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Review Paper: Androgens and COVID-19: A Double-Edged Sword

Mahmoud Sadeghi Ataabadi[1], Soghra Bahmanpour[1, 2], Saeed Yousefinejad[3], Sanaz Alaee[1,4*], Roohollah Esmati Gharehchah[5]

1. 1Department of Reproductive Biology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
2. Department of Anatomy, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
3. 3Research Center for Health Sciences, Institute of Health, Department of Occupational Health Engineering, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran
4. Stem Cells Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran5. Provost, Techno India JNR, Institute of Technology, Udaipur 313003, Rajasthan, India
5. Department of Nursing, Faculty of nursing and midwifery, Islamic Azad University of Bushehr, Bushehr, Iran

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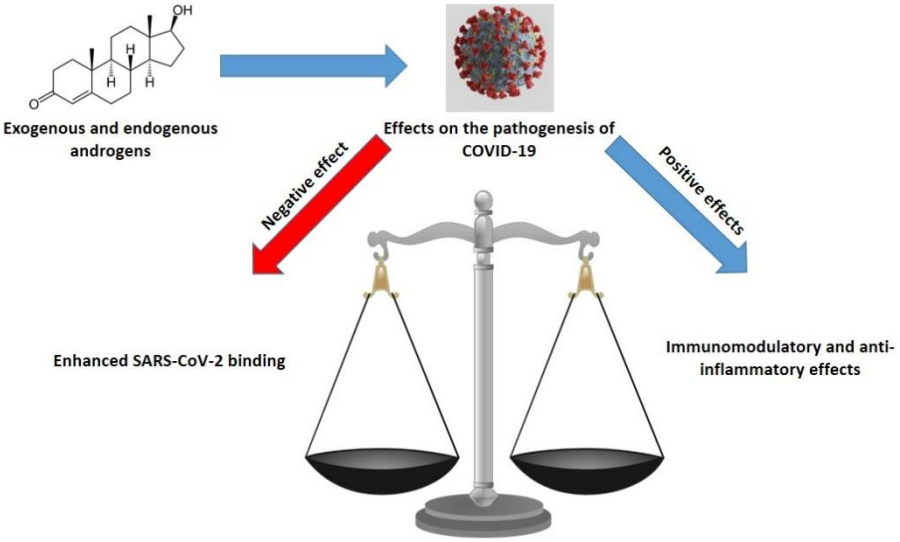
ABSTRACT

The world is still affected by the major public health threat of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The evidence has shown that men are more likely to die from SARS-CoV-2 infection. Numerous studies are devoted to investigating the causes of this disparity, which seems to be multifactorial. The immune response can be affected by sex hormones, especially androgens. It has been revealed that SARS-CoV-2 targets the cells through ACE2 and TMPRSS2 receptors both of which are regulated by the androgen receptor. The relationship between these receptors and androgens may explain the difference in COVID-19 disease severity and mortality in different genders. On the other hand, it has also been found that severe testosterone and dihydrotestosterone deficiencies or low testosterone in critically ill male COVID-19 patients could be a prognostic marker of severe disease. Nonetheless, as a double-edged sword, androgens have positive effects on immunomodulation and immune protection, while causing negative effects as they facilitate the entrance of the virus into the cell. The present study is thus aimed to investigate the different aspects of the influence of androgens on COVID-19 development.

**** Corresponding Author:***
Sanaz Alaee, PhD
Address: *Department of Reproductive Biology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran*
E-mail: *sanaz620@gmail.com*

Graphical abstract



1. Background

In December 2019, a novel infectious respiratory illness with dry cough, fever and decreased or normal white blood cell (WBC) counts appeared in Wuhan, Hubei, China. Afterward, it spread worldwide, leading to a pandemic situation. The World Health Organization (WHO) called it the coronavirus disease 2019 (COVID-19), with the virus being classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). Since then, the COVID-19 outbreak has marched the world nonstop like a tireless warrior.

