Clinical Importance of Histopathological Inflammation in Patients with Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: A Prospective Study of 222 Patients

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Abstract

Objective: To investigate the relationship between the severity of histopathological prostatic inflammation with lower urinary tract symptoms and prostate specific antigen (PSA) levels. Methods: We prospectively included 222 consecutive patients eligible for transurethral resection of the prostate in a non-academic referral center by a single surgeon. Patients with proven urinary tract infection or prostate cancer were excluded. Preoperative assessment included PSA levels, International Prostate Symptom Score (IPSS), mean peak flow, mean resected prostate weight and post-residual volume. Finally, the presence and severity of inflammation was determined histopathologically. Results: Mean patient age was 69.1 ± 8.6 years with mean preoperative PSA levels of 4.7 ± 5.4 ng/mL and IPSS of 15.7 ± 6.9. Mean peak flow was 10.7 ± 6.5 ml/s and the mean resected prostate weight 39.4 ± 27.3 g. Positive correlations between PSA (log) and prostate weight (r = 0.54, p < 0.001) and between PSA (log) and active (r = 0.30, p < 0.0001) and chronic inflammation (r = 0.19, p = 0.005) were observed. No correlations were found between IPSS and PSA (log) (r = -0.14, p = 0.040) or between IPSS and active inflammation (p = 0.659) or chronic inflammation (p = 0.125). Conclusion: The study showed a weak correlation between PSA and the active or chronic inflammation. It also showed that there was no correlation between the active or chronic histopathological inflammation and IPSS.

Introduction

An acute bacterial prostatitis is common in the urological practice with a life-time incidence of 25% but less than 10% has a proven bacterial infection [1, 2]. However, chronic inflammation is assumed to play a role in the pathogenesis of lower urinary tract symptoms (LUTS), which can be treated by medical therapy or by surgery (transurethral resection of the prostate (TURP)) [3].

This study aims to prospectively investigate the value of histopathological inflammation in the resected specimen by TURP in patients with LUTS due to benign prostatic hyperplasia (BPH) and to investigate the correlations between inflammation and prostate specific antigen (PSA) and International Prostate Symptom Score (IPSS).
**Methods**

The study was approved by the hospitals ethics committee and was conducted according to the established good clinical practice criteria. We prospectively included 222 consecutive patients eligible for TURP in a non-academic referral center by a single surgeon between May 2008 and June 2010. Only patients with a clear indication for TURP according to EAU guidelines were eligible. Patients with proven urinary tract infection or prostate cancer were excluded. Pre-operative assessment included PSA levels, IPSS, mean peak flow, mean resected prostate weight and post-residual volume. Endoscopic procedures were performed under loco-regional anesthesia using an Olympus resectoscope 26 (6%) or 28 charrière (94%), depending on the estimated prostate volume. All patients underwent complete TURP and no separate tissue mapping was performed. The resected prostate specimens were weighted and the fragments were embedded until 4 cassettes, each containing 2 g of tissues, were filled. Each additional 10 g of prostate tissues was used to fill an extra cassette. The tissue was fixed in formalin and embedded in paraffin. One slide was made from every paraffin block and examined after staining by hematoxylin and eosin [4]. The inflammatory infiltrate was first divided into an active (mixed infiltrate of lymphocytes, plasma cells and polymuclear cells) and chronic (mononuclear infiltrate of lymphocytes and plasma cells) component, after which the density of both components was scored 0–3 according to a semi-quantitative scoring system: 0 being no infiltrate and 3 severe infiltrate. The analysis of inflammation biomarkers (i.e. cytokines and growth factors) is more reliable than presence of cell infiltrate; however this was not performed in our series. Two senior pathologists analyzed all tissue sections of each patient independently and were blinded for clinical data. They scored the mean value of the infiltrate considering all tissue sections.

**Statistical Analysis**

Initially, data were analyzed with descriptive statistics and Pearson correlation was used to investigate simple correlations between variables. Appropriate linearity tests and lack-of-fit tests were performed to ensure that these relationships were linear and adequate. Secondly, an in-depth analysis of the PSA levels and the covariates was performed using a multiple regression model. Since the histogram of PSA is severely skewed due to the prevalence of lower PSA values in a normal population, PSA values were transformed with a natural log transformation, resulting in a more realistic normality assumption of the log PSA than the original PSA scale. We preferred to examine inflammation as a categorical rather than a continuous variable, due to the heterogeneity in degree of inflammation.

**Results**

**Patient Characteristics**

The mean patient age was 69.1 ± 8.6 years and the mean preoperative PSA value 4.7 ± 5.4 ng/ml. Mean IPSS was 15.7 ± 6.9 and mean peak flow 10.7 ± 6.5 ml/s. Mean post-residual volume was 83.8 ± 130.3 ml. The mean resected prostate weight was 39.4 ± 27.3 g and the mean operating time 31.1 ± 11.9 minutes.

**Correlations**

We investigated the relationship between log PSA and several parameters, including IPSS, peak flow, post-residual volume, histopathology and the weight of the resected prostate tissues. A significant correlation between log PSA and the resected prostate weight was observed (r = 0.54; p < 0.001). A non-significant correlation was found between log PSA and IPSS (r = -0.14; p = 0.04). No correlation was observed between log PSA and peak flow (r = 0.00; p = 0.99) and between log PSA and post-residual volume (r = 0.08; p = 0.28). These findings were also confirmed in a multiple regression model. We also investigated the potential correlation between inflammation (active and chronic) and log PSA, IPSS and the resected prostate weight. A significant but weak correlation was observed between log PSA and active (r = 0.30; p < 0.0001) and chronic (r = 0.19; p = 0.005) inflammation.

