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Post-COVID-19 erectile dysfunction: A review

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Abstract
Purpose: This study was conducted to define the association between ED and COVID-19.
Data sources: Through a search and review of the Medline databases (Pub Med and Medscape) and male genitourinary system, erectile dysfunction information through 2023, and Coronavirus disease 2019.
Study selection: A comprehensive examination of the erectile dysfunction and male genitourinary system information available through 2023 was conducted using the Medline databases (Pub Med and Medscape) and Coronavirus disease 2019.
Data extraction: Studies that failed to meet the predetermined inclusion criteria were omitted. In evaluating the quality of a study, factors such as obtaining ethical approval, defining eligibility criteria, implementing appropriate controls, providing adequate information, and establishing well-defined assessment measures were considered. Using a data collection form, we independently extracted data from each eligible study that pertained to the outcomes of interest to us.
Conclusion: COVID-19, a coronavirus disease pandemic, has the potential to negatively impact the sexual and reproductive health of males and females alike. This may occur via systemic, psychological, or immunological effects.

Keywords: Coronavirus disease 2019, COVID-19, male genitourinary system, erectile dysfunction

Introduction
On 11 March 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused coronavirus disease 2019 (COVID-19), which was subsequently designated a pandemic, emerged as a significant global health concern [1].
Approximately 760 million individuals worldwide were reported to have contracted SARS-CoV-2, with 6.6 million fatalities confirmed [2].
It is currently understood that COVID-19 can impact numerous tissues and organs. By binding to the angiotensin-converting enzyme 2 (ACE-2) receptors on the host via spike proteins on its surface, the virus is capable of invading cells. Prior to this binding occurring, transmembrane serine protease 2 of the host cell must activate spike proteins (TMPRSS2). It has been reported that tissues with overexpressed TMPRSS2 enzyme and ACE-2 receptor are more severely affected by COVID-19 [3].
Covid-19 may induce severe endothelial dysfunction as a result of the overexpression of these two proteins in endothelial cells. Endothelial cells are abundant in the genitourinary tissues, as evidenced by their substantial blood supply; thus, these tissues are prospective targets for SARS-CoV-2 [4].
Defining erectile dysfunction (ED) as the incapacity to attain or sustain an erection of adequate strength to facilitate sexual activity. Occurrences of ED may be organic, psychogenic, or a combination of both [5].
The relationship between COVID-19 and endothelial dysfunction-associated ED has been the subject of some studies [6]. Furthermore, the expression of (ACE-2) receptors on Leyding cells provides evidence that testicular damage may transpire subsequent to COVID-19 infection, which induces hypogonadism and ultimately results in ED [7].
Another study explains how the relationship between ED and COVID-19 in critically ill patients depends on the disease mechanism. Patients inflicted with COVID-19 experience immunosuppression and hyper-inflammation, which results in an overabundance of cytokines known as a "Cytokine Storm".

This can ultimately cause organ dysfunction and disseminated intravascular coagulation (DIC) [8].
Finally, In COVID-19, there is increased rates of post-traumatic stress disorder (PTSD), depression and anxiety are expected in the general population, and even more in COVID-19 survivors, following the pandemic with the resulting negative effects on sexual health and couple dynamics [9].
The objective of this study is to determine the frequency of ED following COVID-19 recovery, to examine the changes in erectile function at three and six months after recovery, and to identify potential aetiologies for this association.

Materials and methods

Data sources: By searching and reviewing Medline databases (Pub Med and Medscape) and native arterial-venous fistula creation failure available till 2023.

Study selection: All studies were independently assessed for inclusion. They were included if they fulfilled the following criteria: Published in English language, Published in peer-reviewed journals, discuss the association between ED and COVID-19**.**

Data extraction: Studies that failed to meet the predetermined inclusion criteria were omitted. An element of the study quality assessment was the acquisition of ethical approval, eligibility criteria specified, appropriate controls and adequate information and defined assessment measures. Data from each eligible study were independently abstracted using a data collection form to capture information related to our concerned study outcomes.

