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Short-term effects of COVID-19 on semen parameters: A multicenter study of 69 cases

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Abstract

Objective: COVID-19, which is known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global health problem that can cause multiorgan damage because of its use of the angiotensin-converting enzyme 2 (ACE2) receptor in its pathophysiology. We aimed to investigate whether SARS-CoV-2 had a short-term effect on spermatogenesis, which plays an important role in male reproductive health as it has abundant ACE2 expression in testicular tissue.

Material and methods: This multicenter study included 69 patients aged 20–45 years, who admitted to our hospitals between April 2020 and October 2020 with a history of a positive test result for SARS-CoV-2 based on the nasopharyngeal or oropharyngeal swab samples and had recovered from the disease at least three months earlier and who had undergone a spermiogram test in the hospital database within the last year before the onset of disease. The patients were divided into two groups according to their COVID-19 symptoms being mild or moderate, depending on whether they had received home treatment or required hospitalization for oxygen therapy. Semen samples taken before and after COVID-19 were compared within and between the groups in terms of sperm parameters.

Results: The mean age of the patients included in the study was 30.4±4.8 years in the mild symptomatic COVID-19 group and 31.06±4.2 years in the moderate symptomatic group. When the spermiogram samples of the patients before and after COVID-19 were evaluated, it was found that motility and vitality significantly decreased in the mild symptomatic group, while the decrease in all semen parameters was statistically significant in the moderate symptomatic group.

Conclusion: Although the mechanism by which COVID-19 causes testicular involvement remains uncertain, its short-term results on spermatogenesis reveals that COVID-19 negatively affects sperm parameters.

KEYWORDS
COVID-19, male infertility, SARS-CoV-2, semen, spermatogenesis

1 | INTRODUCTION

With the severe acute respiratory syndrome (SARS) epidemic in 2002, it was first identified that coronaviruses could cause severe respiratory infections in humans. It was shown that this disease was caused by the SARS coronavirus (SARS-CoV), a member of the coronavirus family previously unreported in humans.[1] At the end of December 2019, the novel coronavirus disease, called SARS-CoV-2 because of its similarity to SARS-CoV which is much more contagious, was first detected in China.[2] Although the epidemic was predicted to occur as a result of zoonosis in the livestock market, current transmission is via human-to-human droplets.[3] Then, the SARS-CoV-2 disease was named as COVID-19 by World Health Organization (WHO) in February 2020. Since then, the virus has spread very rapidly, and according to the current WHO report, 222 countries have been affected worldwide, with 102 million confirmed cases and 2.2 million confirmed deaths being reported, and the numbers are increasing dramatically day by day.[4]

Because of the COVID-19 pandemic, almost all research around the world has focused on investigating the characteristics of the virus, ways of transmission, etiology, diagnosis, and treatment options.[5] Almost a year after the first case, unknowns about the virus have begun to come to light, and current studies have evolved into investigating the long-term consequences of the disease, long-term irreversible damage, and morbidity in organs and tissues. It is now clearly known that the SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells, similar to the SARS-CoV virus.[6] In addition to being abundantly expressed from the type II alveolar cells of the lungs, ACE2 also has significantly high expression levels in other organs such as the small intestine and kidney.[7] Although the lungs seem to be the target organ mainly affected because of the high amount of ACE2 expression, cardiovascular system damage and kidney damage also have a critical role in the prognosis of the disease.[8] Theoretically, any tissue which expresses ACE2 can become a target for SARS-CoV-2. Previous studies have shown that spermatogonia, Leydig cells, and Sertoli cells express high levels of ACE2 receptor protein in their cell membranes.[9] Furthermore, COVID-19 affects men 2.5 times more than women, and it has been observed that testosterone levels change in those that have had the disease.[10] Based on this information, we aimed to investigate the effect of COVID-19 on spermatogenesis, which plays a crucial role in male fertility, and to determine the effects of the disease on semen parameters, which has not been previously evaluated in the literature.

