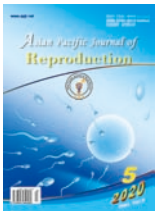

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Possible links between COVID-19 and male fertility

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have a ripple effect that puts men at a risk of infertility. This article reviews the possible link between SARS-CoV-2 infection and male reproduction following speculations that the single-stranded RNA viruses could directly invade the testes. SARS-CoV-2 enters the human lung cells *via* angiotensin converting enzyme 2 (ACE2). ACEs, its products, angiotensin-(1-7), and its receptor, MAS receptor, are expressed in the testes. Although the binding of SAR-CoV-2 to ACE2 could lead to excess angiotensin II with possible enhanced inflammation, angiotensin II could also promote sperm motility. In addition, the pathophysiology of SAR-CoV-2, especially in relation to male fertility, is yet to be fully understood; the suppression of androgen observed in COVID-19 infected men calls for the need for andrological assessment in infected male.

KEYWORDS: SARS-CoV-2; COVID-19; Angiotensin converting enzyme; Steroidogenesis; Spermatogenesis

1. Introduction

Coronaviruses (CoV) are single-stranded RNA viruses that primarily target the human respiratory system. Microscopically, CoV has glycoprotein spikes on its envelope which gives it a crown-like appearance. The betacoronaviruses (coronaviridae family) have several genera that affect humans and other vertebrates like mice, bats, cats, dogs, and bats[1]. The α-CoV and β-CoV cause infection of the respiratory, gastrointestinal, and central nervous systems in human and several mammals, while the σ-CoV and γ-CoV primarily affect birds[2,3].

At the tail of December 2019, there was an outbreak of a pneumonia-like infection, now called coronavirus disease 2019 (COVID-19) caused by a novel coronavirus (2019-nVoV) that was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its similarity to SARS-CoV[4]. This infectious illness was declared a global pandemic by the World Health Organization on the 11th March 2020[5]. Although there are claims that the first case was transmitted from animal to human[6], human-to-human transmission is fast spreading with a high mortality rate. Established mode of transmission is through respiratory droplets from sneezing and coughing with symptomatic and possibly asymptomatic infected persons being the primary source of spread. As on the 2nd September, 2020, 11:35 GMT, (about eight months from the outbreak), 26 149 876 cases of COVID-19 and 866 015 of mortalities from COVID-19 has been reported[7].

2. Pathogenesis of COVID-19

Studies have shown that similar to SARS-CoV, SARS-CoV-2 enters the human cells by binding to angiotensin-converting enzyme 2 (ACE2)[8,9]. ACE2 is a zinc-containing transmembrane aminopeptidase that was initially identified as a variant of ACE. It is widely expressed, especially in the lung type II alveolar cells, endothelial cells of the arteries and veins, arterial smooth muscle cells, enterocytes of the small intestine, cortical neurons and glia[10]. Primarily, ACE2 acts as a counterbalance to ACE.

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Renin activates angiotensinogen to angiotensin Ⅰ. This is cleaved by ACE into angiotensin Ⅱ, which exerts its effect through angiotensin Ⅱ type 1 receptor (AT1R) and angiotensin Ⅱ type 2 receptor (AT2R). In addition, ACE also cleaves the C-terminal dipeptidyl residue to inactivate bradykinin and enkephalins. ACE2 cleaves phenylalanine from angiotensin Ⅱ and hydrolyzes it into angiotensin-(1-7) which exert their activities through AT2R and MAS receptors[11]. The spike S1 protein of SARS-CoV-2 binds to the enzymatic domain of ACE2, peptidase domain, on the cell surface and results in endocytosis and translocation of both the virus and enzyme into the cells[11]. The viral entry is facilitated by priming of the S protein by the host serine protease, transmembrane protease serine 2[11]. Following viral entry, it replicates, increases the pH of endosomes and lysosome and activates p38 mitogen activated protein kinases and extracellular regulated protein kinases, which causes hyper-inflammatory response. In the incident of COVID-19, ACE2 becomes overwhelmed, causing a rise in the level of angiotensin Ⅱ that cannot be hydrolyzed to angiotensin-(1-7) due to unavailability of ACE2. This explains the pulmonary manifestations of the viral infection.

3. Possible links between COVID-19 and male fertility

Studies have revealed the presence of SARS-CoV-2 RNA in stool, urine, and blood samples. Although urine and blood reportedly have a low SARS-CoV-2 RNA detection frequency, the detection rate in the stool is relatively high with longer clearance time than in the nasopharyngeal swabs from respiratory secretions[12-14]. This infers that the virus could be contracted and spread through other means besides respiratory droplets.

