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Covid-19; an Emerging Impact Possibility on Male Fertility

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Abstract
COVID-19 as an emerging pandemic, Expression patterns for COVID-19 is angiotensin converting enzyme 2 (ACE2) receptors that exists within the testicular tissue (spermatogonia, Leydig and Sertoli cells) providing a rich site for viral replication. Hence, an impact on testicular tissue could be observed within males seeking fertility post COVID-19 infection. Another interesting factor is the structure of the sperm glycocalyx which could serve as an adequate carrier for COVID-19. Similar to a degree to SARS-CoV, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) forming a protein complex. Another mediator with SARS-CoV-2 is the cellular serine protease (TMPRSS2). ACE2 Located on X chromosome (cytogenetic location: Xp22.2) while TMPRSS2 located on chromosome 21 (cytogenic location: 21q22.3). COVID-19 triggers an elevated immune response in a "cytokine storm" like action. resulting in an extensive tissue damage mediated by interleukin 6 (IL-6). Such aggressive immune response along with the extensive tissue damage impairs its control over various native bacteria leading to an active infection. Testicular damage could progress rapidly to intercellular oedema. Testicular ultrasonography, semen analysis and male hormone profiling is recommended. Post recovery repetition for the previously mentioned tests would provide a useful insight to the andrological observations. Semen cryopreservation is highly recommended for vulnerable patients, as a high possibility of pathogenicity for the testicular tissue might be present.

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I. Introduction

COVID-19 has generated an emerging pandemic causing panic all over globe with a sudden and acute infectivity occurring through the population. In China, Italy, USA and other countries the COVID-19 pandemics 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. All mentioned above has led the world into a state of panic we are witnessing nowadays all over the globe with no knowledge what so ever regarding what to witness later from the post recovery individuals.

While still early to assume the possibility of other pathogenicity emerging within the male gonads due to poor data available on such matter. Expression patterns for COVID-19 target site angiotensin converting enzyme 2 or ACE2 receptors and Transmembrane Protein Serine Protease exist within the male gonad tissue(**NCBIHPA ACE2**) (**NCBIHPA TMPRSS2**). Hence, a future impact on testicular tissue could be observed within males seeking ART post COVID-19 infection. 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(**R. Roy et al.** 2007).

In literature review we concern on COVID-19 virus origins, epigenetic expression patterns in various body organs including testicular tissue, the possibility of its presence in human semen and the approach that should be adopted in ART. Another discussed topic will be a novel technology that can be routinely applied in the future for removing viruses from semen.

II. Literature Review

2.1 Family of corona viruses

According to (**Cascella M. et al**2020)CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (coronam 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) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). 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. 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) — capable of infecting humans — have been identified. Some of 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 of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.

Common human CoVs 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 subjects 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). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. 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(**Cascella M. 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% and above), cationic surfactants (benzalkonium chlorides 0.3% and above), peroxyacetic acid and chloroform except for chlorhexidine. Thus, using other products as lipid solvents in this particular case is not considered effective with COVID-19(**WHO Lab. Biosafety COVID-19** 2020).

