

A Review of the Impact of Covid-19 on the Male Genito-Urinary Tract

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Abstract

Introduction and Objectives: Since its advent in 2019, Corona Virus Disease 19 (Covid-19) has changed everyday life in many unprecedented ways. With the availability of Covid-19 vaccines, clinical practice has stepped gradually towards its everyday routine. The clinician, however, needs to address such concerns as “Can Covid-19 present with urinary tract symptoms predominantly?”, “Can the urinary tract develop long-term Covid-19 symptoms?”, “Can Covid-19 vaccines/drug therapy cause male infertility?” **Methods:** This mini-review of the current literature has been carried out by searching the Pubmed database. **Results and Conclusions:** Our literature review suggests that there is insufficient evidence to conclude a significant impact on the urinary tract from Covid-19 infection. There is supporting evidence that mRNA anti-SARS-CoV-2 vaccines are safe for male gonads. Research to further support these conclusions is required.

Keywords

Covid-19, SARS-Co2, Urinary Tract, Male Subfertility

1. Introduction

At the time this article was written, Corona Virus-19 (Covid-19) cases world-wide almost exceeded half a billion while deaths associated with Covid-19 were above 6,000,000. The aforementioned disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is highly transmissible, which has emerged as a global pandemic since 2020 and is an established threat to public

health and safety [1] [2]. Typical presenting symptoms include malaise, fever, cough, shortness of breath, headache as well as some gastro-intestinal manifestations [3] [4] [5] [6]. SARS-CoV-2 attacks human cells via binding to the extra-cellular part of angiotensin-converting enzyme 2 (ACE2) receptors [7]. ACE2 is a transmembrane protein encoded by a gene located on chromosome X [8]. ACE2 is highly expressed in Sertoli, Leydig cells as well as spermatogonia in human males [9]. There is also evidence that SARS-CoV-2 could be transmitted through the reproductive system [10] [11]. This review aims to summarize the literature on Covid-19 related male genitourinary tract symptoms.

2. Materials and Methods

We reviewed the current literature regarding Covid-19 related, male genitourinary tract symptoms, and signs as well as associated findings by searching the Pubmed database. Although this is not a systematic review, compliance with PRISMA criteria has been maintained wherever possible.

2.1. Research Inclusion Criteria

A spectrum of meta-analyses, systematic reviews, and clinical trial as well as clinical reports has been included.

2.2. Types of Patients

Adolescents that have evidently been through the Covid-19 infection from the beginning of pandemic until March 2022 as well as men that have been vaccinated with the mRNA type of vaccine against SARS-CoV-2.

2.3. Complications

All complications are from the urinary tract as well as the male genital system that required either hospitalisation or review from a specialist. Such complications have been divided into 3 main arms: 1) presenting symptoms; 2) “long-term Covid” complications; 3) the impact of mRNA vaccines on male fertility.

3. Results

3.1. SARS CoV-2 and Urinary Tract

It has been broadly documented that SARS-CoV-2 viral RNA can be detected in human urine, the duration of viral shedding though remains unclear [12]. However, there have only been scarce reports that the main onset of Covid-19 infection’s symptoms could be the excretory urinary tract (**Table 1**). In a publication from Luciani *et al.* [13] three patients had hematuria as a presenting symptom of Covid-19 infection. Sighinolfi *et al.* [14] expressed concern that symptoms of Covid-19 infection may overlap those of urosepsis. In another study, 7/57 male Covid-19 patients had increased urinary frequency as a presenting symptom [15].

The concentration of proinflammatory cytokines in the urine of patients who

Table 1. Primary presenting symptoms are from urinary tract in Covid-19 patients.

Presenting symptom from Urinary Tract	Number of patients	Reference
Hematuria	3	Luciani <i>et al.</i> [13]
Increased urinary frequency	7	Mumm <i>et al.</i> [15]

complain of high urinary frequency appears to be higher than that of controls [16]. On the other hand, acute kidney injury (AKI) turns out to be one of the common pathologies of Covid-19 the extremely high mortality of which should make it an alarming sign for the clinician. The link between AKI and SARS-CoV-2 is believed to be ACE receptors [17] [18] because of C5b-9 deposition through CD68+macrophage mediation [19]. A special subcategory is renal-transplant patients. In a review paper published in 2021 regarding patients before the vaccines era [20], 31.6% of the patients required non-invasive ventilation while mortality rate was 15.4%, both appeared to be higher than that of the general population [21].

As early as May 2020, Mumm *et al.* [15] observed high urinary frequency in 7 males out of 57 hospitalized patients all of which did not have any documented urinary tract infection or AKI. In another report [22], 39 African American Covid-19-positive patients, including seven females and 32 males, developed *de novo* lower urinary symptoms (LUTS) without urinary tract infection per standard urine culture and sensitivity testing. Such observations led to the hypothesis that the lower urinary tract symptoms in Covid-19 positive patients are secondary to the increased concentration of inflammatory cytokines that are excreted in the urine or expressed in the bladder [16] [23]. Respecting the long-term LUTS following the infection, Lamb *et al.* [16] further hypothesized an ongoing chronic inflammation, hence full recovery from Covid-19 was questioned. Those symptoms however appear to have a mild onset; as in a comparison between 5617 Covid-19 patients and 11,225 healthy individuals in Ontario Canada, no group of individuals was in higher need of cystoscopies, specialist consultation or medication for overactive bladder.

3.2. SARS CoV-2 and Male Reproductive System

According to “the human protein atlas” [24] ACE 2 receptors are expressed in testis, epididymis, seminal vesicles and prostate (Table 2). In addition, orchitis has been reported as a consequence of SARS-Co-V-1 infection [25]. Given the fact that SARS-CoV-2 clings to the ACE2 receptors, it could be hypothesized that male reproductive tissue damage could be an event of the Covid-19.