Review of literature

Coronavirus Disease (2019): Coronaviruses pose a significant threat to both humans and animals. A novel coronavirus was identified as the causative agent of a cluster of pneumonia cases in Wuhan, Hubei Province, China, by the end of 2019. It spread at an accelerated rate, leading to a pandemic that ravaged China before reaching a global scale. The World Health Organization assigned the designation COVID-19, an abbreviation for coronavirus disease 2019, to the disease in February 2020. Prior to its current designation as SARS-CoV-2, the virus responsible for COVID-19 was known as 2019-nCoV (severe acute respiratory syndrome coronavirus 2 [10].

Virology: Coronaviruses are positive sense single-stranded RNA viruses with an envelope and a diameter of 80–220 nm. Coronavirus derives its name from the crown-shaped, 20-nanometer-long spikes on the envelope that, when observed through electron microscopy, resemble the corona of the sun. Diseases can be caused by the virus in both humans and animals. It possesses the most extensive genome among the RNA viruses presently recognized [11].
Coronaviruses are taxa belonging to the order Nidovirales and the subfamily Coronavirinae of the family Coronaviridae. The four genera comprising this subfamily are betacoronavirus, alphacoronavirus, gammacoronavirus, and deltacoronavirus. As of now, there are six coronaviruses identified as causative agents of human diseases. SARS-CoV and MERS-CoV are two of them that caused human coronavirus epidemics [12].
A nucleoprotein (N) encases the RNA genome in a coiled tubular structure within the coronavirus particle. This helical nucleocapsid is surrounded by the viral envelope (E). There are two to three structural proteins that comprise the viral envelope. Composed of matrix protein (M) and envelope. Envelop-anchored spike structural protein (S) is the target of neutralising antibodies. An abundance of hemagglutinin esterase has been identified in beta-coronaviruses [12].
Coronaviruses possess five essential genes, four of which code for structural proteins (N, E, M, S) and two for transcription and viral replication (RNA dependent RNA polymerase, RdRp). The structure of the genome is 5'-RdRp-S-E-M-N-3'. This coronavirus gene sequence is exceptionally conserved [12]. According to the sequencing of the entire genome, SARS-CoV-2 is an entirely new betacoronavirus that is separate from SARS-CoV [13].
SARS-nucleotide CoV-2's sequence exhibited 79.0% and 51.8% similarity to that of SARS-CoV and MERS-CoV, respectively. Furthermore, it maintains a close relationship with bat-origin SARS-like coronavirus (bat-SL-CoVZC45), sharing 87.6% to 89.9% identity [14, 15].
Upon its initial emergence, the virus was designated as 2019-novel coronavirus (2019-nCoV). However, on February 11, 2020, the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses adopted the name severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) after conducting a phylogenetic analysis [16].

Transmission: The transmission risk is not fully comprehended. Epidemiologic investigations conducted in Wuhan during the onset of the outbreak established an initial correlation with a seafood market specializing in the sale of live animals. This market was frequented or worked at by the majority of patients, and it was subsequently disinfected. As the outbreak progressed, however, person-to-person contact emerged as the predominant mode of transmission [17].

Diagnosis of COVID-19: The determination to conduct COVID-19 testing ought to be linked to the evaluation of the probability of infection, taking into consideration clinical and epidemiological factors [18]. Individuals who have had close contact with a patient who has laboratory-confirmed COVID-19 within 14 days of the onset of symptoms, or who have a history of travel from affected geographic areas within 14 days of the onset of symptoms, are considered epidemiological factors [19].
For symptomatic and asymptomatic individuals, the U.S. CDC advises using viral tests to diagnose acute infections in order to direct contact tracing, treatment options, and isolation requirements. Additionally, those who are at a high risk of repeated exposure, including healthcare workers and first responders, should undergo virological testing [19].
The assessment of symptomatic patients encompasses several criteria, namely the manifestation of clinical symptoms, recent travel to countries prone to COVID-19, exposure to such patients, and the ability to identify the resolution of the disease. A known recent exposure to COVID-19 patients, an unknown exposure to COVID-19 patients, olfactory dysfunction, loss of smell and/or taste, transplant donors, and recipients are all criteria for testing asymptomatic patients [19].

