Original article

# Relation between histological prostatitis and lower urinary tract symptoms and erectile function

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**Short title:** Prostatitis, LUTS, and erection

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**Abstract**

**Background:** Chronic prostatitis (CP) significantly worsens patient quality of life, but its etiology is heterogeneous. Although the inflammatory process must be associated with CP symptoms, not all patients with benign prostatic hyperplasia and histological prostatitis complain of CP symptoms. The relation between the severity of histological inflammation and lower urinary tract symptoms (LUTS) and erectile function is not fully understood.

**Methods:** This study comprised 26 men with suspected prostate cancer but with no malignant lesion by pathological examination of prostate biopsy specimens. LUTS were assessed by several questionnaires including the International Prostate Symptom Score (IPSS), Quality of Life (QOL) index, Overactive Bladder Symptom Score (OABSS), and the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), and erectile function was assessed by the Sexual Health Inventory for Men (SHIM). Prostate volume (PV) measured by transabdominal ultrasound, maximum flow rate by uroflowmetry, and serum concentration of prostate-specific antigen were also evaluated. All data collections were performed before prostate biopsy. Histological prostatitis was assessed by immunohistochemical staining with anti-CD45 antibody as the Quick score. The relation between the Quick score and several factors was assessed by Pearson correlation coefficient and a multivariate linear regression model after adjustment for PV.

**Results:** The Pearson correlation coefficient showed a correlation between the Quick score and several factors including PV, IPSS, QOL index, OABSS, and NIH-CPSI. A multivariate linear regression model after adjustment for PV showed only the NIH-CPSI to be associated with the Quick score. The relation between the Quick score and each domain score of the NIH-CPSI showed only the subscore of urinary symptoms to be an associated factor.

**Conclusion:** We found a correlation only between histological prostatitis and LUTS but not erectile dysfunction. Especially, the subscore of urinary symptoms (residual feeling and

urinary frequency) was associated with histological prostatitis.

**Keywords:** CD45, erectile function, histological prostatitis, lower urinary tract symptoms

## 1. Introduction

In the clinical setting, we often see patients with benign prostatic hyperplasia (BPH) who complain of lower abdominal pain and/or perineal discomfort as well as dysuria. In such cases, a diagnosis of chronic prostatitis (CP) is predominantly considered. Generally, prostatitis is classified into 4 categories by the National Institutes of Health: acute (I) or chronic bacterial prostatitis (II), CP/chronic pelvic pain syndrome (CPPS) (III), inflammatory (IIIa) or non-inflammatory (IIIb), and asymptomatic inflammation of the prostate gland (IV).[1] Among them, CP/CPPS is the most frequency category that significantly worsens the quality of life (QOL), but its etiology is heterogeneous and generally unknown. Although the inflammatory process must be associated with CP symptoms, not all patients with BPH whose prostatic tissue shows histological inflammation complain of CP symptoms, i.e., class IV type. Furthermore, it was reported that histological prostatitis may serve as a major risk factor for sexual dysfunction.[2] Thus, the basic clinical question has arisen of whether the degree and severity of prostatic tissue inflammation correlate with the degree of several symptoms including lower urinary tract symptoms (LUTS) and erectile function in patients with BPH.

The positive staining rate for anti-CD45 antibody by histological examination in prostatic tissue was recently reported to be significantly and positively correlated with inflammatory scoring.[3] The degree of inflammatory infiltration can be assessed with this method in quantitative terms. Regarding subject symptoms, the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) has been used in several clinical studies and has already gained credibility in aiding the diagnosis of CP.[4] Thus, in the present study, we investigated both the relation between histological inflammation of the prostate tissue by anti-CD45 staining and the severity of LUTS including CP symptoms and the relation between

histological prostatitis and erectile function in patients with BPH.

## 2. Subjects and methods

### *2.1 Patients*

This study comprised 26 men with suspected prostate cancer based on a high serum concentration of prostate-specific antigen (PSA) and/or the detection of a tumorous mass by magnetic resonance imaging but who had shown no malignant lesion by pathological examination of prostate biopsy specimens between April 2014 and March 2015. LUTS were assessed by several questionnaires including the International Prostate Symptom Score (IPSS), QOL index, Overactive Bladder Symptom Score (OABSS), and NIH-CPSI, and erectile function was assessed by the Sexual Health Inventory for Men (SHIM). Prostate volume (PV) measured by transabdominal ultrasound, maximum flow rate by uroflowmetry, and serum concentration of PSA were also evaluated. All data collections were performed before prostate biopsy. The present study was approved by the Regional Ethics Committee of the Juntendo University Urayasu Hospital.

