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MINI-REVIEW

Effect of COVID-19 on male reproduction

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Abstract

There is a structural basis for invasion of the male reproductive system by the novel coronavirus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Current evidence suggests this virus can cause substantial damage to male testicles, leading to decreased testosterone levels, increased luteinizing hormone levels, and a decrease in sperm production and quality. Potential mechanisms for this damage include local inflammation of the testes, cytokine storms and fever. SARS-CoV-2 has strong transmissive ability, and its impact on the male reproductive system deserves attention. In view of the limited existing research, the aim of this study was to review the impact of the novel coronavirus on male reproduction and the potential mechanism.

Keywords

SARS-CoV-2; Male reproductive system; Male fertility; COVID-19; Reproductive hormones; Damage mechanism

1. The discovery of COVID-19

Scientists isolated and sequenced a novel coronavirus from human samples for the first time in December 2019. In February 2020, the International Committee on Taxonomy of Viruses officially named it "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" [1]. In the same month, the World Health Organization named the disease caused by this virus as SARS-CoV-2 coronavirus disease 2019 (COVID-19).

2. Pathological characteristics of COVID-19

SARS-CoV-2 belongs to the β-coronavirus family and is a type of enveloped linear, single-stranded, positive-sense RNA virus. Soon after being infected with COVID-19, the human body typically develops fever, dry cough and fatigue, whereas upper respiratory symptoms (*e.g.*, runny nose, nasal congestion) are rare. About 50% of patients experience breathing difficulties after one week, and critically ill patients can rapidly progress to life-threatening acute respiratory distress syndrome, metabolic acidosis, septic shock or coagulation dysfunction.

3. How COVID-19 attacks the male reproductive system

SARS-CoV-2 invades the human body and initiates the infection process by binding to angiotensin converting enzyme 2 (ACE2) on host cells. A variety of cell types in the male testis show high expression of ACE2, suggesting it could serve as a potential gateway for the invasion of novel coronavirus. Some studies have shown that COVID-19 can invade the male reproductive system and cause hormone imbalance and damage to sperm production. This study reviews the impact of COVID-19 on male reproductive health, together with the potential mechanisms involved.

4. Molecular basis underlying the effects of COVID-19 on male reproductive health

SARS-CoV-2 is composed of a protein coat that surrounds RNA. The protein component contains four structural proteins: nucleocapsid (N), envelope (E), membrane (M), and spike (S) proteins [2]. N protein binds to nucleic acids and facilitates viral genome encapsulation, while E protein forms an envelope around the nucleocapsid. The M and S proteins are embedded within the envelope, with S protein being the most important structural protein for viral invasion into the human body. Transmembrane protein serine 2 (TMPRSS2) is a family of proteases that anchor to the cell membrane through the amino terminal transmembrane region and have the ability to cleave S proteins into S1 and S2 subunits. During the process of virus invasion into the human body, the S1 subunit first binds to the host cell surface receptor angiotensin converting enzyme 2 (ACE2). Under the action of the S2 subunit, it then fuses with the host cell membrane and enters the cell through endocytosis, thereby completing the replication and proliferation cycle. High expression levels of TMPRSS2 and ACE2 in host cells therefore comprise the molecular basis for virus infection and host damage [3]. ACE2 is expressed in various tissues of the human body, particularly in type II alveolar epithelial cells, respiratory epithelial cells, myocardial cells, ileal and esophageal epithelial cells, renal proximal tubule cells, and

urinary tract epithelial cells in the bladder. Single cell RNA sequencing data has shown that ACE2 is highly expressed in the three main cell types that comprise testicular tissue (spermatogenic, stromal, and supporting cells) [4]. TMPRSS2 is highly expressed in spermatogenic cells, whereas its expression is relatively low in the other two cell types. The co-expression of ACE2 and TMPRSS2 in testicular tissue suggests the testis could be a potential target organ for SARS-CoV-2 infection in the human body. Once the virus invades the target cells in testicular tissue, it can damage the physiological functions of spermatogenesis and hormone levels in the pituitary-testicular axis, thus affecting male fertility. A correlation has been observed between the expression of testicular ACE2 and age, with the highest expression observed in male patients aged around age 30 years, relatively low expression at age 20, and the lowest expression at age 60. This indicates that young male patients are more likely to experience testicular problems following SARS-CoV-2 infection than elderly patients [3].

