Infection/Inflammation

Effect of Prostatitis on Lower Urinary Tract Symptoms: Retrospective Analysis of Prostate Biopsy Tissue

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Purpose: Most patients, even some urologists, assume that prostate volume is the most important prognostic factor for lower urinary tract symptoms (LUTS). In some cases, however, prostatic inflammation is a more important factor in LUTS than is prostate volume. For this reason, comparison of the impact on LUTS of inflammation and prostate volume is an attractive issue.

Materials and Methods: From January 2000 to May 2009, 1,065 men aged between 47 and 91 years (who underwent transrectal ultrasound-guided prostate needle biopsy and transurethral prostatectomy) were retrospectively investigated. Components such as age, serum prostate-specific antigen (PSA) level, prostate volume, and the presence of prostatitis were investigated through independent-sample t-tests, chi-square tests, and univariate and multivariate analyses.

Results: Chi-square tests between prostatitis, prostate volume, serum PSA, and severe LUTS showed that prostate volume (R=0.173; p=0.041) and prostatitis (R=0.148; p $<$ 0.001) were related to LUTS. In particular, for a prostate volume under 50 ml, prostatitis was a stronger risk factor than was prostate volume. Among the multivariate predictors, prostatitis (odds ratio [OR]: 1.945; p $<$ 0.001) and prostate volume (OR, 1.029; p $<$ 0.001) were found to be aggravating factors of LUTS.

Conclusions: For patients with prostate volume less than 50 ml, prostatitis was found to be a more vulnerable factor for LUTS. For those with prostate volume over 50 ml, on the other hand, the volume itself was a more significant risk factor than was prostatitis. In conclusion, the presence of prostatitis is one of the risk factors for LUTS with increased prostate volume.

Key Words: Inflammation; Prostate; Prostatic hyperplasia

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is an increasingly common condition in aged males. By the age of 60 years, more than 50% of men will have microscopic evidence of the disease, and more than 40% of men beyond this age will have lower urinary tract symptoms (LUTS) [1]. Many risk factors may lead to progression of LUTS, for instance, prostate volume, metabolic syndrome, and inflammation [2-4]. In particular, inflammation of the prostate is an emerging constituent of BPH and LUTS [5]. It is difficult and complicated to prioritize these risk factors. For practitioners,

however, the priority is clinically critical.

Prostate hyperplasia triggers bladder outlet obstruction and this obstruction disturbs urine outflow. Several structural and functional changes, for instance, collagen predisposition and fibrosis in the detrusor muscle, are regarded in part as a positive compensatory response aiming to overcome resistance to bladder empting [6,7]. To prevent these disasters, the operative management of BPH is an inevitable treatment choice unless the patient ignores inconvenient catheterization [8]. However, patients with normal or even small prostate volumes complain of a similar degree of LUTS as do BPH patients, who do not complain

that much. Thus, it is certain that many other factors influence LUTS.

Chronic prostatitis is one of the most common urologic diseases of 30 to 40-year-old men [9]. There have been abundant discussions about prostatitis, but the particularity of this inflammatory disorder is hard to control and the recurrence rate is over 20 to 30% [10]. Chronic prostatitis is one of the obvious causes of BPH itself and its symptoms overlap in many cases of BPH patients. Accordingly [11], it is hard to differentiate prostatitis from BPH and to weigh the gravity of these symptoms.

In many cases of patients with LUTS, the diagnostic and therapeutic approach should be directed to the prostate enlargement or prostatitis. However, it is hard to separate most patients by prostatitis and BPH. For that reason, comparison of the effects of prostatitis and prostate enlargement on LUTS is important to both urologists and patients.

MATERIALS AND METHODS

From January 2000 to May 2009, after the exclusion of patients with psychological problems, neurogenic bladder, asymptomatic elevation of prostate-specific antigen (PSA), acute prostatitis, and prostate cancer, 1,065 male patients aged between 47 and 91 years with LUTS who underwent transrectal prostate biopsy and transurethral prostatec-

tomy were enrolled in this study retrospectively. Not only general considerations such as age, height, and body weight but also International Prostate Symptom Score (IPSS), PSA, and prostate volume measured by transrectal ultrasonography were documented. Prostatitis was pathologically defined as significant lymphocytic infiltrate in the stroma immediately adjacent to the prostatic acini and confirmed by pathologic consultation. Pathologically uncertain specimens were discussed and confirmed by two or more pathologists for therapeutic guidance. Patients with prostatitis were classified into group A and patients without prostatitis (no prostatitis) were classified into group B. For statistical consideration, severe LUTS was defined as patients with IPSS over 20, and mild LUTS as a score under 7.

