

Relationship of Semen Quality and Reproductive Hormones with Susceptibility to COVID-19 Infection

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ABSTRACT

Objective: There is increasing evidence that semen quality reflects the overall health status of individuals and is a marker of future health. In addition, reproductive hormones have significant regulatory effects on the immune system and the function of inflammatory cells. In this study, it was aimed to investigate whether baseline semen quality and serum reproductive hormone levels are potential indicators of susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Materials and Methods: The medical records of a total of 1303 patients who underwent semen analysis and hormonal evaluation including total testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL) for infertility or other medical reasons, were retrospectively analyzed. Among these patients, 316 were determined to have previously been exposed to SARS-CoV-2 infection.

Results: There was no statistically significant difference in baseline hormone profiles (FSH, LH, PRL, and T) and semen parameters between patients exposed to SARS-CoV-2 infection and non-exposed patients.

Conclusion: This study demonstrated that baseline semen quality and serum reproductive hormone levels (T, PRL, FSH, and LH) are not indicators of susceptibility to SARS-CoV-2 infection.

Keywords: COVID-19, hormone, SARS-CoV-2, semen quality, susceptibility

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INTRODUCTION

A novel beta-coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly worldwide and caused the coronavirus disease 2019 (COVID-19) pandemic.^[1] Since it was first identified in China in December 2019, more than 767,750,000 cases of COVID-19 have been reported worldwide as of June 2023.^[2] Clinical studies have demonstrated that comorbidities such as hypertension, diabetes, dyslipidemia, and obesity weaken the immune system through various mechanisms, increasing individuals' susceptibility to COVID-19 and worsening the prognosis of the disease.^[3,4]

There is increasing evidence that semen quality reflects the overall health status of individuals and is a marker of future health.^[5-8] Various studies have indicated that infertile men have a higher rate of comorbidities than fertile men.^[6,9] In addition, poor semen parameters and male infertility have been shown to be early indicators of an increased risk of cardiovascular disease, diabetes, hyperlipidemia, cancer, and even overall mortality.^[9-14] Although the link between male reproductive health and somatic health has not been fully elucidated, it is suggested that genetic, hormonal, environmental and epigenetic factors play a role in this relationship.^[8] Moreover, comorbidities may directly impair male reproductive



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function.^[15] Therefore, it has been hypothesized that semen analysis may serve as a potential biomarker for overall health counseling, such as potential preventive health measures and chronic disease management, beyond fertility counseling.

SARS-CoV-2 infects the host via angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), which are expressed in different tissues such as lung, heart, testis, prostate, and kidney.^[16] The transcription of the TMPRSS2 and ACE2 genes is regulated by the androgen receptor.^[17] It has been shown that the suppression of androgen hormones causes a decrease in ACE2 expression and activity.^[18] In addition, reproductive hormones have significant regulatory effects on the immune system and the function of inflammatory cells.^[19] Testosterone increases the susceptibility to both viral and bacterial infections by suppressing the adaptive and innate immune system.^[20] The negative effect of testosterone on the immune response has been evaluated in numerous studies and can be summarized as follows: androgens (1) suppress antibody response to vaccination and infection, (2) suppress inflammatory immune cells like dendritic cells and macrophages, (3) promote regulatory immune cells like myeloid-derived suppressor cells, and (4) dampen the development and function of T and B cells.^[21] In contrast, prolactin (PRL) plays a key role in stimulating both innate and adaptive immunity.^[22,23] PRL can support immunity by triggering T cell activation leading to NK cell activation and inflammatory cytokine production. Additionally, PRL can stimulate B cell activation to produce antibodies.^[24] It has been reported that hypoprolactinemia may even cause death due to opportunistic infections.^[25] These findings suggest that the hormonal status of individuals might play an important role in susceptibility to COVID-19 and severity of clinical course.

In the present study, it was aimed to investigate whether baseline semen quality and serum reproductive hormone levels are potential indicators of susceptibility to SARS-CoV-2 infection.

MATERIALS and METHODS

Study Design and Population

The medical records of patients who underwent semen analysis and hormonal evaluation due to couple's infertility or other medical reasons in a tertiary center between January 2020 and January 2022 were retrospectively analyzed. Men between the ages of 18–49 were included in the study. Before semen analysis and hormonal evaluation, patients who (i) had a history of COVID-19 disease and (ii) were previously exposed to treatments that could affect their basal parameters, such as gonadotropins, antioxidants, anti-estrogens and testosterone replacement were

excluded from the study. In addition, patients who had received at least one dose of any COVID-19 vaccine were also excluded.

