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SYSTEMATIC REVIEW

Effect of SARS-CoV-2 viral infection on male sexual hormones levels post COVID-19 exposure: A systematic review and meta-analysis

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Summary ***Introduction: The COVID-19 can affect human testicles, thus will interfere the production of important male sexual hormone such as testosterone. Our study provides scientific evidence through systematic reviews and meta-analyses that focus on the effects of SARS-CoV-2 virus infection on male sexual hormonal disorders in patients post-exposure to COVID-19.***

Methods: This meta-analysis was made in accordance with the PRISMA guidelines. The outcomes of this study were the level of total testosterone, free testosterone, LH and FSH. Chi-square and I^2 tests were used to evaluate heterogeneity between studies. The standardized mean deviation (SMD) with 95% CI were used and analysis was performed using the Review Manager 5.4 software.

Results: The four included studies reported a total of 256 patients with COVID-19 with time of follow-up time post COVID-19 varying from one month to 7 months. The mean age distribution in the study was 34-57 years old. Total testosterone level (SMD = -158.71; 95% CI= -205.30 – -112.12; p < 0.00001) was significantly higher at follow-up post COVID-19, while LH (SMD = 0.40; 95% CI = 0.15-0.65; p = 0.002) was lower. The free testosterone level and FSH level showed no significant difference between baseline and after following up post COVID-19.

Conclusions: At follow up, the total testosterone level in patients with SARS-CoV-2 infection appeared to be elevated while LH was lower compared to the baseline.

KEY WORDS: *COVID-19; Male sexual hormones; Total testosterone; Free testosterone; Luteinizing hormone; Follicle stimulating hormone.*

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INTRODUCTION

Coronavirus disease, known as COVID-19, is an acute respiratory syndrome caused by coronavirus type-2 or SARS-CoV-2. As of 2021, there have been approximately 200 million COVID-19 infections worldwide, resulting in more than 4 million deaths (1). Although many people with COVID-19 infection are asymptomatic or have very mild symptoms, a small number of patients develop severe symptoms and potentially long-term consequences. COVID-19 has been linked to more than 50 long-term side effects, such as impact to the blood vessels, heart, lungs, kidneys, and brain. Also it was just discovered to have an effect on human testes, interfering with the production of vital male hormones such as testosterone (2).

As a result of SARS-CoV-2 virus infection, systemic or local cytokine synthesis has the potential to inhibit Leydig cell differentiation, thereby compromising testicular cells by affecting testosterone production and the process of spermatogenesis (3). This inflammatory process was further identified in the testicles of six males who died from SARS-CoV-2 (4). This study focused on total testosterone since it is one of the easiest and basic male sexual hormone parameters to measure with acceptable precision in most hospital laboratories. Furthermore, the impact of lower testosterone is becoming an issue when there is concern regarding the long-term impact of the SARS-CoV-2 virus on decreased sexual desire and impaired male fertility. Other characteristics, such as free testosterone, *Luteinizing Hormone* (LH), and *Follicle Stimulating Hormone* (FSH), were included in the study as supporting data to better understand the pattern of male sexual hormone alterations.

There is still no consensus or global agreement regarding the management of sexual and hormonal disorders after COVID-19 infection. Therefore, researchers are interested in providing scientific evidence through a systematic review and meta-analysis focusing on the effects of SARS-CoV-2 virus infection on male sexual hormonal abnormalities in patients after exposure to COVID-19.

MATERIALS AND METHODS

Protocol registration

The protocol of this systematic review and meta-analysis is registered at PROSPERO (CRD42023445406)