### *2.2 Immunohistochemistry and histopathological assessment*

Briefly, 4-μm paraffin sections were deparaffinized and hydrated, 3% hydrogen peroxide was used to remove endogenous peroxidase, and antigen retrieval was done by boiling in 0.01M citrated buffer and blocking with normal serum. Sections were incubated with primary antibody of rabbit anti-human CD45 polyclonal antibody (1:500 dilution, Sigma-Aldrich Inc., USA) in TBST overnight at 4°C and then were incubated with biotinylated secondary antibody (Vectastain ABC kit, Vector Laboratories, Inc., USA) against rabbit IgG with 2.5% normal serum for 60 minutes. Thereafter, sections were incubated with ABC reagent (Vectastain ABC kit, Vector Laboratories, Inc.) for 30 minutes at room temperature. The

enzyme reaction was developed with liquid chromogen-DAB (EnVision+ Kit/HRP, Dako). Finally, Mayer's hematoxylin (MUTO PURE CHEMICALS Co., Ltd., Japan) was used for nuclear counterstaining according to standard protocol. For each specimen, 5 areas were randomly selected, and at least 200 cells were counted overall. Immunoreactivity was classified by estimating the percentage (P) of cells showing characteristic staining (from an undetectable level [0%] to homogeneous staining [100%]) and by estimating the intensity (I) of staining (1, weak staining; 2, moderate staining; and 3, strong staining). Results were scored by multiplying the percentage of positive cells by the intensity, i.e., by the so-called Quick score (P × I; maximum = 300).[5]

*2.3 Statistical analysis*

The results are expressed as mean ± standard error. The relation between the Quick score and other factors was assessed by the Pearson correlation coefficient. Subsequently, to identify the contributors to histological prostatitis, the association between the Quick score and several factors with significant correlation coefficients was also assessed in a multivariate linear regression model after adjustment for PV. Thereafter, to identify the contributors of NIH-CPSI subscore to histological prostatitis, the associations between Quick score and each domain (pain, urinary symptoms, and QOL) score were also assessed in a multivariate linear regression model after adjustment for PV. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS (Version 18.0, SPSS, Chicago, IL).

**3. Results**

Patient characteristics are shown in Table 1. The mean age of the patients was 67.35 years, and the mean PV was 46.22 ml. The mean scores were 13.19 for the IPSS, 3.27 for the

QOL index, 4.04 for the OABSS, 10.76 for the NIH-CPSI and 8.19 for the SHIM. Maximum flow rate and serum concentration of PSA were 14.81 ml/s and 7.53 ng/ml, respectively. There was a wide distribution in the Quick score (from 20.5 to 142.5) for CD45 staining, and the mean score was 73.56 (Figure 1). According to the Pearson correlation coefficient, there was a correlation only between the Quick score and several factors including PV, IPSS, QOL index, OABSS, and the NIH-CPSI (Table 2). A multivariate linear regression model with these questionnaire scores after adjustment for PV showed only the NIH-CPSI to be associated with the Quick score (Table 3, Figure 2a). Regarding the relation between the Quick score and each domain score of the NIH-CPSI, only the subscore of urinary symptoms was shown to be an associated factor (Table 4, Figure 2b).

## 4. Discussion

It has been unclear whether the degree and severity of prostatic tissue inflammation really correlate with several symptoms including LUTS and erectile function in patients with BPH. In general, LUTS and sexual function are closely linked and are the most common complaints relating to QOL in the field of urology. A large-scale, questionnaire-based study showed that the prevalence of sexual dysfunction was 49.0% in patients with CP, in which erectile dysfunction (ED) accounted for 14.9%.[6] In terms of histological prostatitis, an association between decreased sexual function and histological inflammation of the prostate tissue was reported.[7] Another histological study showed that the mean international index of erectile function-5 (IIEF-5) score in prostatitis patients was significantly lower (16.5 ± 6.6) than that in those without prostatitis (19.6 ± 3.9).[2] In that study, histological prostatitis certainly affected erectile function, although the erectile status of both patient groups was not so severe, equally classified as mild ED (12-21 points) by evaluation with the IIEF-5 score.

