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Mini Review

The Role of SARS-CoV-2 in Male Reproduction

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Abstract

COVID19 is an infectious disease transmitted by the SARS-CoV-2 virus, whose outbreak was declared a pandemic in March 2020. To date, on November 17, 2020, 55,243,538 confirmed cases had been reported worldwide. Epidemiological studies in different countries have shown higher morbidity and mortality in male than in female patients. The relationship between the COVID-19 disease and the renin-angiotensin-aldosterone (RAA) system has also been documented. The SARS-CoV-2 enters cells through a receptor called angiotensin-converting enzyme-2 (ACE2) and a serine protease (TMPRSS2), both widely expressed in the body, including the testes. ACE2 belongs to the RAA system, which is also expressed in the male reproductive system, and its absence causes infertility. Moreover, ADAM17 is a metalloprotease responsible for inflammation and spermatogenesis and is activated by SARS-CoV-ECA2. Knowledge about the consequences of SARS-CoV-2 infection on male reproduction, as well as the possibility of sexual transmission, is still limited. This review summarizes the available evidence to analyze the effect of SARS-CoV-2 infection on male reproduction and its possible sexual transmission. The reproductive consequences caused by COVID-19 are currently unknown. Although most studies have shown the absence of SARS-COV-2 in the semen and prostate secretion, there is evidence of testicular tissue alteration accompanied by inflammatory infiltration in viral orchitis. These results suggest that there may be a deterioration in the testicular function that could lead to infertility. Also, more studies are needed to assess the risk of sexual transmission.

Keywords: SARS-CoV-2, ACE2, TMPRSS2, ADAM17, Infertility

Introduction

Numerous pneumonia cases of unknown etiology appeared at the end of December 2019 in Hubei's province in China, where the virus was identified as a severe respiratory syndrome, named as coronavirus-2 (SARS-CoV-2).[1,2] The World Health Organization (WHO) declared the infection caused by SARS-CoV-2, a pandemic, and named the disease COVID-19. Since its discovery, the new pneumonia caused by this virus continues to spread around the world, with a current count of 55,243,538 confirmed cases and 1,330,930 deaths worldwide.[3] The COVID-19 disease is transmitted mainly by a direct contact with the infected person through the droplets expelled when talking, coughing, or sneezing; and through contact with surfaces contaminated with secretions from the respiratory tract of infected people.[4] The incubation period is 6-14 days.[5] Viral transmission from presymptomatic and asymptomatic individuals has promoted viral shedding throughout the world.[6,7] Diverse clinical manifestations appear in the population infected by SARS-CoV-2, some of them include the asymptomatic carrier, the acute respiratory disease, and pneumonia; which present common signs and symptoms, such as fever, dry cough, headache, asthenia, myalgia, sore throat, and less common rhinorrhoea, diarrhea, hemoptysis, nausea, or vomiting, and conjunctival congestion. Anosmia and ageusia have been recognized as prevalent early symptoms in both asymptomatic and COVID-19-positive patients.[8–11]

In early 2020, SARS-CoV-2 was identified as a member of the family Coronaviridae.[1,2] Coronaviruses, that includes four genera (α, β, γ, and δ) SARS-CoV-2, SARS-CoV, and MERS-CoV belong to the genus β-coronavirus and can cause acute respiratory distress syndrome in humans.[12] SARS-CoV-2 is an enveloped virus with a single-stranded RNA genome, a non-segmented

and positive sense, a part of its genome encodes the spike (S), envelope (E), membrane (M), and nucleocapsid (N). The spike protein (S) binds to the receptor on the host cell membrane's surface, the membrane protein that participates in viral assembly and budding, and the nucleocapsid protein, which binds to the genome and participates in assembly and viral lysis.[13,14] SARS-CoV-2 and SARS-CoV enter cells through the interaction of their protein S with the receptor called angiotensin-converting enzyme (ACE2),[15,16] which is highly present in the human body. It can be found in the oral, nasal and nasopharynx mucosa, lungs, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, brain, testis, and prostate.[17–19] Due to the presence of ACE2 in male reproduction organs, SARS-CoV-2 infection may have an impact in male reproduction. The review aims to analyze the available information of the SARS-CoV-2 infection and its potential effects on male fertility, and its sexual transmission. For this purpose, Pubmed, Science Direct and MedRxiv databases were employed to identify publications in this regard.

