Androgens' Role in Severity and Mortality Rates of COVID-19

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ABSTRACT

By the end of December 2019 new corona virus began to spread from Wuhan, China and caused a worldwide pandemic. COVID-19 deaths and prevalence represented sex discrepant patterns with higher rate of deaths and infection in males than females which could be justified by androgen-mediated mechanisms. This review aimed to assess the role of androgens in COVID-19 severity and mortality. Androgens increase expressions of Type II transmembrane Serine Protease (TMPRSS2) and Angiotensin Converting Enzyme 2 (ACE2), which both facilitate new corona virus entry into host cell and their expression is higher in young males than females. According to observational studies, prevalence of COVID-19 infections and deaths was more in androgenic alopecic patients than patients without androgenic alopecia. The COVID-19 mortality rates in aged men (>60 years) were substantially higher than aged females and even young males caused by high inflammatory activities such as cytokine storm due to hypogonadism in this population. Use of anti-androgen and TMPRSS2 inhibitor drugs considerably modified COVID-19 symptoms. Androgen deprivation therapy also improved COVID-19 symptoms in prostate cancer: overall the role of androgens in severity of COVID-19 and its associated mortality seemed to be very important. So, more studies in variety of populations are required to define the absolute role of androgens.

Introduction

The new coronavirus pneumonia began to spread in Wuhan, China, by the end of December 2019. On February 11, 2020, the World Health Organization (WHO) named this disease as coronavirus disease 2019 (COVID-19). Since the initiation of outbreak, COVID-19 has caused significant damage and challenges around the world. As of September 2021, there have been 231 703 120 confirmed cases of COVID-19, including 4 746 620 deaths, reported to WHO. Recently, many studies have been conducted on the pathogenic characteristics of the new corona virus and its associated factors [1, 2]. These studies have linked increased COVID-19 associated deaths to age, male gender, leukocytosis, high levels of lactate dehydrogenase, heart damage, hyperglycemia, and high corticosteroid use [2]. The female immune system often responds significantly to viral infections, which can be explained by the role of estrogens in strengthening the immune system, as this has led to an increase in autoimmune diseases among women [3, 4]. According to a review study conducted by Li et al., who analyzed 1994 patients' information, the incidence of COVID-19 in men was significantly higher, which could suggest the role of sex hormones [1]. In another clinical trial study, gender was mentioned as a primary factor in determining the severity of the disease, which is highly significant [5]. Such a role for sex hormones, especially androgens, in the exacerbation of COVID-19 disease, mentioned in a number of studies, may raise hope for the use of anti-androgens as a treatment for COVID-19 [6, 7]. The infectivity mechanism of the severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2) is mediated through Type II transmembrane Serine Protease (TMPRSS2), Angiotensin Converting Enzyme 2 (ACE2), and the androgen receptor (AR) whose expression is increased by androgens.

The aim of this review is to define the pathophysiology of this sex-discrepancy in COVID-19 deaths with a focus on androgens role. In this review, the androgens' role was also explained by relation of androgen levels, immune system activity and aging.

Sex and gender aspects in COVID-19

According to previous research, in the COVID-19 pandemic, there were more deaths in males than females. Other deadly coronaviruses (CoVs), such as the Middle East respiratory syndrome (MERS)-CoV and the severe acute respiratory syndrome (SARS)-CoV, have also shown a sex-dependent pattern. The high number of severe male cases could reveal information on CoV's androgen-mediated pathogenic effects as well as the immune responses to these impacts [8]. After adjusting for age and baseline diseases, the risks of dying from COVID-19 were 1.7 times greater in males than females, according to an observational study by Vahedian-Azimi et al. the gender difference was most noticeable at older ages, with males aged > 59.5 years old having a 2.32-fold higher risk of mortality than females in the same age range [9]. Because women's X-linked genes are functional mosaics, and the X chromosome has a high density of immune-related genes, women's innate and adaptive immune responses are often stronger than men. Females have faster pathogen clearance and vaccine efficacy than males, but this also contributes to their increased vulnerability to inflammatory and autoimmune disorders [10]. Uneven levels of progesterone, a steroid hormone with anti-inflammatory properties, may be responsible for the gender differences in illness severity and mortality outcomes in COVID-19. Premenopausal women's natural and adaptive immune cells express progesterone receptors, which control regional and systemic inflammation. The function of estrogen in female immune responses has drawn a lot of interest. Severe COVID-19 complications are less likely to occur in younger women or those with higher estrogen levels. The direct antiviral activity of T-lymphocyte cells may be better promoted by higher levels of estrogen, and the uncontrolled immune response (cytokine storm) that has been seen in COVID-19-related respiratory failure may be better modulated [11–13] .

