

## REVIEW ARTICLE

# Androgenetic alopecia and COVID-19: A review of the hypothetical role of androgens

Hamideh Moravvej<sup>1</sup>  | Mohammad Reza Pourani<sup>1,2</sup>  | Moein Baghani<sup>1</sup> | Fahimeh Abdollahimajd<sup>1,2</sup> 

<sup>1</sup>Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Clinical Research Development Unit of Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Correspondence

Fahimeh Abdollahimajd and Mohammad Reza Pourani, Skin Research Center, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: fabdollahimajd@sbm.ac.ir, fabdollahimajd@yahoo.com and mreza.pourani92@gmail.com

## Abstract

The coronavirus disease 2019 (COVID-19) has become the most emerging health issue globally. A prompt investigation regarding disease management and treatment is crucial for decreasing the burden of the disease. Many explorations and hypotheses have been posed, but the definite treatment has not been determined for COVID-19. Recent studies described a substantial prevalence of COVID-19 and also a higher rate of morbidity and mortality in men afflicted with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The gender-related discordance in COVID-19 infection may be due to hormonal differences, socioeconomic factors, genetic susceptibility, gender-related comorbidities, and habits like alcohol consumption. On the other hand, several studies proposed that androgens could improve the immune system and have a protective role in COVID-19, and decreased levels of androgens might be associated with unsatisfactory outcomes. In the field of dermatology, androgenetic alopecia (AGA) is correlated with a hyperandrogenic state and may be related to COVID-19 severity. Furthermore, recent research has assessed the plausible association of AGA and COVID-19. In this review, we investigate all evidence on AGA and its relationship with COVID-19, including the possible role of androgens in COVID-19 severity and outcomes as well as candidate androgen-related drugs for the treatment of COVID-19.

## KEYWORDS

androgenetic alopecia, coronavirus disease 2019, COVID-19, SARS-CoV-2 infection, treatment

## 1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused around 50 million confirmed cases of coronavirus disease 2019 (COVID-19) and roughly 1.230 million deaths to date throughout the world.<sup>1</sup> The elevated prevalence and escalated rate of COVID-19 morbidity and mortality have given rise to a global health emergency.<sup>2</sup> Recent studies reported COVID-19 severity in 20% of cases that led to hospitalization and admission in an intensive care unit (ICU), and a mortality rate of 10% in afflicted patients with associated comorbidities.<sup>2,3</sup>

Several investigations have described a higher prevalence of COVID-19 together with poorer outcomes in males. Furthermore, many researchers around the world have evaluated the possible etiologies and pathogenesis for the male predominance of the disease.<sup>2,3</sup> Gender discordance may be due to different factors including socioeconomic, immunologic, genetic, and hormonal factors, as well as gender-related comorbidities and habits (e.g., smoking and alcohol consumption).<sup>4,5</sup>

Current studies on the higher prevalence of COVID-19 in men are focused on hormonal differences.<sup>4</sup> Moreover, androgens are acclaimed to have a vital role in the disease pathogenesis.<sup>3,4</sup> In the

field of dermatology, present investigations have established impelling data on the higher prevalence of androgenetic alopecia (AGA) in patients who contract SARS-CoV-2.<sup>6</sup> However, the prevalence of AGA (about 50%) in men is substantial by 50 years of age.<sup>7</sup> Therefore, a precise evaluation of AGA in men with COVID-19 is essential to assess its role as a risk factor.<sup>3</sup> In this study, we aimed to review articles about AGA and the plausible role of androgens in the pathogenesis of COVID-19.

## 2 | MATERIALS AND METHODS

In this study, we reviewed the investigations related to androgens and AGA in COVID-19 patients. We searched all recent research about the COVID-19, the effects of androgens on the disease, and AGA in SARS-CoV-2 afflicted patients with the keywords of “androgenetic alopecia,” “alopecia,” “androgens,” “hair loss,” “sex hormones” in conjunction with “COVID-19” and “SARS\_CoV\_2” in the Medline, Scopus, Google Scholar, and Web of Science databases. In the primary research with mentioned keywords, we found a total of 72 related articles. Regarding the title and abstract of studies and eliminating repeated and unrelated studies, finally, we have studied 56 relevant reports from 2012 to 2020.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Androgenetic alopecia and COVID-19

In the first study, Goren et al.<sup>8</sup> reported 41 Caucasian males hospitalized with COVID-19. Twenty-nine patients (71%) had significant AGA (Hamilton–Norwood scale >2) and 16 (39%) subjects had severe AGA (Hamilton–Norwood scale 4–7).<sup>8</sup> The prevalence of AGA was higher in comparison with the population of Caucasian age-matched (31%–53%). The authors hypothesized increased frequency of AGA in patients with SARS-CoV-2 infection and suggested anti-androgen drugs as a possible treatment for COVID-19.<sup>8</sup>

