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Research Article

Evaluation of Levels of Angiotensin-converting Enzyme 2 (ACE2) and Sex-related Hormones in Males Recovered from COVID-19

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A B S T R A C T

Introduction: The first case of COVID-190 infection was verified and recorded in December 2019, and since then, COVID-19 has spread all over the world. Testes, comprising spermatogonia, Leydig cells, and Sertoli cells, were shown to have high expression levels of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2 entry into target cells. There is currently no evidence that the SARS-CoV-2 virus can harm a man's ability to reproduce.

Methods: In this investigation, the sex hormones of 50 males in their reproductive years who had recovered from SARS-CoV-2 infection were compared to those of 50 men who were healthy and of a similar age.

Results: In the patient group, the mean serum luteinizing hormone (LH) level was (7.2 ± 3.3 mIU/ml). The mean serum testosterone level was significantly lower (3.2 ± 1.7 IU/ml) in the patient group as compared to the control group. There was also a strong correlation between the levels of ACE2 and serum testosterone in the patient group, according to a multivariable regression analysis.

Conclusion: This work offers the first scientific evidence of COVID-19's effects on male sex hormones, underscoring the significance of monitoring gonadal health among SARS-CoV-2-infected patients, especially in males of reproductive age.

Keywords: Reproductive System, Sex Hormones, Androgens, SARS Coronavirus 2, ACE2, COVID-19

Introduction

Since it was first identified in December 2019 in Wuhan, a novel coronavirus-induced pneumonia (designated by the WHO as COVID-19) has been aggressively spreading around the globe, creating a pandemic.[1] SARS-CoV-2, a previously unnamed beta-coronavirus, was identified as the COVID-19 causal agent due to its staggering 80% sequence match to SARS-CoV.[2] Besides the obvious wheeze, it may cause fever and even severe respiratory failure. There have been reports of COVID-19 attacks on multiple organs, including the digestive, cardiovascular, and urinary systems.[3]

Angiotensin-converting enzyme 2 (ACE2) is thought to serve as the receptor for COVID-19 binding and entry into host cells. Theoretically, all cells expressing ACE2 could be

vulnerable to COVID-19 infection. The testes express the maximum protein and mRNA levels of ACE2 in the body, as indicated by the online index, An Atlas of Human Proteins.[4] These three cell types spermatogonia, Leydig cells, and Sertoli cells, have a significantly higher concentration of ACE2 as shown by human testis scRNA-seq profiling.[5] All of these results suggest that COVID-19 may have an effect on the male gonad and, consequently, on male sex hormones.

When viraemia is present, the blood-testis barrier is not completely successful in stopping the virus, allowing it to penetrate the male reproductive system.[6] HIV or measles-induced orchitis are examples of how virus-caused damage to the testes might interfere with gonadal hormone release and spermatogenesis.[7] Orchitis has been linked to SARS-CoV in the past.[8] Fortunately, there is no current clinical data to confirm the claim that COVID-19 infection can impact male reproductive function.

Objective

Evaluation of ACE2 and male reproductive hormones in COVID-19-recovered men

Material and Methods

This case-control research was evaluated and approved by the Medical Ethics Committee of the AL-Najaf Health Directorate, Ministry of Health, Iraq in Najaf Province. One hundred male patients were selected, all of reproductive age (median age 33 years, range 25–50 years), admitted to the Fertility Center's laboratory in AL-Sader Medical City, AL-Najaf Health Directorate between September 1, 2022, and January 31, 2023, for semen analysis. The patients were recruited on a continuous basis as long as they met the inclusion criteria using convenient sampling. After laboratory testing was concluded, residual serum was collected for ACE20 estimation. There was no additional burden or risk associated with the procedure because of the fact that the leftover specimens of sera were thrown away as biohazardous waste and the method did not impose any additional burdens or cause any damage to the patients. The patients and controls comprised males who underwent sex hormone testing and sperm analysis prior to marriage as part of a fertility assessment or when their spouses intended to get pregnant. The patient group (N = 50) was cured of COVID-19 and had children prior to infection, whereas the control group (N = 50) was uninfected and fertile. Each participant provided verbal consent for participation after being informed about the study.

