Late Impact of COVID-19 Pneumonia on Testosterone Levels in Recovered, Post-Hospitalized Male Patients

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Abstract

Background: Recent studies reported lower androgen levels in coronavirus disease 2019 (COVID-19) hospitalized patients which linked to a worse prognosis. However, these studies were conducted in patients with active disease and long-term consequences are still not yet known. Therefore, we aimed to evaluate the late impact of COVID-19 pneumonia on testosterone levels in late recovered, post-hospitalized males.

Methods: We enrolled 55 COVID-19 pneumonia-recovered, post-hospitalized male patients after an average of 60 days of discharge from the hospital and 40 age, body mass index (BMI), and waist-matched participants enrolled in this case-control study. The total testosterone cut-off point was set as 300 ng/dL and the cut-off point for luteinizing hormone (LH) was set as 9.4 IU/L.

Results: Testosterone deficiency prevalence was 50.9%, and testosterone deficiency was mainly hypogonadotropic (60.7%). Late recovered COVID-19 pneumonia patients had significantly lower total testosterone and calculated free testosterone and higher testosterone to LH ratio and prevalence of testosterone deficiency in comparison with the control group. Testosterone-deficient COVID-19 pneumonia patients had significantly higher anthropometric parameters such as waist circumference and BMI, higher Charlson Comorbidity Index, and longer hospitalization time in comparison with testosterone-sufficient patients. Visceral obesity estimated with waist circumference was a significant predictor for total testosterone levels in COVID patients in regression analysis.

Conclusion: Late recovered post-hospitalized COVID-19 pneumonia patients still have lower androgen levels and a higher prevalence of testosterone deficiency in comparison with matched control participants. Moreover, visceral obesity was the most significant predictor of low testosterone levels in recovered COVID-19 patients.

Keywords: COVID-19; Pneumonia; Testosterone; Male; Obesity

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Introduction

On March 12, 2020, World Health Organization (WHO) declared coronavirus disease (COVID-19) a global pandemic. COVID-19 is caused by a previously unknown beta-coronavirus, which is now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its high sequence similarity with SARS-CoV. At the time of finishing this work, it has infected more than 180 million people worldwide and caused nearly 4 million deaths globally. COVID-19 is a systemic disease, affecting the respiratory, cardiovascular, digestive, endocrine, and neurologic systems [1]. Hyper-inflammation and immunosuppression are the prominent features in COVID-19 [2].

Many research had shown that men are more likely to get worse symptoms with higher hospitalization and mortality rate compared to females [3]. Furthermore, sex differences in the prevalence of smoking, drinking habits, and heart diseases do not fully explain the differences between both sexes regarding SARS-CoV-2 infection [4]. Consequently, a potential role for testosterone was hypothesized.

On the other hand, studies have identified angiotensin-converting enzyme 2 (ACE2) as a host cell receptor that SARS-CoV-2 can use to establish an infection and consequently provide a critical link between immunity, inflammation, ACE2, and cardiovascular disease [5]. In the same consent, many studies reported that ACE2 is widely expressed in testicular tissue, Leydig cells, and Sertoli cells [6]. ACE2 is a constitutive product of adult-type Leydig cells and may participate in the control of testicular function [7].

Therefore, the impact of COVID-19 infection on the hypothalamic-pituitary-gonadal axis attracted attention. Recent studies reported lower androgen levels in COVID-19 hospitalized patients which linked to worse prognosis and even fatal outcomes [8, 9]. However, these studies were conducted in patients with active disease and long-term consequences are still not yet known and consequently, the effects of COVID-19 on the male reproductive system are not clarified. So, recovered patients from COVID-19 pneumonia should be evaluated to

detect the late impact of COVID-19 pneumonia on male reproductive hormones levels.

Therefore, in this study we aimed to evaluate the late impact of COVID-19 pneumonia on male reproductive hormones, total testosterone (TT), and luteinizing hormone (LH), in recovered, post-hospitalized males in comparison with matched participants as controls.

Materials and Methods

Fifty-five COVID-19 pneumonia-recovered, post-hospitalized male patients, aged 35 - 65 years (mean age 52.1 ± 7.41 years) after recovery and discharge from governmental isolation hospitals and 40 matched participants according to age, body mass index (BMI) and waist circumference (WC) were recruited in this study from January 2021 to March 2021 in Mansoura General Hospital, Mansoura University, Egypt. The control group was selected from the outpatient clinics of other departments at Mansoura University General Hospital. Our control participant group was treated for other medical disorders. The control group was matched according age and anthropometric parameters including BMI and WC. Our Institutional Research Board at Mansoura Faculty of Medicine reviewed and approved the study protocol (IRB no. R.21.03.1261). The study was conducted in compliance with the Declaration of Helsinki.