Studies have elucidated the roles of ACE, ACE2 and AT2R in male reproduction (Figure 1). ACE has been reported to be well distributed in human prostate, testis, epididymis, and semen[15]. It has been linked to testicular development in puberty[16], germ cell maturation[17], regulation of epididymal fluid and electrolyte balance[18], and sperm capacitation[19]. On the other hand, ACE2 has been reported to be expressed in adult testicular Leydig cells, and speculated to play a key role in steroidogenesis[20]. A study by Reis *et al* confirmed the expression of ACE2, angiotensin-(1-7) and MAS receptors in the Leydig and Sertoli cells, as well as their possible roles in steroidogenesis and spermatogenesis[21]. AT1R, which has

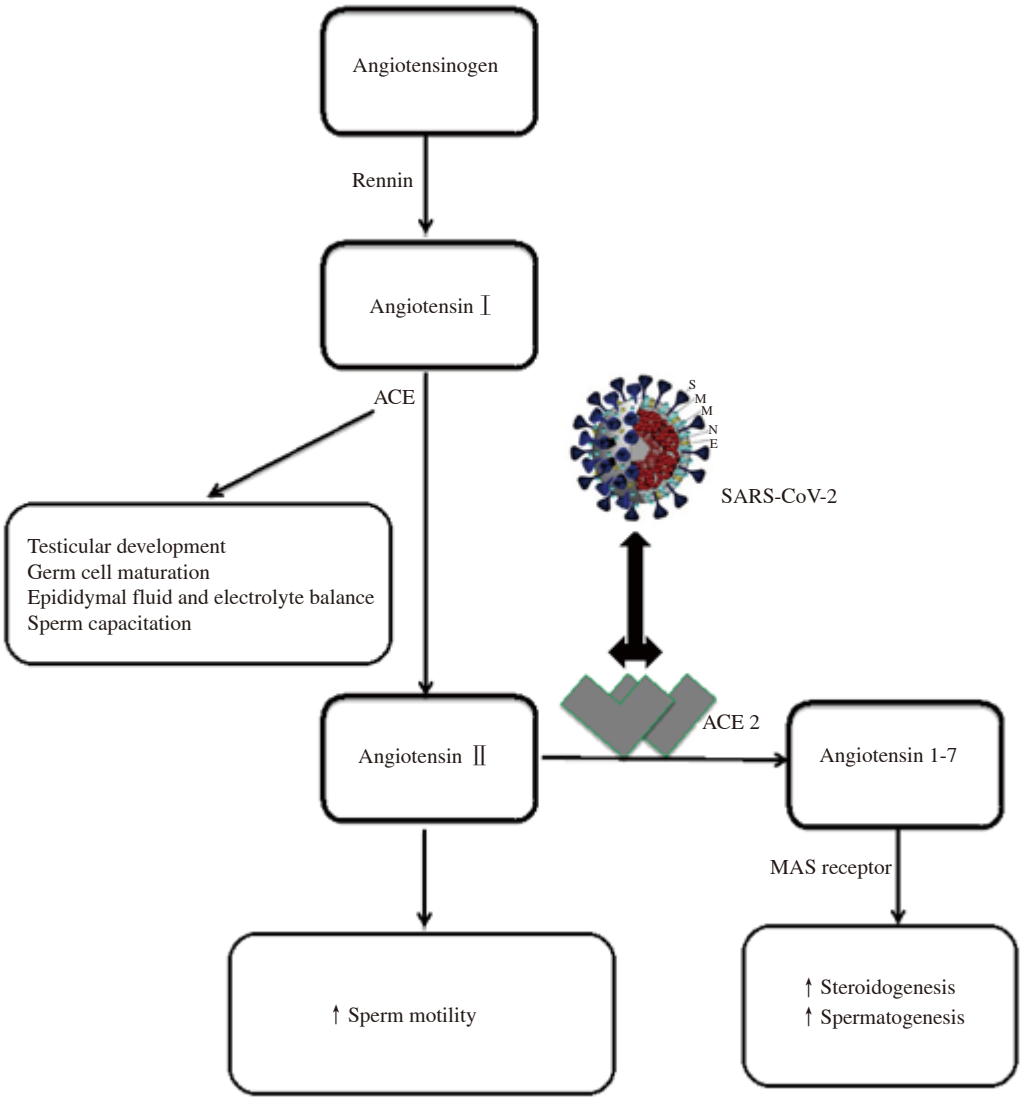

Figure 1. Possible link between SARS-CoV-2 and male reproduction. ACE: Angiotensin converting enzyme; S: Spike glycoprotein; M: Membrane protein; N: RNA and nucleocapsid protein; E: Envelope.

been reported to be expressed in developing human spermatids and mature sperm cell[22], has been linked to sperm capacitation and acrosome reaction[23]. AT2R has been documented to be expressed in human testis, epididymis, prostrate and sperm cells[24]. Studies have shown that exposure of human sperm cells to angiotensin Ⅰ and angiotensin Ⅱ enhances sperm motility[23].