Wambier et al.<sup>6</sup> conducted research on 175 patients with SARS-CoV-2 infection including 122 (69.7%) males and 53 (30.3%) females. The prevalence of AGA in males and females was 79% and 42%, respectively. In a similar age-matched population of males (similar to the study of Goren et al.<sup>8</sup>), the frequency of AGA was 31%–53%, while the maximum prevalence of AGA in a female population over the age of 70 was 38%. The outcomes revealed a considerable proportion of AGA in patients admitted with COVID-19.<sup>6</sup>

Nanes et al.<sup>9</sup> criticized the study by Wambier et al. and stated that the age-matched population announced in the study was not detailed clearly. The prevalence of AGA in females mentioned in the study (42%) was similar to the 38% or 54% prevalence published in the referred studies.<sup>9</sup>

Another study by Lee et al.<sup>10</sup> assessed the severity of hair loss in 1941 admitted male symptomatic patients that tested for SARS-CoV-2 infection. The study consisted of 1605 negative-tested and

336 positive-tested COVID-19 patients.<sup>10</sup> Classification of hair loss was obtained from the UK Biobank data based on the Hamilton–Norwood Scale (HNS). Severe AGA (HNS 4–7) was significantly associated with a higher rate of positive COVID-19 tests.<sup>10</sup> In addition, severe AGA had a higher odds ratio than other important risk factors consisting of increased BMI, hypertension, dyslipidemia, and diabetes. However, mild and moderate AGA (in comparison with patients with no hair loss) did not correlate significantly with increased COVID-19 positivity. The main limitation of that study was that the AGA characterization of patients was based on self-reported data.<sup>10</sup>

Thatiparthi et al.<sup>11</sup> commented on the study by Lee et al.<sup>10</sup> and propounded that premature alopecia may aggravate the risk of scalp damage due to solar elastosis, thereby disrupting the protective epidermal barrier. In addition, the angiotensin-converting enzyme 2 (ACE2) receptor, as an important receptor for SARS-CoV-2 pathogenicity, is expressed in epidermal keratinocyte cells as well as pulmonary pneumocytes; it is also affected by androgens.<sup>11</sup> Hence, the authors proposed that the ACE2 receptor in injured epidermal keratinocytes may be a possible route for SARS-CoV-2 entry to the host cells. Thatiparthi et al. concluded that hyper-androgenic conditions like AGA might augment the severity of COVID-19 and anti-androgenic medication should be assessed as a therapeutic option.<sup>11</sup>

Yousaf et al.,<sup>12</sup> in response to the previous paper,<sup>11</sup> expounded that the ACE2 receptor, as a possible route of entry in epidermal keratinocytes for SARS-CoV-2, should be assessed in other conditions with epidermal disruption like hand eczema.<sup>12</sup> Furthermore, alopecia, as a manifestation of a hyper-androgenic state, could be a presentation of immunosenescence, which comprises another important risk factor for COVID-19 morbidity and mortality. Consequently, the correlation between alopecia and severity of COVID-19 is one of the possible factors that influence the disease outcome.<sup>12</sup>

Wambier et al.<sup>13</sup> delineated an Indian pilot, observational, prospective study that evaluated 44 hospitalized COVID-19-positive men according to the severity of AGA. The most severe consequences like ventilator usage due to respiratory failure or mortality were associated with HNS scores above 2 (Gabrin sign). This study propounded that worse outcomes, including demand for ventilator and mortality, developed in adult men without any comorbidities aged 35–45 years with the Gabrin sign.<sup>13</sup>

Ramos et al.<sup>14</sup> performed a cross-sectional study through an online questionnaire to examine COVID-19 characteristics and associated risk factors. A total of 43 595 eligible subjects were enrolled in this study including 39 789 controls, 2332 suspected COVID-19 cases, and 1474 definite COVID-19 cases. The frequency of AGA and excessive gray hair was correlated with the age group.<sup>14</sup> Interestingly, COVID-19 severity was significantly associated with extensive gray hair and also AGA. This survey explained that AGA and gray hair were correlated with cardiovascular disease (an important risk factor for COVID-19 severity). The major limitation of the study was the absence of a professional examination; thus, other etiologies of hair loss like telogen effluvium could not be assessed.<sup>14</sup>

Wambier et al.,<sup>15</sup> in a recent study, described SARS-CoV-2 infectivity through transmembrane protease serine 2 (TMPRSS2), which is

associated with androgen sensitivity.<sup>15</sup> Moreover, the prospective cohort study of Goren et al.<sup>16</sup> involved 77 men admitted with COVID-19; ICU admission was significantly lower (1 out of 12 patients; 8%) in the group taking anti-androgens (dutasteride, finasteride, spironolactone, etc.) relative to the group that did not use anti-androgens (38 out of 65 patients; 58%).<sup>16</sup>