Eligibility criteria were patients post-hospitalized and recovered from COVID-19 pneumonia, after discharge from hospital, aged between 18 and 65 years, and male sex. While exclusion criteria were female sex, abnormal albumin levels, acute or chronic liver cell failure, history of the gonadal disease, malignancy, and endocrinal disease affecting testosterone levels (including diabetes mellitus (DM), pituitary disorders particularly hyperprolactinemia, and abnormal thyroid functions), testosterone replacement, medications or diseases that affect testosterone levels such as gonadotropin therapy, and patients on corticosteroid therapy in the last 4 weeks. Hospitalization for COVID-19 pneumonia was indicated in patients with blood oxygen saturation < 90%. Intensive care unit (ICU) admission was indicated for patients who need mechanical support for their respiration by either continuous positive airway pressure-bilevel positive airway pressure (CPAP-BPAP) or mechanical ventilation. We excluded mild COVID pneumonia case to ensure homogeneity of the patients. Most of hospitalized patients for COVID pneumonia received corticosteroid therapy in form of dexamethasone or methyl prednisolone for variable time tailored according to patients' status, yet, we tested patients at least 4 weeks after the end of corticosteroid therapy to avoid interaction between corticosteroid and testosterone levels.

All data of the participants were checked and reviewed. Each participant underwent a detailed history with special stress for disease that affected gonadal functions and history of drug intake, particularly corticosteroid, and clinical examination. Most of our patients in this study were still on anticoagulant therapy. The comorbidity burden was assessed by the Charlson Comorbidity Index (CCI) [10]. Blood pressure, weight, height, BMI (calculated by the standard formula: weight (kg)/height^2 (m)^2), and WC were done for all partici-

pants. WC was taken as the smallest circumference around the abdomen without any clothing at the umbilical level.

Laboratory evaluation

All laboratory tests were performed after an average of 60 days of discharge from isolation governmental hospitals. The participants and recovered patients were tested in the morning after night fasting. Blood samples were taken at 10 a.m., including liver functions test, creatinine, serum albumin, C-reactive protein (CRP), TT, sex hormone-binding globulin (SHBG), and LH. Laboratory tests were measured by enzyme-linked immunosorbent assay (ELISA) (Roche Diagnostics). Calculated free testosterone (cFt) levels were calculated from TT and SHBG and serum albumin with Vermeulen's formula according to mass action laws [11].

Definition

The American Urological Association [12] defined testosterone deficiency as TT levels below 300 ng/dL according to testosterone deficiency guidelines, while elevated LH levels more than 9.4 IU/L was used to define hyper-gonadotropic hypogonadism according to the European Male Aging Study criteria [13].

Statistical analysis

We conducted statistical analysis by using Statistical Package for the Social Sciences (SPSS), Version 23. All data were checked for suitability for a normal distribution with the Shapiro-Wilk test. All continuous variables were expressed as the mean ± standard deviation for variables and were compared with independent t-test while non-normally distributed expressed as the median and interquartile range (IQR) and were compared using Mann-Whitney test. Categorical variables were expressed as a percentage and Chi-square was carried out to compare between them. Linear regression was used to assess the association of TT as the dependent variable with other statistically significant correlated variables in Pearson correlation (independent variables) in the patients' group. P value less than 0.05 was considered statistically significant.

Results

A total of 55 recovered, post-hospitalized COVID-19 pneumonia male patients, and 40 age, BMI, and WC-matched participants were enrolled in this study from January 2021 to March 2021. The mean age of the patients was 53.02 ± 7.385 years, the prevalence of testosterone deficiency was 50.9% (28 patients), while the prevalence of hypogonadotropic hypogonadism was 60.7% (17 patients).

