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COMMENTARY

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Androgen sensitivity gateway to COVID-19 disease severity

Carlos Gustavo Wambier[1] | Andy Goren[2] | Sergio Vaño-Galván[3] | Paulo Müller Ramos[4] | Angelina Ossimetha[5] | Gerard Nau[6] | Sabina Herrera[3] | John McCoy[2]

[1]Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, Rhode Island

[2]Applied Biology, Inc., Irvine, California

[3]Trichology Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain

[4]Department of Dermatology and Radiotherapy, São Paulo State University – UNESP, São Paulo, Brazil

[5]Brown University, Providence, Rhode Island

[6]Division of Infectious Diseases, Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island

Correspondence
Carlos Gustavo Wambier, Department of Dermatology, Rhode Island Hospital, 593 Eddy Street, APC, 10th Floor, Providence, RI 02903.
Email: carlos_wambier@brown.edu

Abstract

In this communication, we present arguments for androgen sensitivity as a likely determinant of COVID-19 disease severity. The androgen sensitivity model explains why males are more likely to develop severe symptoms while children are ostensibly resistant to infection. Further, the model explains the difference in COVID-19 mortality rates among different ethnicities. Androgen sensitivity is determined by genetic variants of the androgen receptor. The androgen receptor regulates transcription of the transmembrane protease, serine 2 (TMPRSS2), which is required for SARS-CoV-2 infectivity. TMPRSS2 primes the Spike protein of the virus, which has two consequences: diminishing viral recognition by neutralizing antibodies and activating SARS-CoV-2 for virus-cell fusion. Genetic variants that have been associated with androgenetic alopecia, prostate cancer, benign prostatic hyperplasia and polycystic ovary syndrome could be associated with host susceptibility. In addition to theoretical epidemiological and molecular mechanisms, there are reports of high rates of androgenetic alopecia of from hospitalized COVID-19 patients due to severe symptoms. Androgen sensitivity is a likely determinant of COVID-19 disease severity. We believe that the evidence presented in this communication warrants the initiation of trials using anti-androgen agents.

KEYWORDS

alopecia, androgens, anti-androgen, clinical trial, COVID-19, pandemic, SARS-CoV-2, TMPRSS2

Individual vulnerability to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been linked to pre-existing conditions in each host. Individual risk has been attributed to multiple co-morbidities including COPD, metabolic, cardiovascular and pulmonary disease (Bialek et al., 2020). However, this disease mortality risk model fails to explain gender disparities in COVID-19 mortality. Additionally, the small but not insignificant amount of otherwise healthy young adults that have died following SARS-CoV-2 infection, most notably, Dr Li Wenliang, a previously healthy 34-year-old Chinese doctor that first alerted the world to the SARS-CoV-2 epidemic (Petersen et al., 2020).

A recent report from 5,700 patients with COVID-19 in New York showed a drastic difference of over six times more male fatalities in a very productive age range (40–49 years) and approximately two times more male admissions from 30 to 49 years. (Richardson, Hirsch, Narasimhan, et al., 2020). In Germany, the mortality proportion of males to females has been approximately 1.5–1 among the tested patients (Koptyug, 2020). However, it is important to note that the population > 70 years-old is predominantly female. Analyzing those younger than 70 years, the ratio of male to female mortality is over 3–1 (Koptyug, 2020).

Males are known to be at an increased risk for severe symptoms following SARS-CoV-2. The only study to date that utilized a multivariable analysis showed that male gender was the most important independent risk factor for COVID-19 complications. Within 487 cases from Wuhan, China, male gender showed an odds-ratio (OR) of 3.68

(95% confidence interval [CI] 1.75–7.75), compared to the diagnosis of hypertension, which had an OR 2.71 (95% CI 1.32–5.59), and age over 50 years, which had OR 1.06 (95% CI 1.03–1.08) (Shi et al., 2020). Several other studies have reported a significant difference in the incidence of severe cases between females and males. Among 1,099 cases reported in one study, 58% were male, and among the 67 patients with severe disease needing intensive care, noninvasive ventilator, or that died 67% were male (Guan et al., 2020). Epidemiologic reports usually fail to look at obesity and smoking as covariates in analysis of the impact of gender. And obesity is particularly confounding as obesity in elderly men may be associated with reduced, rather than enhanced, androgen activity. And current smoking seems to have a paradoxical protective effect (Propper, 2020). All epidemiological data published so far reported that COVID-19 patients show a very low prevalence of smokers, with no significant association between current smoking and severe disease in COVID-19 patients (Rossato et al., 2020). At the same time, chronic obstructive pulmonary disease is likely to be more common in the older male population than in the female population, as a consequence of occupational and smoking habits.