Recent investigations suggested that the shorter CAG repeat length in the first exon of the androgen receptor gene is associated with a higher rate of COVID-19 morbidity and mortality.<sup>17</sup> Besides, decreased CAG repeat length is correlated with hyper-androgenic conditions like AGA and acne.<sup>17</sup> Interestingly, different ethnicities experienced divergent courses of COVID-19; for instance, African Americans had a shorter length of CAG repeats and featured a disproportionate rate of COVID-19-associated deaths.<sup>18</sup>

McCoy et al.<sup>17</sup> evaluated the polyglutamine repeats (CAG repeat) located in the AR gene in 65 COVID-19 positive patients. All subjects were divided into two groups, one with CAG < 22 (48%) and the other with CAG ≥ 22 (52%).<sup>17</sup> The length of hospitalization and the total number of ICU admissions were significantly higher in the group with CAG < 22 compared with CAG ≥ 22 (25 days, 14 of 31 subjects (45.2%) vs. 47.5 days, 24 of 34 subjects (70.6%), respectively). In that study, increased AR CAG scores were associated with a more severe course of COVID-19 and also a higher rate of ICU admission. The authors proposed the AR CAG repeat length as a biomarker for evaluating the risk of ICU admission among COVID-19 patients.<sup>17</sup>

Sabharwal et al.<sup>19</sup> established that the geographical divergence of COVID-19 might be due to genetic differences in distinct ethnicities. For instance, the HSD3B1 gene that encodes 3 β-hydroxysteroid dehydrogenase-1, an enzyme responsible for the conversion of dehydroepiandrosterone to more active androgens, is more common in Italy and Spain. This could elucidate why the first reports of AGA were from Spain.<sup>19</sup>

### 3.2 | Sex-related differences in COVID-19

Recent studies suggest higher prevalence, comorbidity, and mortality rates of COVID-19 in males than females. In a comprehensive review of 59 254 individuals from 11 countries, higher mortality of SARS-CoV-2 infection was reported in males.<sup>2</sup>

Foresta et al.<sup>3</sup> discussed gender susceptibility to SARS-CoV-2 infection and implied a higher rate of severe cases (females (42%) vs. males (58%)) and mortality in men, similar to SARS and MERS as other diseases caused by the *Coronaviridae* family.<sup>3</sup> Channappanavar et al. reported elevated SARS-CoV load in male mice pneumocytes examined in vivo.<sup>18</sup> Besides, sex-related risk factors might aggravate the course of COVID-19.<sup>4</sup> Several etiologies have been described to affect the gender divergence in SARS-CoV-2 infection including habitual history of smoking cigarettes and alcohol consumption as well as psychosocial factors and dissimilar sex-related comorbidities.<sup>4</sup>

One of the most important routes for COVID-19 pathogenicity is the ACE2 receptor in alveolar epithelial cells. Besides, SARS-CoV-2 utilizes the TMPRSS2 that is expressed in type II pneumocytes for

spike protein priming. This leads to decreased viral identification by the immune system and facilitates viral connection to host cells.<sup>18,20</sup> ACE2, as the modulator of the renin-angiotensin system (RAS), has an important preservative role against organ damage and conditions like hypertension, cardiovascular disease, and acute respiratory distress syndrome (ARDS).<sup>4</sup> Also, SARS-CoV-2 attaches to the ACE2 receptor of host cells through its spike protein and decreases the expression of ACE2. An increased level of angiotensin II in conjunction with a decreased level of ACE2 may cause higher permeability of pulmonary vessels, leading to dreadful outcomes of COVID-19 including ARDS and pulmonary failure.<sup>4</sup>

