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**Covid-19: A possible emerging impact on male
fertility**

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Covid-19: A possible emerging impact on male fertility

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ABSTRACT

SARS-CoV-2 is an emerging pandemic; main complementary protein and mediator for SARS-CoV-2 has been identified to be the angiotensin converting enzyme 2 (ACE2) that exists in various organs and highly expressed within the testicular tissue (spermatogonia, Leydig and Sertoli cells). SARS-CoV-2 binds to ACE2 and TMPRSS2 forming protein complexes mediating viral replication within the male gonads. Hence, an impact on testicular tissue could be observed post-infection. The structure of the sperm glycocalyx could serve as an adequate carrier for SARS-CoV-2. SARS-CoV-2 complex protein formation triggers an elevated immune response in a "cytokine storm" like action. Such leads to extensive tissue damage mediated by TFN- α , IL-1 β , IL-18 and IFN- γ . ROS elevation is noted during the infection from the viral-induced cellular damage. Such aggressive immune response, ROS accumulation, complex proteins formation and renin system failure could also progress to intercellular oedema which could lead to intratesticular obstruction with forming consequences including sperm count reduction and elevated Sperm DNA Fragmentation Index (SDFI). Testicular ultrasonography, semen analysis and male hormone profiling are recommended. Post recovery repetition for the previously mentioned tests would provide a useful insight into the andrological observations. Semen cryopreservation is highly recommended for vulnerable patients. Semen purification techniques could be adopted prior to cryopreservation and handling.

Keywords: Covid-19; fertility, male, SARS-CoV-2

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INTRODUCTION

COVID-19 has generated an emerging pandemic causing panic all over the globe with sudden and acute infectivity occurring through the population. In China, Italy, USA and other countries, COVID-19 pandemic has had huge severe impacts on the population showing increasing shortage within healthcare systems and adequate hospitalization provided for the exponentially emerging cases every day (WHO Covid-19 strategy, 2020). Infected patients express mainly pneumonia-associated symptoms (fever, fatigue, shortness of breath and sputum production) (Huang et al., 2020). While the majority are showing pneumonia-related symptoms, some did show other symptoms such as diarrhoea, poor appetite, nausea, vomiting and headache as well as other cardiovascular symptoms such as chest distress and cardiac injury. One study did show among 99 patients infected with SARS-CoV-2 that

females were less susceptible to infection than males and older males (Chen et al., 2020).

While it is still early to assume the possibility of other pathogenicity emerging within the male gonads due to poor data available on such matter. The expression for COVID-19 target site angiotensin-converting enzyme 2 or ACE2 and Transmembrane Protein Serine Protease exist within the male gonad tissue (HPA & GTEX RNA ACE2 2020) (HPA & GTEX RNA TMPRSS2 2020) (Wang et al., 2020). Hence, a future impact on the male gonads and particularly testicular tissue could be observed within males seeking ART or natural conception post-COVID-19 infection, an issue which can be observed with some forms of rubella and mumps as well (Azmat and Vaitla, 2020). Another interesting factor is the structure of the sperm glycocalyx which could serve as an adequate carrier for a glycoprotein coated lipid enveloped virus as COVID-19 (Roy et al., 2007).

In this literature review, first, we focus on SARS-CoV-2 origin, its human cell mediators ACE2 and TMPRSS2 and where they exist within different body organs including testicular and prostate tissues. Second, we predict testicular pathogenicity following an active SARS-CoV-2 infection, impact on male fertility potential, if it is possible for SARS-CoV-2 to exist within the semen and why. Third, recommendations to be followed for susceptible males seeking Assisted reproduction Technology.

COVID-19: A Brief

CoVs (coronaviruses) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (Casella et al., 2020). corona is the Latin term for crown due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) is classified into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV) (Casella et al., 2020). Furthermore, the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs (Cavanagh D. et al. 2007) Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) which are capable of infecting humans have been identified (Peiris et al., 2004).

