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Urogenital complications of COVID19

A Scientific dissertation submitted to the College of Medicine/Diyala University in partial fulfilment of the requirement of M.B.Ch.B.

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Introduction:

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and began in Wuhan, China in December 2019 and a few months later in March 2020 the World Health Organization (WHO) declared it as a pandemic. (1)

The COVID-19 infection affects the lung and causes diffuse alveolar damage resulting in an acute respiratory distress syndrome. (2) However, it may involve other organs such as the kidneys. (3)

The development of acute kidney injury (AKI) in patients with COVID-19 infection ranges from 1% to 46%. (1)

The most common kidney biopsy findings associated with COVID-19 infection are acute tubular damage, collapsing glomerulopathy (CG) that is a variant of focal segmental glomerulosclerosis (FSGS), and thrombotic microangiopathy (TMA). In addition, acute tubular injury (ATI) has been reported to be the most common finding in patients with COVID-19 and AKI. (3)

There have been a few glomerular diseases associated with COVID-19 infection including CG, minimal change disease (MCD), FSGS, vasculitis (including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane (GBM) disease, and immunoglobulin A (IgA) vasculitis with nephritis), membranous nephropathy (MN), lupus nephritis, and TMA. In addition, there have been reports of mixed pathologic renal lesions,

acute interstitial nephritis (AIN) as secondary findings, and treatment-related AKI in COVID-19 patients. (3)

Currently, different types of COVID-19 vaccines are being used around the world. The Pfizer BNT162b2 (Pfizer-BioNTech) and Moderna (mRNA-1273) are mRNA vaccines. They both use a lipid nanoparticle nucleoside-modified mRNA encoding the SARS-CoV-2 spike (S) protein that is involved in the host attachment and viral entry. The Astra-Zeneca vaccine is a chimpanzee adenovirus vector that is deficient in replication and contains the SARS-CoV-2 spike (S) protein. (4)

mRNA vaccines have minimal risk of infection and insertion-induced mutagenesis, produce antiviral neutralizing immunoglobulins (Igs) and stimulate strong immune responses by activating both CD8+ and CD4+ T cells. (5)

It has been reported that mRNA COVID-19 vaccine results in antibody production, activation of virus-specific CD4+ and CD8+ T cells, and release of cytokines such as interferon-γ (IFN-γ). IFN-γ along with type I INFs inhibits the replication of the SARS-CoV2 virus (6) .With millions of COVID-19 vaccinations administered globally, side effects are being reported. (7, 8)

In addition,there are concerns about the possibility that COVID-19 vaccines might cause immunologic events, such as autoimmunity or exacerbation of pre-existing autoimmune disorders. (9-11) Therefore, pharmacovigilance of COVID-19 vaccines seems important for determining the incidence of the potential complications.

COVID19 and Renal impairment:

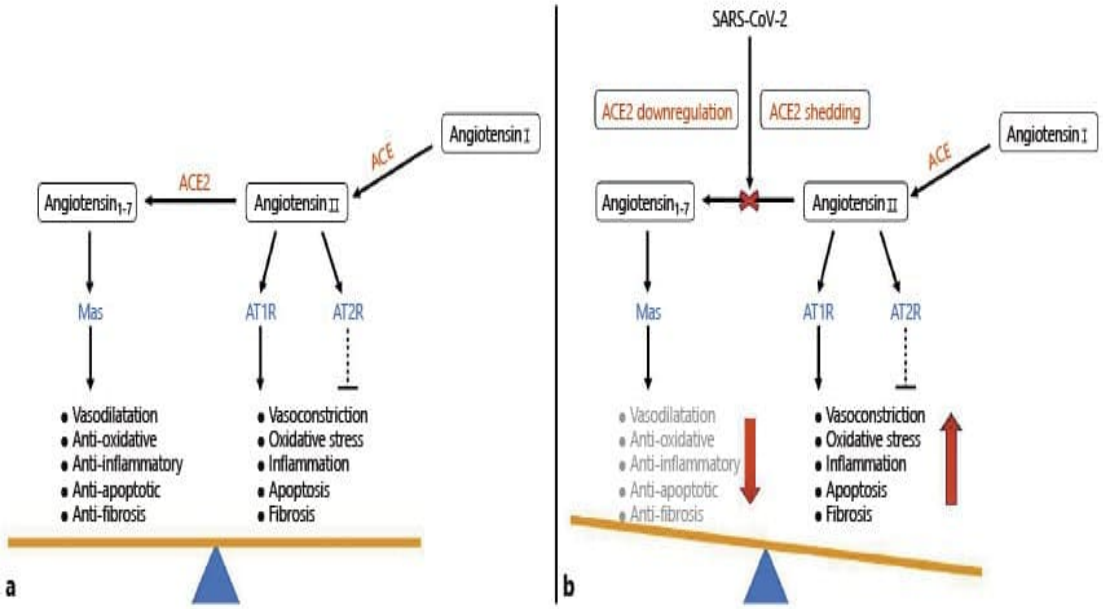
There is accumulating evidence indicating that SARS-CoV2 infection may lead to acute kidney injury (AKI). Several clinical observations have shown characteristics of renal dysfunction such as increased serum creatinine (SCr), variable degrees of proteinuria and hematuria, and even renal fibrosis.