Similar findings were also reported in another study, in which the IIEF-5 score of the histological CP group was significantly lower (15.13 ± 6.8) than that of the simple BPH group (18.93 ± 7.15).[8] A study with relatively older patients (> 70 years of age) showed a significant difference in the IIEF-5 scores between the histological prostatitis group (7.35 ± 4.38) and the uncomplicated BPH group (14.80 ± 5.93).[9] In that study, erectile function seemed to be severe (IIEF5 score, 7.35) because 32 of 80 patients (40.0%) had moderate ED and 38 (47.5%) had severe ED in the prostatitis group. Unexpectedly, we found no correlation between the SHIM score and Quick score in the present study. The mean SHIM score of our patients was low (8.19 ± 1.34). Fifteen of the 26 patients (57.7%) had severe ED because most of our patients possibly had other risk factors for ED, such as diabetes, hyperlipidemia, hypertension, atherosclerosis, heavy smoking, obesity, and depression. These patient characteristics may be a reason for the lack of correlation between the SHIM score and histological inflammation of the prostate in our study, although detailed information of comorbidities was missing.

Although the main and severe symptoms of CP/CPPS are certainly perineal and lower abdominal pain and discomfort, LUTS, and especially storage symptoms, are often observed in the clinical setting.[10,11] The level of tumor necrosis factor-α, which is a cell signaling cytokine involved in systemic inflammation, was recently reported to be high in semen and prostatic secretion in patients with CP/CPPS.[12,13] Thus, there is no doubt that the inflammatory process must be associated with LUTS in patients with CP/CPPS. In contrast, it was reported that chronic prostatic inflammation was found in all patients who had undergone transurethral resection for BPH in one study[14] and 50% in another one.[15] Another interesting study showed that the distribution of chronic inflammation of the prostatic tissue varied according to PV.[16] It is also well known clinically that not all patients with histological prostatitis complain of severe LUTS or CP symptoms. CP symptoms are sometime caused by

psychiatric factors, especially depression. Indeed, a correlation was shown between a change in pain scores and a change in personality characteristics scores.[17] The complicated etiology of CP symptoms makes diagnosis and treatment difficult. The guideline for CP/CPPS states that several trials of antibiotics should be avoided if there is no obvious symptomatic benefit from infection control or cultures do not support an infectious cause.[18]

In this clinical background, a few studies have been conducted to clarify the relation between the degree of histological inflammation of the prostate and the severity of LUTS. However, these associations remain controversial. The Reduction by Dutasteride of Prostate Cancer Event study showed a significant correlation between the mean chronic inflammation score and the IPSS.[19] Another study showed that there was a statistically significant difference between the histological CP group (22.73 ± 5.81) and the simple BPH group (18.23 ± 8.04).[8] It was also reported that the mean IPSS was lower in patients with lower inflammation (12) than those with higher inflammation (21).[20] A literature review of 30 clinical studies recently stated that BPH patients with concomitant chronic prostatic inflammation have more severe LUTS and are at an increased risk of the development of urinary retention.[21] Conversely, even in the studies showing a significant difference in IIEF-5 score between the histological prostatitis group and the non-prostatitis group, there was no significant difference in the IPSS between the two groups.[2,9] The IPSS of the patients in these two studies was 20.50 in the prostatitis group and 18.65 in the non-prostatitis group in one study[9] and 19.0 in the prostatitis group and 17.6 in the non-prostatitis group in the other study.[2] Thus, LUTS of most patients in those studies were classified at the severe level according to the IPSS classification. We found a correlation between the Quick score of CD45 staining and LUTS as evaluated by the IPSS, QOL index, OABSS, and NIH-CPSI (Table 2). Particularly, we found that the NIH-CPSI was associated with the Quick score by a multivariate linear regression model after adjustment for PV. We reconfirmed that the NIH-

CPSI may be an adequate questionnaire tool for estimating the severity of inflammatory infiltration into the prostate tissue. Few patients in the present study complained of perineal discomfort or pain. Thus, the subscore of the NIH-CPSI associated with the Quick score was urinary symptoms, not pain, regardless of a recent report showing that the positive degree of CD163, which is a macrophage marker, was significantly reflected in the subscore of pain on the NIH-CPSI in the patients with prostate inflammation after finding lymphocytic infiltration in the prostate biopsy specimen.[22] The questions for the subscore of urinary symptoms are "How often have you had a sensation of not emptying your bladder completely after you finish urinating, over the last week?" and "How often have you had to urinate again less than two hours after you finished urinating, over the last week?" Because these are questions related to residual feeling and urinary frequency, equivalent to questions 1 and 2 in the IPSS, we also found a correlation between the Quick score and the scores for IPSS questions 1 and 2 (data not shown). We consider that at a minimum, these two urinary symptoms must be associated with histological prostatitis.