Epidemiological observations note milder symptoms and infection rates in children. In a review of 72,314 cases by the Chinese Center for Disease Control and prevention, children less than 10 years of age accounted for less than 1% of the total cases, with no fatal reports (Wu & McGoogan, 2020). In the series of 1,099 laboratory confirmed cases, only nine (less than 1%) were below 14 years of age, among which, only one had severe disease (Guan et al., 2020). In another study, among 1,391 children from 0 to 15 years-old actively tested for suspected SARS-CoV-2, only 171 (12%) had a positive test (60.8% were male), among the 171 positive tests, 15% were asymptomatic and 20% were oligosymptomatic (Lu et al., 2020). Another epidemiologic study in 36 children younger than 16 years reported higher prevalence of COVID-19 in males (64%) (Qiu et al., 2020). Another case report of a male newborn was documented with uneventful rhinitis and cough. The newborn was in close contact with his father suffering from upper airway infection and conjunctivitis (Canarutto et al., 2020).

A possible explanation for the higher mortality rate and disease severity among male patients and the extremely low mortality rate among pre-pubescent may be due to the action of androgens on target tissues, such as the lung (Goren et al., 2020). These sex-based differences in vulnerability to SARS-CoV infection, and increased viral load in the lungs in males has been reported in vivo experiments in mice (Channappanavar et al., 2017).

The intracellular androgen mediated mechanisms for SARS-CoV-2 infection have been previously summarized (Wambier & Goren, 2020). The role of anti-androgen medications prophylactically or after infection by SARS-CoV-2 are still unknown, however, the cellular mechanisms of SARS infection provide important clues to the development of therapies (Figure 1). For example, the first biological step required for viral infectivity of the SARS-CoV-2 virus is priming of the spike proteins by transmembrane protease, serine 2 (TMPRSS2). TMPRSS2 is expressed on the surface of type II pneumocytes in human lung tissue. Although other proteases have been found to activate the spike proteins in vitro, only TMPRSS2 activity is regarded as essential for viral entry and replication in infected hosts (Hoffmann

