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Resolution of sperm quality impairment following SARS–CoV–2 infection: A prospective study

Marzieh Derakhshan^{1,2}, Maryam Derakhshan³, Elham Naghshineh^{1,2}, Minoo Movahedi¹, Hatav Ghasemi–Tehrani¹, Fatemeh Bamarinejad⁴, Atefeh Bamarinejad⁴, Zeinab Omidvar^{4✉}¹Department of Obstetrics and Gynecology/Anatomy, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran²Shahid Beheshti Fertility Center, Isfahan University of Medical Sciences, Isfahan, Iran³Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran⁴School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Objective: To investigate the length of time required to resolve COVID-19 effects on semen quality and DNA integrity.**Methods:** A prospective cohort study was conducted among 42 men who tested positive for SARS-CoV-2 and underwent semen analysis at baseline and four months' post-recovery. Semen samples were collected and evaluated for macroscopic and microscopic parameters, sperm chromatin maturation, and DNA fragmentation.**Results:** The mean age of participants was 37(±7) years, and 14% had normozoospermia at baseline. After a four-month recovery from COVID-19, 48% of patients had normozoospermia. Sperm count, motility, and morphology increased significantly, while sperm DNA fragmentation and sperm chromatin maturation decreased significantly post-recovery from COVID-19.**Conclusions:** Sperm parameters improve after a four-month recovery from COVID-19. The findings indicate significant improvements in sperm count, motility, morphology, DNA fragmentation, and chromatin maturation after a four-month recovery period.**KEYWORDS:** SARS-CoV-2; Male fertility; Recovery; Sperm DNA fragmentation; Sperm parameter

Understanding the impact of SARS-CoV-2 infection on sperm parameters is crucial, as it may have significant implications for reproductive health, assisted reproductive techniques, and potential long-term consequences for affected individuals and their offspring. While the majority of studies have reported temporary alterations in sperm parameters following SARS-CoV-2 infection[5–7], there is limited data on the long-term consequences of these changes[8]. It is essential to assess the resolution of COVID-19 impacts on male fertility beyond the acute phase of the infection. Longitudinal studies following individuals over extended periods will be crucial

Significance

The outbreak of the COVID-19 caused concerns in various medical fields, especially men's reproductive health. The findings of the study demonstrate a significant improvement in sperm quality, count, motility, and DNA integrity after a four-month recovery from COVID-19. This suggests that the virus may have a temporary effect on sperm quality, with potential implications for fertility counseling and management strategies. This study adds valuable evidence to the limited understanding of COVID-19's impact on male reproductive health.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus has emerged as a global health crisis, affecting millions of individuals worldwide[1]. While the primary respiratory symptoms and complications of COVID-19 have been extensively studied, emerging evidence suggests that the virus may also impact other organs, including the male reproductive system[2,3]. Specifically, concerns have been raised regarding the potential effects of COVID-19 on sperm quality and male fertility[4].

✉To whom correspondence may be addressed. E-mail: z.omidvar1377@gmail.com

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in determining the recovery trajectory of sperm quality and the implications for male fertility. The results of such studies underscore the importance of monitoring male reproductive health post-SARS-CoV-2 infection and provide valuable insights for fertility counseling and management strategies in the context of the COVID-19 pandemic. This study aims to contribute to the growing body of knowledge regarding the length of time required for the resolution of COVID-19's effects on semen quality and DNA integrity.

2. Subjects and methods

2.1. Study design

This prospective cohort study was conducted between July 2022 and May 2023 among patients who were referred for infertility assessment to two university-affiliated andrology clinics in Isfahan, Iran.

2.2. Participant selection

A total of 42 adult males with a history of infertility from 18 to 45 years old and a positive COVID-19 test were included in the study. The SARS-CoV-2 infection was proven by detecting SARS-CoV-2 viral RNAs in throat swabs or respiratory specimens by RT-PCR assays, and they were referred to give semen samples as soon as possible after a positive COVID-19 test result. Participants were requested to return at least 4 months after complete recovery to evaluate and compare their sperm analysis. Participants who did not return for the second sampling were excluded from the study. To calculate the sample size required for our study, we used the formula $N = ((z_{\alpha/2} + z_{\beta}/d)^2 * 2 * \sigma^2 / d^2)$. We considered a significance level (α) of 0.05 and a statistical power (β) of 0.8, with an estimated mean difference (d) of 7.2 and a standard deviation of differences (σ) of 9.61, based on data gathered from the first 10 participants in our study. The minimum sample size required was estimated to be 28; however, the actual sample size achieved in this study was 42.

