



COVID-19 INFECTION AND TEMPORAL RECOVERY OF TESTOSTERONE AND LH IN MALES

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) emerged as a global pandemic in 2019 with primary respiratory involvement. Altered angiotensin-converting enzyme-2 (ACE-2) receptor expression has been linked to extrapulmonary effects, including disturbances in male reproductive hormones.

Objectives: To investigate the impact of COVID-19 infection on male reproductive hormones during early and late recovery phases.

Methods: This cross-sectional comparative study was conducted in Mirpur, Azad Jammu and Kashmir, from September 2023 to November 2023. After ethical approval and informed consent, 90 males were enrolled and divided into three equal groups: Group A (healthy controls), Group B (recovered from COVID-19 within the last four months), and Group C (recovered from COVID-19 approximately one year earlier). Data were analyzed using SPSS version 23.0. The Shapiro–Wilk test assessed normality, while Kruskal–Wallis and Mann–Whitney U tests were applied. A p-value ≤ 0.05 was considered statistically significant.

Results: COVID-19-infected individuals had significantly lower serum testosterone levels, particularly in the four-month post-COVID group (Group B: 4.48 ± 2.56) compared with the one-

year post-COVID group (Group C: 5.17 ± 2.78) and controls (Group A: 6.57 ± 1.50). Luteinizing hormone levels were significantly elevated in the four-month post-COVID group (8.03 ± 3.42) compared with the control group (3.99 ± 1.05) and the one-year post-COVID group ($p < 0.05$).

Conclusion: Recent COVID-19 infection is associated with transient disruption of testosterone biosynthesis accompanied by elevated luteinizing hormone levels. Hormonal recovery is evident over time, with near-normal testosterone and LH levels observed at one year post-infection, indicating that COVID-19-related male reproductive endocrine dysfunction is largely reversible.

Keywords: COVID-19, Testosterone, Luteinizing Hormone, Male Reproductive Health

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first emerged in late 2019 and rapidly evolved into a global public health crisis [1]. Although initially recognized as a predominantly respiratory illness, COVID-19 is now well established as a multisystem disease with significant extrapulmonary manifestations, including cardiovascular, neurological, and endocrine involvement [2]. The endocrine system has received increasing attention due to the widespread expression of viral entry receptors in hormone-producing tissues. SARS-CoV-2 gains cellular entry through angiotensin-converting enzyme-2 (ACE2) receptors, which are abundantly expressed in several organs, including the testes [3]. This raises important concerns regarding potential disruption of male reproductive function following COVID-19 infection.

Experimental and clinical evidence indicates that ACE2 receptors are highly expressed in Leydig and Sertoli cells, rendering the testes particularly susceptible to direct viral injury [4]. Disruption of testicular steroidogenesis following SARS-CoV-2 infection has been proposed as a key mechanism leading to alterations in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels [5]. Several clinical studies have reported significantly reduced serum testosterone concentrations in men with acute or recent COVID-19 infection, often accompanied by elevated gonadotropin levels, suggesting primary testicular dysfunction [6,7].

Beyond the acute phase, persistent endocrine abnormalities have also been documented. Long-term follow-up studies have shown that hormonal imbalance, particularly low testosterone levels, may persist for several months after recovery from COVID-19 [8]. Time-dependent analyses demonstrate that hormonal disruption is more pronounced during the early post-COVID period, with gradual improvement over time [9]. Elevated LH levels in the presence of reduced testosterone have been interpreted as evidence of compensatory pituitary response secondary to Leydig cell impairment [10]. Additionally, age has been suggested as an important modifying factor, with middle-aged and older men showing delayed or incomplete hormonal recovery compared to younger individuals [11]. These findings collectively indicate that SARS-CoV-2 infection can disrupt the hypothalamic–pituitary–gonadal axis, with recovery patterns varying over time.

Despite growing evidence of COVID-19–related disturbances in male reproductive hormones, most available studies focus on either the acute phase or short-term follow-up. There is limited comparative data evaluating hormonal status at distinct post-infection intervals, particularly between early recovery (approximately four months) and longer-term recovery (around one year). Furthermore, the relationship between age and post-COVID hormonal recovery remains inconsistently reported. The absence of time-stratified analyses limits a clear understanding of whether COVID-19–associated hypogonadism is transient or persistent.