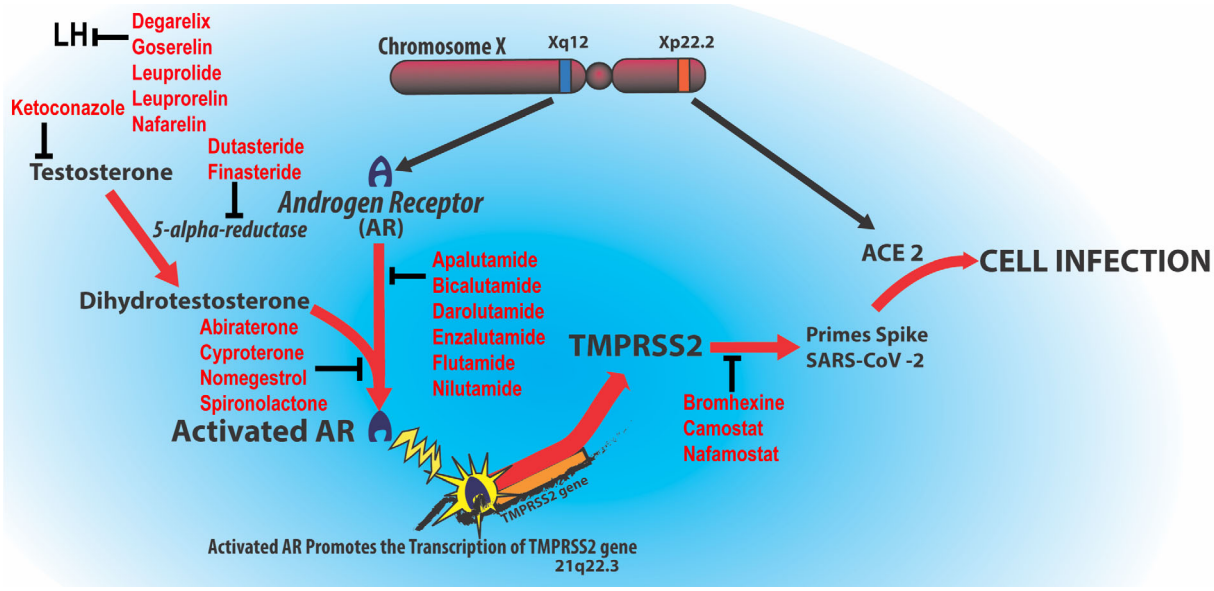

FIGURE 1 Androgen pathway in COVID-19 infection. Red arrows show the steps that are targeted by androgen blockers, which include: GnRH analogs (Degarelix, Goserelin, Leuprolide, Leuprorelin, Nafarelin), which stop LH secretion and induce chemical castration. Dutasteride and Finasteride are 5-alpha-reductase inhibitors, which are safe for men and women after menopause, because dihydrotestosterone (DHT) is the most potent intrinsic androgen hormone. Testosterone is regarded as the main androgen hormone, its production in inhibited by ketoconazole, an inhibitor of steroidogenesis. Androgen receptor inhibitors may be steroidal, such as Abiraterone, Cyproterone, Nomegestrol, or Spironolactone; or nonsteroidal (Apalutamide, Bicalutamide, Darolutamide, Enzalutamide, Flutamide, and Nilutamide). TMPRSS2 blockers include Bromhexine, Camostat, and Nafamostat

et al., 2020). TMPRSS2 may also cleave angiotensin converting enzyme 2 (ACE2) for augmented viral entry, as has been shown for SARS-CoV-1 (Heurich et al., 2014).

The TMPRSS2 gene is located on the human chromosome 21q22.3, it encodes a 492 amino acid polypeptide (Paoloni-Giacobino, Chen, Peitsch, Rossier, & Antonarakis, 1997). Androgen receptor activity is required for the transcription of *TMPRSS2*, as no other regulatory element of the *TMPRSS2* promoter has been described in humans to date (Lucas et al., 2014; National Institutes of Health, 2020). The human *TMPRSS2* promoter has a 15-bp androgen response element at position 148 relative to the putative transcription start site. In addition, TMPRSS2 mRNA expression was found to be androgen regulated in prostate cells (Lin et al., 1999), and the androgen receptor is responsible for the upregulation of TMPRSS2 mRNA (Afar et al., 2001). Additionally, androgen treatment increased TMPRSS2 zymogen activation in cell culture and in a mouse xenograft model, suggesting androgens regulate TMPRSS2 on transcription and post-translation levels (Afar et al., 2001).

The TMPRSS2 gene is expressed mainly in the adult prostate, but also expressed in multiple other tissues, particularly in human adult colon, small intestine, pancreas, kidney, lung, and liver (Jacquinet et al., 2001); additionally, it is found in fetal lung and kidney (Paoloni-Giacobino, Chen, Peitsch, Rossier, & Antonarakis, 2001). TMPRSS2 is expressed in the target organs for COVID-19: lungs, liver, and kidneys (Gu, Han, & Wang, 2020). ACE2 expression shares many similarities with TMPRSS2, it is also expressed in lungs, liver, kidneys and in the prostate (Xu et al., 2020). ACE2 is implicated in SARS-CoV-2 viral anchoring to the cell surface. ACE2 is also affected by androgens, with higher activity found in males (Dalpiaz et al., 2015). Although direct evidence that the TMPRSS2 gene is androgen receptor (AR) regulated in the lung is pending in literature, *TMPRSS2* transcription occurs in lungs, at high levels, in adult males and females (Stopsack, Mucci, Antonarakis, Nelson, & Kantoff, 2020).

Androgen sensitivity may be an important factor for disease severity in men who are more prone to these effects because the AR gene is on the X chromosome. Several studies have demonstrated that androgen sensitivity is associated with the CAG repeat length polymorphisms in the first exon of the androgen receptor gene. Shorter CAG repeats length predispose men to develop androgenetic alopecia, acne and oily skin. Similarly, we believe that shorter CAG repeats in the androgen receptor gene may be associated with increased COVID-19 disease severity and mortality. An interesting observation supporting our theory is the disproportionate mortality rate observed in African American COVID-19 patients (Thebault, Tran, & Williams, 2020). African Americans, as an ethnic group, tend to carry a shorter version of the CAG repeat in the androgen receptor gene (Bennett et al., 2002). Thus, AR polymorphisms could be a very important factor in the known ethnical vulnerability (McCoy, Wambier, Vano-Galvan, et al., 2020).

