Short Communication

Adverse Effect of COVID-19 on Male Fertility and Male Sex Hormones

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Abstract

Background: Coronaviruses (CoVs) cause infections in human testes and may affect seminal fluid analysis (SFA) because the testes widely express angiotensin-converting enzyme 2 receptors. **Objectives:** This study identifies adverse effects of COVID-19 infection on the male reproductive system and their effects. **Materials and Methods:** A cross-sectional study included 102 male patients with secondary infertility, who had a previous history of COVID-19 infection, seeking medical advice at urosurgery consultations and private infertility clinics. These patients were divided into two groups: group (1) includes 40 patients with a history of testicular involvement associated with COVID-19 infection, and group (2) includes 62 patients with no previous history of any testicular involvement. All patients were tested for serum male sex hormones and underwent SFA. **Results:** The results indicated that CoVs have a high affinity for infecting testicular tissue in comparison with other tissues. Also, infection with COVID-19 adversely affected the serum levels of male sex hormones, especially if there was testicular involvement as 20% had low early morning serum testosterone levels and 55% had higher levels of pituitary hormones. In group 2 patients, only 1.6% had low serum testosterone levels and (9.7%) had high S.L.H and S.FSH. Finally, the study revealed that COVID-19 infection adversely affects sperm count and motility in both groups but more in group 1, as (15%) revealed by the oligospermia, compared with (9.7%) in the group 2. **Conclusion:** Coronaviruses have a high affinity to infect the male genital tract, especially the testes, and this affinity increases with the severity of infection. COVID-19 infection significantly affects male sex hormone secretion and motility of sperms in patients with testicular involvement.

Keywords: Asthenospermia, COVID-19, male sex hormones, oligospermia

Introduction

Male infertility is the inability of couples to conceive after 6 months of unprotected and regular sexual intercourse due to causes in the male. It is either primary (when the couple has no previous conceptions) or secondary (when the couple has had previous conceptions including abortion and miscarriage).[1]

The name coronavirus (CoV) is derived from the crown-like antigen in their membranes when observed under ultramicrography. It was first discovered in 1965, and some subtypes have been detected to cause infections in animals and humans.[2-6] Now, there are 46 species of (Covs).[7] Coronaviruses cause many diseases for humans, ranging from simple flu-like to severe life-threatening conditions such as severe acute respiratory syndrome (SARS)-CoV-1.[8,9] In December 2019, a new generation of (CoVs) had emerged and was termed SARS-CoV-2 by the International Virus Taxonomy Committee[10] with genetic similarities to the SARS-CoV-1 virus (79.5%).[11] Infection with this new generation is called "COVID-19" (coronavirus disease-19). This virus has a higher infectious rate and has rapidly spread from Wuhan in China, where it initially appeared.[12,13] There are spike (S) proteins projecting from the surface of the virus assisting in viral cell entry, while the assembly is maintained by envelope "E" and membrane "M" proteins.[12]

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Angiotensin-converting enzyme 2 (ACE2) receptors are the main receptor that allow S1 protein binding to host cells with high affinity for SARS-CoV-2 to enter and gain access to the host cells.[12-17] The testes widely expressed these receptors in addition to the lungs, gastrointestinal, neurological, and cardiovascular tissues.[11,18,19] Because of the presence of these ACE2 receptors in the cells of testicular tissues, SARS-CoV-2 has affinity for testicular infection.[12,17] The initial presenting symptoms of patients infected with COVID-19 are mostly due to respiratory and gastrointestinal infections such as fever, sore throat, dry cough, productive cough, nausea, vomiting, and diarrhea. Although many studies try to identify the adverse effects of the virus on the male reproductive system depending on the ability of the virus to infect testicular tissue and cause orchitis, but still there is no clear evidence supporting the possible adverse effects of SARS-CoV-2 on the reproductive system.[20-22]

In this study, we try to identify the adverse effects of COVID-19 infection on the male reproductive system and their effects.

Material and Methods

This is a cross-sectional study investigating 102 male patients seeking medical advice for secondary infertility at urosurgery consultations and private infertility clinics from February 2021 to February 2023, who were included in this study. All those patients reported a positive past history regarding infections with COVID-19 by positive nasal and/or throat swabs. Those patients were divided into two groups: the 1st group includes 40 patients with a history of testicular pain with or without swelling during or shortly after (10–14 days) post-acute symptoms of COVID-19 infections, while the other 62 patients had no previous history of any testicular pain or swelling. A medical and surgical history was taken from all patients with a complete physical examination, and patients were sent for a new seminal fluid analysis (S.F.A.) twice (1 month apart) by using an automated sperm quality analyzer (LensHooke -Germany) and sent for hormonal assay (F.S.H., L.H. and Testosterone) by using VIDAS (BIOMERIEUX) and Doppler scrotal ultrasonography. Patients with primary infertility, those not having a history of previous COVID-19 infections, and patients with clinical or radiological evidence of varicocele were excluded from the study.

