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Would It be Possible for a SARS-CoV-2 Infection to Affect the Male Reproductive System?

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Abstract

The male reproductive system may be affected by the systemic infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The precise mechanisms of male reproductive impairment are not well known. There are two possible mechanisms for the effect of SARS-CoV-2 on the male reproductive system either directly through the impact of the angiotensin-converting enzyme 2 (ACE2) receptor on testicular tissue or indirectly through the effect of the secondary autoimmune response on testicular functions. The second mechanism is more likely. Extensive studies need to be conducted on the impact of SARS-CoV-2 on the functional characteristics of sperm and the results of natural fertilization or assisted reproductive technology.

Keywords: SARS-CoV-2, Male reproductive system, ACE2 receptor, Inflammation

Introduction

The family of coronaviruses infects bronchial epithelial cells and type II pneumonocytes, causing acute respiratory syndrome. Coronavirus disease 2019 (COVID-19), which was first observed in China in late 2019, is caused by a new species of coronavirus called SARS-CoV-2 [1]. The emerging virus has clinical features including cough, fever, shortness of breath, and severe complications such as pneumonia. These symptoms are common to all types of influenza [2]. Renal dysfunction, liver dysfunction, gastrointestinal complications, mediastinal symptoms, cardiac manifestations, neurological abnormalities, and hematological manifestations are among the reported extrapulmonary features of SARS-CoV-2 [3-6]. It is likely that SARS-CoV-2 also affects the reproductive system [7].

Viruses, bacteria, and protozoa are microorganisms that can disrupt the reproductive system and affect fertility in men [8]. These adverse effects include sperm death as well as decreased motility and sperm count. Infections caused by microbial agents may indirectly affect sperm production in the seminiferous tubules and thus impair fertility [9,10]. Infection caused by a virus through the circulatory system probably influences the male reproductive system [11]. Mumps virus frequently causes inflammation of the testicles and can lead to infertility in men after puberty [12]. Human immunodeficiency virus infection also induces severe inflammation of the testicles and impairs male fertility [13]. Zika virus damages the reproductive tract in mice and results in male infertility [14]. Thus, a wide range of viruses may infect the male reproductive system and thus affect fertility [15]. The goal of the current review was to investigate the possible impact of SARS-CoV-2 infection on the male reproductive system.

Methods of the Search Strategy

In the current study, a literature search was done on PubMed,

SCOPUS, Embase, Google Scholar, and Ovid according to the reported items for male reproductive manifestations related to SARS-CoV-2 infection. The keywords used were 'SARS-CoV-2', 'COVID-19', 'fertility', 'semen', 'reproductive system', and 'reproductive manifestations'.

The Association of SARS-CoV-2 Infection with the Reproductive System in Men

There are several reports with different results about the relationship between SARS-CoV-2 and semen. Most reports did not find SARS-CoV-2 in the semen of male patients with SARS-CoV-2 infection. These studies reported the characteristics of the patients and the severity of their disease. Penn *et al.* evaluated the semen of patients diagnosed with mild SARS-CoV-2 thirty days after diagnosis. Nineteen percent of these patients had testicular pain due to viral orchitis, however, SARS-CoV-2 was not found in their semen [16]. Paoli and colleagues studied the presence of SARS-CoV-2 in the urine and semen of patients with SARS-CoV-2 infection. The result of the presence of SARS-CoV-2 in the urine and semen samples was negative. Two hypotheses have been suggested in this study. First, viral clearance in the testes may occur as the patient progresses. Second, the virus was never present in the semen [17]. In the study of Pavone *et al.*, patients recovering from mild SARS-CoV-2 infection showed no evidence of SARS-CoV-2 in their semen [18]. In a study, it was attempted to detect SARS-CoV-2 in the semen of patients with SARS-CoV-2 infection. SARS-CoV-2 was not found in the semen of these patients 4-5 weeks after the diagnosis of COVID-19 infection. Six males diagnosed with COVID-19 had pain in the testicles indicating viral orchitis. In this study, it was stated that there were scattered expression patterns of ACE2 and TMPRSS2 in the testis [19] (**Table 1**).