We used independent-sample t-tests to compare IPSS with prostate volume and chi-square tests and logistic regression analysis to compare the relative risk of prostate volume, prostatitis, and PSA. Technical statistics were performed by use of SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The enrolled subjects were 1,065 men, their mean age was 73.28 ± 0.31 years old, the average PSA was 11.11 ± 0.26 ng/ml, and the average prostate volume was 41.77 ± 0.64 ml. group A included 321 patients (30.1%), and group B included 744 (69.9%). The average PSA was 10.95 ± 8.71 ng/ml in group A and 11.17 ± 8.57 ng/ml in group B (Table 1). The PSA of group B was slightly higher and the difference was statistically significant, though weakly. Chi-square tests between prostatitis, prostate volume, and PSA showed prostate volume and prostatitis to be significant risk factors for severe LUTS (p=0.041, p < 0.001). In particular, when respective IPSS values were compared with each count of prostate volume or presence of prostatitis, the relative risk of prostate volume was exclusively higher (R= 0.148) and there was statistical significance for any level of prostate volume over 50 ml on the t-test (p < 0.001).

TABLE 1. Characteristics of the patients

Characteristic	Prostatitis patients (group A)	No prostatitis patients (group B)	p-value
Total population	321 (30.1)	744 (69.9)	-
Age (yr)	73.28±9.26	68.02±5.39	0.052
sPSA (ng/ml)	10.95±8.71	11.17±8.57	0.170
Mean prostate volume (ml)	43.10±21.14	41.19±20.96	0.369

Values are presented as number (%) or mean±SD.
sPSA, serumprostate-specific antigen.

TABLE 2. Odds ratio according to prostate volume.

Prostate volume (ml)	Population	Ave. IPSS	p-value	OR	Confidence interval	
					Lower	Upper
-20[a]	60	16.72±6.51	-	-	-	
20-29	307	19.32±8.83	0.300	1.353	0.764	2.396
30-39	189	20.35±7.98	0.133	1.588	0.868	2.905
40-49	251	20.94±6.79	0.085	1.666	0.932	2.980
50-59	37	22.41±6.09	< 0.001[b]	6.751	2.419	18.839
60-69	89	24.90±5.95	< 0.001[b]	10.012	4.479	22.380
70-79	59	24.89±5.43	< 0.001[b]	5.697	2.536	12.797

Values are presented as number (%) or mean±SD.
Ave, average; IPSS, International Prostate Symptom Score.
[a]: reference variable, [b]: p < 0.05.

TABLE 3. Comparison of average IPSS between prostate volume and prostatitis

Prostate volume (ml)	Ave. IPSS of patients with prostatitis (group A)	Ave. IPSS of patients without prostatitis (group B)	p-value
-20	18.91±7.71	16.22±6.19	0.039[a]
20-29	20.59±9.19	18.82±8.66	<0.001[a]
30-39	21.81±7.30	19.75±8.22	0.028[a]
40-49	22.83±6.87	20.12±6.61	0.030[a]
50-59	24.08±5.64	19.07±5.75	0.075
60-69	27.23±6.51	23.75±5.34	0.122
70-79	27.06±5.81	23.98±5.05	0.120
80-	25.94±7.03	25.98±7.54	0.170
Total[a]	22.86±7.80	20.37±7.80	<0.001

Values are presented as mean±SD.
Ave, average; IPSS, International Prostate Symptom Score.
[a]: $p < 0.05$.

However, stepwise volume-controlled analysis showed no statistically significant difference between prostate volume and the severity of LUTS under 50 ml (Table 2). For that range of prostate volume, prostatitis instead showed statistical significance (Table 3).

