INTRODUCTION

Angiotensin-converting enzyme 2 (ACE2) receptors play an important role in the pathogenesis of COVID-19 infection (Hoffmann et al., 2020). SARS-COV2 binds to ACE2 receptors and acts by entering into the cell (Hoffmann et al., 2020). Although COVID-19 mostly manifests in respiratory tract infections such as cough, fever and respiratory distress, other indicators of the virus are nausea, vomiting, palpitations and orchitis. ACE2 is expressed in the respiratory system, digestive system, cardiovascular and urinary system (Zou et al., 2020). Testicular tissue shows high ACE2 mRNA and protein expression (Fan et al., 2020). ACE2 expression has been demonstrated in testicular tissue, seminiferous duct tissues, spermatogonia, Leydig cells and sertoli cells (Fan et al., 2020; Shen et al., 2020; Wang & Xu, 2020). The blood testicular barrier is not cannot adequately function to prevent passage through the urogenital system during viraemia (Li et al., 2012). The fact that orchitis due to COVID-19 has been reported before is evidence of this (Xu et al., 2006). It can therefore be posited that COVID-19 infection will damage testicular structures. Sperm cells are produced in seminiferous tubules by follicle-stimulating hormone (FSH) effect. Leydig cells are cells that produce testosterone by the luteinising hormone (LH) effect. In the acute period, a decrease in total testosterone (T) values and an increase in LH values can be expected due to the change in the Leydig cells. However, it is likely that FSH will not be impacted during the acute period, as a longer period of time is required for changes to occur in spermatogenesis.
In this study, we have aimed to estimate the potential testicular damage caused by this viral infection by evaluating testicular hormone levels in patients at the time of active infection by COVID-19. With a particular focus on pneumonic patients, we evaluated how this situation was in the group with more severe disease.

2 | MATERIAL AND METHODS

After obtaining approval from the Ministry of Health and the Ethics Committee of Hacı Bektaş University, we evaluated patients who had applied to the COVID-19 outpatient clinic with suspicions of COVID-19 between March 2020 and July 2020. Male patients’ ages differ from 18 to 50 years being included in the study. Ages of the patients, polymerase chain reaction (PCR) test results of patients with swabs for COVID-19, presence of pneumonia in thoracic computed tomography (CT), total testosterone, LH and FSH values were recorded. Qiagen Rotor-Gene Q 4® was used for COVID-19 PCR evaluation. The normal value of the testosterone level was between 9.71 and 27.76 mmol/L. The normal value of LH level was between 1.7 and 8.6 mIU/ml. The normal value of FSH was between 1.5 and 12.4 mIU/ml. The blood for hormonal evaluation was taken at 10 a.m., while the other evaluation blood was taken. It was assessed whether there was a difference between those who were positive for COVID-19 and those who were not. It was also assessed whether there was a significant disparity between the hormones of those who had COVID-19 induced pneumonia and those who did not.

SPSS (17.0) were used for statistical analysis. Statistical evaluation results were reported as mean ± SD or median (minimum – maximum values) according to the normal distribution of variables. The data’s distribution was evaluated by the Kolmogorov-Smirnov test. Mann-Whitney U tests and independent samples tests were used to evaluate the differences between groups. p < 0.05 was considered statistically significant in all evaluations.

3 | RESULTS

Between March 2020 and July 2020, 44 patients were included in the study. The mean age of the patients was 35.5 ± 9.85 years. Only one patient described testicular pain. None of the patients had testicular swelling. The COVID-19 PCR test of 24 patients was positive, and the COVID-19 PCR test of 20 patients was negative. The median FSH value was 3 (1–8) mIU/ml. The median LH value was 5 (2–12) mIU/ml. The mean total testosterone value was 11.82 ± 5.91 mmol/L. There was no statistically significant difference between the FSH, LH and total testosterone values of the COVID-19 PCR positive and negative patients (p = 0.80, p = 0.62, p = 0.56 respectively) (Table 1). When FSH, LH and total testosterone values were divided into categories of low, normal and high, FSH and total testosterone values were similar (p = 1, p = 0.61 respectively). LH values were statistically significantly higher in the COVID-19 PCR positive group (p = 0.04) (Table 2).

Thoracic CT was performed on 42 patients. COVID-19 pneumonia was detected in 23 patients. Thorax CT of 19 patients was normal. The FSH and LH values of the patients with COVID-19 pneumonia and those without it were similar (p = 0.61, p = 0.93 respectively) (Table 3). When FSH, LH and total testosterone values were separated as low, normal and high, there was no difference found in FSH and LH values (p = 1, p = 0.2 respectively). Total testosterone levels were found to be significantly lower in patients with COVID-19 pneumonia (p < 0.001) (Table 4).