SARS-CoV-2 is highly aggressive and rapidly transmitted to other parts of the world posing serious risks to human life. COVID-19 has disrupted public health around the world, global financial markets, health care foundations, and social stability. Therefore, the identification of pathogenesis and molecular mechanism of COVID-19 for the available treatment choices is an unmet and even urgent medical need (3). Fatality following infection of COVID-19 was thought to be solely related to pre-existing conditions and aging (4, 5). As the COVID-19 outbreak ensued, additional risk factors, such as gender and race, have been identified (6, 7).

Epidemiological studies among several countries revealed higher intensity and mortality due to COVID-19 in the male population. Epidemiological data from Italy showed that 58% of COVID-19 patients were men, and 70% of them died of COVID-19 (8). Walter and McGregor compared the lethality potential of the COVID-19 pandemic in male and female cases of the same age and reported that the rate of death increased with age in both populations and was higher in males than their age-matched female peers (9).

2. Epidemiological data of sex differences in respiratory infections

Sex differences have previously been documented in some respiratory infection-specific epidemiological data. The most severe outbreak recorded in the history of medical science was the “Spanish flu” that caused the death of almost 50 million people in 1918/19. A review of the epidemiological information regarding influenza-induced mortality in the US and other nations revealed that the 1918 outbreak had a remarkable sexual bias as mortality was higher in men compared to women (10).

Epidemiological studies conducted in Denmark and Canada confirmed an enhanced risk of influenza in men of all ages concerning the H1N1 and H3N2 influenza virus pandemics between 1995–1999 and 1992–2001 (11, 12). An epidemiological study from severe acute respiratory syndrome /SARS (2003) and Middle East Respiratory Syndrome/ MERS (2012) pandemic showed a significantly higher susceptibility rate in men as compared to women (13, 14). In contrast, some epidemiological studies have shown the superiority of women in morbidity and mortality of viral diseases. For instance, in the US, the H2N2 outbreak in 1957 caused higher rates of fatality in female cases aged 1–44 years old (15). Universally, as of 2008, mortality of women due to H5N1 infection was 1.6 times higher than men (16).

3. Probable causes of gender disparity

Investigation of the gender bias mechanism of COVID-19 may lead to the efficient treatment of patients of a specific gender. A combination of gender-specific factors such as genetic architecture, sexual hormone, behavioral and cultural variables, and lifestyle may be associated with the disproportion. Smoking rates and the prevalence of cardiovascular diseases are lower in women, both of which are correlated with a bad prognosis for COVID-19 patients (17, 18). However, smoking is not a risk factor in males or other subgroups for COVID-19 infection (19).

Hormonal milieu variation can play an important pathophysiological role associated with COVID-19. Males and females are different in terms of their reproductive system, as well as the related sex hormone levels. The women's ovaries secrete higher levels of steroids, mostly progesterone and estrogens; in contrast, men mostly secrete androgens, like testosterone in their testes (20, 21). Such hormonal differences start sex-specific gonadal growth and influence nongonadal tissues, like the immune system in life (22). Males and females are different in the inflammation process due to different factors. Females have stronger immune reactions due to encoding the majority of the immune regulatory genes by X chromosomes; however, the sex difference in inflammatory reaction could be caused by sex hormones [35]. Hormone receptors, like the estrogen receptors α and β, progesterone, and androgen receptor (AR) mediate an interaction between the immune system and sex hormones. Their expression is done on the immune cells of the innate and adaptive immune system response. Generally, estradiol plays an immunostimulatory role, whereas progesterone and testosterone are immunosuppressive and neutralize the pathways influenced via estradiol (23, 24). Thus, men generate fewer strong immune reactions and are more vulnerable to infectious agents (25). Also, in males, after an initial surge during fetal development, testosterone concentration remains low, it then rapidly increases with the onset of puberty (26). In normal males, testosterone production peaks at roughly the age of 20-30 years followed by a gradual decrement (at the annual rate of 0.4% to 2%) with progressing age. Clinically low testosterone levels are observed in 19% of males in their 60's increasing to 49% of males in their 80's (27). The reasons for age-related decline in androgenic function are believed to be related to the decreased Leydig cell responsiveness to LH stimulation leading to a reduction in total testosterone production (28), as well as age-associated increases in sex hormone-binding globulin (SHBG) (29).