Mechanism of Pathogenesis

The pathogenesis SARS-CoV mechanism involves the expression of the ACE2 receptor, although SARS-CoV2 has a 20-fold greater affinity to receptor.[16] To get into cells, the S proteins of SARS-Cov-2 associate with the ACE2 receptor. Protein S is formed by two subunits that facilitate the viral-host cell union; the S1 domain interacts and binds through the ACE2 receptor binding domain, while the S2 domain participates in the fusion of the virus-host cell membranes. To complete its entry, S2 is cleaved by the transmembrane protease serine 2 (TMPRSS2), contributing to receptor separation and subsequent membrane fusion, thus facilitating SAR-CoV entry SARS-CoV2 through endocytosis.[14,16,20] Also, protein S binding to ACE2 decreases its expression and the loss of the ACE2 expression turn into a severe acute respiratory failure.[21]

ACE2 is a transmembrane metalloproteinase that shows significant homology to the classic ACE isoform. Both isoforms are part of the renin-angiotensin-aldosterone system (RAAS), a critical system that regulates the cardiovascular system and glucose homeostasis among others.[22,23] Renin is a proteolytic enzyme secreted by the kidney in response to blood pressure or sodium concentration. Renin cleaves angiotensinogen, generating angiotensinogen I.[24] While ACE catalyzes angiotensin I to angiotensin-II, ACE2 is responsible for the generation of angiotensin 1-9 and 1-7 from angiotensin I and II, respectively.[25] Meanwhile, angiotensin II acts on AT1 receptors producing vasoconstriction, sympathetic activation, inflammation, oxidative stress, and insulin resistance, while angiotensin 1-7 provokes anti-inflammatory, antifibrotic, and diuretic actions through the Mas receptor.[26,27]

Role of ACE and TMPRSS2 Isoforms in Testes

The expression of various RAAS molecules has been identified in testes, epididymis, and spermatozoa in different animal and human species.[25,28–35] Several studies have shown that ACE expression is involved in the processes of spermatogenesis, spermiogenesis, sperm capacitation, as well as in fertilization.[34,36–40] ACE2 is also expressed in spermatogonia, Leydig cells, and Sertoli cells in human testes.[41,42] Angiotensin 1-7 is expressed in Leydig cells and interstitial cells; the Mas receptor is expressed in tubular compartments and the seminiferous epithelium. Likewise, the null expression of ACE shows alterations in male fertility[43], including the loss of the ability to bind to the zona pellucida of the oocyte[40] and oocyte-sperm fusion.[36,44]

Interestingly, in patients with infertility due to azoospermia, the angiotensin 1-7 and the Mas receptor expression seems to significantly have decreased.[30] Mas receptor deficiency has been shown to be involved in the regulation of spermatogenesis and testicular apoptosis.[29] The participation of ACE2 as a regulator of spermatogenesis and sperm function has been recognized.[39] On the other hand, TMPRSS2 and ACE2 are co-expressed in prostate cells; in particular, the expression of TMPRSS2 in the epithelium of the prostate gland is dependent on androgens and is a component of the seminal fluid proteasome, whose function is associated with the protection of sperm. Furthermore, the expression of TMPRSS2 increases in prostate cancer cells in response to androgens,[45,46] and it has been suggested that the predominance of TMPRSS2 over testosterone contributes to the predominance of COVID-19 in men.[47] There are no studies focused on evaluating infection by SARS-CoV2 and the RAAS system that involves the male infertility receptor ACE2. Furthermore, a family of transmembrane metalloproteases known as ADAM has an important role in the processes of fertilization and cellular communication. ADAM17 is a membrane-bound enzyme present in testicular germ cells and is expressed

during spermatogenesis and induction of apoptosis by increasing the level of FAS-L on the cell surface.[48] In addition, ADAM17 cleaves and activates various substrates such as receptors of TNF I and II IL-6 participating in the inflammation process and, interestingly, it also cleaves the ACE2 receptor. Likewise, ADAM17 activity is increased by internalization of SARS-CoV2-ACE2 helping viral entry and tissue injury.[49] Also, increased ADAM17 activity has been evidenced with some comorbidities such as heart failure, chronic lung inflammation, diabetes, and kidney diseases.[50] Therefore, the reduction of ACE2 expression on the cell surface causes an imbalance in the RAAS system, increasing Ang II that induces ADAM17 activity.[26] This metalloprotease is involved in inflammation by cleaving and activating cytokines and cytokine receptors.[51] These results suggest that the processes of inflammation and apoptosis could have an impact on male fertility (Figure 1).