2 | MATERIAL AND METHODS

2.1 | Study design

For this multicenter study, ethics committee approval was obtained from the local clinical research ethics committee of our institution on January 27, 2021 with the approval number 01-2021/07. Patients who were diagnosed with COVID-19 according to the results of the reverse transcription polymerase chain reaction (RT-PCR) test of combined oropharyngeal and nasopharyngeal swabs between April 2020 and October 2020 and who had the spermiogram data from the last year available in the database of each hospitals were included in the study. Patients with spermiogram tests in the hospital database before COVID-19 consisted of those who had been previously examined in the urology outpatient clinic for infertility. Only patients with laboratory-confirmed positive RT-PCR results were included. Written informed consent was obtained from all patients. As spermatogenesis lasts for 74 days,[11] the inclusion criteria were determined as being sexually active, age of 20–45 years, diagnosis of COVID-19, and were proven to recover according to the analysis of two consecutive combined nasopharyngeal swab samples at least three months ago. Patients who met these inclusion criteria were called using the contact information obtained from the hospital database and asked to visit the hospital after sexual abstinence for 3–5 days. Detailed medical history was obtained from all patients included in the study. Age, smoking, body mass index, COVID-19 treatment applied, systemic diseases, and surgery history were questioned in detail. The patients were classified as mild symptomatic (outpatient treatment) and moderate symptomatic (SpO_2 < 93%, requiring hospitalization for oxygen therapy). Patients younger than 20 and older than 45 years, those with a history of hormonal drug use that could affect spermatogenesis, those with oligozoospermia or azoospermia, those with a history of testicular surgery (undescended testis, varicocoele, hydrocele, testicular torsion, testicular tumor), those with a history of pelvic radiotherapy, those that had undergone assisted reproduction techniques, and those that received medical therapy to increase total sperm number and sperm motility were excluded from the study. In addition, patients who received steroid therapy for COVID-19 treatment were also excluded considering that it could affect spermatogenesis. Semen samples obtained by masturbation from the patients included in the study were examined manually under a microscope according to the WHO 2010 criteria within 30 minutes after being liquefied at room temperature.[12] Quality control of each internal and external laboratories were assessed according to the WHO 2010 recommendations.[12] Spermiograms were evaluated by a single biologist in each center to prevent individual differences that could occur during the evaluation. As leukocyte count, a well-known inflammatory marker of the testis, and sperm morphology were not studied in some centers, these parameters were not included in analyses because of the multicenter design of the study. The spermiograms of the mild and moderate symptomatic patient groups before and after COVID-19 were compared in terms of semen volume, total sperm number, total and progressive motility and vitality.

2.2 | Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (SPSS). The compliance of the data with the normal distribution curve was evaluated using the Shapiro-Wilk test. For the comparison between the mild and moderate groups, Student's *t* test was used for the continuous data that met

the distribution criteria of normality, the Mann-Whitney *U* test for continuous data without normal distribution, and the chi-square test for categorical data. The *t* test and Wilcoxon test were used in dependent groups to compare semen analysis before and after COVID-19. A *p* value below 0.05 was considered statistically significant.

3 | RESULTS

The study population consisted of 26 men with a mild course of the disease and 43 men with a moderate course of the disease. The demographic data of the patients and the distribution of the treatments administered for COVID-19 according to the mild and moderate symptomatic groups are shown in Table 1. There was no statistically significant difference between the groups in terms of demographic data and medical treatments applied for COVID-19. As a standard COVID-19 treatment protocol, the patients with COVID-19 were treated with oral favipiravir or hydroxychloroquine tablets for 5 days. As no clinical findings indicating bacterial infection were observed during the follow-up of the patients, no antibiotic treatment was applied. Each patient was administered enoxaparin sodium subcutaneously at a dose appropriate for the weight for thromboembolism prophylaxis. Acetaminofen was administered symptomatically if the patients have fever and pain. Fever was present in 18 out of 26 patients in the mild symptomatic group and 31 out of 43 in the moderate symptomatic group. Other common symptoms were cough (39/69), dyspnea (28/69), headache (25/69), muscle pain (22/69), and anosmia and loss of taste (19/69). Endotracheal intubation was not required for any patient in both group.

When the spermiograms before and after COVID-19 were examined, it was found that progressive and total motility (p = 0.02 for both) and vitality (p = 0.03) decreased in the mild symptomatic group. In addition, in the moderate symptomatic group, the decrease in all sperm parameters including semen volume was statistically significant ($p < 0.05$ for all) (Table 2). In addition, we divided the mild symptomatic group into two subgroups according to the presence or absence of fever to examine the effect of fever on semen parameters. Although it was observed that sperm motility and vitality decreased in both groups with and without fever, it was observed that fever did not contribute to this situation (Table 3).

4 | DISCUSSION

In this study, the semen analyses of the patients diagnosed with COVID-19 were compared between the pre-disease period and at least three months after recovery from the disease. The patients were divided into two groups as mild and moderate symptomatic COVID-19. In the mild symptomatic group, progressive and total motility and vitality decreased compared with the pre-disease period, while in the moderate symptomatic, all the sperm parameters were negatively affected by the disease. When the patients in the mild symptomatic group were further divided into two subgroups as those with and without fever, and the effect of fever on semen parameters was examined, we observed that there was no negative effect on semen parameters because of fever within both subgroups.