Based on various studies, endogenous androgens enhance the susceptibility of men to COVID-19-related morbidity and mortality. Moreover, COVID-19 can cause an acute transient phase of male hypogonadism and a reduction in androgenic action stimulating a severe or even deadly course of the COVID-19. Therefore, the role of androgens in COVID-19 disease should be determined to decide whether we should use anti-androgens or androgens to manage this disease (30).

4. Mechanism of SARS-CoV-2 virus entry into the cell and its relationship with androgens

Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 belongs to the family of beta coronavirus. The particular characteristics of SARS-CoV-2 are usually near to those of SARS-CoV. Coronaviruses have structural (nucleocapsid, spike, envelope, and matrix) and nonstructural (the proteases nsp3 and nsp5) proteins (31, 32). The entrance of the virus relies on Transmembrane Serine Protease 2 (TMPRSS2) and Angiotensin-Converting Enzyme 2 (ACE2) as two proteins on the epithelial cells of the host organ. TMPRSS2 can prime the spike-protein via cleaving spike-protein from two areas, by which fusion of

the membranes of the virus and host is achievable. Entrance to the cell is then activated via ACE2 (33). The TMPRSS2 gene expression is done in the prostate of adults, however, it is expressed in many tissues, especially in the pancreas, small intestine, colon, lung, kidneys, and liver (34). The lungs, kidneys, and liver are targeted organs in COVID-19 via TMPRSS2 expression (35). TMPRSS2 is expressed on the surface of the type II pneumocytes in the human lung tissues. In type II pneumocytes, the regulation of TMPRSS2 is commonly linked to androgen receptor (AR) signaling, Androgen regulates TMPRSS2 mRNA expression in the target tissues and the AR up-regulates TMPRSS2 mRNA (36). Also, androgen therapy increases the activation of TMPRSS2 zymogen in the cell culture as well as in a mouse xenograft type; that is, androgens control TMPRSS2 in transcription and post-translation stages (37). Moreover, ACE2 which regulates blood pressure by the renin-angiotensin-aldosterone pathway attaches the viral spike surface protein, also called the "receptor of SARS-CoV-2". ACE2 expression shares several commonalities with TMPRSS2; it is expressed in the kidneys, lungs, liver, and prostate (38, 39). ACE2 is one of the main factors in the anchoring of SARS-CoV-2 on the cell surface. The virus susceptibility and severity can be influenced via ACE2 expression which is under the influence of numerous factors such as renin-angiotensin-aldosterone pathway inhibitors, smoking, and androgens (17, 40, 41). The elevated mortality and morbidity due to the virus in males may be linked to the elevated ACE2 expression in males (the ACE2 gene is on the X chromosome) (42). However, others have shown similar levels of ACE2 expression in male and female subjects (43, 44). Nonetheless, its amount elevates in boys by aging, and females have lower levels of soluble ACE2 compared with men aged 15 years (45). ACE2 over-expression caused a severe type of SARS-CoV disease in mice (46). Sward et al. reported a higher risk for severe COVID-19 in 40 cases with higher soluble ACE2 (male>female) (45).

5. Reasons for anti-androgen therapy in COVID-19

On the other hand, two different small-scale studies have shown higher rates of hospitalization among male COVID-19 patients with androgenetic alopecia patterns. This pattern of alopecia is correlated with elevated levels of dihydrotestosterone (DHT) in the scalp (47, 48). A study reported that 71% of 41 Spanish adult men hospitalized due to COVID-19 had androgenetic alopecia, while the expected prevalence of androgenetic alopecia in the Caucasian population with similar age-matched subjects is approximately 31-53% (47). In the second study, 79% of 122 COVID-19 male patients in Madrid hospitals showed androgenetic alopecia (48). These field data suggest that hyperandrogenism might be involved in the pathogenesis of the COVID-19 disease.

According to the described entry mechanism, if the TMPRSS2 and ACE2 expression levels are essential factors regarding the entry, infection, and spread of SARS-CoV-2, a noteworthy treatment for better management of SARS-CoV-2 infection could be achieved through downregulation of TMPRSS2 and ACE2 expression at the lungs. This goal can be obtained by controlling the androgen receptor (49).