Clarifying the temporal pattern of reproductive hormonal changes following COVID-19 infection is essential for clinical counseling, follow-up planning, and early identification of men at risk for prolonged endocrine dysfunction. Understanding whether hormonal disturbances resolve spontaneously or persist over time has important implications for fertility assessment and endocrine management. A comparative evaluation across defined post-COVID time points can provide clinically relevant insights into recovery dynamics of the male reproductive endocrine axis.

This study was conducted to determine whether COVID-19 infection is associated with short-term (four-month) and long-term (one-year) alterations in male reproductive hormone profiles. Specifically, it aimed to assess the pattern of hormonal recovery by comparing serum luteinizing hormone and testosterone levels between four-month and one-year post-COVID groups, and to analyze the relationship between age and reproductive hormonal parameters across all participants.

MATERIALS AND METHODS

This cross-sectional comparative study was conducted on 90 male participants aged 25 to 57 years. The study population was divided into three equal groups ($n = 30$ each) based on COVID-19 infection status and duration since recovery. Group A (control group) comprised healthy males with no history of COVID-19 infection. Group B (post-COVID one-year group) included males who had recovered from laboratory-confirmed COVID-19 infection in 2022, while Group C (post-COVID four-month group) consisted of males who had recovered from COVID-19 infection within the past four months (2023).

Participants were recruited after obtaining ethical approval and informed consent. Individuals with a history of chronic systemic illnesses, including diabetes mellitus, malignancy, chronic renal or hepatic disease, known hormonal disorders, or those receiving testosterone therapy or other hormonal medications were excluded to minimize confounding effects. COVID-19 infection status was verified through patient-reported reverse transcription polymerase chain reaction (RT-PCR) test results and/or available medical records documenting prior infection.

For hormonal assessment, venous blood samples were collected in the morning hours to minimize diurnal variation in hormone secretion. Blood was drawn under standardized aseptic conditions from the antecubital vein. Serum was separated by centrifugation and analyzed in a certified clinical laboratory. Serum concentrations of luteinizing hormone (LH) and testosterone were measured using standardized laboratory techniques, following manufacturer-recommended protocols and quality control procedures.

DATA ANALYSIS

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. Continuous variables were assessed for normality using the Shapiro–Wilk test. As hormonal variables did not follow a normal distribution, they were expressed as Mean $\pm$ SD. Comparisons among the three study groups (control, four-month post-COVID, and one-year post-COVID) were performed using the Kruskal–Wallis test. Where a statistically significant difference was observed, Mann–Whitney U test was applied for post-hoc pairwise comparisons.

Correlation between age and hormonal parameters (luteinizing hormone and testosterone), as well as between luteinizing hormone and testosterone levels, was assessed using Spearman's rank correlation coefficient. A p -value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1 shows that the mean age of participants was comparable across groups. The median age of participants did not differ significantly among the three groups, indicating that age was not a confounding variable.

Table 1: Descriptive Statistics (Mean $\pm$ SD) of Age, LH, and Testosterone Across Study Groups			
Group	Age Mean $\pm$ SD	LH Mean $\pm$ SD	Testosterone Mean $\pm$ SD
Control (A)	36.57 $\pm$ 8.05	3.99 $\pm$ 1.05	6.57 $\pm$ 1.50
Post-COVID 4 Months (B)	35.90 $\pm$ 8.07	8.03 $\pm$ 3.42	4.48 $\pm$ 2.56
Post-COVID 1 Year (C)	38.03 $\pm$ 8.00	5.72 $\pm$ 3.59	5.17 $\pm$ 2.78

Table 2: Pairwise Mann–Whitney U Test Results for LH and Testosterone Across Study Groups

Hormone	Comparisons	U Value	p Value	Interpretation
LH	Control vs 4 Months	114.0	4.36×10^{-7}	Highly Significant ($p < 0.001$)
	Control vs 1 Year	428.5	0.754	Not Significant
	4 Months vs 1 Year	636.0	0.0058	Significant ($p < 0.01$)
Testosterone	Control vs 4 Months	654.5	0.0022	Significant ($p < 0.01$)
	Control vs 1 Year	551.0	0.132	Not Significant
	4 Months vs 1 Year	313.0	0.0415	Significant ($p < 0.05$)