2.3. Collection of semen samples

The semen samples were obtained through masturbation after 3–7 days of sexual abstinence and collected in sterile containers for analysis. Instructions for proper semen sample collection were provided for all of the participants.

2.4. Evaluation of macroscopic and microscopic parameters

The collected semen samples underwent a comprehensive evaluation of macroscopic and microscopic parameters. Macroscopic parameters were assessed, including volume, viscosity, liquefaction time, and agglutination. The evaluation of microscopic parameters involved the assessment of sperm concentration, motility using the

computer-assisted sperm analysis (CASA) system, and morphology using the Papanicolaou staining method. The viability of sperm cells was determined using the eosin-nigrosin method. All measurements were taken according to the guidelines established by the World Health Organization (WHO)[9].

2.5. Evaluation of sperm chromatin maturation

To perform the sperm chromatin maturation assay method, aniline blue (AB) staining was used. The staining procedure started by applying a droplet of unprocessed semen to a glass slide. The air-dried smear was then immersed in a 3% glutaraldehyde solution in phosphate buffered saline (PBS) for 30 min to fix it. Next, the slide was immersed in a PBS solution twice, for 5 min each time, and allowed to dry naturally. Once dried, the slide was stained with a 5% aqueous solution of AB mixed with acetic acid to maintain a pH of 3.5 for 7 min. The stained slide was then cleansed using a PBS solution, dried by exposure to air, and finally protected with a cover glass[10,11].

To examine the stained smear, a light microscope with an oil immersion objective (100×) was used to evaluate a minimum of 200 spermatozoa. Spermatozoa with unstained nuclei were classified as normal (mature chromatin), while those displaying blue staining were defined as abnormal (immature chromatin). The results were quantified as percentages of sperm with nuclear staining and without nuclear staining.

2.6. Evaluation of DNA damage

DNA damage in sperm cells was assessed using the Halo test method. Fresh, frozen, or unthawed sperm that had not been fixed was placed in an agarose microgel on a slide that had been pre-treated. An initial acid treatment denatured the DNA in fragmented sperm cells, followed by a lysis solution that removed most of the nuclear proteins. Following staining and drying of the slides, at least 200 sperm cells were counted. Sperm heads with elongated DNA strands that do not show any breakage indicate the absence of DNA damage and have a dispersion of a large to medium halo. On the other hand, nucleoids from sperm with fragmented DNA either show a small halo or no dispersion halo at all.

2.7. Statistical analysis

The statistical analysis was conducted using IBM SPSS version 24. Differences in semen parameters between baseline and four-month follow-up measurements were assessed using the Wilcoxon rank sum test. A waterfall plot was used to visualize changes in sperm DNA fragmentation (SDF) and sperm chromatin maturation (SCM). All semen parameters, including baseline and post-recovery measurements, were reported with medians and interquartile ranges

Table 1. The frequency of sperm phenotypes in COVID-19 patients; baseline and after four months follow-up [n(%)].

Parameters	Baseline (n=42)	Follow up (n=42)
Concentration		
Oligozoospermia	8(19.0)	3(7.1)
Normal	34(81.0)	39(92.9)
Sperm motility		
Asthenozoospermia	35(83.3)	22(52.4)
Normal	7(16.7)	20(47.6)
Morphology		
Teratozoospermia	31(73.8)	16(38.1)
Normal	11(26.2)	26 (61.9)
Abnormal viability	7(16.7)	4(9.5)
SCMI, %		
≤20	20(47.6)	22(52.4)
>20	3(7.1)	39(92.9)
SDFI, %		
<15	6(14.3)	17(40.5)
15-30	35(83.3)	25(59.5)
>30	1(2.4)	0(0.0)

SCMI: sperm chromatin maturation index; SDFI: sperm DNA fragmentation index.

(IQRs). Additionally, the results of this study were obtained through the use of frequency tables. A two-tailed *P*-value less than 0.05 was determined to be statistically significant.

