Association Between Inflammation and Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia

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Purpose: To evaluate the association between inflammation in prostatic tissue/serum sample and BPH-LUTS

Patients and Methods: The prostatic tissue and serum sample were collected from 183 patients who underwent transurethral plasmakinetic resection of the prostate (TUPKRP). The association between inflammation detected on prostatic tissues/ serum sample and LUTS related parameters, including International Prostate Symptom Score (IPSS) and peak flow rate (Qmax) were analyzed with SPSS version 13.0, and *P*-value < 0.05 was chosen as the criterion for statistical significance.

Results: There was a positive association between prostate tissue inflammation and LUTS. The differences of IPSS, VSS and SSS were seen with the increase in grade of prostate tissue inflammation (*P* < .001; .001; =.014, respectively). Qmax and IPSS 12months after surgery were better in no inflammation group (*P* = .016; .031). Logistic regression analysis revealed a statistically significant association between the NEUT% NLR and prostate tissue inflammation (*P* = .010; .004), but ROC curve showed the NEUT%, NEUT, and NLR area under the curve (.526; .452; .513, respectively) were calculated as < 0.600. Patients with Qmax over 7.12 had more WBC count in peripheral blood (7.56 ± 1.77 VS 6.37±1.86, *P* = .026). The NLR was significantly higher in the group of IPSS over 20 and AUR presence (*P* = .018; .017). The NEUT%, LYMPH%, LYMPH, and NLR showed a statistical significance in different obstruction classification (*P* = .047; .046; .028; .014, respectively).

Conclusion: There was a correlation between chronic Inflammation and LUTS related to BPH. The patient without inflammation could acquire more sustained and steady relief than those with inflammation in LUTS related to BPH after TUPKRP.

Keywords: inflammation; lower urinary tract symptoms; benign prostate hyperplasia.

INTRODUCTION

In recent years, the relationship between inflammation and biological characteristics of benign prostate hyperplasia has drawn significant academic interest. Evidence from MTOPS and REDUCE clinical studies revealed that risk for Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) is correlated with intra-prostatic infiltration of inflammatory cells[(1,2)]. The REDUCE trial shows that chronic prostatic inflammation can be detected in 77.6% of patients with BPH who underwent prostate biopsies, and many studies have shown a significant correlation between chronic prostatic inflammation and LUTS severity, prostate volume, and increased risk of acute urinary retention[(3-5)]. Since not all the patients with BPH need undergo a prostate biopsy (only for suspicion of prostate cancer), it is a problem how to evaluate the influence of chronic prostatic inflammation on BPH-LUTS. So some researchers analyzed the association between clinical inflammatory markers (white cell count, neutrophil-lymphocyte ratio, and C-reactive protein) and BPH, and the results suggested a positive correlation [(6,7)]. But two key questions are not clear. First, is there an association between serum inflammatory markers and LUTS-BPH? Second, if we could assess the chronic prostatic inflammation status by measuring the clinical inflammatory markers? Our study aims to evaluate the correlation between inflammation in prostatic tissue/ serum sample and BPH-LUTS, and analyze the association between inflammation in prostatic tissue and serum sample, and to preliminarily discover an indicator of inflammation that showed the severity of LUTS and predict the recovery after transurethral resection of the prostate.

MATERIALS AND METHODS

Patient selection

From March 2013 to October 2016, 183 patients who

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Table 1. Comparison of BPH/LUTS parameters between two groups

[a]Group	BPH/AIP	BPH alone	*P*-value
No. of patients	113	70	
BMI, kg/m^2	25.51 ± 2.46	25.83 ± 2.16	0.142
IPSS	23.57 ± 3.44	16.75 ± 3.92	0.000
SSS	12.00 ± 2.11	9.25 ± 1.97	0.000
VSS	9.67 ± 1.39	6.60 ± 3.44	0.000
QOL	4.40 ± 1.02	3.05 ± 1.54	0.000
Qmax	5.33 ± 2.46	8.20 ± 2.10	0.000
WBC	6.87 ± 1.83	7.46 ± 2.90	0.296
NEUT%	65.68 ± 10.31	64.82 ± 9.77	0.741
LYMPH%	24.11 ± 8.93	24.31 ± 8.74	0.932
MONO%	7.10 ± 2.18	6.52 ± 1.55	0.252
NEUT	4.58 ± 1.87	5.06 ± 2.54	0.367
LYMPH	1.58 ± 0.57	1.75 ± 0.75	0.278
MONO	0.49 ± 0.19	0.48 ± 0.17	0.938
NLR	3.68 ± 3.91	3.38 ± 3.02	0.759
N (%)			
Obstruction classification			0.043
III	43	40	
IV	25	18	
V	24	10	
VI	21	2	
AUR			0.009
Abesnt	41	52	
Present	72	18	

