

Case – Sperm DNA fragmentation associated with COVID-19 infection

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has ravaged healthcare systems worldwide and has manifested with a diversity of clinical presentations in humans. There is accumulating evidence that the male reproductive system is a susceptible target for COVID-19 infection.¹

Recent studies have suggested that COVID-19 may negatively impact spermatogenesis and reduce semen quality, thereby reducing fertility potential. Angiotensin-converting enzyme (ACE-2) is the mediating receptor for SARS-CoV-2 infection and is unsurprisingly found within the respiratory epithelium but is also highly expressed within the male gonads. Somatic testicular cells and germ cells both harbor a high concentration of ACE-2 on their cell surface, which may lead to a range of reproductive sequelae, including hypogonadism, testicular parenchymal damage, inflammatory infiltration, anti-sperm antibody production, and disrupted spermatogenesis.²

The sperm DNA fragmentation index (DFI), a measure of DNA damage, has emerged as an important tool in the evaluation of male fertility potential. High levels of sperm DNA damage have been associated with spontaneous pregnancy loss and poor assisted reproductive technology outcomes.^{3,4}

Although early studies have begun elucidating the effects of COVID-19 on traditional semen parameters, there is a paucity of published data measuring DFI in this context. Here, we present a case of a man under investigation for infertility with semen analyses and DFI measurements prior to, and following, COVID-19 infection.

Case report

The ethics review board at our institution approved this study. All patient information remained confidential.

We report the case of a 45-year-old male with a 24-month history of secondary infertility. His partner was a 56-year-old-female being monitored for high prolactin, without any other known gynecological issues. The couple had a history of recurrent miscarriages in a period of two years prior to evaluation. The patient had no contributory past medical or surgical history. He was not on any medications, did not have any known allergies, and did not consume alcohol, drugs, or cigarettes. The physical exam was unremarkable: his estimated testicular volumes were 18 ml and 16 ml on the right and left, respectively, the vas deferens was palpable bilaterally, and there was no clinical varicocele.

The patient underwent four semen analyses (SA) in the period of two years. The first two SAs (December 2019 and July 2020) demonstrated normal semen volume (2.7 and 3.5 ml), normozoospermia (112 and 120 million sperm/ml), and normal progressive motility (53 and 64%). The morphology was only tested in the first SA, and it was normal (4% normal forms). On his second SA (July 2020), a sperm DFI was requested to investigate the cause of the recurrent miscarriages. All DFI analyses were performed in a single laboratory with the same TUNEL assay.⁵ The patient's baseline DFI was found to be moderately elevated at 29%. During the following visit (November 2020), the patient was counseled to modify his lifestyle habits and he was prescribed a multivitamin supplement (Fertil-Pro[®] Men + L-Carnitine), which he continued to take until his fourth SA in April 2021.

The patient tested positive for COVID-19 (via SARS-CoV-2 RNA PCR) six months after the second SA (January 2021). He suffered mild symptoms, including fatigue, anosmia, and ageusia while remaining afebrile. The course of his infection was self-limited, and he did not require intervention or hospital admission.

The third SA was done four weeks following his COVID-19 infection (February 2021); the patient produced a semen

volume of 3.5 ml with a sperm concentration of 50 million sperm/ml. On this SA, the sperm DFI was significantly elevated at 76% (Figure 1).

The fourth SA was performed four months following his COVID-19 infection (April 2021). The semen volume was 2.8 ml with a sperm concentration of 25 million/ml. The DFI was 22%, which was similar to his baseline sperm DFI prior to COVID-19.

Discussion

The acute and chronic effects of COVID-19 on semen quality and spermatogenesis are still largely unknown, however, studies suggest that COVID-19 may be detrimental to men seeking natural or assisted conception.

The patient described in the case report demonstrated a substantial decrease in sperm concentration following SARS-CoV-2 infection, dropping to less than half of his initial sperm concentration prior to COVID-19 (~116 million/ml to 50 million/ml). Although this is a notable decline, the interpretation of SA can be challenging due to the normal biological variation in conventional sperm parameters, particularly, sperm concentration. However, a recent prospective study found that the median sperm number and concentration in the ejaculate of men infected with SARS-CoV-2 was significantly lower than uninfected controls, suggesting that COVID-19 may, in fact, impair spermatogenesis in the short-term.⁶

Sperm DFI has a reportedly lower degree of biological variability than conventional semen parameters.⁷ Given the low variability in sperm DFI measurements, it is notable that our patient demonstrated an increase in DFI from 29% to 76% in the span of seven months. It is unlikely that the substantial increase in DFI (Figure 1) was due to intra-individual variation without a possible precipitating factor. Moreover, the sperm DFI returned to baseline levels four months (more than one full cycle of spermatogenesis) after the COVID-19 infection.

The significant elevation and subsequent reduction in DFI temporally associated with COVID-19 infection suggests a possible link between COVID-19 infection and sperm DNA fragmentation. It is important to acknowledge that there are several precipitants that could temporarily elevate sperm DFI other than COVID-19 (e.g., other febrile illness, genitourinary infection),⁸ however, there were no other known triggers in this patient.