TABLE 1 Distribution of the demographic data of the patients according to the severity of COVID-19 symptoms

Characteristics	Mild (n = 26)	Moderate (n = 43)	p value
Age (years)	30.04 ± 4.8	31.06 ± 4.2	0.611[a]
BMI, kg/m^2	25.55 ± 3.1	25.11 ± 3.4	0.624[a]
Smoker, *n* (%)	16 (61.5%)	20 (46.5%)	0.226
Time between last negative oropharyngeal swab to semen analysis, (d)	119.42 (94–144)	127.66 (96–190)	0.297[b]
Duration of symptoms, (d)	7.6± 6.3	15.3± 9.7	0.004[b]
Duration of hospitalization, (d)	—	11.6± 7.3	—
Duration of bed rest, (d)	5.6± 4.5	—	—
Duration of fever, (d)	5.6± 3.3	7.1± 4.7	0.049[b]
No fever (<37.2°C), *n* (%)	8 (30.7%)	12 (27.9%)	0.421
Low grade fever (37.2–37.8°C), *n* (%)	7 (26.9%)	10 (23.2%)	0.357
Moderate fever (37.8–39.4°C), *n* (%)	5 (19.2%)	8 (18.6%)	0.548
High grade fever (>39.4°C), *n* (%)	6 (23%)	13 (30.2%)	0.138
Medical Treatment for COVID–19			
Hydroxychloroquine, *n* (%)	13 (50%)	21 (48.8%)	0.722
Favipiravir *n* (%)	10 (38.4%)	18 (41.9%)	0.865

The results are shown as mean ± SD.

[a]Student's *t* test.

[b]Mann-Whitney *U* test.

TABLE 2 Comparison of semen parameters before and after COVID-19 according to the severity of symptoms

Semen parameters	Mild	Moderate	*p* value
Semen volume, mL			
Before COVID−19	3.24 ± 1.6	3.34 ± 1.1	0.762[b]
After COVID−19	3.08 ± 0.8	2.74 ± 0.9	0.159[b]
p value[d]	0.548	**<0.001**	
Sperm concentration (millions/mL)			
Before COVID−19	32.24 ± 12.8	35.01 ± 14.1	0.392[b]
After COVID−19	28.62 ± 12.4	30.63 ± 17.2	0.065[b]
p value[d]	0.055	**0.008**	
Total sperm number (millions)			
Before COVID−19	90.72 ± 85.39	114.53 ± 93.66	0.325[b]
After COVID−19	75.57 ± 58.53	90.38 ± 83.66	0.320[b]
p value[d]	0.160	**0.001**	
Progressive motility, (%)			
Before COVID−19	28.81 ± 9.7	30.16 ± 12.1	0.765[a]
After COVID−19	20.92 ± 9.1	21.40 ± 10.1	0.847[a]
p value[c]	**0.002**	**<0.001**	
Total motility, (%)			
Before COVID−19	48.69 ± 12.1	50.74 ± 13.4	0.365[a]
After COVID−19	33.41 ± 12.3	31.42 ± 13.3	0.234[a]
p value[c]	**0.002**	**<0.001**	
Vitality, (%)			
Before COVID−19	62 ± 7.0	64.6 ± 5.6	0.116[a]
After COVID−19	58.1 ± 7.1	57.4 ± 6.8	0.475[a]
p value[c]	**0.030**	**0.001**	

The results are shown as mean ±SD.

[a] Student's *t* test.

[b] Mann-Whitney *U* test.

[c] Paired *t* test.

[d] Wilcoxon test.

Bold indicates significant *p* values.

TABLE 3 Comparison of semen parameters according to presence or absence fever in the mild symptomatic group