Although there have been hopes in vaccines (Gates, 2020), SARS-CoV-2 may escape humoral response directed at Spike proteins through TMPRSS2 cleavage, therefore, males would tend to respond less to neutralizing antibodies, and monoclonal antibodies targeting the Spike protein. (Glowacka et al., 2011).

A preliminary observation in men hospitalized due to severe COVID-19 revealed a very high incidence of androgenetic alopecia compared to what would be expected to the same population (Goren, Vano-Galvan, Wambier, et al., 2020). The androgen gateway to COVID-19 has multiple checkpoints for therapeutic targets, which include commonly used drugs that are routinely used in clinical practice for therapy of hyperandrogenic features such as androgenetic alopecia, acne, early-onset puberty, hirsutism, and chemotherapy for prostate cancer (Figure 1). Androgenetic alopecia induced low density of scalp hair is an interesting clinical sign that would be worth testing as a valid predictor of vulnerability, since it is an irreversible, cumulative evidence of increased androgen expression over decades. If androgenic expression is directly related to vulnerability, a spectrum ranging from resistance to susceptibility could be used to predict severity of disease and transmissibility, such as what is presented in Figure 2. Curiously, when evaluating the mortality rates and severity rates in multiple epidemiologic reports, they tend to follow a pattern that relates to expected testosterone levels in the population, Figure 3. As in other diseases, severity may be amplified by sex-based genetic architecture (Ober, Loisel, & Gilad, 2008). The androgen levels, combined synergistically with the fragility imposed by aging could explain the overall severity and mortality observed in the general population.

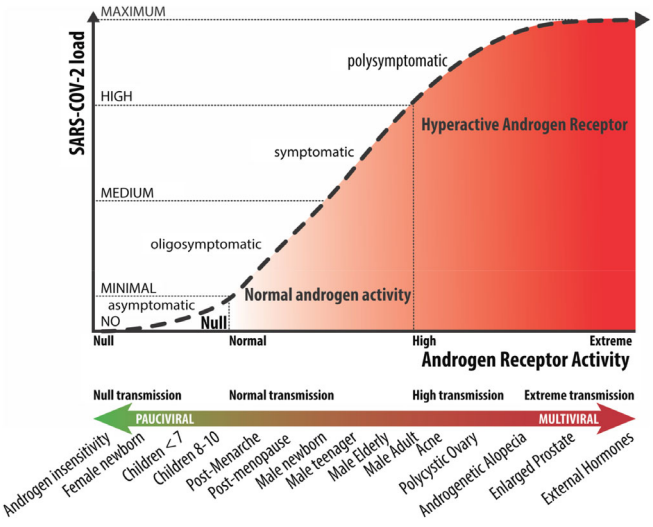

FIGURE 2 Proposal of host vulnerability stratification following the androgen-driven COVID-19 hypothesis, subjects with increased androgen receptor activity through androgen receptor gene polymorphism or through hyperactivation by androgen hormones would be predisposed to increased viral infectivity and cumulative viral load, which would reflect on pronounced symptoms and transmissibility from cell lining of the airways and digestive tract. A spectrum of androgenic activity would imply in *polar pauciviral* COVID-19 (e.g., children < 7), with null airway/fecal transmission potential, women with normal androgen activity would have low transmission potential (*borderline pauciviral COVID-19*), male teenagers and adults would have high transmission potential (*borderline multiviral COVID-19*), and infected individuals with abnormally high androgen receptor activity (genetic or acquired) would represent the *multiviral COVID-19* pole of the spectrum, with extremely high transmission

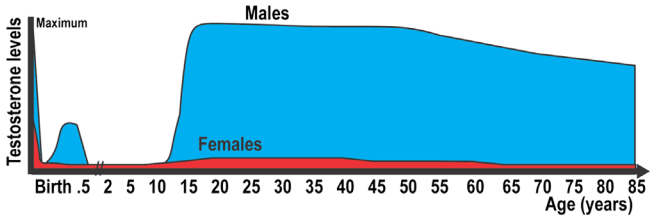

FIGURE 3 Gross testosterone levels per gender, from birth to 85 years of age. Note peak in newborn males, and increase in testosterone levels in both genders after puberty. There is a subtle decrease in testosterone levels with aging. Adapted from: "Sex-specific genetic architecture of human disease," C. Ober et al., 2008, *Nature Reviews. Genetics*, *9*(12), 911–922

