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Chapter

Crosstalk between SARS-CoV-2 and Testicular Hemostasis: Perspective View

R.G. Ahmed

Abstract

The infection of SARS-CoV-2 and its COVID disease caused several economic and social disturbances worldwide. This chapter aimed to determine the severity of SARS-CoV-2 infection on the testicular hemostasis. This overview showed the possible mechanisms of how the SARS-CoV-2 can infect the testes. SARS-CoV-2-induced pneumonia, cytokine storm, and immunosuppressive state may transfer from the respiratory tract to the blood circulation, binding to testicular angiotensin-converting enzyme 2 receptors (ACSE2) and initiate its intracellular replication and action (cytotoxicity), that disrupting the testicular hemostasis. In severe states, COVID-19 disease can increase body/testes temperature, which may destroy the germ cell in the long term. The final mechanism is that SARS-CoV-2 infection causes stress, panic, and anxiety states, causing brain disorders that may perturb the hypothalamic–pituitary-testes-axis (HPTA). This disturbance may then lead to testicular dysfunction. The severity of COVID-19 may be age-dependent and depending on the expression and distribution of testicular ACSE2 receptors. Also, this chapter not only showed the sexual transmission of SARS-CoV-2 but also followed its impact on sexual behavior, pregnancy, and progeny. Thus, maintaining the testicular hemostasis may play a vital role in a healthy life for the offspring. Further research and clinical studies are required to explore this issue.

Keywords: SARS-CoV-2 (COVID-19), Testes, angiotensin-converting enzyme 2 receptor (ACSE2) HPTA, Pregnancy

1. Introduction

The World Health Organization (WHO) confirmed that the infection of SARS-CoV-2 could transfer from human to human via the airway droplet spread, infected surfaces, or fecal route [1–3]. SARS-CoV-2 causes COVID-19 respiratory disease belonging to β-CoV (lineage B) with a duration of 3–6 days [4]. Seah et al. [5] reported that coronaviruses (CoVs) consist of nucleocapsid protein (N) for bounding to RNA genome to make up nucleocapsid, spike protein (S) for binding of host cell receptors to facilitate entry of host cell, an envelope protein (E) for interacting with M to form a viral envelope, and membrane protein (M) for the central organizer of CoV assembly and determining the shape of the viral envelope. SARS-CoV-2 is dissimilar to SARS-CoV in the absence of 8a, longer 8b, and shorter 3b segments and different in the presence of Nsp 2, Nsp3, open reading frame (orf) 2,

Name of virus	Hosts			Classification and incubation period	Transmission of disease/its onset	Epidemiology	Recovery	Complications
	Natural host	Intermediate host	Final host					
SARS-CoV	Bats	Palm civets	Human	β-CoV, lineage B (2–11 days)	Human to human/ sudden	• 2002-2003 in China • Globally thereafter	5–6 weeks	It can damage the testes causing orchitis.
SARS-CoV-2		Malayan pangolins		β-CoV, lineage B (3–6 days)		• 2019-2020 in China • Globally thereafter	2–8 weeks	• It may cause a spermatogenic failure. • It may diminish the sperm concentration and motility.

Table 1.
Overview about the SARS-CoV and testicular complications [10–12].

and orf10 proteins [6–9]. This variance might be the cause of the highly contagious SARS-CoV-2 worldwide. The infection of SARS-CoV-2 can transfer from bats (natural host) to Malayan pangolins (intermediate host) and then to human, as shown in **Table 1** [10–12]. In general, the infection of SARS-CoV-2 can cause a dry cough, diarrhea, fatigue, and disorders in respiratory, circulatory, and renal systems [13–15], and then death [16]. Also, SARS-CoV-2 infection can disrupt the hemostasis of the urinary system [17]. Similar results are recorded in the Middle East respiratory syndrome (MERS-CoV, 2012) and severe acute respiratory syndrome (SARS-CoV, 2002–2003) infected animal models [18].