Lots of reports have demonstrated that angiotensin-converting enzyme 2 (ACE2) is the host cell receptor for SARS-CoV-2. The binding affinity is approximately 10-to 20-fold higher than for SARS-CoV, which shares the same cellular receptor. (12)

The functions of ACE2 in SARS-CoV-2 infection can be divided into two categories: a peptidase function and a peptidase-independent function. ACE2, a homologue of ACE, is a powerful negative peptide of the renin-angiotensin system (RAS) and balances the various functions of ACE. The RAS plays a key role in maintaining blood pressure homeostasis and water-salt balance.

Renin, cleaving angiotensinogen, produces angiotensin I (Ang I), which is transformed by cleavage of ACE into Ang II. Ang II binds to two G protein-coupled receptors, angiotensin II receptor type 1 (AT1R) and angiotensin II receptor type 2 (AT2R), performing biological functions: vasoconstriction, elevating blood pressure, and promoting inflammation, oxidative stress and cell apoptosis. Evidence suggests that by degrading Ang II into Ang (1-7), ACE2 negatively regulates the activated RAS, and shows protective effects: vasodilation, as well as suppression of inflammation, oxidative stress and cell apoptosis. During SARSCoV-2 infection, after binding to

SARS-CoV-2, the external domain of ACE2 is cleaved, and the transmembrane domain is internalized, leading to downregulation of ACE2 and an increase in Ang II levels, thereby promoting the "immunoinflammatory storm". (13)



Additionally, ACE2 was recognized as a functional receptor for cellular entry of SARS-CoV-2. Like other coronaviruses, S proteins on the envelope of SARS-CoV-2 can be functionally divided into S1 and S2 subunits. S1 is crucial for binding to receptors, while S2 is responsible for membrane fusion of cell entry (15).When S1 binds to the peptidase domain of ACE2 by the receptor-binding domain, the cleavage site on S2 is cleaved by host proteases, leading to membrane fusion between the virus and target cell, enhancing the S protein-driven viral infection (16) . Apart from direct membrane fusion, pH-dependent endocytosis may be another way for viral infection (17) . During cellular entry, the coronavirus is likely to bind to and internalize with ACE2, resulting in downregulation of the ACE2

protein and an increase in Ang II levels, promoting the inflammatory effects of the RAS, which is involved in acute lung injury and the severest form of acute respiratory distress syndrome. (14, 13)

Clinical Manifestations: A large retrospective cohort study reported that the most common symptoms were fever and dry cough. The frequency was 88.0 and 70.2%, respectively, followed by fatigue (42.8%) and sputum production (36.0%). (18)

The other, uncommon symptoms were headache (11.8%), sore throat (14.0%), gastrointestinal symptoms (anorexia, nausea, or vomiting (8.9%), upper airway symptoms (rhinorrhea, sneeze, or nasal congestion (7.6%), and diarrhea (6.1%). A majority of patients had lymphocytopenia and electrolyte imbalance including hypocalcemia, hypokalemia, and hyponatremia. Severe complications of SARS-CoV-2 infection included acute respiratory distress syndrome, shock, and acute renal failure. (19)