In this study, using an enzyme-linked immunosorbent assay, the levels of ACE2 were determined in line with the manufacturer's recommendations (BT Lab Inc., Shanghai Korain, China). The normal range was 30–40 ng/ml according to the test manual and reagent description of BT Lab Inc. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), serum testosterone (T), and prolactin (PRL) were measured using electrochemiluminescent immunoassays, as per the manufacturer's instructions (Cobas E411, Roche, Switzerland). The patient data on demographics, comorbidities, signs and symptoms, laboratory results, and complications were collected. All data were statistically analysed with SPSS v.28 and Microsoft Excel 2019. Data were expressed as mean ± SD (standard deviation). Independent t-test was used to compare continuous variables between groups. Multiple comparisons between groups were performed by one-way ANOVA with Tukey's post hoc. Categorical variables were analysed by the chi-square test. Correlation coefficient analysis was completed with Pearson correlation and linear regression. Binary and nominal multiple regression analyses were performed to predict the independent variables. The significance of differences was detected at $p < 0.05$.

Exclusion Criteria

Patients with a history of varicocele, cryptorchidism, congenital disorders, immunological and inflammatory diseases, hormone disruptions, diabetes, alcohol abuse, and smoking were excluded from the study. Patients less than 25 or more than 50 years of age were also excluded.

Blood Collection

Blood samples (5 ml) were obtained from males who had recovered from COVID-19. The samples were placed in a clot activator tube.[9] They were centrifuged (5000 rpm) for 5 minutes to separate serum after being placed in a clot activator tube and were left at room temperature for 30 minutes to coagulate the blood. The serum was collected using a micropipette, deposited in six Eppendorf containers, and frozen at -20 ^{o}C.[10]

Results

Sex Hormones in COVID-19-recovered Patients

To better understand the male reproductive function after SARS-CoV-2 infection and because sex-related hormones may also be used to determine the condition of the male gonad, we measured sex hormone levels in the sera of these 50 patients. The patients exhibited substantially greater blood LH ($p < 0.0001$) and lower serum testosterone ($p < 0.0001$) than the control group, despite the lack of a statistically significant variation in follicle-stimulating hormone blood level (FSH) ($p > 0.05$) and prolactin ($p > 0.05$) among both groups (Table 1).

All men in the study exhibited typical male genitalia, including typical-sized and textured testes. On closer inspection, neither the epididymis nor the testicles were sensitive. No patient complained of scrotal discomfort since the start of COVID-19 symptoms.

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Table 1.Levels of Sexual Hormones in Completely Recovered COVID-19 Patients

Hormone	Patient Group Mean ± SD* (N = 50)	Control Group Mean ± SD (N = 50)	Statistical Test (t)	p Value
Testosterone (IU/ml)	3.2 ± 1.7	5.9 ± 1.7	7.4	< 0.001
Luteinizing hormone (mIU/ml)	7.2 ± 3.3	4.7 ± 1.5	4.7	< 0.001
Follicle-stimulating hormone (mIU/ml)	4.7 ± 1.8	4.2 ± 1.8	1.1	> 0.05 NS
Prolactin (mIU/ml)	11.6 ± 5.1	10.06 ± 3.6	1.8	> 0.05 NS

*Significant at p < 0.05
*NS: Not significant

Evaluation of Serum Angiotensin-converting Enzyme (ACE2)

In the patient group, the mean serum ACE2 concentration was higher (5.3 ng/mL) than in the control group (3.4 ng/ml). As seen in Table 2, ACE2 levels were significantly elevated (p < 0.001) in patients as compared to the control group, according to what we see in Table 2.