The current chapter aimed to determine the severity of SARS-CoV-2 infection on the testicular hemostasis and showed the possible mechanisms of how the SARS-CoV-2 can infect the testes. Also, this chapter showed the sexual transmission of SARS-CoV-2 and followed its impact on sexual behavior, pregnancy, and progeny.

2. Observations and discussion

2.1 Possible mechanisms of how the SARS-CoV-2 can infect the testes

As angiotensin-converting enzyme 2 receptors (ACSE2) expression is rich in testes, SARS-CoV-2 may bind these receptors to penetrate cells and initiate its intracellular replication and action (cytotoxicity) that disrupting the testicular hemostasis. Similarly, several studies reported that ACSE2 receptor expression is rich in human male gonads (spermatogonia, Leydig, Sertoli cells, and seminiferous ducts), thus SARS-CoV-2 can bind ACSE2 receptor to disrupt gonadal hemostasis and increase the risk of testicular dysfunction [19–22]. SARS-CoV-2 may cause spermatogenic failure [20]. However, **t**he detection of SARS-CoV-2 in human semen was 1 to 15 patients (6.66%) [23]. More importantly, Li et al. [24] detected the SARS-CoV-2 in the semen of patients with COVID-19 and the semen of recovering cases. However, this study was limited to 50 patients only and a short time. Previously, SARS-CoV and NL63 coronavirus (NL63-CoV) can propagate inside the host cells by binding the cell surface ACE2 [25, 26]. SARS-CoV can disrupt spermatogenesis causing orchitis [27] and infect Leydig cells and testicular epithelial cells [28]. The previous findings could be attributed to SARS-CoV-2-induced pneumonia, neutropenia, lymphopenia, and hypo-albuminemia [29], and immunosuppressive state and cytokine storm [13, 14]. This state could be illustrated by the variation in the levels of several interleukins (IL-1β, IL-10, and IL-4), interferons (interferon-inducible protein 10, and interferon-gamma (IFN-γ)), and monocyte chemoattractant protein 1 (MCP-1) [13, 14]. Alternatively, SARS-CoV can elevate the levels of lipid peroxidation (LPO) and generally reactive oxygen species (ROS), causing oxidative stress (OS) and testicular dysfunction [30].

Another possible mechanism is that in severe states, COVID-19 disease can increase body/testes temperature, which may destroy the germ cell in the long term. Concomitantly, the viral infection-induced fever disrupts the male reproductive homeostasis [22]. In similar, severe fever in SARS-CoV causes congestion and mild fibrosis in the testes, disrupting the testicular hemostasis [27]. There was a reduction in the sperm number and fragmentation in the sperm DNA in males recovering from COVID-19 disease and fever [31, 32]. This variation can deteriorate fertility, delay embryo development, and augment abortion [33]. Importantly, fever alone can damage the spermatogenesis process [34] and destruct the Sertoli and germ cells [27].

The final mechanism is that SARS-CoV-2 infection causes stress, panic, and anxiety states, causing brain disorders that may perturb the hypothalamic–pituitary-testes-axis (HPTA). Also, the disturbance in the hypothalamic–pituitary

axis can vary the sex hormones and adrenaline that support sexual activities [35]. SARS-CoV might cause leukocyte infiltration in testes [36], disrupt the functions of Leydig cells and the production of testosterone, destroy the seminiferous epithelium, and damage the blood-testis barrier [27]. Interestingly, the elevation in the level of serum IgG was reported in SARS-CoV patients [37]. This elevation could degenerate the Sertoli and germ cells, causing autoimmune orchitis [27]. Mumps orchitis could be attributed to the reduction in the level of testosterone and an increase in the follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels [38]. In general, the virus can cause orchitis and sterility and increase the risk of the testicular tumor [39–41]. This damage may lead to hypogonadism [42] and decrease the number of Leydig cells [43]. In similar, male infertility might initiate by several viruses such as human papillomavirus (HPV) [44], herpes simplex viruses (HSVs) [45], human immunodeficiency viruses (HIV) [46], hepatitis B virus (HBV) [47], hepatitis C virus (HCV) [48], *Mumps orthorubulavirus* virus (MuV) [49], and Bluetongue virus (BTV) (an arbovirus of ruminants) [50].