	With fever	Without fever	*p* value
Individuals, *n*	18	8	**0.009**
Semen parameters			
Sperm concentration (millions/mL)			
Before COVID−19	35.12 ± 10.6	33.02 ± 12.3	0.712[b]
After COVID−19	29.52 ± 10.7	28.48 ± 15.8	0.695[b]
p value[d]	0.095	0.108	
Total sperm number (millions)			
Before COVID−19	88.65 ± 45.62	94.53 ± 63.72	0.458[b]
After COVID−19	78.37 ± 48.67	81.42 ± 62.39	0.672[b]
p value[d]	0.198	0.218	
Progressive motility, (%)			
Before COVID−19	30.03 ± 8.6	29.19 ± 11.7	0.643[a]
After COVID−19	21.08 ± 6.7	22.38 ± 9.2	0.671[a]
p value[c]	**0.002**	**0.006**	
Total motility, (%)			
Before COVID−19	51.38 ± 10.9	54.26 ± 10.1	0.789[a]
After COVID−19	33.49 ± 10.1	30.82 ± 12.7	0.652[a]
p value[c]	**0.004**	**0.008**	
Vitality, (%)			
Before COVID−19	59 ± 6.1	62.7 ± 5.8	0.229[a]
After COVID−19	54.3 ± 8.7	59.5 ± 8.0	0.432[a]
p value[c]	**0.022**	**0.015**	

The results are shown as mean ± SD.

[a] Student's *t* test.

[b] Mann-Whitney *U* test.

[c] Paired *t* test.

[d] Wilcoxon test.

Bold indicates significant *p* values.

Currently, there are only few studies evaluating semen parameters with COVID-19 in the literature. In one of these studies, Li et al[1] showed increased apoptotic cell concentrations in testicles and epididymis in testicular autopsies of patients that died because of COVID-19. The authors also found oligozoospermia, leukospermia, and increased levels of interleukin-6 in some of the patients who had recovered from the disease. Increased apoptotic cells and increased cytokine levels suggest that the current manifestation occurs in the background of autoimmune orchitis. In another study in the literature, Holtmann et al[13]. grouped patients according to the severity of COVID-19 symptoms as mild and moderate symptomatic and examined whether there was any change in semen parameters compared with a control group. They showed that both the total sperm number and total motility decreased in patients with moderate symptoms compared to the control group; however, they observed no change in semen parameters in patients with mild symptoms. In another recent study by Gacci et al[14], the presence of SARS-CoV-2 RNA in saliva, urine, and semen and the effect of the disease on semen parameters were investigated in 48 sexually active men who were proven to have recovered from COVID-19. They reported that the SARS-CoV-2 genome was detected in biological fluids, albeit at low rates. On the other hand, they observed oligozoospermia and azoospermia in some of the patients and found that the occurrence of azoospermia correlated with the severity of the disease. Our study differs advantageously from the studies in the literature at this point as it compares both the pre-disease semen parameters and post-disease semen parameters of the same individuals. Another advantage can be considered as the inclusion criteria used. In addition, eighty percent of patients with COVID-19 are reported to have fever,[15] and it has also been shown that the increase in testicular temperature because of fever may negatively affect semen parameters, and it may take up to three months for semen parameters to return to basal state.[16] In the current study, considering that spermatogenesis lasts for 74 days and the negative effect of fever on semen parameters takes up to three months to return to basal state, we excluded patients with a last negative RT-PCR test result within less than three months in order not to affect the results of our study.

It has been proven in previous studies that the SARS-CoV virus, which is the causative agent of the SARS epidemic, affects the male reproductive system by damaging the seminiferous tubules and causing orchitis findings.[17] Although the virus could not be isolated from the semen of those who had the disease, on the contrary, it was shown that the virus was isolated in testicular samples obtained from autopsy series.[18] On the other hand, SARS-CoV and the new-generation SARS-CoV-2, showing 80% genetic similarity in full genomic sequences, both use the viral spike protein and the ACE2 receptor to enter the cell. The spike protein (protein S) is primed by transmembrane serine protease (TMPRSS2). Male reproductive system cells such as spermatogonia, Sertoli and Leydig cells and prostatic epithelial cells are known to express both ACE 2 receptor and TMPRSS2 protease.[19] However, TMPRSS2, a serine protease, was found to be highly expressed in prostate lumen cells while relatively low levels in testicular cells.[19] Considering this genetic similarity and ways of transmission, the SARS-CoV-2 virus is known to affect men more than women (male-to-female ratio: 2.7:1) compared with SARS-CoV, and therefore the effects of this novel coronavirus on male reproductive health have become a subject worth researching.[20] In addition, a higher level of ACE2 expression has been detected in young male gonads, suggesting that young patients may be more vulnerable in spermatogenesis with an important role in male reproductive health,[21] which emphasizes the importance of the current study.

