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Original Article

Are prostatic calculi independent predictive factors of lower urinary tract symptoms?

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Abstract

We determined the correlation between prostatic calculi and lower urinary tract symptoms (LUTS), as well as the predisposing factors of prostatic calculi. Of the 1 527 patients who presented at our clinic for LUTS, 802 underwent complete evaluations, including transrectal ultrasonography, voided bladder-3 specimen and international prostatic symptoms score (IPSS). A total of 335 patients with prostatic calculi and 467 patients without prostatic calculi were divided into calculi and no calculi groups, respectively. Predictive factors of severe LUTS and prostatic calculi were determined using uni/multivariate analysis. The overall IPSS score was 15.7 ± 9.2 and 14.1 ± 9.1 in the calculi and no calculi group, respectively ($P = 0.013$). The maximum flow rate was 12.1 ± 6.9 and 14.2 ± 8.2 mL s^{-1} in the calculi and no calculi group, respectively ($P = 0.003$). On univariate analysis for predicting factors of severe LUTS, differences on age ($P = 0.042$), prostatic calculi ($P = 0.048$) and prostatitis ($P = 0.018$) were statistically significant. However, on multivariate analysis, no factor was significant. On multivariate analysis for predisposing factors of prostatic calculi, differences on age ($P < 0.001$) and prostate volume ($P = 0.001$) were significant. To our knowledge, patients who have prostatic calculi complain of more severe LUTS. However, prostatic calculi are not an independent predictive factor of severe LUTS. Therefore, men with prostatic calculi have more severe LUTS not only because of prostatic calculi but also because of age and other factors. In addition, old age and large prostate volume are independent predisposing factors for prostatic calculi.

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1 Introduction

Prostatic calculi are common in men who are evaluated for benign prostatic hyperplasia (BPH) or prostate cancer, but the significance of prostatic calculi with respect to urological diseases and symptoms is obscure. In most cases, when symptoms are present, they are usually nonspecific. The majority of calculi are discovered incidentally, usually by means of a radiological investigation for other medical conditions. The incidental finding of prostatic calculi often produces a diagnostic and therapeutic dilemma.

Prostatic calculi are presumed to form by the precipitation of prostatic secretions and calcification of the corpora amylacea under inflammatory conditions [1, 2]. The precise mechanisms by which calculi form and the association of calculi with benign and malignant conditions of the prostate gland are unknown. Most authors agree that prostatic calculi simply accompany the presence of prostatic hyperplasia and carcinoma [3].

BPH produces lower urinary tract symptoms (LUTS) by mechanical obstruction of the prostatic

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urethra, in which the smooth muscle of the prostate and bladder neck contracts and an enlarged adenoma is present [4, 5]. Many authors reported that prostatic calculi only produce nonspecific LUTS [6]. There is a clear correlation between age and incidence of prostatic calculi, although the presence of prostatic calculi in younger men is often associated with symptoms of inflammation and prostatitis [7]. Konig *et al*. [8] reported that prostatic calculi induce prostatitis, which produces and aggravates LUTS. Prostatitis produces LUTS by contraction of the smooth muscle of the prostate and bladder neck. Inflammation of the prostatic parenchyma is suggestive of an important role for LUTS in men who have prostatic calculi.

Prostatic calculi usually coexist with prostatitis or BPH in elderly men. These patients suffer LUTS for underlying prostatic disease, such as prostatitis or BPH. It is unclear whether prostatic calculi independently produce LUTS. Therefore, we evaluated the independent predictive factors of severe LUTS in patients who have prostatic calculi, and determined the predisposing factors of prostatic calculi.

To determine the effect of prostatic calculi on LUTS, we evaluated subjective symptoms and the urinary stream. The voided bladder-3 (VB3) specimen and prostate volume were analyzed to determine the underlying prostatic disease and predisposing factors of prostatic calculi. We then ascertained whether prostatic calculi are independent predictive factors for severe LUTS and also determined the predisposing conditions of prostatic calculi.