Univariate analysis of the risk factors for severe LUTS indicated that there was a statistically significant correlation between severe LUTS and prostatitis and prostate volume (odds ratios [OR], 1.967 [1.492 to 2.592] and 1.029 [1.022 to 1.037]; $p < 0.001$). The multivariate analysis showed this also (odds ratios, 1.945 [1.464 to 2.586] and 1.029 [1.022 to 1.037]; $p < 0.001$). PSA, however, was not a statistically significant risk factor (OR, 1.018 [0.879 to 1.013]; p=0.089).

DISCUSSION

There are so many factors influencing LUTS that physicians cannot target the patient's symptoms all at once. Previous studies have revealed a relationship between LUTS and obesity, metabolic syndrome, smoking, alcohol consumption, and urinary tract infection. The Veterans Administration Normative Aging Study reported that increased body mass index was a significant predictor of a clinical diagnosis of BPH [12,13]. Patients who complain of LUTS have not only one risk factor but also a list of complex problems. Some of them can be managed by lifestyle modification or counseling only. On the other hand, assertive treatment is inevitable for other risk factors such as bladder outlet obstruction by prostate hyperplasia.

Most of all, prostate enlargement is the most important factor for male LUTS management. It is the first consideration of urologic clinical research on adult male LUTS without physiologic or neurologic problems. In autopsy studies, histological evidence of BPH is found in 8% of men aged between 31 and 40 years, and the proportion increases to more than 70% of men by the seventh decade of life. The

average prostate weight increases from approximately 20 g at the age of 40 to 38.8 g in men older than 80 [13]. In addition, there is a close relationship between prostate volume and LUTS. LUTS based on IPSS is mirrored by changes in prostate volume, and the changes in LUTS and other measures of urinary function are associated with change in prostate volume even though there is no definite proportion between prostate volume and LUTS or IPSS [14]. In general, a decrease in prostate volume by any treatment method occurs simultaneously with improvement in LUTS.

It was suggested several years ago that prostate inflammation may be a third component in determining the association between BPH and LUTS. There is even evidence of a weak relationship between the degree of LUTS and the degree of chronic inflammation [5,15]. This is a reminder that detection of prostatitis in patients with LUTS is simply important. Sometimes, pyuria is combined with prostatitis, but in most cases of chronic prostatitis, there is no evidence of urinary tract infection. Elevated PSA can be a clue to chronic prostatitis [16]. Ninety-nine percent of patients with PSA over 4 ng/ml without prostate cancer showed chronic prostatitis compared with 77% of the control group in research by Nadler et al. [17]. Mostly, however, there is no specific laboratory evidence for chronic prostatitis or a definite tool for measuring improvement. This is why consideration of prostatitis in patients with LUTS has priority in the diagnostic schema.

As we discussed above, BPH and prostatitis are the most common benign diseases of the prostate (and probably the entire genitourinary tract) and affect a significant majority of men over time [18]. There are many approaches to the diagnosis of BPH, and prostate volume detection is the most important. Prostate volume is detectable precisely today by transrectal ultrasound. Clinical use of 3D ultrasound has spread rapidly in many specialties, including urology, over the past 10 years. In particular, the clinical application of volume estimation by 3D ultrasound has recently gained much attention. This precise method of prostate volume measurement has shown more satisfactory results recently in BPH treatment [19]. With the use of all these volume-detecting methods, LUTS without prostate hyperplasia or any other obstruction of urine flow should be considered in connection to prostate inflammations such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Confirmative differential diagnosis of BPH and prostatitis is difficult because the symptoms are similar. More than 6% of visiting patients with a primary diagnosis of prostatitis have a concomitant diagnosis of BPH. Some older men with LUTS may be incorrectly diagnosed with BPH simply because of their symptoms and their old age, or they may have prostatitis as well as BPH [20]. Recently, there has been much research on this. In many cases of LUTS, prostate inflammation is combined with BPH. The association between BPH and intraprostatic inflammation was first proposed on the basis of the histological coexistence of hyperplastic nodules and chronic inflammatory infiltrates in

a high proportion of BPH tissues [5,21]. In a subgroup of randomly selected patients from the reduction by dutasteride of prostate cancer events trial, the association between inflammation and the severity of BPH symptoms was described [22]. Now, the relationship between LUTS and BPH is gradually being clarified. In that mechanism, continuous prostate enlargement can be a result of recurrent prostate inflammation. Moreover, this is another reason to control prostatitis as well as prostatic hyperplasia.

