

Does Coronavirus Disease 2019 Kill More Elderly Men than Women Due to Different Hormonal Milieu

Apurva Tandon, Vishal R Tandon¹, Sudhaa Sharma², Annil Mahajan³

Acharya Shri Chander
College of Medical Sciences
& Hospital Sidhra Jammu,
Sidhra, Departments
of ¹Pharmacology and
Therapeutics, ²Obstetrics and
Gynaecology and ³Internal
Medicine, Government
Medical College,
Jammu and Kashmir, India

Submitted: 04-Feb-2022
Revised: 23-Feb-2022
Accepted: 24-Feb-2022
Published: 16-Sep-2022

INTRODUCTION

Preliminary published data worldwide depicts a much greater prevalence and high case-fatality rate among advanced age males in comparison to age-matched women afflicted with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infections showing high morbidity, mortality, high referral, and admission to intensive care unit (ICU) with severe sequelae.

Therefore, a very important research question arises for the research community that whether different hormonal milieu in advancing age men and women with andropause and menopause could have a prominent pathophysiological role in association with SARS-CoV-2, with deficiency of testosterone, thus, evincing men more prone as compared to advancing age menopausal women, in whom, testosterone levels drop before menopause and relatively increase with advanced age, hence, developing more serious complications

ABSTRACT Preliminary data depicts a much greater prevalence and high case-fatality rate in advanced age males as compared to age-matched women with severe acute respiratory syndrome-coronavirus-2 infections with high morbidity, mortality, high referral, and admission to intensive care unit with severe sequelae. However, the literature search revealed both for and against studies in this context. Thus, at present, in light of the mixed studies, it cannot be established whether low testosterone levels in aging hypogonadal males create a permissive environment for severe response to coronavirus disease 2019 (COVID-19) infection and can it increase the morbidity or mortality, or on the contrary if the virus inhibits androgen formation. Hence, it is highly warranted to establish the said hypothesis by conducting large statistically powered clinical studies in future. Further, it is highly indicated that impact of sex hormones and gender on the incidence and case fatality of the disease and hormones as a treatment according to sex and gender for COVID requires further scientific research by the research community before it is actually recommended to mitigate the COVID-19 disease course among elderly men and women at large.

KEYWORDS: *Andropause, coronavirus disease 2019, menopause, severe acute respiratory syndrome-coronavirus-2, testosterone*

related to the SARS-CoV-2 infection. Further, the research question is that if SARS-CoV-2 infection parse causes an acute stage of male hypogonadism, the depletion of androgenic action, triggering a serious or even fatal course of the disease. However, the literature search revealed both for and against studies in this context at present.

SUPPORTIVE STUDIES-TESTOSTERONE AND CORONAVIRUS DISEASE 2019

A prospective, cohort study demonstrated that coronavirus disease 2019 (COVID-19) is associated with decreased level of total testosterone (TT) and increased level of luteinizing hormone (LH) and prolactin. More serious COVID-19 causes more reduction in TT

Address for correspondence: Dr. Vishal R Tandon, Professor, PG Department of Pharmacology, Government Medical College, Jammu, Jammu and Kashmir, India.
E-mail: dr_vishaltandon@yahoo.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Tandon A, Tandon VR, Sharma S, Mahajan A. Does coronavirus disease 2019 kill more elderly men than women due to different hormonal milieu. *J Mid-life Health* 2022;13:96-9.

Access this article online	
Quick Response Code: 	Website: www.jmidlifehealth.org
	DOI: 10.4103/jmh.jmh_37_22

levels and prolongs hospitalization period. Correlation analysis of the said study revealed a significant negative correlation between serum TT levels and hospitalization time of patients with COVID-19. In addition, a significant positive correlation was observed between SpO₂ and serum TT levels in patients with COVID-19. Serum LH levels and serum prolactin levels were higher in patients with COVID-19 and patients with non-COVID-19 respiratory tract infection than in control cases.^[1]

Similarly, a recent case-control study demonstrated significantly lower levels of LH and TT in patients with COVID-19 compared to healthy controls ($P < 0.0001$); conversely, healthy controls depicted lower values of circulating E₂ ($P < 0.001$). Testosterone levels suggestive for hypogonadism were observed in (89.8%) COVID patients at hospital admission and in (85%) cases, hypogonadism was secondary. SARS-CoV-2 infection status was independently associated with lower TT levels ($P < 0.0001$) and greater risk of hypogonadism ($P < 0.0001$) after accounting for age, body mass index, charlson comorbidity index (CCI), and interleukin IL-6 values in the said study. Lower TT levels were associated with a higher risk of ICU admission and death outcomes ($P \leq 0.05$) after accounting for clinical and laboratory parameters. Thereby, indicating an independent association between SARS-CoV-2 infection status and secondary hypogonadism already at hospital admission, with lower testosterone levels predicting the most severe clinical outcomes among COVID-19 patients.^[2]

