

Does COVID-19 cause testicular damage? A cross-sectional study comparing hormonal parameters

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Abstract. – **OBJECTIVE:** We aimed to predict the potential testicular damage of COVID-19 by comparing the hormones FSH, LH, and TT before COVID-19 with values measured after COVID-19.

PATIENTS AND METHODS: A total of 348 patients – who were followed up in our urology clinic for varicocele, premature ejaculation, erectile dysfunction and infertility, had FSH, LH and TT levels measured one year before COVID-19 and were positive for COVID-19 after a Polymerase Chain Reaction (RT-PCR) tests – were included in the study. Presence of pneumonia compatible with COVID-19, hospitalization in the intensive care unit and FSH, LH and TT values before and after COVID-19 were recorded, along with lung computed tomography (CT).

RESULTS: The post-COVID-19 LH value (9.72 ± 3.27 mIU/mL) of the patients was significantly higher than the pre-COVID-19 LH value (5.72 ± 2.50 mIU/mL) ($p < 0.001$). The post-COVID-19 TT (253.85 ± 88.03 ng/dl) value was significantly lower than the pre-COVID-19 TT value (351.08 ± 106.19 ng/dl) ($p < 0.001$). In addition, while there was a mean decrease of 127.8 ng/dl in TT level in patients with pneumonia, a decrease of 39.03 ng/dl was observed in patients without pneumonia ($p < 0.001$).

CONCLUSIONS: COVID-19 may cause an increase in serum LH levels while decreasing TT levels. Additionally, those with COVID-19 pneumonia may experience a greater decrease in serum TT levels than those with COVID-19 without pneumonia.

Key Words:

COVID-19, Luteinizing hormone, Follicle-stimulating hormone, Total testosterone, Pneumonia.

ACE2 are likely to be targets of SARS-CoV-2². ACE2 is widely distributed in the heart, kidney, lung, and testicles³. Some studies^{4,5} analyzed ACE2 expression in the kidney and testis, especially in spermatogonium, Sertoli and Leydig cells, suggesting possible effects on spermatogenesis and possible orchitis formation in male SARS-CoV-2 patients. During the past SARS-CoV-2 epidemic, some studies⁶ showed that the coronavirus family (SARS-CoV) causes orchitis. Even if SARS-CoV-2 is not detected in the testis⁷, testicular damage was detected in these cases⁶. As with previous coronaviruses, tissue inflammation occurs as a result of viral binding to the ACE2 receptor in the testis, causing painful epididymo-orchitis. SARS-CoV-2 is also thought to cause systemic vasculitis of small vessels, causing testicular damage and orchitis⁸.

In light of these data, it may be considered that SARS-CoV-2 infection can potentially target the testicles. In this study, we aimed to estimate the potential testicular damage caused by COVID-19 by comparing the levels of FSH, LH and total testosterone (TT) measured in the year before COVID-19 and six months after COVID-19. In addition, we aimed to determine the hormonal differences between those with COVID-19 pneumonia, those admitted to the intensive care unit, and those who survived the disease without COVID-19 pneumonia and without being admitted to the intensive care unit.

Patients and Methods

Study Design and Patients

After our study was approved by the Local Ethics Committee of our hospital, the files of 6653 patients who applied to our hospital's COVID-19 clinic between April 2020 and December 2021 and underwent RT-PCR for SARS-CoV-2 RNA

Introduction

COVID-19 is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)¹. Angiotensin-converting enzyme 2 (ACE 2) is required for SARS-CoV-2 to enter host cells. Therefore, cells with