A total of 1,303 patients met the study criteria. Among these patients, those previously exposed to SARS-CoV-2 infection were identified through a reverse transcription-polymerase chain reaction test of pharyngeal and nasal swab samples and/or the detection of typical COVID-19 pneumonia (ground glass opacities and consolidation areas, especially in the peripheral and lower lobes) on chest imaging in their medical records.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the institutional review board of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital (number: 2024.07.158).

Semen Analysis

Semen samples were collected by masturbation after three days of abstinence and analyzed within the first hour after ejaculation by the experienced andrology laboratory staff. Semen volume, sperm concentration, motility and morphology of each case were determined in accordance with the recommendations of the WHO laboratory manual for the examination and processing of human semen (6th ed.). The patients were categorized into two groups: those whose semen parameters were within normal standard values according to WHO 2021 criteria (semen volume ≥ 1.4 mL, sperm concentration $\geq 16 \times 10^6$ /mL, total motility $\geq 42\%$, progressive motility $\geq 30\%$ and morphology $\geq 4\%$) and those below these values.

Hormonal Evaluation

For hormonal assessment, peripheral blood samples were collected from all cases between 8:00 a.m. and 11:00 a.m. following a 10–12 hour overnight fasting. The serum levels of total testosterone (T), PRL, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured. Laboratory tests were repeated a few days later when any abnormal findings were encountered.

Statistical Analysis

Statistical analysis was performed using STATA version 11 (StataCorp LP, College Station, TX). The normality of the distribution of the variables was analyzed using the Kolmogorov-Smirnov test. Student's t-test and Mann-Whitney U test were used for the comparison of normally distributed and non-normally distributed variables, respectively. Categorical variables were compared with the chi-square test. $P < 0.05$ was considered statistically significant.

Table 1. Comparison of patients exposed to COVID-19 infection and COVID naive patients in terms of hormone profile and semen parameters

	Patients exposed to COVID-19 (n=316)	COVID-19 naive patients (n=987)	p
Age (year)	31.2±6.6	30.5±6.4	0.73
Hormone profile			
FSH (mIU/mL)	5.8±5.5	6.9±10.2	0.08
LH (mIU/mL)	6.3±2.9	7.2±5.6	0.67
Prolactin (ng/mL)	12.7±8.1	12.7±5.9	0.95
Total testosterone (ng/dL)	4.3±2.1	4.1±1.7	0.44
Semen parameters			
Semen volume (mL)	3.3±1.6	3.2±1.6	0.17
Sperm concentration (million/mL)	28.1±25.9	27.9±25.4	0.94
Progressive motility (%)	37.9±19.2	38.9±19.4	0.39
Total motility (%)	44.4±20.9	45.9±21.1	0.27
Total motile sperm count (million)	41.3±37.3	40.4±38.2	0.78
Morphology	3.7±2.6	3.6±2.4	0.63

Data are expressed as mean±standard deviation. FSH: Follicle-stimulating hormone; LH: luteinizing hormone

Table 2. Distribution of patients with normal and abnormal semen analysis parameters according to whether they were exposed to COVID-19 infection or not

	Patients with normal semen parameters		Patients with abnormal semen parameters		p
	n	%	n	%	
Patients exposed to COVID-19	130	41	186	59	0.54
COVID-19 naive patients	425	43	562	57	

Data are presented as number and percentage of patients

RESULTS

A total of 1303 patients were included in the study. Of these patients, 316 (24.2%) were previously exposed to SARS-CoV-2 infection, while the remaining 987 (75.8%) patients were COVID-19 naive. The mean ages of the exposed and non-exposed patients were similar (31.2±6.6 vs. 30.5±6.4, $p=0.73$). There was no statistically significant difference in hormone profile (FSH, LH, PRL, and T) and semen parameters between patients exposed to COVID-19 infection and non-exposed patients. Detailed results are provided in Table 1.

Semen parameters of 555 (42.6%) patients were within the normal standard values according to WHO 2021 criteria. For 748 (57.4%) patients, at least one of the semen parameters was be-

low the reference values. There was no significant difference in exposure to SARS-CoV-2 infection between patients with normal and abnormal semen analysis parameters ($p=0.54$) (Table 2).