In 12 studies reviewed by Sengupta *et al.* [20] the presence of SARS-CoV-2 has been detected in only 2/12 studies. Li *et al.* [26] detected the virus in 6/38 patients 2 in acute stage, and 4 in recovery stage. Gacci *et al.* [27] found that in a sample of 43 men who have recovered from Covid-19, only one’s semen tested positive for the presence of SARS-CoV-2. Similarly, Ma *et al.* [28] recorded that viral RNA has been detected in 1/12 patients who have moderately been

Table 2. ACE2: location, class, and expression. Source: The human protein atlas Bladder dysfunction and Covid, a class of its own.

Gene name	ACE2
Gene description	Angiotensin I converting enzyme 2
Location	membrane
Class	Enzymes, metabolic proteins, transporters
Protein expression	Proximal renal tubules, intestinal tract, seminal vesicle, epididymis, exocrine pancreas, gallbladder, Sertoli, Leydig cells, trophoblasts. nasal mucosa, bronchus, and fallopian tube

impacted by Covid-19. However, in a large number of other studies, no virus has been detected either in semen [29]-[38] or in testicular cadaveric samples [39].

Men who have recovered from Covid-19 infection appear to have 0.2 ml less sperm volume than healthy individuals [40]. Additionally, the comparison between healthy individuals and men who recovered from Covid-19 infection showed a 16.59×10^6 less sperm concentration for the latter group while sperm motility was decreased by just 1.73% in men that have recovered from Covid-19 compared to healthy individuals. The severity of the infection could play a role as in a study from Holtmann *et al.* [34], patients who underwent a moderate infection, had significantly lower total number of sperm per ejaculate, total number of motile sperm and progressively motile sperm compared to those who underwent a mild infection.

3.3. RNA Vaccines and Sperm Parameters

Unfortunately, toxicity on the male reproductive system has not been evaluated in the clinical trials of both RNA vaccines BNT162b2 (Pfizer-BioNtech) and mRNA-1273 (Moderna) no matter the association of SARS-CoV-2 with decreases in sperm parameters [41]. A small-sample-based, single-center, prospective study at the University of Miami concluded that sperm parameters in men who have received any of the 2 RNA vaccines, actually improved approximately 75 days after the second dose of any of these two vaccines [42]. In the same study, 8/45 men were oligospermic before vaccination, surprisingly 7/8 of these men became “normospermic” after the second dose while parameters like semen volume and sperm motility also significantly improved.

4. Discussion

Covid-19 has been a major public health issue since 2019 requiring millions of hospital admissions and causing millions of deaths. The presence of ACE receptors in the testis and bladder led to the assumption that those two organs might be affected by Covid infection. However, the impact on the male genito-urinary tract, either on a short or long-term basis, is under investigation with no clear outcome. Unfortunately, the great pressure to expand our knowledge in this field has led to many publications, the vast majority of which have been under-

sized, observational, and reporting rather heterogenous outcomes.

Especially for the cases of sperm deregulation during Covid infection, it is known that even a short-term period of fever can induce autophagy, alter sperm DNA integrity, and compromise many sperm parameters [43] [44] irrespective of SARS-CoV-2 infection. Given the fact that the medications used for the treatment of Covid-19 vary a lot, it is reasonable that we could not source any credible papers researching the link between medications for Covid-19 treatment and the impact on male testes.

Additionally, a number of viral infections like HIV, HTLV-1, BK polyomavirus, and CMV can cause lower urinary tract symptoms (LUTS) like nocturia, urgency, and dysuria [16] [45] [46] [47]. The concentration of inflammatory cytokines in the urine of patients with LUTS, like interstitial cystitis, urinary incontinence, and chronic bladder pain syndrome is higher compared to healthy individuals [16] [48]-[53]. It is as well-known that cytokines excreted in urine can harm the bladder urothelium [16] [54] [55]. SARS-CoV-2 infection can result in an abnormal cascade of cytokines production within the frame of irregular immune response, [21] [56] [57] [58] and this has been known as a “cytokine storm syndrome” [54] [59]. Lamb *et al.* [53] reported increased concentrations of cytokines in the urine of patients suffering with Covid-19 associated LUTS and, therefore, hypothesized that this could be the basis of the so-called Covid-19 associated cystitis. However, this mechanism appears to be non-specific for Covid-19 and most importantly does not appear to have a significant long-term clinical impact like the need for cystoscopy or medication on consultation from an expert [23].

5. Conclusion

Although our impression is that Covid-19 primary manifestations from the male genitourinary tract are rare and not disease-specific, while long-term complications are relatively mild and RNA vaccines appear to be safe on the male genital and urinary systems, further research is required to either support or reject these hypotheses.

Consent for Publication

All authors consent for publication.

Author Contributions

All authors contributed in writing, editing, and finalizing the manuscript. Georgios Kallinikas: conceptualization, writing, reviewing, and editing; James N. Tsoporis: writing, reviewing, and editing; Diomidis Kozyrakis: reviewing, and editing; Anastasios Zarkadas: reviewing, and editing; Dimitrios Bozios: reviewing, and editing; Despoina Mitiliniou: reviewing, and editing; Konstantinos Saffioleas: reviewing, and editing; Panagiotis Filios: reviewing, and editing; Athanasios Filios: reviewing, and editing; Evangelos Rodinos: reviewing, and editing;

Vasileios Konstantinopoulos: reviewing, and editing; Gerasimos Vlassopoulos: reviewing, and editing; Ioannis Gerzelis: reviewing, and editing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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