Impact of COVID-19 on male genitourinary system

Kidney: Cheng *et al.* [20] have observed renal dysfunction in COVID-19 patients. Initially, a computed tomography (CT) scan of the kidney identified inflammation and edoema as indicated by a decrease in density.

In a study of 59 patients with COVID-19 and kidney impairment, Li *et al.* [21] found that proteinuria was present in 63% of the patients, increased plasma creatinine levels were detected in 19% of the patients, and elevated urea nitrogen levels were detected in 27% of the patients.

In another study, 178 patients with COVID-19 from Wuhan Union Hospital participated. Five out of 178 patients (2.8%) had elevated BUN levels, while none of the patients (0% of the total) exhibited elevated Scr. Out of a total of 83 patients who were hospitalised and did not have a history of renal impairment, 45(54.2%) presented with urinalysis abnormalities, including proteinuria, leukocyturia, and hematuria. Urinalysis was superior to blood chemistry tests in identifying potential renal impairment in patients with COVID-19, and it could also predict the severity of the disease, according to the findings [22].

Furthermore, an eGFR retrospective analysis encompassing 85 patients was performed in Wuhan. 23 patients out of 85 (Or 27.06%) presented with acute renal failure (ARF). Patients who were elderly or had comorbidities such as hypertension and heart failure developed ARF more readily [23].

The incidence of AKI in patients inflicted with COVID-19 is extremely variable. AKI has been identified in as many as 27% of patients [23].

29% of 52 patients with severe COVID-19 pneumonia had complications associated with AKI, according to Yang *et al.* [24] Furthermore, Huang *et al.* [25] reported that three out of forty-one patients (7 percent) developed AKI.

A comprehensive study comprising 6395 patients inflicted with COVID-19 revealed that the incidence of AKI was 4.3%. AKI was correlated with the severity of pneumonia; the severe group had a significantly higher comorbidity of chronic kidney disease (CKD) and complications of AKI than the no severe group. In addition, the levels of Scr, the ratio of abnormal Scr, BUN, and the ratio of abnormal BUN were significantly increased in the severe group relative to the control group [26].

Pei *et al.* [27] discovered that severe AKI was associated with a high mortality rate among COVID-19 patients, with 11.2% (28/251) dying in the AKI group compared to 1.2% (1/82) in the control group. In the study by Zhou *et al.* [28] which included 191 COVID-19 patients, 32 patients perished out of 33 confirmed COVID-19 patients who subsequently developed AKI.

Bladder: A systematic review was conducted by Chan *et al.* [29] to investigate the detection of SARS-CoV-2 viral RNA in urine. Analyzing a collection of 21 studies involving 3,764 SARS-CoV-2 patients, it was discovered that 5.74 percent of patients had positive viral RNA in urine samples, although the duration of viral shed in urine remained unknown.

In a similar systematic review, Kashi *et al.* [30] examined urinary samples from 533 SARS-CoV-2 patients. The crude overall detection rate of SARS-CoV-2 in urinary samples was 4.5 percent, while the viral shed-ding frequency was estimated to be 1.18 percent. The incidence of urinary shedding was highest among patients afflicted with moderate to severe illness.

Prostate: Controversy surrounds the pathophysiology of SARS-CoV-2 infection of prostatic tissue. Pecoraro *et al.* [31] established that their ten patients with a COVID-19 infection who underwent prostate biopsy but prior to prostatectomy did not exhibit any inflammation of the prostate caused by SARS-CoV-2.