Abbreviations: PSA, Prostate Specific Antigen; BMI, Body Mass Index; IPSS, International Prostate Symptom Score; Qmax, Maximum urine flow rate; AUR, Acute Urinary Retention.
a Continuous variables were compared by independent samples *t*-test

underwent transurethral plasmakinetic resection of the prostate (TUPKRP) for LUTS were diagnosed histologically as benign prostatic hyperplasia at Baotou Central Hospital affiliated to Inner Mongolia Medical University. Studies were performed with full approval of the ethics committee of the Baotou Central Hospital affiliated to Inner Mongolia Medical University (No. YKD2017016). Before the TUPKRP, Height and weight data were recorded. BMI (weight in kilograms divided by height in meters squared, kg/m^2) was calculated and assigned from the National Institutes of Health classification of normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), obese (≥30 kg/m^2). Digital rectal examination (DRE) and transrectal ultrasonography were performed for all patients to evaluate the prostate volume. Serum PSA was obtained using screening test. WBC count and differential white cell count [neutrophils (NEUT), lymphocytes (LYMPH), monocytes

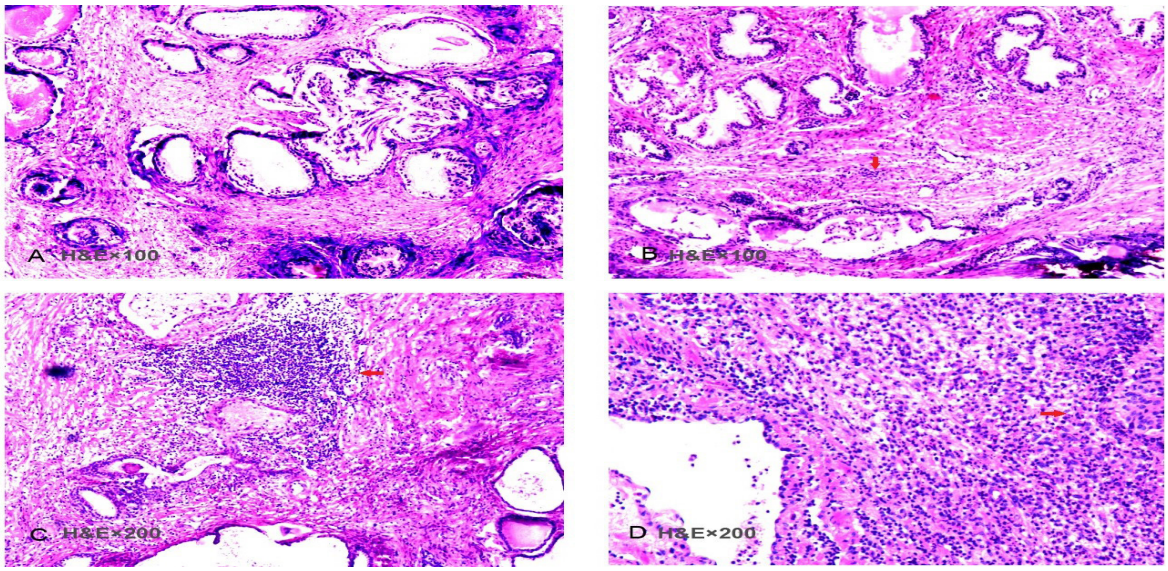

Figure 1. The assessment of prostate tissue inflammation. (A. BPH without inflammation. B. BPH with mild inflammation [scattered inflammatory cell infiltration within the stroma without lymphoid nodules]. C. BPH with moderate inflammation [nonconfluent lymphoid nodules]. D. BPH with severe inflammation [large inflammatory areas with confluence of infiltrates])

Table 2. Logistic regression analysis of factors predicting prostate tissue inflammation

Variable	odds ratio	95%C	*p*-Value
WBC	0.626	0.208—1.210	0.412
NEUT%	0.070	0.017—0.122	0.010
LYMPH%	0.246	0.121—0.479	0.381
MONO%	0.312	0.156—0.621	0.821
NLR	0.140	0.047—0.234	0.004

(MONO), and their percentage (NEUT%, LYMPH%, MONO%) were measured with blood routine test by the clinical laboratory. Neutrophil-lymphocyte ratio (NLR) was calculated from the peripheral serum sample for all patients.