Sex hormones affect the RAS. For instance, estrogen augments the expression of ACE2, possibly leading to protective impacts against COVID-19. Furthermore, with the same viral load, SARS-CoV-2 infectivity was found to be more severe in males than females.<sup>3,4</sup> Moreover, ACE2 is encoded by the gene located on the X chromosome, the expression of which is modified by DNA methylation at the cytosine-phosphate-guanine (CpG) sites.<sup>3</sup> Besides, the DNA methylation level differed significantly across male and female populations. In addition, ACE2 expression is increased due to RAS modification by estrogen and diminished significantly in adult males. Therefore, according to the hypothesis of higher expression of ACE2 in females, sex dissimilarities in SARS-CoV-2 affliction may be justified.<sup>2,3</sup> However, several studies have not found significant sex and age differences in the expression of ACE2.<sup>3,4</sup> The serine protease TMPRSS2 is another factor that raises the ACE2 level and can be upregulated by androgens. Recent studies established the expression of TMPRSS2 in the specific end organs targeted by SARS-CoV-2 like the lung, liver, and kidneys.<sup>18</sup> Furthermore, the expression of TMPRSS2 mRNA in prostate cells was found to be modulated by androgens.<sup>18</sup> Also, TMPRSS2 expression could be upregulated by estrogen and glucocorticoids. These findings may confirm the occurrence of severe COVID-19 in some females.<sup>21</sup> In contrast, a recent study by Asselta et al. did not report significant variation in the expression of TMPRSS2 based on sex and age distinction analysis.<sup>22</sup> Hypothetically, anti-androgen treatments in men may decrease TMPRSS2 function and reduce SARS-CoV-2 virulence and COVID-19 complications.<sup>4,23</sup> Additionally, lower expression of TMPRSS2 is expected in females due to lower androgen levels, which may be associated with better outcomes of COVID-19 in women.<sup>3,24</sup> On the other hand, in a preprint study, no evidence of escalated TMPRSS2 expression was discovered in the lungs of male humans and mice in comparison with females.<sup>25</sup> Consequently, further investigations about sex-related differences in expression and activity of TMPRSS2 should be encouraged.

A current research propounded that circulating TMPRSS2 may affect cells without membrane expression; as a result, the assessment of the function of circulating TMPRSS2 in viral infections is an appealing subject.<sup>26,27</sup> Moreover, a recent investigation detailed that camostat mesylate (a TMPRSS2 blocker) impeded SARS-CoV-2 entry into TMPRSS2-expressing pneumocytes. This finding corroborates camostat mesylate as a putative treatment against COVID-19.<sup>28</sup>

Sex-related dissimilarities in immune system responses may also affect the gender-specific COVID-19 outcomes.<sup>29,30</sup> Most of the

genes associated with immune modulation are on X chromosomes, which may justify the domination of the immune system response in women.<sup>29</sup> For example, a recent examination described that severe COVID-19 in women leads to a higher concentration of serum IgG and a more robust IgG Ab response in the early phase of SARS-CoV-2 infection in comparison with men.<sup>30</sup>

### 3.3 | Androgens and COVID-19

Sex hormones have a major and dimorphic role in innate and adaptive immune system modulation.<sup>27</sup> Recent studies suggested both high and low androgen levels could lead to a severe course of COVID-19.<sup>31,32</sup> Increased tissue dihydrotestosterone (DHT) levels are seen in hyperandrogenic conditions like AGA, benign prostatic hyperplasia, and prostate cancer.<sup>33</sup> Notably, Motopoli et al. studied androgen-deprivation therapy (ADT) in 118 prostate cancer patients and demonstrated that ADT might have a protective role against SARS-CoV-2 infection.<sup>34</sup> Moreover, Patel et al.<sup>35</sup> examined 22 and 36 patients who underwent ADT and non-ADT, respectively; and postulated that ADT was significantly associated with lower hospitalization rates and decreased need for supplemental oxygen. Also, they reported a non-significant lower rate of intubation and mortality in the ADT group.<sup>35</sup> On the other hand, Caffo et al. evaluated 1949 metastatic prostate cancer (PC) patients under ADT and questioned the protective effects of ADT on COVID-19 among PC patients.<sup>36</sup> Koskinen et al. also reported that ADT in 532 prostate cancer patients was not associated with a higher frequency of COVID-19 or increased disease severity.<sup>37</sup> Additionally, Ory et al. declared that reduced expression of TMPRSS2 due to ADT might improve the outcomes of COVID-19.<sup>38</sup> In addition, a recent study appraised the effect of ADT on TMPRSS2 expression and COVID-19 susceptibility. The authors noted that ADT had decreased TMPRSS2 mRNA expression in the mouse lung.<sup>39</sup> Another new study demonstrated a robust immune response in male mice that received ADT and explained that human genes correlated with a weak immune response to the virus are related to androgens.<sup>40</sup>

Appealingly, Ehdaie et al.<sup>41</sup> documented a correlation between ADT and two comorbidities that lead to unfavorable consequences in the SARS-CoV-2 affliction, namely cardiac adverse events and venous thromboembolism.<sup>41</sup> In some investigations, the association between testosterone and thrombotic events like microthrombi and venous thromboembolism (one of the characteristic events in severe cases of COVID-19) has been revealed.<sup>4</sup> In contrast, testosterone therapy in males with hypogonadism has a protective role against pro-thrombotic conditions.<sup>31</sup>

A reduction in testosterone level is associated with aging and comorbidities like obesity, diabetes, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD), all of which are major risk factors for COVID-19.<sup>32</sup> These findings posited the possible dimorphic role of androgens in the course of COVID-19.