Due to the aforesaid point, androgenic management of ACE2 and TMPRSS2 is possibly attained via androgen deprivation therapy (ADT) and anti-androgen drugs (50). Anti-androgens compete with endogenous androgens for binding to the ligand-binding pocket of the androgen receptor, inducing conformational changes that prevent optimum transcriptional activity. Anti-androgens are generally used for treating alopecia or acne; They are also prescribed for treating prostate cancer (51). Flow cytometry and qPCR test results showed ADT by the interruption of androgen signaling is correlated with impressive prostate cancer cell killing and decrease of TMPRSS2 expression (52). Importantly, the same effects were also shown in other tissues. For example, using ADT in the lung culture of rats was correlated to a decrease in lung TMPRSS2 transcriptions (52). Thus, this idea suggested that the same ADT prescribed in prostate cancer might be an appropriate option for down-regulation of the SARS-CoV-2 receptors (ACE2 and TMPRSS2) in the lung tissue to ameliorate the consequences of the COVID-19 infection in male cases. For example, finasteride, an FDA-approved 5-alpha reductase inhibitor (5-ARIs), reduces activation of AR in multiple tissues (53). Previous data also showed that flutamide, as a prophylactic anti-androgen drug, could have protective effects against SARS-CoV in the male mice models (14).

Wu and coworkers conducted a clinical study on

1339 COVID-19 patients through in silico and in vitro analysis and came up with some interesting results. They demonstrated higher disease progression and mortality in men with COVID-19. They also showed that during virus infection, M1 macrophage polarization was commonly activated. M1 macrophages could secrete inflammatory cytokines like TNF-α, IL-6, and iNOS. Since it has been previously reported that the cytokine release syndrome (CRS) or cytokine storm is linked to the severity of COVID-19, Wu and coworker concluded that it is possible to repress the over-exuberant inflammatory response of male COVID-19 patients via AR inhibition. They indicated that AR antagonists by suppression of AR-ACE2/TMPRSS2 key axis might be a promising treatment for male COVID-19 patients (54).

To identify possible medicines to intervene with SARS-CoV-2 cell receptor (ACE2), evaluation of the protein-protein interactions (PPIs) network containing the genes co-expressed with ACE2 in the epithelial lung cells was explored using a computational approach. The result showed a network of 193 genes, 222 interactions, and 36 potential drugs with crucial roles. Among possible interesting drugs for Covid-19 treatment, they found Nimesulide, Fluticasone Propionate, Thiabendazole, Photofrin, Didanosine, and Flutamide. The activity of flutamide on the ACE2-related network could be mediated by the regulatory role of AR on ACE2 (55). Other potential anti-androgen drugs that could be studied are listed in Table 1 and illustrated in (56).

Table 1. Different classes of anti-androgen drugs

AR antagonists	Steroidal Antiandrogens	Spironolactone	Cyproterone Acetate	Oxendolone	Osaterone	Megestrol Acetate	Chlormadinone Acetate
	Nonsteroidal Antiandrogens	Bicalutamide	Flutamide	Nilutamide	Topilutamide	Enzalutamide	Apalutamide
Androgens synthesis inhibitor	CYP17A1 inhibitors	Aminoglutethimide		Ketoconazole	Abiraterone Acetate		Seviteronel
	5α-reductase inhibitors	Finasteride		Dutasteride	Epristeride		Alfatradiol
Antigonadotropins	GnRH modulators	GnRH agonists			GnRH antagonists		
	Progestogens	Chlormadinone Acetate			Medrogestone		
	Estrogens	Alfatradiol					
others	Isotretinoin						

A limited number of studies have addressed the safety of anti-androgens in the era of the COVID-19 outbreak. A retrospective study showed that the rate of COVID-19 infection was significantly lower among men who used ADT or/and 5-alpha reductase inhibitors drug compared to men over 40 years who did not take these medications (4.2 vs. 14.9%; $p<0.0001$) (57). Montopoli et al, in the Veneto Italian region, applied a population-registry-based approach to analyze the data of 9280 patients (4532 males). They reported that compared with all COVID-19 patients, cancer patients had an elevated risk of SARS-CoV-2 infections. Nonetheless, data analysis showed that the mortality rate was four times lower in prostate cancer patients with COVID-19 infection who took ADT as compared to those who did not use ADT (58). The same protection effect was shown by comparing prostate cancer cases with COVID-19 who used ADT and COVID-19 cases with any other cancer without ADT use. Five-fold lower mortality risk was linked to the use of ADT drugs (58).