However, Connely *et al.* [32] acknowledged the significant limitations of this study, including its small sample size, absence of follow-up, and selection bias. Furthermore, it is worth noting that each patient had prostate cancer, which could have modified the microenvironment of prostatic tissue and thus may not accurately reflect the response of the prostate gland to SARS-CoV-2 infection.

In their study, Chakravarty *et al.* [33] discovered that patients who were diagnosed with SARS-CoV-2 in addition to prostate cancer exhibited elevated rates of hospitalisation and mortality in comparison to patients with other solid tumours. Patients who were diagnosed with prostate cancer and SARS-CoV-2 exhibited elevated rates of hospitalisation in comparison to those who were afflicted with other genitourinary cancers, including those of the bladder and kidney. This study brought attention to the susceptibility of the prostate gland to SARS-CoV-2.

Testes: Due to the virus's notable affinity for the TMPRSS2 Receptor, there is conjecture regarding its potential for infiltration into testicular tissue [34]. The testicular architecture of twelve SARS-CoV-2-positive patients was found to have been severely compromised upon autopsy; nevertheless, only one patient's testicular tissue contained a detectable amount of the virus. Furthermore, the presence of detectable virus in multiple organs of this patient is suggestive of a substantial viral load [35].

An additional autopsy examination of six individuals revealed an accumulation of apoptotic cells in the seminiferous tubules, accompanied by the presence of T-lymphocytes and macrophages in the interstitium [36]. An additional autopsy examination of five men infected with SARS-CoV-2 identified pathogens within the lumen of seminiferous tubules. Testicular tissue electron microscopy revealed the presence of SARS-CoV-2 in one living biopsy and one deceased biopsy. Three out of every six SARS-CoV-2 patients in this study had Tuberculous involvement [37].

Impact of COVID-19 vaccination on genitourinary system

COVID-19 vaccination and LUTs: In their study, Valera-Rubio *et al.* [38] examined the adverse effects (AEs) associated with COVID-19 vaccination through the use of an online questionnaire. The researchers found that urinary urgency was the most prevalent urological AE, occurring at rates of 0.75 percent and 1.16 percent, respectively, after receiving the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) and the COVID-19 mRNA-1273 vaccine (Moderna). Urinary frequency was the second most frequently reported adverse urological effect, occurring at rates of 0.37 and 0.69 percent, respectively, after administration of the BNT162b2 mRNA and mRNA-1273 vaccines. Additional adverse effects associated with the urinary system comprised nocturia and urinary incontinence.

Certain urinary proteins associated with regulated exocytosis and immune response changed significantly before and after COVID-19 vaccination, as demonstrated by Pan *et al*. [39]. After vaccination, urinary protein can reveal the immune response of the body two to four hours later.
Chen *et al*. [40] examined the adverse effects of the first dose of the coronavirus disease 2019 (COVID-19) vaccine on storage lower urinary tract symptoms (LUTS) prior to and subsequent to vaccination, as well as the correlation between pre-vaccinated overactive bladder (OAB) and the exacerbation of storage LUTS after COVID-19 vaccination. OAB was diagnosed utilizing OABSS that had been pre-vaccinated. The assessment of storage LUTS deterioration was conducted using the elevated OABSS score subsequent to vaccination. Up to 13.4% of 889 subjects developed worsened storage LUTS subsequent to vaccination.

Haematuria after vaccination: A number of instances of macroscopic haematuria were documented in patients who had previously undergone biopsy-confirmed IgA nephropathy subsequent to receiving the COVID-19 vaccines. Gross haematuria manifested in patients hours or days following vaccination, and it typically resolved with supportive care alone [41].