were reviewed. Positive results (RT-PCR) were investigated and that 596 of these patients were followed in our urology clinic. Patients who were followed by our urology clinic due to varicocele, premature ejaculation, erectile dysfunction and infertility and who had their FSH, LH and TT measurements in the last year before they had COVID-19 were included in our study. Those whose FSH, LH and TT levels were not checked in the last year before COVID-19, those who had comorbidities that directly affect testosterone level such as obesity, hypertension, diabetes or heart disease before COVID-19, and those who use drugs (such as aldactone) that may cause low testosterone levels, those diagnosed with testicular disease such as epididymoorchitis and those who had testicular surgery were not included in the study. Our study was carried out with 348 patients after re-evaluation according to exclusion criteria. Patients were invited to our outpatient clinic six months after suffering from COVID-19 and blood samples were taken from all patients. Serum hormonal evaluation, including FSH, LH and TT levels, was performed. Hormone levels were measured using an electrochemiluminescence immunoassay (normal ranges of values: FSH 1.4-18.1 IU/L; LH 1.5-9.3 IU/L; TT 165-753 ng/dl). Age of patients, presence of COVID-19 compatible pneumonia on thoracic computed tomography (CT), intensive care unit admission for COVID-19, and FSH, LH, and TT values within one year before COVID-19 and 6 months after COVID-19 were recorded. COVID-19 pneumonia was identified with major radiological findings, defined as ground glass opacities, consolidations, cobblestone appearance, air bronchogram and airway changes, vascular enlargement, and nodules. The results for those with COVID-19 pneumonia, those who were admitted to the intensive care unit and those who survived the disease without COVID-19 pneumonia and without being admitted to the intensive care unit were compared.

Data Collection

The principles of the Declaration of Helsinki were applied when creating the data. All methods were carried out abiding by the guidelines and regulations indicated by these principles. Written informed consent was obtained from each patient. The electronic hospital information system was used to obtain epidemiological data, including demographic, clinical and laboratory findings. Considering the circadian rhythm of testosterone release (before 10:00 a.m.), total testoster-

one, FSH, and LH levels which were measured in venous blood samples were recorded. Peripheral venous blood samples were evaluated in the Central Laboratory of Adana City Training and Research Hospital central laboratory by using the standard procedures. Biochemical hormonal parameters were measured using a Siemens ADVIA 1800 automatic biochemistry analyzer (Siemens Healthcare Diagnostics Inc, Advia Centaur XPT, Laboratory Diagnostics, Erlangen, Germany, manufactured in Ireland).

Statistical Evaluation

The SPSS 23.0 package program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Categorical measurements are summarized as numbers and percentages, continuous measurements are summarized as mean, standard deviation and minimum-maximum. The fit of the variables to normal distribution was investigated by using Shapiro-Wilk test. The independent Student's *t*-test was used for normally distributed parameters and Mann-Whitney *u* test was used for non-normally distributed parameters. The Wilcoxon test was used to determine the differences between the pre-COVID-19 and post-COVID-19 findings of the FSH, LH and TT values. Statistical significance level was taken as 0.05 in all tests.

Results

The mean age of 348 patients was 50.0 ± 14.9 years (20-74). Baseline values of FSH, LH and TT were 5.9 ± 2.5 mIU/mL, 5.7 ± 2.5 mIU/mL, and 351.1 ± 106.1 ng/dl, respectively (Table I).

The post-COVID-19 LH value was 9.7 ± 3.2 , and the post-COVID-19 LH value was statistically and significantly higher than the pre-COVID-19 LH values ($p < .001$). The post-COVID-19 FSH value was 6.2 ± 2.8 , and the increase in FSH value after COVID-19 was not statistically significant ($p = 0.124$). The TT level after COVID-19 was 253.8 ± 88.0 , and the TT level was found to be statistically and significantly lower after COVID-19 ($p < .001$) (Table II).

While there was a mean decrease of 127.8 ng/dl in TT level in patients with pneumonia due to COVID-19, a decrease of 39.03 ng/dl was observed in patients who did not have pneumonia. This difference was considered statistically significant ($p < .001$). While LH level increased by 3.3 mIU/mL in patients with pneumonia, it increased by 5.2 mIU/mL in patients without pneumonia.

Table I. Epidemiology of mood disorders in adults¹.