Search strategy and study selection

This meta-analysis was made in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) guidelines (5). The review topic was determined based on *Population, Intervention, Comparison, Outcome* (PICO) methods. The population was male over 18 years old without country or race restrictions. The

intervention was condition on when admitted for COVID-19 (baseline). The comparison was condition on follow up after COVID. The outcomes were total testosterone levels, free testosterone, LH and FSH. The inclusion criteria for studies were: (1). Observational study, (2). Studies that report the level of total testosterone and at least one of free testosterone, LH, and FSH level at baseline and follow up in patients with SARS CoV-2. Studies that were case reports, conference abstracts, reviews, editorials letters, not available in full text as well as non-English studies were omitted. The systematic search was carried out across *PubMed*, *Scopus*, *ScienceDirect*, *Web of Science*, and grey literature. The keywords used to search are "*COVID*", "*SARS-CoV-2*", "*COVID-19*", "*Corona virus*", "*Testosterone level*", "*Androgen*", "*FSH*", "*Follicle Stimulating Hormone*", "*LH*", "*Luteinizing hormone*", "*Free Testosterone*".

Quality assessment and data extraction

Two authors worked independently to extract data by filling out tabulation templates that had been produced in advance of time. When there are disputes during data extraction, the ultimate choice will be discussed with the senior author. The data obtained comprises study characteristics (first author's name, year of publication, sample size, study design, range data collection), and basic characteristics of the research sample (age, severity of covid, follow-up range, laboratory outcome, and sexual function outcome). The risk of bias was determined using the *Newcastle Ottawa Scale* (NOS), with a score of 7-9 indicating a low risk of bias, 4-6 suggesting a high risk of bias, and 0-3 indicating a very high risk of bias.

Statistical analysis

Data analysis was performed using the Review Manager 5.4 software. The outcomes of this study were the level of total testosterone, free testosterone, LH and FSH. Chi-square and I^2 tests were used to evaluate heterogeneity between studies. The random-effects model analysis was applied if the heterogeneity test was high (I^2 test > 50% and chi-square $p < 0.05$). If the heterogeneity test was low (I^2 < 50%, chi-square $p > 0.05$), the fixed-effect model analysis was used. The pooled *standardized mean and deviation* (SMD) with 95% CI were used to perform the analysis on continuous data i.e., testosterone level, free testosterone, LH and FSH. If there is Median (IQR) or Median (Range) data, it will be converted to Mean ± SD with Median (Range) using scenario 1 and Median (IQR) using scenario 2 from the following online calculator https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html. Studies featuring Mean ± SD data that have been stratified by COVID-19 severity will be combined with the following online calculator https://www.statstodo.com/ CombineMeansSDs.php. The results are significant when the P value < 0.05.

Results

The results of a systematic search for studies using predetermined keywords identified a total of 606 studies in five databases, namely *PubMed/MEDLINE*, *Scopus*, *ScienceDirect*, *Web of science*, and grey literature. The number of studies found in each database can be seen in Figure 1. All these studies were then checked for duplication, resulting in 287 duplicate studies. Selection was then carried out on 319 studies by reading titles and abstracts, as many as 15 articles that met the criteria and selection continued by reading the full text. The result obtained four studies that met the inclusion criteria and were included in the systematic review of meta-analysis. The four cohort studies revealed a total of 356 COVID-19 patients (6-9). These studies are carried out in a variety of nations, including Italy, Turkey, Russia, and Iran. The first study was conducted in February 2020. At the time of the study,

Figure 1.
PRISMA diagram of the study search and selection process.

