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Relationship between COVID-19 and the male reproductive system

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Abstract. – OBJECTIVE: The objective of this review is to provide currently available information on the potential effects of coronavirus disease 2019 (COVID-19) on male fertility.

MATERIALS AND METHODS: This is a mini-review. Due to the similarity between the COVID-19 and severe acute respiratory syndrome (SARS) virus, we searched for the following keywords: "SARS-CoV, male reproductive system, infertility, COVID-19, SARS-CoV-2, and orchitis". By reviewing and analyzing the literature, we analyzed the influence of temperature on sperm, the expression of angiotensin-converting enzyme 2 (ACE2) in the testes, and the impact of SARS-CoV-2 on the male reproductive system.

RESULTS: SARS-CoV-2 enters the body through the ACE2 receptor. The high expression of ACE2 on the surface of spermatogonia and supporting cells in the testes, as well as the immune response caused by COVID-19, can lead to testicular spermatogenesis dysfunction and reduced sperm count.

CONCLUSIONS: COVID-19 infection can affect male reproductive function, and standard treatment strategies should be established in time to help male patients infected with COVID-19.

Key Words:
COVID-19, SARS-CoV-2, Male reproductive system, Orchitis, SARS.

Abbreviations

ACE2: angiotensin converting enzyme 2; BTB: Blood-testis barrier; COVID-19: Coronavirus disease 2019; MERS: Middle East respiratory syndrome; MERS-CoV: MERS coronavirus; RBD: receptor binding domain; S: spike protein; SARS: severe acute respiratory syndrome; SARS-CoV: SARS coronavirus; SARS-CoV-2: SARS coronavirus 2; WHO: World Health Organization.

Introduction

Recently, the official website of the people's government of Hubei Province posted a bulletin encouraging men infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to undergo fertility tests. SARS-CoV-2 is the pathogen that has caused the coronavirus disease 2019 (COVID-19). COVID-19 is known to damage many organs in the body, especially the lungs, but little is known about its effects on the reproductive system. However, this bulletin was indicative of a possible link between this novel disease and the male reproductive system.

SARS-CoV-2 and COVID-19

At the end of 2019, a novel coronavirus disease leading to Severe Acute Respiratory Syndrome first broke out in Wuhan, China, and then, spread quickly worldwide. According to the statistics of the World Health Organization (WHO), patients with novel coronavirus have appeared in more than 100 countries, with more than 700,000 deaths. The emergence of the novel coronavirus disease was a challenge to the Chinese people and the whole world because there was limited information on this virus. Gradually, more information on the virus has been obtained as the disease continuously spreads. On February 11, 2020, the WHO officially named the novel coronavirus pneumonia as COVID-19. Infected people typically develop symptoms such as fever, cough, and difficulty in breathing. These symptoms may appear 2-14 days after exposure or even longer after exposure, and an infected person can infect another person *via* aerosol-mediated transmission[1]. As COVID-19 spreads from one

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person to another[2] *via* this mode of transmission, infected individuals should be isolated to reduce the possibility of transmission.

Thus far, we have found a total of seven kinds of coronavirus that infect humans. Among the six known types, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), causing COVID-19 and MERS, respectively, are infectious and harmful, and the other four viruses have little impact on people. SARS-CoV and MERS-CoV caused infectious disease outbreaks in 2003 and 2012, respectively. The seventh type, SARS-CoV-2, is homologous with SARS-CoV. Although SARS-CoV-2 has affected a larger population, the mortality rate associated with the infection with this virus is lower than that in case of SARS and MERS[3-5]. Immunocompromised individuals, such as the elderly and those with serious underlying diseases such as diabetes, high blood pressure, heart disease, and so on, are at a higher risk of infection with SARS-CoV-2. As a new disease, there is no specific drug for COVID-19. Notably, China is the first to implement plasma replacement therapy for COVID-19 treatment; this is a method of replacing plasma that has not produced antibodies with plasma that has.