In this study, when we compared clinical and laboratory characteristics between late recovered COVID-19 pneumonia patients and matched participants as the control group, we

Table 1. Demographic, Clinical, and Laboratory Characteristics of Study Participants

	COVID-19 pneumonia patients (n = 55)	Matched control (n = 40)	P value
Age (years)	53.02 ± 7.385	51.80 ± 7.498	0.432
Smoker ratio	21 (38.2%)	16 (40%)	0.858
ICU admission	15 (29.3%)		
Hypertension	29 (52.7%)	19 (47.5%)	0.615
Body weight (kg)	105.93 ± 15.677	102.73 ± 16.123	0.334
Height (m)	1.7416 ± 0.05862	1.7358 ± 0.06842	0.654
BMI (kg/m^2)	35.0776 ± 5.87218	34.2703 ± 6.06213	0.516
WC (cm)	120.20 ± 16.875	115.55 ± 17.255	0.192
CRP (mg/L)	15.8782 ±7.82614	14.175 ± 7.00417	0.277
CCI	3 (3)	3 (2)	0.128
Albumin (g/dL)	4.23 ± 0.19108	4.1564 ± 0.27200	0.145
SHBG (nmol/L)	49.0091 ± 9.81952	49.8350 ± 9.21400	0.679
TT (ng/dL)	335.8182 ± 148.116	401.35 ± 145.734	0.35
cFT (ng/dL)	5.342909 ± 2.40896	6.3615 ± 2.314652	0.41
LH (mIU/L)	7.6836 ± 2.69298	7.03 ± 2.47596	0.23
T/LH	0.4731 (0.51)	0.6584 (0.43)	0.022
Testosterone deficiency prevalence	28 (50.9%)	12 (30%)	0.042

COVID-19: coronavirus disease 2019; ICU: intensive care unit; BMI: body mass index; WC: waist circumference; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; TT: total testosterone; cFT: calculated free testosterone; LH: luteinizing hormone; SHBG: sex hormone binding globulin; T/LH: testosterone to LH ratio.

found statistically significant differences of mean testosterone to LH ratio, TT, and cFT. Moreover, we found a higher prevalence of testosterone deficiency in the COVID-19 patients group. There were no significant differences between the two groups in mean CCI. Other clinical and laboratory differences between the two groups are detailed in Table 1.

Table 2 demonstrates the comparison of clinical and laboratory parameters between 28 post-COVID-19 testosterone-deficient patients and 27 post-COVID-19 testosterone-sufficient patients. We found significant differences in the means of hospitalization duration, CCI, BMI, WC, and LH. An unexpected result is an insignificant mean difference of CRP between the testosterone-deficient and sufficient patients. Other differences are shown in Table 2.

In this study, Pearson's correlation test was used for exploring any significant relationships between serum TT levels and other parameters. We studied in regression analysis the association between TT as the dependent factor with other significantly correlated parameters as independent variables, hospitalization duration, LH, BMI, WC, and the square root of CCI among 55 COVID-19 patients. We found that WC diameter was the only significant predictor of TT levels. Moreover, after controlling the age, we found that the square root of CCI and WC could significantly predict TT levels as shown in Table 3.

Discussion

Several studies have highlighted a statistically significant de-

crease in testosterone levels with COVID-19 infection; however, the majority of these studies have been conducted in patients with active disease and long-term consequences are still not known and need exploration [14].

In our study, we aimed to evaluate the late impact of COVID-19 pneumonia on androgen levels after recovery. Our main current findings show that recovered COVID-19 pneumonia patients still have lower androgen levels and a higher prevalence of testosterone deficiency in comparison with matched control participants after an average of 60 days. Moreover, visceral obesity was the most significant predictor for low testosterone levels in recovered COVID-19 patients.

The late effect of COVID-19 has been evaluated in rare studies. Our results partially coped with a single-center Chinese study that reported a lower ratio of TT to LH in recovered COVID-19 patients in comparison with age-only matched control and low TT levels were observed only in critically ill patients [15]. On the other hand, our findings were in contrast with another recent Chinese study's findings on recovering COVID-19 patients which did not observe any significant change in comparison with healthy control participants [16]. This contrast may be explained by different patients' selection regarding ethnicity and disease severity.

In the same consent, few studies on hospitalized COVID-19 patients reported generally lower androgen levels with mainly hyper-gonadotropic which pointed to testicular origin. Lower testosterone and higher LH levels in comparison of active COVID-19 patients with age-matched healthy controls were reported [8, 17, 18].