2.2 Sexual transmission, sexual behavior, pregnancy, and progeny

The SARS-CoV-2 can transfer via respiratory droplets from human-to-human [51], feces [52], blood [53], or semen [24, 54, 55]. SARS-CoV-2 can form a systemic local infection in the male reproductive system due to the disruption in the barriers between testes, blood, vas deferens, and epididymis barriers [24, 54, 55]. However, the transportation of SARS-CoV-2 through semen was absent during the sexual process [56]. This absence may be due to the defense barrier between the testes and blood [57]. Importantly, real-time polymerase chain reaction (RT-PCR) has failed to designate SARS-CoV-2 sequences in the testicular tissues [43, 58].

The infection of SARS-CoV-2 may transfer during the sexual activity between the couples who have COVID-19 disease [59]. Moreover, saliva contact (physical process) between couples can increase the risk of virus transmission [12, 60]. On the other hand, pregnant women during the last trimester of pregnancy are more vulnerable to SARS-CoV-2 infection [61]. Moreover, cerebral vasculitis [62] and maternofetal T helper 2 (Th2) disorder [63] could damage the placenta. In Iran, 7 from 9 infected pregnant women with SARS-CoV-2 were dead [64]. A few data have supported this route [64]. However, most studies neglected the risk of the vertical route of SARS-CoV-2 between dams and their offspring [65–67]. On the other hand, the infected breast milk with SARS-CoV-2 or the close contact between neonates and infected dams with COVID-19 disease can be other routes for the possibility of SARS-CoV-2 transmission [68].

More importantly, the outbreak of infectious diseases can put the dams and their neonates in a risky state [69]. Likewise, SARS-CoV 2003 might disrupt the maternofetal immune system, causing abortion [70] or intrauterine growth restriction (IUGR) [71]. This disruption may delay neonatal health and cause neurodevelopmental disorders [72]. However, the severity and duration of this disruption on offspring are not identified completely. A healthy dietary supplementation and proper awareness during the perinatal period should be followed during this epidemic period to avoid this disorder. Also, anti-inflammatory treatments will be supportive to treat fertility problems [22].

3. Conclusion

This chapter showed three possible mechanisms of how the SARS-CoV-2 can infect the testes (**Figure 1**): **(1)** SARS-CoV-2 may bind ACSE2, disrupting the