The Structure and Origin of SARS-CoV-2

The spike (S), membrane, envelope, and nucleocapsid proteins are the four main structural proteins of coronavirus particles[6]. The coronavirus genome encodes the spike protein, which is a distinct feature of coronaviruses, but also the most variable part of the coronavirus[7,8]. The virus binds to the angiotensin converting enzyme 2 (ACE2) located on the host cell membrane through the virus surface enzyme of its S glycoprotein and enters the cell. The S protein mediates the connection of the virus to the host receptors; it is cleaved by an enzyme of the host cell into two separate peptides labeled the S1 protein and S2 protein, which form the receptor-binding domain of the S protein and constitute the stalk of the spike, respectively[6]. All coronaviruses rely on spike proteins to infect other cells. The S1 proteins bind with cellular receptors to mediate infection, completing the invasion process by the virus. The S2 proteins use their functional elements to help the virus interact with the target cell membrane[7]. This process decides the characteristics of virus transmission and pathogenesis. Genomic data from SARS-CoV-2 suggest that its S1 protein contains some unique adaptations, which increases the affinity of SARS-CoV-2 for human ACE2; this might be the reason why COVID-19 spreads widely among people[9,10]. Of note, the sequence consistency between SARS-CoV and SARS-CoV-2 of N protein was more than 90% by National Center for Biotechnology Information amino acid blast[2].

ACE2 is a carboxypeptidase that binds to endothelial cells; it is highly expressed in multiple human organs, such as the lungs, heart, gastrointestinal tract, testes, and so on[11]. SARS-CoV-related studies[12,13] have reported that SARS-CoV enters cells by binding to the ACE2 receptor SARS-CoV-2 which shares 79.6% of its consensus sequences with SARS-CoV and is shown to have 96% genome-wide similarity to the bat coronavirus[13]. Researchers[7,13] analyzed the molecular structure of the novel coronavirus and observed 94.4% similarity between SARS-CoV-2 and SARS-CoV, indicating that the two viruses belonged to the same species. However, some pangolin coronaviruses also show strong similarities with SARS-CoV-2[9]. In brief, we believe that the new coronavirus is spread through wild animals as the intermediate hosts, but it is still unclear if this host is a bat, pangolin, or mink.

The Relationship Between SARS-CoV and Orchitis

Recent evidence[14,15] confirmed that SARS-CoV-2 acts on the ACE2 receptor to enter cells and this could cause pathological injuries in multiple organs, including the lungs, heart, kidney, and testes which show a high expression of ACE2 on the cell surface. In addition, many viruses, such as the HIV and mumps virus can invade testicular cells, resulting in orchitis, which can lead to male infertility and testicular cancer[14]. Among these organs, testicular ACE2 expression is abundant, mainly concentrated in testicular spermatogonial cells, interstitial cells, and supporting cells, which are closely related to male reproductive function.

The testicular parenchyma is composed of testicular lobules that contain seminiferous tubules, the site of sperm production, and interstitial cells, which are responsible for the synthesis and secretion of androgens. The seminiferous tubules are made up of spermatogenic cells and supporting cells, and the spermatogonia are the precursor cells of spermatogenic cells. The supporting cells are located in the tube wall of the seminiferous tubules and play an important role in the formation and development of spermatozoa. Androgens promote spermatogenesis and the development of

male reproductive organs, as well as the maintenance of male secondary characteristics and sexual function.

Although SARS-CoV has not been detected in the testes, SARS-CoV infection can still cause severe immune damage to the testes and result in widespread destruction of reproductive cells. These pathological changes may be directly caused by the local replication of SARS-CoV-mediated cytopathic effects, or indirectly as a result of a harmful immune response and cytokine response to a viral infection or systemic toxicity due to respiratory failure[15]. At present, there is no direct evidence to prove that SARS-CoV can directly infect the testicle, but this possibility cannot be ruled out. Currently, testicular injury is a more convincing explanation for the complications or sequelae. We know that temperature is crucial to the growth and development of cells, and 37°C is the optimal temperature for cell growth. However, almost all patients with SARS-CoV infection have persistent fever. When the human body is in a state of high fever for a long time, changes in testicular temperature occur, and germ cells will be damaged and degenerate[15]. Under normal circumstances, the appropriate temperature for sperm formation and survival is 1-2°C below the body temperature. High temperature has been reported to induce cell apoptosis[14,16].

