

Could COVID-19 have an impact on male fertility?

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Abstract

The pandemic caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to several hypotheses of functional alteration of different organs. The direct influence of this virus on the male urogenital organs is still to be evaluated. However some hypotheses can already be made, especially in the andrological field, for the biological similarity of the SARS-CoV and SARS-CoV2. As well as SARS-CoV, SARS CoV-2 uses the 'Angiotensin Converting Enzyme-2' (ACE2) as a receptor to enter human cells. It was found that ACE2, Angiotensin (1-7) and its MAS receptors are present, over in the lung, also in the testicles, in particular in Leydig and Sertoli cells. A first hypothesis is that the virus could enter the testicle and lead to alterations in testicular functionality. A second hypothesis is that the binding of the virus to the ACE2 receptor, could cause an excess of ACE2 and give rise to a typical inflammatory response. The inflammatory cells could interfere with the function of Leydig and Sertoli cells. Both hypotheses should be evaluated and confirmed, in order to possibly monitor fertility in patients COVID-19+.

KEYWORDS

angiotensin-converting enzyme 2, COVID-19, male infertility

Betacoronaviruses (Coronaviridae family) have a positive-sense RNA genome, which are 26–32 kilobases in length. They are called coronaviruses due to their 'crown-like' appearance with spiked glycoproteins in the outer layer (Su et al., 2016). Coronaviruses have been identified in various hosts, including mammals such as camels, bats, mice, cats, and dogs (Su et al., 2016). Most of the coronaviruses that are pathogenic to humans are associated with rather mild respiratory symptoms (Su et al., 2016).

At the end of December 2019, a novel Coronavirus (2019-nCoV, subsequently named severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] due to its similarity to SARS-CoV; the disease is known as coronavirus disease-19 [COVID-19]) was identified in Wuhan (China). This virus appears to be more contagious than those previously encountered. In fact, on 30 January 2020, the World Health Organization (WHO) declared it to be a Public Health Emergency of International Concern (PHEIC) as it had spread to 18 countries (with 7,818 confirmed cases; Puliatti et al., 2020). On 12 March 2020, WHO declared it a pandemic, with the virus having spread to every continent (123 countries), affecting broad and

localised areas (132,758 confirmed cases, 4,955 deaths; Puliatti et al., 2020). The first case was transmitted from animal to human, but now human-human transmission occurs through respiratory droplets from coughing and sneezing, with symptomatic individuals being the main vehicle for its spread. The incubation period varies from a minimum of 3 days to a maximum of 15 days.

One recent theory proposed that the SARS-CoV-2 virus uses the 'angiotensin-converting enzyme 2' (ACE2) as a receptor to enter human cells (Lu et al., 2020), which is similar to the mechanism of the entry of SARS-CoV into cells (Dimitrov, 2003). The extracellular domain of ACE2 is a cell surface receptor for the glycoproteins (S domain) on the SARS-CoV-2 envelope (Lu et al., 2020). Viral glycoproteins comprise an exocellular domain, a trans-membrane domain and an intracellular domain. The exocellular domain is formed by an S1 unit that bonds to the ACE2 peptidase domain (PD) through the receptor-binding domain (RBD; Lu et al., 2020); a second S2 unit facilitates membrane fusion simultaneously with virus-receptor binding (Lu et al., 2020; Figure 1). The PD domain breaks angiotensin I down into angiotensin-(1-9), which

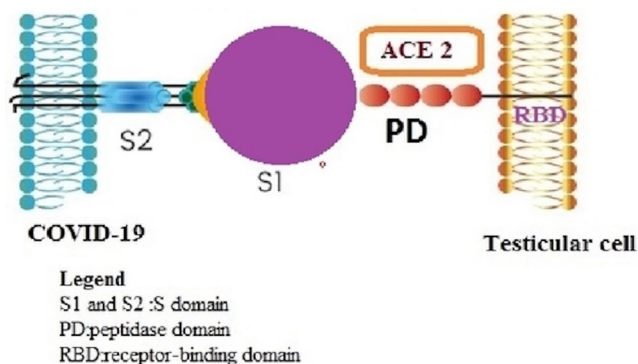


FIGURE 1 Link between SARS CoV2 and ACE2

is then transformed into angiotensin (1-7) by other enzymes (ACE; Dimitrov, 2003). ACE2 can also directly convert angiotensin II into angiotensin (1-7) (Dimitrov, 2003). angiotensin II binds to the ART1 receptor and can cause inflammation and fibrosis. ACE2 antagonises the activation of the classical rennin-angiotensin system (RAS) and protects against organ damage.

In the COVID-19 infection process, ACE2 receptors are saturated by binding with the virus, giving rise to the increased availability of angiotensin II, which cannot be converted (Dimitrov, 2003). The excess angiotensin II explains the pulmonary symptoms that are characteristic of COVID-19. The process is blocked by the conversion of angiotensin II into angiotensin (1-7) by ACE2. Angiotensin (1-7) binds to the ART2 and MAS receptors (Dimitrov, 2003).

Reis et al. (2010) has also confirmed the presence of ACE2, angiotensin (1-7) and its MAS receptors in the testicles, specifically in Leydig and Sertoli cells.

