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Impact of COVID-19 on male urogenital health: Success of vaccines

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Throughout 2021, the scientific and medical communities were concentrated on dealing with the acute morbidity and mortality induced by the COVID-19 pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We reviewed the present data for adverse effects of COVID-19 on the different parts of the male urogenital system during the dynamic situation of the COVID-19 pandemic. With the approval of COVID-19 vaccinations, there is a ray of hope at the end of this dark tunnel and a chance to look ahead for the management of long-term consequences in males with urogenital illness. A multidisciplinary investigation of these cases could provide information for establishing and optimizing treatment protocols.

Keywords: COVID-19; Urinary bladder; Erectile dysfunction; Prostate; Angiotensin-converting enzyme 2

Introduction
The COVID-19 pandemic has caused a dramatic loss of human life as a principal public health challenge. In fact, those with chronic urinary disorders might be more susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) than patients without chronic urinary diseases, according to certain theories. Men with comorbidities, such as prostate cancer, benign prostatic hyperplasia (BPH), infertility and erectile dysfunction (ED), are particularly vulnerable to COVID-19.

SARS-CoV-2 infects the cell via connecting to the angiotensin-converting enzyme 2 (ACE2) transmembrane protein via its viral spike proteins and priming the spike protein by transmembrane serine protease 2 (TMPRSS2). TMPRSS2, which facilitates S protein division at the S1/S2 site, serves as a primer for sequential SARS-CoV-2 interaction with ACE2 and cell entrance. ACE2 is the receptor protein of SARS-CoV-2, and TMPRSS2 seems to promote its proliferation and transmission. ACE2 receptor expression in testicular tissues such as spermatogonia, Leydig and Sertoli cells suggests that a testis is likely to be targeted by SARS-CoV-2. Androgen receptor signaling has lately been linked to the severity of COVID-19, clarifying why men are more prone to severe COVID-19 symptoms. The emphasis of this review is on the impact of the COVID-19 pandemic on male urogenital health (Fig. 1). Furthermore, we evaluated the progress made during the pandemic regarding the potential impacts of vaccines on COVID-19-related urogenital disorders.

Prostate cancer
Prostate cancer remains one of the most prevalent cancer types and it is responsible for most of the cancer deaths in men worldwide, especially in developed countries. ACE2 and TMPRSS2 are found abundantly in prostate tissue. Clinical data showed...
infiltration of the prostate by SARS-CoV-2 through ACE2 and TMPRSS2.\textsuperscript{13–16} It is likely that downregulation of ACE2 expression associated with elevated ACE activity leads to increased prostate carcinogenesis.\textsuperscript{17} TMPRSS2 gene fusion changes in the prostate cancer cells over the course of carcinogenesis.\textsuperscript{5,6,18–20} TMPRSS2 is overexpressed in locally advanced and metastatic prostate cancer cases.\textsuperscript{21} Bahmad \textit{et al.} indicated the presence of a change in TMPRSS2 expression and protein transcription, indicating a link between SARS-CoV-2 and prostate cancer.\textsuperscript{22} Anti-androgens and TMPRSS2 inhibitors are indicated as viable treatment options for prostate cancer patients with COVID-19.\textsuperscript{22} It is thought that androgens could contribute to developing severe COVID-19.\textsuperscript{5}

Many researchers have hypothesized that the increased TMPRSS2 expression levels and their part in the pathogenesis of COVID-19 and prostate cancer might be convenient for identifying new therapy modalities for COVID-19 regarding androgen deprivation therapy (ADT) and TMPRSS2 inhibition. Repurposing prostate cancer treatments for COVID-19 has many benefits including the low risk regarding the adverse effects of monotherapy and combination options with different drugs.\textsuperscript{22,23}