Macrophages in the testicular mesenchyme can secrete tumor necrosis factor, interleukins, and other cytokines, which can participate in the local regulation of testicular function in a paracrine or autocrine manner. A prominent feature of the testes infected by SARS-CoV is leukocyte infiltration[14]. Macrophages and leukocytes cells express ACE2 and can affect testosterone production by testicular interstitial cells, destroying the blood testicular barrier and spermatogonial cells. In addition, these cells and the inflammatory cytokines they produce may activate an autoimmune response in the seminiferous tubules to form autoantibodies. It has been shown that there is a large amount of IgG deposition in the vas deferens epithelium, including that in some degenerated germ and supporting cells. This result suggests that SARS-CoV may not directly infect the testes, but that it triggers a secondary autoimmune response. Like other viral orchitis, SARS orchitis is an autoimmune orchitis[14].

SARS-CoV-2 and Orchitis

SARS-CoV and SARS-CoV-2 are highly similar with regard to several aspects. First, they use the same ACE2 receptor to invade cells and this indicates that the pathogenesis of their infections is similar. Second, they have approximately 80% sequence consistency. Lastly, the symptoms (fever, cough, and dyspnea) caused by their infection are very similar. Therefore, it is not surprising that patients infected with SARS-CoV-2 have the same complications or sequelae as those infected with SARS-CoV.

Although SARS-CoV and SARS-CoV-2 are highly similar, there are still some differences among them. The receptor binding domain (RBD) in the S protein is the most variable part of the coronavirus[13]. Studies have shown that six amino acids of the RBD are essential for ACE2 receptor binding and selection of hosts; these are L455, F486, Q493, S494, N501, and Y505[17]. Moreover, several key residues in SARS-CoV-2 RBD, especially Q493, are essential for good interactions with human ACE2[17]. Hence, this shows that compared to SARS-CoV, SARS-CoV-2 is equipped to bind to ACE2 more efficiently and has high pathogenicity, which enables it to spread rapidly among the population[7,17].

ACE is an important part of the renin-angiotensin-aldosterone system and plays a crucial role in regulating blood pressure and body fluids. ACE2 is widely expressed in many tissues, including the heart, kidneys, lungs, liver, and intestinal tissues, as well as the testes[18,19]. However, what is noteworthy is that the existing epidemiology showed that men are more likely to contract SARS-CoV-2 than women in China and Italy[20,21]. The high infection rate and susceptibility rate of men had undoubtedly aggravated the harm caused by COVID-19 to men. A large-scale prospective cohort study[22] conducted in the United Kingdom found that 60% of the patients diagnosed with COVID-19 are men. A recently performed single-cell RNA sequencing profiling analysis of human testicular cells showed that ACE2 was highly expressed in the spermatogonia and Leydig and Sertoli cells[23], which was suggestive of a high potential of SARS-CoV-2 infection in human testes. If the spermatogonia are infected and destroyed by the SARS-CoV-2, spermatogenesis will also be disturbed. Briefly, these results emphasize the risk posed by COVID-19 to testicular cells and the process of spermatogenesis.

The testes also have their own anti-infection defense system, which mainly relies on the function of the blood-testis barrier (BTB). The BTB provides protection from autoimmune cell destruction, making the testes an immune-privileged

site. The composition of BTB includes its physical and immunomodulatory components. The physical components comprise a layer of Sertoli cells connected by tight junctions[24]; the immunomodulatory components are mainly composed of the constitutive expression of anti-inflammatory factors by testicular cells, most prominently, transforming growth factor beta[25,26]. The high expression of ACE2 on Sertoli cells makes the physical barrier of BTB vulnerable to attack by viruses. When cells are attacked by viruses, the testicular immune response will be spontaneously initiated, which will cause immune cells such as T-lymphocytes and macrophages to gather in the testes. Although the immune system plays an important anti-viral role, excess production of immune factors is also disadvantageous and may cause orchitis. The massive release of inflammatory factors and chemokines is the body's adaptive immune response after a SARS-CoV-2 infection, but it may also lead to uncontrolled inflammation, which results in a large decrease in the number of lymphocytes and the dysfunction and low initiation efficiency of the adaptive immune response. This may even lead to secondary autoimmune orchitis[27].