The present study has some limitations. First, although a relation between histological prostatitis and LUTS, particularly as evaluated by the NIH-CPSI, was clearly shown, the number of subjects is too small to derive definitive conclusions. Second, few of the study patients complained of CP symptoms such as perineal discomfort or pain. This may provide poor power to clarify the association between histological prostatitis and CP symptoms. Third, the data was completely obtained by the anti-CD45 antibody immunohistochemical staining method. More detailed and reliable evaluation of histological inflammation, such as with CD163 staining, may increase the value of our findings.

In conclusion, we found a correlation only between the severity of inflammation of the prostate tissue and LUTS as evaluated by the IPSS, QOL index, OABSS, and NIH-CPSI, and not with ED. Furthermore, only the NIH-CPSI, and especially the subscore of urinary

symptoms (residual feeling and urinary frequency), was associated with histological prostatitis by a multivariate linear regression model after adjustment for PV. A larger-scale study that includes patients with severe CP symptoms will be necessary to further assess the relation between histological prostatitis and LUTS and ED.

**Conflict of interest**

None.

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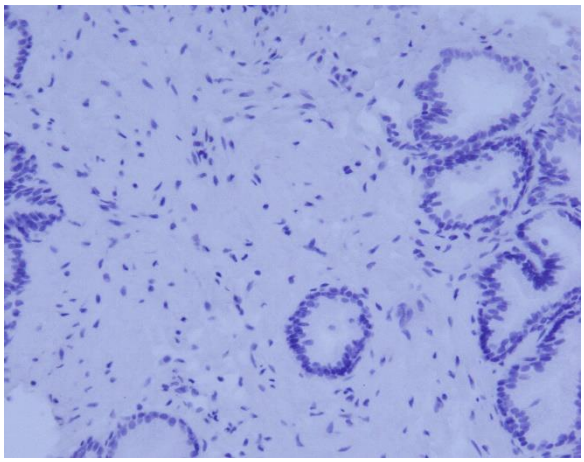
**Figure legends**

**Fig. 1.** Specimen immunohistochemically stained with anti-CD45 antibody from a case of typical prostatic inflammation (20 × 10). The Quick score for cases was 20 (2.5 % × 1) (a) and 123 (41.0 % × 3) (b).

**Fig. 2.** Relations between the Quick score for CD45 staining and NIH-CPSI score (a) and the subscore of urinary symptoms of the NIH-CPSI (b).

Figure 1.

a



b

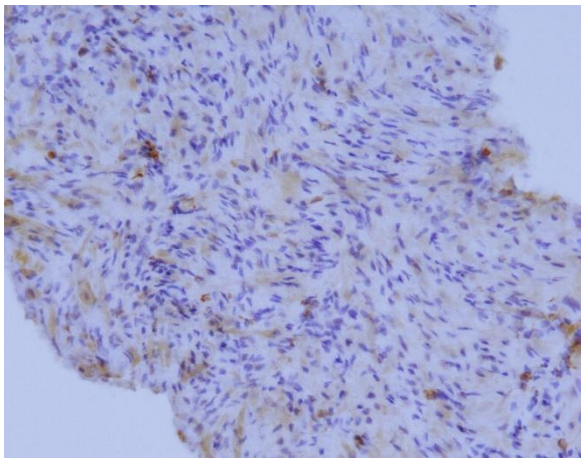


Figure 2.