Testosterone levels were found to be connected with COVID-19 clinical severity even before admission to the hospital, with testosterone levels being significantly lower in elderly males who required the most intensive care and were at the highest risk of mortality [14]. In vitro exposure of endothelial cells to dihydrotestosterone (DHT), which is a testosterone derivative, worsened spike protein S1-mediated endothelial injury and elevated monocyte adhesion to endothelial cells. Findings from patients hospitalized due to COVID-19 also showed higher circulating VCAM-1 and E-Selectin levels in men, in comparison to women indicating higher endothelial injury [15]. Endothelial injury leads to dysregulated vascular tone, elevated permeability, elevated procoagulant activity, and impaired vascular formation, collectively contributing to more severe disease [16]. The study by Karkin et al. showed that COVID-19 may cause erectile dysfunction. The results of this study represented that the levels of testosterone of patients before and after COVID-19 were significantly different. They also concluded that high testosterone levels increase the rate of hospitalization in the intensive care unit by intensifying the disease [17].

This shows that severe COVID-19 symptoms could be caused by androgen-mediated pathways as it will be explained.

Androgens' role in ACE2 and TMPRSS2 expression regulation as well as regulation of viral entry and fusion in COVID-19

ACE2 is a zinc-dependent metalloprotease, a terminal carboxypeptidase and a type I transmembrane glycoprotein that is highly expressed in the heart, testis, and kidney, as well as at lesser levels in other tissues [18, 19]. ACE2 is expressed in human Airway Smooth Cell (ASM) and also the epithelial of the lung. ACE2 is expressed at a lower level in female ASM than in male ASM, and estrogen reduces ACE2 expression in human ASM cells, whilst testosterone increases it [20, 21]. Trimers of the transmembrane spike (S) glycoprotein of SARS-CoV-2 facilitate viral entry into the host cell. S binds to ACE2, which acts as a cellular receptor on the surface of host cells, then this enzyme mediates subsequential viral uptake and fusion into the host cell, dependent on process by target cell proteases [22]. Both ACE2 protein and mRNA are present in the highest concentrations in the testis of men. It is proved that ACE2 expression, which is an independent luteinizing hormone and is androgen dependent is restricted to Leydig and Sertoli cells in testis of human and it is also a fundamental production of adult Leydig cells [23]. TMPRSS2 transcription was also observed in human Leydig-like cells [24]. These findings suggest that Leydig cells and Sertoli cells of testis could also be potential targets for SARS-CoV-2 and sex discrepancy of COVID-19 deaths can also be justified by this information. TMPRSS2 is one of the target cell proteases that has been

