Is there an impact of the COVID-19 pandemic on male fertility? The ACE2 connection

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Younis JS, Abassi Z, Skorecki K. Is there an impact of the COVID-19 pandemic on male fertility? The ACE2 connection. Am J Physiol Endocrinol Metab 318: E878–E880, 2020. First published May 19, 2020; doi:10.1152/ajpendo.00183.2020.—The viral pandemic of the coronavirus disease 2019 (COVID-19), generated by a novel mutated severe acute respiratory syndrome coronavirus (SARS-CoV-2), has become a serious worldwide public health emergency, evolving exponentially. While the main organ targeted in this disease is the lungs, other vital organs, such as the heart and kidney, may be implicated. The main host receptor of the SARS-CoV-2 is angiotensin converting enzyme 2 (ACE2), a major component of the renin-angiotensin-aldosterone system (RAAS). The ACE2 is also involved in testicular male regulation of steroidogenesis and spermatogenesis. As the SARS-CoV-2 may have the potential to infect the testis via ACE2 and adversely affect male reproductive system, it is essential to commence with targeted studies to learn from the current pandemic, with the possibility of preemptive intervention, depending on the findings and time course of the continuing pandemic.

INTRODUCTION

The pandemic of novel coronavirus disease 2019 (COVID-19), mediated by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) viral infection, is a serious, geometrically expanding, worldwide public health emergency, with newly recognized manifestations being appreciated and reported daily. The very high contagiousness of COVID-19 is largely attributed to its rapid community transmission, high virulence, and sustained surface viability. The presentation of COVID-19 varies considerably from rare asymptomatic cases, to mild flu-like symptoms, including high fever, to severe respiratory illness. The SARS-CoV-2 pathogen is a single-stranded RNA virus, with the gravest clinical pathophysiology, being a severe acute respiratory syndrome (SARS). The newly evolved virus has an estimated 10- to 15-fold greater mortality rate than the usual seasonal Haemophilus influenzae-mediated respiratory illness (2a). Critical cases are characterized by rapid respiratory deterioration, septic shock, and/or multiple organ dysfunction or failure (3, 29). Contemporary infection rates and rolling updates are continuously displayed on the World Health Organization (WHO) COVID-19 website.

In this perspective report, we focus on the role of angiotensin-converting enzyme 2 (ACE2) as a key receptor for SARS-CoV-2 in different organs of the body, including the lung, heart, and kidney. We shall also discuss the physiological role of ACE2 in the testis and the theoretical adverse effects of SARS-CoV-2 on the male reproductive system, as the virus may have the potential to use ACE2 as a route to infect this part of the body. Since there is only anecdotal evidence and concern in the literature as to the adverse effect of the coronavirus family, specifically SARS-CoV-2, on male fertility, we call for urgent targeted research on this topic to clarify this aspect from the current wave of the pandemic.

SARS-COV-2 AND ITS HOST RECEPTOR

SARS-CoV-2, which belongs to the Betacoronavirus genus, has been recently sequenced (14) and has been shown to have many similarities with the original SARS-CoV, first reported in 2002. Spike proteins of SARS-CoV-2 and SARS-CoV have almost identical three-dimensional structures in the receptor-binding domain that maintains van der Waals forces. They have been shown to share 76.5% identity in amino acid sequences and to possess a high rate of homology (32). Similar to most viruses, the SARS-CoV and SARS-CoV-2 enter the host cell (type 2 alveolar epithelial cells) by receptor binding followed by endocytosis, genome replication, exocytosis, and budding (7). While both viruses have been shown to recognize human angiotensin-converting enzyme 2 (ACE2) receptor as their host receptor, SARS-CoV-2 binds to ACE2 receptor more efficiently than SARS-CoV, increasing its damaging pathogenicity and its ability of SARS-CoV-2 to transmit from person to person (8, 25, 26). ACE2 receptor recognition is the first step of viral infection, as it is the key determinant of host cell and tissue tropism, pathogenicity, and subsequent viral replication. However, ACE2, the entry receptor of the virus, also plays a crucial role against lung injury (33).

ACE2 A PART OF THE RENIN-ANGIOTENSIN SYSTEM

ACE2 is a transmembranal zinc metallopeptidase with high homology to the classic ACE, but contains a single catalytic domain. Both ACE isoforms are part of the renin-angiotensin-aldosterone system (RAAS), a cardinal endocrine system that plays a key role in the regulation of blood pressure and fluid balance. Whereas ACE catalyzes the conversion of angiotensin I (ANG I) into angiotensin II (ANG II), ACE2 is responsible for the generation of angiotensin 1–7 (ANG 1–7) from ANG II. While ANG II exerts deleterious effects on the heart, lungs, kidneys, and the brain via angiotensin II type 1 (AT1) receptors (10), the ANG 1–7-Mas receptor axis provokes beneficial balancing and salutary actions on these vital organs, as evident
ACE2 IN THE TESTIS

Among several extra-respiratory organs, ACE2 is highly expressed in the human testis (5, 23). This raises the question of whether COVID-19 in males, via the ACE2, may have adverse reproductive implications, especially in young men planning to have children.