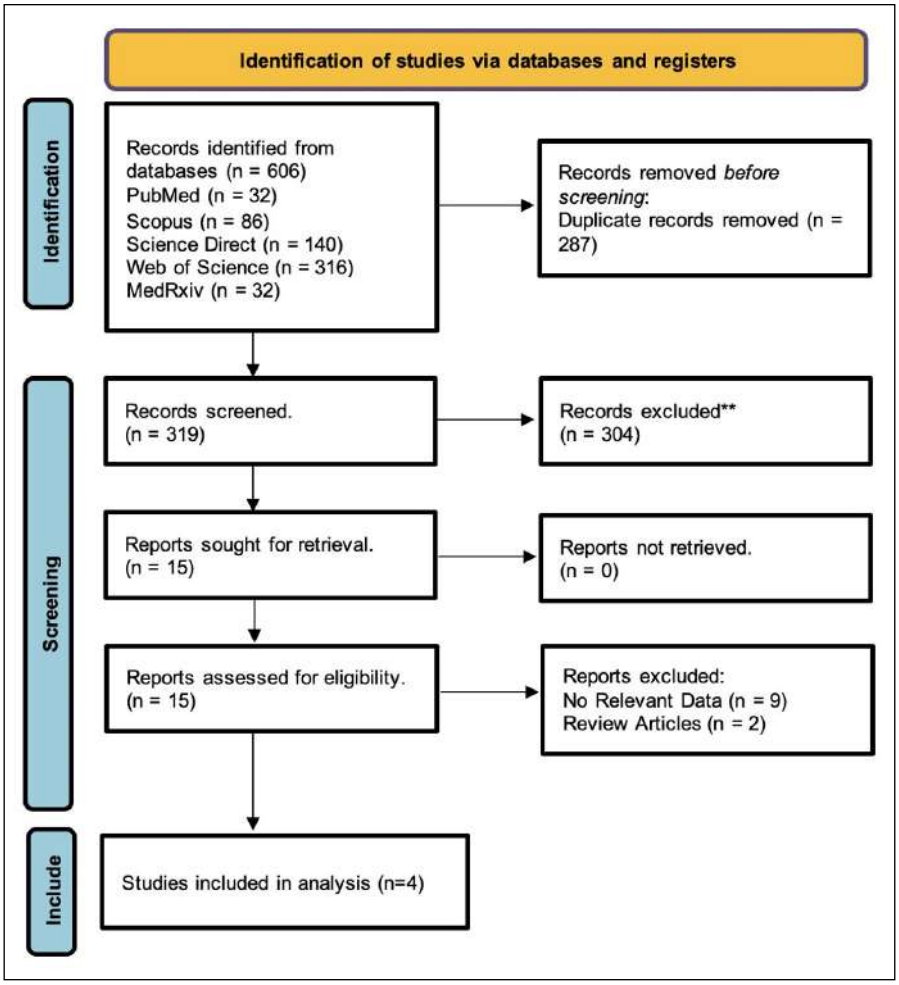


Table 1.
Basic characteristics of the study.

No.	Author (year)	Data collection	Country	Design	N	Covid severity	Follow-up	Age (years) Mean ± SD	Laboratory Outcome	Sexual Function Outcome
1.	*Salonia et al. (2022)* (6)	February 29 - May 2, 2020	Italy	Cohort	121	NR	7 months	57 ± 12	WBC, neutrophils, lymphocytes, NLR, creatinine, CRP, IL-6, FSH, LH, tT	NR
2.	*Apaydin et al. (2022)* (7)	April - October 2020	Turkey	Cohort	29	NR	6 months	43.3 ± 28.6	FSH, LH, tT, fT, Bioavailable testosterone, SHBG, lymphocyte, thrombocyte, creatinine, ALT, KDH, ferritin, D-dimer	NR
3.	*Enikeev et al. (2022)* (8)	NR	Russia	Prospective	44	NR	3 months	46.7±9.9	Testosterone, prolactin, LH, FSH	IIEF-5
4.	*Afshari et al. (2022)* (9)	July 2020 - February 2021	Iran	Prospective	162	Severe, moderate	1 month	39.88 ± 7.04	LH, FSH, tT, fT	NR
Total sample size					**356**					

NR: Not reported; tT: Total testosterone; fT: Free testosterone; WBC: White Blood Cell; NLR: Neutrophil Lymphocyte Ratio; SHBG: Sex Hormone Binding Globulin; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; IL-6: Interleukin-6; CRP: C-reactive protein; IIEF-5: The International Index of Erectile Function 5.

Table 2.
Characteristic of study Outcomes.

