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REVIEW

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Does COVID-19 cause or worsen LUT dysfunction, what are the mechanisms and possible treatments? ICI-RS 2023

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and produced a worldwide pandemic in 2020. There have been 770,875,433 confirmed cases and 6,959,316 attributed deaths worldwide until September 19, 2023. The virus can also affect the lower urinary tract (LUT) leading to bladder inflammation and producing lower urinary tract symptoms (LUTS) in both the acute and chronic phases of disease.

Methods: At the 2023 meeting of the International Consultation on Incontinence-Research Society (ICI-RS), the literature relating to COVID-19 and bladder dysfunction was reviewed. The LUTS reported, as well as the pathophysiology of these bladder symptoms, were the subject of considerable discussion. A number of different topics were discussed including lower LUTS reported in COVID-19, how SARS-CoV-2 may infect and affect the urinary tract, and proposed mechanisms for how viral infection result in new, worsened, and in some persisting LUTS.

Conclusions: The workshop discussed the interaction between the virus and the immune system, covering current evidence supporting theories underlying the causes of acute and chronic LUTS related to COVID-19 infection. Research questions for further investigation were suggested and identified.

KEYWORDS

COVID-19, long-COVID, lower urinary tract symptoms, SARS-CoV-2, urinary frequency, urinary urgency

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has significantly impacted public health, and has posed numerous challenges for healthcare systems worldwide. There have been 770,875,433 confirmed cases of COVID-19 and 6,959,316 deaths as a result of infection up to September 19, 2023.[1]

Respiratory distress is the most significant consequence of SARS-CoV-2 that leads to hospital admission. However, it is increasingly recognized that there are nonrespiratory results of infection and that organs such as liver, kidney, gut, and heart can also be severely damaged.[2,3] During the pandemic, a patient group was recognized who after an

acute viral infection experienced a variety of chronic symptoms. Up to as many as 10% of patients have continued or developed new symptoms following their initial illness, some of which have persisted for years.[4] These continuing symptoms have been named the disease entity known as long COVID or postacute sequelae of COVID-19 (PASC).[5] Symptoms reported include chronic fatigue, joint pain, cough, shortness of breath, "brain-fog," chest pain, and in some patients, new bladder symptoms or lower urinary tract symptoms (LUTS).[6] We are continuing to define long COVID and learn about it as its impact on patients globally including those of working age emerges.[7]

Grabbert et al. published a report of increased urinary frequency in patients hospitalized with SARS-CoV-2.[8] Since this publication, there have been several reports of similar observations of new LUTS, even beyond the acute infection. Dhar et al. found that urinary frequency and the incidence of nocturia increased with COVID-19 infection, and that some patients also reported bladder pain.[9] Continued research into long COVID is essential as the societal and economic burden reveals itself postpandemic. With so many individuals having experienced infection and reinfection worldwide the long-term effects of SARS-CoV-2 on various tissues, and the impact on different organs' functioning, remains unknown.[10,11] Understanding the impacts of SARS-CoV-2 infection on the bladder may be useful:

- To help diagnose and treat LUTS associated with acute COVID-19 infection and long COVID.
- To understand the inflammatory mechanisms of COVID-associated LUTS which may reveal more about other inflammatory conditions of the bladder that remain poorly defined—such as interstitial-cystitis/bladder pain syndrome (IC/BPS).

In this paper, we aim to explore the existing literature surrounding the connection between COVID-19 and bladder function, with a specific focus on the development and exacerbation of LUTS. By examining the available evidence, we hope to gain insights into the underlying mechanisms that lead to LUTS in COVID, the clinical implications, and the future directions for research to lead to improved treatment of symptoms.

2 | SYMPTOMATOLOGY

The lower urinary tract has arisen as one of the many organ systems that can be impacted by COVID-19. COVID infection has been reported to have an effect on the bladder, urethra, and prostate producing a spectrum of LUTS, including asymptomatic microscopic and gross hematuria, bladder-storage symptoms, and voiding dysfunction (Figure 1).[12,13]