Some of human corona viruses (HCoVs) were identified in the mid-1960s, while others were only detected in the new millennium. In general, estimates suggest that 2% of the population are healthy carriers for CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections (Casella et al., 2020). The common HCoVs are HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage), HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised host and

the elderly, lower respiratory tract infections can occur. Other human CoVs are SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively) (Peiris et al., 2004) (Lu et al., 2020). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations (Wang et al., 2020). SARS-CoV-2 has been found in several autopsies located within the testicular tissue which lead to reduction of the Leydig cells number compared to control individuals (Ming yang et al., 2020). Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively. SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat (Casella et al., 2020). Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant (e.g. hypochlorite 0.1%), cationic surfactants (benzalkonium chlorides 0.3%), peroxyacetic acid and chloroform except for chlorhexidine. Thus, using other products as lipid solvents in this case is not considered effective with COVID-19 (WHO, 2020).

Angiotensin-Converting Enzyme 2 and cellular Serine Protease TMPRSS2: The mediators of COVID-19 cellular entry

Like SARS-CoV, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) forming a protein complex. Another mediator for SARS-CoV-2 cell entry is the cellular serine protease (TMPRSS2). Such complexes formed with both mediate viral entry into the cell through a pre to post-fusion confirmation process of transition (Song et al., 2018) (Hoffmann et al., 2020; Harmer et al., 2002; Li et al., 2003; Li et al., 2020). Hence, both proteins are considered as mediators to the various organs and tissues where the virus could exist and form complex proteins. The Human Protein Atlas GTEX RNA data (HPA), as well as other recent analysis, revealed ACE2 and TMPRSS2 RNA data expression to be within various sites (ACE2 Located on X-chromosome (cytogenetic location: Xp22.2) while TMPRSS2 located on chromosome 21 (cytogenetic location: 21q22.3). According to (Harmer et al., 2002), RNA-sequence in normal tissues exists in the

gastrointestinal tract (GIT), gall bladder, kidney, prostate, testis, heart, fat, liver, thyroid, brain, lung, skin and bladder for both proteins. Such an abundance of distribution and variability could serve as an opportunity for viral entry and replication within the previously mentioned target sites. ACE2 RNA data indicate high expression in testicular tissue while TMPRSS2 RNA data indicate high expression in prostate tissue (HPA & GTEX RNA ACE2, 2020; HPA & GTEX RNA TMPRSS2, 2020; Harmer et al., 2002; Li et al., 2020). According to Wang et al. (2020), gene ontology (GO) analysis indicated a predominant enrichment for ACE2 in spermatogonia, Leydig and Sertoli cells. Such high expression in Leydig, Sertoli and spermatogonia provide a rich site for viral replication and transmission which could lead to cellular damage, apoptosis and reduction of these cell types within the tissue (Ming yang et al., 2020). One of the recent reports indicated a reduction in sperm count in males 72-90 days post SARS-CoV-2 infection (Segars et al., 2020). ACE2 levels of expression within spermatogonia were found to be close to Alveolar Type 2 (AT2) cells while Leydig and Sertoli cells had a significantly more frequency of ACE2 expressing cells which may enhance the possibility of an ongoing infection within the testis during COVID-19 infection periods (Wang et al., 2020). Another interesting fact is that the sperm glycocalyx contains lectins, such as an affinity towards glycoprotein parts of various viruses and could serve as an aid in COVID-19 transmission (Roy et al., 2007). Thus, Human semen could become a potential source for viral spread and transmission among the population.

Proposed Testicular Pathogenicity

Similar to AT2 cells regarding the existence of ACE2, where SARS-CoV and recently COVID-19 infection triggers an elevated immune response in a cytokine-storm-like action. The result is extensive tissue damage mediated by interleukin 6 (IL-6), and Tumour Necrosis Factor (TFN- α), interleukin 1 beta (IL-1 β), interleukin 18 (IL-18) and interferon gamma (IFN- γ) (Sun et al., 2020; Tisoncik et al., 2012; Mehta et al., 2020). Such an aggressive immune response along with the extensive tissue damage leads to acute inflammation. It also impairs its control over various native bacteria leading to an active

bacterial infection (Nieto-Torres et al., 2014) (Sun et al., 2020). According to Kuba et al. (2005), SARS coronavirus S protein could progress to acute lung failure through deregulation of the renin-angiotensin system. According to recent literature, Reactive Oxygen Species (ROS) from viral replication mediated cell damage and is elevated during an active SARS-CoV-2 infection which mediates extensive tissue damage. ROS is considered a risk factor and an important event that take place during the infection leading to various cells apoptosis and further viral pathogenesis (Livan et al. 2020; Nasi et al., 2020). The same principle could be applied to other infected tissues within various organs and particularly to testicular tissue for the similarity to AT2 cells regarding ACE2 expression. Such could progress in time to ROS accumulation with renin-angiotensin system exhaustion and deregulation to intercellular oedema (Kuba et al., 2005; Livan et al., 2020). Hence, the possibility of high oxidative damage, complex proteins formation coupled with oedema within the testicular tissue could lead to intratesticular obstruction with forming consequences such as reduction of Leydig cells number (Yang et al., 2020). which in time could result in a reduction for both sperm count and DNA integrity of the formed spermatozoa.