Results from a recent prospective study demonstrated the protective effect of Dutasteride (a 5ARi) in male COVID-19 cases. So that, the total remission time was significantly reduced in the men who took Dutasteride (9.0 versus 15.6 days in the

placebo group ($p < 0.001$)) (59).

According to the mentioned data, it seems that sex-specific treatment approaches should be considered to ameliorate the clinical period of the infection and anti-androgen drugs or ADT can be helpful in the prevention and treatment of COVID-19.

6. Reasons for androgens therapy in COVID-19

Despite higher COVID-19 severity and mortality in males (9), the reasons why males at younger ages are highly protective of adverse outcomes should be assessed. The same situation has been already reported with influenza. Descriptive reports have consistently shown that each year in the US, the expenses of influenza are higher in cases aged over 65. Thus, 90% of mortalities due to seasonal influenza are seen in cases older than 65 [31]. In unvaccinated people ≥ 65 years, the possibility of hospitalization due to seasonal influenza is higher in men compared to females [32]. Regarding the H7N9 outbreak in China, the likelihood of death among older male subjects was 2.4 times higher after exposure to H7N9 as compared with the age-matched females [33].

As previously explained, circulating testosterone concentrations decreases in men by aging. Thus, the decreased testosterone could be possibly linked to the age-related increase in COVID-19 severity (60).

In addition to the age-related declines in testosterone, genetic conditions (e.g. Klinefelter's syndrome and congenital gonadotropin deficiency), medically induced hypogonadism, tissue damage from infection (e.g., mumps associated orchitis), or trauma can result in low testosterone concentrations in males at reproductive-age (61). Age-associated decreases in testosterone generation are linked to symptoms such as reduced libido, erectile impairment, depression, fatigue, decreased strength, bone loss, and elevated abdominal fat (62). Testosterone replacement in older male cases with hypogonadism leads to health and quality-of-life benefits (63). Also, lower testosterone concentrations are associated with elevated vulnerability of respiratory disorders, like asthma and chronic obstructive pulmonary diseases (COPD) (64), cardiovascular diseases, and diabetes (65). All of these conditions greatly contribute to the severity of COVID-19 (66, 67).

Testosterone possibly decreases the requirement for assisted ventilation due to its anti-catabolic effect in respiratory muscles (68). Low testosterone concentrations decrease the activity and exercise capacity of the respiratory muscles as well as overall strength (69), whereas normal circulating testosterone concentrations protect against different respiratory outcomes (forced expiratory volume in 1 second and forced vital capacity) (70). The peak oxygen use showed an improvement in males receiving testosterone replacement therapy (71). The results of a study showed the high prevalence of low testosterone levels in intubated patients with acute respiratory failure which can be linked to a longer stay at intensive care unit (ICU) (72). Many small-scale clinical investigations reported an improvement in the outcomes of hospitalized COPD cases following testosterone therapy (73).

Testosterone exerts its anti-inflammatory effects by suppressing the humoral and cellular immune systems. Similar to estrogen, it lowers IL-6 and TNF-α by inhibiting the NF-κB pro-inflammatory pathway (74). Moreover, testosterone deficiency can increase inflammatory markers, like C-reactive protein (CRP) and autoimmune disease (75). Anti-inflammatory and protective effects of testosterone were assessed using a murine model. Like the male subjects, aged male C57BL/6 mice showed lower testosterone levels compared to young ones. After influenza A virus (IAV) inoculation, the aged male mice showed higher pulmonary inflammation, clinical disorder, and morbidity in comparison with young males. Decreased total anti-influenza IgG and neutralizing antibody reactions were also found. The aged and young male mice were similar in terms of the peak titers of IAV in the lungs; however, aged male mice showed a delay in virus clearance. Among some young male mice, the testes were removed. Treatment of gonadectomized mice with testosterone decreased the pulmonary pathology, clinical illness, and morbidity; however, viral replication showed no changes after hormone replacement therapy (HRT) in young male mice. Treating old male mice with testosterone ameliorated the survival after infection with IAV, but did not change the pulmonary pathology or virus replication. Accordingly, low levels of testosterone, whether naturally occurring in aged male mice or induced surgically in young male mice, negatively influenced the consequence of influenza. Generally, testosterone ameliorated the consequences of IAV