Exclusion criteria of patients were: 1) infection 2) connective tissue diseases 3) neurologic diseases 4) hematological malignancy history 5) medical therapy (e.g. Chemotherapy or Immunotherapy) which may influence the level of peripheral blood parameters(e.g., chemotherapy or immunotherapy, using anti-inflammatory drugs, acetylsalicylic acid, diuretics, and anticholinergic).

Inflammation assessment

The assessment of prostate tissue inflammation was supported in a blinded manner by a certified pathologist according to the International Histopathological Classification System of Prostatic Inflammation (**Figure 1**). The prostate specimens, obtained from TUPKRP, were stained by hematoxylin and eosin (H&E×100).

LUTS assessment

The objective clinical parameters of LUTS were collected from the urodynamic. The peak flow rate (Qmax) was measured by uroflowmetry at a voided volume of >150ml. The extent of bladder outlet obstruction (BOO) was evaluated by pressure-flow studies (PFS) according to the Schafer line. The patients with detrusor overactivity (DO) were excluded.

The subjective clinical parameters of LUTS, including International prostate symptom score (IPSS), Storage symptoms score (SSS), Voiding symptoms score (VSS), and QOL were collected from the medical records before TURP to evaluate lower urinary tract symptoms.

Follow-up

Patients with a follow-up of 12 months after TURP were considered eligible for the study. Follow-up consisted of physical examination, IPSS, and uroflowmetry at 3, 6, and 12 months. Two patients were excluded due to other complications. (One patient with cerebral infarction at 7 months, another one with myocardial infarction at 9 months)

Statistical Analysis

Categorical variables were described by frequencies and percentages. Continuous variables are presented as mean± standard deviation. Comparison of the clinical characteristics between BPH with inflammation and BPH alone were analyzed by chi-square tests in case of categorical characteristics and Mann-Whitney U tests in case of continuous characteristics. The clinical LUTS parameters in different inflammatory groups were compared with one-way analysis of variance (ANOVA). The Tukey test was used in post hoc multiple comparisons between the two groups. Logistic regression analysis was used to evaluate the independent effect of each routine clinical inflammation markers on the extent of prostate tissue inflammation. The cut-off values were revealed by receiver operating ROC curve analyses. Friedman's test was used to compare Qmax and IPSS before and after 3, 6, and 12 months. Postoperative variables within groups were compared by independent samples t-test. All analyses were performed by using the routines of the SPSS ver13.0, and statistical significance was defined as $P < .05$.

RESULTS

According to the International Histopathological Classification System of Prostatic Inflammation, the patients were divided into inflammation group and no inflammation group. The clinical characteristics and laboratory data of patients were summarized in **Table 1**. The median age and BMI have no significance between the two groups ($P = .249$; .142). The initial PSA and PV showed a statistically significant difference ($P = .040$; .014) between two groups, and the initial PSA and PV were found to be higher in the inflammation group (8.26 ± 6.28 VS 4.31 ± 2.06, 74.99 ± 34.78 VS 54.40 ± 25.41). There was a positive association between prostate tissue inflammation and LUTS (IPSS, SSS, VSS, QOL [$P < .001$], Qmax [$P < .001$], Obstruction [$P = .043$], and AUR [$P = .009$]). We were unable to find evidence for significant associations between prostate tissue inflammation and blood differential white cell count (WBC [$P = .296$], LYMPH and LYMPH% [P=.278, .932], NEUT and NEUT% [$P = .367$, .741], MONO and MONO% [$P = .938$, .252], NLR [$P = .759$]).

