Review

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Comprehensive Review of COVID-19 on Benign Prostate Hyperplasia Patient Symptoms

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Since the outbreak of the global Coronavirus disease (COVID-19) pandemic in 2019, the number of confirmed cases has increased steadily worldwide. The most common symptom of COVID-19 (SARS-CoV-2) is respiratory symptoms. On the other hand, increased voiding frequency and lower urinary tract symptoms (LUTS) have also been reported. Regarding the relationship between LUTS and COVID-19, only small size (n<100) retrospective studies have been reported, but the post-International Prostate Symptom Score (IPSS) increases compared to pre-IPSS after a COVID-19 infection in those older than 50 years. α-blockers and phosphodiesterase-5 inhibitors are relatively safe, but there are conflicting reports on 5 α-reductase inhibitors; hence, further research is needed. Four major theories have been argued regarding the relationship between LUTS and COVID-19: renin-angiotensin system-related, androgen-related, inflammation-related, and metabolic derangement-related. In conclusion, elderly male patients often have benign prostate hyperplasia as a co-morbidity, and the severity of COVID-19 is high in this group. Therefore, voiding symptoms in these patient groups is of particular concern.

Keywords: COVID-19; SARS-CoV-2; Lower urinary tract symptoms; Prostatic hyperplasia

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INTRODUCTION

The number of confirmed cases of the global Coronavirus disease (COVID-19) has increased worldwide since the outbreak of the pandemic in 2019. The most common symptom of COVID-19 (SARS-CoV-2) is respiratory symptoms [1,2]. On the other hand, non-respiratory symptoms reported, such as digestive symptoms (nausea, vomiting, and diarrhea), have been reported [3]. An increase in voiding frequency and lower urinary tract symptoms (LUTS) have been reported [4]. As a condition for a COVID-19 infection, angiotensin-converting enzyme 2 (ACE2) acts as the receptor of COVID-19. COVID-19 can theoretically infect any organ if the co-expression of ACE2 and transmembrane serine protease 2 (TMPRESS2) occurs [5].

Regarding the benign prostate hyperplasia (BPH) and COVID-19, the two diseases are potentially more likely to coexist than show a direct relationship. First, male patients more susceptible to COVID-19 and have a higher incidence and mortality rate with severe conditions [6]. Although it varies from country to country, there are reports that as many as 70-80% of COVID-19 deaths are male [6]. In addition, more severe diseases are expressed in older patients, and BPH also occurs in an age-dependent manner [7].

Therefore, older male patients are more likely to have severe COVID-19 infections and have BPH as a co-morbidity. Furthermore, there is a possibility of the correlations as both ACE and TMPRESS2 are co-expressed in the prostate [8]. Therefore, studies on the correlations between BPH and COVID-19 are needed. Nevertheless, a well-designed prospective study for COVID-19 is difficult to establish because of its ongoing status and the lack of high-level evidence. Therefore, this study evaluated the current situation of BPH with COVID-19 to provide information that would be helpful for urologists through a literature review related to this issue.

MAIN BODY

1. Literature Search Strategy and Selection Criteria

This study systematically reviewed the papers on BPH and COVID-19 related to the urology field. A literature search was performed using a combination of keywords including "COVID-19," "SARS-CoV-2," "BPH," "LUTS," and "voiding." MEDLINE and Google Scholar databases were searched for papers published until March 20, 2022. Two reviewers (J.Choi and J.J.Kim) screened all returned articles. Case reports and papers not written in English were excluded to narrow the scope and improve the clarity of the manuscript.

2. LUTS and COVID-19

A few small-sized (n<100) retrospective studies related to BPH and COVID-19 have been published. Elaimeri and Alemairy [9] compared the pre-IPSS (International Prostate Symptom Scores, i.e., IPSS score performed when visiting an outpatient clinic before COVID-19) and post-IPSS in 85 COVID-19 patients. The study claimed that when the IPSS score was divided into mild (0-7), moderate (8-19), and severe (20-35), the proportion of 'mild' decreased from 46% to 22% after a COVID-19 infection. The ratio of 'moderate' increased from 54% to 77%, reflecting the worsening BPH symptoms.

