International Journal of Biomedicine 12(4) (2022) 526-529
http://dx.doi.org/10.21103/Article12(4)_RA5

SHORT REVIEW

INTERNATIONAL JOURNAL OF BIOMEDICINE

Hair Loss and Androgen's Role in the Era of COVID-19

Ramadan S. Hussein[1, 2*]

[1]*Department of Internal Medicine, College of Medicine, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia*
[2]*Department of Dermatology, Andrology and STDs, Assuit Police Hospital, Assuit, Egypt*

Abstract

The new coronavirus (SARS-COV2), which causes coronavirus illness, has expanded globally, impacting millions of individuals. In comparison to female patients, males have a higher prevalence, morbidity, and death rate from this condition, according to international statistics. Androgens have been implicated in the pathophysiology of COVID-19. This review's objective is to explain the potential connection between the pathophysiology of androgen and the infectivity mechanism of the coronavirus as well as the association between SARS-COV2 and hair disorders. This might assist in clarifying androgen's involvement in COVID-19 prognosis and therapy. (**International Journal of Biomedicine. 2022;12(4):526-529.**).

Keywords: COVID-19 • androgen • androgenetic alopecia • hair loss

For citation: Hussein RS. Hair Loss and Androgen's Role in the Era of COVID-19. International Journal of Biomedicine. 2022;12(4):526-529. doi:10.21103/Article12(4)_RA5.

Abbreviations

AR, androgen receptor; **ACE2**, angiotensin-converting enzyme 2; **AGA**, androgenetic alopecia; **CAG**, cysteine-adenine-guanine; **DHT**, dihydrotestosterone; **TMPRSS2**, transmembrane serine protease 2.

Introduction

The new coronavirus (SARS-COV2), which causes coronavirus illness, has expanded globally, impacting millions of individuals.[(1)] SARS-CoV-2-infected males are more likely to be admitted to the ICU than females – the most common observation.[(2)] Several investigations have revealed that the virus's cellular entrance is aided by angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2).[(3)] Androgens promote TMPSS2 gene expression, so COVID-19 illness has also been associated with alterations in androgen sensitivity. Androgenetic alopecia (AGA) has been connected to developing severe COVID-19, particularly in admitted patients. The role of androgen and anti-androgenic drugs could be important in the pathophysiology and management of SARS-COV2.[(4)] The PRISMA checklist was used to carry out this review, based on scientific articles published between 2020 and 2022 in English databases such as PubMed and Google Scholar with the keywords "SARS-COV2," "androgens," "hair loss," and "TMPSS2." We chose papers from a vast number of publications based on the role of androgens and TMPSS2 in the infectivity mechanism of the current COVID-19 virus pandemic and the therapeutic potential of anti-androgenic drugs.[(5)]

SARS-CoV-2 pathophysiology

SARS-CoV-2 is a member of the beta-coronavirus genus, which involves enclosed, infectious single-strand RNA viruses with similar shapes.[(2)] The bat is the most probable main host of coronavirus, which is why it is referred to as a zoonotic virus. By activating spike proteins with the enzyme TMPSS2 and binding to ACE2 receptors, the novel coronavirus infects host cells. The virus's cellular entrance is aided by ACE2 and TMPSS2. Androgens increase the *TMPSS2* gene expression.[(4)]

Possible impact of androgen on COVID-19 pathogenesis

The expression of the TMPSS2 geneis enhanced by androgens and decreased by androgen deprivation treatment. [(4)] The production of testosterone and TMPPRSS2 modifies the

***Corresponding author**: Ramadan S. Hussein. Department of Internal Medicine, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia. E-mail: ramadangazeera@yahoo.com*

tendency of the new coronavirus infection of cells and the affinity of the spike proteins to bind to ACE2 receptors. Androgens exert their effects by binding to the androgen receptors (Ars), also known as nuclear receptors, encoded by the AR gene located in chromosome Xq11-12. Variants of this gene have varying androgen responses.[5] Because androgens increase the AR transcriptional activity, it is hypothesized that androgen-deficient individuals would have a decreased amount of active ARs; consequently, the transcription potential of TMPRSS2 will be diminished, and the possibility of new coronavirus entry into host cells will be reduced.[6] Androgen deficiency is associated with systemic inflammation and high amounts of pro-inflammatory cytokines in young and aged men.[7,8] Furthermore, there is evidence that even when testosterone levels are low, interpersonal differences in AR susceptibility caused by CAG polymorphisms may produce sensitivity.[9] The AR has 3 key domains: the DNA-binding domain, the ligand-binding domain, and the transactivation domain. The polymorphism of CAG triplet repeat (polyCAG), in the N-terminal transactivation domain of the AR protein, has been involved either in endocrine or neurological disorders in humans. Elevated AR expression may raise the risk of severe COVID-19 infection by stimulating TMPRSS2 transcription. In addition, the length of CAG repeats was identified as a potential reason for racial disparities in COVID-19 mortality rates.[10,11]