According to the International Histopathological Classification System of Prostatic Inflammation, we divided the BPH with inflammation to three groups (mild, moderate and severe), and then we compared the clinical parameters of LUTS among three groups. AS **Figure 2** shows, no difference was observed in Qmax among

Table 3. The association between Clinical parameters of LUTS and different serum parameters.

[a]Group Qmax				IPSS			AUR			Obstruction Classification				
	≥7.12	<7.12	*P*	≥20	<20	*P*	Yes	No	*P*	III	IV	V	VI	*P*
WBC	7.56 ± 1.77	6.37 ± 1.86	0.026	7.33 ± 2.14	6.77 ± 2.36	0.311	7.42 ± 2.06	6.80 ± 2.38	0.391	6.85 ± 2.00	7.16 ± 2.33	7.27 ± 2.62	7.35 ± 1.80	0.933
NEUT%	68.90 ± 8.68	64.46 ± 10.72	0.072	66.88 ± 8.55	64.04 ± 6.51	0.256	66.44 ± 9.98	65.58 ± 10.53	0.716	61.96 ± 9.50	62.41 ± 10.23	67.24 ± 9.69	69.16 ± 8.37	0.047
LYMPH%	22.50 ± 8.42	23.27 ± 8.76	0.238	23.02 ± 6.53	26.48 ± 6.10	0.102	24.18 ± 8.85	24.09 ± 8.57	0.962	21.51 ± 7.18	22.86 ± 8.10	26.73 ± 10.66	27.87 ± 8.56	0.046
MONO%	6.63 ± 1.76	7.22 ± 2.06	0.222	7.15 ± 2.08	6.75 ± 1.73	0.404	7.19 ± 2.12	6.79 ± 1.77	0.380	6.56 ± 1.48	7.58 ± 2.56	7.45 ± 2.37	6.95 ± 1.55	0.280
NEUT	5.34 ± 2.43	4.58 ± 1.81	0.125	5.05 ± 2.15	4.39 ± 1.79	0.190	4.96 ± 1.87	4.68 ± 2.28	0.073	4.28 ± 1.47	4.75 ± 2.57	5.05 ± 1.81	5.08 ±2.15	0.609
LYMPH	1.59 ± 0.74	1.65 ± 0.57	0.671	1.57 ± 0.60	1.75 ± 0.67	0.241	1.72 ± 0.72	1.52 ± 0.47	0.896	1.43 ± 0.45	1.59 ± 0.40	1.76 ± 0.67	1.93 ± 0.89	0.028
MONO	0.50 ± 0.22	0.49 ± 0.17	0.869	0.52 ± 0.19	0.45 ± 0.17	0.159	0.53 ± 0.20	0.50 ± 0.19	0.543	0.48 ± 0.20	0.51 ± 0.17	0.52 ± 0.21	0.52 ± 0.18	0.886
NLR	4.17 ± 3.55	3.49 ± 3.95	0.461	4.25 ± 0.71	2.62 ± 0.94	0.018	3.97 ± 2.36	2.89 ± 2.66	0.017	2.60 ± 1.59	3.55 ± 2.22	4.10 ± 3.14	4.28 ± 2.88	0.014

Abbreviations: IPSS, International Prostate Symptom Score; Qmax, Maximum urine flow rate; AUR, Acute Urinary Retention.

[a] Continuous variables were compared by independent samples t-test

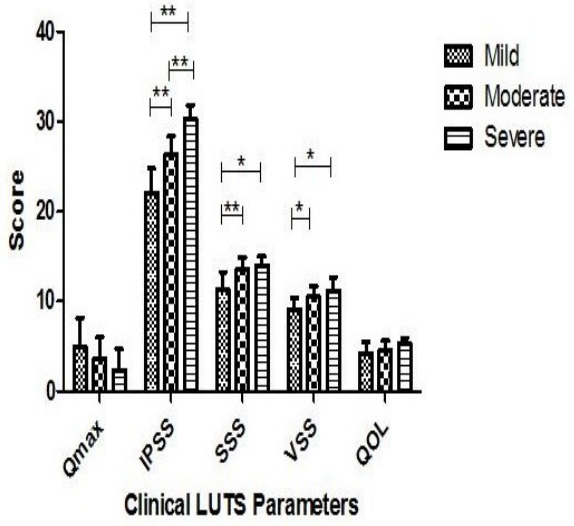

Figure 2. Comparison of clinical parameters of LUTS stratified by grade of inflammation (**P < 0.01; *P < 0.05)

three groups (P = .144); the IPSS showed a statistically significant difference among three groups (P < .001): The IPSS in the severe group is higher than that in the mild group (30.33 ± 1.53VS22.12 ± 2.65, P < .001), and the same differences in the IPSS were observed between mild group VS moderate group and moderate group VS severe group (22.12 ± 2.65VS26.36 ± 2.03, P < .001; 26.36 ± 2.03VS30.33 ± 1.53, P = .030).