Commonly reported LUTS in patients with COVID-19 infection include urinary urgency, frequency, nocturia, and bladder pain, it has not been possible to separate the increasing overactive bladder (OAB) symptoms and the possibility of viral cystitis.[9] One study showed that the degree of LUTS seems to correlate with the severity of COVID-19, with the worst bladder symptoms attributed to those with more severe respiratory symptoms.[14] Increased urinary frequency has also been reported in patients with COVID-19 infection independent of acute renal injury or urinary tract infection in a small series of hospitalized patients.[15] In a similar study, LUTS, especially storage symptoms, were found to occur early in COVID infection and the authors of this article recommended that clinicians include questions about the urinary tract during routine history taking in patients with suspected infection.[16] A survey-based symptomatic assessment completed in 350 patients with COVID, with a median age and length of hospital stay of 64.5 years (range 47–82) and 10 days (range 5–30), respectively, showed that new ($n = 250$, 71.4%) or worsening OAB symptoms ($n = 100$, 28.6%) persisting for many weeks after discharge home, had a significant negative impact on quality of life.[17] However, these findings may not be applicable for those with asymptomatic, mild, or moderate COVID infection that did not require admission to the hospital.

There have also been some studies showing that COVID infection is not associated with a significantly increased incidence of urinary symptoms, and that there was no reported change in prescription rates for OAB during the

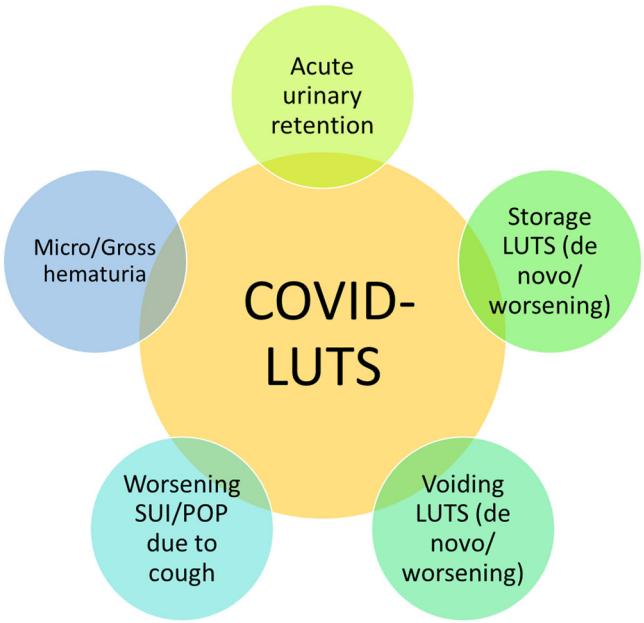

FIGURE 1 Spectrum of LUTS in patients diagnosed with COVID-19.[12,13] LUTS, lower urinary tract symptoms; POP, pelvic organ prolapse; SUI, stress urinary incontinence.

pandemic.[18] In one study, approximately 25% of participants with positive urine viral RNA, denied any LUTS.[19]

3 | PATHOPHYSIOLOGY

Regarding the potential mode of action of the virus within the lower urinary tract, several theories exist (Table 1).

Data from the pediatric literature shows an increased incidence of children with urinary retention after COVID infection.[27] Neurological examination and imaging findings of these children did not reveal any abnormality and the median time from diagnosis of COVID-19 infection to the onset of LUTS was recorded to be 3 months. Incomplete bladder emptying/urinary retention was supported by urodynamic findings of increased bladder compliance, high residual urine volumes, and absence of detrusor pressure increase during the voiding phase.[24]

A systematic review of 52 articles investigating the association of COVID-19 infection with benign prostatic hypertrophy (BPH) in men, found that COVID-19 infection may accelerate BPH and therefore worsen LUTS such as acute urinary retention. The authors have suggested that pro-inflammatory pathways triggered by COVID may lead to prostate damage and enlargement.[23]

4 | VIRAL CYSTITIS

In acute COVID-19 infection, it has been hypothesized that the SARS-CoV-2 virus itself may directly cause a viral cystitis. This would be unsurprising as other viruses such as HIV and HTLV-1 are also associated with LUTS and urodynamic abnormalities have been documented independent of urinary tract infection.[25–27]

The main virulence factor of SARS-CoV-2 is the spike protein, responsible for viral attachment to host cells via angiotensin-converting 2 enzyme receptors (ACE-2), TMPRSS-1 receptors, and vimentin (extracellular), then enabling viral entry.[21,28] A single-cell RNA-sequencing study, which examined datasets from multiple organs, revealed that approximately 1% of type II alveolar cells in the lungs exhibited ACE2 positivity, with a standard deviation of 1%. On this basis, cell types with >1% of ACE2-positive cells were considered at "high risk" of SARS-CoV-2 infection. This group found that 2.4% of bladder urothelial cells expressed the ACE2 receptor, putting the bladder into this "high risk" category for viral invasion.[20] Therefore, it has been postulated that SARS-CoV-2 may directly infiltrate the urinary tract, resulting in local inflammation and subsequent disruption of normal bladder physiology.

