Is There a Relationship between Lower Urinary Tract Symptoms and C-reactive Protein Levels in Men? A Cross-Sectional Study

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ABSTRACT

Objective: Lower urinary tract symptoms (LUTSs) increase with benign prostatic hyperplasia and age in men. The mechanism underlying this increase is not well known. In literature, an increase in inflammation is suggested as the reason for LUTSs. C-reactive protein (CRP) is a commonly used and important marker for inflammation. The aim of this study was to question the relationship between LUTS and CRP levels and to determine if inflammation may cause LUTSs.

Methods: Our study was retrospective and cross-sectional. One hundred and eighty-three patients who were LUTS (+) and (–) and who were suggested to undergo prostate biopsy because of high PSA were included in this study in a urology polyclinic. For all patients suggested to undergo biopsy, CRP levels were routinely requested by the polyclinic. CRP levels were compared to LUTSs both based on their value in the report and their cut-off value of 0.50 mg/dL. For statistical analyses, $p<0.05$ was considered significant.

Results: While the average age in LUTS (+) patients was 62.71±0.87 years, in LUTS (–) patients, it was 61.67±1.01 years ($p=0.625$). When the CRP levels of the patients with and without symptoms were compared, a statistically significant difference was not found ($p=0.189$). Additionally, in the evaluation made, by considering pathological if the cut-off values of CRP were 0.5 mg/dL or more, there was no difference between LUTS (+) and (–) patients ($p=0.921$).

Conclusion: In our study, we could not find a relationship between LUTSs and CRP levels. There are many factors affecting CRP levels. Currently, to determine the relationship between LUTSs and CRP levels, wider, community-based studies where all factors affecting CRP levels are excluded and containing sub-analyses are required. *(JAREM 2016; 6: 105-9)*

Keywords: Prostate specific antigen, lower urinary tract symptoms, C-reactive protein, prostate, biopsy

INTRODUCTION

Lower urinary tract symptoms (LUTS) are related to a pathophysiological process involving the bladder and bladder outlet dysfunction and represent a clinical entity consisting of one or more symptoms that mostly occur because of benign prostatic hyperplasia (BPH) and overactive bladder (OAB) in men. At least one LUTS symptom is found in 62.5% of men over 40 years of age (1, 2).

The prevalence of LUTS has been reported to be 28% in a different study because of the fact that the structure of the society and regions and personal characteristics vary according to countries (3). It is true that the incidence of LUTS increases with age (4). In addition, LUTS may occur because of several pathological conditions such as urolithiasis and tumors (5, 6). In the etiology of LUTS, the relationship with the potential power of chronic inflammation has been shown in many studies. Studies have shown that chronic inflammation plays a role in BPH and OAB (7, 8). However, the detailed mechanism underlying LUTS is still not well understood and there is no single mechanism that has been described (5).

C-reactive protein (CRP) is a widely used, inexpensive, and easily found biomarker for inflammation (1). Although the distribution of CRP levels changes at different rates, CRP is seen as a valuable tool in inflammation studies, and high-sensitive (hs) CRP has been applied lately along with the use of more accurate measurements; it provides more accurate and precise measurements (9, 10) but does not exist in every work environment.

In the studies conducted to date, the CRP levels have also been shown to be increased in men with a poor peak urinary flow rate and filling symptoms (11). A positive correlation with CRP has been found in men with nocturia and voiding difficulties in the Boston Area Community Health (BACH) study (5). Considering the CRP and LUTS studies, the NHANES III study is a comprehensive study in which despite the high levels of CRP, no significant correlation has been shown in patients with three or four symptoms, which could be considered as all the symptoms that constitute almost all the LUTS cases in men over 60 years of age (12). When the Olmsted County Study results were evaluated and the age groups assessed for prostate-specific antigen (PSA) were reviewed (the age group between 40 and 79 years), the increase in CRP levels showed a significant correlation in patients with poor flow rates and poor filling symptoms (11). When studies examining the relationship between the presence of LUTS and CRP were assessed, it was observed that there were studies different from each other reporting that both the relationships between them show a positive correlation and they do not have any association.

The aim of the present study was to determine whether there was a significant relationship between LUTS and CRP in patients who were LUTS positive in comparison with those who were not LUTS positive.