About a quarter of patients have at least one underlying chronic disorder, including hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease (20) . Numerous studies have suggested that renal functional impairment mainly manifests as kidney dysfunction (elevated blood urea nitrogen (BUN) and SCr), abnormal urinary analysis (proteinuria and hematuria), and radiographic abnormalities of the kidneys (21,22) . The most common clinical presentation is proteinuria, which is found in more than half of the patients before or after admission, followed by hematuria, elevated BUN, and elevated SCr (33.7, 14.3, and 10.7%, respectively). A metaanalysis further revealed that patients presented with varying degrees of

albuminuria (+ in 38.8% of the patients, and ++ or +++ in 10.6% of the patients). During SARS-CoV-2 infection, especially in critically ill patients, AKI was proved to be an important risk factor for mortality. (21)

Among those with SARS-CoV-2 infection and AKI, 33.9% of the patients were reported dead after hospitalization, and the mortality of SARS-CoV-2 infection plus AKI was significantly higher than without renal injury ($p < 0.001$) (23) . Furthermore, inflammation and edema of the renal parenchyma, seen by CT scan, are equally common. (21)

The main manifestations of renal injury are summarized in Table 1.

Table 1. Key parameters of clinical manifestations

First author	Subjects, *n*	HU, %	PU, %	Elevated BUN, %	Elevated SCr, %	Imaging abnormality, %	AKI, %	Ref.
Li et al.	193	48.3 (71/147)	58.9 (88/147)	30.6	22.2	96.4 (106/110)	28.5	[23]
Cheng et al.	710	26.9	44.0	14.1	15.5	N	3.2	[24]
Pei et al.	333	41.7	65.8	N	N	N	7.5	[25]
Yang et al.	4,963	N	57.2	13.7	9.6	N	4.5	[26]
Total	6,199	33.7	55.8	14.3	10.7	96.4	5.3	

Imaging abnormality: inflammation and edema of the renal parenchyma by CT scan. HU, hematuria; PU, proteinuria; BUN, blood urea nitrogen; SCr, serum creatinine; AKI, acute kidney injury; N, not mentioned.

Calculating the estimated glomerular filtration rate, endogenous creatinine clearance, and urine microalbumin/creatinine ratio may help in detecting early renal injury in infected patients. (15)

Currently, there are no specific therapies for the treatment of SARS-CoV-2 infection. We should pay more attention to the treatment of

renal lesions and the protection of renal function of severely infected patients. Given the current clinical studies reporting that patients with combined chronic disease and SARS-CoV-2 infection were easier to develop AKI, these patients need to strengthen management of their fluid balance and closely observe the urine volume, color of urine, any signs of edema, and blood pressure; avoid the usage of nephrotoxic drugs; and enhance their monitoring of early biological diagnostic indices for identifying AKI, such as blood and/ or urine neutrophil gelatinase-associated lipocalin. AKI could be diagnosed following one of the following conditions: (1) SCr is increased by ≥26.5 μmol/L within 48 h; (2) SCr has been increased to 1.5 times the baseline value within the previous 7 days; (3) the urine volume is < 0.5 mL/kg/h for 6 h. (24,25)

Possible effective antiviral therapy, symptomatic treatment, and promoting renal functional recovery are the principles of renal management. In addition, it has been proved that immunosuppressive drugs such as cyclosporin and mycophenolic acid may be good candidates for therapeutic medicines against renal damage by SARS-CoV-2 (26,27) , and specific inhibitors of IL-6 appear to be beneficial in severely infected cases. (28)

COVID19 and Hematuria

Proteinuria and hematuria are reported to have an even higher prevalence in COVID-19 than AKI (29) .Retrospective studies in China have reported that proteinuria and hematuria are associated with COVID-19 (30) and with higher mortality. (31,29)

Proteinuria was defined by presence of ≥1+ protein on urinalysis, **hematuria** was defined as the presence of >4 red blood cells per high-power field on urinalysis, and **urinary tract infection** was defined as presence of a positive urine culture.

Patients were categorized as having proteinuria or hematuria "on admission" if they had these findings within the first 48 h of presentation to the emergency department. If these findings appeared on later urinalyses, they were defined as "in-hospital" values.

Data on indwelling Foley catheter placement and anticoagulation use were also documented as these factors could influence in-hospital proteinuria and hematuria measurements.

In patients with a documented baseline serum creatinine (SCr) within 3 months prior to admission, "AKI on admission" was defined as a rise in SCr of 0.3 mg/dL or an increase 1.5 times the baseline based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition. (32)

For patients without a 3-month baseline SCr, "AKI on admission" was retroactively defined as a SCr >1.2 mg/dL (upper limit of normal in Stony Brook University Medical Center Lab) within the first 48 h of presentation to the emergency department with subsequent improvement by 50% during the hospitalization. (29)

"In-hospital AKI" was diagnosed based on KDIGO in those without admission AKI. Renal replacement therapy was defined as the need

for either hemodialysis, continuous kidney replacement therapy, or both.