2.8. Ethics statement

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Isfahan University of Medical Sciences (ethical approval number: IR.MUI.MED.REC.1402.184). Informed consent was obtained from all of the study participants.

3. Results

3.1. Baseline characteristics

The study included a cohort of 42 male patients who were referred for fertility assessment and were found to be positive for COVID-19. The mean ($\pm$ SD) age of participants was 37($\pm$ 7) years. Also, they

reported a previous history of infertility within a median (IQR) of 1 (0-11) years.

3.2. Frequency of sperm phenotypes before and after recovery from COVID-19

Considering the WHO-defined reference[9], 6 males (14.3% of the total) had normozoospermia at baseline, which increased to 20 (47.6%) patients at the follow-up point. In the initial assessment as well as during the follow-up, none of the patients showed azoospermia. Additionally, it was observed that 19% of the study participants revealed oligozoospermia during the initial assessment (mean $\pm$ SD of sperm concentration: 8.50 $\pm$ 3.54), which reduced to 7.1% after recovery from COVID-19 (mean $\pm$ SD of sperm concentration: 7.00 $\pm$ 1.73). The frequency of sperm phenotypes in initial as well as follow-up assessments is presented in Table 1.

3.3. Changes in sperm quality parameters after COVID-19 recovery

The follow-up assessment revealed an increase in semen analysis parameters, including volume, concentration, progressive and total motility, viability, and morphology, as compared to the initial measurement. All observed changes exhibited statistical significance except for semen volume. Table 2 shows details of the baseline and follow-up values for sperm parameters.

3.4. Analysis of sperm DNA fragmentation index (SDFI) and sperm chromatin maturity index (SCMI)

There was a significant difference in sperm DNA fragmentation index (SDFI) and sperm chromatin maturation index (SCMI) at the follow-up sampling, in comparison to the initial sampling [median (IQR): 17 (11-19) *vs* 21 (16-24) and 20 (15-30) *vs* 30 (25-32); *P*<0.001, respectively]. SCMI and SDFI decreased in 85.7% and 78.5% of patients who followed up $\geq$ 4 months after SARS-CoV-2 infection, respectively. Within-participant changes in SCMI and SDFI from baseline (range, -19 to 5 and -10 to 4, respectively) are presented in the waterfall plots (Figures 1, 2).

Table 2. Change in semen analysis parameters in COVID-19 patients; baseline and four months follow-up.

Parameters	Normal value [#]	Baseline (n=42)	Follow up (n=42)	<i>P</i> -value
Volume, mL/ejaculation	≥ 1.4 (1.3-1.5)	2.2 (1.57-3.29)	2.5 (1.97-3.08)	0.130
Concentration, 10 ⁶ /mL	≥ 15.0 (12.0-16.0)	30.0 (16.5-46.0)	34.5 (20.0-55.0)	<0.001
Total sperm count, 10 ⁶ /ejaculation	≥ 39 (35-40)	60 (40-100)	86 (48.7-137.2)	<0.001
Progressive motility, %	≥ 30 (29-31)	23 (20-28)	29 (22-35)	<0.001
Total motility, %	≥ 42 (40-43)	48 (40-50)	50 (42-60)	<0.001
Viability, %	≥ 54 (50-56)	74 (60-80)	80 (70-90)	<0.001
Morphology, %	≥ 4 (3.9-4.0)	3 (2-4)	4 (3-6)	<0.001
SCMI, %	≤ 20	30 (25-32)	20 (15-30)	<0.001
SDFI, %	< 15	21 (16-24)	17 (11-19)	<0.001

Wilcoxon rank sum test was used; data are presented as median (IQR). SCMI: sperm chromatin maturation index; SDFI: sperm DNA fragmentation index; #: based on the sixth WHO report.