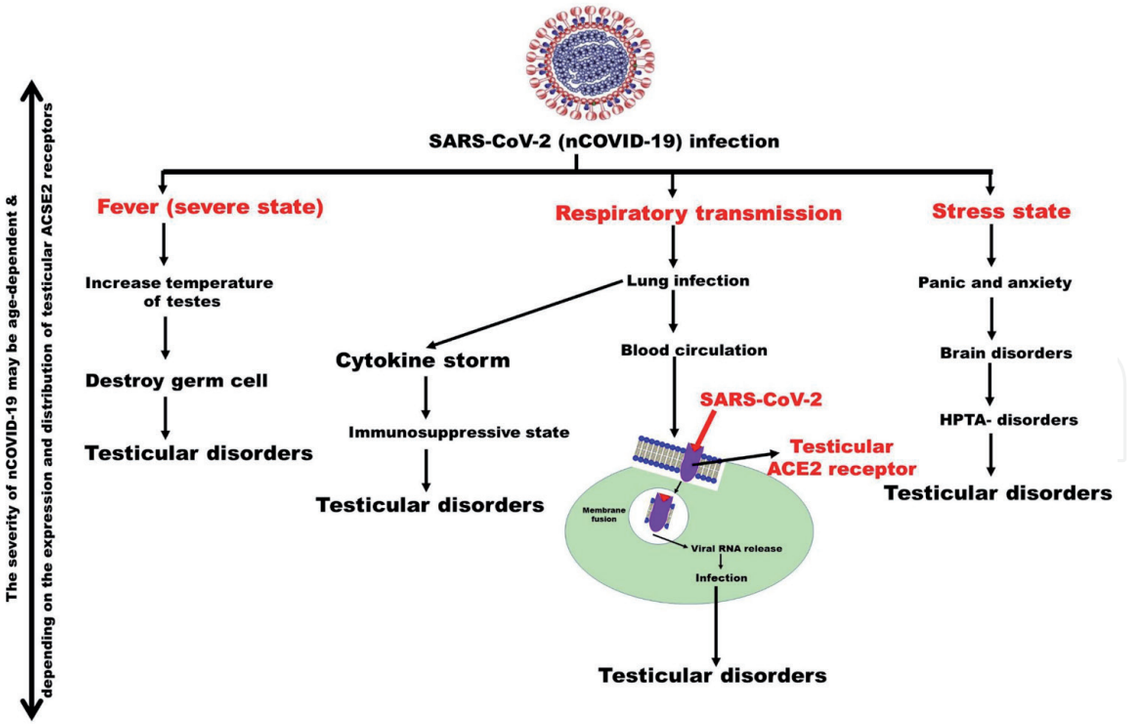

Figure 1.
Summary about the expected mechanisms of SARS-CoV-2 (COVID-19) on testicular hemostasis. Here, ACSE2 is angiotensin-converting enzyme 2, and HPTA is hypothalamic–pituitary-testes-axis.

testicular hemostasis. **(2)** SARS-CoV-2 and its COVID disease can increase the temperature of the testes, destroying the germ cell in the long term. This severity may be age-dependent and depending on the expression and distribution of testicular ACSE2 receptors. **(3)** SARS-CoV-2 and its COVID disease may perturb the HPTA. In the future, SARS-CoV-2 may directly or indirectly change the world's demographics [73]. Thus, preserving the testicular hemostasis may play a dynamic role in a healthy life for the offspring. Additional studies are desired to explore these issues.

4. Recommendations

As there is limited information about the complications of SARS-CoV-2 on reproductive organs, the current findings warrant the risk of the occurrence of orchitis and recommend the following-up and evaluation of the testicular hemostasis (andrological health) in the infected males with SARS-CoV-2. Also, avoid sex activity between the couples who have SARS-CoV-2 infection or symptoms of COVID-19 was recommended. In cases that recovered from COVID-19, the endothelial disorder may cause erectile dysfunction as a pathophysiological condition [74, 75]. Importantly, couples should be avoided the fear of virus transmission during the sexual process because this fear can decrease the sexual desire and quality of sex activity [76]. Moreover, these severe conditions can increase abortion, menstrual disorders, and psychological problems (depression, poor mood, nervousness, or irritability) [77].

On the other hand, recovered dams from symptoms of COVID-19 should use an artificial feeding pump, wash their hands, and wear a mask before and during the breasting feeding process [78]. Evaluation of gonadal function and genital examination for patients recovered from COVID-19 should be warranted. More importantly, the American Society for Reproductive Medicine (ASRM) recommended suspending all types of assisted reproductive techniques (ART),

including intrauterine inseminations (IUIs) or in vitro fertilization (IVF) during the COVID-19 pandemic [79], particularly, for patients who have immunocompromised diseases (AIDS, cancer, or malnutrition) or chronic diseases (cardiovascular, hepatic, or renal diseases, hypertension, and diabetes mellitus) [80, 81]. Similarly, the French Biomedicine Agency (ABM) suspended ART during this period [82]. Finally, the social contact between ART professional groups and patients should be online during this period.

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Conflict of interest

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