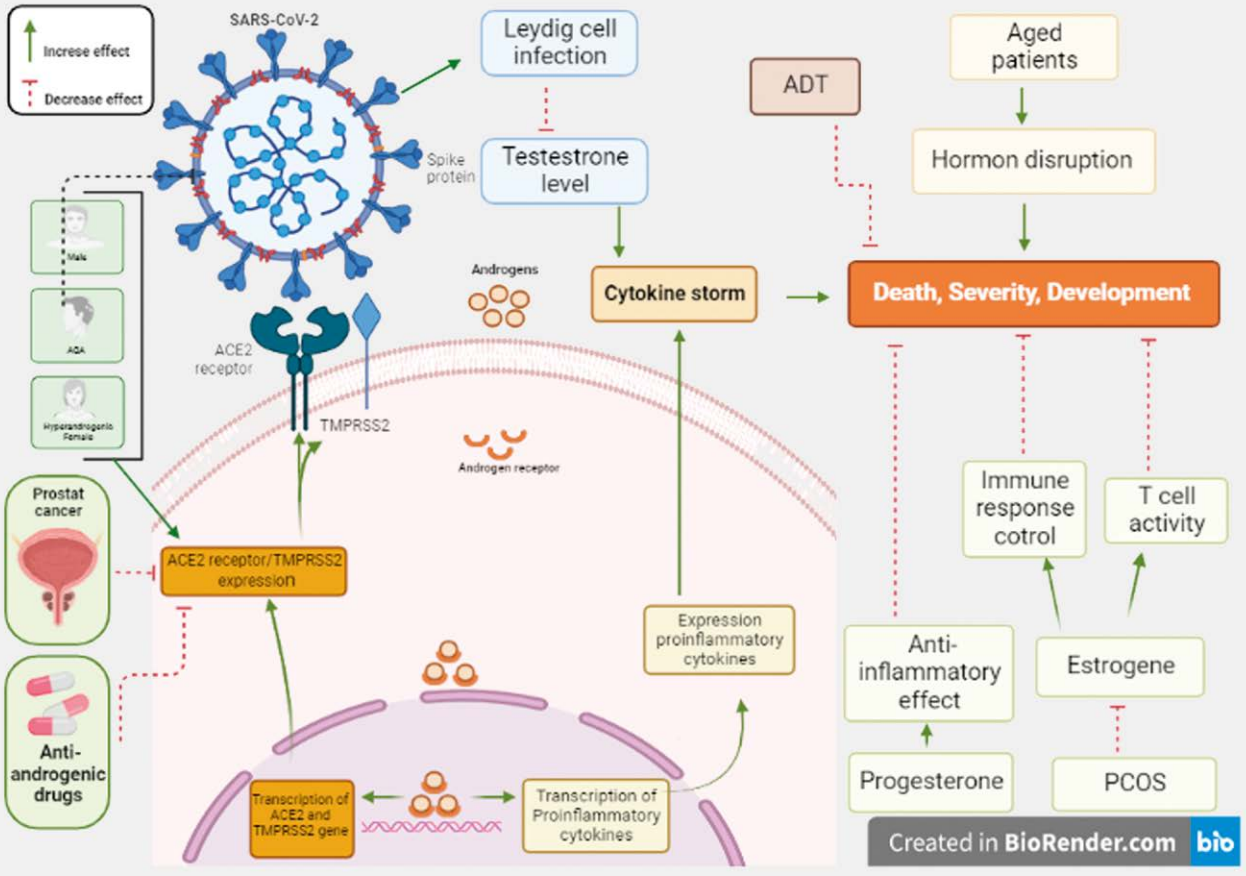
implicated in SARS-CoV-2 entrance. S is activated for fusion into the cell through its membrane, after cleavage by TMPRSS2 via substantial, irreversible conformational changes [25–27]. The expression of TMPRSS2 is positively modulated by androgens [28, 29]. Thereby elevated expression of ACE2 and TMPRSS2 by androgens can lead to increased viral entry as well as infectivity and thereby disease severity [30]. Based on these information ACE2 and TMPRSS2 can be considered as targets for reduction of viral entry and subsequently prevents disease development, but based on previous studies ACE2 downregulation, they are linked to a worsening of severity of SARS-induced lung injury. It has also been reported that when the SAR-SCoV-2 spike protein binds to ACE2, it causes ACE2 to downregulate, resulting in reduced angiotensin1–7 synthesis in the lungs and acute respiratory injury [31, 32]. It was also observed that androgen depletion in older men was associated with lower ACE2 levels [33] and this may explain the higher mortality due to COVID-19 in this population; thereby, TMPRSS2 is an appealing target because it has no obvious detrimental phenotype when it is knocked out [34]. Furthermore, in animal models of coronavirus infection, TMPRSS2 expression levels have been associated to COVID-19 severity [35] and its inhibition has recently been found to prevent SARS2-spike-facilitated entrance into the lung cell [22]. It is reported that TMPRSS2 knockout meaningfully prevented SARS-CoV-2 infection and significantly decreased its severity in vivo [36]. However, new studies have shown that dependence on TMPRSS2 varies according to the variant. Zhao et al. concluded that in VeroE6/TMPRSS2 cells, Omicron variant displayed weaker cell-cell fusion activity when compared to Delta variant. By considering all aspects, their findings imply that TMPRSS2 does not contribute to omicron variant infection and cell entry, which is primarily mediated by the endocytic pathway. The clinical symptoms or severity of the COVID-19 may be impacted by the difference in route of cell entry between the Omicron and Delta variants [37]. Meng et al. showed in their study that when compared to Delta, the Omicron spike protein has a higher affinity for ACE2. Higher cellular RNA expression of TMPRSS2 was significantly correlated with the defect in Omicron pseudo-typed virus entry to specific cell types, and deletion of TMPRSS2 adversely affected Delta entry more than Omicron [38].