The direct evidence for the effect of COVID-19 on male reproductive function comes from a study where the sperm parameters and immune factors, among other characteristics, were compared between semen specimens from rehabilitated COVID-19 patients and those who died. Epididymides from decreased COVID-19 patients showed noticeable changes compared to those from age-matched controls, such as the presence of interstitial edema and congestion both in the testes and epididymides and the thinning of the seminiferous epithelium[28], which demonstrates that spermatogenesis can be markedly impaired by SARS-CoV-2. Furthermore, the sperm concentration of inpatients with COVID-19 was significantly decreased, compared to that of age-matched control men[28].

Although there are no reports of infertility due to SARS-CoV-2 infection, current clinical data indicate that SARS-CoV-2 affects the male reproductive system.

Conclusions and Future Directions

SARS-CoV-2 is associated with a higher occurrence of infection and stronger infectivity than the other coronaviruses; thus, we have reason to believe that the sequelae or complications in COVID-19 patients are more severe. In view of this, it is necessary that infected men be examined for fertility soon after recovery, especially for marriageable men and married men who want to have children. Furthermore, measures should be taken to safeguard the reproductive health of men infected with COVID-19, and it is necessary to screen these patients. We can help these patients by formulating screening criteria and via timely screening and formulating standard treatment strategies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

All authors drafted, edited, and approved the final manuscript.

References

1) Wang J, Du G. COVID-19 may transmit through aerosol. Ir J Med Sci 2020; 189: 1143-1144.
2) Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. Eur Rev Med Pharmacol Sci 2020; 24: 2006-2011.
3) Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) Coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses 2020; 12: 194.
4) Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect 2020; 9: 687-690.
5) Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. Microbes Infect 2020; 22: 69-71.
6) Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282: 1-23.

7) Djomkam ALZ, Olwal CO, Sala TB, Paemka L. Commentary: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Front Oncol 2020; 10: 1448.
8) Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q, Zhou H, Yan J, Qi J. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 2020; 181: 894-904 e9.
9) Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med 2020; 26: 450-452.
10) Ortega JT, Serrano ML, Pujol FH, Rangel HR. Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: an in silico analysis. EXCLI J 2020; 19: 410-417.
11) Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020; 14: 185-192.
12) Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. Clin Infect Dis 2020; 71: 870-874.
13) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
14) Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S, Gu J. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 2006; 74: 410-416.
15) Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, Geng J, Cai J, Han H, Li X, Kang W, Weng D, Liang P, Jiang S. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004; 203: 622-630.
16) Docampo MJ, Hadziselimovic F. Molecular pathology of cryptorchidism-induced infertility. Sexual Development 2015; 9: 269-278.
17) Wan Y, Shang J, Graham R, Baric RS, Li F, Gallagher T. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94: e00127-20..
18) Song C, Wang Y, Li W, Hu B, Chen G, Xia P, Wang W, Li C, Diao F, Hu Z, Yang X, Yao B, Liu Y. Absence of 2019 novel coronavirus in semen and testes of COVID-19 patientsdagger. Biol Reprod 2020; 103: 4-6.
19) Clarke NE, Turner AJ. Angiotensin-converting enzyme 2: the first decade. Int J Hypertens 2012; 2012: 307315.
20) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China medical treatment expert Group for C. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.
21) Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020; 323.
22) Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJM, Baillie JK, Semple MG. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020; 369: m1985.
23) Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells. Cells 2020; 9: 920.
24) Fijak M, Bhushan S, Meinhardt A. Immunoprivileged sites: the testis. Methods Mol Biol 2010; 459-470.
25) Watanabe M, Kashiwakura Y, Kusumi N, Tamayose K, Nasu Y, Nagai A, Shimada T, Daida H, Kumon H. Adeno-associated virus-mediated human IL-10 gene transfer suppresses the development of experimental autoimmune orchitis. Gene Ther 2005; 12: 1126-1132.
26) Pollanen P, Euler M, Jahnukainen K, Saari T, Parvinen M, Sainio-Pollanen S, Soder O. Role of transforming growth factor/3 in testicular immunosuppression. J Reproduct Immun 1993; 24: 123-137.
27) Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, Su X, Cao B. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020; 395: 1517-1520.
28) Li H, Xiao X, Zhang J, Zafar MI, Wu C, Long Y, Lu W, Pan F, Meng T, Zhao K, Zhou L, Shen S, Liu L, Liu Q, Xiong C. Impaired spermatogenesis in COVID-19 patients. EClinicalMedicine 2020: 100604.