Numerous scientists stated their theories on the effects of testosterone regarding the severity of COVID-19.\textsuperscript{24–28} Furthermore, there were beneficial effects of ADT on less severe disease and decreased incidence rate of COVID-19.\textsuperscript{22,29–33} In a cohort study, the difference in 30-day mortality rates between the control and ADT group was statistically insignificant.\textsuperscript{34} In addition, Klein \textit{et al.} have not found any association between the risk of infection and ADT.\textsuperscript{35} A randomized clinical trial has concluded that ADT had no beneficial effect on COVID-19.\textsuperscript{36}

**Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS)**

BPH is among the most common disorders in aged male patients and is identified as an increment in the stromal and epithelial cell count in the prostate gland transition zone.\textsuperscript{37} BPH displays in several forms involving irritative and obstructive LUTS, urinary incontinence and retention.\textsuperscript{38} BPH and LUTS are evaluated by

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\textsuperscript{10} It is likely that downregulation of ACE2 expression associated with elevated ACE activity leads to increased prostate carcinogenesis.\textsuperscript{17}

\textsuperscript{11} TMPRSS2 gene fusion changes in the prostate cancer cells over the course of carcinogenesis.\textsuperscript{5,6,18–20} TMPRSS2 is overexpressed in locally advanced and metastatic prostate cancer cases.\textsuperscript{21}

\textsuperscript{12} Anti-androgens and TMPRSS2 inhibitors are indicated as viable treatment options for prostate cancer patients with COVID-19.\textsuperscript{22}

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\textsuperscript{16} BPH is among the most common disorders in aged male patients and is identified as an increment in the stromal and epithelial cell count in the prostate gland transition zone.\textsuperscript{37} BPH displays in several forms involving irritative and obstructive LUTS, urinary incontinence and retention.\textsuperscript{38} BPH and LUTS are evaluated by
approved international prostate symptom score (IPSS) and serum prostate-specific antigen (PSA) measurement. The first step in the management of BPH is 5-alpha-reductase inhibitors (5-ARIs) with 1-adrenergic receptor (1-AR) antagonists.

Given that inhibition of the ACE2/Ang(1–7)/Mas pathway in SARS-CoV-2 infection increases proinflammatory cellular function and cytokine production, this eventually causes inflammatory responses that lead to worsening of BPH. The previous study demonstrated that LUTS has risen significantly in elderly men after COVID-19 infection but did not observe the same in younger patients. In three patients with the diagnosis of microhematuria, SARS-CoV-2 caused viral cystitis exacerbating local inflammation in urothelial cells which eventually led to irritative LUTS. Nabeeh et al. showed that immunosuppression is associated with increased LUTS, severe pyuria and urinary tract infections. A previous study found increased urinary frequency, as one of the symptoms of COVID-19, in seven out of 57 COVID-19 patients. Marand et al. showed the existence of white and red blood cells in COVID-19 patient urine; in patients who had no previously diagnosed urinary tract disorders, for example urinary retention, incontinence or LUTS. COVID-19 patient urine samples were very rarely contaminated with SARS-CoV-2 viral RN. Fever and repetitive urination must be appraised as significant symptoms that overlap with urosepsis in COVID-19 differential diagnosis.

The increase in IPSS of male COVID-19 patients was significant compared with IPSS before infection. Nabeeh et al. indicated that, among men receiving COVID-19 treatment, 13 patients experienced acute urinary retention and required urethral catheters and 15 patients underwent transurethral resection of the prostate. They also noticed that patients requiring intensive care with the complaint of severe respiratory distress had higher IPSSs than patients hospitalized in the ward. Similarly, a different study revealed that COVID-19 patients with high IPSSs had a significantly higher need for intensive care and mortality rates than those with low IPSSs.