The androgen-based hypothesis in the severity of SARS-CoV-2 infection could not explain better outcomes of COVID-19 in younger males with higher levels of testosterone compared with elderlies with

lower testosterone levels and dreadful consequences.<sup>4,29</sup> Hence, the evaluation of androgen effects on the immune system may clarify age-related differences in males with SARS-CoV-2 infection.<sup>4</sup>

Androgens modify the immune system by attenuating inflammatory responses. This includes the suppression of cytokine storms and the reduction of peripheral blood monocytes and natural killer cells.<sup>4,27,32</sup> Further, sex hormones like estrogen and testosterone may minimize the pro-inflammatory state, and its reduction may exacerbate unfavorable outcomes of COVID-19 in elderly patients.<sup>29</sup> Also, androgens augment the generation of suppressive cytokines like interleukin-10 and transforming growth factor- $\beta$ . Moreover, androgens play an important role in thymic evolution, which decreases T cell function.<sup>4</sup> Rastrelli et al. indicated diminished total and calculated free testosterone levels were associated with higher ICU admission and mortality rates in 31 male patients with severe COVID-19, suggesting a protective effect of androgens in SARS-CoV-2 infection.<sup>42</sup> Similarly, Salciccia et al. evaluated 29 admitted men with SARS-CoV-2 affliction, and demonstrated that total testosterone levels were substantially lower in ARDS patients and were associated with poor outcomes in COVID-19 patients. The study findings supported the preservative impacts of testosterone in COVID-19 afflicted patients.<sup>43</sup> Correspondingly, Schroeder et al. reported low levels of testosterone and DHT in severely ill COVID-19 males.<sup>27</sup> Similarly, Ma et al.<sup>44</sup> found a significantly decreased ratio of testosterone to luteinizing hormone (LH) besides elevated serum LH and prolactin in 81 COVID-19 patients in comparison with 100 healthy controls; however, no significant variation in the level of serum testosterone was found.<sup>44</sup> In that study, the diminished ratio mentioned may have been due to impaired testosterone generation and the compensatory secretion of LH in COVID-19 patients.<sup>24</sup> These studies proposed that the severity of COVID-19 could be correlated with a lower level of testosterone due to pre-existing conditions or increased SARS-CoV-2 virulence.<sup>4</sup>

Rambhatla et al.<sup>45</sup> performed a retrospective study comparing 32 male COVID-19 patients on testosterone replacement therapy (TRT) against a control group of 63 COVID-19 afflicted males lacking TRT. The researchers concluded that TRT was not correlated with increased COVID-19 severity or worsened consequences.<sup>45</sup>

Cadegiani et al.<sup>46</sup> conducted a cross-sectional, case-control study with a total of 233 afflicted patients to assess the characteristics of COVID-19 in hyperandrogenic females with polycystic ovary syndrome (PCOS). Several common clinical symptoms of COVID-19 occurred more in the hyperandrogenic group than the non-hyperandrogenic group.<sup>46</sup> Interestingly, shorter lengths of CAG repeats in the AR gene were related to PCOS.<sup>18</sup> These findings suggest the need for further evaluation of COVID-19 outcomes in hyperandrogenic conditions.<sup>46</sup>

### 3.4 | Anti-androgenic treatments and COVID-19

In the COVID-19 pandemic, researchers throughout the world have conducted several clinical trials to assess plausible treatment

options.<sup>20</sup> For instance, some clinical trials have planned to target sex hormones or TMPRSS2.<sup>24</sup> Additionally, chloroquine and nitric oxide as COVID-19 treatment candidates are reported to decrease testosterone levels in animals and diminish AR activity in patients with PC, respectively.<sup>31</sup>

Based on the aforementioned content, some studies evaluated ADT consequences on patients with SARS-CoV-2 infection and proposed that anti-androgens have protective effects against COVID-19.<sup>39,47</sup> Moreover, ADT causes diminished expression of TMPRSS2 and decreased RAS overexpression.<sup>24,31</sup> Anti-androgenic treatments consist of gonadotrophic releasing hormone (GnRH) agonists (leuprolide, goserelin, and triptorelin) and antagonists (degarelix), androgen receptor inhibitors (ARIs; cyproterone, spironolactone, eplerenone, and flutamide), and 5 alpha-reductase inhibitors (5ARIs) (finasteride and dutasteride).<sup>47</sup> Liaudet et al.<sup>48</sup> considered spironolactone as a mineralocorticoid receptor (MR) antagonist that has an anti-androgenic function, which may suppress the expression of TMPRSS2. Therefore, the mentioned mechanisms and characteristic action of spironolactone to decrease pulmonary edema would be favorable in COVID-19 treatment.<sup>48</sup>

Lazzeri et al.<sup>49</sup> designed an observational investigation with 421 COVID-19-positive patients. The study results indicated that only 4.22% of the population was under treatment with 5ARIs, which was significantly lower compared with general population data (14.97%). The mortality rate was higher in male patients receiving 5ARIs (27.78%) than all males with SARS-CoV-2 affliction that may be justified with older age in the 5ARIs group. They postulated that androgen inhibition might have a preservative effect against COVID-19.<sup>49</sup>