2 Patients and methods

2.1 Patients selection

Between January 1998 and December 2005, 1 527 males were examined by one physician at the prostate clinic of our hospital. Exclusion criteria were acute infections of the urinary tract, a history of lower urinary tract surgery or irradiation and a history or evidence of prostatic cancer. The indications for prostatic biopsy included a suspicious digital rectal examination (DRE) and/or an elevated prostate-specific antigen (PSA) level (≥ 4.0 ng per 100 mL). Of the 1 527 patients, 802 underwent complete evaluations. A total of 335 patients with prostatic calculi and 467 patients without prostatic calculi were divided into calculi and no calculi groups, respectively.

2.2 Measurements

Prostatic calculi and prostate volume were measured by transrectal ultrasonography (TRUS). The Meares-Stamey four-glass test was carried out to determine the presence of prostatitis defined as > 10 WBC and/or positive culture. It included chronic bacterial and nonbacterial prostatitis. All patients had a complete history, physical examination, uroflowmetry and an international prostatic symptoms score (IPSS) at the first visit. Severe LUTS was defined as an overall IPSS score ≥ 20.

2.3 Definition of prostatic calculi

In all, 335 patients with prostatic calculi and 467 patients without prostatic calculi were divided into calculi and no calculi groups, respectively. All patients underwent TRUS to measure prostatic calculi. Hyperechoic areas without shadowing and tiny stippled calcifications (< 3 mm in largest diameter) were not considered as prostatic calculi for the purpose of this analysis. All patients had a complete history, physical examination and uroflowmetry. Severe LUTS was defined as an overall IPSS score ≥ 20.

2.4 Statistics

Statistical analysis was performed using SPSS, version 12 (SPSS Inc. Chicago, IL, USA). Parametric continuous variables were compared with the unpaired *t*-test, and categorical variables were compared with the χ^2-test. The parametric variables are reported as mean ± SE. Statistical significance was set at $P = 0.05$. Factors associated with severe LUTS and the formation of prostatic calculi were studied by univariate analysis. Of these variables, only those that were statistically significant ($P < 0.05$) on univariate logistic analysis were included in the multivariate logistic model. Multivariate logistic regression was used to determine the independent predisposing factors for severe LUTS and the formation of prostatic calculi.

3 Results

The average age of patients was 70.5 ± 10.7 and 64.8 ± 12.8 years in the calculi and no calculi groups, respectively ($P < 0.001$). The mean prostate volume was 29.7 ± 17.3 and 25.5 ± 16.5 mL ($P = 0.001$) and the overall IPSS was 15.7 ± 9.2 and 14.1 ± 9.1 in the calculi and no calculi groups, respectively ($P = 0.013$).

A total of 109 (32.5%) and 134 patients (28.7%) in the calculi and no calculi groups, respectively, complained of severe LUTS ($P < 0.001$). The maximal flow rate (Q_{max}) was 12.1 ± 6.9 and 14.2 ± 8.2 mL s^{-1} in the calculi and no calculi groups, respectively ($P = 0.003$). The results of VB3 showed that 24 (7.2%) and 22 (4.7%) had prostatitis in the calculi and no calculi groups, respectively ($P = 0.094$; Table 1).

To identify the factors related to severe LUTS, we examined age and presence of prostatic calculi and prostatitis by univariate analysis. It indicated that age ($P = 0.042$) and presence of prostatic calculi ($P = 0.048$) and prostatitis ($P = 0.018$) were possible risk factors for severe LUTS. However, prostatic volume did not induce severe LUTS. On the basis of multivariate analysis performed for predictive factors of severe LUTS, no factors had statistical significance (Table 2).

Old age ($P < 0.001$) and large prostate volume ($P < 0.001$) were important predisposing factors of prostatic calculi in univariate analysis. However, prostatitis was not related to prostatic calculi ($P = 0.109$). On the basis of multivariate analysis performed for predisposing factors of prostatic calculi, age ($P < 0.001$) and prostate volume ($P = 0.001$) had statistical significance (Table 3).

4 Discussion

Prostatic calculi are commonly diagnosed by TRUS. However, it is unknown whether prostatic calculi are clinically insignificant or whether they have the potential to cause symptoms, especially LUTS. We sought to determine whether prostatic calculi are an independent predictive factor for LUTS and predisposing factors for prostatic calculi.