In the management of BPH, 5-ARIs alone or in combination with alpha-blockers are suitable and effective therapeutic alternatives for men with BPH/LUTS. S-ARIs are used to reduce prostate volume for the management of BPH. Drug-target analysis of 5-ARIs revealed androgen signaling as a crucial modulator of ACE2 levels and mitigation of TMPRSS2 expression. Treatment with dutasteride, a 5-ARI, reduced ACE2 levels and recombinant spike-receptor-binding domain. Randomized clinical trials have demonstrated that chronic and acute dutasteride treatment could be protective against severe COVID-19 in male patients. In earlier studies, 5-ARIs could change androgen metabolism in the lungs and potentially affect COVID-19 infection.

1-AR antagonists have been shown to reduce hyperinflammation and sequelae cytokine release syndrome against COVID-19. Additionally, there was a much larger impact size in decreasing mortality in men who received doxazosin and tamsulosin 1-AR antagonists. A previous retrospective analysis of COVID-19 patients showed a significant inverse relationship between hospital stay and 28-day mortality rate after the use of 1-AR antagonists.

These results emphasize the crucial requirement for future-oriented trials testing whether preventive 1-AR antagonists improve outcomes in diseases with hyperinflammation, such as COVID-19. Clinical investigations to test the effectiveness and safety of 1-AR antagonists, such as doxazosin and tamsulosin, to avoid hyperinflammation and reduce mortality in COVID-19 patients would be beneficial.

**Urinary bladder**

The urinary bladder mucosa senses bladder fullness and modulates the functioning of nerves and muscles. Bladder mucosa damage can cause irritative symptoms. ACE2 receptors are mostly found in the bladder. Lamb et al. showed medium expression levels in the bladder. Kaya et al. indicated the storage symptoms as possibly-one of the earlier manifestations of COVID-19. Increased urinary frequency and nocturia with elevated markers of inflammation were detected by Lamb et al. in COVID-19 patients with no previous LUTS. These findings of LUTS are also supported by a survey-based study including 350 patients who recovered from COVID-19. It can be suggested that physicians attending COVID-19 patients should be mindful of any urinary symptoms such as COVID-19-associated cystitis, overactive bladder and other bladder dysfunctions caused by bladder inflammation. Well-planned clinical trials are required for further recommendations.

**Male reproductive function**

Androgens secreted by the Leydig cells are necessary for spermatogenesis and maintenance of secondary sex characteristics. Moreover, testicular macrophage and lymphocyte numbers are regulated by Leydig cells. ACE2 receptors are mostly found in testicular cells, expressed primarily by Leydig, Sertoli cells and spermatogonia. Furthermore, SARS-CoV-2 can affect the physiological process of germ cell environment control, which impedes spermatogenesis by secreting and transporting nutrients and regulatory components. Therefore, the tests might be a potential SARS-CoV-2 target.

When compared with the control group, men infected with SARS-CoV-2 showed elevated serum luteinizing hormone (LH) levels, and the testosterone:LH ratio was found to be reduced. Owing to negative-feedback regulation, decreased testosterone production in SARS-CoV-2-infected males promotes LH release during the early phases of hypogonadism. Two out of five patients with COVID-19 presented symptoms resembling Sertoli-cell-only syndrome.

Previous reports indicated that the spike protein of SARS-CoV-2 was present in the testes, the blood–testis barrier endothelial and seminiferous tubules and sperm in the epididymis in autopsy cases of male COVID-19 patients. However, another study indicated that SARS-CoV-2 genetic material was not present in the testes and semen samples obtained from men with COVID-19. In addition, Yang et al. indicated that, in the testes, SARS-CoV-2 was present only in one case out of ten; however, high viral load in the blood was the reason for the positive result instead of testicular tissue affinity. Therefore, COVID-19 can induce testicular spermatogenic dysfunction by inflammatory or immune reactions. Autopsied testicular samples reported injury of testes consistent with autoimmune orchitis.
and epididymitis. Moreover, elevated proinflammatory cytokine levels [tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6] with declined gene expression (claudin, occludin and connexin-43) and disrupted blood–testis barrier integrity in the testes were all associated with COVID-19 infection. Previous research in 12 postmortem testis samples from male COVID-19 patients found interstitial edema and mild lymphocytic infiltration consistent with orchitis symptoms but no significant changes in spermatogenesis.