To evaluate the testicular damage caused by COVID-19, a prospective study evaluated 44 patients and suggested that there was no difference between the follicle-stimulating hormone (FSH), LH, and testosterone values of the COVID-19 polymerase chain reaction (PCR) positive and negative patients. However, when LH values were separated as low, normal, and high, LH values were statistically significantly higher in the COVID-19 PCR positive group ($P = 0.04$). Thoracic computed tomography was performed in 42 patients. Testosterone levels were significantly lower in patients with COVID-19 pneumonia ($P = 0.01$). When FSH, LH, and testosterone values were separated as low, normal, and high, there was no difference in FSH and LH values ($P = 1$, $P = 0.2$). Testosterone levels were found significantly lower in patients with COVID-19 pneumonia ($P < .001$). Thereby, this study also proposed that testosterone levels seem to decrease during acute COVID-19 infection, especially in the patient group with viral pneumonia.^[3]

Another 7-month cohort study suggested that TT levels increased, whereas LH and 17 β -estradiol levels

significantly decreased (all $P \leq 0.02$). Over time, after COVID-19, more than 50% of men who recovered from the disease still had circulating testosterone levels suggestive for a condition of hypogonadism at 7-month follow-up. In as many as 10% of cases, testosterone levels even further decreased.^[4]

A prospective study also suggested low TT levels play a role on the pathogenesis of the disease in COVID-19 patients with poor prognosis and a mortal course and may guide clinicians in determining the clinical course of the disease. In this study, the measured serum TT level of the COVID-19 patients' group was found to be significantly lower than that of the control group ($P < 0.001$). The serum TT levels were significantly lower in severe COVID-19 patients compared to mild-to-moderate COVID-19 patients ($P < 0.001$). In COVID-19 patients in need of intensive care compared to COVID-19 patients who did not need intensive care ($P < 0.001$) and in COVID-19 patients who died compared to survivors ($P < 0.001$).^[5]

Similarly, another cohort study reported serum TT level at baseline to decrease in the COVID-19 ICU patients significantly and as serum TT level at baseline decreases, the probability of mortality significantly increases. Thereby, COVID-19 might deteriorate serum testosterone level in SARS-CoV-2 infected male patients. Low serum TT level at baseline has a significantly increased risk for the ICU and mortality in patients with COVID-19.^[6]

CONTRARY STUDIES-TESTOSTERONE AND CORONAVIRUS DISEASE 2019

However, contrary to the above reports, few studies^[7,8] suggested that in males infected with SARS-CoV-2, most sex-related hormones (TT, FSH, and LH levels) remain within the normal reference ranges after recovery from COVID-19, and no significant associations were observed between testosterone level and disease duration or severity.^[7]

Similarly, in another study showed that men who contract COVID-19 do not appear to have worse clinical outcomes compared with women which raises the possibility of androgen-independent effects, as the testosterone replacement therapy is not associated with a worse clinical outcome in men diagnosed with COVID-19.^[8]

Pan *et al.* in their study revealed that SARS-CoV-2 was not detected in the semen of patients recovering from COVID-19, 1 month after COVID-19 diagnosis. Angiotensin-converting enzyme-2 (ACE-2)-mediated viral entry of SARS-CoV-2 into target host cells is unlikely to occur within the human testicle based

on ACE-2 and transmembrane protease serine type 2 (TMPRSS2) expression. The long-term effects of SARS-CoV-2 on male reproductive function thus remain unknown.^[9]

Stanley *et al.*^[10] in their study suggested that SARS-CoV-2 infection is unlikely to have long-term effects on male and female reproductive function. Although the results cannot be considered definitive, they imply that procedures in which oocytes are collected and fertilized *in vitro* are associated with very little risk of viral transmission from gametes to embryos and may indeed have the potential to minimize exposure of susceptible reproductive cell types to infection in comparison with natural conception.