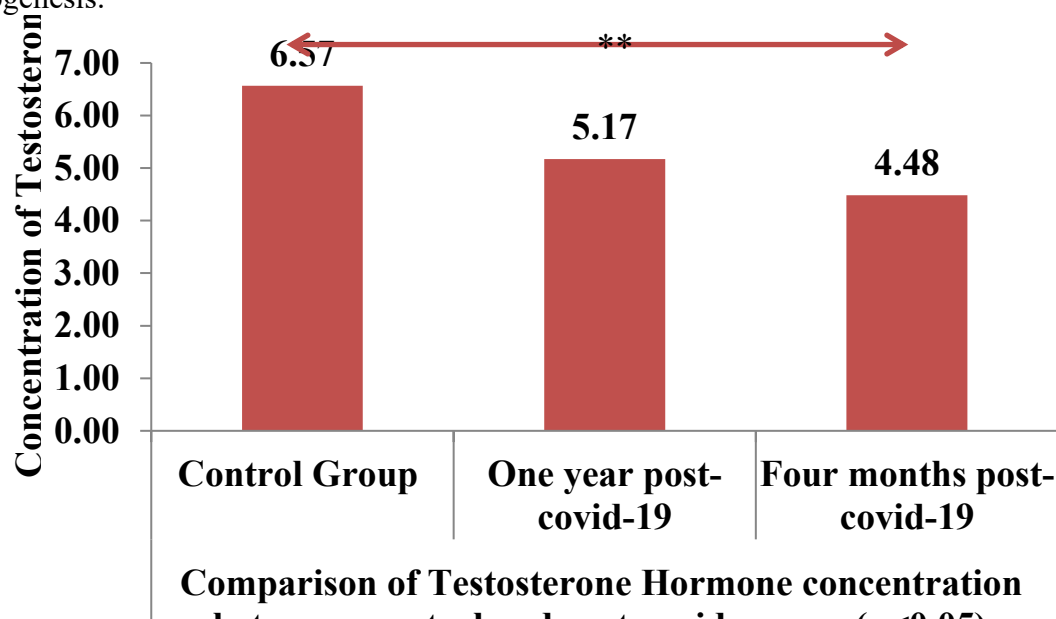
Table 2 depicts that serum luteinizing hormone levels showed a highly significant difference across groups ($p < 0.001$). The four-month post-COVID group demonstrated markedly elevated LH levels compared to both the control and one-year post-COVID groups. LH levels in the one-year post-COVID group approached those observed in controls, indicating recovery of pituitary–gonadal axis function.

Table 3: Overall (Kruskal–Wallis) and Post-hoc (Mann–Whitney U) Comparison of Age and Hormonal Variables Across Groups			
A) Kruskal–Wallis Overall Comparison			
Variable	H Statistic	p-value	Interpretation
Age	1.456	0.483	Not significant
LH	21.166	0.0001	Highly significant
Testosterone	10.505	0.005	Significant
B) Post-hoc Mann–Whitney U Pairwise Comparisons LH			
Group Comparison	U Value	p-value	Interpretation
Control vs 4 Months	114.0	0.0001	Highly significant
Control vs 1 Year	428.5	0.754	Not significant
4 Months vs 1 Year	636.0	0.001	Significant
C) Post-hoc Mann–Whitney U Pairwise Comparisons Testosterone			
Group Comparison	U Value	p-value	Interpretation
Control vs 4 Months	654.5	0.001	Significant
Control vs 1 Year	551.0	0.132	Not significant
4 Months vs 1 Year	313.0	0.05	Significant

Table 3 shows that serum testosterone levels also differed significantly among groups ($p < 0.001$). The four-month post-COVID group exhibited significantly reduced testosterone levels compared to controls. Testosterone levels in the one-year post-COVID group showed partial normalization, being significantly higher than the four-month group but slightly lower than controls.

Table 4: Spearman Correlation Between Age, LH, and Testosterone Among Study Participants			
Variable Pair	Spearman r	p-value	Interpretation
Age ↔ LH	0.12	0.28	No significant correlation
Age ↔ Testosterone	−0.19	0.05	Weak negative trend (not significant)
LH ↔ Testosterone	−0.43	0.001	Moderate negative correlation (significant)

Correlation analysis revealed no significant association between age and LH or testosterone levels (Table 4). A moderate, statistically significant inverse correlation was observed between LH and testosterone, suggesting compensatory pituitary activity in response to reduced testicular steroidogenesis.



DISCUSSION

The present study evaluated the temporal effects of COVID-19 infection on male reproductive hormones and demonstrated significant, time-dependent alterations in luteinizing hormone (LH) and testosterone levels. The most pronounced hormonal disturbances were observed in males assessed four months after recovery from COVID-19, while partial normalization was evident in individuals evaluated one year post-infection. These findings support the concept that COVID-19 induces transient disruption of the hypothalamic–pituitary–gonadal (HPG) axis, with gradual endocrine recovery over time.