Although in earlier research SARS-CoV-2 was considered to exist in the semen, recent studies indicate the absence or infrequent existence of SARS-CoV-2 in the semen of men at acute and convalescent stages of COVID-19. In a cross-sectional clinical study, patients infected with SARS-CoV-2 had considerably diminished sperm concentration and elevated seminal IL-6, monocyte chemoattractant protein-1 and TNF-α when compared with controls. Furthermore, ~40% of men had oligoazoospermia, and 60% had higher leucocytes. A case-controlled longitudinal research study by Maleki et al. reported a noteworthy reduction in sperm concentration, semen volume and progressive motility with altered morphology. These changes were correlated with enhanced ACE2 enzymatic activity in semen, increased seminal inflammation, oxidative stress and raised seminal apoptotic marker activity compared with controls. Furthermore, SARS-CoV-2 could lead to sperm DNA fragmentation by inducing cellular oxidative stress, which leads to reduced embryo development, implantation rate and an increase in miscarriage rate. Previous case-control studies demonstrated a significant reduction in semen parameters such as sperm concentration, total sperm count, progressive motility and total motility. As per the result, disease severity correlated with sperm concentration and men had reduced total sperm counts a long time after recovery. Segars et al. demonstrated reduced sperm counts and motility for 72–90 days following the infection. Similarly, Gacci et al. indicated oligo-azoospermia in sexually active men recovered from COVID-19 and a 76% increase in IL-6 levels in the semen of the patients. This situation was correlated with disease severity and exceeded the average population rates. Furthermore, Ma et al. reported that 67% of men with COVID-19 displayed normal sperm parameters and low sperm DNA fragmentation, whereas 33% of men displayed decreased sperm motility with higher sperm DNA fragmentation. However, previous clinical studies indicated total sperm count, total motility and morphology within the normal range in men with acute or convalescent COVID-19.

The effects of COVID-19 infections can be related to orchitis accompanied by testicular ultrasonography changes, a decline in testosterone and an increase in the inflammatory response. The influence of SARS-CoV-2 on spermatogenesis and male fertility has extended a problematic matter to provide biological evidence for clinicians. According to the results mentioned above, it can be suggested that the clinical assessment of the male reproductive tract including seminal parameters and reproductive hormones is necessary for men who have had COVID-19 before fertility treatment.

| TABLE 1 | Disrupting effects of SARS-CoV-2 on the physiological processes in testes, Leydig cells, spermatogonia, semen and testosterone. |
| -------- | ---------------------------------------------------------------------------------------------------------------------- |
| **Methods** | **Results and conclusions** | **Refs.** |
| Sertoli cells | Autopsies of COVID-19-positive (n = 10) and -negative men (n = 10) | Changes for testicular cells and decreased number of Sertoli cells resulted in impaired spermatogenesis | 77 |
| Sertoli cells and Leydig cells | The testes (n = 12), RT-PCR, light and electron microscopy | Significant seminiferous tubular injury, decreased Leydig cells, mild lymphocytic inflammation | 70 |
| Sertoli and Leydig cells | The testes (n = 11), RT-PCR, light and electron microscopy, IHC | A combination of orchitis, vascular changes, basal membrane thickening, Leydig and Sertoli cell scarcity, and reduced spermatogenesis | 127 |
| Spermatogonia | The testes, epididymis and the semen specimen (n = 6), TUNEL assay and IHC | Impairment of spermatogenesis and autoimmune orchitis in COVID-19 patients Interstitial edema, congestion, red blood cell exudation in testes and epididymides | 76 |
| Spermatogonia | The testes COVID-19-positive (n = 6) and -negative (n = 3), immunofluorescence, TEM | A converse connotation between ACE-2 receptor levels and spermatogenesis, supports a possible mechanism between COVID-19 and infertility | 128 |
| Spermatogonia | Semen samples in patients with mild or moderate COVID-19 were taken before and after COVID-19 (n = 69) | In short-term results, COVID-19 has negative effects on spermatogenesis sperm parameters in the moderate symptomatic group | 129 |
| Semen | Semen (n = 23) | Sperm parameters of the patients were within normal ranges | 89 |
| Semen and testosterone | The testicles of patients who died of COVID-19 (n = 20); healthy controls (n = 44) and cases (n = 44) | COVID-19 affects hormone levels such as decrease in testosterone levels and enhanced luteinizing hormone and follicle-stimulating hormone as well as sperm quality | 130 |
| Testosterone | Serum follicle-stimulating hormone, luteinizing hormone, sex-hormone-binding globulin and total testosterone levels (n = 81) | A high rate of hypogonadism and oligoazoospermia and impaired progressive motility were found, especially secondary hypogonadism, and about half of the patients had hypogonadism in the 6-month follow-up | 131 |
Erectile dysfunction