Table 2. Comparison of Demographic, Clinical, and Laboratory Characteristics Between COVID-19 Pneumonia Male Patients With Testosterone Deficiency and Patients Without Testosterone Deficiency

	Non-deficient testosterone (n = 27)	Deficient testosterone (n = 28)	P value
Age (years)	53.89 ± 7.617	52.18 ± 7.191	0.396
Smoker ratio	10 (37%)	11 (39.3%)	0.864
Hospitalization time (days)	5.19 ± 1.733	7.46 ± 3.226	0.002
ICU admission	3 (11.1%)	8 (28.6%)	0.106
Hypertension	12 (44.4%)	17 (60.7%)	0.227
Body weight (kg)	102.00 ± 16.502	109.71 ± 14.108	0.068
Height (m)	1.7496 ± 0.05977	1.7339 ± 0.05750	0.325
BMI (kg/m^2)	33.4579 ± 5.87564	36.6395 ± 5.52875	0.043
WC (cm)	112.93 ± 16.146	127.21 ± 14.647	0.001
CRP (mg/L)	14.1 ± 7.90569	17.5929 ± 7.49004	0.098
CCI	3 (2)	5 (4)	0.007
Albumin (g/dL)	4.2000 ± 0.26890	4.1143 ± 0.27314	0.246
SHBG (nmol/L)	51.2222 ± 9.86257	46.8750 ± 9.46348	0.101
cFT (ng/dL)	7.302593 ± 1.624783	3.453214 ± 1.2331	0.0001
LH (mIU/L)	6.6889 ± 1.47187	8.6429 ± 3.23642	0.006
T/LH	0.2449 (0.17)	0.7058 (0.29)	0.001

COVID-19: coronavirus disease 2019; ICU: intensive care unit; BMI: body mass index; WC: waist circumference; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; LH: luteinizing hormone; cFT: calculated free testosterone; SHBG: sex hormone binding globulin; T/LH: testosterone to LH ratio.

Similarly, male patients with COVID-19 had lower testosterone levels even in comparison with non-COVID-19 respiratory tract infections and age-matched controls [19]. This may point to a specific pathogenic impact on testicular functions rather than acute phase hypogonadism [20]. Furthermore, testosterone could predict the outcomes of hospitalized COVID-19 patients. Hypotestosteronemia was linked with increased risk in terms of ICU and mortality [19], need of mechanical ventilation or mortality [17], and higher risk of ICU admission and death outcomes [21]. Moreover, testosterone levels were significantly associated with a longer time of hospitalization [19].

However, in contrast to previous studies which pointed to the testicular origin of hypogonadism in active COVID-19 patients, a recent finding from a large case-control study [21] reported a very high prevalence of testosterone deficiency around 90%. However, in contrast with other studies, hypogonadism patients were predominately hypogonadotropic hypogonadism pointing to hypothalamic and/or pituitary origin. Hypogonadism patients in our study were predominately hypogonadotropic suggestive of hypothalamic or pituitary origin.

Few pathogenic mechanisms can explain testosterone deficiency in COVID-19 pneumonia. Acute stage hypogonadism in male COVID-19 patients like other critical infections may be explained via the mechanism of secondary immune reactions and oxidant sensitive-inflammatory pathways. The SARS-CoV-2 infection could induce secondary inflammation and oxidative stress is more likely to impair androgen synthesis [22], yet, our patients in this study were recovered with average 60-day period. Another mechanism could be via prolactin levels change. Few studies reported abnormally elevated prolactin

Table 3. Linear Regression Models Predicting Total Testosterone Levels in Recovered, Post-Hospitalized for COVID-19 Pneumonia Male Patients

	Model 1			Model 2		
	B	β	P value	B	β	P value
WC	-5.895	-2.932	0.005	-5.941	-2.991	0.004
BMI	7.217	1.238	0.221	7.709	1.337	0.188
LH	-3.154	-0.470	0.641	-1.600	-0.238	0.813
Hospitalization time	-9.768	-1.599	0.116	-9.866	-1.635	0.109
Sqrt CCI	-67.069	-1.976	0.054	-78.849	-2.288	0.027

Model 1 was unadjusted. Model 2 adjusted for age. COVID-19: coronavirus disease 2019; WC: waist circumference; BMI: body mass index; LH: luteinizing hormone; Sqrt CCI: square root of Charlson Comorbidity Index.