To further test this hypothesis, it would be interesting to observe for severe COVID cases in female patients who present with increase androgens, for example, females with metabolic syndrome, or whom are using birth control methods with progestogen hormones that bind to androgen receptor. Additionally, there are many medical conditions that could increase androgen activity in females and might correlate with increasing vulnerability to COVID-19. Generally, in the same age group, females have much lower levels of testosterone than males (Ober et al., 2008) however, some conditions are known to increase androgen hormone levels in female patients. Congenital adrenal hyperplasia (CAH) is a class of autosomal recessive disorders characterized by a specific hormone deficiency referred to as 21-hydroxylase deficiency. 21-hydroxylase deficiency results in excess

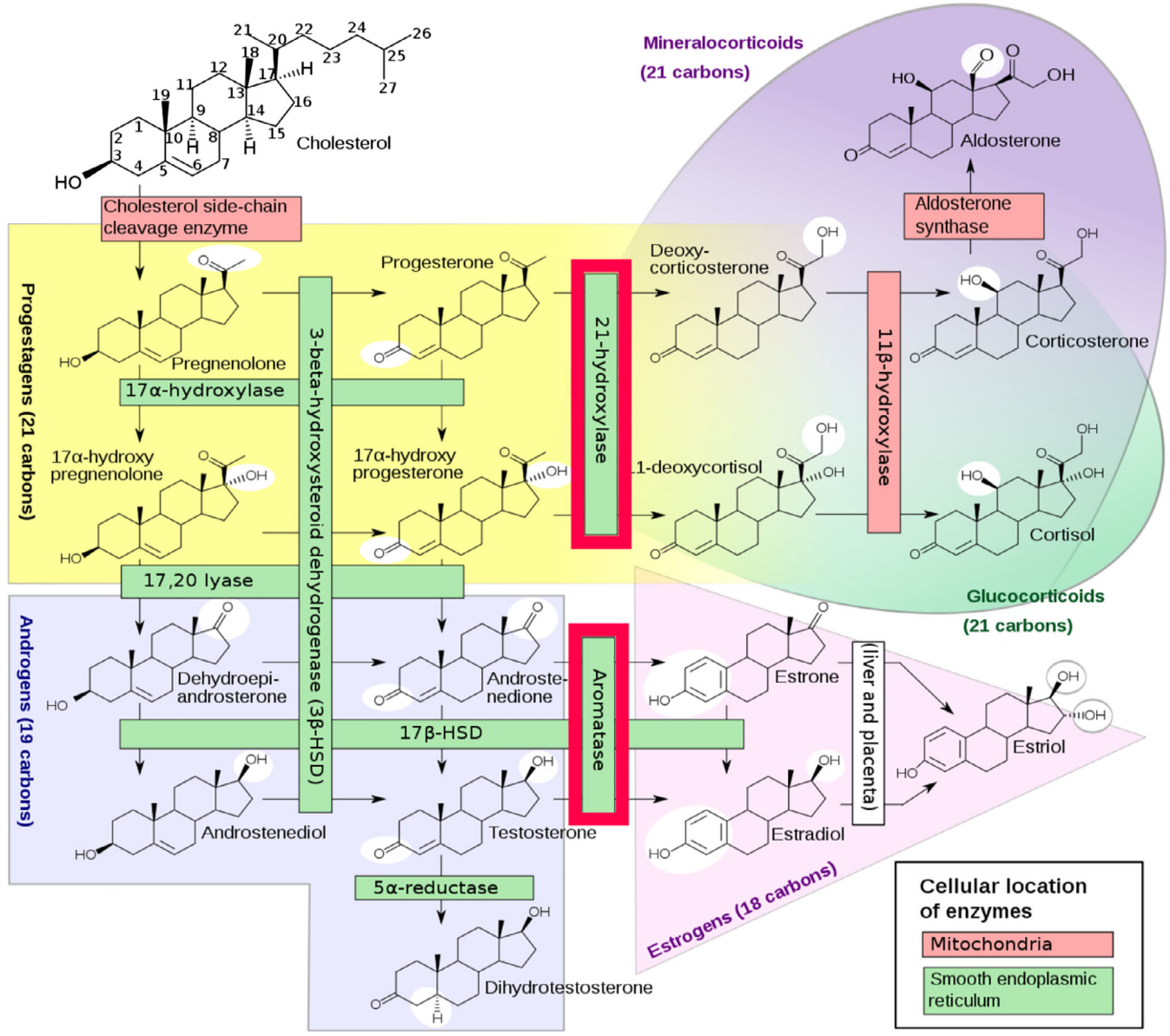

FIGURE 4 Steroidogenesis. Enzyme activities that reduce androgen steroid levels: 21-hydroxylase and aromatase (red boxes). 21-Hydroxylase deficiency causes increased production of androgen hormones in females. Male patients who take external androgens may accumulate dihydrotestosterone, particularly when combined with aromatase inhibitors. (Figure source: Wikimedia commons)