COVID-19 vaccination and fertility: Diaz *et al*. [42] investigated public concerns regarding vaccine side effects using Google Trends and discovered a substantial surge in queries pertaining to COVID-19 and fertility. This finding implies that a primary factor contributing to vaccine hesitancy was apprehension regarding the potential consequences on fertility.
Thankfully, a recent investigation conducted by Gonzalez *et al*. [43] compared the semen parameters of 45 males three months prior to and subsequent to vaccination. Importantly, after vaccination, neither sperm concentration nor total motile sperm count decreased, and no males developed azoospermia.
The aforementioned data offer substantial assurance concerning the safety of COVID-19 vaccination in relation to prospective pregnancy. Furthermore, as previously mentioned, infection with COVID-19 may be linked to decreased fertility; therefore, COVID-19 vaccination aids in the maintenance of reproductive function by preventing COVID-19 infection. Vaccination might potentially elicit additional protective effects within the genitourinary tract. An extensive retrospective study encompassing more than 10 million men provided evidence that vaccinated males had a reduced likelihood of developing orchitis and/or epididymitis in comparison to their unvaccinated counterparts. While further extensive research is required, the available evidence indicates that the COVID-19 vaccine is a secure and efficacious method of averting infection, as well as safeguarding fertility and sexual health [44].

Erectile dysfunction and COVID-19: ED, commonly known as "impotence," is the inability to attain or maintain an erection of sufficient strength to enable sexual activity. Irregular sperm count is present in one in every two men aged 40 and older. Additional forms of male sexual dysfunction may encompass challenges pertaining to libido, orgasm, or ejaculation [45].

Classification: The most widely employed classification system for ED includes organic, psychogenic, and mixed etiologies. This system has the official endorsement of the International Society for Impotence Research. Ninety percent of cases of ED were attributed to psychogenic factors in the 1950s. Current consensus among authors is that mixed ED is the most prevalent [46].

Mechanisms of post-COVID-19 ED: COVID-19 has the potential to influence penile erection-related physiology via neurogenic, vasculogenic, and endocrine mechanisms. Among the potential mechanisms implicated in the emergence of ED in COVID-19 survivors, impaired pulmonary hemodynamics, endothelial dysfunction, and subclinical hypogonadism have all been identified [47].

1. Vascular mechanisms and endothelial dysfunction
Proper vascular structure is critical for erectile function. The vascular endothelium, which comprises specialised cells lining the inner surfaces of blood vessels, spaces such as the sinusoidal surface, and tissues including the corpus cavernosum of the penis, is compromised by SARS-COV-2. SARS-COV-2 gains access to host cells via the angiotensin-converting enzyme 2 (ACE2) protein, which is expressed by the endothelium [48].
Additionally, Sansone *et al*. [47] assessed the probability of an individual reporting a prior infection with COVID-19 subsequent to receiving a diagnosis of ED. With a 5.27 odds ratio, logistic regression models adjusting for age and BMI revealed a significant association between ED and COVID-19. The evaluation of the hypothalamic-pituitary-testicular axis and penile color-doppler ultrasound may provide information regarding the degree to which COVID-19 has compromised vascular function and erectile function.
COVID-19 may also influence the prevalence and severity of ED via the virus's indirect effect on the cardiovascular system of men and the indirect effects of COVID-19 treatments. An instance of acute cardiac injury caused by COVID-19 may result in a reduction in blood flow to the genitalia. Also considered to be at risk for ED [49] are COVID-19 patients admitted to the intensive care unit who are prescribed thiazide-type diuretics, aldosterone receptor blockers, B-adrenergic receptor blockers, or ACE inhibitors for blood pressure control [49].

2. Neurological mechanisms
Research has shown that individuals inflicted with COVID-19 frequently exhibit neurologic symptoms [50]. The majority of COVID-19 patients exhibit disorders affecting the central and peripheral nervous systems; however, severe cases are more prone to experiencing stroke, ataxia, seizures, and a diminished level of consciousness [51].
Potential adverse effects of the neurological effects observed in certain cases of COVID-19 on ED have been documented [49]. Neurogenic ED comprises a substantial subset of ED, comprising approximately 10 to 19 percent of all cases [52].