There are lots of speculations about the male gender preponderance to COVID-19 infection, and COVID-19-induced male infertility. Although studies of Xu *et al*[25] reported infiltration of inflammatory cells into the testes of SARS-CoV-infected patients, no similar reports have been documented on SARS-CoV-2 infection. Semen samples from patients who recovered from COVID-19 and testicular biopsies from a dead COVID-19 patient did not detect SARS-CoV-2 RNA[26]. This finding was corroborated by other studies that reported absence of SARS-CoV-2 viral RNA in the semen of male patients with active or resolving infection[27-29]. On the contrary, COVID-19 confirmed patients had significantly higher serum luteinizing hormone (LH) and prolactin, but normal levels of circulatory testosterone when compared to their healthy counterparts, indicating a likely initial suppression of testosterone biosynthesis which resulted in a negative feedback thus stimulating increased LH release[30]. These findings suggest that the testis is possibly not directly infected and male are not more predisposed to the virus, but the viral infection could impair androgen production. Interestingly, a cohort study revealed that 6 out of 38 (15.8%) COVID-19 confirmed patients expressed SARS-CoV-2 in their semen; 4 out of the 6 COVID-19 confirmed patients (66.7%) were in the acute stage of infection while 2 out of the 6 COVID-19 confirmed patients (33.3%) were recovering[31]. Although it is unclear whether or not the expressed virus was viable, this calls for caution especially in patients who require assisted reproductive technology/*in vitro* fertilization interventions. A repeat SARS-CoV-2 RNA testing might be necessary in semen donors to reduce the chance of possible spread and increase the success rate of the artificial reproductive technology.

Since ACE2, angiotensin-(1-7), and MAS receptors are expressed in the testis, SARS-CoV-2 could invade the testes and alter testicular functions. Also, the binding of the virus to ACE2 could lead to an excess of angiotensin Ⅱ which would give rise to a robust inflammatory response with subsequent impairment of the Leydig and Sertoli cell functions. Although there are limited studies with a small sample size that evaluated the presence of the virus in the testes or semen, it is important to note that no study has reported the presence of the virus in the testes or semen. Since angiotensin Ⅱ is known to promote sperm motility, excess angiotensin Ⅱ following overwhelmed ACE2 could precipitate inflammation, and may not override its positive effect on sperm motility, especially if the inflammation is not localized in the testes.

Furthermore, some studies have reported no gender bias in SAR-CoV-2 infection[32], while others observed a slightly higher prevalence in men[33,34]. In addition, studies have reported that men are at more risk for worse outcomes and mortalities independent on age[32]. The observed higher prevalence, poorer outcome and increased mortality in male are likely not SARS-CoV-2-specific. It has been established that men are more susceptible to infection than women. Estrogen exerts more vigorous immune system response when compared to testosterone, thus suppressing inflammatory cytokine release with resultant increased poor outcome and death in male from viral respiratory infections[35]. In addition, it is not unlikely that the X chromosome which carries the highest number of immune-related genes accounts for the robust immunologic response seen in females[36]. Health-related risky behaviour which impairs immune system response such as smoking and poor utilization of medicare may also explain the higher morbidity and mortality seen in men. When compared with the female counterpart, a higher percentage of men smoke[37] and lower percentage of them utilizes medicare[38].

4. Conclusion

SAR-CoV-2 remains novel and much is yet to be unraveled about this highly contagious virus. The higher prevalence and mortality from COVID-19 observed in men are likely secondary to hormonal factor, genetic makeup, and health-related risky behaviour. Although just a study has demonstrated direct testicular invasion of the virus, the suppression of androgen observed in COVID-19 infected men suggests the need for andrological assessment in infected men. Studies evaluating the direct testicular invasion of SARS-CoV-2 *via* ACE2 or other mechanisms, and the likely effect of the viral infection on male fertility are necessary to better understand the possible pathophysiology of SARS-CoV-2 on male reproduction and also unravel new preventive strategies and therapeutic opportunities.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

Roland Eghoghosoa Akhigbe and Moses Agbomhere Hamed contributed equally to the study.

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