Of course, there are some differences between the symptoms of BPH and those of prostatitis. The symptoms of BPH are various but those of prostatitis are mainly irritative symptoms such as chronic pelvic pain. Accordingly, LUTS may be divided into two categories, namely, obstructive and irritative symptoms in order to compare BPH with prostatitis.

In a symptomatic approach to LUTS, prostatitis without evidence of bacterial infection is a dilemma for therapeutic modalities. A multidisciplinary approach to patients with chronic prostatitis is a recent therapeutic consideration [23].

Chronic prostatitis is a long-standing disease resistant to medication therapy. The age of patients with chronic prostatitis is not limited to older men as in BPH. In addition, prostatitis patients are generally treated in the outpatient setting [16]. Many enrolled patients disappear, come to the clinic very irregularly, or receive concomitant management from other hospitals. Some of the cases are prescribed antibiotics such as quinolones or alpha-blockers [24,25], and for such cases there was a little improvement in symptoms and quality of life. However, most of them were not that effective. Nevertheless, most CP/CPPS patients needed to be managed aggressively by various medications, such as antibiotics, analgesics, and antidepressants or other invasive managements, such as botulinum injection as well as the current medications [23,26].

It is confusing that the prostatitis of the enrolled patients was found incidentally, and this suggests that these cases should be classified as CP/CPPS. Also, this study was a retrospective analysis, which means that case-control study was difficult and the initially enrolled cases were too limited to be engaged. For instance, some items were discarded or skipped from the medical records. Also, it is virtually impossible to confirm CP/CPPS retrospectively; thus, the confirmative diagnostic method was pathologic confirmation of prostate tissues, and this limitation resulted in some problems such as the relatively higher PSA level of the enrolled cases than of the normal population or the narrowed range of BPH patients who were managed operatively. Practically, however, a larger number of patients with LUTS do not need operative procedures. Most BPH patients receive alpha blockers and 5-alpha reductase inhibitors to reduce their LUTS, and prostatitis patients primarily receive antibiotics, with additional prescription of alpha blockers. Because BPH and prostatitis share some symptoms and features, many physicians handle prostatitis and BPH medications indistinctively. This may make the results confusing or distorted when the prostate volume is relatively small.

In this study, post-managed urodynamic and pressure-flow analysis might have been included for quantification, classification of LUTS origin, or exclusion of neurogenic bladder for all the patients, but as we discussed above, chronic prostatitis patients are hard to follow up and are resistant to repetitive consultation. Therefore, we had to exclude all patients with a history of neurologic or psychological problems or with suspicious neurogenic bladder by selective post-managed urodynamic study. However, because the IPSS is a well-designed voiding symptom scaling system, we at least achieved subjective quantification of symptoms.

Pathologic confirmation of benign prostate enlargement, prostatitis, and combined BPH with prostatitis was made by pathologic specialists, but the severity of inflammation was not recorded. The severity of inflammation is known to be a factor affecting LUTS [15].

Prescribed medications could affect LUTS. In this study, the patients did not have any urologic or antibiotic medication history for their LUTS within 6 months. However, they were prescribed antibiotics for 3 days before prostate biopsy and prophylactic antibiotics for transurethral prostate resection. This could have affected the results of this study.

A well-designed prospective study is needed to avoid these biases. First of all, chronic prostatitis should be diagnosed in at least 6 months after the first visit to the clinic. Precise prostate volume detection and annual PSA confirmation should be included. Prophylactic antibiotics and prescription for prostate biopsy should have consensus.

CONCLUSIONS

Prostatitis is a more vulnerable factor for LUTS in patients with a normal to moderately enlarged prostate volume. On the other hand, for patients with a large prostate volume over 50 ml, the volume is a more significant risk factor than is prostatitis.

For counseling and workup of patients with LUTS, prostatitis as a disease entity that can be controlled by medication and other procedures should be given priority in the problem list. In other words, if volume reduction of prostate tissue hyperplasia is the target of LUTS with BPH, controlling prostatitis is the primary target of any kind of LUTS management regardless of whether the prostatitis comes with BPH or not.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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