Recommendations and protocol to be adopted

Observation for the individuals undergoing COVID-19 current infection is recommended for a high possibility of pathogenicity for the testicular tissue might be present. Testicular ultrasonography, semen analysis and male hormone profiling (particularly testosterone) are recommended. Such hormone profiling results in better monitoring to the status as well as the number of cells under cellular stress from the infection. Post recovery repetition for the previously mentioned tests would provide a useful insight to the andrological observations pre and post-infection period. The reason for such recommendations come from a recent study where autopsies have been performed for COVID-19 patients post-mortem where Leydig cells were found to be reduced in number compared to control. Hence, testosterone can be used as a marker for Leydig cells status within the testicular tissue (Yang et al., 2020).

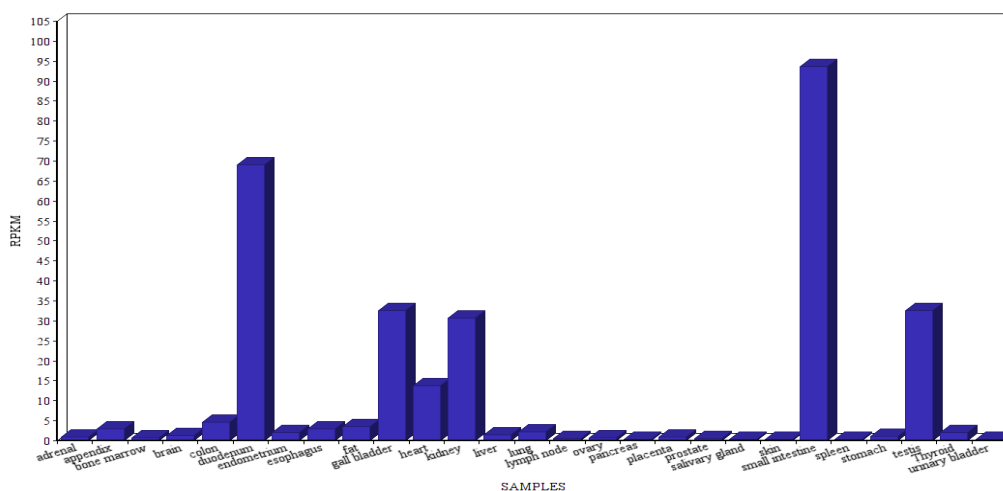


Figure 1. Illustrates the variations in ACE2 RNA expression in various body tissue samples

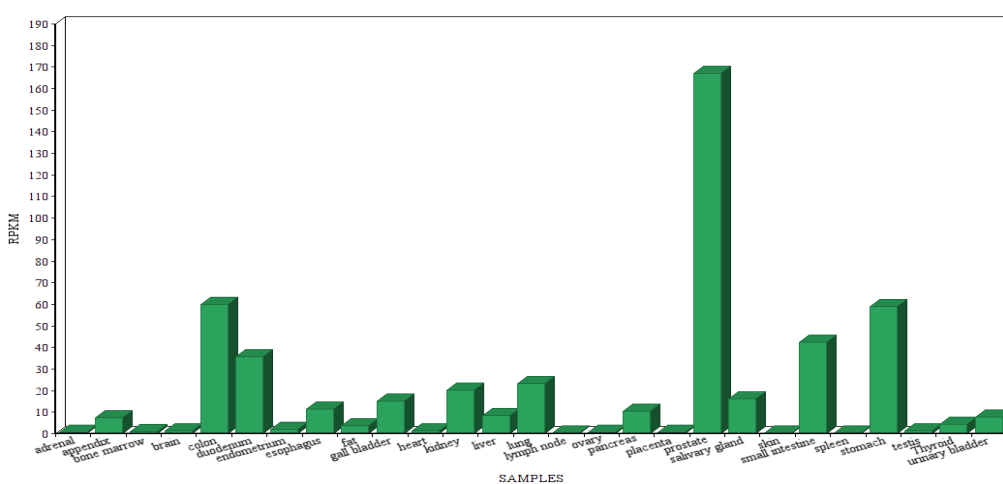


Figure 2. Illustrates the variations in TMPRSS2 RNA expression in various body tissue samples