Adamowicz et al.<sup>50</sup> posited that 5 alpha-reductase (5AR) in lungs lessens the activity of androgens, and 5ARIs might lead to focal androgen excess that could impair the lung regeneration process and cause severe symptoms in COVID-19 patients.<sup>50</sup> Comparably, Kroumpouzou et al.<sup>51</sup> assumed 5AR in the lungs minimizes the effects of androgens and leads to regeneration of the surfactant layer. Usage of 5ARIs in COVID-19 patients (by elevation of androgen levels in lungs) disabled the regenerative process in the lungs, thereby exacerbating disease severity.<sup>51</sup> Interestingly, these data suggest that SARS-CoV-2 infection may be worsened by the use of anti-androgens. McCoy et al.<sup>33</sup> examined COVID-19 patients with AGA and analyzed 48 patients who had received 5ARIs for at least 6 months with a control group of 65 patients and concluded that a lower frequency of COVID-19-related clinical symptoms was associated with 5ARI usage.<sup>33</sup> Lee et al.<sup>52</sup> carried out a retrospective cohort study on 5061 confirmed COVID-19 patients and reported significant higher rates of oxygen requirement (6.46% vs. 4.63%) and ICU admission (2.69% vs. 1.87%) as well as non-significant increased mortality rate (1.88% vs. 1.48%) in males relative to females. In an analysis of patients who had received hormone replacement therapy (HRT) with the control group, no statistically significant correlations were found; however, oxygen therapy requirement was higher in the non-HRT group and the length of ICU admission was escalated in the recent HRT user group.<sup>52</sup>

Ilanhez et al.<sup>53</sup> performed population research via an electronic questionnaire. Among 41 529 participants, 4.7% of healthy and 4.5% of COVID-19-afflicted males had a history of using anti-androgens.

Anti-androgen usage was not associated with increased prevalence or worsened outcomes of COVID-19.<sup>53</sup> Cadejani et al.<sup>54</sup> performed an observational research with a total of 305 non-hospitalized COVID-19 males (192 non-AGA, 71 AGA non-5ARIs, and 52 AGA-5ARIs). Most of the patients who had received 5ARIs (82.7%) were asymptomatic; AGA patients who had not received any 5ARIs experienced more COVID-19 symptoms than non-AGA patients. In terms of the length of clinical symptoms and viral shedding, AGA patients experienced a more severe course of COVID-19 compared to non-AGA patients (9.4 vs. 14.2 days, and 14 vs. 17.8 days, respectively). The mentioned durations were alleviated by chronic 5ARI consumption.<sup>54</sup>

Along with anti-androgen clinical trials, other studies have been carried out to evaluate the effect of direct TMPRSS2 blockers like nafamostat, camostat, bromhexine, plasma alpha-1-antitrypsin, and leupeptin on COVID-19.<sup>4,18,27</sup> All clinical trials related to the sex hormones are summarized in Table S1.

## 4 | CONCLUSION

Considering the points discussed, androgens appear to have a dimorphic role in the immune system and may affect COVID-19 severity. Current research hypothesized different mechanisms of androgens in relation to the pathogenesis of SARS-CoV-2 infection. Consequently, recent studies assessed the association of COVID-19 with hyperandrogenic conditions, ADT and TRT therapies, and sex hormone levels. These investigations have propounded the dimorphic role of sex hormones like testosterone in SARS-CoV-2 affliction and have suggested the necessity of additional studies. As a hyperandrogenic state, AGA can be associated with a more severe course of COVID-19. However, some studies debate the escalated prevalence of AGA in cases of severe COVID-19. In the aforementioned investigations, anti-androgenic therapies like testosterone and dutasteride in AGA and spironolactone in polycystic ovarian disease revealed favorable outcomes in less severe symptoms of COVID-19. It might be reasonable for practitioners to continue prescribing these medications for patients who underwent the treatment in the COVID-19 era. AGA patients referred to clinic or hospitalized might experience a more severe course of COVID-19, but some studies have not confirmed it. In conclusion, further studies should examine the association between AGA and COVID-19.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## ORCID