Twelve patients were exposed to COVID-19 twice, and the remaining patients were exposed to it once. According to the WHO 2021 criteria, the semen parameters of two of these 12 patients were within normal ranges. In the remaining 10 patients, at least one of the semen parameters was below reference values.

DISCUSSION

To our knowledge, this retrospective case-control study is the first to investigate the relationship between semen quality and susceptibility to SARS-CoV-2 infection. The results of the study showed no significant difference between the pre-disease se-

men parameters of patients exposed to SARS-CoV-2 infection and those of SARS-CoV-2 naïve individuals. Additionally, there was no significant difference in exposure to SARS-CoV-2 infection between patients with normal and abnormal semen analysis parameters according to WHO 2021 criteria. Moreover, serum FSH, LH, PRL, and T levels were comparable between patients exposed to SARS-CoV-2 infection and naïve individuals.

There is growing evidence that male fertility and sperm quality are closely related to overall health. Various studies have shown that the severity of comorbidities is inversely correlated with semen quality.^[6,15] In a cross-sectional study involving 9,387 patients, men with higher Charlson comorbidity index scores had lower semen volume, sperm concentration, motility, total sperm count, and morphology scores.^[6] The deficiency of some common regulatory genes effective on both spermatogenesis and cell division has been held responsible for the coexistence of infertility and comorbidities.^[26–28] Additionally, it has been suggested that hormonal, environmental and intrauterine factors may also explain the link.^[29,30] Taking these data together, we hypothesized that patients with poorer semen quality might be more susceptible to SARS-CoV-2 infection since semen quality and comorbidities are closely related, and comorbidities increase individuals' susceptibility to SARS-CoV-2. However, based on our findings, there does not seem to be any relationship between sperm quality and susceptibility to SARS-CoV-2 infection.

Despite existing evidence for the immunosuppressive effects of testosterone against bacterial and viral infections, the results of the present study revealed no significant relationship between susceptibility to SARS-CoV-2 infection and serum T levels.^[31] Serum T levels of patients exposed to SARS-CoV-2 infection and naïve individuals were comparable. Various studies have examined the susceptibility to SARS-CoV-2 infection in patients receiving androgen deprivation therapy (ADT) for prostate cancer, yielding conflicting results.^[32, 33] Montopoli et al.^[32] reported lower SARS-CoV-2 infection rates in patients receiving ADT compared to those not receiving ADT [odds ratio (OR) 4.05, 95% confidence interval (CI) 1.55–10.59, $p=0.00043$]. In contrast, more recently, Klein et al.^[33] did not observe a protective effect of ADT against SARS-CoV-2 (OR 0.93, 95% CI 0.54–1.61, $p=0.8$). Further studies are needed to confirm the effect of testosterone on susceptibility to SARS-CoV-2 infection.

PRL, a lactogenic hormone, is also known to play an important role in regulating immune function during viral infections.^[25] Sen^[34] suggested that low serum PRL levels increase susceptibility to SARS-CoV-2 infection, while high PRL levels are protective against SARS-CoV-2 infection. They further hypothesized that controlled enhancement of serum PRL

levels through dopamine antagonists may provide an advantage in avoiding COVID-19 by stimulating both acquired and innate immunity. However, these hypotheses were not confirmed in the present study, as our results revealed no significant difference in serum PRL levels between patients exposed to SARS-CoV-2 infection and naïve individuals.

This retrospective study has several limitations. First, all patients were collected from a single center. Further studies involving various centers and populations will be necessary to confirm our findings. Second, data were not available regarding comorbidities of the patients included in the study that might affect their susceptibility to SARS-CoV-2 infection. Third, some patients in our study group may have had COVID-19 mildly symptomatic or asymptomatic and may not have been tested for COVID-19 at that time. Therefore, these patients may have been missed. Fourth, we do not have data on the severity of COVID-19 infection experienced by the patients. Finally, some patients whose semen parameters were below standard values according to WHO criteria did not have a second confirmatory semen sample.

CONCLUSION

This study demonstrated that baseline semen quality and serum reproductive hormone levels (T, PRL, FSH, and LH) are not indicators of susceptibility to SARS-CoV-2 infection. Therefore, there seems to be no relationship between these parameters and susceptibility to COVID-19. Further research, particularly multi-center studies, is needed to validate these findings and address the aforementioned limitations.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (No: 2024.07.158, Date: 11/07/2024).

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