Statistical analysis

Excel 2010 was used to apply all data collected, which were then subjected to analysis by the Statistical Package for Social Science (SPSS version 27). Independent *t* test was used to compare the means between the two groups in the study.A *P* value of <0.05 is considered significant, while *P* value < 0.001 was considered highly significant.

Ethical approval

This study has been approved by the ethical committee of Hammurabi College of Medicine, University of Babylon (Issue No: 2500; date: February 19, 2021). All patients were informed regarding the research study, and verbal consent was obtained from these patients about the investigation that had been conducted apart from the work done to reach the diagnosis and for research purposes.

Results

COVID-19 and testicular invasion

Forty patients (39.2%) of the total patients included in this study were suffering from testicular involvement with COVID-19 infection, while 62 patients (60.8%) did not have any features of testicular involvement. Most of those patients (32 out of 40 (80%)) who reported testicular involvement had moderate-to-severe symptoms of COVID-19 infection, which required hospital admission, while only 15 out of 62 (24%) patients of group 2 had a history of moderate-to-severe symptoms that required hospital admission.

The predictive value of the occurrence of testicular involvement related to the severity of COVID-19 infection is highly significant (*P* value < 0.001), as shown in Table 1 and Figures 1 and 2.

Effect of COVID-19 infection on male sex hormones, as shown in Table 2. Regarding group 1 patients, 8 (20%) patients had low early morning serum testosterone levels and 22 (55%) patients had high S.L.H, S.FSH. While in

Table 1: COVID-19 and testicular involvement

	COVID-19 and testicular involvement	COVID-19 without testicular involvement
Number of patients	40	62
percentage	39.2%	60.8%
Previously hospitalized (moderate-severe COVID-19)	32 (80%)	15 (24%)
P value (severity of COVID and occurrence of orchitis)	<0.001	

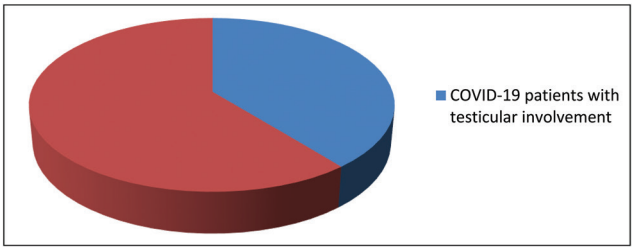

Figure 1: Percentage of testicular involvement in COVID-19 patients

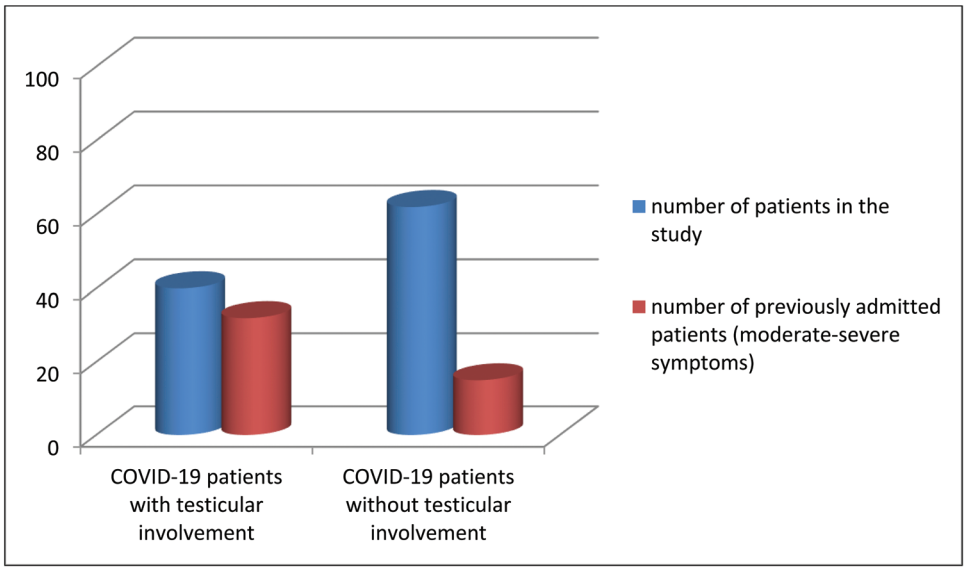

Figure 2: Severity of COVID-19 and occurrence of testicular involvement

Table 2: Effect of COVID-19 on the serum level of male sex hormones

COVID-19 patients	Low s. testosterone	P value	High LH, FSH	P value
With testicular involvement	8 (20%)	< 0.001	22 (55%)	< 0.05
Without testicular involvement	1 (1.6%)		4 (9.7%)	