Testosterone measured before COVID-19 can be directly related, inversely related, or unrelated to COVID-19 severity and mortality. Since testosterone is not measured on a regular basis in all persons unlike other clinical lab test, it is hard to find studies that measured testosterone before COVID-19, additionally testosterone measured during or after COVID-19 is not as accurate for assessing the relation between testosterone level and COVID-19 severity and mortality, because during COVID-19 infection or even long after COVID-19 (even after 3 months) testosterone levels are affected due to detrimental effects of SARS-CoV-2 infection on Leydig cells. Testosterone post-COVID levels cannot be considered as accurate as pre-COVID due to absence of post-COVID testosterone levels of persons who died as well. One study that dosed testosterone before COVID-19 showed a direct relationship between testosterone level and COVID-19 severity as well as mortality [39]. Still, testosterone is not necessarily the major determinant of androgens in terms of prediction of COVID-19 severity. If that were the case, young men would be the ones who would suffer the most, while the old men are the ones that suffer the most, as it will be explained in next section of this study. Additionally, anabolic steroids, which are DHT derivatives may put their users at higher risk of COVID-19 infection and severity [40]. These results may be explained by the fact that higher level of androgens including testosterone causes higher expression of TMPRSS2 specially in Leydig cells, which poses cells to higher SARS-CoV-2 entry and infection and resultantly more severe disease.

The AR is a nuclear receptor that belongs to the family of steroid receptors and its expression is increased by androgens. It is a transcription factor that is activated by ligand binding (by endogenous androgens, such as testosterone and DHT) and then translocates from the cytoplasm to the nucleus, where it forms a homodimer with regulatory areas of target genes, after that, the activated receptor promotes transcription of genes (▶ **Fig. 1**) [41, 42]. Several molecular studies have proved that TMPRSS2 is a target gene of AR in prostate cancer cells [28, 43, 44]. Activation of AR escalates TMPRSS2 levels in various tissues, most notably in prostate. Also, multiple lung lines have been reported to express functional AR in vitro studies [45–47]. The evidence shows that men have higher TMPRSS2 expression in their lungs [48]. Autopsy studies showed a strong correlation between AR expression and SARS-CoV-2 infectivity [49]. Further assessment upon clinical information on patients with COVID-19 proved that some specific genetic variants of AR (different in polyQ/AGA length) are associated with more advanced COVID-19 severity, which shows that AR sensitivity matters as much or even more than hormonal levels, as demonstrated in women with Poly Cystic Ovarian Syndrome (PCOS) or hyperandrogenism [50, 51].

Androgens, aging, and immune system

From another point of view, the COVID-19 severity can be justified by correlation between aging, immune system activity, and androgen levels; depressed androgen levels known as "hypogonadism," begins at advanced ages, around the age of 30 [52–54]. As testosterone levels fall with age, 20 percent to 50 percent of males over 60 have significantly lower testosterone levels [55, 56]. Furthermore, low testosterone levels have a substantial relationship with frailty [57] and mortality in older men [58], with the latter being particularly prominent in older men with metabolic syndrome [59]. A variety of co-morbidities have been linked to getting older. Metabolic syndrome, obesity, diabetes mellitus, and other chronic health disorders that might induce hypogonadism are more common in older men. These same co-morbidities also predispose older men to a higher risk of serious disease and death. A variety of causes of hypogonadism in older men are controllable, according to multiple studies, and hypogonadism can be reversed with weight loss or better illness control [60]. A number of studies have found that androgen deprivation, which fundamentally decreases androgens level in PCa patients, causes components of the metabolic syndrome [61–63] and treatment with testosterone reduces insulin resistance, obesity, and dyslipidemia in hypogonadal men [58, 64]. Low testosterone is strongly associated with multiple metabolic diseases – almost accurately dividing healthy from truly unhealthy ones – and low testosterone worsens these diseases. Low testosterone leads to worse outcomes in all diseases in an inde-



▶ **Fig. 1** The viral spike protein must first recognize the host cell ACE2 receptor before the host cell TMPRSS2 can proteolytically activate the viral spike protein, which is the dominant mechanism by which SARS-CoV-2 enters host cells; androgens bind to androgen receptors, and then androgen receptor move from cytoplasm to nucleus and elevates transcription of genes related to inflammatory cytokines, ACE2 and TMPRSS2, and subsequently their expression. In aged men with COVID-19, decreased levels of testosterone, due to hypogonadism, which is further decreased by SARS-COV-2 infection leads to cytokine storm that makes the COVID-19 mortality and severity worse. ADA: Androgenic Alopecia; ADT: Androgen Deprivation Therapy; PCOS: Poly Cystic Ovarian Syndrome; ACE2: Angiotensin Converter Enzyme 2; TMPRSS2: Transmembrane Serine Protease 2. (Created with BioRender.com). [rerif]

pendent manner, even when it is in the presence of metabolic diseases [65, 66].