Similarly, Hussain *et al.*^[11] in their study suggested that high testosterone levels can lead to thrombosis which is also one of the fatal manifestations in COVID-19 patients. Thus, they suggested that a critical evaluation of the serum testosterone and its relevance to COVID-19 is warranted before it is recommended protective against COVID-19.

WOMEN HORMONE AND CORONAVIRUS DISEASE INFECTION

In a retrospective study of Seeland *et al.*,^[12] hormone therapy in female COVID-19 patients shows that the fatality risk for women >50 years receiving estradiol therapy (user group) is reduced by more than 50%; the odds ratio (OR) was 0.33, 95% confidence interval (CI) (0.18–0.62) and the hazard ratio was 0.29, 95% CI (0.11–0.76). For younger, premenopausal women (15–49 years), the risk of COVID-19 fatality is the same irrespective of estradiol treatment, probably because of higher endogenous estradiol levels.

Similarly, Chedraui and Pérez-López *et al.*^[13] in their study proposed that postmenopausal women seem to present a more severe infection as compared to premenopausal ones. Estradiol protects the vascular system, mediating with the renin–angiotensin–aldosterone system, whereas testosterone enhances the levels of ACE-2 and the TMPRSS2, thus, delaying viral clearance in men as compared to women.

In a study by Costeira *et al.*,^[14] menopausal women had higher rates of predicted COVID-19 ($P = 0.003$). Combined oral contraceptive pill (COCP) users had lower rates of predicted COVID-19 ($P = 8.03E-05$), with a reduction in hospital attendance ($P = 0.023$). Menopausal women using hormone replacement therapy (HRT) or hormonal therapies did not exhibit consistent associations, including increased rates of predicted COVID-19 for HRT users alone. The findings

of the study support a protective effect of estrogen exposure on COVID-19, based on a positive association between predicted COVID-19 with menopausal status and negative association with COCP use. HRT use was positively associated with COVID-19, but the results should be considered with caution due to lack of data on HRT type, route of administration, duration of treatment, and potential unaccounted for confounders and comorbidities.

PATHOGENESIS

The link between testosterone and the immune system, male aging is well-established. In men testosterone progressively decline with aging and andropause, whereas in women, testosterone levels drop before menopause and variably increase with advanced age relatively. Testosterone coregulates the expression of ACE-2 and TMPRSS2 in host cells, which may facilitate SARS-CoV-2 internalization. Further, low serum testosterone levels may predispose to endothelial dysfunction, thrombosis, and defective immune response, leading to both impaired viral clearance and systemic inflammation.^[15,16]

Contrariwise, low levels of serum testosterone, which may be associated with aging and obesity and other chronic diseases, lead to systemic inflammation, endothelial dysfunction, and increased platelet activity, predisposing to thrombosis and thromboembolism and promoting atherosclerosis and CVD. Further, male hypogonadism may trigger a detrimental cytokine dysfunction, including high circulating levels of IL-6, tumor node factor (TNF)-alpha, and IL-1beta, responsible for poor prognosis in COVID-19.^[15]

Further, it has been proposed that elevated IL-6 is a characteristic biomarker of patients infected with COVID-19 and has been linked to the development of acute respiratory distress syndrome (ARDS). Low testosterone is associated with ARDS. Thus, low testosterone levels may exacerbate the severity of COVID-19 infection in elderly men more than women. Further, normal testosterone levels may offer some protection against COVID-19.^[15-17]

Similarly, estrogen hormone has been proposed to reduce SARS-CoV-2 infectivity through modulation of pro-inflammatory signaling pathways. Estrogen is known to cause activation of CD4 cell, activation of anti-inflammatory cytokines IL-4, and IL-10 and causes inhibition of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-17, and TNF- α . Further, it has been reported that estrogen increases the expression of ACE-2 and the production of angiotensin-1-7, so it may counteract the deleterious effect of high angiotensin II-induced

ARDS. Estrogen also inhibits TMPRSS2, necessary for trimming and activation of SARS-CoV-2 spike protein to bind ACE-2. It also ameliorates airway inflammation and hyperresponsiveness through inhibition of NLRP3 inflammasome-induced pro-inflammatory cytokine release.^[18]

Thus, both HRT after menopause and the use of combined contraceptive pills may produce a similar potent immune response and protection against viral infections.

Therefore, emergence of future clinical trials and large-scale prospective studies are warranted in this regard to confirming the supreme importance of estrogen therapy in the management of COVID-19 mainly in postmenopausal women.

