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Impact of COVID-19 on the progression of benign prostatic hyperplasia and aggravation of related symptoms: A prospective study

Mehmet Sevim MD | Okan Alkiş MD | İbrahim Güven Kartal MD | Şeref Coşer MD | Hüseyin Akman MD | Bekir Aras MD

Department of Urology, Faculty of Medicine, Kutahya Health Sciences University, Kutahya, Turkey

Correspondence
Mehmet Sevim, MD, Department of Urology, Faculty of Medicine, Kutahya Health Sciences University, Kutahya, Turkey.
Email: drmehmetsevim@gmail.com

Abstract

Objective: This study aims to evaluate the lower urinary tract symptoms (LUTS) of the patients with benign prostatic hyperplasia (BPH) who were admitted due to coronavirus disease (COVID-19) and to show the effect of COVID-19 on BPH.

Methods: This prospective study included patients over the age of 45 admitted due to COVID-19 between June 2021 and December 2021 and treated with alpha-blockers for BPH. During admission, the patients were evaluated by prostate volumes, prostate-specific antigen (PSA) values, and International Prostate Symptom Scores (IPSS). Furthermore, treatment duration due to COVID-19, frequency, nocturia, and voided volumes obtained from the voiding diary was recorded. Finally, the sequent IPSS values were compared by inviting the patients to the urology polyclinic in the first month.

Results: The mean age of 142 patients was 72.42 ± 10.21 years. The IPSS scores of the patients increased from 10.66 ± 4.46 to 12.99 ± 3.58 1 month after the diagnosis ($p < 0.01$). Moreover, the IPSS quality of life (QoL) scores were 2.44 ± 0.58 and 2.75 ± 0.51, respectively ($p < 0.01$). The mean frequency obtained from the voiding diary data increased from 5.10 ± 1.5 to 5.65 ± 1.36 ($p < 0.01$), mean nocturia count increased from 1.13 ± 0.05 to 1.39 ± 0.66 per day ($p < 0.01$), and the mean voiding volume decreased from 320.56 ± 46.76 ml to 298.84 ± 39.74 ml ($p < 0.01$).

Conclusion: In this study, we detected an increase in LUTS during COVID-19 treatment. Therefore, it should be noted that symptomatic or asymptomatic COVID-19 patients may refer to urology polyclinics due to aggravation of LUTS.

KEYWORDS

benign prostatic hyperplasia, COVID-19, International Prostate Symptom Score, lower urinary tract symptoms

1 | INTRODUCTION

Benign prostatic hyperplasia (BPH) causes lower urinary tract symptoms (LUTS) and has a detrimental effect on the quality of life (QoL).[1] The risk factors for BPH include metabolic syndrome, diabetes, obesity, hypertension, diet, sex hormone levels, prostate inflammation, age, genetic tendency, and geographical location.[2] The studies investigating BPH have shown a strong association between the development and progression of BPH and histological inflammation. Furthermore, inflammatory cytokines are overexpressed in BPH

tissues.[3] Autoimmune diseases, metabolic factors, and various bacteria and viruses defined in the prostate gland may be possible triggers of the inflammatory response observed in the prostate gland in patients with BPH.[4]

The cytokine storm caused by hyperinflammation and immunosuppression, resulting in microthrombosis and disseminated intravascular coagulation development is discussed in the pathophysiology of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5,6] Although the clinical symptoms most commonly appear in respiratory and circulatory systems, the cytokine storm affects the whole body through endothelial damage, microangiopathy, and vasculitis.[7] Furthermore, it may be thought that suppression of angiotensin-converting enzyme-2 (ACE2) after SARS-CoV-2 infection may lead to activation of pro-inflammatory pathways, increased cytokine secretion, and an eventual inflammatory response in the prostate gland.[8] Therefore, SARS-CoV-2 might cause irritative symptoms and trigger the inflammatory process in the prostate gland.[9] Moreover, previous studies showed that COVID-19 might cause different LUTS during and after the disease.[10]

Based on this literature data, we aimed to evaluate the LUTS due to BPH before and after COVID-19 and to show the effect of COVID-19 on BPH.

2 | MATERIALS AND METHODS

The study was conducted after the approval of the Ethical Committee of Kütahya Health Sciences University with approval number 2021-02/11 on 31.05.2021. Our prospectively designed study included patients over the age of 45 hospitalized in the pandemic clinics of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between June 2021 and December 2021. The SARS-CoV-2 diagnosis was made with a positive COVID-19 oropharyngeal swap PCR test. Each patient included in the study was under alpha-blocker treatment due to BPH. The informed consent form was obtained from the participants. Patients with a serum total prostate-specific antigen (PSA) value above 4 ng/dl, history of previous prostate and urethral surgery, diagnosis of diabetes mellitus, and patients whose prehospitalization data could not be obtained were excluded from the study. In addition, patients requiring intensive care monitoring during the progression of the disease were not included. Demographic data of 142 patients who met the inclusion criteria were collected. The patients were evaluated using the International Prostate Symptom Score (IPSS) form, which consists of eight questions validated in Turkish. The prostate volumes were measured by abdominal ultrasonography and PSA values from the hospital data system.[11] The voiding diary, which started at the onset of the treatment for COVID-19, was recorded for 3 days. Then, the IPSS form and the 3-day voiding diary were obtained 1 month after the initial evaluation. To determine the effect of COVID-19 on BPH patients, we compared the initial and first monthly results. The frequency, nocturia, and voiding volumes were compared by taking the average of the 3-day values.