The menopausal transition is defined by a change in sex steroid profile in women who have seen a significant decrease in ovarian estrogen production. After menopause, the ovaries stop producing estrogen, and estrogen is generated primarily from adipose tissue. Androgens are produced by both the ovaries and the adrenal glands in women [67, 68]. Between the ages of 20 and 40, serum testosterone levels in women drop by half [68–70]. These decreases also happen for androgen dehydroepiandrostenedione sulfate and androstenedione. Following the last menstrual period, there is no further decrease in testosterone [71]. There is an increase in serum testosterone reaching levels in older 60 to 80 year old women, albeit the amount of this increase is quite varied [68, 69]. Testosterone has been demonstrated to play a role in frailty in older males, but its role in frailty in older women appears to be less important [57]. Although the age-related decline in testosterone happens in both men and women, it begins significantly earlier in men and continues throughout their lives, whereas it reaches a maximum reduction in women just before menopause. Unlike men, older women have a recovery in circulating testosterone levels, which, while variable, occasionally approaches levels that is seen in the young [69]. Furthermore, as estrogen production declines, the overall androgenicity ratio (androgen/estrogen) in women increases with age [69, 71]. The phenotypic alterations found in postmenopausal women, such as hirsutism, are likely due to an increase in androgenicity [72]. It remains to be explored whether this rise in testosterone and androgenicity contributes to fewer severe outcomes and fatalities in old women compared to males. Inflammation is the immune system's response to infections and other potentially damaging stimuli. It might be the cause or a symptom of disorders that affect the cardiovascular, respiratory, or reproductive systems. The activation of innate and adaptive immune cells, as well as the proteins produced by these cells, causes inflammation [73].

Aging is linked to immune system decline and remodeling, which increases the chance of severe complications from infectious illnesses [74, 75]. Increased systemic inflammation [e. g., higher serum concentrations of interleukin (IL)-6 and tumor necrosis factor (TNFα)] and a diminished ability to respond to specific immunological challenges are both linked to aging [76, 77]. Enhanced mortality in aging is caused by a general impairment of overall immune function and an increased inflammatory response. Indeed, people over 65 account for the majority of influenza-related hospitalizations and more than 70 % of influenza-related deaths [78, 79]. Furthermore, males are more likely than females to be hospitalized and succumb to influenza virus infections in those aged 80 and up [80, 81]. Sex steroids, such as testosterone, can have a major impact on inflammatory cell activity and immune response modulation. Testosterone alters metabolic, cardiovascular, and immunological processes, which has a significant impact on health and disease [82–84]. Testosterone primarily suppresses immunological functions through acting on ARs in immune cells, which regulate target gene expression [85]. Testosterone inhibits immune cell activity by lowering inflammatory and boosting anti-inflammatory mediator expression in macrophages and T lymphocyte cells, protecting against a number of inflammation mediated illnesses [85, 86]. Role of testosterone in the pathophysiology of inflammation was reviewed by Traish et al. [87]. Low testosterone levels have been associated with higher rates of infection-related hospitalizations and all-cause mortality in male hemodialysis patients [88]. Testosterone levels have also been linked to higher mortality and illness severity following influenza infections as individuals get older [89]. Additionally, administration of testosterone replacement therapy (TRT) in elderly male mice reduces mortality and decreases illness severity independent of alterations in pulmonary inflammation or viral replication [90].