The possible link between COVID-19 and AGA, gray hairs, and trichodynia

Testosterone and DHT stimulate AR activity. Activated AR regulates the transcription of the *TMPRSS2* gene. SARS-CoV-2 engages ACE2 as the entry receptor and uses TMPRSS2 for spike protein priming.[12] In a population-based investigation, individuals with prostate cancer who had androgen restriction therapy were partly protected against COVID-19.[13] Thus, the dermatological symptoms of AR hyperactivation, such as AGA, might identify people at a greater risk for adverse consequences of COVID-19. AGA is the most common cause of moderate and severe alopecia in adults, accounting for the majority of reported cases, and this reflects the DHT level and AR sensitivity.[14] Gray hair and AGA were previously linked to an increased risk of cardiovascular disease, a recognized risk factor for COVID-19 with a poor prognosis.[15,16] In contrast, severe stress may accelerate the loss of melanocyte stem cells, leading to premature graying of the hair. Additionally, diffuse hair graying and telogen effluvium should be explored as COVID-19 side effects. Scalp allodynia has not been a common occurrence.[17]

Telogen effluvium pathophysiology in SARS-CoV-2 patients

Numerous conditions may cause pathologically excessive hair loss. Regardless of the source, the follicle tends to act similarly. While post-infectious hair disorders have been conventionally classified as telogen effluvium, they might have various pathophysiological causes and clinical characteristics. Depending on the nature and severity of the injury, the infection may cause either early-onset dystrophic anagen effluvium or late-onset telogen effluvium in the hair follicle. There have been isolated cases of dystrophic anagen and telogen effluvium associated with COVID-19; however, the former has yet to be verified by hair light microscopy. In a study performed by M. Shanshal, trichogram, of dystrophic anagen was compatible with telogen effluvium.[18] In a study by Domínguez-Santás et al., in 10 individuals with COVID-19, the onset and intensity of post-infectious hair loss were correlated with the disease's clinical severity, and fever was observed.[19] In general, hair loss is attributable to a multi-systemic, febrile inflammatory condition. To date, the etiology of hair loss in COVID-19 has not yet been understood. A pathogenic inflammatory response at the hair follicle level, or a direct invasion of the hair follicle by SARS-CoV-2, causing inflammation and cell death, has yet to be demonstrated. Interleukin-6 (IL-6), a pro-inflammatory cytokine implicated in severe COVID-19, may have a role in hair loss, according to one idea. It is believed that IL-6 contributes to hair loss by suppressing the elongation of hair shafts and the development of hair follicles.[20,21] Only a few COVID-19 patients needed hospitalization in the included trials, indicating that hair loss was most prevalent in people with moderate disease. Given the significant female predominance among individuals with hair loss, female sex hormones like estrogen and progestin could potentially play an important role in the pathophysiology behind hair loss. Estrogens and progesterone have anti-inflammatory and immunomodulating properties, suppressing pro-inflammatory cytokines.[22,23] Research is now being conducted to reuse estrogens and progestin for COVID-19 therapy.[24] Estrogen and progestin also have a protective effect on the hair follicle. Through its receptors, estradiol is known to influence hair follicle development and the hair cycle. At the same time, progestin might reduce testosterone transformation to DHT, an active metabolite of androgen that causes hair loss.[25] As a result, hair loss in female COVID-19 patients may be attributed to an acute insult caused by the viral infection, which causes a substantial decline in serum estrogens and progestin levels in female patients.

Anti-androgens impact on COVID-19 treatment

The androgen function may be significant in SARS-CoV-2 management. ARs regulate nitric oxide (NO) synthesis and activity to a certain degree, and blocking these receptors reduces NO synthesis. Moreover, NO suppresses the activities of adrenoceptor enhancers that might change the transcription of the TMPRSS2 and ACE2 genes, decreasing the virus's capacity to infiltrate host cells. NO has been shown to suppress SARS-COV-2 multiplication and also affects the virus spike proteins and their connections with ACE2, indicating that it serves many purposes in COVID-19. These data revealed that testosterone pathways are most likely the primary mechanism causing the reported NO beneficial impact. Dexamethasone, a steroid, decreased fatality by one-third in ventilated patients and one-fifth in oxygen-treatment patients without ventilators.[26] Dexamethasone has been found to suppress testosterone production in human patients and animal models. Lower testosterone levels might contribute to dexamethasone's beneficial effects, but these preliminary findings should be interpreted with care.[27] Testosterone blockers have been effective in reducing ACE2 levels, showing the utility of this strategy. Anti-androgen drugs that demonstrated therapeutic promise in current clinical studies are 5-reductase inhibitors (dutasteride, finasteride), AR blockers (apalutamide, cyproterone, spironolactone), and TMPRSS2 blockers. Anti-

androgen drugs that have shown therapeutic promise in recent clinical studies are 5-reductase inhibitors, AR blockers, and TMPRSS2 blockers (camostat, nafamostat, bromhexine).[28]