SARS-CoV-2 may mediate damage to the male reproductive system via both direct and indirect mechanisms, or a combination of both. The biological basis for a direct mechanism of viral-induced damage can be explained by the expression of ACE-2 receptors on various testicular cells that may mediate the effects of SARS-CoV-2 infection. Post-mortem testicular analysis of five COVID-19 patients (ranging from 51–83 years old) compared to uninfected controls demonstrated widespread germ cell degeneration with very

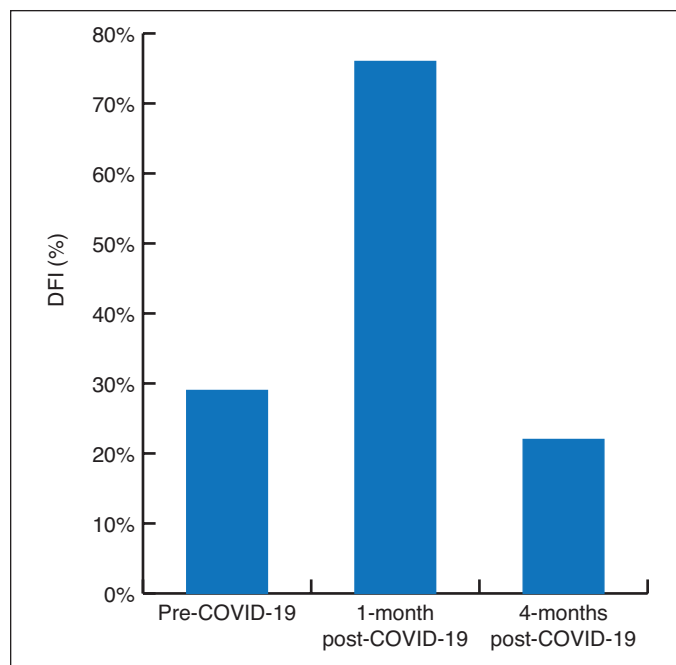


Figure 1. DNA fragmentation index (DFI) (%) before and after COVID-19 infection.

few viable spermatocytes, increased parenchymal apoptosis, and marked immune cell infiltration (lymphocytes and macrophages) in the interstitium.⁹ The authors suggested that SARS-CoV-2 may trigger a maladaptive autoimmune response, contributing to viral orchitis and subsequent parenchymal damage. Similarly, in another postmortem analysis of 12 COVID-19 patients, there was marked seminiferous tubular injury, lower numbers of Leydig cells, and lymphocytic inflammation compared to controls.¹⁰ This testicular pathological pattern is similar to the viral orchitis noted in autopsies of men infected with SARS-CoV-1, the virus underlying the 2003 SARS pandemic, which used similar mechanisms of host cell entry via ACE-2 receptors.¹¹

Indirect mechanisms of COVID-19-mediated impairment in testicular function likely also play a significant role. Interestingly, 90% of postmortem testicular samples did not demonstrate SARS-CoV-2 virus via RT-PCR, thus supporting the contributions of indirect mechanisms as well.¹⁰ Fever is a common symptom in COVID-19 patients and an elevated body temperature is an established factor known to impair spermatogenesis and sperm DNA integrity.^{12,13} Profound inflammation and cytokine secretion is an important prognostic marker for severe COVID-19 infection and can contribute to oxidative DNA damage and apoptosis.¹² Genitourinary infection (e.g., mumps, hepatitis B virus, hepatitis C virus, human immunodeficiency virus) and inflammation with ensuing oxidative stress are common causes of male infertility and likely represent some of the mechanisms by which COVID-19 elevates sperm DFI.¹⁴ Furthermore, hypothalamic-pituitary-testicular (HPT) axis dysregulation can be implicated through

various mechanisms, including direct hypothalamic/pituitary effects of SARS-CoV-2 and profound psychological stress or anxiety stemming from COVID-19.¹²

There is relatively little published on sperm DFI and COVID-19. Ma et al examined a cohort of reproductive-aged males (ranging from 20–49 years old) who endured mild to moderate COVID-19 infection. The median time between disease onset and semen collection was 78.5 days (range 56–109). The authors measured DNA fragmentation with the sperm chromatin dispersion assay and found that one-third of patients demonstrated high DFI (mean 20.05 ± 3.80 %), as well as low sperm motility (defined as progressive and nonprogressive <40%).¹⁵ The authors inferred that impaired sperm quality, reflected by a high sperm DFI, may represent a complication of COVID-19 in certain men. However, in the aforementioned study, DFI was not measured prior to COVID-19 infection, thus limiting the ability to attribute the differences in DFI as a result of COVID-19.

In a recent longitudinal study, investigators examined 41 reproductive-age males (interquartile range [IQR] 22–34 years old) who recovered from COVID-19 infection and required hospitalization. Following discharge, these men submitted a SA at a median of 76 days (IQR 73–87) after the onset of symptoms and demonstrated significantly lower total sperm counts, concentration, and motility compared to controls. A repeat SA of the men that recovered done at a median of 106 days (IQR 102–127) after symptom onset showed a significant increase in the sperm count, concentration, and normal morphology compared to their initial SA.¹⁶ It is important to note that this study did not have baseline SA values for participants, thus limiting the interpretation of results. Nevertheless, the temporal association between COVID-19 infection and SA abnormalities (attributable to both direct and indirect mechanisms), followed by enhancement of sperm quality after a complete cycle of spermatogenesis, suggests a temporary and reversible insult to spermatogenesis.

Conclusions

There is accumulating evidence to support an adverse effect of COVID-19 infection on male fertility. Direct (possibly via ACE-2 receptors in testicular cells) and indirect mechanisms may be responsible for the observed pathophysiological damage and reproductive function impairment. Our patient presented with a substantial elevation in sperm DFI shortly following his course of COVID-19, further supporting these emerging data. As such, men who contract COVID-19 may

be at risk for temporary alterations in sperm quality, which may adversely impact fertility outcomes, and thus, should be counseled accordingly.

Competing interests: Dr. Zini is a shareholder in YAD Tech. The remaining authors declare no competing personal or financial interests related to this work.

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