CONCLUSION

Thus, currently, in light of the mixed studies, it cannot be established whether low testosterone levels in aging hypogonadal males create a permissive environment for severe responses to COVID-19 infection or could it increase the morbidity or mortality or rather the virus inhibits androgen formation. Hence, in view of the worldwide preponderance of COVID-19-related morbidity and mortality in elderly males, additional testing for gonadal function and impact of testosterone replacement treatment is highly warranted to be established in the near future by conducting large statistically powered clinical studies. Further, it is highly warranted that impact of sex hormone replacement and gender on the incidence and case fatality of the disease and hormones as a treatment according to sex and gender for COVID requires further scientific research by the research community before it is actually recommended to mitigate the COVID-19 disease course among elderly men and women.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kadihasanoglu M, Aktas S, Yardimci E, Aral H, Kadioglu A. SARS-CoV-2 pneumonia affects male reproductive hormone levels: A prospective, cohort study. *J Sex Med* 2021;18:256-64.
2. Salonia A, Pontillo M, Capogrosso P, Gregori S, Tassara M,

- Boeri L, *et al.* Severely low testosterone in males with COVID-19: A case-control study. *Andrology* 2021;9:1043-52.
3. Okçelik S. COVID-19 pneumonia causes lower testosterone levels. *Andrologia* 2021;53:e13909.
4. Salonia A, Pontillo M, Capogrosso P, Gregori S, Carezzi C, Ferrara AM, *et al.* Testosterone in males with COVID-19: A 7-month cohort study. *Andrology* 2022;10:34-41.
5. Cinislioglu AE, Cinislioglu N, Demirdogen SO, Sam E, Akkas F, Altay MS, *et al.* The relationship of serum testosterone levels with the clinical course and prognosis of COVID-19 disease in male patients: A prospective study. *Andrology* 2022;10:24-33.
6. Çayan S, Uğuz M, Saylam B, Akbay E. Effect of serum total testosterone and its relationship with other laboratory parameters on the prognosis of coronavirus disease 2019 (COVID-19) in SARS-CoV-2 infected male patients: A cohort study. *Aging Male* 2020;23:1493-503.
7. Xu H, Wang Z, Feng C, Yu W, Chen Y, Zeng X, *et al.* Effects of SARS-CoV-2 infection on male sex-related hormones in recovering patients. *Andrology* 2021;9:107-14.
8. Rambhatla A, Bronkema CJ, Corsi N, Keeley J, Sood A, Affas Z, *et al.* COVID-19 infection in men on testosterone replacement therapy. *J Sex Med* 2021;18:215-8.
9. Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, *et al.* No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. *Fertil Steril* 2020;113:1135-9.
10. Stanley KE, Thomas E, Leaver M, Wells D. Coronavirus disease-19 and fertility: Viral host entry protein expression in male and female reproductive tissues. *Fertil Steril* 2020;114:33-43.
11. Hussain AN, Hussain F, Hashmi SK. Role of testosterone in COVID-19 patients-A double-edged sword? *Med Hypotheses* 2020;144:110287.
12. Seeland U, Coluzzi F, Simmaco M, Mura C, Bourne PE, Heiland M, *et al.* Evidence for treatment with estradiol for women with SARS-CoV-2 infection. *BMC Med* 2020;18:369.
13. Chedraui P, Pérez-López FR. The severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) infection and the climacteric woman. *Climacteric* 2020;23:525-7.
14. Costeira R, Lee KA, Murray B, Christiansen C, Castillo-Fernandez J, Ni Lochlainn M, *et al.* Estrogen and COVID-19 symptoms: Associations in women from the COVID symptom study. *PLoS One* 2021;16:e0257051.
15. Papadopoulos V, Li L, Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone? *Andrology* 2021;9:65-72.
16. Giagulli VA, Guastamacchia E, Magrone T, Jirillo E, Lisco G, De Pergola G, *et al.* Worse progression of COVID-19 in men: Is testosterone a key factor? *Andrology* 2021;9:53-64.
17. Salonia A, Corona G, Giwercman A, Maggi M, Minhas S, Nappi RE, *et al.* SARS-CoV-2, testosterone and frailty in males (PROTEGGIMI): A multidimensional research project. *Andrology* 2021;9:19-22.
18. Al-kuraisy HM, Al-Gareeb AI, Faidah H, Al-Maihy TJ, Cruz-Martins N, El-Saber Batiha G. The looming effects of estrogen in COVID-19: A rocky rollout. *Front Nutr* 2021;8:649128.