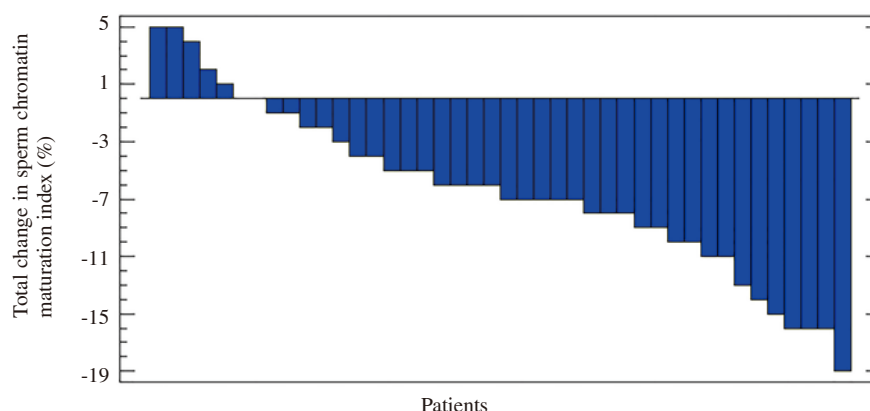


Figure 1. Waterfall plot to demonstrate change in sperm chromatin maturation index (SCMI) among COVID-19 patients and after recovery.

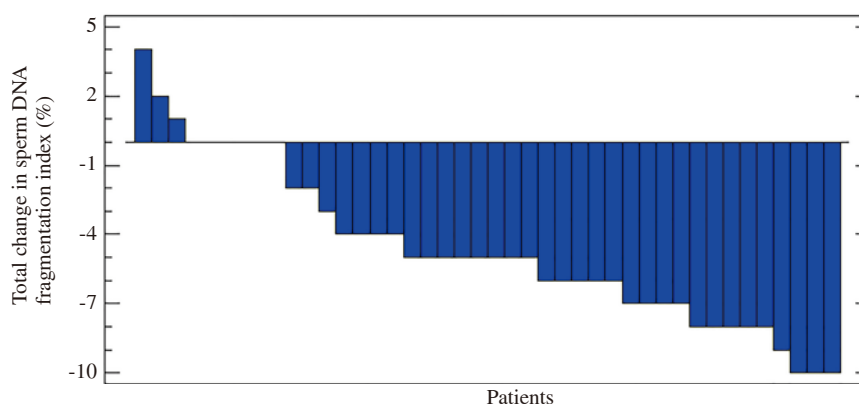


Figure 2. Waterfall plot to demonstrate change in sperm DNA fragmentation index (SDFI) among COVID-19 patients and after recovery.

4. Discussion

This prospective cohort study examined the sperm parameters of 42 COVID-19-positive patients. We compared the second sampling, taken after a 4-month recovery period, with the first sampling. The results indicated that all parameters, except semen volume, exhibited a statistically significant difference between the baseline and follow-up measurements. Furthermore, there was a notable decrease in the levels of DNA fragmentation and sperm chromatin immaturity in the follow-up samples compared to the baseline measurements.

The initial hypothesis that the testis might serve as one of the target organs in the SARS-CoV-2 infection originated from the fact that high expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) as SARS-CoV-2 receptors showed up in seminal vesicles and seminiferous tubules[12,13]. In addition to these, investigations into the subject expanded after SARS-CoV-2 mRNA was detected in the semen sample for the first time[14]. The following research, however, has shown contrasting results[15–20], and additional analysis has revealed that SARS-CoV-2 mRNA is only detected in semen samples in the acute phase of COVID-19[21]. Following that, additional research looked into the potential impact of SARS-CoV-2 infection on male fertility and sperm parameters. Recently, researchers in cohort studies were looking into how these parameters alter after recovery from COVID-19.

A recent meta-analysis was conducted to investigate a total of

973 participants across 7 case-control studies and 5 retrospective cohort studies that were published up until February 2022. The findings demonstrate that infection with SARS-CoV-2 has an adverse effect on the quantity of semen, concentration of sperm, total count of sperm, and sperm motility, which leads to a decline of these measures in individuals with COVID-19. Though the mentioned study did not examine the impact of COVID-19 on the extent of DNA fragmentation. Furthermore, it should be noted that the majority of the studies incorporated in their analysis were of the case-control design, which limits the ability to assess the long-term impact of COVID-19 on sperm parameters[22].

Currently, there is insufficient evidence available on the length of time required for improvements in sperm parameters. Studies in this field have shown diverse results[6,18,23–25]. In a study with a sample size close to the present study, Gacci *et al*[5] reported that semen parameters would be impaired even after recovery from COVID-19. Nevertheless, the duration of the recovery period was not specified in their study. On the other hand, it appears that the investigations that have serially examined semen during follow-up are better able to explain the alterations in sperm parameters and their subsequent restoration in individuals affected by COVID-19.