3. Endocrinal mechanisms and hypogonadism
COVID-19 has the potential to influence ED via endocrine mechanisms. Hyperinflammation induced by the same inflammatory cytokines that have been linked to the clinical

progression of sexual dysfunction is a characteristic feature of COVID-19 (tumor necrosis factor [TNF]-a, interleukin [IL]-6 and IL-1b) [47].

4. The psychological impact of COVID-19 on ED

Amidst the COVID-19 pandemic, it is critical to consider the impact of increased stress, anxiety, and physical health on men with ED [53]. Post-pandemic increases are anticipated in the prevalence of depression, anxiety, and post-traumatic stress disorder (PTSD) among the general population, and among COVID-19 survivors in particular. [47].

An investigation examining the correlation between depression and sexual activity among 544 hospital employees and acquaintances in Italy during the COVID-19 lockdown examined data collected via the Beck Depression Inventory, FSFI (Female sexual function index), and IIEF-15. The levels of sexual satisfaction were assessed using the intercourse satisfaction (IS) and overall satisfaction (OS) domains of the IIEF-15. Unsatisfactory levels were characterized by a cut-off score of 12.5 or less, which was an arbitrary sum of the IIEF-IS and IIEF-OS domains. In addition, the sexual desire (SD) domain of the IIEF was documented, and a cut-off score of ≤5 was arbitrarily employed to delineate low sexual desire. The IIEF-Erectile Function score had a median of 10 (interquartile range: 3–11), while the score for IIEF-Orgasmic Function was 3. (3, 5). The IIEF-Sexual Desire score was 4, the IIEF-Overall Satisfaction score was 5, and the IIEF-Intercourse Satisfaction score was 5 (0, 7). (3, 5) [54].

Treatment of post-COVID-19 ED

PDE5 inhibitors are among the most efficacious treatments for ED. Since receiving FDA approval in 2013, Tadalafil and Sildenafil have been widely used to treat ED [55]. In theory, the potential benefits of daily tadalafil administration include the potential to enhance vascular endothelial function and mitigate fibrosis. Hence, the administration of this medication has the potential to ameliorate both pulmonary fibrosis and the ED induced by COVID-19 [56].

Shamohammadi *et al*. [57] confirmed that ED caused by COVID-19 can be ameliorated with daily administration of 5 mg tadalafil. Sexual function parameters of patients in the intervention group treated with tadalafil improved significantly more than those in the control group, as measured by the complete IIEF questionnaire.

Isidori *et al*. [58] have suggested that PDE5 inhibitors, specifically sildenafil, could function as modulators of the NO-cGMP-PDE5 axis. This is because PDE5 is primarily expressed in the lungs, which are the organs most severely impacted by COVID-19. Therefore, inhibiting it could potentially decrease the infiltration of pro-inflammatory cytokines and alveolar hemorrhage-necrosis. Furthermore, sildenafil and tadalafil prevent clotting and thrombotic complications by inhibiting the transition of endothelial and smooth muscle cells to mesenchymal cells in the pulmonary artery.

Conclusion

Protection and sexual health of both males and females may be negatively impacted by the coronavirus disease-2019 pandemic. Such effects may manifest as systemic, psychological, or immunological in natura. As an economical and expeditious initial evaluation of the pulmonary and cardiovascular complications associated with COVID-19, erectile function may also prove to be an exceptionally valuable surrogate indicator of cardiovascular and pulmonary health. As an effective predictor of complete Restitutio AD Integrum, we advised that an assessment of the hypothalamic-pituitary-testicular axis and penile color-doppler ultrasound would be required to determine the extent to which COVID-19 has compromised vascular function and, ultimately, erectile function. Furthermore, in order to provide students who develop sexual dysfunction as a result of the containment measures with the necessary support, individualised psychological interventions would be required.

Conflicts of interest: There are no conflicts of interest.

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