Similarly, Nabeeh et al. [10] compared 50 patients infected with COVID-19 after being diagnosed with BPH. The IPSS, Qmax (maximum flow rate), and PVR (post-void residual urine) were compared objectively. The IPSS score increased from 13 to 26 or higher during hospitalization and after infection. Voiding parameters, such as Qmax, PVR, IPSS, and QOL (quality of life), were deteriorating. In addition, approximately 26% of patients required catheterization with acute urinary retention during hospitalization. This study argued that COVID-19 directly affects the general condition, increases the immuno-compromised state, and increases corticosteroid use, causing an underactive bladder, worsening the voiding symptoms.

Another study conducted a prospective cross-sectional study, dividing 94 COVID-19 patients into those older or younger than 50 years [11]. In patients hospitalized for COVID-19 for more than three weeks, the pre-IPSS was recorded as memory-dependent and compared with the post-IPSS. There was no significant difference in younger patients. Although IPSS of older patients increased from 5.1 to 9 points, they claimed that COVID-19 substantially affected voiding disorder in older patients. Overall, the level of evidence is low, generally with less than 100 retrospective case-control studies or cross-sectional studies. Fig. 1 and Supplementary Fig. 1 presents a forest plot of meta-analysis for IPSS studies in male patients over 50 years.

3. Medications related to LUTS and COVID-19

Various drugs had positive and negative effects on COVID-19. Non-steroidal anti-inflammatory drugs (NSAIDs) can increase

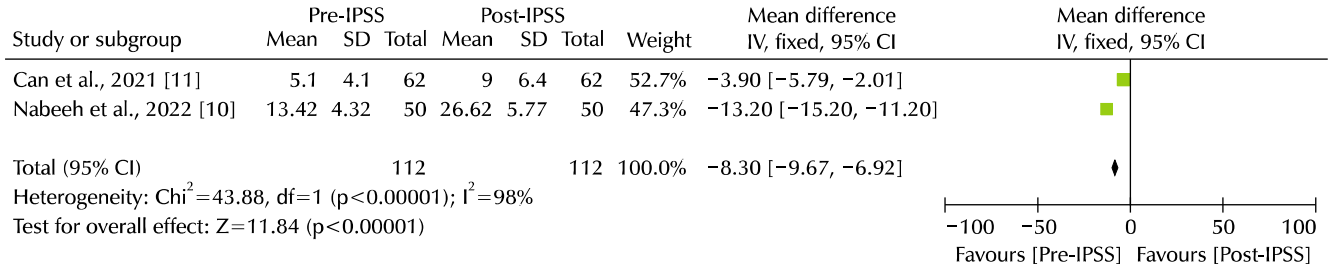

Fig. 1. Forest plot of the pre- and post-IPSS score in male COVID-19 patients over the age of 50 years. Two studies show a consistent increase in IPSS after COVID-19 infection in male patients over the age of 50 years. IPSS: International Prostate Symptom Score, SD: standard deviation, CI: confidence interval.

Table 1. Correlation between urological drugs with COVID-19

Medication	Considerations	Drug-drug interaction related to COVID-19
α-blockers	Potential to decrease acute respiratory distress syndrome.	None
5α-reductase inhibitors	Mixed reports that they will play a protective or worsening role.	None
PDE-5 inhibitors	Theoretically, respiratory symptoms of COVID-19 can be reduced.	Avoid concomitant use with lopinavir/ritonavir.

PDE-5: phosphodiesterase-5.

the likelihood of thrombosis or kidney injury, so NSAIDs should be used carefully in case of a COVID-19 infection [12]. Table 1 lists the effects of α-blockers, 5α-reductase inhibitors (5-ARIs), and phosphodiesterase-5 (PDE-5) inhibitors.

1) α-blockers

COVID-19 can cause cytokine storm syndrome, which drives the secretion of interleukin (IL)-6, IL-8, and TNF-α, resulting in acute respiratory distress syndrome [13]. On the other hand, in releasing catecholamine, an α-blocker may potentially be effective in preventing these syndromes because the immune cell acts on the a-adrenergic receptor. In particular, there is a clinical trial to prevent the cytokine storm using prazosin, a short-acting α-blocker [13]. Therefore, there is a possibility that other α-blockers have potential benefits. Furthermore, there are no drug-drug interactions with a COVID-19 treatment, so there might be no severe problems with using α-blocker in COVID-19 patients.

