culture was higher in group 1 than that of group 2 ($P=.046$). BPH patients with bladder calculi may be more likely to have a positive urine culture. We assumed that UTI caused by bacteria may alter urinary PH and citrate concentration, which could contribute to the formation of crystal. Moreover, the change of urinary micro-environment associated with bacteria may be the underlying mechanism of bladder calculi. However, the data in our study are limited and the mechanisms of how bacteria leading to bladder stone are still not obscure. And more further studies are still needed to be investigated.

Our study also revealed that the TPV, PSA, and disease duration were significantly lower in group 1 than those of group 2. As bladder calculi was an absolute indication for the surgical treatment of BPH, patients in group 1 might undergo surgical therapy earlier than those of group 2, which might contribute to the lower TPV and disease duration in group 1. The level of PSA could be influenced by many factors, such as age, TPV, UTI, and indwelling catheter. A higher TPV and incidence of indwelling catheter in group 2 might contribute to a higher level of PSA value in this group.

As many studies reported that metabolic abnormalities were associated with lithogenesis,^[10,19] we hypothesized the change of urinary micro-environment is also a risk factor for the pathogenesis of bladder calculi. However, it needs to be confirmed by trials in the future.

According to our study, the incidence of bladder calculi in patients with BPH was tended to be closely associated with preoperative positive urine culture and longer IPP in our study. Furthermore, the IPP was presented to be an independent risk factor for the formation of bladder calculi. Above all, we proposed that BPH patients with great IPP may benefit from early surgical intervention. Besides, the prevention of UTI is also important for the prevention of bladder calculi.

However, the main aim of our study is to reduce the surgical intervention related to bladder calculi in patients with BPH but not to increase the rate of early surgical intervention. As a main risk factor for the presence of bladder calculi in patients with BPH, the presence and lengthening of IPP is difficult to be prevented. Recently, a novel study reported that the degree of IPP

could not be reduced by combining therapy using the with α -blocker and 5α -reductase.^[20] And IPP could also contribute to the failure of medication and tend to increase the risk of progression in patients with BPH.^[20,21] But the prevention and treatment of UTI is easy to be achieved. By performing the urine routine and urine culture in BPH patients complaining about LUTS or other associated symptoms, we are able to confirm the diagnosis of UTI early. And these will help us to select the proper antimicrobials and complete antibacterial therapy effectively, which may help to prevent the presence of bladder calculi in patients with BPH.

There are some limitations in our study. First, this study was retrospective, which might introduce recall bias. And the sample size included into our study is small. Second, the preoperative urine culture was only conducted once, so the results of which may have contingency. Third, some included patients did not have urine culture. Besides, quite a few patients lacked urodynamic data before surgery. Prospective randomized controlled trials are needed to confirm our conclusions.

5. Conclusions

In conclusion, the incidence of bladder calculi in patients with BPH was proved to be closely associated with preoperative positive urine culture and longer IPP in our study. Furthermore, the IPP was presented to be an independent risk factor for the formation of bladder calculi. And early antibacterial therapy of UTI may help to prevent the presence of bladder calculi in patients with BPH.

References

- [1] Papatsoris AG, Varkarakis I, Dellis A, et al. Bladder lithiasis: from open surgery to lithotripsy. *Urol Res* 2006;34:163–7.
- [2] Gratzke C, Bachmann A, Descalcaud A, et al. EAU Guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2015; 67:1099–109.
- [3] McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1793–803.
- [4] Philippou P, Moraitis K, Masood J, et al. The management of bladder lithiasis in the modern era of endourology. *Urology* 2012;79:980–6.
- [5] Elzayat EA, Elhilali MM. Holmium laser enucleation of the prostate (HoLEP): the endourologic alternative to open prostatectomy. *Eur Urol* 2006;49:87–91.
- [6] Mebust WK, Holtgrewe HL, Cockett AT, et al. Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol* 2002;167:999–1003.
- [7] Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. *J Urol* 2010;183:1105–9.
- [8] Matlaga BR, Miller NL, Terry C, et al. The pathogenesis of calyceal diverticular calculi. *Urol Res* 2007;35:35–40.
- [9] Husmann DA, Milliner DS, Segura JW. Ureteropelvic junction obstruction with a simultaneous renal calculus: long-term follow-up. *J Urol* 1995;153:1399–402.
- [10] Raj GV, Auge BK, Assimos D, et al. Metabolic abnormalities associated with renal calculi in patients with horseshoe kidneys. *J Endourol* 2004;18:157–61.
- [11] Nose H, Foo KT, Lim KB, et al. Accuracy of two noninvasive methods of diagnosing bladder outlet obstruction using ultrasonography: intravesical prostatic protrusion and velocity-flow video urodynamics. *Urology* 2005;65:493–7.
- [12] Griffiths D, Hofner K, van Mastrigt R, et al. Standardization of terminology of lower urinary tract function: pressure-flow studies of voiding, urethral resistance, and urethral obstruction. International Continence Society Subcommittee on Standardization of Terminology of Pressure-Flow Studies. *Neurourol Urodyn* 1997;16:1–8.

- [13] Yoshida O, Okada Y. Epidemiology of urolithiasis in Japan: a chronological and geographical study. *Urol Int* 1990;45:104–11.
- [14] Childs MA, Mynderse LA, Rangel LJ, et al. Pathogenesis of bladder calculi in the presence of urinary stasis. *J Urol* 2013;189:1347–51.
- [15] Park S, Pearle MS. Pathophysiology and management of calcium stones. *Urol Clin North Am* 2007;34:323–34.
- [16] Chia SJ, Heng CT, Chan SP, et al. Correlation of intravesical prostatic protrusion with bladder outlet obstruction. *BJU Int* 2003;91:371–4.
- [17] Lim KB, Ho H, Foo KT, et al. Comparison of intravesical prostatic protrusion, prostate volume and serum prostatic-specific antigen in the evaluation of bladder outlet obstruction. *Int J Urol* 2006;13:1509–13.
- [18] 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;84:1026–9.
- [19] Schwartz BF, Stoller ML. The vesical calculus. *Urol Clin North Am* 2000;27:333–46.
- [20] Liu Q, Zhu Y, Liu J, et al. Ultrasound image features of intravesical prostatic protrusion indicated failure of medication therapy of finasteride and doxazosin in patients with benign prostatic hyperplasia (LUTS/BPH). *Int Urol Nephrol* 2017;49:399–404.
- [21] Matsukawa Y, Ishida S, Majima T, et al. Intravesical prostatic protrusion can predict therapeutic response to silodosin in male patients with lower urinary tract symptoms. *Int J Urol* 2017;24:454–9.