	Frequency (n)	Percent (%)
Pneumonia		
No	120	34.5
Yes	228	65.5
Hospitalized in the intensive care unit		
No	256	73.6
Yes	92	26.4
	Mean±SD	Med (Min-Max)
Age	50.01±14.91	52 (20-74)
FSH Before COVID-19 (mIU/mL)	5.93±2.55	6 (1-15)
LH Before COVID-19 (mIU/mL)	5.72±2.50	6 (1-15)
FSH After COVID-19 (mIU/mL)	6.24±2.84	6 (1-15)
LH After COVID-19 (mIU/mL)	9.72±3.27	9 (2-18)
TT Before COVID-19 (ng/dl)	351.08±106.19	360 (112-680)
TT After COVID-19 (ng/dl)	253.85±88.03	240 (100-600)

*TT, Total Testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

This difference was considered statistically significant ($p = .034$). In addition, an increase of 0.63 mIU/mL ($p=.243$) was observed in patients with pneumonia, while the FSH level increased by 0.14 mIU/mL (Table III).

No statistically significant difference was observed in the pre-COVID-19 and post-COVID-19 FSH, LH and TT levels of patients hospitalized in the intensive care unit (ICU). In patients who were not hospitalized in the intensive care unit (ICU), there was no difference between pre- and post-COVID-19 FSH, LH and TT levels ($p = .486$, $p = .158$, $p = .758$) (Table IV).

Discussion

The testes are considered the target of SARS-CoV-2 due to ACE2 expression in the testicles⁹. Wang et al¹⁰ conducted a study on transcriptome analysis of human testicular tissues and concluded that there is significant expression of ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) in spermatogonia, spermatids, Leydig and Sertoli cells. Ricardo et al¹¹ claimed that testicular cells could be a target for SARS-CoV-2 due to the presence of ACE2 receptors in testicular cells. Verma et al¹² compared ACE2 and

Table II. Differences in the hormonal values of patients in the study group before and after COVID-19.

	Before COVID-19	After COVID-19	p^*
FSH (mIU/mL)	5.93±2.55	6.24±2.84	.338
LH (mIU/mL)	5.72±2.50	9.72±3.27	<.001
TT (ng/dl)	351.08±106.19	253.85±88.03	<.001

* $p < 0.05$, Wilcoxon test; *TT Total Testosterone; LH luteinizing hormone; FSH follicle-stimulating hormone.

Table III. Hormonal differences before and after COVID-19 in patients who had pneumonia and who did not.

	Pneumonia		p^*
	No	Yes	
Difference in FSH (u)	0 (-2-9)	0 (-3-5)	.317
Difference in LH (t)	5.21±4.45	3.35±3.42	.034
Difference in TT (u)	-35 (-170-58)	-113 (-400-0)	<.001

* $p < 0.05$, (u): Mann-Whitney U test, (t): Independent samples t -test; *All patients with pneumonia were hospitalized. *TT Total Testosterone; LH luteinizing hormone; FSH follicle-stimulating hormone.

Table IV. Hormonal differences before and after COVID-19 in patients who were hospitalized in the intensive care unit and who were not.

	Hospitalized in the intensive care unit		<i>p</i> *
	No	Yes	
Difference in FSH (u)	0 (-3-9)	0 (-2-4)	0.342
Difference in LH (t)	4.30±4.13	3.13±3,0	0.214
Difference in TT (u)	-79 (-400-58)	-76 (-315-22)	0.788

**p*<0.05, (u): Mann-Whitney U test, (t): Independent samples *t*-test. *TT Total Testosterone; LH luteinizing hormone; FSH follicle-stimulating hormone.

cell-specific gene expression in normal adult human testes ($n = 3$) using a microarray analysis. They found high levels of ACE2 transcripts in normal adult testicles. Yang et al¹³ showed that the number of Leydig cells decreased in the testicular tissues of 12 COVID-19 patients who were autopsied, while edema and inflammation were present in the interstitium. Data about the presence of SARS-CoV-2 in the testis are limited. Zhao et al¹⁴ showed the presence of SARS-COV-2 in testicular tissue. However, Pan et al¹⁵ reported that SARS-CoV-2 was not detected in sperm samples taken from 34 patients within an average of 31 days after the diagnosis of COVID-19. In another study¹⁶, SARS-CoV-2 was not detected in semen samples from twelve asymptomatic to mildly symptomatic COVID-19 patients in Wuhan 14 to 42 days after diagnosis of COVID-19. Although there was no direct study in our research to detect the presence of the virus in the testis or semen and damage in the testis, an increase in LH level, decrease in serum TT level and low serum TT:LH ratio after COVID-19 indicate primary hypogonadism. We think that this hypogonadism is due to damage caused by COVID-19 in the testicles.