Table 2.Comparison of Levels of ACE2 in the Two Groups

Variable	Study Group	Mean ± SD	p Value
ACE2 (ng/mL)	(N = 50) Patient	± 2.4 5.3	< 0.001**
	Control (N = 50)	± 1.03 3.4	

p < 0.001: Highly significant (**), N: number of participants

In the current investigation, the level of ACE2 of the patient group showed a statistically significant difference (5.3 ± 2.4 ng/ml) when compared to that of the control group (3.4 ± 1.03 ng/ml) with p value < 0.001.

Correlations between Serum ACE2 Activity and Testosterone

As shown in Figure 1, the statistical results showed a highly significant (p ≤ 0.001) inverse correlation between the mean level of ACE2 and the mean level of testosterone (r = -0.323).

Comparing the patient group and the control group, the current study revealed that ACE2 levels were elevated, whereas testosterone levels were low in the patient group. Lower testosterone levels result in the upregulation of ACE2 and TMPRSS2 receptors, which facilitate SARS-CoV-2 entrance into alveolar cells and downregulate a lung-protective pathway.[11] The ligand-activated transcription factor androgen receptor is known to have TMPRSS2 as a target, and androgen receptor activation raises TMPRSS2 levels in several organs.

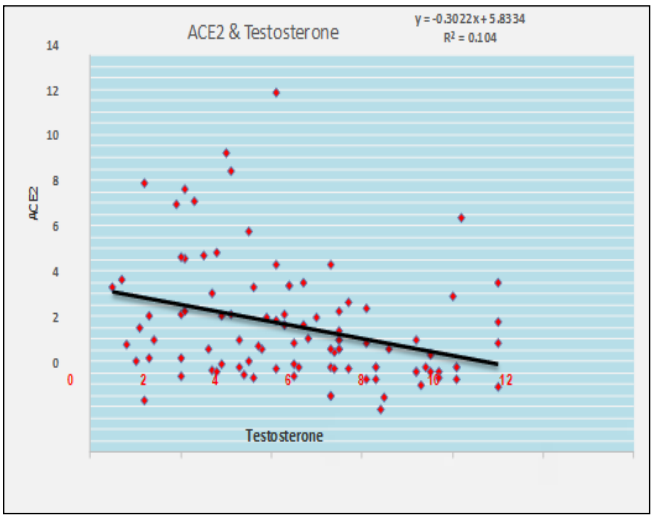

Figure 1.Correlation between ACE2 (ng/ml) and Testosterone (IU/ml) in the Patient Group (p value ≤ 0.001, r = -0.323, R2 = 0.104)

Discussion

Table 1 demonstrates a statistically significant difference (p value < 0.001) between the LH levels of the patient group and those of the control group. This result is consistent with a few previous studies.[12,13]

Sertoli or spermatogenic cell injury is a leading cause of male infertility.[14] Higher LH concentrations in males with infertility are believed to be associated with low levels of testosterone and these androgen receptor cells may make the situation worse. Corticosteroids impede LH secretion.[15] As per a previous study, in severe cases of COVID-19, testosterone decreases while LH increases.[13]

Testosterone levels were found to be highly significant (p value < 0.001) on comparing the patient group to the control group. Under the control of LH, the generation of testosterone occurs in the interstitial Leydig cells.[16] The cellular transmembrane protease serine 2 (TMPRSS2) ACE2 is used by COVID-19, for entrance into human

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cells. Testicular Leydig cells secrete testosterone after being stimulated by pituitary luteinizing hormone (LH) and regulated by hypothalamic gonadotropin-releasing hormone (GnRH).[17]

Reportedly, testosterone has anti-inflammatory effects by dampening the functioning of the body's immune cells and antibody defences. Testosterone works to decrease IL-6 and TNF-a by blocking the NF-kB proinflammatory mechanism.[6] It is hypothesised that male infertility is accompanied by a decrease in testosterone concentrations and an increase in LH. The ratio of testosterone to luteinizing hormone was substantially lower in patients with COVID-19 infection, according to a recent study.[15] The idea that COVID-19 infection may be connected to acute testicular damage is supported by an analysis of testicular hormones. Furthermore, patients with viral pneumonia had significantly reduced total testosterone levels. In addition, this finding revealed that infection with COVID-19 may cause damage to testicular tissues,[18] which explains why the patients' group had substantially lower total and free testosterone and higher LH than the control group.