This theory is supported by some reports of SARS-CoV-2 viral RNA being detected in urine; however, the exact localization of urothelial ACE2 receptors is unknown.[21] Zou et al. produced cell scatter plots by analyzing published scRNA-sequencing data from the urinary system and found high expression of ACE-2 receptors on urothelial cells but this finding does not reveal whether there is one or many cell layers responsible for this high receptor expression (apical, intermediate, or basal).[21] Effect on the bladder may be due to a COVID-viraemia with viral entry from the bloodstream and therefore basal side, or from urine, with viral invasion from the luminal side. It is still unknown whether the virus can be isolated routinely in urine, and at what stage of the disease there is viral shedding into the urinary system.[13] It remains undetermined whether viral replication in urothelial cells themselves produces LUTS, or whether symptoms are the result of local and/or systemic inflammation.[29]

5 | INFLAMMATORY CYTOKINES

Another possible explanation for LUTS experienced during acute COVID-19 is the effect of pro-inflammatory cytokines on the bladder. During severe acute systemic infection, the normal homeostasis of pro- and anti-inflammatory cytokines is disrupted leading to widespread abnormal activation of

TABLE 1 Proposed pathophysiological mechanisms underlying COVID-LUTS.[13]

Local	*Bladder inflammation*: Increased expression of urinary inflammatory cytokines (IL-6, IL-8) Expression of ACE2 receptors on urothelial cells.[20,21] Mast cell activation by COVID-driven cytokines/growth factors augmenting inflammatory response of the cytokine storm.[22] *Prostatic inflammation*: Inflammatory mediators have been shown to play an important role in the progression and severity of LUTS secondary to benign prostate obstruction in men.[23]
Neurological	Neuroinflammation and/or demyelination secondary to cytokine storm might be involved in the development of OAB symptoms.[24–26]
Psychological	Fear and anxiety related to prolonged hospitalization, including ICU care because of COVID.

Abbreviations: ICU, intensive care unit; LUTS, lower urinary tract symptoms; OAB, overactive bladder.

immune cells and an unregulated extensive release of pro-inflammatory mediators known as a cytokine storm. Such a generalized response has a widespread and potentially damaging effect on host tissue including the bladder. It is well documented that elevated urinary cytokine levels are found in many patient groups with LUTS, including those with OAB and those with painful bladder syndrome (PBS).[30–32] Lamb et al. reported elevated urinary cytokine levels of IL-6, IL-8, and IP-10 in a small cohort of patients with COVID-19 when compared to those without COVID infection or any urological diagnoses. This group went further to suggest that persistent LUTS found in patients with long COVID, may represent a chronic inflammatory cycle in the bladder.[20] This may be supported by the finding that the SARS-CoV-2 virus can produce toxin-related peptides such as conotoxins, phospholipases, phosphodiesterases, zinc metal proteinases, and bradykinins in urine, as these peptides may produce a direct inflammatory response in the bladder.[33,34]

6 | VIRAL PERSISTENCE/ REACTIVATION

The relationship between the inflammation seen in acute COVID infection, and the pathophysiology of long COVID is not yet understood. The reason why a subset of patients should develop LUTS or go on to have chronic LUTS also remains unknown.

However, there is a growing body of evidence to support that in some, SARS-CoV-2 may persist long beyond the acute infection. Both viral messenger RNA and the spike protein itself have been detected in the gut and urinary tract many months after primary infection.[35] This may mean that SARS-CoV-2 could behave in a similar fashion to herpes viruses or Lyme, which stay dormant and then reactivate opportunistically.[36] Viral persistence or reactivation may both trigger intermittent immune responses that lead to long-term LUTS.