No.	Author (year)	Data collection	Group	N	Total testosterone (ng/dL)	Free testosterone (ng/dL)	LH (mIU/L)	FSH (mIU/L)	IIEF
1.	*Salonia et al. (2022)* (6)	February 29 - May 2, 2020	Baseline	121	86 ± 76	NR	5 ± 2.1	6.01 ± 3.37	NR
			Follow-up 7 months	121	289.28 ± 144.21	NR	4.3 ± 2.25	8.2 ± 3.9	NR
2.	*Apaydin et al. (2022)* (7)	April - October 2020	Baseline	29	273.25 ± 175.8	7.74 ± 5.32	9.06 ± 7.77	9.06 ± 7.77	NR
			Follow-up 6 months	29	349.5 ± 164.5	7.18 ± 2.8	11.1 ± 14.6	5.01 ± 2.44	NR
3.	*Enikeev et al. (2022)* (8)	NR	Baseline	44	210.54 ± 77.87	NR	3.3 ± 0.5	5.1 ± 1.11	20.7 ± 5.3
			Follow-up 3 months	37	395.13 ± 129.84	NR	2.975 ± 0.76	5.05 ± 1.32	23.1 ± 4.3
4.	*Afshari et al. (2022)* (9)	July 2020 - February 2021	Baseline	162	124 ± 84	5.14 ± 2.94	7.02 ± 4.83	4.08 ± 2.16	NR
			Follow-up 1 month	69	259 ± 111	4.76 ± 2.19	6.55 ± 5.48	5.89 ± 3.4	NR
Total Sample Size			**Baseline**	**356**					
			Follow-up	**256**					

NR: Not reported.

Table 3.
Quality assessment of the study New Ottawa-Scale (NOS).

Author (year)	Study design	Selection	Comparability	Outcome	Total
Salonia et al., 2022	Cohort	***	**	***	8
Enikeev et al., 2022	Cohort	***	**	***	8
Apaydin et al., 2022	Cohort	***	**	***	8
Afshari et al., 2022	Cohort	***	**	**	7

participants ranged in age from 34 to 57 years old. The reported follow-up time spans from one month to seven months. Tables 1 and 2 indicate the features of the studies. Newcastle Ottawa Scale was used to measure the quality of the studies. Table 3 shows the quality assessment results, which found three studies with a total score of 8 and one studies with a total score of 7 that were considered to have low risk of bias.

Mean total testosterone level

Analysis of four studies reporting testosterone level on COVID-19 showed a significant difference between total testosterone level on baseline and after following up (pooled SMD = -158.71; 95% CI = -205.30 - -112.12; $p < 0.00001$) (6-9). The total testosterone level appears to be lower at baseline.
The forest plot for total testosterone level is provided in Figure 2.

Mean free testosterone level

Analysis of two studies reporting free testosterone level on

Figure 2.
Forest plot of mean total testosterone level.

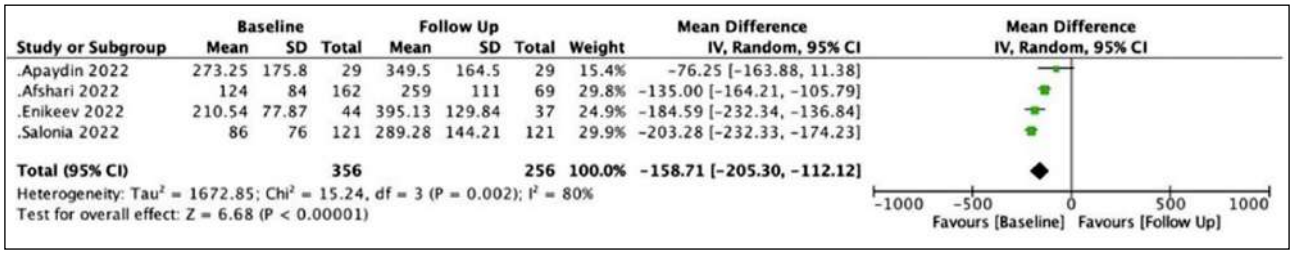


Figure 3.
Forest plot of mean free testosterone level.