AKI classes for in-hospital AKI were assigned to all patients based on the Acute Kidney Injury Network (AKIN) criteria (33). Class 1 was assigned for an acute increase in SCr by 50%, class 2 for an increase by 100%, and class 3 for an increase of 200% or if the patient required renal replacement therapy during the hospitalization. (33) "Recovery from AKI" was defined as improvement to the patient's baseline or normal SCr. (34)

"Admission" values for AKI, proteinuria, and hematuria were all analyzed against outcomes of ICU admission, IMV, and death, while "in-hospital" kidney abnormalities were analyzed against the outcome of death alone.

Patients with proteinuria at admission were older and had a higher prevalence of hypertension, CKD, and angiotensin receptor blocker use compared to those without. Admission ferritin, D-dimer, NT-

proBNP, and peak values for BUN, ferritin, CRP, and inflammation score were associated with proteinuria . Those with admission proteinuria had a higher incidence of in-hospital AKI, ICU admission, and death compared to those without proteinuria . After controlling for multiple covariates, admission proteinuria remained significantly associated with in-hospital AKI (OR 4.71, 95% CI 1.28–17.38, p = 0.02) .

Admission hematuria was associated with increased baseline D-dimer, NT-proBNP, and peak BUN. Those with hematuria at

admission had a higher incidence of in-hospital AKI, ICU admission, IMV, and death compared to those without hematuria . On multivariable analysis, admission hematuria remained significantly associated with ICU admission (OR 4.56, 95% CI 1.12–18.64, p = 0.03), IMV (OR 8.79, 95% CI 2.08–37.00, p = 0.003), and death (OR 18.03, 95% CI 2.84–114.57, p = 0.002) .

Combined proteinuria/hematuria was associated with an increased risk of ICU admission, IMV, and death . These relationships did not show statistical significance on multivariable analysis, although there was a trend toward significance for ICU admission (OR 5.35, 95% CI 0.88–40.24, p = 0.08) and IMV (OR 6.99, 95% CI 1.08–59.12, p = 0.05) .

Patients with in-hospital proteinuria had higher LDH, while those with in-hospital hematuria had higher LDH, D-dimer, and CRP on admission. Patients with proteinuria, hematuria, and combined proteinuria/hematuria during hospitalization were more likely to be male and had an independent association with in-hospital AKI, indwelling Foley catheter use, use of anticoagulation, increased inflammatory scores, ICU admission, IMV, and death .

proteinuria and hematuria at admission significantly influenced in-hospital outcomes. Those with admission proteinuria had a 4.7 times higher risk of in-hospital AKI, while those with admission hematuria had a 4.6 times higher risk of ICU admission, an 8.8 times higher risk of requiring IMV, and an 18 times higher risk of death.

COVID19 and Infertility :

Reproduction is a fundamental process that permits organisms to pass on their genetic imprint to the individuals of the next generation. Inability to bear a child is a major setback on the social, mental, and physical wellbeing of both men and women. Unfortunately, infertility has become a common health problem affecting around 8–12 % of the global population. Infertility rates differ greatly in various regions of the world, while the males could be responsible for up to 50 % of overall infertility cases. (35)

The SARS-CoV-2 virus targets cardiac, gastro-intestinal, hepatic, cutaneous, and renal organs to elicit organopathy and uses angiotensin converting enzyme 2 (ACE-2), transmembrane serine protease 2 (TMPRSS2), and other entry factors to colonize host cells. Hence, organs expressing these entry factors are at greater risk of COVID-19 mediated pathology and organ dysfunction. Studies have claimed the expression of these entry factors in gonads and other accessory reproductive organs (36,37) . Therefore, it is possible that this virus might be able to invade reproductive organs and disrupt the reproductive health of infected individuals.

SARS-CoV-2 infection impaired sperm quality has been reported from patients with moderate infection (38) . It is further suggested that enhanced immune response in testicular cells might adversely impact the process of spermatogenesis (39) . Furthermore, females of child bearing age, when infected with COVID-19, exhibited decrease in menstrual volume and a prolongation of their menstrual cycle.