2.1 | Statistical method

The Statistical Package for Social Sciences for Windows 22.0 (SPSS Inc.) program was used for statistical analysis. The normal distribution of the data was tested with the Kolmogorov–Smirnow/Shapiro–Wilks test. Numbers, percentages, mean, and standard deviation expressions were used for descriptive statistics. Paired sample *t*-test was used to compare before and after measurements in dependent groups. For statistical significance, $p < 0.05$ was accepted. The quality of reporting outcomes was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12]

3 | RESULTS

The mean age of 142 patients enrolled in the study was 72.42 ± 10.21 years. The mean BMI was detected as 25.71 ± 4.17 kg/m^2. The average number of hospitalization days of the patients in the pandemic service was 11.05 ± 3.36 days. The mean PSA value was 2.32 ± 1.52 ng/ml. The mean prostate volume was 58.85 ± 24.86 ml (Table 1).

The IPSS and IPSS QoL investigation forms during admission revealed a mean IPSS score of 10.66 ± 4.46 at the beginning of hospitalization. Moreover, it was detected that the score increased to 12.99 ± 3.58 a month after COVID-19 ($p < 0.01$). The IPSS-QoL score at the beginning of COVID-19 and in the first month were 2.44 ± 0.58 and 2.75 ± 0.51 overall, respectively ($p < 0.01$).

We investigated the data of a 3-day voiding diary that was filled in at the beginning of COVID-19 and after 1 month, and we detected an increase in frequency from 5.10 ± 1.51 to 5.65 ± 1.36 ($p < 0.01$). We noticed that the mean nocturia count increased from 1.13 ± 0.05 to 1.39 ± 0.66 ($p < 0.01$). Moreover, the mean voiding volumes obtained from voiding diary data at the beginning of COVID-19 and in the first month were 320.56 ± 46.76 and 298.84± 39.74 ml, respectively ($p < 0.01$) (Table 2). Eight patients were catheterized because of globe vesicale during hospitalization. Six patients were

TABLE 1 Patients' characteristics

	***n* = 142**
Age (years) (mean ± SD)	72.42 ± 10.21
BMI (kg/m^2) (mean ± SD)	25.71 ± 4.17
Duration of hospital stay (day) (mean ± SD)	11.05 ± 3.36
PSA (ng/ml) (mean ± SD)	2.32 ± 1.52
Prostate volüme (ml) (mean ± SD)	58.85 ± 24.86

Abbreviations: PSA, prostate specific antigen.

TABLE 2 Change of IPSS, IPSS_QoL score, frequency, nocturia, and AVV

	Beginning of COVID-19	Post-COVID-19 1st month	*p* Value
IPSS (mean ± SD)	10.66 ± 4.46	12.99 ± 3.58	<0.01[a]
IPSS-QoL (mean ± SD)	2.44 ± 0.58	2.75 ± 0.51	<0.01[a]
Frequency (mean ± SD)	5.10 ± 1.51	5.65 ± 1.36	<0.01[a]
Nocturia (mean ± SD)	1.13 ± 0.05	1.39 ± 0.66	<0.01[a]
AVV (mean ± SD)	320.56 ± 46.76	298.84 ± 39.74	<0.01[a]

Abbreviations: AVV, average voided volüme; IPSS, International Prostate Symptom Score; QoL, quality of life.
[a]Paired *t*-test.

catheterized after discharge. Transurethral prostatectomy operation was conducted on 10 patients, and transvesical prostatectomy operation was performed on one patient during further follow-ups.

4 | DISCUSSION

Recent studies have revealed that COVID-19 has common effects on various organs. The increase in LUTS was shown as the first possible finding of COVID-19 as one of the effects above.[13] COVID-19 is accepted as an inflammatory disease that affects the whole body. Our study which was designed from this point of view showed an increase in LUTS by IPSS in the patients with BPH after COVID-19. Furthermore, IPSS-QoL showed a significant decline in QoL compared to the period before COVID-19. This prospective study has the largest population of COVID-19 patients admitted to the hospital and diagnosed with BPH to the best of our knowledge.