There were no significant differences in the SSS between moderate and severe groups (13.59 ± 1.28VS14.00 ± 1.00, P = .722), but the SSS in the mild group tended to be lower than the moderate and severe groups (11.28 ± 1.99VS13.59 ± 1.28, P < .001; 11.28 ± 1.99VS14.00 ± 1.00, P = .016). The QOL was not different in the different grades of prostate tissue inflammation (4.26 ± 1.03VS4.59 ± 1.00VS5.33 ± 0.58, P = .117).

The VSS showed a statistically significant difference among three groups (P = .014): The VSS in the mild group is lower than that in the moderate and severe groups (9.14 ± 1.21VS10.53 ± 1.17, P = .017; 9.14 ± 1.21VS11.67 ± 1.53, P = .037), and no differences in VSS were observed between the severe and moderate groups (11.67 ± 1.53VS9.14 ± 1.21, P = .364).

Preoperative and postoperative variables at the different follow-up points areillustrated in **Figure 3**. Qmax and IPSS 12 months after surgery were better in no inflammation group (P = .016; .031). Qmax was significantly higher (P < .001; .010), and IPSS were significantly lower than preoperative values in both groups at 3-month follow-ups (P = .013; .036). Qmax in no inflammation group was significantly higher at 6- and 12-month follow-up compared with the Qmax at 3-month (P = .032; .041), but Qmax in the inflammation group remained stable at 6- and 12-month follow-up (P = .213; .331). IPSS at 6months after TURP was significantly lower compared with IPSS recorded at 3month follow-up in the inflammation group (p = 0.018), but no significant difference exists in the no inflammation group (P = .131). No significant IPSS values reduction was observed at 12-month follow-up in both groups (P = .301; .532).

Logistic regression analysis adjusted for age and prostate volume (**Table 2**) revealed a statistically significant association between the NEUT%, NLR, and prostate tissue inflammation (P = .010; .004).

ROC curves in **Figure 4** showed that the NEUT%, NEUT, and NLR as an indicator of prostate tissue inflammation have no statistically significant difference (P = .725; .609; .855), so NEUT%, NEUT, and NLR has no power of prediction in prostate tissue inflammation. The NEUT%, NEUT and NLR's area under curve (0.526, 0.452, 0.513) were calculated as < 0.600.

The differences of serum parameters in clinical parameters of LUTS were summarized in Table 3. Patients with Qmax over 7.12 had more WBC count in peripheral blood (7.56 ± 1.77 VS 6.37 ± 1.86, P = .026). The NLR was significantly higher in the group of IPSS over 20 and AUR presence (P = .018; .017). The NEUT%, LYMPH%, LYMPH and NLR showed a statistically significance in different obstruction classification (P = .047; .046; .028; .014).

DISCUSSION

The correlation between inflammation and BPH/LUTS

Present studies have suggested that inflammation play an important role in the progression and pathogenesis

