

## Effects of coronavirus disease 2019 (COVID-19), including its prevention and treatment, on the male reproductive system

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*To the Editor:* The current coronavirus disease 2019 (COVID-19) pandemic has resulted in an unprecedented worldwide health crisis. The Chinese government incorporated the syndrome into the B class of infectious diseases stipulated in the Law of China on the Prevention and Treatment of Infectious Diseases, with prevention and control measures implemented according to A class infectious diseases. On February 11, 2020, the World Health Organization named the syndrome COVID-19. Subsequently, the International Committee on Taxonomy of Viruses (ICTV) named the causative virus 2019 novel coronavirus (2019-nCoV). As we have been achieving a deeper understanding of COVID-19, its potential effects on the genitourinary system have gradually gained the public's attention. The virus itself may have an impact on the male reproductive system, but the impacts of drugs, environmental factors, psychological factors, and other aspects on reproduction during the epidemic period should not be ignored.

The 2019-nCoV genome encodes four structural proteins (S, E, M, and N), which together mediate viral infection and replication. The 2019-nCoV protein binds to target cells expressing angiotensin-converting enzyme 2 (ACE2); its binding affinity for ACE2 is much higher than that of severe acute respiratory syndrome coronavirus, which may explain the higher infectivity of 2019-nCoV. *In vitro* infection studies of cells from horseshoe bats, masked palm civets and mice demonstrated that 2019-nCoV shows tropism for all ACE2-expressing cells except those from mice. However, the virus could not infect cells that did not express ACE2, further confirming that ACE2 was the major receptor for 2019-nCoV, nor did the virus infect target cells expressing other coronavirus-like receptors. Recently, studies have shown that ACE2 transcripts and proteins can be detected in many organs such as the lung, ileum, esophagus, kidney, and testis.<sup>[1]</sup> In a subsequent study, high levels of ACE2 mRNA in human testis (higher than in kidney or lung) were confirmed by bioinformatic

analyses of sequence data. Based on these data, it has been speculated that the testis is a potential target organ for 2019-nCoV infection.

Previous studies showed that ACE2 can participate in reproductive physiological processes such as penile erection, spermatogenesis, and sperm motility regulation through the renin-angiotensin-aldosterone system (RAAS) system [Figure 1]. RAAS is a biaxial system: one axis is the ACE-angiotensin II (AngII)-angiotensin type 1 receptor (AT1R) axis, and the other is the ACE2-angiotensin-(1-7) [Ang-(1-7)]-Mas receptor axis. The catalytic activity of ACE2 for hydrolysis of AngII is 400 times higher than that for hydrolysis of angiotensin I in the ACE-Ang II-AT1R axis, indicating that the main function of ACE2 is to hydrolyze AngII to produce Ang-(1-7). Moreover, ACE2 is the main enzyme responsible for the formation of Ang-(1-7), which exerts regulatory effects on the cardiovascular system including vasodilation, anti-proliferation, and anti-fibrosis effects through the Mas receptor. Ang-(1-7) has a negative regulatory effect on the RAAS system. In the male testis, Ang-(1-7) is mainly concentrated in the testicular interstitium and is detected in lesser amounts in the seminiferous tubules. The Mas receptor is also expressed in seminiferous tubule epithelial cells. Neither Ang-(1-7) nor Mas could be detected in testicular biopsies of patients with non-obstructive azoospermia and normal spermatogenic function. This expression pattern suggests that the ACE2-Ang-(1-7)-Mas axis may be involved in testicular spermatogenesis. Mas is also expressed in the head and tail of human spermatozoa. Mas agonists can improve sperm motility in patients with asthenospermia through the phosphoinositide 3-kinase/AKT (Protein kinase B) pathway *in vitro*, but do not affect the acrosome reaction. Mas knockout mice had an abnormal cardiac function but remained fertile despite the decreased testicular weight, abnormal spermatogenesis, and changes in testicular steroid-related gene expression profiles. These data suggested that Mas may affect the androgen synthesis pathway. Analysis of plasma from COVID-19 patients and