A highly recommended procedure to be undertaken for individuals at high risk to COVID-19 infection is semen cryopreservation. In case of a pathogenic development that would lead to failure of sperm production, such would ensure a chance for conceiving via ART. In currently infected patients, semen cryopreservation should be performed in a closed system to ensure contamination prevention (WHO 2010). In case of an open system for cryopreservation, viral removal from semen samples can also be performed using multiple density gradients for possibly infected semen samples. This processing technique has been adopted in HIV-1 and HCV infected semen samples for ART purposes (Loskutoff et al., 2005). Ferromagnetic micro and nano-beads coated with various lectins as mannose-binding lectins could serve as novel alternatives for purification of samples from COVID-19 (Jack et al., 2003).

CONCLUSIONS

TMPRSS2 and ACE2 complex formation with COVID-19 mediate viral entry and production. Expression sites for both receptors provide potential target sites for COVID-19 such as spermatogonia, Sertoli and Leydig cells. The general exhaustion of ACE2 system through constant complex formation with the viral molecules might lead to an impaired renin-angiotensin system as complex proteins keep forming. Such constant vasodilatation and complex proteins coupled with ROS accumulation from viral replication and immune response could lead to testicular oedema which in turn leads to intratesticular obstruction with forming consequences. Semen analysis, testicular ultrasonography, as well as semen cryopreservation, is of great importance as a precaution prior to the development of such

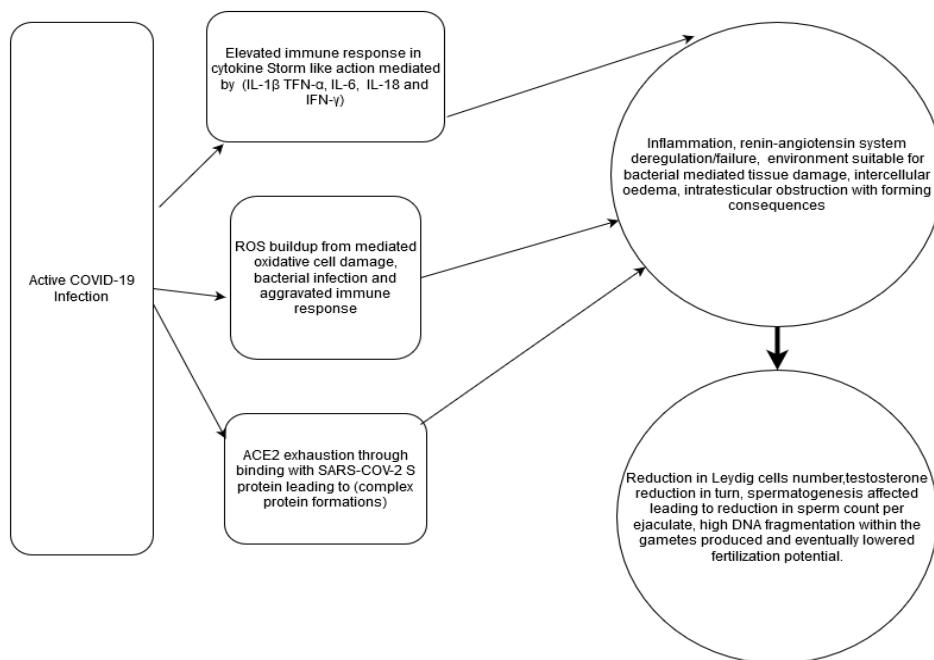


Figure 3. Diagram shows the various factors affected during an active SARS-CoV-2 infection and how can this pathogenic progression affect male fertility

pathogenicity within the testis with precaution to the viral presence within the samples undergoing cryopreservation. Samples can be purified pre-cryopreservation with various current and novel emerging techniques.

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Conflict of interest

Authors declare that they have no conflicts of interest.

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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (<http://acdd.tanta.edu.eg>). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: <https://jcbjournals.ekb.eg>) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

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