infection in the male mice and its physiological levels were associated with ameliorated consequences of subsequent infection with two various IAV strains (76). On the other hand, testosterone is decreased upon facing an immune challenge and traumatic injury (77). For example, males infected with malaria showed declined testosterone compared with uninfected ones, but normal concentrations were observed following successful therapy of the disease (78). It is ambiguous in the human study that how finely calibrated testosterone responses are associated with immune activation because malaria infections, as well as critical damages, are extreme events. Even moderate immune reactions are linked to an enhancement in metabolic rate and energy expenditure. Testosterone is declined in milder events (79). The immunosuppressive impacts of testosterone are possibly a homeostatic mechanism for turning off the immune reaction. Such effectiveness of testosterone also contributes to the balance in the outcomes of reduced immunity against infection (80).

Schroeder et al. measured the sex hormones, cytokine, and chemokine in COVID-19 patients admitted to an ICU at the University Hospital Hamburg-Eppendorf of Germany. The result showed that most male COVID-19 cases presented low testosterone (68.6% / <8.86 nMol/l) and dihydrotestosterone (48.6% / <10 ng/dl) levels, so that 14.3%, 28.6% and 25.7% of males were found to have low (5-8.68 nMol/l), very low (3-4.9 nMol/l), and 25.7% extremely low (<3 nMol/l) testosterone levels, respectively. Significantly, among 9 male dead COVID-19 patients, 1 male showed normal testosterone concentration (8.69-29 nMol/l), 1 had normal testosterone concentration at the lowest percentage, whereas 7 of them had low testosterone level. On the other hand, most women with COVID-19 showed increased testosterone concentration (60% / > 1.6 nMol/l) with no changes in dihydrotestosterone concentration (≤30 ng/dl). Of the 3 dead women, 1 showed increased testosterone level. Both male and female COVID-19 cases can have increased estradiol concentration (45.7% in male upper 52.2 pg/ml and 40% in female cases upper 50-100 pg/ml). Disease severity matches up with increased cytokine reactions (e.g. IL-6) in males and IL-2 in female cases. In male COVID-19 cases, testosterone concentrations showed a negative correlation with inflammatory IL-2 and IFN-γ. In contrast, most female COVID-19 cases (60%) showed increased testosterone concentrations linked to increased inflammatory cytokine expression, like IL-6 and IL-1ß. Therefore, high testosterone concentration in women (> 1.6 nMol/l) and its low concentration in men (<8.86 nMol/l) accord with inflammatory cytokines reactions in a sex-specific type. Accordingly, testosterone presented a protective immune reaction in male cases, whereas it accelerated the inflammation in females (81). It was also shown that testosterone possesses protective and sex-specific effects on vascular aging by reducing oxidative stress and inflammation (82). Testosterone-treated male rats showed a two-fold increase in the activity of the antioxidants catalase and superoxide dismutase (83). In humans, testosterone supplementation decreased TNF-α and increased the anti-inflammatory cytokine interleukin-10 in hypogonadal older men (84).

Nonetheless, testosterone concentration in COVID-19 patients should be interpreted according to its type. Low testosterone concentrations (hypogonadism) possibly are due to hypothalamic-pituitary (secondary hypogonadism) or testicular (primary hypogonadism) reasons or sometimes due to both factors, as detectable in the male elderly (61). Acute critical diseases suppress the hypothalamic-pituitary-gonadal (HPG) axis. Additionally, a direct invasion and injury by the virus and different parameters like inflammation, fever, hypoxia, or medicines can influence the male HPG axis.