Different pathophysiological pathways were described to explain BPH-induced LUTS caused by COVID-19. One of these explanations is inflammation. Recent studies have shown inflammation's involvement in the disease pathogenesis, symptomatology, and progression.[14] Chronic activation of T-lymphocytes is primarily responsible observed in patients with BPH. Furthermore, the cytokines and growth factors released from the inflammatory cells create a pro-inflammatory environment that may support fibromuscular growth. These may be responsible for inducing a relative hypoxia state due to the increased oxygen need of the cells. This inflammatory state may play a role in the clinical presentation or progression of BPH.[15] The progression of BPH is not only associated with local inflammation that appears on the prostatic tissue but also with systemic inflammation. Since there is a significant association between prostate diameter/volume and the number of components of the metabolic syndrome, there is evidence that systemic inflammation may play a role in BPH.[14,16] Furthermore, another study showed a positive association between gout disease, which causes a systemic inflammatory response, and BPH.[17] In our study, we showed the clinical aggravation of LUTS after COVID-19 which the inflammatory microenvironment of SARS-CoV-2 might have caused.

Another inflammation pathway is the signal change of ACE2. Studies demonstrated that ACE2 has antifibrotic and anti-inflammatory activities.[9] Furthermore, previous studies on the characteristics of SARS-CoV-2 revealed that the virus binds to the ACE2 receptor on many human tissues such as the lungs, kidneys, prostate, and pancreas and infects the target tissue.[18] Therefore, the progression of BPH may occur due to the decrease in antifibrotic and anti-inflammatory activities following the functional loss of ACE2 and a reduction of ACE2 expression on cellular membranes of the prostate tissue due to viral invasion. Consequently, it is considered that this appears as a result of BPH and LUTS increase caused by COVID-19.[10]

Although the expression of ACE2 is highest in the lungs, intestines, and kidneys, such expression is higher in 2.4% of urothelial cells, which increases the susceptibility to possible viral cystitis infection caused by COVID-19. The inflammatory conditions that appear due to viral cystitis or bacterial infection may increase the symptoms of LUTS through another pathophysiological pathway.[19,20] Furthermore, previous studies stated that glycosuria, proteinuria, and hemoglobinuria might cause an increase in LUTS through irritative symptoms.[21,22] Mumm et al.[23] showed in their retrospective study on 57 patients that frequency increased in seven patients, which might have appeared due to viral cystitis. In line with the studies mentioned above, a significant increase in voiding frequency was observed when compared to the pre-COVID-19 period. Moreover, we believe that increased nocturia and decreased voiding volume may aggravate LUTS.

Another pathophysiological pathway for the development of BPH can be the mechanisms related to androgen receptors (AR). Sex hormones and AR play an essential role in the development of BPH.[24] Wambier and Goren[25] demonstrated that infection by SARS-CoV-2 has an androgen-mediated process. Therefore, it may be concluded that the progression of BPH may be a complication of COVID-19, and such probability should be investigated in further studies, given the important role of AR in the pathophysiology of BPH.

Another factor for the aggravation of BPH symptoms might be administering intravenous fluids during hospitalization. However, the treatment algorithms must not be abandoned in serious diseases like COVID-19 on suspicion of BPH symptoms aggravation.

The use of questionnaire forms that have been validated, was a limitation. Furthermore, other limitations include a lack of urinary flow rates of the patients admitted to pandemic clinics since there was no uroflowmetry device and a lack of urine analysis of the patients without dysuria complaints, routinely. In addition, another limitation is that crystalloid fluids and diuretic drugs given during treatment may have increased LUTS. However, limited contact with COVID-19 patients caused the study to be designed in this form.

5 | CONCLUSION

In this study, we revealed that an increase in LUTS can be seen after COVID-19. However, further studies are required to clarify whether COVID-19 increases BPH or if the increase is due to other causes such as intravenous fluid therapy. Thus, it should be considered that symptomatic or asymptomatic COVID-19 patients may refer to urology polyclinics due to aggravation of LUTS. Clinicians should be aware that LUTS of patients diagnosed with COVID-19 may be aggravated, and they should be cautious and take necessary actions. We believe that multi-centered prospective studies are required to evaluate LUTS more accurately due to COVID-19.

AUTHOR CONTRIBUTIONS

Mehmet Sevim set up the main idea and hypothesis of the study. Okan Alkiş, Mehmet Sevim, Hüseyin Akman, and Bekir Aras developed the theory and edited the material method section. Mehmet Sevim, Okan Alkiş, İbrahim Güven Kartal, and Şeref Coşer made the evaluation of the data in the results section. The discussion part of the article was written by Mehmet Sevim, Okan Alkiş, Hüseyin Akman, İbrahim Güven Kartal, Bekir Aras, and Şeref Coşer have reviewed and made the necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

ORCID

Mehmet Sevim http://orcid.org/0000-0002-7571-7669
Okan Alkiş http://orcid.org/0000-0001-6116-9588
İbrahim Güven Kartal http://orcid.org/0000-0002-2313-3522
Şeref Coşer http://orcid.org/0000-0002-8856-8084
Hüseyin Akman http://orcid.org/0000-0002-3414-442X
Bekir Aras http://orcid.org/0000-0002-7020-8830

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