levels in COVID-19 pneumonia which has a known suppressive effect on pituitary gonadotropin secretion although hyperprolactinemia might be attributed to other etiologies like drugs and stress [19, 23, 24]. Furthermore, direct damage of testicular tissue by the SARS-CoV-2 virus was hypothesized. High expression of ACE2 receptors in Leydig and Sertoli cells could suggest direct SARS-CoV-2 impact at the testicular level in active COVID-19 patients; however, the extent of this damage still needs to be verified. There are recent studies that reported injury to Sertoli cells and seminiferous tubules, Leydig cells loss in COVID-19 patients [25], and damage of seminal tubules in post mortem COVID-19 patients [26]. Another mechanism via the ACE2 pathway was postulated. The high expression of ACE2 receptors at Leydig cells and its decreased expression by SARS-CoV-2 leads to subsequently enhanced angiotensin II levels [27]. Angiotensin II could reduce both basal and LH-stimulated testosterone synthesis by Leydig cells [7]. Another mechanism could be postulated by the obesity effect. Obesity is one of the risk factors for severity of COVID-19 disease and connects with COVID-19 by few mechanisms as immune system activity attenuation and chronic inflammation [28]. At the same time, obesity particularly visceral obesity is a well-known risk factor for testosterone deficiency in males [29]. Similarly, in our study result, visceral obesity was the most significant predictor for low testosterone levels in recovered COVID patients. Hence, obesity is considered a risk factor for both COVID-19 and testosterone deficiency, therefore, visceral obesity may be the main link between COVID-19 and hypogonadism. Another mechanism that could postulate testosterone deficiency in COVID-19 pneumonia is corticosteroids. Corticosteroids likely are involved in testosterone deficiency in COVID-19 disease. The use of corticosteroids and stress-induced hypercortisolism might have a suppressive impact on the hypothalamus-pituitary-gonadal axis. Cortisol can disrupt and suppress the hypothalamus-pituitary-gonadal axis. Corticosteroid could suppress gonadotropin-releasing hormone at the hypothalamic level and could affect the pituitary gonadotropin action at the testicular level [30]. We excluded patients with corticosteroid use in the last 4 weeks to avoid cortisol disruption on hypothalamus-pituitary-gonadal axis. Lastly, a recent hypothesis of the production of anti-sperm antibodies was postulated. Following damage to the blood-testicular barrier, anti-sperm antibodies were postulated to be produced and involved in hypogonadism pathogenesis [31].

To the best of our knowledge, despite this article does not present first the evaluation of reproductive hormonal levels in patients with COVID-19, our study for the first time demonstrated lower testosterone levels in hospitalized patients with COVID-19 after recovery. Our study has some points of strength. Firstly, it evaluates the late effect of the SARS-CoV-2 virus on testosterone levels after recovery. Secondly, our participants as control were matched according to age, and anthropometric parameters such as WC and BMI, which are known to affect testosterone levels by a large number of studies. Thirdly, we excluded any history of disorders known to affect androgen levels even DM. Lastly, we evaluated both free testosterone and TT levels.

The current study is certainly not devoid of limitations, which include relatively smaller sample size, single center-based study, and the study could not evaluate these COVID-19 patients prospectively. Another limitation is that we did not evaluate follicle-stimulating hormone (FSH) and prolactin due to limited funding for this research as this study was funded by the authors themselves. Another limitation is that a pre-existing testosterone deficiency could not be excluded in all our participants although few patients have normal testosterone report with variable time, yet, we excluded all disease which could affect androgen level and set our inclusion criteria for age between 18 and 65 for avoiding known impact of age on androgen level and match our control group. Lastly, we recruited hospitalized patients only. Hence the effect of mild COVID-19 was not evaluated even our control participants may have asymptomatic COVID-19 and our results could be applied to moderate and severe cases of COVID-19 only.

In this study, we highlighted the need for gonadal function evaluation among patients recovered from SARS-CoV-2 infection particularly severe and critical patients, and further studies are invited to verify our study findings.

Conclusion

Late recovered post-hospitalized COVID-19 pneumonia patients still have lower androgen levels and a higher prevalence of testosterone deficiency in comparison with matched control participants. Moreover, visceral obesity was the most significant predictor of low testosterone levels in recovered COVID-19 patients. These results need more confirmation in other communities and more follow-up studies.

Acknowledgments

Financial Disclosure

Conflict of Interest

None to declare.

Informed Consent

Written informed consent was obtained from each participant.

Author Contributions

MA and AA contributed to the conception and interpretation of the data. AN and ES performed the laboratory tests. MA performed the statistical analysis. MA and AA were involved

in writing, reviewing, and editing the manuscript. All authors read and approved the final manuscript.

Data Availability

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

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