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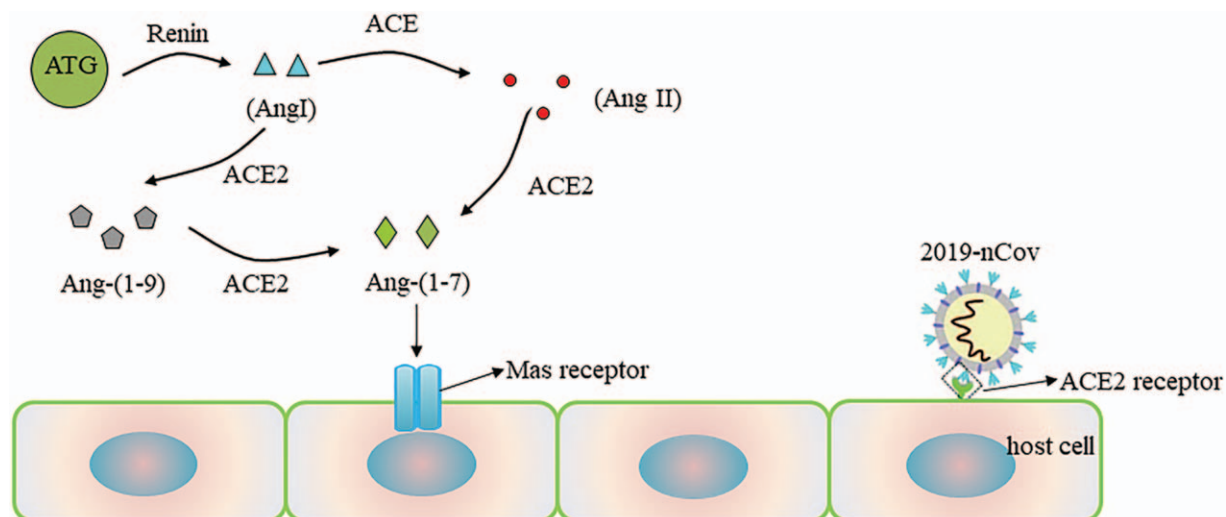
DOI:  
10.1097/CM9.0000000000001375

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Chinese Medical Journal 2021;134(20)

Received: 22-12-2020 Edited by: Peng Lyu



**Figure 1:** The process of 2019-nCoV combining ACE2 receptor and ACE2 participate in reproductive physiological processes such as penile erection, spermatogenesis, and sperm motility regulation through the RAAS system. 2019-nCoV: 2019 novel coronavirus; ATG: Angiotensinogen; ACE2: Angiotensin converting enzyme 2; Ang I: Angiotensin I; Ang II: Angiotensin II; RAAS: Renin angiotensin aldosterone system.

healthy controls showed that AngII was significantly increased in COVID-19 patients and showed a linear correlation with viral load; elevated AngII eventually aggravated hypertension. While the high-affinity interaction between 2019-nCoV and ACE2 in the genitourinary system may have direct effects, the effects of increasing hypertension should not be ignored. Hypertension can damage the cavernous vessels and sinusoid endothelial cells of the penis, including damaging or even occluding the lumen, and can also lead to a decrease in elastic fibers in the white membrane of the penis, causing erectile dysfunction. Other studies have found that hypertension can mediate penile vasoconstriction through endothelin-1, resulting in pudendal artery contraction of penile blood supply.

In the study of Li *et al*,<sup>[2]</sup> concerns were raised following a subsequent study in which semen samples were collected from 38 COVID-19 patients (15 in the acute phase and 23 in recovery). 2019-nCoV was detected in semen from six patients, four in the acute stage (15.8%) and two in the convalescent stage (8.7%). This is a rare study to demonstrate the presence of 2019-nCoV in semen. So far, only one study has analyzed gonadal function in COVID-19 patients. The results showed that luteinizing hormone levels were increased in 2019-nCoV-infected patients and that the ratio of testosterone to luteinizing hormone was decreased, indicating potential gonadotropin toxicity. Further studies are needed to confirm this result.