Conclusion

Androgen activity affects the *TMPRSS2* gene. As the *ACE2* and *TMPRSS2* genes are required for SARS-CoV-2 to enter host cells, they might be utilized as COVID-19 targeted therapies. The effects of androgen on TMPRSS2 may explain the reduced risk of mortality in teenagers and the gender differences in COVID-19 illness. The severity of AGA and hair loss may be considered a prognostic factor in COVID-19 infection. Even though there is still a considerable measure of the potential for the establishment of COVID-19 therapies based on androgen deprivation, ongoing studies will provide crucial information that will lead to improved management alternatives.

Acknowledgment

This publication was supported by the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University.

Competing Interests

The authors declare that they have no competing interests.

References

1. World Health Organization; 2020. Coronavirus disease (COVID-19): situation report, 51. Geneva: Available from: https://apps.who.int/iris/handle/10665/331475.
2. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020 Sep 1;174(9):882-889. doi: 10.1001/jamapediatrics.2020.1467.
3. Jian L, Yi W, Zhang N, Wen W, Krysko O, Song WJ, Bachert C. Perspective: COVID-19, implications of nasal diseases and consequences for their management. J Allergy Clin Immunol. 2020 Jul;146(1):67-69. doi: 10.1016/j.jaci.2020.04.030.
4. Bennani NN, Bennani-Baiti IM. Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy. Ann Oncol. 2020 Nov;31(11):1585-1586. doi: 10.1016/j.annonc.2020.08.2095.
5. Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, Giguere V, Hochberg RB, McKay L, Renoir JM, Weigel NL, Wilson EM, McDonnell DP, Cidlowski JA. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. Pharmacol Rev. 2006 Dec;58(4):782-97. doi: 10.1124/pr.58.4.9.
6. Rastrelli G, Di Stasi V, Inglese F, Beccaria M, Garuti M, Di Costanzo D, Spreafico F, Greco GF, Cervi G, Pecoriello A, Magini A, Todisco T, Cipriani S, Maseroli E, Corona G, Salonia A, Lenzi A, Maggi M, De Donno G, Vignozzi L. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology. 2021 Jan;9(1):88-98. doi: 10.1111/andr.12821.
7. Bobjer J, Katrinaki M, Tsatsanis C, Lundberg Giwercman Y, Giwercman A. Negative association between testosterone concentration and inflammatory markers in young men: a nested cross-sectional study. PLoS One. 2013 Apr 18;8(4):e61466. doi: 10.1371/journal.pone.0061466.
8. Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, Bandinelli S, Valenti G, Ferrucci L. The relationship between testosterone and molecular markers of inflammation in older men. J Endocrinol Invest. 2005;28(11 Suppl Proceedings):116-9.
9. Zitzmann M. The role of the CAG repeat androgen receptor polymorphism in andrology. Front Horm Res. 2009;37:52-61. doi: 10.1159/000175843.
10. Giovannucci E, Stampfer MJ, Krithivas K, Brown M, Dahl D, Brufsky A, Talcott J, Hennekens CH, Kantoff PW. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc Natl Acad Sci U S A. 1997 Apr 1;94(7):3320-3. doi: 10.1073/pnas.94.7.3320. Erratum in: Proc Natl Acad Sci U S A 1997 Jul 22;94(15):8272.
11. Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G, Herrera S, McCoy J. Androgen sensitivity gateway to COVID-19 disease severity. Drug Dev Res. 2020 Nov;81(7):771-776. doi: 10.1002/ddr.21688.
12. McCoy J, Wambier CG, Vano-Galvan S, Shapiro J, Sinclair R, Ramos PM, Washenik K, Andrade M, Herrera S, Goren A. Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19? J Cosmet Dermatol. 2020 Jul;19(7):1542-1543. doi: 10.1111/jocd.13455.
13. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, Carbone GM, Cavalli A, Pagano F, Ragazzi E, Prayer-Galetti T, Alimonti A. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). Ann Oncol. 2020 Aug;31(8):1040-1045. doi: 10.1016/j.annonc.2020.04.479.
14. Goren A, Vaño-Galván S, Wambier CG, McCoy J, Gomez-Zubiaur A, Moreno-Arrones OM, Shapiro J, Sinclair RD, Gold MH, Kovacevic M, Mesinkovska NA, Goldust M, Washenik K. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain - A potential clue to the role of androgens in COVID-19 severity. J Cosmet Dermatol. 2020 Jul;19(7):1545-1547. doi: 10.1111/jocd.13443.
15. ElFaramawy AAA, Hanna IS, Darweesh RM, Ismail AS, Kandil HI. The degree of hair graying as an independent risk marker for coronary artery disease, a CT coronary angiography study. Egypt Heart J. 2018 Mar;70(1):15-19. doi: 10.1016/j.ehj.2017.07.001.
16. Trieu N, Eslick GD. Alopecia and its association with coronary heart disease and cardiovascular risk factors: a meta-analysis. Int J Cardiol. 2014 Oct 20;176(3):687-95. doi: 10.1016/j.ijcard.2014.07.079.
17. Zhang B, Ma S, Rachmin I, He M, Baral P, Choi S, Gonçalves WA, Shwartz Y, Fast EM, Su Y, Zon LI, Regev A, Buenrostro JD, Cunha TM, Chiu IM, Fisher DE, Hsu YC. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. Nature. 2020 Jan;577(7792):676-681. doi: 10.1038/s41586-020-1935-3.