Table 1. Details of patients in various studies.

Study	SARS-CoV-2 patient (s)	Clinical features related to reproductive system	Semen tested for SARS-CoV-2	Ref
Observational	Six patients 31 days (interquartile range, 29-36 days) from COVID-19 diagnosis	Scrotal discomfort suggestive of viral orchitis	Not detected	[19]
Case report	31-year-old man, eight days after SARS-CoV-2 infection	No sign	Not detected	[17]
Observational	9 patients recovering from mild SARS-CoV-2	No sign	Not detected	[18]
Observational	34 patients recovering from SARS-CoV-2	Six males had pain in the testicles indicating viral orchitis	Not detected	[16]
Observational	12 patients in the recovery phase Among the 9 IgG-positive patients, 8 showed negative pharyngeal swab 2019-nCoV RNA test results while one remained positive. Patients 9–12 displayed negative 2019-nCoV RNA test results, but their IgG remained positive during hospitalization.		Not detected	[20]
Cohort	23 male patients recovered from SARS-CoV-2	No sign	Not detected	[21]
Observational	16 SARS-CoV-2-positive men in the acute phase of disease	No sign	Not detected	[22]
Pilot cohort	18 semen samples from recovered men were obtained 8–54 days after absence of symptoms, 14 from control subjects, and 2 from patients with an active SARS-CoV-2 infection	Impairment of sperm quality	Not detected	[23]
Case report	43-year-old man	low-grade fever and severe bilateral testicular pain that had started 3 days earlier	Not detected	[24]

Case report	37-year-old male recovered from COVID-19	bilateral orchitis	Not been evaluated	[25]
Observational	38 participants 23 participants had achieved clinical recovery 15 participants were at the acute stage of infection	No sign	6 patients had results positive for SARS-CoV-2, including 4 of 15 patients who were at the acute stage of infection and 2 of 23 patients who were recovering	[27]
Original research	COVID-19 male patients (n=6) and recruited recovering COVID-19 inpatients (n=23)		Not detected Concentration of CD3+ and CD68+ increased in the interstitial cells of testicular tissue. Semen from COVID-19 inpatients showed that 39.1% of them have oligozoospermia, and 60.9% showed an increase in leucocytes in semen. Also, levels of IL-6, TNF-α, and MCP-1 increased in semen samples.	[28]

The study of Song *et al.* included patients with SARS-CoV-2 infection. The results showed that the virus did not directly infect the genitals in men who were in the acute stage of infection or had recovered [20]. Men diagnosed with SARS-CoV-2 were tested for viral RNA in the semen in the acute and recovery stages of SARS-CoV-2 infection. The results showed that there was no virus in their semen [21] (**Table 1**).

Kayaaslan and Holtmann examined semen samples in patients in the acute stage of SARS-CoV-2 infection. All semen samples were negative for the detection of SARS-CoV-2 [22,23]. Moreover, Holtmann *et al.* stated that a moderate SARS-CoV-2 infection impaired semen parameters [23] (**Table 1**).

There are also some reported cases of orchitis in SARS-CoV-2 patients which increases the likelihood of the virus affecting the reproductive system. In Marca's case report, a young man who was referred to a hospital for orchitis was diagnosed with SARS-CoV-2. This study suggested that SARS-CoV-2 may enter the cell by binding to the angiotensin-converting enzyme receptor in testicular cells and explained the occurrence of testicular pain in this patient [24]. A case of SARS-CoV-2 with bilateral orchitis was referred to a hospital for testicular pain. No epididymitis was observed in this patient. This study suggested that based on previous data on the severe acute respiratory syndrome (SARS) infection which occurred in 2002, SARS-CoV-2 infection may occur due to secondary spermatocyte dysfunction [25] (**Table 1**).

However, there are some contradictory studies. A study reported that SARS-CoV-2 was detected in the semen of six men among thirty-eight male patients with SARS-CoV-2 infection who still had symptoms or had improved [26]. A cohort study has also shown that SARS-CoV-2 can be present in the semen of men diagnosed with SARS-CoV-2 infection [27] (**Table 1**).