7 | SARS-CoV-2 AS A BACTERIOPHAGE

Contrary to our initial understanding that SARS-CoV-2 replicates solely in eukaryotic cells, there is evidence that it may invade and even replicate in bacteria of the gut. Petrillo et al showed that SARS-CoV-2 replicates spontaneously in the gut bacteria of those infected with COVID.[37] Brogna et al. also found viral particles in bacteria cultured from the stool samples of COVID-infected individuals and demonstrated viral replication.[38] This suggests that SARS-CoV-2 can live within the gut, hidden within the gut microbiome. Some groups have shown that those with COVID-19 have altered gut flora. The "COVID gut microbiome" has been shown to have reduced bacterial diversity, with pathogenic and pro-inflammatory bacteria increasing in number, and normal anti-inflammatory and beneficial species diminished.[39] These changes in the gut bacterial populations cause gut dysbiosis which has been associated with many chronic inflammatory conditions such as Crohn's disease and ulcerative colitis. Gut dysbiosis, which increases epithelial permeability and dysfunction through damage, allows for the passage of pathogenic material from the gut into the bloodstream causing an immune response. This could be another mechanism by which there is promotion of a chronic systemic inflammatory response that may be affecting many organ systems in long COVID.[40]

There are data showing that the microbiome of the bladder and the gut are closely linked.[41] One group has shown that over 60% of urinary flora are also found in the intestine.[42] There is therefore a possibility that COVID-19 not only causes a gut dysbiosis but also potentially a bladder dysbiosis, causing urothelial dysfunction, a vulnerability to infection, and a local inflammatory response in the bladder.[43]

8 | CONCLUSION

The link between COVID-19 and LUTS is well documented in the literature. There is evidence that de novo and worsening of pre-existing LUTs are seen both in acute covid infection, and in those who are unfortunate enough to develop long COVID. The exact mechanisms of how COVID results in bladder symptoms are not known for sure but may be different in the acute and chronic phases.

In the initial primary infection with SARS-CoV-2, the virus itself may be able to access the urinary system by targeting the ACE-2 receptors expressed on the urothelial cells of the bladder. This may cause local inflammation and a viral cystitis. The systemic effect of COVID and the initiation of a cytokine storm also has potential to damage the bladder tissue in the same way that it damages other organs such as the lungs.

Following acute COVID infection, chronic bladder symptoms could be caused by viral reservoirs in the gut allowing SARS-CoV-2 to intermittently reactivate and trigger immune response. COVID's effect on the microbiota of the intestines may dampen the body's defense against pathogenic bacteria by inducing epithelial dysfunction, in turn promoting a systemic inflammatory response. Furthermore, we may find evidence in the future that dysbiosis as a consequence of COVID is not only reserved to the gut but also may affect the bladder.

Research questions

1. What is the correlation between LUTS and initial COVID infection severity? The following studies are suggested:

- Population study of hospitalized patients and those not requiring hospitalization
- Symptom questionnaires to assess COVID severity (respiratory symptoms)
- Validated symptom questionnaires for LUTS, that is, ICIQ-FLUTS

2. How does COVID-19 vaccination influence the development of LUTS? The following study is suggested:

- Large population study of vaccinated and unvaccinated individuals with validated symptom questionnaire for LUTS, that is, ICIQ-FLUTS

3. Can urine or blood-based biomarkers be used to predict the onset and severity of LUTS? The following study is suggested:

- Urinary and bladder biopsy cytokines in acute COVID, long COVID, and asymptomatic individuals

4. How does COVID-LUTS evolve? Is spontaneous resolution likely? When and how should we treat patients with persistent/prolonged COVID-LUTS? The following studies are suggested:

- Long-term follow-up of cohort of hospitalized patients with COVID-associated LUTS in the acute phase
- Long-term follow-up of patients who develop LUTS as part of long COVID

5. Association between long COVID symptoms and types of urinary tract bacteria infections—are they acting as bacteriophages? The following studies are suggested:

- Differences in bladder microbiome in COVID infection, long COVID, and asymptomatic individuals—in bladder tissue
- Associations between gut and bladder microbiome changes in association with COVID
- Any evidence of SARS-CoV-2 as bacteriophage in the bladder

6. Treating urinary tract bacterial infections and do they have an impact on long COVID symptoms? The following study is suggested:

- Long-term antibiotics/rotational antibiotics/promotion of healthy urinary microbiome as treatment modalities for COVID-associated LUTS

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