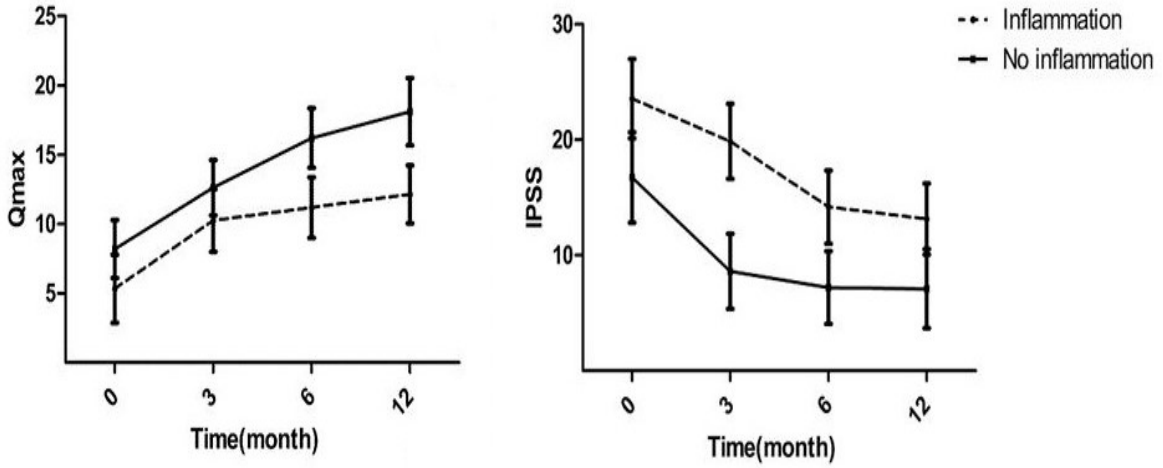

Figure 3. Trend in peak flow rate (Qmax) at uroflowmetry and IPSS during follow-up of TUPKRP

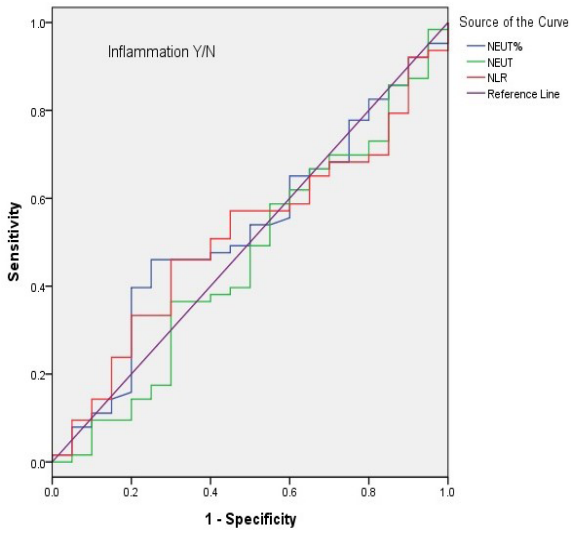

Figure 4. ROC curves of inflammation for different serum parameters cut-off values

of BPH[8-10]. Histological inflammation is commonly found in BPH specimens, and it affects the biological characteristics of benign prostate hyperplasia, such as patient symptoms, prostate volume, and PSA levels. The Reduce trail [2] showed a relationship between the degree of chronic inflammation and the degree of LUTS related to BPH. Among 8224 men, 77.6% had chronic inflammation, and only 21.6% had no inflammation. For those men with chronic inflammation, 89% had mild, 10.7% had moderate and 0.3% had severe inflammation. In addition, this trail revealed that total IPSS and subscores were higher in the group of patients with histological chronic inflammation at baseline compared with those with no chronic inflammation. After the longitudinal evaluation for 4 years, Nickel et al. [4] confirmed that chronic inflammation is associated with severity and the progression of LUTS related to BPH, and chronic inflammation at baseline was associated with an increased risk of acute urinary retention. In the Robert's study[11], the results reveal the strong correlation between histological inflammation, IPSS, and prostate volume. Inamura et al[12] reported that the location of inflammation in the prostate might be an important factor affecting the severity of LUTS, especially voiding dysfunction. In this study, prostate inflammation was diagnosed by histopathology in 113/183 patients. Of the 61.7% who had prostate inflammation, 68.3% had mild, 27.0% had moderate and 4.7% had severe inflammation. Because our study was conducted in BPH patients with severe symptoms requiring surgical treatment and as the Uzun et al.[13] showed that Qmax correlated with LUTS at the strong desire to void, these limitations may result in the difference with the REDUCE Trail. However, our study still suggested that local prostatic histological inflammation is positively associated with prostate volume, initial PSA, and LUTS (IPSS, SSS, VSS, QOL, Qmax, Obstruction, and AUR). Furthermore, our results showed that total IPSS and subscores VSS significantly increased with the degree of the inflammation. So we assume that prostatic inflammation may have a major impact on voiding symptoms. Above all, we think that inflammation may be a trigger of LUTS.