In the study by Achua et al., immunofluorescence-stained slides from male participants of the patient group revealed a correlation between increased ACE2 concentrations in the tissues and spermatogenesis impairment.[1] These results, particularly levels of ACE2 receptors correlate negatively with spermatogenesis, offering a possible mechanism for infertility after COVID-19, by indicating that the virus may target the testes.

Circulating ACE2 levels are typically low in healthy individuals[19] and are elevated in individuals with a variety of cardiovascular disorders, including arrhythmia, heart failure, high blood pressure, and narrowing of the aorta[20]. COVID-19 infection itself can increase ACE2 levels, and our results imply that individuals with already high ACE2 levels may be at an increased risk of a serious illness. On the cell surface, ACE2 expression is downregulated following virus binding. This reduces the cellular transformation of angiotensin II to Ang 17 and angiotensin I to Ang 19, resulting in an increase in angiotensin II concentration.[21] It is consistent with other studies, such as a study by Kamel et al., in which the mean of ACE2 was 3.83 ± 0.82 ng/ml in patients.[22] The level of ACE2 rises depending on how much the lungs are affected because of increased ACE2 shedding caused by ACE2-expressing cell death brought on by severe lung infection.[4,23–25] In another study, the ACE2 values of the COVID-19 group were found to be significantly lower than those of the post-treatment group.[26]

The process of spermatogenesis may be disrupted if viruses get access to these cells, posing a threat to male fertility. Intriguingly, ACE2 expression in the testes declines with age, with higher levels of expression seen in younger groups as compared to the elderly.[27] COVID-19 may affect male fertility by targeting ACE2 and TMPRSS2, which are expressed in the testis and seminal vesicles and the prostate gland and testis, respectively.[28] The COVID-19 virus may lower testosterone levels and have a deleterious effect on sperm production and parameters through ACE2 receptors and Leydig cells.[29] Seminal plasma electrolyte management, steroidogenesis regulation, spermatogenesis regulation, and sperm function regulation are all responsibilities of the Renin-Angiotensin System (RAS).[30]

Various medications can also influence the expression of ACE2. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are widely used to treat cardiovascular diseases. In addition to their pharmacological effects, they enhance the expression of ACE2 in the heart.[3] Testicular expression of ACE2 and TMPRSS2 are both highly correlated with COVID-19 viral loads, suggesting that males who have these genes highly expressed may be more susceptible to infection.

The negative correlation between ACE2 and testosterone observed in our study was consistent with findings from other studies indicating that testosterone affects COVID-19 infection via a mechanism that does not involve cytokine production. According to a study, the initial biological steps required for the potential infectivity of COVID-19 are the activation of TMPRSS2 in the cell to make spike protein and the activation of ACE2 as the entrance receptor.[31]

Through this mechanism, studies indicate that elevated testosterone levels are associated with low prognosis in SARS-CoV-2. Wambier and Goren reported that the hyperandrogenic phenotype may be associated with increased COVID-19 viral load, viral dissemination, and severity of lung involvement.[32] Rozhivanov et al. reported that individuals with hyperandrogenism showed a more severe coronavirus infection and TMPRSS2 levels.[33]

Conclusion

This study gives first-hand data on how COVID-19 affects testosterone levels in men, highlighting the importance of evaluating gonadal function in patients who have recovered from SARS-CoV-2 infection, particularly in men of reproductive age.

Conflict of Interest: None

Source of Funding: None

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