Analysis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) for assessing the cause of the testosterone deficiency (very severe / <3 nMol/l) in male COVID-19 cases indicated the increased LH concentrations in 31.4% of them (≥8.7 mIU/ml), whereas it was normal in all female cases. Also, 6 men out of the 35 cases with low testosterone concentrations had increased LH levels, suggesting the impaired Leydig cell steroidogenesis in 17.1% of men. FSH concentrations showed an elevation in 4 out of 35 men (11.4%/ 12.5-25 mIU/ml). Increased FSH concentrations in these men were accompanied by incremented LH concentrations. Moreover, 40% of females showed decreased FSH concentrations, indicating the loss of ovarian function. Accordingly, a certain number of males (6 from 35; 17.1%) showed primary hypogonadism. However, the rest (18 out of 35; 51.4%) of males COVID-19 cases presented low testosterone concentrations, which

is not of testicular, but probably of hypothalamic reasons (81).

A consecutive series sampling of 31 Italian males COVID-19 patients showed a significant gradual decrease in total testosterone (TT) and calculated free testosterone (cFT) concentrations, indicating a strong association with the requirement to transfer from the general ward to respiratory ICU. TT and cFT indicated a remarkable negative correlation with inflammatory markers, like the neutrophil number, LDH, ferritin, and CRP, as well as a positive correlation with lymphocyte number. Moreover, TT exhibited a negative correlation with ferritin and CRP concentrations. A sharp elevation was observed in both ICU transfer or fatality risk in males with TT levels below 5 nmol/L or cFT smaller than 100 pmol/L. The lower baseline concentrations of TT and cFT were correlated with poor prognosis and mortality in COVID-19 male cases admitted to respiratory ICU (85).

Another study assessed 81 males with COVID-19 and indicated the lower serum TT (not statistically significant) levels, whereas they had higher serum LH in comparison with 100 healthy males at the same age. COVID-19 patients were found to have a significantly lower serum T: LH that showed a negative association with disease severity [49]. Higher serum LH in males with COVID-19 can negate the probability of the HPG axis inhibition which is affected by the primary Leydig cell damage. Moreover, orchitis is an identified SARS complication (86). In another study, the sex hormone profiles were compared in 119 COVID-19 cases and age-matched 273 male controls. The serum T concentrations showed no remarkable changes in the COVID-19 group, but they had a higher serum LH concentration and a lower serum T: LH rate than the controls. The basal T concentration extensively varied in the population; therefore, the ratio between hormones, like T: LH rate, was regarded as the more appropriate factor for male gonad performance evaluation (or appropriate response to the HPG axis). An Impairment in T secretion can induce LH release which temporarily preserves the T concentration. Using multiple linear regression, the researchers found that T: LH ratio had a negative association with inflammation indicators including WBC (White Blood Cells) count and CPR (C - Reactive Protein) concentration in COVID-19 patients. As the acute-phase protein, increased CRP is linked to cytokine secretion, which is a reflection of the inflammation severity (87). Emotional, physical, or psychological stresses, as well as pain accompanied by infections, activate the hypothalamo-hypophyseal axis. Thus, the impaired hypothalamic-pituitary and the dysfunction in the LH release rhythm are considerable.

These results should be considered in the interventional strategies for male cases of COVID-19, to treat male hypogonadism with exogenous testosterone. Thus, assessing testosterone concentrations could be helpful as hypoandrogenism can deteriorate the systemic inflammatory reactions in COVID-19 patients.

7. Discussion and Conclusion

The sex and age disparity of COVID-19 was confirmed by available clinical data (8, 88). These disparities were shown in all three recent coronavirus epidemics (13, 14). In this context, male patients' mortality and susceptibility rate due to SARS-CoV-2 infection were higher than female patients; elevated mortality was also observed in older cases of COVID-19 (9). Therefore, various hormonal milieu has a pathophysiological effect on SARS-CoV-2. Therefore, as a double-edged sword, androgens have positive effects on immunomodulation and immune protection, as well as negative effects since it facilitates the entrance of the virus into the cell.