IL-6 is a tightly regulated, pro-inflammatory cytokine that is expressed at low levels except during infections, trauma, or other stresses. Testosterone is among the factors that have been shown to negatively regulate the expression of the IL-6 gene. Low testosterone levels in young men have been linked to low-grade systemic inflammation and are considered part of the mechanism underlying the negative health outcomes in male hypogonadism [91]. IL-6 levels are increased in LOH even when there is no infection, trauma, or stress. The age-related rise in IL-6 is believed to be responsible for some of the phenotypic changes in advanced aging in men, especially those that resemble chronic inflammatory disease [76]. In addition, levels of the soluble IL-6 receptor, the inflammatory marker are also elevated in older men [92] and higher levels of IL-6 have been shown to suppress androgen generation [93]. TRT has been shown to decrease levels of TNFα, another inflammatory cytokine, in hypogonadic men with chronic inflammatory disease [94], indicating that testosterone may reduce the inflammatory process and decrease the burden of illness. TRT has also been reported to reduce the spontaneous, but not inducible, generation of inflammatory cytokines by monocytes [95], suggesting that the impact of TRT is probably limited. Evidence shows that, although TRT was more efficacious in lowering inflammation in hypogonadic men than in eugonadal men, in general testosterone protects against inflammation regardless of clinical status [96]. The studies has shown that IL-6 levels were increased in the blood of the patients infected with SARS-CoV-2, which can be considered as a characteristic biomarker [97, 98]. Reports on the administration of tocilizumab for COVID-19 at doses similar to those used for the remedy of cytokine release syndrome have represented rapid improvement in patients. In these reports, rapid administration of anti IL-6 receptor therapy for patients with acute respiratory distress syndrome (ARDS) was critical [99, 100]. The society for immunotherapy of cancer sponsors the use of IL-6 or IL-6 receptor blocking antibodies [101]. According to a previous observational study about half of the COVID-19 positive patients developed ARDS [102]. Fifty percent of ARDS patients died, and older patients were more likely to develop ARDS. Critical diseases, like ARDS, are linked to neuroendocrine alterations associated with increased morbidity and mortality [103]. Critical disorders develop in two steps, the acute and chronic stages. Cytokines are thought to be responsible for early response changes, and other endogenous and exogenous (e. g., medications) factors contribute to the chronic changes. It is assumed that cytokines are behind the early response changes, and other endogenous factors, like dopamine and cortisol, and exogenous factors like medications, are proved to contribute to the chronic changes [103, 104]. Testosterone levels reduce during the early phase and continue to decrease during the chronic phase. The reduction in testosterone appears to be independent of LH levels, suggesting dysfunction of the hypothalamic-pituitary-gonadal axis [105, 106]. It was found that 50 % of men older than 65 years who were hospitalized for acute illnesses, such as respiratory infections, had hypogonads, and low testosterone levels, which were associated with in-hospital mortality [107, 108]. ARDS, a complication of severe sepsis, and sepsis-related morbidity and mortality, which were more common in men than women, were shown to be associated with high levels of IL-6, and occurred regardless of age or disease [109]. Low levels of testosterone were observed in male patients with severe sepsis and respiratory failure [110, 111] indicating that hypogonadism may provide a permissive environment for serious complications in men. Testosterone is one of the pharmacological therapies available for mitigating the catabolic response in critical diseases [112]. Actually, low testosterone level is a component of the proinflammatory profile linked to ARDS [113], and it is proved that TRT reduces airway inflammation in asthma [114]. As a result, interactions between aging, low testosterone, comorbidities, and inflammation provide a rich environment for severe complications associated with COVID-19, including cytokine storm; a condition which is highly mediated by IL-6-STAT3 signaling and is responsible for high number of deaths in COVID-19 patients specially older men; As previously noticed, gender difference was most noticeable at males aged > 59.5 years [9], because old men in addition to testosterone drop than young men experience following SARS-COV-2 infection, have metabolic diseases due to hypogonadism prior to SARS-COV-2 infection, which worsens COVID-19 outcomes and subsequently put them at higher risk of all cause death as well as severe COVID-19. A recently published study states men with hypogonadism are at greater risk of severe COVID-19 compared to healthy persons [115]. This is why aged male COVID-19 patients experience more mortality than young male patients.

Testosterone decrease after SARS-CoV-2 infection and its relation to COVID-19 severity and mortality

According to data noted in the previous section of the present study, direct probable effects of SARS-CoV-2 on testis and subsequently reduction in testosterone production, which may lead to cytokine storm as well as hyper catabolic states, contribute to the severe complications of COVID-19. SARS-CoV-2 has high tropism for Leydig cells and levels of testosterone substantially decreases following viral infection by SARS-CoV-2 [116]. A study proved that men with a severe COVID-19 infection had lower serum total testosterone levels compared to healthy ones [117]. In another study it is shown that during COVID-19, levels of testosterone were significantly decreased in comparison to healthy controls [118].

Post-COVID testosterone measurement is possibly strictly linked to persisting symptoms, many of them related to low testosterone. Because testosterone recovery predicts COVID-19 recovery, which means that, obviously, lower testosterone during or even after 1 month of COVID-19 (as measured by this study) could mean worse disease course, confounding cause and effect [119]. However results of an study showed similarity between median testosterone concentrations measured 7 months before COVID-19 and 3–9 months after [115].

It is proved in a study that even more than 90 days after recovery from COVID-19, when compared with healthy control, sperm concentration, total sperm count, and total motility were significantly declined, showing a persistent effect of COVID-19 on male testicles, reinforcing that these are not only affected but affected for prolonged periods of time [120].