COVID-19 induces deleterious effects on erectile function and men’s health involving mental, biological and healthcare access mechanisms\(^9\) (Fig. 3). COVID-19 infection can exacerbate ED by causing widespread corporeal endothelial dysfunction even long after the initial infection. The onset or the development of subclinical to advanced ED in COVID-19 patients can be due to non-symptomatic hypogonadism, hampered pulmonary hemodynamics, endothelial dysfunction and profound psychological burden (Fig. 3). ED has been described among the possible consequences for COVID-19 for survivors.

The pandemic caused deterioration in sexual function in some adult men. The risk factors include raised depression, anxiety and reduced frequency of sexual life during the COVID-19 pandemic.\(^{92}\) Pre-existing hypertension, obesity, diabetes and a cardiovascular disease history increase the prevalence and severity of ED and COVID-19.\(^{93}\) Furthermore, ED is a clinical marker and predictor of chronic systemic, particularly cardiovascular, disease and the presence of ED can be correlated with the increased risk of contracting COVID-19. Moreover, it has been emphasized that COVID-19 can aggravate former cardiovascular disorders by doing so, contributing to the progression of ED.
In a preliminary study, COVID-19 was associated with ED independently from well-known confounding factors like age and body-mass-index. In a previous cross-sectional retrospective study, male COVID-19 patients were shown to be 3.3-times more likely to develop ED. ED can also be seen in healthy individuals as a complication after recovery from severe COVID-19. Baseline erectile function and severity of COVID-19 are the strongest predictors of ED among these patients.

Because the sense of taste and, particularly, smell are crucial for normal sexual activity, anosmia and ageusia during COVID-19 also contribute to the onset of ED. These symptoms are seen in the initial phase of COVID-19. Anosmia is a characteristic concern on the sexual health of men. The release of odor can be understood as a favorable health trait leading to attraction and copulation by either the male or female. Ageusia is another main trigger on the sexual health of the male. Taste is one of the senses which serves individuals to experience intimacy better (Fig. 3).

When compared with couples that include normozoospermic males, azoospermia causes a decrease in the quality of sexual function and a significant level of psychological distress. In fact, healthcare professionals are exposed to psychological trauma, and their sexual welfare is possibly negatively affected during the COVID-19 outbreak. In addition, ED prevalence among healthcare professionals under high COVID-19 risk conditions was greater than in control cohorts. To minimize the social–environmental effects of COVID-19, adequate psychological support and development of quality of life, with special attention to sexual health, are essential. Male sexual frequency has surged during the COVID-19 pandemic, according to a study by Chen et al., and mental health is a major issue that should be addressed in the development of male sexual health. In a case study, researchers reported that a COVID-19 patient experienced ED for ~1 week, followed by recurring spontaneous ejaculation.