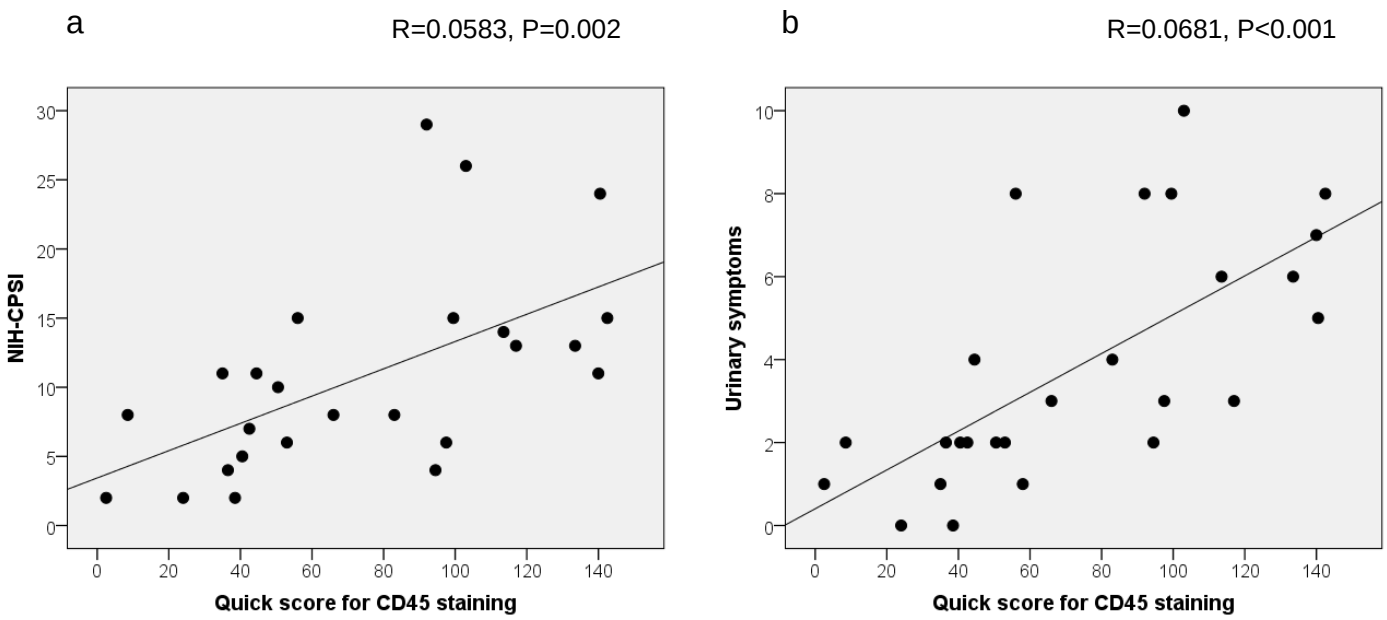

a
R=0.0583, P=0.002
NIH-CPSI
Quick score for CD45 staining
b
R=0.0681, P<0.001
Urinary symptoms
Quick score for CD45 staining

**Table 1**
Patient background.

| N = 26 | | |
|---|---|---|
| Age (y) | 67.35 ± 1.35 | (54-78) |
| Prostate volume (ml) | 46.22 ± 5.72 | (17.1-165.3) |
| IPSS | 13.19 ± 1.43 | (2-17) |
| QOL | 3.27 ± 0.317 | (0-5) |
| OABSS | 4.04 ± 0.49 | (1-10) |
| NIH-CPSI | 10.76 ± 1.44 | (2-29) |
| SHIM | 8.19 ± 1.34 | (1-20) |
| Maximum flow rate (ml/s) | 14.81 ± 1.21 | (3.2-26.2) |
| PSA (ng/ml) | 7.53 ± 0.77 | (2.00-16.97) |
| Quick score for CD45 staining | 73.56 ± 8.23 | (2.5-142.5) |

IPSS, International Prostate Symptom Score; QOL, Quality of Life; OABSS, Overactive Bladder Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; SHIM, Sexual Health Inventory for Men; PSA, prostate-specific antigen.
Values are expressed as mean ± SE.

**Table 2**
Correlation between Quick score and several factors.

| | Correlation coefficient | P |
|---|---|---|
| Age (y) | 0.145 | NS |
| Prostate volume (ml) | 0.394 | 0.046 |
| IPSS | 0.668 | 0.000 |
| QOL | 0.601 | 0.001 |
| OABSS | 0.522 | 0.006 |
| NIH-CPSI | 0.583 | 0.002 |
| SHIM | -0.100 | NS |
| Maximum flow rate (ml/s) | -0.220 | NS |
| PSA (ng/ml) | 0.068 | NS |

IPSS, International Prostate Symptom Score; QOL, Quality of Life; OABSS, Overactive Bladder Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; SHIM, Sexual Health Inventory for Men; PSA, prostate-specific antigen.
Values are expressed as mean ± SE.

**Table 3**
Multivariate linear regression model with questionnaires after adjustment for prostate volume.

| | Standardized partial regression coefficient | P | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| IPSS | 0.052 | NS | -2.752 | 3.347 |
| QOL index | 0.243 | NS | -3.917 | 16.771 |
| OABSS | 0.363 | NS | -0.691 | 13.012 |
| NIH-CPSI | 0.397 | 0.047 | 0.032 | 4.541 |

CI, confidence interval; IPSS, International Prostate Symptom Score; QOL, Quality of Life; OABSS, Overactive Bladder Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index.

**Table 4**
Multivariate linear regression model with questionnaires after adjustment for prostate volume.

| | Standardized partial regression coefficient | P | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Pain | 0.077 | NS | -0.378 | 5.682 |
| Urinary symptoms | 0.550 | 0.027 | 1.010 | 15.023 |
| QOL | 0.048 | NS | -6.553 | 8.075 |

CI, confidence interval; QOL, Quality of Life.