In the current study, males evaluated four months after COVID-19 infection exhibited significantly reduced serum testosterone levels accompanied by elevated LH concentrations. This hormonal pattern is indicative of primary testicular dysfunction with compensatory pituitary overactivity. Similar findings have been reported in earlier studies. Salonia et al. observed suppressed testosterone levels with concomitant elevation of LH in men shortly after COVID-19 infection, suggesting Leydig cell impairment rather than central hypogonadism [6]. Dhindsa et al. also reported significantly lower testosterone levels in COVID-19 patients, which correlated with systemic inflammatory markers, reinforcing the link between inflammation and impaired steroidogenesis [7]. These findings closely parallel the early post-COVID hormonal disturbances observed in the present study.

The biological plausibility of COVID-19-related testicular dysfunction is supported by molecular and histopathological evidence. SARS-CoV-2 enters host cells via angiotensin-converting enzyme-2 (ACE2) receptors, which are highly expressed in Leydig and Sertoli cells [4]. This receptor distribution renders the testes vulnerable to direct viral injury. Additionally, inflammatory cytokine release, oxidative stress, fever, and microvascular damage during COVID-19 may further impair Leydig cell function and testosterone biosynthesis. Achua et al. demonstrated inflammatory infiltration and structural damage in testicular tissue of deceased COVID-19 patients, providing histological confirmation of testicular involvement [12]. These mechanisms collectively explain the elevated LH and suppressed testosterone levels observed during early recovery in the present cohort. An important finding of this study is the evidence of hormonal recovery at one year post-COVID-19 infection. LH levels showed significant reduction and approached values observed in the control group, while testosterone levels demonstrated partial normalization. These results suggest

progressive restoration of testicular endocrine function over time. Similar recovery patterns have been reported in longitudinal studies. Carnegie et al. documented improvement in testosterone levels within 8–12 months following COVID-19 infection, indicating that COVID-related hypogonadism is often reversible [13]. Gacci et al. also reported recovery of testicular function in a substantial proportion of men one year after infection [14]. Richer et al. demonstrated declining inflammatory markers and improving testosterone levels during late recovery phases, further supporting a time-dependent recovery trajectory [15].

The inverse relationship between LH and testosterone observed in this study provides further insight into the underlying endocrine dynamics. A moderate and statistically significant negative correlation between LH and testosterone suggests intact hypothalamic–pituitary feedback mechanisms, with increased LH secretion attempting to compensate for reduced testosterone production. This compensatory pattern has been consistently reported in post-COVID studies. Dutta et al. observed elevated LH levels in men with persistently low testosterone during early recovery, highlighting compensatory pituitary activation [16]. Klein et al. demonstrated that COVID-19 is associated with sex-specific endocrine dysregulation, including suppression of testosterone with compensatory gonadotropin responses, supporting the concept that post-COVID reproductive hormonal disturbances are predominantly due to primary testicular involvement rather than central hypothalamic–pituitary dysfunction [17]. Age was evaluated as a potential confounding factor in hormonal recovery. In the present study, age did not show a significant association with luteinizing hormone or testosterone levels. This finding contrasts with earlier evidence suggesting delayed or incomplete endocrine recovery in older men following COVID-19 infection. Cinislioglu et al. and Pozzilli et al. reported that advancing age was associated with more pronounced testosterone suppression and slower recovery of gonadal function after COVID-19, indicating increased vulnerability of Leydig cells in older males [18, 19]. The absence of a significant age effect in the current study may be attributed to the relatively narrow age range of participants and exclusion of individuals with chronic comorbidities known to affect hormonal status.

CONCLUSION

Overall, the findings of this study add to the growing body of evidence indicating that COVID-19-related male reproductive endocrine dysfunction is most pronounced during early recovery and improves over time. The demonstration of partial hormonal recovery at one year supports the concept that COVID-19-associated hypogonadism is largely transient in many individuals. However, persistent subclinical abnormalities in some patients highlight the importance of long-term follow-up.

Future studies should incorporate semen analysis, sperm DNA fragmentation testing, and testicular imaging to better characterize the functional implications of hormonal disturbances. Additionally, evaluating the impact of disease severity, vaccination status, and comorbid conditions may further clarify recovery trajectories and identify men at risk of prolonged reproductive dysfunction.

Conflict of Interest

Authors declare that they have no conflict of interest.

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