Hamideh Moravvej  <https://orcid.org/0000-0002-9425-7282>

Mohammad Reza Pourani  <https://orcid.org/0000-0003-3222-7528>

Fahimeh Abdollahimajd  <https://orcid.org/0000-0002-9463-0665>

## REFERENCES

- WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int>
- Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med*. 2020;9(4):941.
- Foresta C, Rocca M, Di Nisio A. Gender susceptibility to COVID-19: a review of the putative role of sex hormones and X chromosome. *J Endocrinol Invest*. 2020;44:1-6.
- Cattrini C, Bersanelli M, Latocca MM, Conte B, Vallome G, Boccardo F. Sex hormones and hormone therapy during covid-19 pandemic: implications for patients with cancer. *Cancer*. 2020;12(8):2325.
- Barat T, Abdollahimajd F, Dadkhahfar S, Moravvej H. Evaluation of the efficacy and safety of cow placenta extract lotion compared to minoxidil 2% in the treatment of female pattern androgenetic alopecia. *Int J Womens Dermatol*. 2020;6:318-321.
- Wambier CG, Vaño-Galván S, McCoy J, et al. Androgenetic alopecia present in the majority of hospitalized COVID-19 patients—the “Gabrin sign”. *J Am Acad Dermatol*. 2020;83:680-682.
- Mirmirani P. Age-related hair changes in men: mechanisms and management of alopecia and graying. *Maturitas*. 2015;80(1):58-62.
- Goren A, Vaño-Galván S, Wambier CG, et al. 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;19:1545-1547.
- Nanes BA. Androgenetic alopecia in COVID-19: compared to what? *J Am Acad Dermatol*. 2020;83(6):e451.
- Lee J, Yousaf A, Fang W, Kolodney MS. Male balding is a major risk factor for severe COVID-19. *J Am Acad Dermatol*. 2020;83(5):e353-e354.
- Thatiparthi A, Liu J, Martin A, Wu JJ. Letter to the editor: a response to ‘male balding is a major risk factor for severe COVID-19’. *J Am Acad Dermatol*. 2021;84(2):e87-e88.
- Yousaf A, Kolodney M. Reply to letter to the editor: “a response to ‘male balding is a major risk factor for severe COVID-19’”. *J Am Acad Dermatol*. 2020;84(2):e89.
- Wambier CG, Vaño-Galván S, McCoy J, Pai S, Dhurat R, Goren A. Androgenetic alopecia in COVID-19: compared to age-matched epidemiologic studies and hospital outcomes with or without the Gabrin sign. *J Am Acad Dermatol*. 2020;83(6):e453-e454.
- Müller Ramos P, Ianhez M, Amante Miot H. Alopecia and Gray hair are associated with COVID-19 severity. *Exp Dermatol*. 2020;29(12):1250-1252.
- Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *J Am Acad Dermatol*. 2020;83(1):308-309.
- Goren A, Wambier CG, Herrera S, et al. Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men. *J Eur Acad Dermatol Venereol*. 2021;35(1):e13-e15.
- McCoy J, Wambier CG, Herrera S, et al. Androgen receptor genetic variant predicts COVID-19 disease severity: a prospective longitudinal study of hospitalized COVID-19 male patients. *J Eur Acad Dermatol Venereol*. 2021;35(1):e15-e17.
- Wambier CG, Goren A, Vaño-Galván S, et al. Androgen sensitivity gateway to COVID-19 disease severity. *Drug Dev Res*. 2020;81:771-776.
- Sabharwal N, Sharifi N. HSD3B1 genotypes conferring adrenal-restrictive and adrenal-permissive phenotypes in prostate cancer and beyond. *Endocrinology*. 2019;160(9):2180-2188.
- Pourani MR, Abdollahimajd F. CD147 as a novel receptor in the pathogenesis of SARS-CoV-2: is there any correlation with risk of COVID-19 in dermatological diseases? *Dermatol Ther*. 2020;33:e14443.
- Xu Z, Wang Y, Xiao ZG, et al. Nuclear receptor ERR $\alpha$  and transcription factor ERG form a reciprocal loop in the regulation of TMPRSS2: ERG fusion gene in prostate cancer. *Oncogene*. 2018;37(48):6259-6274.
- Asselta R, Paraboschi EM, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *Aging (Albany NY)*. 2020;12(11):10087-10098.
- Pourani MR, Nekooghdam SM, Youssefian L, Vahidnezhad H, Abdollahimajd F. CD147 inhibitors as a treatment for melanoma: promising agents against SARS-CoV-2 infection. *Dermatol Ther*. 2020;33:e14449.
- Bhowmick NA, Oft J, Dorff T, et al. COVID-19 and androgen targeted therapy for prostate cancer patients. *Endocr Relat Cancer*. 2020;27(9):R281-R292.
- Baratchian M, McManus JM, Berk M, et al. Sex, androgens and regulation of pulmonary AR, TMPRSS2 and ACE2. *bioRxiv*; 2020.
- Ziegler CG, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. 2020;181:1016-1035.e19.
- Strope JD, Chau CH, Figg WD, eds. Are sex discordant outcomes in COVID-19 related to sex hormones? *Sem Oncol*. 2020;47:335-340.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271-280.e8.
- Al-Lami RA, Urban RJ, Volpi E, Algburi AM, Baillargeon J. Sex hormones and novel corona virus infectious disease (COVID-19): Mayo Clinic Proceedings; 2020; Elsevier.
- Zeng F, Dai C, Cai P, et al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between sex. *J Med Virol*. 2020;92(10):2050-2054.
- Kalra S, Bhattacharya S, Kalhan A. Testosterone in COVID-19—foe, friend or fatal victim? *Eur Endocrinol*. 2020;16(2):88.
- Pozzilli P, Lenzi A. Commentary: testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism*. 2020;108:154252.
- McCoy J, Cadegiani FA, Wambier CG, et al. 5-alpha-reductase inhibitors are associated with reduced frequency of COVID-19 symptoms in males with Androgenetic alopecia. *J Eur Acad Dermatol Venereol*. 2020;35(4):e243-e246.
- Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n= 4532). *Ann Oncol*. 2020;31:1040-1045.
- Patel VG, Zhong X, Liaw B, et al. Does androgen deprivation therapy protect against severe complications from COVID-19? *Ann Oncol*. 2020;31(10):1419-1420.
- Caffo O, Zagonel V, Baldessari C, et al. On the relationship between androgen-deprivation therapy for prostate cancer and risk of infection by SARS-CoV-2. *Ann Oncol*. 2020;31(10):1415-1416.
- Koskinen M, Carpen O, Honkanen V, et al. Androgen deprivation and SARS-CoV-2 in men with prostate cancer. *Ann Oncol*. 2020;31:1417-1418.
- Ory J, Lima TFN, Towe M, et al. Understanding the complex relationship between androgens and SARS-CoV2. *Urology*. 2020;144:1-3.
- Leach DA, Isac A-M, Bevan CL, Brooke GN. TMPRSS2, required for SARS-CoV-2 entry, is downregulated in lung cells by enzalutamide, a prostate cancer therapeutic; 2020.
- Bennani N, Bennani-Baiti I. Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy. *Ann Oncol*. 2020;31(11):1585-1586.
- Ehdaie B, Atoria CL, Gupta A, et al. Androgen deprivation and thromboembolic events in men with prostate cancer. *Cancer*. 2012;118(13):3397-3406.