While FSH acts on Sertoli cells, LH targets Leydig cells in the testis, leading to testosterone synthesis responsible for spermatogenesis¹⁷. Some studies^{18,19} showed that COVID-19 affects FSH and LH levels. According to Ma et al¹⁸ when reproductive-age men infected with SARS-CoV-2 were compared with healthy controls, they found higher levels of LH in the infected patients. However, they could not find any difference in FSH levels in both groups. According to Cayan et al¹⁹ as the disease caused by COVID-19 worsened, the mean LH and FSH values in the serum increased. It is quite clear that more studies are needed to support the relationship between COVID-19, the hypothalamic-pituitary system, and circulating gonadotropin levels. Similar to the results of the limited studies

in the literature, it was revealed in our study that there was no increase in mean LH levels and no difference in FSH levels after COVID-19. Some studies concluded that COVID-19 lowers serum TT levels. Rastarelli et al²⁰ sought to predict the relationship between TT levels, clinical outcomes of SARS-CoV-2 infection and biochemical prognostic markers of serious disease. In their study, they found that SARS-CoV-2 reduced TT level relatively but did not affect it statistically, while LH was statistically higher. Vanhorebeek et al²¹ explored the endocrine aspects of acute and long-term critical illness. They reported that there was a decrease in TT level in the acute phase of critical diseases. Kadihasanoğlu et al²² stratified COVID-19 patients according to disease severity and compared serum TT levels. They showed that COVID-19 was associated with decreased TT level and increased LH level, and severe COVID-19 caused further reductions in TT levels. Salonia et al²³ compared the circulating sex hormones of 281 healthy male and 286 symptomatic male COVID-19 patients and investigated the relationship between serum TT, COVID-19, and clinical outcomes. They found that patients infected with SARS-CoV-2 had lower TT levels than the healthy control group, and approximately 90% of these patients had TT levels at the level of hypogonadism. They also showed that the lower the testosterone level, the higher the ICU and death outcomes. In another study, Ökçelik evaluated 44 patients who applied to the COVID-19 outpatient clinic to reveal the relationship between COVID-19 and potential testicular damage. Ökçelik²⁴ found that there was no statistical difference between the FSH, LH, and TT values of COVID-19 PCR positive and negative patients, but the testosterone levels of patients with COVID-19 pneumonia were statistically significantly lower. Similarly, in our study, serum TT levels were significantly decreased in patients with COVID-19. The fact that

patients with COVID-19 pneumonia experienced a greater decrease in TT levels than those without pneumonia suggests that testicular damage may be more severe in patients with COVID-19 pneumonia than in patients without pneumonia.

Our study has some limitations. First of all, our study presents the results of a single center, but we think that the number of patients is sufficient. Second, only serum total TT was measured, but free and bioavailable testosterone levels were not evaluated as they were not studied in our clinic. Another limitation is that the presence of COVID-19 in semen and whether it has an effect on the semen could not be evaluated. The biggest reason for this is that our andrology outpatient clinic, where sperm analyses are performed, did not provide services for a very long time, similar to the postponement of many elective cases during the pandemic period. The strength of our study is knowing the pre-COVID-19 FSH, LH and TT levels of our patients followed in the urology outpatient clinic. Our study showed that COVID-19 can cause low serum testosterone and high serum LH levels, proving a greater decrease in serum TT levels in those with COVID-19 pneumonia than in those without pneumonia.

Conclusions

COVID-19 may cause an increase in serum LH levels while decreasing TT levels. Additionally, those with COVID-19 pneumonia may experience a greater decrease in serum TT levels than those with COVID-19 without pneumonia.

Authors' Contributions

K.K. and G.G. made substantial contributions to conception and design, and acquisition of data, and analysis and interpretation of data. K.K. supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability

The data are available from the corresponding author upon request.

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