5. Effect of COVID-19 on male reproductive health

5.1 Effect of COVID-19 on hormone levels of the pituitary-testis axis in male patients

The testis is composed of seminiferous tubules and connective tissue stroma. The seminiferous tubules contain "spermatogenic cells" and "supporting cells", whereas the connective tissue stroma contains "interstitial cells". A three-level regulatory mechanism regulates androgens in the hypothalamus–pituitary–testis, involving mainly the supporting cells and interstitial cells in the testis. A case-control study by Ma *et al*. [5] was the first to report sex hormone levels in male COVID-19 patients. No significant difference in serum testosterone level was found between 81 male patients who entered the recovery period after COVID-19 infection and 100 age-matched healthy men. Moreover, the testosterone/luteinizing hormone (LH) and follicle stimulating hormone (FSH)/LH ratios in the COVID-19 recovery group were significantly lower than those in the control group. In addition, linear regression analysis revealed that the testosterone/LH ratio and the number of white blood cells in COVID-19 patients showed significant negative correlations with the level of C-reactive protein. Another study found that male patients with COVID-19 in the disease period had significantly lower levels of serum testosterone and double serum testosterone compared to the healthy control group [6]. Temiz *et al*. [7] reported significant differences in FSH, LH, and testosterone levels between COVID-19 patients and controls, although the hormone levels in both groups were within the normal range. Rastrelli *et al*. [8] compared the testosterone level between COVID-19 patients with different outcomes. These authors reported that the total testosterone level of COVID-19 patients with poor outcomes was significantly lower than that of COVID-19 patients with good outcomes.

The above results indicate that COVID-19 patients have a lower testosterone level and higher LH level compared with normal controls. There was no significant difference in the testosterone level of COVID-19 patients in the recovery period compared to normal controls, whereas the LH level and testosterone/LH ratio were significantly higher. This indicates that COVID-19 has some effect on testicular function by altering the level of gonadotropin. The slightly increased LH level and slightly reduced FSH/LH and testosterone/LH ratios also indicate slightly damage of testicular tissue, with changes in the gonadotropin level mediated through a negative feedback mechanism involving the hypothalamic–pituitary–gonadal (HPG) axis.

5.2 Effect of COVID-19 on sperm production

The relevant semen parameters show alterations in male COVID-19 patients. A single center cohort study analyzed the semen test results for 20 COVID-19 patients (18 rehabilitation patients and 2 active infection patients) [9]. These were divided into a mild infection group and a moderate infection group according to whether or not hospitalization was required during the infection period. The sperm density, total number of tested sperm, total number of active sperm, and total number of rapidly moving sperm were significantly lower in the moderate infection group compared to the mild infection group and to the normal control group. Another study classified COVID-19 patients into mild and moderate groups according to whether or not they had fever [10]. The sperm quality (sperm density and total number of active sperm) of patients in the moderate group was significantly lower compared to the mild and control groups. However, another small cohort study showed that all semen parameters in the COVID-19 case group were normal, except for sperm morphology [11]. Whether the SARSCoV-2 virus can be detected in semen is currently a subject of debate, with a meta-analysis reporting that 3 out of 12 studies were able to detect viral RNA in patient semen [12]. However, many studies using Reverse Transcription Polymerase Chain Reaction (RT-PCR) were unable to detect SARS-CoV-2 in the semen of COVID-19 patients.

The above observational research results show varying degrees of change in the spermatogenic function of COVID-19 patients with different levels of illness. However, it is still uncertain whether these changes are caused by viral damage to testicular tissue. Patients with more severe disease receive additional treatments such as glucocorticoids and antiviral drugs which may damage spermatogenic cells and cause spermatogenic disorders [13, 14]. Therefore, the possibility of interference by such drugs should be excluded in future relevant studies.

6. Mechanism of testicular injury induced by COVID-19

Yang *et al*. [15] used electron microscopy to observe the testicular tissue from 12 patients who died from COVID-19. The Sertoli cells in the testes showed swelling, vacuolization, and detachment from the basement membrane of the seminiferous tubules. The interstitial tissue of the testis showed edema and inflammatory infiltration, with an inflammatory reaction observed in the local testis. These findings demonstrate that COVID-19 causes substantial damage to testicular tissue.

Many studies using RT-PCR have failed to detect SARS-CoV-2 in the semen of COVID-19 patients following recovery from this disease. Moreover, semen quality improved following recovery from COVID-19.

6.1 Viral orchitis

Viral infection is known to cause viral orchitis, with Li *et al*. [16] reporting the first COVID-19 case with viral orchitis as a complication. A retrospective study by Lin *et al*. [17] showed that 2.7% (3/112) of COVID-19 patients had viral orchitis. Other types of coronavirus, such as SARS-1-CoV, can also cause orchitis. One study reported histopathological results at autopsy for the testicles of seven patients who died from SARS infection. These showed the presence of viral orchitis, with the main site of inflammatory infiltration being in the seminiferous tubules. Immunohistochemical results showed that IgG was mainly deposited in the epithelial cells, stroma, degenerated germ cells and supporting cells of the seminiferous tubules [16, 18]. These pathological processes involved the same cell types as those showing high ACE2 expression [19, 20]. The above results indicate that testicular damage caused by SARS-CoV-2 may be a result of inflammation and immune responses, rather than direct viral attack. Oxidative stress and other mechanisms may also decrease the semen quality of male patients with COVID-19.