There may be different incidences of prostatic calculi with diverse definition and community. In one autopsy study, the incidence was 70.1% and 29.1% in Black men from Washington, DC, and from Ibadan, Nigeria and Accra, Ghana, respectively. They suggest that dietary pattern and age were important factors for determining the incidence of prostatic calculi [9]. We showed prostatic calculi in 41.8% of men who complain of LUTS. These differences may emerge because of selection bias and may obscure the definition of prostatic calculi. Definition and classification of prostatic calculi were not unified. In our study, prostatic calculi diagnosed hyperechoic areas with shadowing and larger than 3 mm in size. Prostatic calculi could be divided into larger and smaller calculi on the basis of formation theories and histopathological characteristics [10]. Symptoms are strongly correlated with the larger-

Table 1. Clinical variables between men with and without prostatic calculi.

	Calculi ($n = 335$)	No calculi ($n = 467$)	P-value
Age			
No. (age < 65 years)	101	195	
No. (age ≥ 65 years)	234	272	
Age (years)	70.5 ± 10.7	64.8 ± 12.8	< 0.001
Prostate volume			
No. (volume < 25 mL)	168	283	
No. (volume ≥ 25 mL)	167	184	
Prostate volume (mL)	29.7 ± 17.3	25.5 ± 16.5	0.001
Total IPSS score	15.7 ± 9.2	14.1 ± 9.1	0.013
No. with severe symptoms (overall score ≥ 20) (%)	109 (32.5%)	134 (28.7%)	< 0.001
Max flow rate			
No. (max flow rate < 10)	142	157	
No. (max flow rate ≥ 10)	193	310	
Max flow rate (mL s^{-1})	12.1 ± 6.9	14.2 ± 8.2	0.003
Prostatitis			
No. (negative)	311	445	
No. (positive) (%)	24 (7.2%)	22 (4.7%)	0.094

Abbreviation: IPSS, international prostate symptoms score. The parametric variables are reported as mean ± SE.

Table 2. Univariate and multivariate logistic regression analysis of covariate influence on severe lower urinary tract symptoms (overall international prostate symptoms score [IPSS] score 20).

	Univariate OR (95% CI)	Multivariate-adjusted OR (95% CI)
Age (years)		
< 65 years	1.00	1.00
≥ 65 years	1.33 (0.99–1.78)	1.25 (0.92–1.59)
P-value	0.042	0.151
Calculi		
No	1.00	1.00
Yes	1.31 (0.98–1.74)	1.26 (0.94–1.70)
P-value	0.048	0.121
Prostate volume		
< 25 mL	1.00	
≥ 25 mL	1.09 (0.82–1.29)	
P-value	0.806	
Prostatitis		
Negative	1.00	1.00
Positive	1.52 (0.97–1.75)	1.36 (0.92–1.55)
P-value	0.018	0.079

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Univariate and multivariate logistic regression analysis of covariate influence on prostatic calculi.

	Univariate OR (95% CI)	Multivariate-adjusted OR (95% CI)
Age		
< 65 years	1.00	1.00
≥ 65 years	2.27 (1.71–3.01)	1.76 (1.30–2.39)
P-value	< 0.001	< 0.001
Prostate volume		
< 25 mL	1.00	1.00
≥ 25 mL	2.00 (1.50–2.69)	1.71 (1.26–2.32)
P-value	< 0.001	0.001
Prostatitis		
Negative	1.00	
Positive	1.47 (0.98–1.75)	
P-value	0.109	

Abbreviations: CI, confidence interval; OR, odds ratio.

sized calculi [3]. These obscure and diverse definitions of prostatic calculi may be a limitation of our study.

The first clinical reports of prostatic calculi associated with symptoms of urinary tract obstruction were published in the late 1 800s [11]. Following these reports, most of the studies have suggested that prostatic calculi are related to nonspecific LUTS [3, 6]. The effects of prostatic calculi on LUTS are unclear, but several explanations may be proposed. Prostatic calculi probably influence a relaxation of the prostatic urethra and thus interfere with the urinary stream. There is a likelihood of a more significant effect on relaxation of the prostatic urethra in periurethral calculi than in scattered stromal calculi. Although the effects on LUTS are probably different between the different types and locations of prostatic calculi, we did not classify prostatic calculi. We used only exit or not-exit classes. Prostatic calculi should be subdivided in future studies to evaluate the probable mechanisms of the effects of prostatic calculi on LUTS. Another mechanism underlying LUTS is spasm of pelvic floor muscles [12]. Men with prostatic calculi had more severe irritative symptoms and voiding symptoms in our study (these results were not described). This observation suggests that prostatic calculi induce not only mechanical obstruction but also smooth muscle contraction.