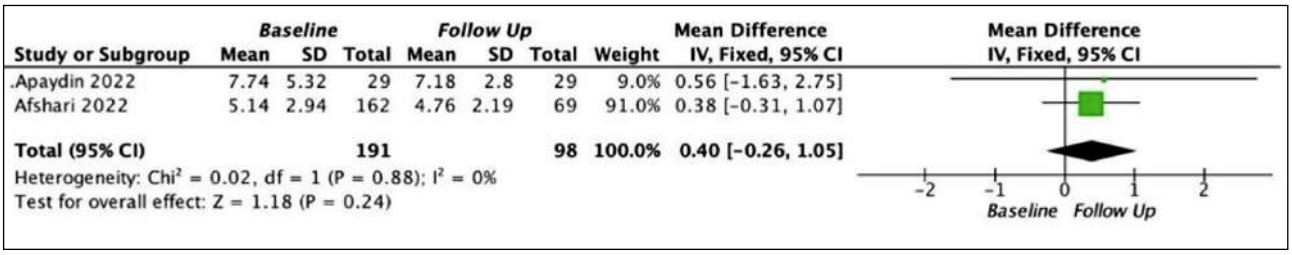


Figure 4.
Forest plot of mean luteinizing hormone level.

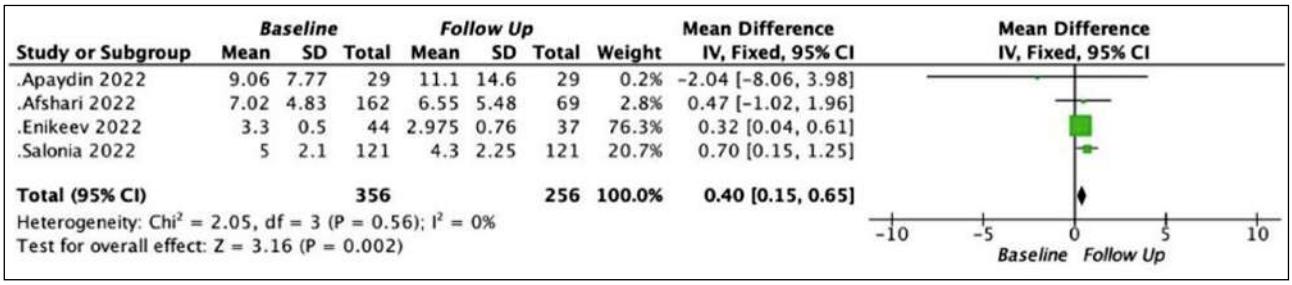
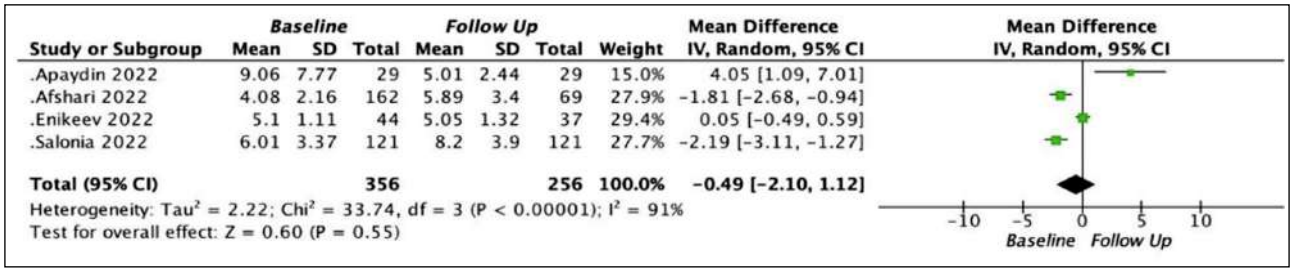


Figure 5.
Forest plot of mean follicle stimulating hormone level.



COVID-19 showed no significant difference between free testosterone level on baseline and after following up (pooled SMD = 0.40; 95% CI = -0.26-1.05; p = 0.24) (7, 9). The forest plot for testosterone level is provided in Figure 3.

Mean luteinizing hormone level

Analysis of four studies reporting LH level on COVID-19 showed a significant difference between LH level on baseline and after following up (pooled SMD = 0.40; 95% CI = 0.15-0.65; p = 0.002) (6-9). The forest plot for LH level is provided in Figure 4.

