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Research Article

The Sars-Cov-2 Pandemic: Its Effects on the Testicular Function and Future Ramifications on Male Reproductive Performance

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Abstract

During the recent century there have been a series of viral pandemics that have collectively infected millions of individuals globally. Recently and with the discovery of the novel coronavirus SARS-CoV-2 that has spread globally, causing the current SARS-CoV-2 (coronavirus disease-19) pandemic. With the recent increase of infections due to the pandemic in the male population, concerns have emerged about the potential impact of SARS-CoV-2 on male reproductive organs and male fertility. Therefore, this study was designed to look at those effects within the same male population at a certain pre and post infection period. We also investigated oxidative stress created by excessive generation of reactive oxygen species (ROS) by the sperm and/or the disruption of antioxidant defense systems in the male reproductive tract of those patients. The generated data from this study clearly depicts a significant effect on almost all of the sperm parameters assessed including DNA fragmentation. The data also very uniquely shows significant effects of the stability of the DNA of the sperm along with increases in the ROS values on those patients that were infected by the Covid virus.

Keywords: *Reactive Oxygen Species (ROS); DNA Fragmentation; Covid Virus; SARS-CoV-2*

Introduction

Male infertility is linked to some viral infections including human papillomavirus (HPV), herpes simplex viruses (HSV) and human immunodeficiency viruses (HIVs). Very limited knowledge exists about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effect on fertility. However, according to several sources, the new coronavirus, known as SARS-CoV-2, enters human cells and can cause tissue damage by binding its spike protein to cell membrane protein angiotensin-converting enzyme 2 (ACE2; See diagram 1).

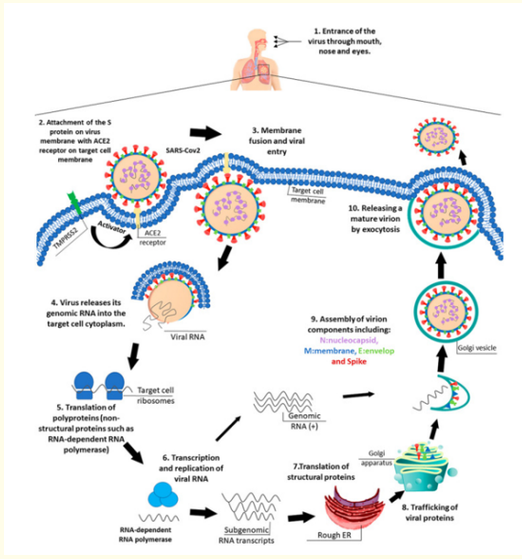

Diagram 1: *Events during the Infection cycle of SARS-CoV2.*

The ACE2 is known to be present in several human organs in addition to the respiratory system (lungs) and can especially be abundant in the human testes. It can be concentrated in several cells which are directly related to the male reproductive system and its overall physiology. These cells present in the parenchymal testes tend to include the germ cells, supporting cells and Leydig cells. It is furthermore postulated that the possible risk factors of coronavirus disease 2019 (SARS-CoV-2) infection on fertility comes from the abundance of angiotensin-Converting Enzyme-2 (ACE2), receptor entry of the virus, on testes, a reduction in important sex hormone ratios and SARS-CoV-2-associated fever [1].

In this study, we wanted to investigate the potential effect of SARS-CoV-2 on male fertility and specifically the quality of ejaculate characteristics and sperm DNA fragmentation qualities between COVID-19 infected males and their non-infected counterparts. Also, our experimental designed aimed to look at those effects within the same male population at a certain pre and post infection period. We also investigated oxidative stress created by excessive generation of reactive oxygen species (ROS) by the sperm and/or the disruption of antioxidant defense systems in the male reproductive tract of those patients.

Materials and Methods

Two groups of patients of similar age characteristics that were attending the Andrology Institute of America (AIA) were isolated and studied. Group one (N = 30) consisted of patients that did not have any infections with SARS-CoV-2 and patients in Group two (N= 30) consisted of SARS-CoV-2 infected patients that underwent andrological evaluation at the AIA prior to being infected and were evaluated approximately 90 days post infection. Seminal collections and evaluations were performed and assessed as previously described [2]. Similarly, DNA fragmentation assessments and reactive oxygen species (ROS) measurements were performed as per previously described methodologies [3-5].

Results

The results from the measurements for the spermatogenic parameters between the two groups of patients are presented in table 1. The ages between the two groups were uniform without any significant differences. Furthermore, the sperm parameters assessed within Group 1 (uninfected by Covid) as compared between the two time periods (96.0 + 5.1 days apart) showed no significant deviations and stayed within normal range (WHO Standards). However, when similar comparisons were made between the two time periods (110 + 9.7 days apart), in Group 2 (infected by covid) one sees significant reductions ($P < 0.05$) in almost all of the sperm parameters assessed. When considering the direct measurements on the stability of the sperm DNA by measuring the level of DNA fragmentation evident in the sperm collected from the same patients but from before Covid infection versus 110 days post infection it is quite evident that the infection not only affected the general spermatogenic parameters measured during a routine semen analysis, but it had a significant effect of the stability of the sperms DNA via measurements of DNA fragmentation (Table 2; $P < 0.05$). Most importantly the highest levels on ROS were found in Group 2 seminal specimens following Covid infection (pre-infection = 0.32 versus post-infection= 14.32; $P < 0.05$) whereas in the non-infected Group 1 patients there was no variation between the two time periods of 96.0 days (0.50 versus 0.60). A strong positive correlation ($r = 0.8147$, $P < 0.0001$) of ROS levels between pre-infection and post-infection specimens was observed.