42. Rastrelli G, Di Stasi V, Inglese F, et al. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. *Andrology*. 2021;9(1):88-98.
43. Salciccia S, Del Giudice F, Gentile V, et al. Interplay between male testosterone levels and the risk for subsequent invasive respiratory assistance among COVID-19 patients at hospital admission. *Endocrine*. 2020;70(2):206-210.
44. Ma L, Xie W, Li D, et al. Effect of SARS-CoV-2 infection upon male gonadal function: a single center-based study. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.03.21.20037267>.
45. Rambhatla A, Bronkema CJ, Corsi N, et al. COVID-19 infection in men on testosterone replacement therapy. *J Sex Med*. 2021;18(1):215-218.
46. Cadegiani F, Lim R, Goren A, et al. Clinical symptoms of Hyperandrogenic women diagnosed with COVID-19. *J Eur Acad Dermatol Venereol*. 2021;35(2):e101-e104.
47. Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. *BMC Endocr Disord*. 2020;20(1):1-19.
48. Liaudet L, Szabo C. Blocking mineralocorticoid receptor with spironolactone may have a wide range of therapeutic actions in severe COVID-19 disease. *Crit Care*. 2020;24(1):1-2.
49. Lazzeri M, Azzolini E, Buffi NM, et al. Impact of anti-androgenic therapies on COVID-19: an observational study in male population from a COVID-19 regional centre of Lombardy (Italy). medrxiv; 2020.
50. Adamowicz J, Juszcak K, Drewa T. May patients receiving 5-alpha-reductase inhibitors be in higher risk of COVID-19 complications? *Med Hypotheses*. 2020;140:109751.
51. Kroumpouzou G. Effects of 5-alpha reductase inhibitors on lung function: a reason for discontinuation during COVID-19 pandemic? *Dermatol Ther*. 2020;33:e13535.
52. Lee JH, Kim YC, Cho SH, et al. The effect of sex hormone on COVID-19: analysis of laboratory-confirmed 5061 patients in South Korea. *Menopause*. 2020;27(12):1376-1381.
53. Ianhez M, Ramos PM, Goren A, Miot HA. Androgen sensitivity in COVID-19 and antiandrogens: prospective data are still needed. *Dermatol Ther*. 2020;33:e14166.
54. Cadegiani FA, Goren A, Wambier CG, McCoy J. Azithromycin with nitazoxanide, hydroxychloroquine or ivermectin, with or without dutasteride, for early stage COVID-19: an open-label prospective observational study in males with mild-to-moderate COVID-19 (The Pre-AndroCoV Male Trial); 2020.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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