Mean follicle stimulating hormone level

Analysis of four studies reporting FSH level on COVID-19 showed no significant difference between FSH level on baseline and after following up (pooled SMD: -0.49; 95% CI = -2.10-1.12; p = 0.55) (6-9). The forest plot for LH level is provided in Figure 5.

Discussion

This study is the first systematic review and meta-analysis to compare male sexual hormone levels in patients with COVID-19 when the SARS-CoV-19 virus was first detected and at follow-up after a negative COVID-19 PCR swab. Four studies were meta-analyzed with a total baseline sample of 356 patients and 256 patients at follow-up with reported follow-up times ranged from 1 month to 7 months. The parameters studied were total testosterone, free testosterone, *Luteinizing Hormone* (LH), and *Follicle Stimulating Hormone* (FSH) levels as Mean ± SD.

ACE-2 receptors are abundant in testicular tissue. As a result, it is hypothesized that SARS-CoV-2 infection may cause testicular tissue injury, which may lead to impaired sexual function and fertility in men. The primary endpoint of this study is the change in total testosterone because it is one of the easiest and simplest male sexual hormone parameter measured with good accuracy in most hospital laboratories. Furthermore, the impact of lower testosterone is concerning given the long-term impact of the SARS-CoV-2 virus on decreased libido levels and impaired male fertility. Changes in free testosterone levels, *Luteinizing Hormone* (LH) levels, and *Follicle Stimulating Hormone* (FSH) levels were secondary outcomes of this study. The resulting decrease in testosterone levels may lead to dysregulation of GnRH production in the hypothalamus followed by abnormal secretion of LH and FSH from the pituitary. These results indicate

a decrease in peripheral organ function and a compensatory increase in central function (29).

Total testosterone

The four studies meta-analyzed in this study showed significant differences in total testosterone levels between baseline and follow-up. At follow up, total testosterone levels in individuals with SARS-CoV-2 infection appeared to be higher in relation to the baseline.

This study also found that the testosterone levels of patients who served as baseline data in this study were below the normal range. Most (95%) testosterone is produced in the Leydig cells of the testes depending on stimulation by LH. Only a small amount (5%) is produced in the adrenal glands. Low testosterone levels can originate from the testes (primary hypogonadism), hypothalamus-pituitary (secondary hypogonadism), or a combination of both, which is mostly found in the aging male population as late onset hypogonadism (30). In patients with COVID-19, the increase in gonadotropin concentration as a form of central function compensation may be insufficient because SARS-CoV-2 virus infection may also disrupt homeostatic and cause HPG axis feedback failure (29).

The influence of testosterone levels in men on COVID-19 prognosis is currently the focus of attention in several research literatures. Suppressive effects on the gonadal axis through inflammatory mediators, decreased testicular response to gonadotropins, and increased metabolic clearance rate of testosterone have been described as potential causes of lower testosterone concentrations during acute illness due to the SARS-CoV-2 virus (31).

Total testosterone levels can be a prognostic factor of disease severity as low testosterone levels are associated with a high risk of intensive care unit admission and death (10). When there is a decrease in total testosterone levels, the probability of death increases significantly (11). The more severe the comorbidities at the time of treatment, the less likely testosterone levels are to improve over time. In general, testosterone has immunosuppressive effects. Testosterone activates CD8 cells and increases T-helper 1 responses while decreasing natural killer cell responses by decreasing TNF-α and increasing anti-inflammatory IL-10 production (13). Therefore, a poor prognosis in COVID-19 patients with low testosterone is predictable. However, the *Salar et al.* study found no significant difference between testosterone levels before the disease in the mild and moderate COVID-19 groups. Possible reasons for this are that severe symptomatic cases were previously excluded and the low number of patients in the study (12).