4 | DISCUSSION

Testicles are mostly composed of seminiferous tubules and intertubular tissues. The seminiferous tubules are the location where sperm cells are produced. They consist of spermatogonia and supporting Sertoli cells. Leydig cells are responsible for the production of testosterone in LH control. SARS-COV2 enters into the cell by binding to ACE2 receptors (Hoffmann et al., 2020). Therefore, the virus infects and causes damage to the cell. This suggests that SARS-COV2 infection can occur in all cells with ACE2 receptors. It has been previously shown that COVID-19 infection shows symptoms in the body.

### TABLE 1 Testicular hormone values according to COVID-19 positivity

|            | COVID-19 negative | COVID-19 positive | p   |
|------------|-------------------|-------------------|-----|
| FSH (mIU/ml) | 3(1–6)           | 3(1–8)           | .80 |
| LH (mIU/ml)  | 5(2–10)          | 5.5(2–12)        | .62 |
| T (mmol/L)   | 11.25 ± 5.63     | 12.29 ± 6.22     | .56 |

*Mann-Whitney U test.

|            | COVID-19 negative | COVID-19 positive | p   |
|------------|-------------------|-------------------|-----|
| FSH (n)    | 0 20 0            | 0 24 0            | 1   |
| LH (n)     | 0 19 1            | 0 17 7            | .04 |
| T (n)      | 6 14 0            | 9 15 0            | .61 |

*Mann-Whitney U test.

|            | COVID-19 negative | COVID-19 positive | p   |
|------------|-------------------|-------------------|-----|
| FSH (n)    | 0 20 0            | 0 24 0            | 1   |
| LH (n)     | 0 19 1            | 0 17 7            | .04 |
| T (n)      | 6 14 0            | 9 15 0            | .61 |

*Independent Samples t test.
outside of the respiratory system (Fan et al., 2020; Shen et al., 2020; Wang et al., 2020). Since ACE2 is expressed in the respiratory system, digestive system, cardiovascular and urinary systems, COVID-19 can also cause disease in these systems (Zou et al., 2020). The amount of ACE2 mRNA and protein expression within the testes is higher than in many other tissues (Fan et al., 2020). Some other viral diseases have also been shown to cause viral orchitis and cause male infertility (Xu et al., 2006). Since the main roles of the testicles are spermatogenesis and the secretion of androgens, sex steroids can be used to assess the male gonad status. A recent study found that testosterone/luteinising hormone ratios were significantly lower in patients with COVID-19 infection (Ma et al., 2020). In our study, when we segregated FSH, LH and total testosterone values into low, normal and high categories, LH values were found to be significantly high. This supports the thesis that acute testicular damage can be linked to COVID-19 infection by the evaluation of testicular hormones. Furthermore, total testosterone values were significantly lower in patients with viral pneumonia. This result also indicated that COVID-19 infection could cause damage to testicular tissues.

Zhao et al. (2003) previously detected SARS-COV2 particles pathologically in seminiferous tubules and Leydig cells. Pan et al. (2020) reported scrotal discomfort in 17.6% COVID-19 positive patients. However, in this study, the presence of COVID-19 could not be seen in the semen samples. This could be in part because semen turnover was not analysed in this study. Contrary to this study, COVID-19 has been shown to be present in semen (Fan et al., 2020; Wang & Xu, 2020). In order to better evaluate the effects of COVID-19 infection on semen, future studies should widen the parameters of factors analysed and semen turnover should be measured in each patient.

Previously, Liu et al. (2019) reported that half of the COVID-19 positive patients had acute respiratory distress syndrome (ARDS). In the acute phase of the disease, decreases in testosterone values were observed (Vanhorebeek et al., 2006). In our study, testosterone levels were found to be significantly lower but especially in patients with viral pneumonia.

The relatively low number of sampled patients was the limitation of our study. It should be noted that the specificity of COVID-19 PCR is not 100% and that the PCR results of some COVID-19 patients showed negative results. We evaluated COVID-19 pneumonia patients in order to circumvent this limitation. Still, the strength of the study is that the study is prospective and for the first time demonstrates that testicular hormones are affected in patients with COVID-19 viral pneumonia.

5 | CONCLUSIONS

Testosterone levels seem to decrease during acute COVID-19 infection, especially in the patient group with viral pneumonia. This suggests to us testicular damage in the acute period. Future studies should evaluate the effect on spermatogenesis by paying attention to sperm turnover, especially in patients with COVID-19 pneumonia.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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