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METHODS

In total, 183 patients who were admitted to the urology clinic were retrospectively evaluated. Some of these patients applied to the clinic because of LUTS and/or other urological complaints, while others applied because of lumbar pain, inguinal pain, and others although they did not have urological symptoms or they applied to have the total PSA (tPSA) checked for the investigation of prostate cancer although they had no complaints. These patients were retrospectively analyzed using the data repository of the urology clinic and the data processing center of our hospital. This study, consisting of retrospective data, was conducted in accordance with the Declaration of Helsinki. The tPSA of a total of 183 patients was 4 ng/dL and above. Prostate needle biopsy was recommended to these patients by the urology clinic. When the clinical data of the patients were analyzed, the patients with LUTS (+) and LUTS (–) were evaluated. Those with LUTS (+) were the patients having at least one symptom and these patients were given a "1" score. The patients with LUTS (–) classification did not have any LUTS symptoms and these patients or healthy individuals were given a "0" score. Although these patients were LUTS (–), their tPSA was 4 ng/ml and above, and a prostate needle biopsy was proposed. The filling, voiding, and post-voiding symptoms of the LUTS are shown in Table 1. The number of patients with a LUTS "1" score was 107, and the number of patients with a LUTS "0" score was 76. Those with diseases such as urinary tract infections, hematuria, urolithiasis, etc. that might affect the serum CRP levels and those with diseases other than urologic diseases that could significantly increase the CRP level were excluded from the study. The drugs taken by the patients were disregarded. Prostate needle biopsy was required for the 183 patients due to elevated PSA, and the serum CRP levels, which are important in terms of the use in the diagnosis, treatment, and management of any complications that may develop after the biopsy, were routinely checked.

Serum C-reactive Protein Analysis

The CRP cut-off value was taken as 0.5 mg/dL. The values over 0.5 mg/dL were considered as inflammation. Evaluations were made by giving a "0" score for the values below 0.5 mg/dL and a "1" score for the values at 0.5 mg/dL and above. In addition, statistical evaluations were made through assessing the quantitative serum CRP values. Using Archem Diagnostics kits (Lot: 862 Ref: 02R04-3), an Architect C8000 autoanalyzer (Abbott Diagnostics, USA, Illinois) device was used with the immunoturbidimetric method.

Statistical Analysis

Age and serum CRP levels (by considering both the quantitative value and cut-off value as 0.5) were compared among the patients with LUTS (+) and LUTS (–). Age and CRP were compared with the Student t-test method. $p<0.05$ was used as the criteria of significance in the statistical analysis.

RESULTS

The number of patients with LUTS was 107 and the number of those without LUTS was 76. Our study was conducted as a cross-sectional study in groups of patients who had PSA>4.0 ng/dL, who were admitted to the urology clinic, and to whom biopsy was recommended. While the mean age of those with LUTS (+) was 62.71+0.87, it was 61.67+1.01 (p=0.625) in those with LUTS (–). When the serum CRP levels of those with and without symptoms were compared, no statistically significant difference was found (p=0.189). Besides, no significant difference was found between those with LUTS (+) and LUTS (–) (p=0.921) in the evaluation in which a serum CRP cut-off value of 0.5 and higher was considered as pathological (Table 2). Serum CRP levels in those with LUTS (+) and LUTS (–) are shown in Figures 1 and 2.

DISCUSSION

There are publications about the relationship between LUTS and CRP not being fully understood and this relationship has been found to be, conversely, both significant and insignificant in the studies conducted (1, 5). Because of the presence of conflicting

Table 1. Lower urinary tract symptoms

Storage symptoms	Voiding symptoms	Post-voiding symptoms
Frequent urination	Slow flow urination	Not feeling the complete complete discharge of urine
Nocturia	Bifurcation	Dribbling of urine after voiding
Urgency	Hesitancy	
Stress incontinence	Strain	
Urge incontinence		