2.2 Angiotensin Converting Enzyme 2 and the cellular serine protease TMPRSS; the mediators of COVID-19 cellular entry

Similar to a degree to SARS-CoV, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) forming a protein complex. Another mediator with SARS-CoV-2 is the cellular serine protease (TMPRSS2). Such complexes formed with both mediates viral entry into the cell through a pre to post fusion conformation process of transition (**Song W. et al.** 2018) (**Markus Hoffmann et al.** 2020) (**Harmer D. et al** 2002). Hence, both proteins expression patterns are considered a mediator to the various organs and tissues were the virus could exist and replicate. The Human Protein Atlas (HPA) reveals ACE2 and TMPRSS2 RNA-sequence expression to be within various sites. ACE2 Located on X chromosome (cytogenetic location: Xp22.2) while TMPRSS2 located on chromosome 21 (cytogenic location: 21q22.3).According to the human protein atlas (**HPA**2020), the RNA-sequence in normal tissues is located in the gastro intestinal tract (GIT), gall bladder, kidney, prostate, testis, heart, fat, liver, thyroid, brain, lung, skin and bladder for both proteins.Such bundance of distribution and variability could serve as an opportunity for viral entry and replication within the previously mentioned target sites (**NCBIHPA ACE2**) (**NCBIHPA TMPRSS2**) (**Harmer D. et al** 2002). According to(**Wang, Z. et al.** 2020), gene ontology (GO) analysis indicated a predominant enrichment in spermatogonia, Leydig and Sertoli cells. Highly enriched sites for both proteins positive Leydig, Sertoli and spermatogonia provide a rich site for viral replication and transmission. While male gamete generation was downregulated, cell to cell junction and immunity was elevated. Human male gametes could then provide a potential source for the viral spread and transmission. According to (**Wang, Z. et al.** 2020), ACE2 level of expression within spermatogonia was found to be close to 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. Another interesting fact is that the sperm glycocalyx contains lectins, such has an affinity towards glycoprotein parts of various viruses and could serve as an aid in COVID-19 transmission (**R. Roy et al.** 2007).

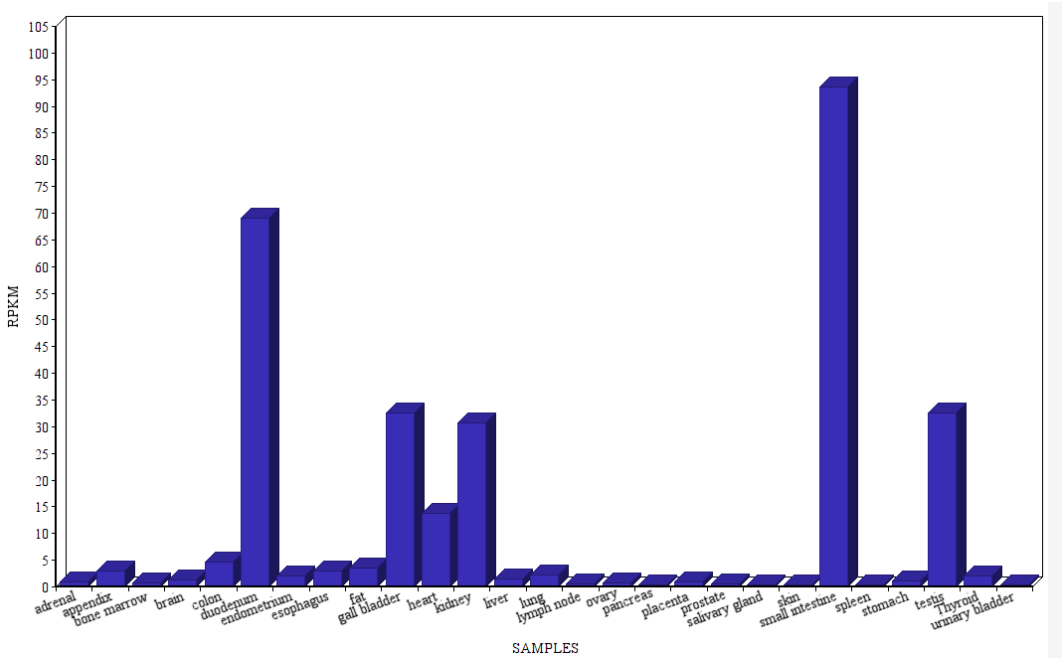

Figure shows ACE2 Human protein Atlas RNA-seq expression in normal tissues (**NCBI HPA ACE2**https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue)