The potential effects of drugs used to treat COVID-19 on the male reproductive system should not be ignored. Common therapies for COVID-19 include antiviral drugs (e.g., interferon, ribavirin, lopinavir, and ritonavir) and glucocorticoids. Patients with severe or complicated bacterial infections may be treated with antimicrobials (such as moxifloxacin or azithromycin). Among antiviral drugs, interferon-alpha, ribavirin, abidor, and chloroquine phosphate are recommended. Ribavirin is a broad-

spectrum antiviral drug. Animal experiments have demonstrated that ribavirin can reduce levels of testosterone, inhibit spermatogenesis, and cause sperm malformation in rats, although these toxic effects were reversible. Clinical studies have shown that combined therapy with ribavirin and interferon can affect male fertility through reproductive toxicity characterized by decreased sperm count. Pharmacokinetic studies showed that the concentration of ribavirin in seminal plasma was twice as high as that in serum, and therefore, strict contraception was recommended during treatment. Studies have also shown that ribavirin caused damage to sperm DNA that persisted for as long as 8 months.<sup>[3]</sup> Thus, strict contraception is recommended for at least 8 months following antiviral therapy. Lopinavir/ritonavir caused oxidative stress damage in rat testicular tissue, leading to abnormal spermatogenesis, while chloroquine phosphate can affect spermatogenesis and epididymal function. COVID-19 patients showing rapid progression on pulmonary imaging and excessive activation of inflammatory reactions may be treated with glucocorticoids. Previous studies showed that glucocorticoids can dilate the intercellular space of the seminiferous epithelium, affecting the blood-testis barrier and enabling harmful substances to enter the testis and inhibit male reproduction. Glucocorticoids can also increase germ cell apoptosis by interacting with receptors on these cells. However, low dose therapy over short periods had little effect on the reproductive system. Therefore, male fertility should be carefully monitored in COVID-19 patients receiving combination antiviral therapy.

Although needed to stop the spread of COVID-19, the potential effects of disinfectant used on the male reproductive system should be taken seriously. Commonly used chemical disinfectants include ethanol, chlorine, biguanidine, quaternary ammonium salts, iodine, aldehydes, phenolics, peroxide, and ethylene oxide. Chlorine-containing disinfectants are widely recommended for

COVID-19 prevention. Previous studies showed a significant increase in sperm head deformities in mice fed with hypochlorite. Peracetic acid, also known as acetic acid, has a wide range of antibacterial activities both in gas form and in solution. Animal experiments showed that phenolic disinfectants can cause defects in embryonic development and spontaneous abortion.<sup>[4]</sup> Excessive intake of iodine can lead to decreased sperm concentration. At present, 75% ethanol and chlorine-containing disinfectants are most commonly used for COVID-19 prevention and control. These disinfectants are formulated within safe concentration limits and will not cause damage to the reproductive system, gametes, or zygotes. However, improper or excessive disinfection may be harmful and should be of concern.

Large-scale outbreaks of COVID-19 may cause panic among the public, triggering episodes of depression, anxiety, fear, and post-traumatic stress disorder. When stimulated by the stress of a sudden crisis, risk perceptions, and cardiac stress levels both increased. The central stress response system is activated, inhibiting the reproductive functions of the body. Studies have shown that stress and negative emotions can affect various sperm parameters at the macroscopic, cellular, and subcellular levels. Effects of stress include decreased semen volume, sperm concentration, and total sperm count decreased sperm motility, and increased sperm DNA fragmentation.<sup>[5]</sup>

In the background of COVID-19 prevention and control, clinicians must not only pay attention to the virus itself but also the potential effects of the virus on the male

reproductive system. Effects of drugs and environmental and psychological factors on the male reproductive system must also be considered.

### Conflicts of interest

None.

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**How to cite this article:** Liu K, Tao W. Effects of coronavirus disease 2019 (COVID-19), including its prevention and treatment, on the male reproductive system. *Chin Med J* 2021;134:2509–2511. doi: 10.1097/CM9.0000000000001375