It is also worth noting that the COVID-19 pandemic has delayed medical procedures of assisted reproductive technology (ART)

throughout the world. ART is a set of medical procedures that are widely used to treat infertility.

Both mental health and depression are also considered as risk factors for infertility.

Renin Angiotensin System (RAS) is precisely tuned machinery that controls fluid homeostasis within the body. Renin, ACE-1, ACE-2, and ACE-3 are the fundamental components of the RAS. In recent years, the influence of the RAS on different reproductive phenomena has been investigated. In males, it has been found that the RAS regulates tubular contractibility, spermatogenesis, sperm maturation, capacitation, acrosomal exocytosis, and fertilization capacity while, in females, it has been found that the RAS maintains ovarian blood pressure and several autocrine/paracrine signaling pathways that control fertility. (40)

Oxidative stress (OS) is a physiological condition in which the redox equilibrium is disrupted as a result of excessive reactive oxygen species (ROS) production at the subcellular level. SARS-CoV-2 mediated disruption of the RAS can lead to accumulation of ANG-II in blood plasma, and then promote ROS production via the NADPH oxidase (NOX)-protein kinase C (PKC) dependent pathway (Box 3) (41) . Hypoxia is a common symptom of COVID-19 and it acts as a stimulant for ROS generation (42) . Meta-analysis of 1210 COVID-19 cases has revealed reduced hemoglobin levels (5.9 g/L-7.1 g/L) , which might be related to anemic hypoxia and cellular ROS production in patients. Excessive ROS and subsequent OS in male gonads can impair genesis, motility, and fertilization capacity of mature sperms. Finally, OS promotes long-term changes in

epididymis and maturing spermatozoa resulting in declined sperm quality .

Furthermore, in women with PCOS, an OS-induced proinflammatory state might result in ovulatory failure and hyperandrogenism .

The majority of COVID-19 cases report moderate to severe fever , The epithelia of the scrotal testes are highly sensitive to changes in temperature of even a few degrees . Slight changes in testicular temperature can cause incidences of morphological abnormality in developing spermatozoa and spermatids. Additional body temperature increases also curtail the sperm-storage capacity of the cauda epididymidis . Furthermore, high fevers (>39 C) for 3 or more days have been associated with declined sperm concentration and semen quality in patients .

Heat stress also has the potential to reduce levels of gonadotropin receptors,aromatase activity of granulosa cells, and follicular fluid concentrations of estradiol in rat follicles . Moreover, high temperatures can threaten development of embryos in mice .

COVID19 and Renal vein thrombosis :

Renal vein thrombosis (RVT) is a relatively rare condition with variable clinical presentation and course. RVT affects males more than females and has been reported in children and embryos. (43,45) Due to the large renal venous system, the left vein is more commonly involved in RVT; despite that, up to two-thirds of the patients have bilateral involvement. The presentation can range from an acute

onset of abdominal pain, costovertebral angle tenderness and gross hematuria to unspecific symptoms. It can be asymptomatic in many instances, especially in chronic cases. (44,46,47)

Flank pain is the most common presentation of RVT; therefore, this disease should always be considered as a rare differential diagnosis of patients with abdominal pain. (43)

Major RVT predisposing factors include trauma, malignancy, infection, hypercoagulopathy and nephrotic syndrome. Factor V Leiden mutation has been particularly associated with RVT (44,46,48) . Membranous glomerulonephritis (MN) is the most common disease that leads to RVT; however, other nephrotic syndromes such as membranoproliferative glomerulonephritis, focal glomerulosclerosis and systemic diseases such as lupus erythematosus are also among the causes. Given the MN's male predominance, it might explain why RVT affects the male population more. (44,49)

Coagulation dysfunction and its correlation with COVID-19 has been well-reviewed and accordingly, the patient's recent COVID-19 infection could have propagated the thrombosis formation. (49-50) Despite all of this information, cases of idiopathic and spontaneous RVT have also been reported in the literature. (43,51)

Since there is no specific laboratory study diagnosis of RVT, imaging remains the main diagnostic tool. In ultrasonography, the involved kidney might become enlarged or atrophic depending on the acute or chronic manifestation of the disease. Color Doppler ultrasound can also be utilized to detect flow. However, as in our case, sonographic methods are not highly sensitive. While angiography remains the

gold standard diagnostic procedure, CT-angiography and MR-angiography are the most commonly used due to their accessibility and noninvasive nature. (44)