The COVID-19 pandemic has become a serious life-threatening health problem, and there are still unclear aspects of the disease. The most common clinical manifestation of the disease is pneumonia because of the presence of ACE2-containing cells among type 2 alveolar cells, and studies have mostly focused on this issue considering the life-threatening nature of pneumonia and acute respiratory distress syndrome.[2,22] However, the ACE2 receptor is present in most organs and tissues, as well as type 2 alveolar pneumocytes. Interestingly, a recent study showed that Sertoli and Leydig cells in the testicles had even higher levels of ACE2 expression than alveolar type II cells.[23] The high level of ACE2 receptor may make the testicles vulnerable to SARS-CoV-2, which uses this receptor in its pathogenesis, and this may lead them to become a target organ for the virus as lungs. This raises the question of why there is no clinically evident testicular infection in COVID-19, despite such intense ACE2 receptor expression in testicular tissue. It is now clearly known that the disease is transmitted from person to person by inhalation through droplets.[24] The virus can easily reach the target organ, the lungs, by inhaling the droplets, but there is no direct way to easily reach the testicle as another potential target organ. This may be the reason for respiratory symptoms being more distinctive and the lungs being more affected than the testicles.

Although the testicles seem to be protected by the presence of a blood testicular barrier and the absence of a window opening out from the body, to date, nearly 30 viruses have been isolated from the testicles. The mumps virus, human immunodeficiency virus, and zika virus are the major viral infection agents that have been found to disrupt the blood testicular barrier by causing complications such as orchitis and epididymitis and reaching the testicle through viremia.[25] Recently, the detection of the SARS-CoV-2 virus in semen has become a serious concern as it reveals the possibility of the disease being sexually transmitted.[13,26] In a study conducted by Machado et al, 15 patients were investigated for the presence of SARS-CoV-2 viral RNA in semen, and viral RNA was detected in only one case. Another study argued against research investigating the presence of viral RNA in semen, suggesting that such unclear information had the risk of revealing fear and anxiety in the scientific world. The authors also criticized the few studies in the literature claiming that SARS-CoV-2 viral RNA could be isolated from semen, explaining that the methodology used for the presence of virus in semen was not clearly specified. On the other hand, they stated that masturbation, which is one of the collection modality of semen samples, may cause viral RNA contamination from semen by hand and cough, and the presence of viral RNA did not necessarily indicate the presence of viable virus.[27] Fortunately, the main consensus in the literature is that the virus cannot be isolated from semen. The current hypothesis concerning how a virus that cannot be isolated in semen can cause possible testicular damage is that inflammatory cytokines produced excessively as a result of the immune response created by the virus may disrupt the blood testicular barrier and cause the impairment of Sertoli and Leydig cell functions.[20,28] As in most infectious diseases, the inflammatory process induced by fever can damage germ cells by leukocyte infiltration and cause a decrease in the testosterone level by affecting Leydig cells.[7,29] Consequently, the mechanism of testicular involvement by which SARS-CoV-2 involves the testis remains unclear. To the best of our knowledge, there is no current study in the literature evaluating semen parameters before and after COVID-19.

Despite its strengths, our study also has certain limitations. First, sperm morphology and leukocyte count could not be analyzed in some of the centers, and therefore they were excluded from the assessment in order to ensure standardization. Second, only one spermiogram test was performed and compared for each patient before and after COVID-19. Our study not reflecting the long-term results of the patients can be considered as another limitation. Third, as the patient group included in the study was a young population whom usually had mild and moderate disease, the patient group requiring follow-up in the intensive care unit, which was defined as the severe symptomatic group, could not be included in our study. Lastly, it should be kept in mind that even if the results we obtained from our study were found to be statistically significant, it may not be clinically significant because of minimal differences in semen parameters between pre-disease and post-disease period.

5 | CONCLUSION

There are very few studies in the literature on the possible damage caused by COVID-19 in the male reproductive system. The results of the few studies in the literature and the current study suggest that the male reproductive system may be adversely affected by COVID-19. We consider that clinicians should focus more on the male genital system, as well as the lung and cardiovascular organs, and these results, which may have permanent effects on human health, should be confirmed through long-term and multicenter studies with larger sample sizes.

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CONFLICT OF INTEREST

The corresponding author states the absence of any conflict of interest for all author involved in the present study.

AUTHORS' CONTRIBUTION

G.E., H.T., and U.Y.: involved in conceptualization. G.E., H.T., U.Y., A.S., M.K., and M.Y.: involved in data collection. A.E., G.E., and A.S.: contributed to statistical analysis. G.E., A.S., and U.Y.: involved in writing—original draft preparation. G.E., M.H.G., M.Y., M.K., andH.T.: involved in writing—review and editing. G.E. and U.Y.: involved in visualization. A. E. and G.E.: involved in data curation. All authors read and agreed to the published version of the manuscript.

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