TABLE 1 Suggested methods to evaluate possible independence of the androgen receptor to TMPRSS2 gene expression

In vitro	AR knock-out cell cultures expressing TMPRSS2 gene that is,: Assay of SARS-CoV-2 in Vero cells cultures.
In vivo	Knock-out AR COVID-19 animal infection experiment.
Epidemiological studies	Total androgen insensitivity syndrome: Single case report.

TABLE 2 Ongoing clinical trials registered at ClinicalTrials.gov addressing the androgen gateway to COVID-19

TMPRSS2 inhibitors	Bromhexine: NCT04355026, NCT04273763, NCT04340349 Camostat: NCT04321096, NCT04355052, NCT04353284. NCT04338906 Nafamostat: NCT04352400
Anti-androgens	Spironolactone: NCT04345887
Other sex hormones	Progesterone: NCT04365127 Estrogen: NCT04359329
Androgen receptor genetics	CAG repeats: NCT04368897

adrenal precursors which are excessively metabolized into androgens, that is, testosterone and dihydrotestosterone (DHT) (White & Speiser, 2000), Figure 4. Studies suggest that females with 21-hydroxylase deficiency have a higher risk for a host of medical conditions. Some females with 21-hydroxylase deficiency fit diagnosis criteria for polycystic ovary syndrome (PCOS) (New & Nonclassical, 2006). A common characteristic of PCOS is hyperandrogenism (Bani Mohammad & Majdi Seghinsara, 2017) PCOS is a very common disease among females of reproductive age. Depending on the criteria used, PCOS prevalence ranges from 4 to 21% (Lizneva et al., 2016). Furthermore, metabolism has a direct relationship with hyperandrogenism in females, genetically higher testosterone levels in females was associated with increased risk of type 2 diabetes (odds ratio (OR) = 1.37 (95% confidence interval [95% CI]: 1.22–1.53)) and polycystic ovary syndrome (OR = 1.51 [95% CI: 1.33–1.72]), while higher testosterone levels reduce type 2 diabetes risk in men (OR = 0.86 [95% CI: 0.76–0.98]; Ruth et al., 2020). Coincidently, PCOS is associated with a shorter CAG repeats in the androgen receptor gene (Schüring et al., 2012). Table 1 lists some strategies to verify if the androgen receptor activity is truly the key to the SARS-CoV-2 infection. Table 2 lists some clinical trials ongoing with medications that target the androgen gateway for COVID-19 Figure 1.

The role of androgens on COVID-19 disease severity and mortality could explain the gender bias in mortality rates. In addition, our androgen sensitivity theory explains the low rate of mortality among prepubescent children and the higher rate of mortality observed in the African American population. The study of androgenetic alopecia among hospitalized COVID-19 patients further strengthen our theory. A future study of genetic variances in deceased COVID-19 patients may enable the development of a diagnostic to identify vulnerable individuals. Finally, if our theory is proven correct, antiandrogen therapy could be used as a treatment for COVID-19 patients. A vaccine might ultimately be found for SARS-CoV-2; however, if a vaccine is not found or found to be ineffective, androgen suppression as a prophylactic treatment could reduce COVID-19 disease burden. Given that certain anti-androgens such as finasteride carry a low risk of serious adverse events, healthcare workers, police officers, and the military personal could potentially use anti-androgens as a prophylactic treatment.

Although authors suggest the main role of androgens by current known mechanisms of the disease, other alternative, unknown pathways for SARS-CoV-2 infection might exist.

ORCID

Carlos Gustavo Wambier https://orcid.org/0000-0002-4636-4489
Andy Goren https://orcid.org/0000-0002-8190-2289
Sergio Vaño-Galván https://orcid.org/0000-0003-2773-7494
Paulo Müller Ramos https://orcid.org/0000-0002-1561-414X
Gerard Nau https://orcid.org/0000-0001-7921-8317

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