The correlation between inflammation and treatment of BPH/LUTS

Accumulating evidence reveals that inflammatory may play essential roles in the development and maintenance of prostate growth and LUTS, but presently available drugs used in the treatment of LUTS related to BPH, whatever alpha 1-blockers or 5-alpha reductase inhibitors, do not exhibit anti-inflammatory activity. So inflammation may be considered as a new rational target for medical therapy for LUTS/BPH, and some studies have made an advance in anti-inflammatory agents used in the treatment of LUTS related to BPH[14-16]. Moreover, Men with higher grade inflammation may be at greater risk for medical treatment failure and at risk for BPH related surgery[17]. Meanwhile, the prostatic inflammation could influence the curative effect of transurethral resection of prostate in BPH. Hu et al [18] found the patients with chronic prostatic inflammation have higher (worse) IPSS scores compared to those with only BPH in 3 years after transurethral resection of the prostate. However, in a study by Nunzio et al.[19], results showed patients with prostate inflammation presented a 50% risk reduction of prostoperative storage urinary symptoms. Our study suggests that Qmax was significantly higher, and IPSS were significantly lower than preoperative values in both groups at 3-month follow-ups. Qmax and IPSS at 12months after TUPKRP surgery were better in no inflammation group. No significant IPSS values reduction was observed at 12 months follow-up in both groups. In another word, TUPKRP surgery is an excellent opportunity to improve LUTS related to BPH. The patient without inflammation could acquire sustained and steady relief in LUTS, but the patient with inflammation only gain the benefit in 3 months after TUPKRP, and subsequently, the improvement in LUTS is not obvious. The main reasons may be due to the inflammatory cells that still exist in residual glandular or surgical capsule after TUPKRP. The inflammatory cytokines (IL-8, 17) released by inflammatory cell could influence the function of smooth muscle contraction.

The association between inflammation in prostatic tissue and clinical inflammatory markers in blood sample

At present, the best method is the histological diagnosis to evaluate chronic prostatic inflammation of BPH, but prostate tissue specimen was obtained by invasive biopsy or surgical TURP. Therefore, it is a problem how to evaluate the influence of chronic prostatic inflammation on BPH-LUTS by noninvasive methods. So some researchers analyzed the association between serum inflammatory markers and LUTS/BPH. Fujita et al. [6] reported that white blood cell count seems to be associated with the degree of prostate enlargement and lower urinary tract symptoms. Our study also showed a similar result, but the correlation is extremely weak. The cause may be that white blood cell count in blood was influenced by systemic inflammatory disease. NLR was proposed as an indicator of systemic inflammatory response and MetS as an indicator which is strongly and positively correlated with parameters of LUTS than with ESR and CRP. Ozer et al. [7] found positive correlation between Neutrophil-Lymphocyte Ratio and severe symptoms and progression of BPH. Tanik et al.[20] reported that NLR can predict BPH progression; NLR was positively correlated with IPSS and negatively correlated with Qmax; In this study, the results showed

NEUT%, LYMPH%, LYMPH and NLR were different in different obstruction classifications, especially, the NLR was significantly higher in the group of IPSS over 20 and AUR presence. Furthermore, our study revealed a statistically significant association between the NEUT%, the NEUT, and NLR and prostate tissue inflammation, but their cut-off value has no power of prediction in prostate tissue inflammation. The NLR, which is an indicator of inflammation, reflects the systemic inflammatory status and Mets[21,22][. The NLR may be a candidate marker for the severity of LUTS in BPH patients, but further studies are needed to access the relation between the NLR/Mets and LUTS related to BPH, and find the predictive cut-off values.

Our study has two limitations: first, it is a single-center study with a small number of patients and a 1-year short-term follow-up. Second, the functions of inflammatory cytokines need further to be confirmed in future studies.

CONCLUSIONS

Our results add to the evidence that correlation between Inflammation and BPH-related lower urinary tract symptoms (LUTS). The patients without inflammation could acquire more sustained and steady relief than those with inflammation in LUTS related to BPH after TUPKRP. Although inflammatory markers in blood sample such as WBC, NEUT and LYMPH have limited indication of inflammation that showed the severity of LUTS, it is difficult to assess the chronic prostatic inflammation status by measuring the clinical inflammatory markers.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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