To determine the effects of prostatic calculi on LUTS, we evaluated the subjective symptoms (IPSS) and objective urine stream (uroflow study). Our study is the first to evaluate the effect of prostatic calculi on the IPSS and Q_{max} scales. The total IPSS scores of men with prostatic calculi were higher than those in men without prostatic calculi. Indeed, voiding and storage symptoms are affected together by prostatic calculi. In these patients, Q_{max} was also decreased. However, multivariate logistic regression analysis revealed that prostatic calculi are not independent factors of severe LUTS in men with prostatic calculi, because men with prostatic calculi are older and have larger prostates. Therefore, men with prostatic calculi have more severe LUTS not only because of prostatic calculi but also because of age and other factors.

The other problematic consideration is when to treat prostatic calculi. Most authors recommend that if there are no complications due to prostatic calculi, periodic follow-up is sufficient [6, 13]. Patients who have intractable infection or prostatic calculi protruding to prostatic urethra causing urinary retention may be treated by transurethral removal, which offers relief, but does not guarantee the removal of all calculi or eliminate the possibility of new calculus formation. If removal of calculi is deemed necessary, a transurethral removal is the procedure of choice in younger patients

in order to preserve sexual function. In older patients, open prostatolithotomy may be performed for a single large stone or large cluster of stones [13].

The predisposing factor of prostatic calculi is not clear. The general acceptance is that prostatic calculi are a consequence of aging in older men [6, 11]. Our study also supports that age is a significant predictive factor for prostatic calculi. On uni- and multivariate analyses performed for possible risk factors of prostatic calculi, age and prostate volume were significant. Therefore, age and prostate volume are independent predisposing factors for prostatic calculi.

However, we did not show that prostatitis causes prostatic calculi. The role of prostatic calculi in the etiology and symptoms of chronic prostatitis and chronic pelvic pain syndrome (CPPS) has been more actively studied. Recently, the majority of studies suggest that prostatic calculi are common in patients with CPPS and are associated with greater inflammation and symptoms [14, 15]. Their studies showed a significant difference in the duration of pelvic pain between prostatic calculi and noncalculi groups, but did not show a significant difference in the WBC count in the prostatic fluid. Ludwig *et al.* [16] concluded that prostatic calculi are typical signs of inflammation, but these sonographic abnormalities do not prove the presence of chronic prostatitis. Our study did not show a difference in the WBC count in VB3 between the prostatic calculi and no calculi groups. It is noteworthy that we defined prostatitis as > 10 WBC and/or positive culture in VB3 We did not examine the symptoms of prostatitis by means of a questionnaire. We defined only chronic bacterial prostatitis and chronic nonbacterial prostatitis, except CPPS, as prostatitis. However, one cannot exclude inflammation in the gland simply on the basis of the absence of leukocytes in prostatic secretions. These definitions of prostatitis are inevitable limitations in these kinds of studies.

In our study, men with a normal PSA and DRE did not undergo a biopsy. Although there was the potential for a missed diagnosis of prostate cancer, justifying a biopsy in the setting of a normal PSA and DRE is difficult. Thus, additional histological studies are needed to confirm such suspicions. Other studies have failed to find a relationship between prostate cancer and prostatic calculi, concluding that prostatic stromal calculi are a dystrophic, inflammation-mediated, benign process [17, 18].

5 Conclusion

Patients who have prostatic calculi complain of severe symptoms and the maximum urinary flow rate are decreased. However, prostatic calculi are not an independent predictive factor of severe LUTS on the basis of multivariate analysis. Therefore, men with prostatic calculi have more severe LUTS not only because of prostatic calculi but also because of age and other factors. In addition, older age and larger prostate volume are independent predisposing factors for prostatic calculi.

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