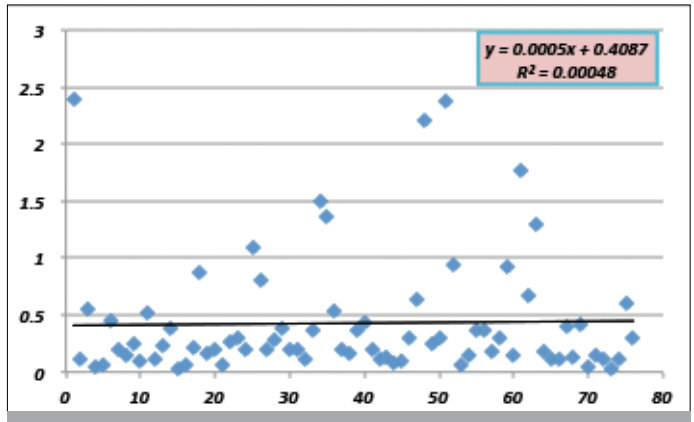

Figure 1. CRP levels in patients with LUTS (–)
LUTS: lower urinary tract symptoms; CRP: C-reactive protein

Table 2. LUTS (+) and LUTS (–) results

	LUTS (+)	LUTS (-)	p
n	107	76	
Age	62.71±0.87	61.67±1.01	0.625
Serum CRP (mg/dL)	0.53±0.10	0.43±0.06	0.189
CRP cut-off 0.5 (mg/dL)	0.23±0.04	0.24±0.05	0.921

LUTS: lower urinary tract symptoms; CRP: C-reactive protein

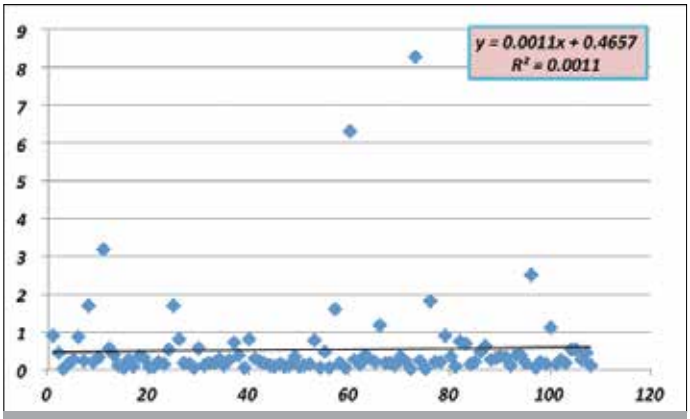

Figure 2. CRP levels in patients with LUTS (+)
LUTS: lower urinary tract symptoms; CRP: C-reactive protein

results, this study was intended to be repeated in our hospital for the purpose of detecting the presence of the relationship. However, when our results were evaluated, it was observed that there was no relationship between LUTS positivity and CRP when both the quantitative and cut-off values were taken as 0.5 mg/dL.

Considering that the average age of our patients was around 60 years old, it is a fact that, in Turkey, they often use anti-inflammatory drugs and other medications either on their own decision or when prescribed and these can affect the CRP levels (5, 13). Therefore, when the impact of inflammation in BPH and OAB due to drug use is considered (14), because LUTS may have become negative or because of the effect of drug use on the CRP level in patient groups with LUTS positivity and fewer symptoms, changes may have occurred in our results. The existence of this condition should be remembered in such studies.

In their study, Hung et al. (1) reported that serum CRP levels increase with age in the association of BPH and LUTS; besides, they identified a positive correlation between the filling symptoms and high LUTS values and the CRP. It may be asked though, why does CRP rise in patients with only high filling symptoms? Why not in others? However, they did not make any comment in these regards. Hung et al. (1) identified this situation in their study, but they could not clarify this issue and could not assert any hypothesis. Only the determination of the situation was made in both articles. In our study, the difference was not significant when the ages of those with LUTS (+) and LUTS (–) were assessed ($p>0.05$). It is not known whether or not the drug use of patients was taken into consideration in the studies conducted related to CRP in the literature. In addition, considering the drug use in this age group, in other words, in the case of a positive correlation between CRP and LUTS, it is very rare to find a patient not using the International Prostate Symptom Score (IPSS). The cessation of drug use is not ethical when the work is planned.