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### Table 1. Correlations between inflammation and PSA

|                   | Log PSA, n | Mean ± SD | p       | Correlation, r |
|-------------------|------------|-----------|---------|----------------|
| **Active inflammation** |            |           |         |                |
| No inflammation   | 25         | 1.4 ± 1.6 | < 0.0001| 0.30           |
| Mild inflammation | 91         | 4.4 ± 4.3 |         |                |
| Moderate inflammation | 88      | 5.9 ± 6.4 |         |                |
| Severe inflammation| 14         | 4.6 ± 6.6 |         |                |
| **Chronic inflammation** |        |           | 0.005   | 0.19           |
| No inflammation   | 4          | 1.0 ± 0.7 |         |                |
| Mild inflammation | 109        | 4.0 ± 5.0 |         |                |
| Moderate inflammation | 91      | 5.7 ± 5.9 |         |                |
| Severe inflammation| 14         | 4.2 ± 4.4 |         |                |
(table 1). Age was related to active (r = 0.24; p < 0.0001) but not to chronic (r = 0.09; p = 0.08) inflammation. Similarly, the weight of the resected prostate tissue was related to active inflammation (r = 0.13; p = 0.011) but not to chronic (r = 0.1; p = 0.34) inflammation. However, IPSS was not correlated with active (r = 0.03; p = 0.6) or chronic (r = -0.03; p = 0.91) inflammation, despite the categorization of IPSS into 3 categories (mild, moderate and severe) which did not result in any association with active (p = 0.659) and chronic (p = 0.125) inflammation (table 2). We used 3 different categories of IPSS (mild, moderate and severe) to differentiate correlations between inflammation and different grades of IPSS and opted as such to use IPSS as a categorical variable instead of a continuous variable.

### Discussion

In our study, nearly all patients had some degree of inflammation (active n = 197 or 89%; chronic n = 218 or 98%) in their prostatic tissue on histopathological examination. However, the meaning of this finding is not yet fully understood. We could not demonstrate a significant correlation between IPPS and inflammation, suggesting only a minimal effect of histopathological inflammation on patients symptoms. Wang et al. [5] retrospectively investigated the correlation of histopathological prostatitis with LUTS in patients who underwent TURP for BPH. They compared 80 patients with uncomplicated BPH with 80 patients with BPH and histopathological prostatitis in which no statistically significant difference in IPSS could be demonstrated. Hu et al. [6] also investigated histopathological TURP specimens and found asymptomatic inflammatory prostatitis in only 55 of the 106 (52%) patients. Inflammation was associated with prostate weight (46.5 vs. 43.4 g; p < 0.0001) and higher IPSS (8.8 vs. 8.2; p < 0.0001). No correlation however could be observed between inflammation and PSA.

The Medical Therapy Of Prostate Symptoms study demonstrated a correlation between inflammation and risk of symptomatic LUTS evolution (21 vs 13.2%; p = 0.083), although the tissue used was from prostate biopsies and not from TURP specimens [7]. The Reduction By Dutasteride Of Prostate Cancer Events study showed similar findings and a significant correlation between chronic inflammation and higher IPSS (8.8 vs. 8.2; p < 0.0001) was observed but also only prostate biopsies were used for histopathologic examination [8]. The group of Umbehr et al. [14] proved an association between higher PSA with inflammation in prostatic biopsy tissue in 224 patients. Stimac et al. [15] described similar findings in 106 patients, after prostate biopsies and showed a correlation between subclinical inflammation and serum PSA.

A large variability in the incidence of prostatic inflammation is present in the quoted studies. This can be explained by the sample differences between prostate biopsies and TURP-specimens. Although no significant correlation was shown in our study, even if inflammation was categorized in three different (mild, moderate, severe) groups, this does not exclude the role of inflammation in the pathogenesis of BPH. Nörstrom et al. [9] characterized 21 extracellular markers on prostate-infiltrating lymphocytes and analyzed expression of 26 soluble proteins in prostate tissue obtained from BPH patients. They found several pro-inflammatory factors

### Table 2. Correlations between IPPS and inflammation

| IPSS categorization | Active inflammation | Chronic inflammation |
|---------------------|---------------------|----------------------|
| Mild                | Moderate            | Severe               |
| No inflammation     | 4                   | 1                    | 5                      |
| Mild inflammation   | 11                  | 47                   | 36                     |
| Moderate inflammation | 15               | 43                   | 30                     |
| Severe inflammation | 2                   | 7                    | 6                      |

| p       |
|---------|
| 0.659   |
| 0.125   |
(lymphocyte subsets) correlated to prostate weight and PSA, highlighting possible involvement in the progression of BPH.

PSA is a well-known sensitive but less-specific prostate marker [10–12]. We showed a correlation between PSA and active or chronic inflammation, although only weak for active (r = 0.30) and very weak for chronic (r = 0.19) inflammation. This finding can be explained due to the presence of inflammation in all patients. PSA is often used in follow-up of chronic prostatitis, but this method should be questioned. We described several studies which have observed a more significant correlation link between PSA and inflammation [13, 16, 17] but all with the limitation that only prostate biopsies were used for histopathologic examination.

Conclusion

Histopathological inflammation is often associated with higher PSA in prostate biopsy tissues. We performed a large, prospective study to investigate the association between PSA and histopathological inflammation in TURP specimen. We could not show a significant correlation between PSA and histopathological acute or chronic inflammation and were not able to prove a correlation between active or chronic histopathological inflammation and IPSS. The role of histopathological inflammation in the pathogenesis of BPH remains unclear, for which further research is needed. Chronic inflammation is however likely responsible for BPH progression given the fact that all patients underwent surgery.

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