Immediate initiation of anticoagulant therapy with parenteral heparin is essential for the management of RVT and the prevention of further renal damage. (44,52)

Mechanical or chemical thrombectomy is not indicated in all cases of RVT. It is implemented in situations such as medical treatment failure, bilateral RVTs, thrombosis extension to IVC, transplanted kidneys, or complications such as pulmonary embolism. In rare cases such as renal carcinoma or complete renal necrosis, nephrectomy might be indicated. (44)

Considering the severe respire atory distress in our case, we can assume pulmonary embolism as a probable cause of death, which unfortunately did not respond to heparin therapy. However, given the unstable clinical condition and azotemia in our patient, it was not possible to perform pulmonary CT angiography to rule out or confirm it.

COVID19 and Erectile dysfunction :

One of the repercussions of COVID-19 is its impact on men's sexual health. COVID-19 infection is expected to be associated with an increased likelihood of erectile dysfunction (ED).Considering the high transmissibility of COVID-19, ED could be a concerning consequence for a large segment of the population. (54)

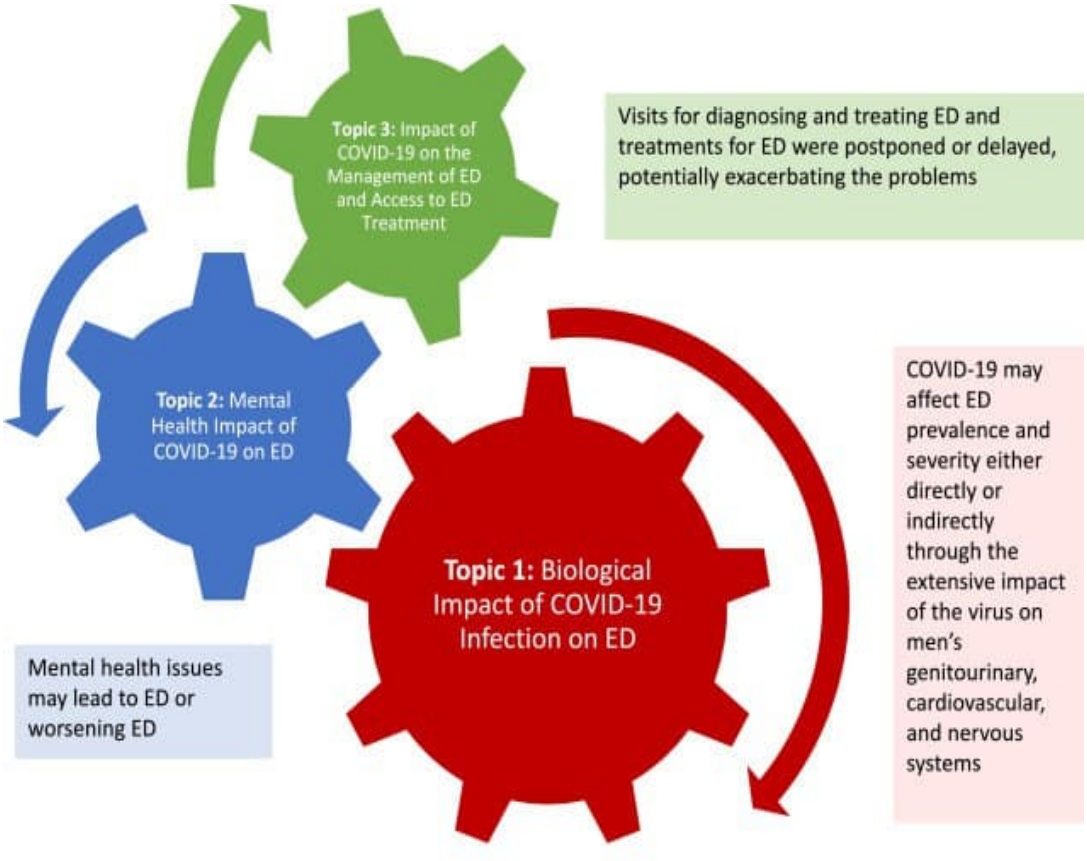
Evidence that COVID-19 may biologically impact ED both in regard to the prevalence of ED (ie, the number of men with ED) and the severity of ED in men with existing ED is beginning to emerge. Vascular integrity is necessary for erectile function. Accumulating evidence suggests that SARS-COV-2 damages the vascular endothelium, the layer of specialized cells lining the inner surfaces of blood vessels and spaces like the surface of the sinusoids of tissues like the corpus cavernosum of the penis.13 The endothelium expresses the protein angiotensin-converting enzyme 2(ACE2), through which SARS-COV-2 can access host cells.