Based on findings of above studies, testosterone measured during or after can be an indirect marker of the level of infectivity, as the virus has strong prediction for the Leydig cells, which produce testosterone. Correspondingly, countless studies that measured testosterone during hospitalization, showed that the lower testosterone levels the worse outcome appears, as testosterone can be considered as a marker of level of viral aggression.

Worse outcomes in COVID-19 patients following decrease in level of testosterone may be justified by the fact that low level of testosterone induces cytokine storm and is associated with metabolic diseases and worse outcomes in all diseases as well as hypercatabolic states as mentioned in previous section which resultantly led to higher severity and mortality in COVID-19 patients. In addition, lower level of androgens is associated with decrease in ACE2 expression, which leads to acute respiratory injury as already mentioned.

Impact of drugs that affect androgen-mediated mechanisms in COVID-19

It is probable that anti-androgens inhibiting androgen signaling will decrease TMPRSS2 expression in the lungs and therefore viral entrance. As a result, anti-androgens have been offered as a COVID-19 therapy option [105–107].

Expression of TMPRSS2 has been reduced in response to anti-androgens at the RNA and protein levels. Enzalutamide (ENZA) successfully reduces the expression of TMPRSS2, blocks the viral entrance and decreases mortality as well. The anti-androgens bicalutamide (BIC) and ENZA, which are AR antagonist significantly reduced the viral entry, the latter reducing the cellular entry by about 50 % [48]. In addition to being an AR antagonist, Enzalutamide inhibits translocation of AR from cytoplasm to nucleus as well as its binding to DNA. In the study of Leach et al., reduction of TMPRSS2 levels by Enzalutamide in human lung cells and mouse lung caused prevention of virus entry [121]. However, Baratchian et al. in a molecular study indicated that ENZA did not suppress TMPRSS2 activity, while ACE2 was moderately affected [122, 123].

Camostat, a TMPRSS2 inhibitor, has been shown to be able to prevent virus entry [124]. Tannic acid by forming a thermodynamically stable complex was another investigated TMPRSS2 inhibitor that could inhibit both SARS-CoV-2 Mpro and TMPRSS2 [125].

Men who use 5α-reductase inhibitors, which are commonly used to treat androgenetic alopecia (AGA) and benign prosthetic hyperplasia, displayed significantly reduced symptoms of COVID-19 and all-cause mortality [126].

Proxalutamide is a second-generation non-steroidal anti-androgen (NSAA), an AR antagonist, with the highest anti-androgenic capacity compared to any NSAA. Proxalutamide has increased the recovery rate, reduced the mortality rate and shortened hospital stay for hospitalized COVID-19 patients [127]. Based on a clinical study the cure rate of patients with COVID-19 treated with proxalutamide was higher than patients treated with placebo on day 14. Overall mortality decreased by 77.7 % in 28 days as well [128]. Substantial improvements seen in immunological, inflammatory and thrombotic markers with proxalutamide can support reduction of hospitalization [129]. Proxalutamide also significantly improves lung injury in patients with COVID-19 [130]. Cadegiani et al. in a double-blind, randomized clinical trial (DB-RCT), investigated the efficacy of proxalutamide 200 mg/day, compared to placebo group regarding viral clearance. The patients were non-hospitalized, with mild to moderate COVID-19. The results showed that seven-day remission was much better in the proxalutamide group as the average clearance time was lower. However, no significant difference was seen between genders in this study. Proxalutamide could be helpful for viral clearance in COVID-19 patients over 40 years old [131].

In a RCT study by Zimerman et al., it was concluded that to achieve the reduction in mortality rate observed by proxalutamide in COVID-19 patients, patients should adhere on and complete the 14-day treatment, otherwise the administration of this drug (if its interrupted too early) has no effect or even may worsen the mortality rates [132].

Recent publication on sabizabulin shows reduction of more than 50 % in mortality rate among hospitalized COVID-19 patients [133]. The strongest actions of sabizabulin are in its ability to disrupt AR through different pathways, developed for castration-resistant prostate cancer that did not respond to NSAAs [134].

For men with mild COVID-19 treated early with nitazoxanide and azithromycin, dutasteride therapy reduces viral shedding and inflammation as well as time-to-remission [135]. Brief administration of finasteride partially improves oxygen saturation, but does not influence other outcomes in hospitalized men over 50 years of age with COVID-19 [136]. Compared to nonhyperandrogenic women, hyperandrogenism had a more severe and prolonged clinical presentation, however, the risk of COVID-19 complications was still not high in any of the groups. Spironolactone reduced any additional hyperandrogenic-related risks [137].