COVID-19 was associated with decreased testosterone levels in most of the participants, suggesting the presence of hypogonadism. Low testosterone levels suppress nitric oxide (NO) synthase expression and also induce vascular smooth muscle cell atrophy. An increasing amount of research substantiated the hypothesis that SARS-CoV-2 targets the endothelium. Most importantly, it is known that ACE2 is expressed by the endothelium, and is the protein which the virus uses to access host cells. It has also been hypothesized that pulmonary fibrosis reduces the availability of NO in the corpus cavernosum and, by doing so, decreases the oxygen saturation which leads to the development of ED in COVID-19 patients. It is also known that men with cardiovascular risk factors, for example diabetes, usually respond poorly to treatment with phosphodiesterase-5 (PDE5) inhibitors. As a result, the ACE2/Ang(1–7)/Mas pathway could be targeted to effectively treat ED in COVID-19 patients. Hospitalized male COVID-19 patients usually have elevated levels of IL-6, which most probably contributes to the development of ED. The cytokine storm in some COVID-19 patients could lead to vascular endothelial cell apoptosis in a reactive oxygen species (ROS)-dependent manner, which could also lead to the development of ED. Higher levels of TNF-α, IL-6 and IL-1β are indicators of a greater risk of vascular dysfunction in hypogonadal patients. Therefore, hypogonadism and low testosterone levels might trigger psychological elements that contribute to the initiation of ED.

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**FIGURE 3**
The effects of SARS-CoV-2 on male erectile function. COVID-19 has a harmful impact on men’s health including mental, biological, hormonal and other healthcare access mechanisms resulting in sexual dysfunction.
Long after the onset of infection, Kresch et al. revealed the existence of the SARS-CoV-2 in the penis.\textsuperscript{106, 116} ED can partly be regarded as an indicator of the situation of the cardiovascular system in COVID-19 patients. After recovery from COVID-19, ED is recognized as a predictive indicator of general health in males and can be utilized as a first-line evaluation tool for pulmonary and cardiovascular problems.\textsuperscript{117} A median of 174 days after COVID-19 recovery, erectile function and psychological distress improved to comparable levels with controls.\textsuperscript{118} In a case study, researchers reported that a COVID-19 patient experienced ED for \textless{}1 week, followed by recurring spontaneous ejaculation.\textsuperscript{102} COVID-19 infection can cause Peyronie’s disease as a potential sequela and physicians should question the patients with Peyronie’s disease about their history of COVID-19 infection.\textsuperscript{119}

COVID-19 and ED patients might benefit from PDE5 inhibitor treatment. Sales data of PDE5 inhibitors demonstrate a significant increase during the pandemic.\textsuperscript{120} As with routine management of ED patients, PDE5 inhibitors should be actively utilized and studied in COVID-19 patients who present with sexual dysfunction.\textsuperscript{117}

During the pandemic, there was a significant increase in the number of people who applied to andrology clinics, and the underlying issues are usually of multifactorial etiology including psychogenic factors.\textsuperscript{121} The direct mechanistic effect of COVID-19 on male erectile performance must be investigated by the evaluation with color Doppler ultrasound of the penis and hypothalamic–pituitary axis. The duration of COVID-19-induced ED is another topic of research which needs studies with adequate follow-up.

**COVID-19 vaccines**

An extremely low number of cases were reported with urological symptoms after vaccination for COVID-19.\textsuperscript{122} Vaccination introduces antigenic parts (i.e., SARS-CoV-2 spike protein) to the system that might inhibit the proliferation of prostate cancer cells and serve as a novel benefit of the vaccines. However, the potential benefit of prostate cancer inhibition by COVID-19 vaccines requires extensive in vivo studies before further conclusions can be drawn.\textsuperscript{124}