Endogenous testosterone enhances the men's susceptibility to severe complications of SARS-CoV-2 infection via influencing ACE2 and TMPRSS2 receptors (38, 89). The difference in TMPRSS2 and ACE2 expression has a mediatory role in SARS-CoV-2 pathogenesis and androgenic signaling. In the future, if a vaccine is not found, a prophylactic approach in hypertensive COVID-19 subjects (such as healthcare workers, police officers and bank employees) could be achieved by avoiding the rise in ACE2 and TMPRSS2 expression (e.g. with by anti-androgens therapy). Antiandrogens are routinely used to treat many diseases, such as prostate and breast cancer, alopecia, and polycystic ovarian syndrome. They are well tolerated in males and females. However, an anti-COVID-19 strategy that targets androgen-mediated TMPRSS2 and ACE2 expression should be cautiously applied. More investigations on TMPRSS2 and ACE2 expression, as well as their modulation in the lungs and some

relevant cells affecting SARS-CoV-2 pathogenesis, should be also considered. In addition to the effectiveness of androgens in the known pathways of the disease, other unidentified mechanisms may exist in COVID-19 infection. Also, sex differences in ACE2 and co-receptor TMPRSS2 expression alone are not responsible for higher COVID-19 burden in males.

Some pharmacokinetic and pharmacodynamics concerns have to be resolved. For example, the effects of anti-androgenic drugs take several days to appear, which contrasts with the rapid treatment of COVID-19 in the acute phases [27]. On the other hand, patient selection seems vital for adequate assessment of this interaction and treatment. Men using ADT are at a higher risk of life-threatening situations, like diabetes, obesity, osteoporosis, and cardiovascular disease (90, 91).

Although the effect of gender on adverse events and life-threatening outcomes can be attributed to higher serum testosterone levels in males, normal serum testosterone concentrations are important to sustain the men's health. In contrast, low serum testosterone concentrations cause systemic inflammation. Regarding the effect of sex hormones on immune reaction, particularly the anti-inflammatory and anabolic impacts of testosterone, their possible effect should be considered in developing treatment approaches for COVID-19 cases, especially older adults as well as those with hormone deficiencies (92). Many conditions involved in males with COVID-19 are linked to low testosterone concentrations (type II diabetes, obesity, aging, cytokine storm) (61). Testosterone makes men susceptible to a less effective immune reaction against infectious agents. Male hypogonadism can cause a detrimental cytokine dysfunction, such as high circulating concentrations of IL-6, TNF-alpha and IL-1beta, involved in poor prognosis in COVID-19. Accordingly, exogenous testosterone therapy may be useful for mitigating the damaging inflammatory reaction against SARS-CoV-2. The association between testosterone and severe acute COVID-19 should be defined. The efficacy of hormone replacement therapy in the treatment of older adults with COVID-19 should be more studied. Further research may suggest the use of anti-androgens as a prophylaxis method and androgens become a part of a COVID-19 therapy protocol. In the end, the following measures are recommended:

1) Developing the international data registry to provide data regarding demographic, epidemiological, and pathological/functional results of COVID-19 in male patients and healthy controls with the same ethnicity and age, considering variations in the case fatality rates and outcomes between different age groups.

2) Assessing the circulating hormonal milieu in patients cross-sectionally and using a case-control study (based on age; comorbidities; symptoms; BMI; ethnicity; therapeutic strategies, and outcomes) and in the healthy controls with the same age.

3) Assessing the genome of specific subsets of COVID-19 male cases at high risk of severe outcomes and higher risk of mortality, linked to specific androgenic profiles.

4) Developing in vitro culture systems for investigating the testosterone effect on various tissues, such as human ACE2 in the testis and the reproductive tract, like the epithelial and endothelial lung cells;

5) Developing an animal model that recapitulates the variations regarding overall outcomes based on gender (females vs. males) as well as the related hormonal milieu.

Compliance with ethical guidelines

There was no animal or human study in this work.

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Author's contributions

Conceptualization: S. Bahmanpour, M. Sadeghi Ataabadi, S. Alaee
Data Curation: S. Alaee, M.R. Arabnezhad, R. Esmati Gharehchah
Review & Editing: S. Bahmanpour, S. Alaee
Visualization: M. Sadeghi Ataabadi
Writing: Supervision: M. Sadeghi Ataabadi, S. Bahmanpour, S. Alaee, S. Yousefinejad,

Conflict of interest

The authors declared no conflict of interest.

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