Typical components of the RAAS have been found in the testis and epididymis in the human and mammalian animal models (2, 11, 18, 20). For instance, the receptor Mas has been identified in rat testis (16a) and mouse (1) testis; it starts to increase around puberty and reaches its maximal expression during reproductive life. ACE2 expression in the testis is restricted to the Leydig and Sertoli cells in humans (6). Similarly, Mas mRNA in the testis is localized to Leydig and Sertoli cells, being much more pronounced in Leydig cells (1). Knockout mammalian models, specifically to various components of the RAAS, such as Mas-knockout mice showed aberrant expression of genes involved in mitochondrial function and testicular steroidogenesis (11, 30). However, unlike the case for alveolar cells, it is not yet known whether cells involved in spermatogenesis depend on intact ANG 1–7 for functional integrity, and this can be studied as a basic question in relevant model systems.

Recently, the expression pattern of ACE2 in adult human testis at the level of single-cell transcriptomes was shown to be predominantly enriched in spermatogonia, Leydig, and Sertoli cells (27). In the clinical setting, ANG 1–7 and Mas were detected in the seminiferous tubules, as well as in the interstitial compartment, mainly Leydig cells, in men with normal spermatogenesis. However, neither components of the RAAS were found in the seminiferous tubules of infertile men with nonobstructive azoospermia (20).

Taken together, the RAAS, specifically ACE2, seems to play an important role in male reproduction. Accumulating evidence suggests that the RAAS components are involved in human male regulation of steroidogenesis, testosterone production, and spermatogenesis in the testis.

ADDITIONAL CONCERNS

An additional concern of the COVID-19 pandemic that might impact male fertility is fever. Particularly high and sustained elevation in body temperature is a major manifestation of the COVID-19 pandemic, which complicates more than 80% of patients (12). The concept that fever and elevation of testicular temperature result in impairment of spermatogenesis is widely accepted (9).

More importantly, emerging evidence indicates that a subgroup of patients with severe COVID-19 might have a secondary cytokine storm syndrome (hemophagocytic lymphohistiocytosis) (16). This is an underrecognized, hyperinflammatory syndrome characterized by sustained fever, with fulminant and fatal hypercytokinemia with multiorgan failure. These patients have a particular serum blood cytokine profile with cytopenia and hyperferritinemia. These findings also suggest that immunomodulatory therapy (IL-6 antagonist) may improve mortality rate considerably in these patients (16, 24).

As cytokines contribute to testicular function and maintenance of male reproductive health, and to the pathologies associated with their abnormal activity in this organ, COVID-19-induced changes in cytokines profile may have further implications to male fertility (13). In addition, immunomodulatory therapies may provoke potential long-term effects on male fertility and are a matter of concern. Furthermore, cytokine microenvironment deviations within the testis may have tumorigenic adverse effects on the cellular level, leading eventually to testicular cancer, a second long-term matter of concern (13).

WHAT EVIDENCE SO FAR?

To the best of our knowledge, no clinical studies on male fertility investigated survivors from the previous coronavirus epidemics, SARS-CoV (commenced in 2002) and MERS-CoV (commenced in 2012). This may be due to the fact that these viruses are much less contagious in comparison to the SARS-CoV-2, and the epidemics were short-lived and of limited scope: to date, only 8,098 and 2,538 people were infected worldwide by the SARS-CoV and MERS-CoV, respectively (WHO website). It is also possible that the effect of these previous epidemics on male fertility were not explored in targeted studies. One study analyzed the pathological changes of testes from six patients who died of SARS, suggesting SARS-CoV orchitis (31). All biopsies displayed widespread germ cell destruction with few or no spermatoozon in the seminiferous tubules. SARS viral genomic sequences by in situ hybridization were not detected in all specimens, although immunohistochemistry demonstrated abundant IgG precipitation, indicating possible immune response as the cause of the damage.

In contrast, as of April 28, 2020, the number of confirmed cases of SARS-CoV-2 is 3,073,356, and the pandemic continues to evolve. The highly contagious nature of the SARS-CoV-2 virus, using ACE2 as the receptor of entry to both the lungs and testis, it is imperative to seize the opportunity to investigate the impact of the COVID-19 pandemic on male fertility. One non-peer-reviewed retrospective study examined the impact of SARS-CoV-2 on male sex hormones in 81 hospitalized patients, in their third to sixth decade of age (15). Serum luteinizing hormone levels were higher in the SARS-CoV-2 group compared with controls, while there were no differences in serum follicular stimulating hormone or testosterone levels. Another recent non-peer-reviewed study examined 34 recovering adult Chinese male patients, 20–55 yr of age, following confirmed COVID-19 diagnosis. While six men had mild scrotal discomfort at the time of disease, suggesting viral orchitis, in none of these men was SARS-CoV-2 detected in their semen 29–36 days following recovery (17). One major limitation of both studies is the fact that the authors did not report sperm counts and viability of COVID-19 patients.

CONCLUSIONS

ACE2 is abundant in the adult human testis, as it is in the lungs, kidney, and heart, and the SARS-CoV-2 virus uses ACE2 as its receptor of entry. Clinical and translational studies are needed without delay to determine the effects of SARS-CoV-2 on human spermatogenesis and steroidogenesis in the testis, to inform medical consultation with infected men, especially those in the reproductive years. This may be of greater importance for men already known to have a sperm production problem. The issue of sperm
banking following SARS-CoV-2 infection and its safety should also be evaluated. Since all infertility and in vitro fertilization and embryo transfer treatments are presently deferred, this may be the best time to conduct these targeted studies before returning to our routine endeavors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

J.S.Y., Z.A., and K.S. created and developed the concept; J.S.Y. drafted manuscript; J.S.Y., Z.A., and K.S. edited and revised manuscript; J.S.Y., Z.A., and K.S. approved final version of manuscript.

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