A Vaccine Adverse Event Reporting System (VAERS) should continuously monitor for urological adverse effects because different populations are included among the candidates for vaccination.\textsuperscript{124} Recent data confirm the urological safety of Pfizer–BioNTech and Moderna vaccines and reassure and help providers counsel patients.\textsuperscript{124} Scarcely amounts of data are available on the effects of COVID-19 vaccination in terms of semen quality.\textsuperscript{125} No significant changes in sperm parameters were seen in 75 fertile men 1–2 months after receiving the second dose of Pfizer’s COVID-19 vaccine, according to Lifshitz and colleagues.\textsuperscript{126}

**Concluding remarks and future perspectives**

Male COVID-19 patients usually develop more-severe disease and mortality rates are higher in men, probably owing to gender-specific alterations in immunological response, besides other factors. COVID-19 has been associated with detrimental effects on male reproductive function including impaired fertility and sexual function, with prostate pathologies. Special attention should be given, and counseling should be provided, for male patients of reproductive age as COVID-19 causes adverse effects on male sexual function.

Because ACE2-positive cells are more abundant in the testis than in the lung, the testis might be an organ with a high risk of infection. The kidney, epididymis, prostate and seminal vesicles all have a high level of TMPRSS2 expression. In the testes, TMPRSS2 is particularly expressed in spermatogonia and spermatids rather than in other testicular cell types. By contrast, ACE2 and TMPRSS2 are the common proteins usually examined for the SARS-CoV-2 infection risk. However, other co-receptors might also promote the entry of the virus into the cells. This is supported by the fact that ACE2 is expressed in \textless{}0.1 % of pulmonary cells, although the lung is the most susceptible organ to infection by SARS-CoV-2. Therefore, studies are needed on the expression of other viral receptors in testicular tissue so that the SARS-CoV-2 tropism in the human reproductive system is better understood.

Viral susceptibility of other organs should also be studied for a clearer understanding of pathogenetic mechanisms. The restricted availability of medical staff and access to health services during the pandemic will probably delay the treatment of urological cancers and negatively influence the disease outcome of many cancer patients.

Sexual and overall health should be viewed as a priority when managing patients in this population. Whereas lifestyle changes might even affect the sexual life and function of healthy men, the pandemic caused extremely dramatic changes in the daily life of most men via the disease-prevention measures, including restrictions on transport and social gatherings, social distancing, among others.

ED is a clinical surrogate for a ‘dysfunctional’ phenotype, which is often associated with early-age cardiovascular events. This pre-existing accumulation of conditions frequently present in subjects with ED could increase the susceptibility to contracting COVID-19. Developing safe and efficacious drugs is warranted for male urogenital disorders in the clinical setting. Psychological health is in direct association with sexual wellbeing. Psychological distress is a universal component of the COVID-19 disease course. Owing to the lockdown of large populations, the limitation of personal freedom can induce catastrophic losses in personal relationships, recreation, social support and even household income. By contrast, lockdowns and social distancing might improve the sex lives of couples who live together. Future research could be helpful for interventions designed to help couples maintain sexual intimacy when they are not forced to spend more time together. A growing body of evidence recently revealed that SARS-CoV-2 is also a neurotropic virus. Thus, it could affect male sexual function via the development of neurological disorders. Further investigations are needed to better explore this intriguing field.

To fulfill this goal, further advances will be required to enable urogenital safety science to keep pace with the everchanging landscape of novel therapeutic and vaccine paradigms. Interventions for promoting male sexual wellbeing during the COVID-19 pandemic should probably also focus on the mental health of the individuals.
Oral PDE5 inhibitors have several off-label implications owing to their anti-inflammatory, antioxidant and antiapoptotic properties as well as their regulation of the immune response. Based on these properties, oral PDE5 inhibitors could be repurposed for adjudvant use in the protocols for treating COVID-19 manifestations. Finally, a meticulous investigation of testosterone deficiency in COVID-19 patients is recommended owing to its possible association with reproductive problems. This could be due to the high viral blood load in the blood in acute phase, which might enable more virus to reach the testes and pass through the blood-testis barrier, mediated by local and/or systemic inflammation.

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