Men (N)	Ages (Yrs.)	Volume (mL)	Count/mL ($x10^6$)	Total Count ($x10^6$)	Motility (%)	Grade (0-4)	Morphology (% Normal)
Uninfected N-30	41.2 ± 3.1	3.2 ± 0.7[a]	37.5 ± 2.6[a]	120 ± 3.1[a]	47.8 ± 7.6[a]	3.5 ± 0.6[a]	13.1 ± 0.4[a]
Time dif. in days	96.0 ± 5.1	3.1 ±.0.6[a]	39.6 ± 2.9[a]	123 ± 3.6[a]	45.9 ± 6.1[a]	3.4 ± 0.5[a]	12.7 ± 0.3[a]
Infected N=30	40.5 ± 4.6	3.7 ± 0.6[a]	34.2 ± 2.5[a]	127±3.8[a]	43.7 ± 4.2[a]	3.3 ± 0.5[a]	12.5 ± 0.5[a]
Time dif. in days	110 ± 9.7	3.2 ± 0.8[a]	19.3 ± 5.1[b]	62 ± 6.3[b]	31.2 ± 6.1[b]	2.1 ± 0.6[b]	6.3 ± 1.7[b]

Table 1: *Depicting all clinical data and spermatogenic parameters assessed among the two groups of patients studied at pre- and post-infection periods (Means +/- SD).[a, b]: Means with different superscripts within columns are significantly different ($P < 0.05$).*

Men (N)	Ages (Yrs.)	DNA Fragment. (%)	ROS RLU/sec/10^6 sperm
Uninfected N-30	41.2 ± 3.1	8.3 ± 1.3[a]	0.50 ± 0.01[a]
Time differ. in days	96.0 ± 5.1	9.1 ± 1.5[a]	0.60 ± 0.01[a]
Infected N=30	40.5 ± 4.6	10.3 ± 1.7[a]	0.32 ± 0.01[a]
Time differ. in days	110 ± 9.7	33.7 ± 5.1[b]	34.32 ± 4.70[b]

Table 2: *Depicting all clinical data and DNA fragmentation along with ROS values among the two groups of patients studied at pre- and post-infection periods (Means+/- SD).*

Discussion

Male infertility is linked to some viral infections including human papillomavirus (HPV), herpes simplex viruses (HSV) and human immunodeficiency viruses (HIVs). Almost nothing is known about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effect on fertility. The possible risk factors of coronavirus disease 2019 (SARS-CoV-2) infection on fertility comes from the abundance of angiotensin-Converting Enzyme-2 (ACE2), receptor entry of the virus, on testes, a reduction in important sex hormone ratios and SARS-CoV-2-associated fever [1]. Recent studies have shown a gender difference for SARS-CoV-2 rates and comorbidity. In the current study, we show very clearly a definite potential effect of SARS-CoV-2 on male fertility by investigating the status of the ejaculate status of patients that were not COVID infected (Group 1) versus patients that were infected (Group 2). The important finding in this study was that we were able to evaluate the status of those patients by providing baseline values of their spermatogenic parameters prior to being infected in both groups and subsequently taking a look at their same parameters approximately 90 days (one spermatogenic cycle) post-Covid infection as compared between the two Groups. The data clearly depicts a significant effect on almost all of the sperm parameters assessed. Data also very uniquely shows significant effects of the stability of the DNA of the sperm on those patients that were infected by the Covid. Furthermore, when considering the oxidative stress and DNA damage to those sperm in the Covid infected group, one can deduct that such damage is very dramatic and could have significant effects on those sperm to cause adequate fertilization and possibly yield a variety of abnormalities to the resulted fetus from such pregnancies.

Going even further, it is well established that defective sperm function could be due to oxidative stress created by excessive generation of reactive oxygen species (ROS) by the sperm and/or the disruption of antioxidant defense systems in the male reproductive tract. Excess free radical generation may involve defective spermiogenesis with high levels of cytoplasmic retention and consequent ROS generation. The consequences of such oxidative stress include a loss of motility and fertilizing potential and the induction of DNA damage in the sperm nucleus [5]. The causes and consequences of oxidative damage to the DNA in the sperm nucleus although not well known with certainty, the available evidence suggests that, in addition to a reduced chance of spontaneous pregnancy [6] and a reduced chance of a live birth following IVF/ICSI [7,8], early pregnancy loss and morbidity in the offspring, including childhood cancer, may also be associated with such damage. Although the current study did not go far enough to evaluate such findings, one needs to consider those results very seriously and agree that further and more intense studies must be undertaken to evaluate the magnitude of the global COVID infection in males that wish to consider procreating in the future.

The Future: Where do we go from here?

The data presented in this study points clearly the link between the SARS-CoV-2 and its possible effects on men's seminal characteristics and strengthens and brings together the findings and observations made in the area of reproductive health during the current pandemic. Furthermore, this is the first study to clearly depict the strong link between SARS-CoV-2 infection in men of reproductive age on

specific spermatogenic parameters. Although other studies pointed out on the presence of SARS-COV-2 in the semen of male patients [1], in the current study, we are able to show and conclude that SARS-CoV2 is not only capable of entering the testicular parenchymal tissues but also affect the end result of the physiology of those tissues, the process of spermatogenesis and affect directly the end product, the sperm cells themselves. The findings in the current study are of immense significance since SARS-CoV2 is now shown to have a significant impact on humans' reproductive status and their ability to procreate and we definitely need to take this matter very seriously.

It is these authors opinion that the reproductive system of any young population is preordained for subsequent disorders, infertility, reduced sperm count and motility but SARS-CoV2 pattern of penetration and accessing the testes as shown in this study may be accelerating those aging alterations and needs to be taken very seriously. Therefore, the research and medical practices should focus on the possible vulnerability being posed by SARS-CoV-2 on gametes and the future generations ability to procreate.

Conflict of Interest Statement

The authors have nothing to disclose.

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