The vascular endothelium regulates the vascular tone, coagulation, metabolism, and permeability of the vessels. Endothelial dysfunction results in abnormal regulation of blood pressure response to inflammation, impairment of the sensitive balance between the vasoconstricting and vasodilating agents and stimuli,and coagulation disorders.Vascular damage associated with COVID-19 is likely to affect the fragile vascular bed of the penis, potentially resulting in impaired erectile function.

ED that manifests during COVID-19 may be a signal for underlying cardiovascular disease and may provide opportunities for earlier assessment of vascular dysfunction. Evidence coming from diagnostic procedures, such as penile color-doppler ultrasound and hypothalamic-pituitary−testicular axis evaluation, may aid in assessing the extent to which COVID-19 has been able to impair erectile,and finally vascular function. (54)

It is important to consider the role of added stress, anxiety,and physical health implications for men with ED amid theCOVID-19

pandemic. 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. Anxiety and depression are commonly seen in men with ED. Psychological and mental health issues may lead to ED or worsening ED. ED has been shown to be 1.3−2.3 times more common in individuals with anxiety and depression. Although the psychological effects such as depression, anxiety, posttraumatic stress, and sleep disturbances are being studied for COVID-19, literature evaluating the relationship between these psychological and mental consequences and ED is rather scarce. (54)



Some evidence has shown that sexual behavior was altered during the pandemic, including a reduction in sexual desire and number of sexual partners during the lockdown. The COVID-19 outbreak has dramatically affected men's quality of life by changing inter-personal relationships, community life, and sexual health.Disruptions in elective and non-emergency medical care access and delivery were observed during COVID-19, particularly during periods of considerable community transmission of SARS-CoV-2. Many elective surgeries for benign urological conditions such as ED were postponed during the COVID-19 outbreak. One example summarizing shifts in men's urological care was published by the Canadian Urological Association. It noted the massive shift in only offering surgeries for emergencies and urgent oncology cases with management shifting to mostly virtual care for male sexual health conditions. Although not explicitly documented in the published medical literature, it is likely that the evaluation and treatment of ED was also postponed or delayed, potentially prolonging and possibly exacerbating ED problems. (54)

Conclusions

- ✓ **In SARS-CoV-2 patients, viral infection and replication are probably the main etiologies of renal dysfunction. SARS-CoV-2 may cause renal injury either by direct renal infection or via systemic effects such as host immune clearance and immune tolerance disorders, endothelial cell injury, thrombus formation, glucose and lipid metabolism disorder, and hypoxia. The mechanism of renal injury caused by SARS-CoV-2 has not yet been fully clarified. However, our current understanding**

suggests that the ACE2 signaling pathway plays a key role in mediating renal injury. It is important to monitor kidney injury in the management of SARS-CoV-2. The earlier treatments achieve a better clinical outcome. Patients with AKI are recommended to receive CRRT in order to both protect renal function and remove inflammatory cytokines, which may accelerate the process of disease recovery.

- ✓ **Proteinuria and hematuria both at the time of admission and during hospitalization are associated with adverse clinical outcomes in hospitalized patients with COVID-19.**

- ✓ **The recent literature provides evidence that male gonads may be potentially vulnerable to SARS-CoV-2 infection, recommending caution to pregnant women and couples planning natural pregnancy or assisted reproduction.**

- ✓ **RVT is a rare cause of abdominal and flank pain if left untreated may lead to renal damage. Current literature emphasizes CT-angiography as the diagnostic modality of choice. Extension to IVC and pulmonary embolism are possible complications of this phenomenon. Anticoagulant therapy should not be hesitated in order to reduce the risks. For the best outcomes, all physicians, especially emergency medicine practitioners should be familiar with this problem.**

- ✓ **COVID-19 has a uniquely harmful impact on men's health and erectile function through biological, mental health, and**

healthcare access mechanisms. As the pandemic wanes, strategies to identify long-term effects and additional health care support may be needed to adequately mitigate the impact of COVID-19 on men's health.

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