The primary function of the Leydig cells is to produce sex steroid hormones, particularly testosterone. As such, the presence of MAS receptors might suggest that angiotensin (1-7) modulates the secretion of testosterone (Reis et al., 2010). The presence of MAS receptors and angiotensin (1-7) in the seminiferous tubules may also explain the involvement of Sertoli cells and germinal cells (Reis et al., 2010). Although the testicular expression of ACE2 may indicate the possible entry of the virus into the testicles, the literature concerning SARS-CoV is not consistent and concordant. Zhao et al. (2003), encountered the presence of SARS-CoV in the testicular epithelial cells and in the Leydig cells, whereas Ding et al. (2004), encountered direct infection in other organs, but not in the testicles.

In a recent study, Song et al. (2020) collected 12 semen samples from survived COVID-19 patients and testicular biopsies from a dead COVID-19 patient. In the semen samples and in testicular biopsy, tissues were not detected 2019-nCoV RNA. These results could indicate that the virus would not directly infect the testes or male genital tract even in the acute phase.

There are currently no studies assessing the possible entry of SARS-CoV-2 in testicles via ACE2 or other mechanisms, but it could be a possible aetiopathogenic hypothesis of future infertility in patients who acquire SARS-CoV-2 infection.

Another aetiopathogenic hypothesis could be that SARS-CoV-2 infection causes an indirect inflammatory/immune response in testicles.

Indeed, a high concentration of testicular inflammatory infiltration has been observed in patients infected by SARS-CoV (Xu et al., 2006). The inflammatory cells could interfere with the function of Leydig cells, thereby impeding testosterone production, as well as destroy the cells of seminiferous tubules (Xu et al., 2006). The cytokines produced by the inflammatory cells could activate an autoimmune response and develop antibodies within the seminiferous tubules (Xu et al., 2006).

However, in an acute phase, these functional alterations of the Leydig cells may not potentially be evident.

Ma et al. (2020), in a recent retrospective study on COVID-19 patients, showed that they had significantly higher serum luteinising hormone (LH) and prolactin than healthy men, but without changes in the levels of serum testosterone. The authors explained these results with an early subtle negative feedback between testosterone and LH. Probably in the early stage, impaired testosterone production may stimulate the release of LH which can maintain testosterone level temporarily, and only after some time, the clinical hypogonadism emerges.

These aetiopathogenic hypotheses should be taken into consideration in cases where COVID-19 is diagnosed in young men, in order to be able to implement a stricter long-term andrological screening and follow-up programme.

Unfortunately, these primary studies have several limitations of small sample size, test methods, the course of disease. Further studies are required to confirm the results and to evaluate the prevention of testicular damage and the possibility of reversing it with new treatments that could be introduced in the market in the short term.

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REFERENCES

- Dimitrov, D. S. (2003). The secret life of ACE2 as a receptor for the SARSvirus. *Cell*, 115(6), 652–653. [https://doi.org/10.1016/S0092-8674\(03\)00976-0](https://doi.org/10.1016/S0092-8674(03)00976-0)
- Ding, Y., He, L. I., Zhang, Q., Huang, Z., Che, X., Hou, J., ... Jiang, S. (2004). Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis and virus transmission pathways. *The Journal of Pathology*, 203, 622–630. <https://doi.org/10.1002/path.1560>
- Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., ... Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet*, 395(10224), 565–574.
- Ma, L., Xie, W., Li, D., Shi, L., Mao, Y., Xiong, Y., ... Zhang, M. (2020). Effect of SARS-CoV-2 infection upon male gonadal function: A single center-based study. *medRxiv*. <https://doi.org/10.1101/2020.03.21.20037267>

- Puliatti, S., Eissa, A., Eissa, R., Amato, M., Mazzone, E., Dell'Oglio, P., ... Rocco, B. (2020). COVID-19 and urology: A comprehensive review of the literature. *BJU International*. <https://doi.org/10.1111/bju.15071>
- Reis, A. B., Araújo, F. C., Pereira, V. M., Dos Reis, A. M., Santos, R. A., & Reis, F. M. (2010). Angiotensin (1–7) and its receptor Mas are expressed in the human testis: Implications for male infertility. *Journal of Molecular Histology*, 41, 75–80. <https://doi.org/10.1007/s10735-010-9264-8>
- Song, C., Wang, Y., Li, W., Hu, B., Chen, G., Xia, P., ... Liu, Y. (2020). Detection of 2019 novel coronavirus in semen and testicular biopsy specimen of COVID-19 patients. *medRxiv*. <https://doi.org/10.1101/2020.03.31.20042333>
- Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C. K., Zhou, J., ... Gao, G. F. (2016). Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends in Microbiology*, 24, 490–502. <https://doi.org/10.1016/j.tim.2016.03.003>
- Xu, J., Qi, L., Chi, X., Yang, J., Wei, X., Gong, E., ... Gu, J. (2006). Orchitis: A complication of severe acute respiratory syndrome (SARS). *Biology of Reproduction*, 74(2), 410–6.
- Zhao, J. M., Zhou, G. D., Sun, Y. L., Wang, S. S., Yang, J. F., Meng, E. H., ... Zhang, T. H. (2003). Clinical pathology and pathogenesis of severe acute respiratory syndrome. *Zhonghua Shi Yan He Lin Chang Bing Du Xue Za Zhi*, 17, 217–221.

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