When the V/S (Voiding/Storage) ratio is >1, in which chronic inflammation can be associated with LUTS, the interpretation of the presence of inflammation in the prostatic tissues is made (1). Serum CRP levels have been reported to show a positive correlation in patients who have LUTS with weighted symptoms of OAB (15). However, when the LUTS is recovered with alpha blocker drugs, high serum CRP levels do not decrease but the clinical symptoms improve. However, antimuscarinic therapy provides an inhibitory effect in both detrusor activity and suburothelial inflammation in patients who have LUTS with weighted OAB symptoms; whereby after the treatment, CRP levels that do not recover in BPH are said to decrease to normal levels in OAB (1, 16). In a study when serum CRP levels > 0.30 mg/dL were used as a base for the cut-off value, those higher than this level were shown to be associated with urgency in LUTS (17). Although prostatic inflammation was observed in the histopathologic examination of the prostate (18, 19), there are studies showing that there is no significant relationship between LUTS and BPH (18, 20, 21). Inflammation can develop in the presence of histologic BPH, and prostatic inflammation may not directly influence the development of LUTS (18). We know that chronic inflammation increases, bladder filling function decreases, and prostate growth increases with age; in addition, it is reported that chronic inflammation is found in prostate biopsy specimens at a rate of about 98% (22); however, it has also been shown that CRP levels have no relationship with prostate growth and uroflow parameters (1).

In our study, assessments were only made on all LUTS. Storage, voiding, and post-voiding symptoms were not evaluated separately. In studies in which LUTS are evaluated, these three categories should separately be examined and should be considered when treatment is applied. This separation will provide us with a clue in terms of determining an approach for the treatment.

Choi et al. (18) defined that LUTS showed a significant association with CRP in their study in which they used hsCRP. There were significant differences when LUTS with medium and severe symptoms were compared with those without symptoms or with mild LUTS. hsCRP levels increased in the scores of IPSS, filling symptoms, voiding symptoms, and QoL, respectively. They argued that the hsCRP level was an independent factor for LUTS (18). However, when those with and without LUTS were compared in our study, we could not find any significant difference between the scores when the quantitative values of serum CRP were considered as well as when the cut-off value was taken as 0.5 mg/dL ($p>0.05$). The reason for this may be that we worked with conventional CRP. Questioning the existence of LUTS is a really simple process, as shown in our study. In addition, several studies questioning the relationship between CRP and LUTS conflict with each other (5, 23-25). When the studies showing that there is no relationship were examined, it was proposed that conventional CRP be used as in our study and that CRP could be close to normal values in chronic infections (18, 26). The assessments of the sub-analysis for LUTS are beyond the topic of this paper. The presence of individual symptoms was important for us. Therefore, evaluations were simply made as LUTS (+) and LUTS (–); here, when (+), the score was 1, and when (–), the score was 0, and the statistical analysis was performed according to these scores. Studies reporting that the CRP levels show significance with LUTS have recently been published (5, 24). Lu et al. (25) found a significant relationship between hsCRP and LUTS. Moreover, when age is taken into consideration, the mean age was 39 years old in the FAMHES study and 69.2 years old in the study of Choi et al. (18). Although there was not much difference between the age groups when both groups were examined, LUTS and CRP had a significant relationship (18, 25). Choi et al. (18), unlike the others,

showed in their study that hsCRP values had a relationship with filling symptoms.

Different from other studies, ours was a cross-sectional study. Therefore, there might be restrictive factors. We conducted this study in groups of patients who applied to our urology clinic, who had and did not have LUTS complaints, who had a PSA level of >4.0 ng/mL, and who were referred to biopsy. Perhaps, it would have been better if a comparison with CRP levels of the patients having a PSA level of <4.0 ng/mL had been planned while designing this study. Such a study could be planned in the following step. The retrospective nature of the study may also be a drawback. Community-based, broad participation, and prospective and controlled studies are needed. Considering the many unknowns and paradoxical results, we confirmed the reality with our study that the results in the literature are confusing; in other words, the presence of a relationship between LUTS and CRP is still not clear.

CONCLUSION

In this study, no correlation between CRP and LUTS was found. There are many factors that affect the CRP levels. Broader, comprehensive, and population-based studies containing sub-analyses and from which all factors affecting the levels of CRP are excluded are needed in order to show whether or not there is a relationship between CRP and LUTS in this regard.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.N.A., A.A.; Design - S.N.A., A.A.; Supervision - A.A.; Resources - A.A.; Materials - E.B., A.A.; Data Collection and/or Processing - S.N.A., E.B.; Analysis and/or Interpretation - A.A., S.N.A.; Literature Search - A.Ç., E.B., A.A.; Writing Manuscript - S.N.A.; Critical Review - A.A., A.Ç.

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