6.2 Cytokine storm refers to an infection in the body

Abnormal overactivation of the immune system in the late stage of infection leads to the rapid release of a large number of different cytokines in body fluids, resulting in cell damage. Yang *et al*. [21] followed up 53 severely ill COVID-19 patients and screened for 48 cytokines. The case group showed increased levels of 14 cytokines compared with the control group. Sustained increases in interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein-3 (MCP-3), and interleukin-1 receptor antagonist (IL-RA) were associated with increased viral load and impaired lung function. Studies have shown that patients with severe COVID-19 may suffer from second-generation cytokine storm syndrome, or hemophilic lymphohistiocytosis. This little-known inflammatory syndrome is characterized by persistent fever and is accompanied by explosive and fatal hypercytokinemia and multiple organ failure. Patients with this syndrome exhibit a specific serum cytokine profile, accompanied by cytopenia and methemoglobinemia [22, 23]. Cytokines are crucial for the maintenance of testicular function, and COVID-19-induced changes in the local cytokine spectrum can affect male reproductive ability [24]. However, due to the failure to detect local cytokines in the testes and to the presence of the blood-testis barrier, it remains to be determined whether virus-induced systemic cytokine inflammation occurs in the testes and causes corresponding damage. Oxidative stress and high-grade fever can affect the HPG axis and testis, and other mechanisms should therefore also be studied.

6.3 Cytokine storm

Cytokine storm refers to the abnormal overactivation of the immune system in the late stage of infection with microorganisms, leading to a large number of cytokines in body fluids and resulting in cell damage. Yang *et al*. [21] studied 53 severely ill COVID-19 patients and screened for 48 cytokines. Compared with the control group, the case group showed increased levels of 14 cytokines. Sustained increases in the levels of IP-10, MCP-3 and IL-1RA were associated with increased viral load and impaired lung function. Patients with severe COVID-19 may suffer second-generation cytokine storm syndrome, or hemophilic lymphohistiocytosis. This little-known inflammatory syndrome is characterized by persistent fever accompanied by explosive and fatal hypercytokinemia and multiple organ failure. Patients with this syndrome exhibit a specific serum cytokine profile, accompanied by cytopenia and methemoglobinemia [22, 23]. Cytokines are crucial for the maintenance of testicular function, and changes in the local cytokine spectrum of the testes caused by coronavirus will affect male reproductive ability [24]. However, due to the failure to detect local cytokines in the testes and to the presence of the blood-testis barrier, it remains to be confirmed whether virus-induced systemic cytokine inflammation occurs in the testes and causes corresponding damage.

6.4 High-grade fever

The process of sperm production is temperature-dependent, with the optimal temperature being slightly lower than the normal human body temperature. Elevated local temperatures in the testicles can therefore adversely affect sperm production.

Both spermatogenesis and sperm quality suffer adverse effects from elevated body temperature. Once the body undergoes disordered temperature regulation, this may damage sperm quality and increase the risk of infertility. Since about 80% of COVID-19 patients show fever symptoms [25], the impact on male reproduction needs to be considered. Carlsen *et al*. [26] reported that the number of normally shaped sperm decreased by 7.4% during fever days in male patients, while the number of inactive sperm increased by 20.4%. During the process of virus resistance, the body produces varying degrees of immune response that share common symptoms with fever. In addition, local inflammation further increases the temperature of the testes. Therefore, fever may play a role in the abnormal spermatogenic function of male COVID-19 patients, but is not a specific manifestation of COVID-19 patients, nor is it a persistent influencing factor.

7. Summary and outlook

COVID-19 has a wide range of impacts, and its strong transmission ability has normalized the epidemic prevention and control. The impact of SARS-CoV-2 on the male reproductive system requires further research. Existing evidence shows that COVID-19 causes substantial damage to testicular tissue, alters sex hormone levels in males, and has adverse effects on sperm production and quality. Local inflammatory reactions in the testicles may be the main mechanism of injury, rather than direct viral damage. Factors such as cytokine storms and fever

may play key roles in this process. In view of the limited data and scale of existing studies and the diversity of conclusions, further research is needed into the effects of COVID-19 on the male reproductive system, particularly with regard to tissue damage and the mechanism of injury.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XZY—wrote the manuscript; JF—performed the literature review; MLM—provided help and advice on the revision of the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Xuezhen Yang is serving as one of the Editorial Board members of this journal. We declare that Xuezhen Yang had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to KSH.

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