In the study of Hu *et al*[8] by examining 36 COVID-19 patients, sperm parameters were analyzed after the recovery time of 90 days and then at intervals of 30 days until 210 days of follow-up. The results were then compared to those of a control group. In this

study, there was no difference in sperm parameters between the control group and the groups of patients with follow-ups of 150-180 days and 180-210 days. However, sperm parameters were different between the groups of patients with follow-ups of <90 days as well as 120-150 days. They pointed out that there may still be an impact on spermatogenesis two months after the discharge of COVID-19 patients, and the decline in sperm quality had a noticeable delayed effect during the course of 120-150 days. This delay can be attributed to the natural cycle of spermatogenesis and the cumulative damage caused by the disease.

Moreover, consistent with our findings, Falahieh *et al*[26] observed an improvement in sperm characteristics, such as motility, morphology, and SDFI, after a duration of 120 days following the diagnosis of COVID-19 in a cohort of 20 individuals who were hospitalized due to a moderate illness. Furthermore, a notable decrease in levels of reactive oxygen species (ROS) in semen and lipid peroxidation was observed at 120 days post-diagnoses of COVID-19, in comparison to the levels observed at 14 days post-diagnoses. In contrast, Mannur *et al*[27] observed persistent changes in sperm morphology and sperm DNA integrity in a mild COVID-19 patient. These abnormalities were shown to endure for an extended period, exceeding four months. Nevertheless, there were other investigations in which they did not identify any differences in sperm parameters between the COVID-19 patients and the control group, even when the follow-up duration was shorter than 120 days[24,25].

With regard to the recent recommendations provided by the WHO, the utilization of the sperm DNA fragmentation index (DFI) can serve as a valuable additional evaluation for male fertility[9]. Based on the results of the current study, there was a statistically significant decline in the levels of SDFI and SCMI in the second sample of patients diagnosed with COVID-19 after four months of follow-up, as compared to the first sample. Conversely, in another investigation carried out by Shi *et al*[28], a cohort of 132 individuals was examined. Among them, 78 participants had previously tested positive for COVID-19 within the past three months, while the remaining 54 individuals had not yet been infected by SARS-CoV-2. The study findings revealed a significantly elevated level of SDFI in the group of participants who had tested positive for COVID-19.

The exact mechanism underlying the increase in SDFI and decrease in DNA integrity in patients with SARS-CoV-2 is still under investigation. Generally, however, SARS-CoV-2 appears to directly and indirectly impact testicular function. At this point, alongside symptoms of orchitis in some patients with COVID-19[29] and histopathological indications of inflammatory infiltration in the seminiferous tubules, as well as the activation of immune responses and the subsequent initiation of the inflammatory cascade leading to excessive production of ROS following SARS-CoV-2 infection, potential mechanisms involve the alteration of sperm parameters, particularly SDFI and SCMI, after SARS-CoV-2 infection[30-32].

It should be noted that our study had limitations that should be considered when interpreting the results. First of all, generalizability is limited because the participants in this study were examined in the context of infertility evaluation. Additionally, in the present study,

the impact of confounding variables such as body mass index (BMI), smoking, and other factors related to lifestyle on changes in sperm parameters in COVID-19 patients was not investigated; other studies also did not find a relationship between these factors and changes in sperm quality parameters in COVID-19 patients[28,33].

In conclusion, the findings of the current study indicate significant improvements in sperm count, motility, morphology, DNA fragmentation, and chromatin maturation after a four-month recovery from COVID-19. Furthermore, these metrics were shown to be more favorable when compared to the initial baseline measurements. Further research is needed to elucidate the length of time required for improvements in sperm parameters after recovery from the SARS-CoV-2 infection.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

Marzieh Derakhshan, Maryam Derakhshan, Elham Naghshineh, Minoo Movahedi, and Hatav Ghasemi-Tehrani contributed to the conception and design of the study. Atefeh Bamarinejad and Fatemeh Bamarinejad conducted the data analysis and were primarily responsible for drafting the manuscript. These authors also played key roles in critically reviewing, and substantially editing the manuscript to ensure the validity and accuracy of the results. Zeinab Omidvar, Maryam Derakhshan, and Marzieh Derakhshan carried out the ethical procedure as well as they contributed to the data collection. All contributing authors approved the final manuscript.

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