A recent study reported that impairment of spermatogenesis was observed in SARS-CoV-2 patients, which could be explained as a result of an elevated immune response in the male reproductive system. Histopathological examination of testicular tissue samples of severely ill SARS-CoV-2 infection showed that thinning of seminiferous epithelium deceased. Furthermore, they observed an increase in apoptotic cells within seminiferous tubules which is an indication of impaired spermatogenesis [28] (**Table 1**).

Discussion

ACE2 is a key enzyme in the renin-angiotensin (Ang) system that can produce Ang (I–VII) from Ang II [29]. ACE2 attaches to the membranes of cells located in the lungs, heart, arteries, kidney, and intestines [30,31]. Furthermore, ACE2 receptors have been identified in spermatogonia, Sertoli cells, and Leydig cells in the human testis [32]. ACE2 may be involved in controlling testicular function through steroidogenesis modulation or some other Leydig cell function [33].

A number of researchers believe that ACE2 may have a key role in the cellular entry of SARS-CoV-2 into testis which

may directly affect men's reproductive system. Several studies suggest that SARS-CoV-2 indirectly affects the male reproductive system through inflammatory processes caused by the effect of SARS-CoV-2 through the ACE2 receptor. Part of the ACE2 receptor at the cellular surface is an extracellular domain that binds to the SARS-CoV-2 glycoprotein [21]. The expression of ACE2 in testicular cells (especially seminiferous cells, Sertoli cells, and Leydig cells) may be affected by the virus [34]. Viral glycoproteins have an intracellular domain, a membrane domain, and an extracellular domain. Unit S1 of the extracellular domain binds to the ACE2 peptidase domain [22]. The ACE2 peptidase domain breaks angiotensin I which in turn can activate the inflammatory cascade [35]. Therefore, the hypothesis that SARS-CoV-2 causes an indirect inflammatory response in the testicles could be more likely. Inflammation can affect the normal function of Leydig cells. In turn, it reduces testosterone production and thus damages seminiferous cells. Therefore, SARS-CoV-2 may lead to abnormal activation of the inflammatory cascade. Thus, excessive secretion of cytokines leads to capillary leakage, edema, and organ failure. Following SARS-CoV-2 infection, a significant increase in tumor necrosis factor-alpha (TNF-α), gamma interferon (IFN-γ), and interleukin (IL) 6 (IL-1, IL-10, IL-2) has been reported [36]. Also, a recent study claims that impairment of spermatogenesis was observed in SARS-CoV-2 patients as a result of immune response in the testis. A significant increase in seminal IL-6, TNF-a, and monocyte chemoattractant protein-1 (MCP-1) levels were observed in semen samples of SARS-CoV-2 patients [28]. During the previous outbreak of the coronavirus (SARS-CoV) in 2002, several studies showed an association between the members of the coronavirus family and orchitis. SARS-CoV virus was also not observed in the semen in many reports [37], though there was testicular damage due to cell destruction [38]. Hence, it can be stated that, like other members of the coronavirus family, SARS-CoV-2 may bind to the ACE2 receptor in the testis which may lead to inflammation and eventually orchitis [39].

In conclusion, according to the reports, SARS-CoV-2 can cause reproductive impairment. The exact mechanism of the effect of SARS-CoV-2 on the reproductive system is not well understood. However, it is thought that SARS-CoV-2 either directly enters the cell through the receptor and affects the reproductive system or indirectly affects the reproductive system by activating the inflammatory factors. The latter mechanism is more likely. Due to the fact that it takes longer for the body of men to be cleansed of SARS-CoV-2 virus than that of women [40] and that SARS-CoV-2 will probably become a long-term problem, further studies should be conducted on the effect of SARS-CoV-2 on various aspects of the male reproductive system such as sperm quality and the results of natural fertilization or assisted reproductive technology.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Authors' Contributions

Akram Ebrahimifar and Kaveh Rahimi participated in the study design, methodological issues, analysis, interpretation of the study, and writing of the manuscript.

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