Table 3: Effect of COVID-19 infection on the seminal fluid parameters

COVID-19 patients	Oligospermia	P value	Asthenospermia	P value
Group 1 with testicular involvement	6 (15%)	> 0.05	26 (65%)	< 0.05
Group 2 without testicular involvement	6 (9.7%)		21 (33.9%)	

group 2 patients, only 1 (1.6%) had low early morning serum testosterone levels and 6 (9.7%) patients had high S.L.H, S.FSH.

So there is a significant difference in the increase in LH and FSH between the two groups with *P* value < 0.05, while the difference in the decrease in testosterone levels between the two groups is highly significant (*P* value < 0.001), as shown in Table 2.

COVID-19 and seminal fluid parameters

Regarding group 1 patients with testicular involvement, 6 (15%) patients revealed decrease sperm count < 15 million/ml or (< 39 million/ ejaculate) compared with 6(9.7%) patients in group 2 who suffered from oligospermia, whereas 26 (65%) patients of group 1 had asthenospermia (motility grade a < 25% or a + b < 40%) compared to 21 (33.9%) patients of group 2 with asthenospermia on SFA. The results of the SFA of the two groups of patients are shown in Table 3.

Discussion

In this study, we try to evaluate patients with secondary infertility who had previous infections with COVID-19 and classify those patients into two groups: group 1 with clinical or radiological testicular involvement and group 2 without testicular involvement. This high abundance of testicular involvement with COVID-19 infection is due to the affinity of SARS-CoV-2 to infect the testicular tissue due to the presence of the ACE2 receptor in the male testes and may be due to the sample taken not being randomized as it includes patients seeking advice for secondary infertility.

Regarding the effect of COVID-19 infection on male sex hormones, there was a significant difference in increase in LH and FSH between the two groups with *P* value < 0.05 while the difference in the decrease in testosterone between the two groups is highly significant (*P* value < 0.001).

The effects of COVID-19 on the male reproductive sex hormones are attributed to the viral effect on the cells of testicular tissue (germ cells, Sertoli cells, and Leydig cells) as it cause pathological changes in the testes as damage to the Leydig and germ cells, basement membrane thickening, and infiltration by leukocytes.[23] Other studies reveal that other pathological changes may occur in patients with post COVID-19 orchitis as lymphocytic infiltration around the small vessels and edema in the testicular interstitial tissues, which subsequently leads to hyalinization of the seminiferous tubules and fibrosis and atrophy of the testes.[24] So the testosterone secretion will be affected, and subsequently LH and FSH secretion.

Although the results in our study show that the proportion of increase in FSH and LH secretion is more common than a decrease in testosterone secretion, even in the group 1 patients with testicular involvement. These results match the findings of Ma *et al*.[25] who suggested an explanation that there is a decrease in the testosterone level, and spermatogenesis in the earlier stage of the disease (acute phase) promotes the increment in LH and FSH. However, these results need further investigation since it may be due to the altered function of secreted testosterone, even though normal range or due to the direct effect of virus on the pituitary and hypothalamus.

Regarding COVID-19 and seminal fluid parameters, although there are high significant differences between the two groups with regard to the effect of COVID-19 on the motility of sperm, but also for group 2 patients, the ratio of asthenospermia (33.3%) patients is higher than the ratio of patients with secondary infertility with no previous history of COVID-19 infection, as shown by Holtmann *et al*. who studied SFA parameters of COVID-19 patients compared with healthy volunteers.[26]

Conclusion

Coronaviruses (CoVs) have high affinity to infect the male genital tract, especially the testes, due to ACE receptors in the testicular tissue, and this affinity increases as the severity of infection increases. COVID-19 infection affects male sex hormone (F.S.H, L.H, and testosterone) secretion in both groups, but more affect group with testicular involvement, and it is statistically significant.

Lastly, COVID-19 infection adversely affects semen parameters in both groups as it causes a decrease in sperm count (oligospermia), but there is no statistical significance between the two groups, while the effect on sperm motility (asthenospermia) is higher in the group of patients with testicular involvement with statistical significance.

Author contribution

This study was designed by Salam Abd-Elameer Yahya, Patients included in the study were collected by all authors. Also, the works on those patients and data collected from each patient were initiated by each author, and then the data were analyzed and interpreted by Muhammed Ibrahim Muhsen. These data were reviewed and approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

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