2) 5-ARIs

A COVID-19 infection requires TMPRESS2 on the cell surface. This TMPRESS gene is located in region 5 of the androgen-response element [14]. Therefore, it has been argued that preventing androgen can reduce the incidence of TMPRESS2 and theoretically reduce the infection rate. On the other hand, there are conflicting arguments. Dhindsa et al. [15] reported that patients with lower testosterone levels (<100 ng/dl) among COVID-19 hospitalized patients showed higher severity. Of the 152 patients, 90 males were included in this single-center cohort study, and patients without severe side effects had a high blood testosterone level. By contrast, patients with severe disease from the beginning or middle of hospitalization usually had testosterone levels less than 100 ng/dl. Dhindsa et al. [15] argued that although the TMPRESS2 gene is located in the androgen receptor, it is not known how the TMPRSS2 function changes as the androgen signaling changes. Therefore, it is difficult to confirm the effects of testosterone or 5-ARI on COVID-19.

3) PDE-5 inhibitors

PDE-5 inhibitors act on angiotensin-II receptor type-I to reduce lung pro-inflammatory cytokines and pulmonary edema [16]. PDE5-i is also used to treat alpine diseases, so there is a high possibility that PDE-5 inhibitors have a low risk, especially with COVID-19, which has many lung complications [17,18]. On the other hand, lopinavir or ritonavir, which has been used as an AIDS treatment and as a COVID-19 treatment, increases the duration of sildenafil [19]. Therefore, its use should be avoided when using sildenafil with these antiviral drugs. Currently, paxlovid and remdesivir are used, so there would be no significant problems with PDE-5 inhibitor use in COVID-19 patients.

4. Possible Mechanisms by Which COVID-19 Causes LUTS

Regarding the correlation between BPH and COVID-19, four theories have been proposed regarding the causes of worsening voiding symptoms during a COVID-19 infection.

1) Renin-angiotensin system (RAS) dysregulation

In the RAS, angiotensinogen switches to angiotensin I and then to angiotensin II; both are involved in BPH symptoms [20,21]. On the other hand, the COVID-19 virus helps downregulate ACE2, preventing the conversion of angiotensin II to angiotensin 1-7, 1-9, and worsening the BPH symptoms.

2) Androgen related

The androgen-related theory is that when dehydrotesterone increases, the androgen receptor activity increases and worsens the BPH symptoms [22,23]. In addition, it also increases TMPRESS2 expression and worsens the severity of COVID-19, so there is a correlation between the BPH and a COVID-19 infection. On the other hand, as mentioned earlier, there is no clear correlation between the increase

in the androgen receptor and TMPRESS2. Furthermore, there are reports showing that patients with high testosterone levels have low severity [15], so further validation between testosterone and COVID-19 is needed.

3) Inflammation related

Viruses, such as COVID-19, can lead to prostate inflammation because viruses cause the release of various inflammatory cytokines [24]. In addition, COVID-19 has an inhibitory effect on ACE2 action that can further cause inflammation and exacerbate voiding symptoms [25].

4) Metabolic derangement related

The metabolic derangement theory suggests that COVID-19 increases new-onset diabetes and cardiovascular complications [26,27], affecting the voiding symptoms [28].

CONCLUSIONS

Elderly male patients often have BPH as a co-morbidity. The COVID-19 severity is high in this group, so there may be an indirect correlation, and voiding symptoms may worsen due to the general condition or steroid use. Despite the various hypotheses, the original articles are still insufficient, and more prospective research is needed. In addition, most BPH drugs can be used safely, but the reports on 5-ARI are controversial; hence, further research will be needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHORS CONTRIBUTIONS

J.C. participated in data collection and wrote the manuscript. H.J.S., D.H.L., and T.K.H. participated in the study design and performed the statistical analysis. J.J.K. participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via https://doi.org/10.14777/uti.2022.17.2.31.

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