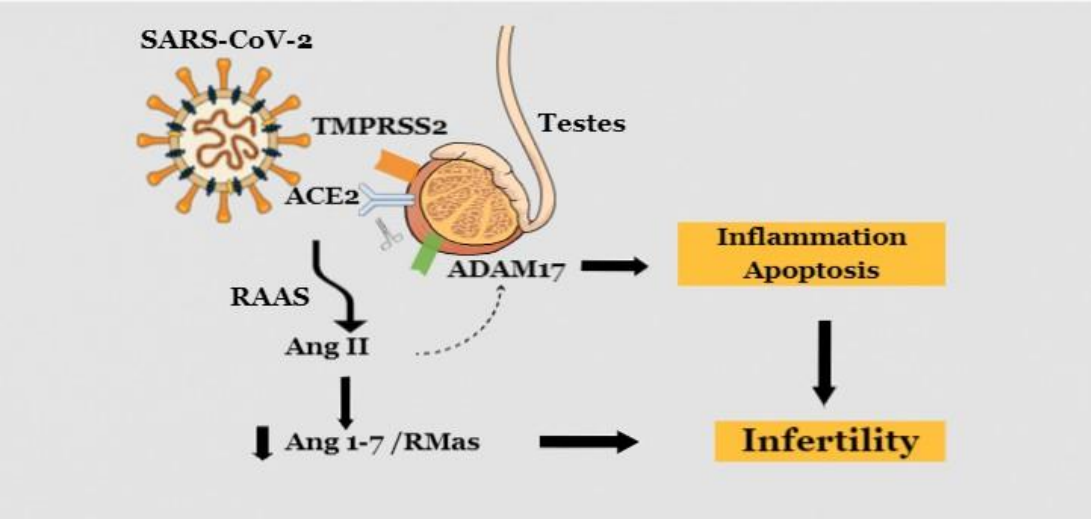

Figure 1. Proposal for the involvement of SARS-CoV-2 infection with the male reproductive system. SARS-CoV-2 enters cells through a receptor called angiotensin converting enzyme type 2 (ACE2). The transmembrane protease serine 2 (TMPRSS2), contributes to the fusion of the membrane, facilitating the entry of the virus through endocytosis. Internalization of SARS-CoV2-ACE2 activates a desintegrin and metalloprotease 17 (ADAM17), which participates in inflammation, apoptosis, and cleavage of ACE2. The reduction of ACE2 expression on the cell surface causes an imbalance in the RAAS system, increasing the Ang II that induces ADAM17 activity. The increase in inflammation and apoptosis could have an impact on male fertility.

SARS-CoV-2 in Male Fertility and Sexual Transmission

A previous study showed that SARS-CoV infection affects the testicles, causing orchitis in humans, showing an alteration of the germ cells with few sperms in the seminiferous tubules accompanied by leukocyte infiltration and abundant IgG in the intestinal tissue.[52] Likewise, another study showed male gonadal dysfunction in 81 patients infected with SARS-CoV-2.[53] This study observed a decrease in the ratio of testosterone/ luteinizing hormone, suggesting it as a marker to assess testicular deterioration by SARS-CoV-2.[54] Also, post-mortem analysis of testicles from COVID-19 positive patients' showed lymphocytic improvement, decrease in several Leydig cells, lesions in Sertoli cells and seminiferous tubules, with the absence of the virus in the testicular tissue.[54]