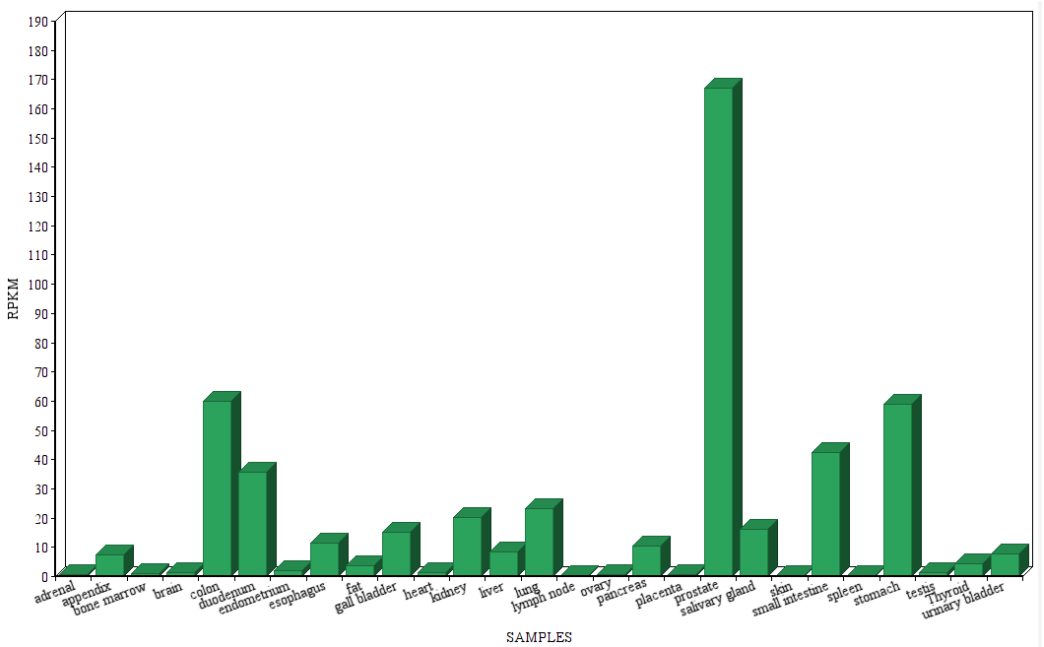

Figure shows TMPRSS2 Human protein Atlas RNA-seq expression in normal tissues (**NCBI HPA TMPRSS2 https://www.proteinatlas.org/ENSG00000184012-TMPRSS2/tissue)**

2.3 Proposed testicularpathogenecity

Similar to AT2 cells, where COVID-19 infection triggers an elevated immune response in a "cytokine storm" like action. The result is an extensive tissue damage mediated by interleukin 6 (IL-6). Such aggressive immune response along with the extensive tissue damage impairs its control over various native bacteria leading to an active infection(**Nieto-Torres et al.** 2014). According to (**Kuba et al.** 2005), SARS coronavirus S protein could progress to acute lung failure through deregulation of the renin-angiotensin system. The same principle could be applied to the majority of infected tissues within various organs and particularly totesticular tissue for the similarity to AT2 cells regarding expression. Such could progress in time to intercellular oedema as the renin-angiotensin system becomes deregulated (**Kuba et al.** 2005).

III. Recommendations Andprotocol 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 is recommended.Post recovery repetition for the previously mentioned tests would provide a useful insight to the andrological observations pre and post infection period.

A highly recommended procedure to undertake for individuals not yet diagnosed with COVID-19 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 current infected patients, semen cryopreservation should be performed in a closed system to ensure contamination prevention (**WHO laboratory manual fifth edition** 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 sample. Such has been adopted in HIV-1 and HCV infected semen samples for ART purposes (**Loskutoff, Naida M. 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, D.L. et al**2003)(**Yavuz Oz. et al 2019)**.

IV. 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. Such constant vasodilatation could lead to testicular intercellular oedema. Semen analysis, testicular ultrasonography as well as semen cryopreservation is of extreme importance as a precaution to the development of such pathogenicity within the testis with precaution to viral presence within the samples undergoing preservation, such can be purified pre-cryopreservation with various current and novel emerging techniques.

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