18. Shanshal M. COVID-19 related anagen effluvium. J Dermatolog Treat. 2022 Mar;33(2):1114-1115. doi: 10.1080/09546634.2020.1792400.
19. Domínguez-Santás M, Haya-Martínez L, Fernández-Nieto D, Jiménez-Cauhé J, Suárez-Valle A, Díaz-Guimaraens B. Acute telogen effluvium associated with SARS-CoV-2 infection. Aust J Gen Pract. 2020 Aug 26;49. doi: 10.31128/AJGP-COVID-32.
20. Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, Vannucchi V, Moroni F, Pelagatti L, Tarquini R, Landini G, Vanni S, Masotti L. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020 Sep;81(3):452-482. doi: 10.1016/j.jinf.2020.06.008.
21. Kwack MH, Ahn JS, Kim MK, Kim JC, Sung YK. Dihydrotestosterone-inducible IL-6 inhibits elongation of human hair shafts by suppressing matrix cell proliferation and promotes regression of hair follicles in mice. J Invest Dermatol. 2012 Jan;132(1):43-9. doi: 10.1038/jid.2011.274.
22. Mauvais-Jarvis F, Klein SL, Levin ER. Estradiol, Progesterone, Immunomodulation, and COVID-19 Outcomes. Endocrinology. 2020 Sep 1;161(9):bqaa127. doi: 10.1210/endocr/bqaa127.
23. Al-Kuraishy HM, Al-Gareeb AI, Faidah H, Al-Maiahy TJ, Cruz-Martins N, Batiha GE. The Looming Effects of Estrogen in Covid-19: A Rocky Rollout. Front Nutr. 2021 Mar 18;8:649128. doi: 10.3389/fnut.2021.649128.
24. Lovre D, Bateman K, Sherman M, Fonseca VA, Lefante J, Mauvais-Jarvis F. Acute estradiol and progesterone therapy in hospitalised adults to reduce COVID-19 severity: a randomised control trial. BMJ Open. 2021 Nov 30;11(11):e053684. doi: 10.1136/bmjopen-2021-053684.
25. Grymowicz M, Rudnicka E, Podfigurna A, Napierala P, Smolarczyk R, Smolarczyk K, Meczekalski B. Hormonal Effects on Hair Follicles. Int J Mol Sci. 2020 Jul 28;21(15):5342. doi: 10.3390/ijms21155342.
26. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436.
27. Mohamed MS, Moulin TC, Schiöth HB. Sex differences in COVID-19: the role of androgens in disease severity and progression. Endocrine. 2021 Jan;71(1):3-8. doi: 10.1007/s12020-020-02536-6.
28. Ghazizadeh Z, Majd H, Richter M, Samuel R, Zekavat SM, Asgharian H, Farahvashi S, Kalantari A, Ramirez J, Zhao H, Natarajan P, Goodarzi H, Fattahi F. Androgen Regulates SARS-CoV-2 Receptor Levels and Is Associated with Severe COVID-19 Symptoms in Men. bioRxiv [Preprint]. 2020 May 15:2020.05.12.091082. doi: 10.1101/2020.05.12.091082.