The gradual recovery of total testosterone levels also indicated progressive recovery from the severe multisystemic symptoms associated with COVID-19 (10). The study by *Xu H et al.* also found improvements in testosterone levels that can even reach the normal range during recovery from COVID-19 (14). The recovery of physiological testosterone levels can occur as lymphocyte and neutrophil homeostasis returns, this is also related to old age factors, with or without comorbidities that may affect the ability of some COVID-19 patients to restore testosterone production (13). Thus, the discovery of an upward trend in testosterone levels at follow-up suggests the effect of this decrease in testosterone levels is reversible.

Free testosterone

The meta-analysis of the two studies in this study did not find any significant changes in baseline and follow-up free testosterone levels. This could be due to the number of studies that could be meta-analyzed only 2 studies with a small sample size and did not include all degrees of COVID-19.

Free testosterone levels are decreased in COVID-19 patients. Some studies found a significant association between free testosterone levels and the risk of ICU care or death. Together with total testosterone, free testosterone levels were significantly associated with higher serum levels of LDH, ferritin, procalcitonin, as well as increased neutrophil levels and decreased lymphocyte counts. Such inflammatory biomarkers are poor prognostic factors for SARS-CoV-2 infection (15). In the *Van Zeggeren et al.* study, free testosterone levels were significantly lower in patients with severe COVID-19 and in patients who died from severe COVID-19 compared to those who survived. SHBG levels were also associated with the outcome of patients treated with COVID-19 (16). Like total circulating testosterone, free testosterone levels were significantly decreased in severe patients compared to the mild-moderate group (13).

SHBG levels are also associated with the outcome of patients treated with COVID-19 Hypoalbuminemia occurs due to increased vascular permeability and capillary leakage is common in critically ill patients and similar mechanisms can lead to low albumin, or CBG concentrations (16). In addition, serum levels of SHBG, the most widely circulated testosterone-binding protein, showed a significant association with older age in mild-moderate patients, but not in severe patients (13). With age, SHBG levels also increase, causing a decrease in bioavailable testosterone and free testosterone, which affects androgenic activity (20). In COVID-19 patients, SHBG levels were also found to be elevated (30). Thus, in some cases, a decrease in testosterone levels can be caused by an increase in SHBG levels. It takes a decrease in bioavailable testosterone levels or a significant increase in SHBG levels to produce a significant decrease in free testosterone levels (30).

Luteinizing Hormone and Follicle Stimulating Hormone

This meta-analysis study conducted on 4 studies found significant changes in LH levels between baseline and follow-up. There was a decrease in LH levels at follow-up. A possible mechanism is that the SARS-CoV-2 virus enters cells through the ACE-2 receptor which is found in many testicular Leydig cells that regulate testosterone through the conversion of Angiotensin II to Angiotensin 1-7 increasing LH levels (7). Elevated serum LH levels indicate primary hypogonadism and testicular failure, rather than secondary causes so this condition is more likely to be influenced by a severe inflammatory state (32). When the inflammatory condition improves characterized by the return of lymphocyte and neutrophil homeostasis, accompanied by the restoration of physiological testosterone levels, according to the negative feedback mechanism of the HPG axis, there will be a decrease in LH and FSH levels (13). However, FSH levels were found to be insignificant. These inconsistent results may be due to the small number of samples, the follow-up time of each

study and the varying age ranges of research subjects and the varying degrees of severity of COVID-19. In their study, *Salar et al.* also found no significant difference between FSH or LH hormone levels before and after exposure to COVID-19 in mild or moderate degree groups (12). This could be due to previous exclusion of cases with severe symptoms and the low number of patients in the study (12).

The elevated levels of circulating LH and FSH reported in COVID-19 cases may indicate transient activation of GnRH due to the initial inflammatory response (3). This compensatory process by LH against decreased testosterone levels is also significantly higher in COVID-19 patients compared to healthy men (21). High luteinizing hormone indicates loss of peripheral organ function and compensatory increase in central function (19). SARS-CoV-2 virus has been shown to alter the hypothalamic-pituitary-testis axis, increasing LH and FSH levels in men by suppressing the HPG axis. According to *Cayan et al.'s* study, blood concentrations of LH and FSH increased with the severity of COVID-19. FSH levels were found to be significantly higher in the ICU group compared to the asymptomatic group (11).