Few studies have focused on evaluating the effects of SARS-CoV-2 infection on male reproduction. The existing studies have performed semen analysis in patients recovered from COVID-19 and mild to moderate pneumonia (Table 1). The presence of SARS-CoV-2 in semen is still contradictory. The virus's presence was evidenced in six COVID-19 positive patients (4 in the acute phase and 2 in the recovery phase).[55] However, several studies have reported the absence of SARS-CoV-2 in semen and prostate secretion.[56-63] In a SARS-CoV-2 positive patient with moderate symptoms, the virus's presence was not found in the semen eight days after the symptoms began.[62] In another study, patients recovered from COVID-19 reported scrotal discomfort suggesting viral orchitis. However, no virus was seen in the semen a month after patients had been diagnosed

with COVID-19.[57] Similarly, in another study, investigators did not find the presence of SARS-CoV-2 in the semen of 12 patients in the recovery phase with severe symptoms, nor in two patients in the acute phase of COVID-19.[59] Complementing this information, in another study, this virus was not found in recovered patients; most of which had mild complications from COVID-19. Another investigation where semen was collected from patients during the acute infection stage who presented mild discomfort (68%) and moderate pneumonia (32%) as a consequence of SARS-CoV-2, did not find the virus in the semen too.[60] Likewise, there was no evidence of SARS-CoV-2 in the semen of nine patients with an asymptomatic level and an asymptomatic patient.[61] Currently, the absence of SARS-CoV-2 has been shown in the prostate secretion of three COVID-19 positive patients in the nasopharyngeal smear, nor seven previously positive at sampling patients. However, the semen was not evaluated, and the number of patients were limited; therefore, more studies are needed to determinate the prostate alteration.[63]

Approximately, 27 viruses can cause viremia in the human semen.[64] Viruses can cross the blood-testicular barrier formed by Sertoli cells adjacent to the seminiferous tubules' basement membrane, which maintains an essential microenvironment with a unique immunity for testicular function.[64,65] Like SARS-CoV, other viruses such as HIV and Epstein-Barr can cause viral orchitis,[52] germ cell apoptosis, and inflammation. It is worth mentioning that germ cell damage causes infertility,[66] in addition to the possibility of contracting sexually transmitted infections.[64] Knowledge about the presence of SARS-CoV-2 in semen is essential due to the clinical and public health implications. There is insufficient evidence to confirm the risk of contagion of SARS-CoV-2 through semen. In addition to the fact that sexual practice is not limited to intercourse, they have recommended abstinence from intercourse, oral or anal sex in SARS-positive patients, because the virus persists in nasal secretions and feces for 10 to 16 days respectively after the absence of COVID-19 symptoms.[67]

Table 1. SARS-CoV-2 in semen

Ref	Patients (N)	Appearance of symptoms* (Days)	Sampling** (Days)	Severity of SARS-COV2 infection in patients	Confirmation of COVID19 (Gen amplified by PCR)	Presence of viral RNA in semen
55	38	6-16	2-13	--	---	Positive (N=6)
62	1	15	8	Mild	E y S	Negative
57	34	-	31	Mild to Moderate	ORF1ab y N	Negative
58	18	-	43.5-47	Mild (14)*** Moderate (4)***	-	Negative
56	12	-	14-42	Mild (92%)*** Asymtomatic (8%)***	-	Negative
59	23	-	32	Mild (78%)*** Moderate (22%) ***	N y ORF	Negative
60	16	-	0-7	Mild (68.7%)*** Moderate (31.3%)***	-	Negative
61	9	-	7-88	Mild (8)*** Asymptomatic (1)***	R, E y N	Negative
63	10	11	3-23	--	N y ORF	Negative****

* Semen collection days after the onset of symptoms.
** Days of semen collection after confirmatory diagnosis.
*** Classification of patients according to the severity of the infection.
**** Negative in prostatic secretion (N=10; 3 positive; 7 recovering patients).

Conclusion

The repercussions on testicular function and infertility caused by the infection of SARS-CoV and SARS-CoV-2 is considerable because the functional receptor ACE2 and TMPRSS2 are expressed in the male reproductive tract. SARS-CoV generates orchitis in humans, whose virus invades cells through the same pathway. ACE2 is an essential part of SAAR, which is involved in fertilization. Furthermore, ADAM17 is a SARS-CoV-activated metalloprotease and participates in the regulation of spermatogenesis, inflammation, and proteolytic cleavage of ACE2. The expression of molecules such as ACE2/TMPRSS2/ADAM17 in the male reproductive tract denotes that SARS-CoV2 infection could be involved in spermatogenesis. It is essential to analyze the viral load and the conditions

that make SARS-CoV-2 cause a testicular alteration and affect its hormonal regulation. Therefore, it should not be underestimated that COVID-19 disease could lead to male fertility.

Conflict of Interest

The authors declare no conflict of interest.

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