In addition to direct damage to the testes by the virus, other factors such as fever, inflammation, and dysregulation of the HPG axis may also play a role in testosterone secretion or sperm production (19). Hypothalamic and pituitary tissues also express ACE-2 receptors and therefore could be targets of the SARS-CoV-2 virus. Low testosterone with normal or low gonadotropins may be caused by the combined effects of COVID-19 on the hypothalamus-pituitary-testis axis and on the testes 7, (13). In addition, emotional, physical, or psychological stress and pain associated with infection may affect the hypothalamic-pituitary axis causing abnormalities in the rhythm of LH secretion (19).

COVID-19 treatment

Medications given to COVID-19 patients in the general ward or ICU can alter sexual hormone levels such as corticosteroids, anticoagulant drugs, and antiviral drugs such as Remdesivir (26). Animal studies have found that antiviral drugs such as ribavirin (the treatment of choice for COVID-19) can induce oxidative stress, lower testosterone levels, and severely impair spermatogenesis (4). A considerable decrease in sperm count was observed upon ribavirin treatment. In addition, sperm DNA fragmentation was found up to 8 months even after discontinuation of such treatment.

Glucocorticoid treatment is also given to patients who must be admitted to the ICU, potentially affecting testosterone levels (7). Corticosteroid use and stress-induced hypercortisolism may have a suppressive impact on the hypothalamic-pituitary-Forest plot of mean follicle stimulating hormone levelgonadal axis. Corticosteroids can suppress gonadotropin-releasing hormone in the hypothalamus and may affect the action of pituitary gonadotropin on the testes (27).

Post COVID-19 hypogonadism

The results of the *Paoli et al.* study show that overall andrological health does not appear to be compromised at 3 months after COVID-19 recovery. After a full spermatogenetic cycle of 3 months there was recovery of semen parameters and sperm DNA fragmentation. This suggests no significant long-term impairment and no sperm autoimmune response. Likewise, the hormone profiles of total testosterone, FSH, and LH showed no relevant changes. Ultrasound examination also showed no damage to the testicular parenchyma. These findings reinforce the hypothesis that once clinical recovery occurs, the SARS-CoV-2 virus does not appear to cause direct damage to testicular function, while the impact of indirect damage appears to be transient (28). In the study of *Xu et al.* using more than 50 days as the cutoff for defining long-term positive cases, Authors found no significant relationship between testosterone levels and the severity of COVID-19. This means that although the disease course of these patients is longer, the tissues and organs, especially the testes, can still maintain normal conditions or can return to normal. This may be due to the low virulence, achieved immunity, and adequate compensatory capacity to cope with the long-term impact of the virus (14). Circulating testosterone levels were also found to continue to increase over time in men recovering from COVID-19. However, nearly 30% of men still showed low testosterone levels even after 12 months during the recovery period (10).

Based on observations, this study is the first systematic review and meta-analysis to compare male sexual hormone levels in COVID-19 survivors when the SARS-CoV-19 virus was first detected and at follow-up. This study can also be the basis for rationalizing the provision of testosterone replacement therapy in cases of acute hypogonadism which has the possibility of being reversible in male COVID-19 survivors. Currently, there is no direct evidence to confirm that SARS-CoV-2 causes testicular injury leading to hypogonadism and infertility, but the potential risk cannot be ignored. This study has several limitations. Most of the studies had varying follow-up times, many patients were lost to follow-up, most studies did not include the severity of COVID-19, as well as other presence of factors that may affect hormone levels, such as age, comorbidities, psychological conditions, use of medications such as antivirals, corticosteroids, and glucocorticoids.

Conclusions

There was a significant differentiation in total testosterone levels between the initial COVID-19 and the follow-up. Total testosterone levels in individuals with SARS-CoV-2 infection appeared to be higher relative to the baseline, implying that testosterone would return once the COVID-19 infection is resolved, while LH was lower during follow-up period. There was no statistically significant difference in free testosterone and FSH levels between baseline and follow-up.

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