According to Nickols and co-workers, randomized clinical trial, androgen suppression via temporary medical castration by degarelix, which is a luteinizing hormone releasing hormone antagonist that binds to the gonadotropin-releasing hormone receptors in the pituitary gland and immediately suppresses secretion of luteinizing and follicle-stimulating hormone, did not improve clinical outcomes for hospitalized men suffering from COVID-19 [138]. This result may be explained by the fact that degarelix, that does not inhibit the androgen receptor and does not increase estradiol, does not seem to work for COVID-19, showing the importance of androgen receptors and proportions between DHT, testosterone and estradiol, compared to testosterone levels alone. It can be also said that decrease in androgen levels by degarelix via luteinizing hormone releasing hormone antagonism may lead to ACE2 downregulation, which is linked to a worsening of severity of SARS-induced lung injury [31, 32].

According to results achieved in the above studies, it can be concluded that two determinants play more important roles more than testosterone levels: The ratio between testosterone, DHT (dihydrotestosterone) and estradiol, and the sensitivity to androgenic hormones through ARs as mentioned earlier as well. Since studies that inhibited only testosterone, instead of the receptor, had little or no results, such as degarelix.

COVID-19 in patients with androgenic alopecia

Androgenic alopecia is a common kind of hair loss in the human scalp induced by two androgens: testosterone and 5-DHT. Although both androgens bind to the AR and trigger androgen-sensitive genes in human hair dermal papilla cells, 5-DHT has a far higher binding affinity and potency in inducing the involved androgen-sensitive genes than testosterone [139]. The highest concentration of ARs are found on the scalp, and there are even more in individuals with androgenic alopecia [140]. We reviewed several studies to explore the potential association between AGA and COVID-19 severity.

According to a cross-sectional study by Miguel et al., among the 98 middle-aged COVID-19 patients in Peru, of those 32.7 % with comorbidities, and 45.9 % with AGA, the severity of the infection was statistically significant in alopecic patients. According to statistical analysis, alopecic patients were at a higher risk of moderate to severe COVID-19 symptoms. Overall, 57.1 % of the patients required oxygen therapy. Among patients with oxygen therapy, patients without alopecia (24.5 %) were considerably less than those with alopecia. Among patients hospitalized for more than 14 days, those without alopecia (32.1 %) were substantially lower than those with alopecia (71.1 %) [141].

Wambier et al. proposed an association between AGA and the severe effects of COVID-19. A total of 175 individuals who developed COVID-19 were assessed. Of the patients, 122 were men and 53 were women. In total, 67 % of patients presented with AGA. In both sexes, who had alopecia, the age was highly variable, while the most people with alopecia had advanced ages. So, this point can also indicate the importance of the androgen depletion in developing COVID-19 symptoms. These results indicate that a significant proportion of people hospitalized for COVID-19 have AGA. The authors added that assumption of the androgen-mediated severity of COVID-19 should be validated in larger studies. They also mentioned that it is still not possible to make a definite conclusion about the relationship between AGA and severity of COVID-19 [142].

In another observational study by Goren et al., a total of 41 Caucasian men admitted to hospitals diagnosed with bilateral SARS-CoV-2 pneumonia were analyzed; the average age of the patients was 58 years. Of those, 29 (71 %) had a clinically significant AGA diagnosis (Hamilton-Norwood scale higher than 2), and 12 (29 %) showed clinically irrelevant signs of AGA (Hamilton–Norwood 1 or 2) and 16 (39 %) were classified as severe AGA (Hamilton–Norwood 4 to 7) [6].

Lee and Yousaf et al. in an observational study examined severity of hair loss in 1941 hospitalized male tested for COVID-19. The examined individuals were divided into following models: model 1: “no hair loss,” model 2: “slight hair loss,” model 3: “moderate hair loss,” model 4: “serious hair loss”. The cohort included 1605 patients with negative COVID-19 result and 336 patients with positive COVID-19. A relation between rate of positive COVID-19 occurrence and baldness severity was observed; COVID-19 was found to be positive in 15.03 percent of the 592 model 1 individuals, 16.83 percent of the 404 model 2 persons, 18.15 percent of the 551 model 3 subjects and 20.05 percent of the 394 model 4 individuals. Model 4 patients were considerably more likely in COVID-19 positive patients ($p = 0.0468$). Models 2 and 3 did not differ significantly from model 1 in terms of the number of positive COVID-19 results. No correlation between rate of COVID-19 positivity and any other variable was observed in this study [143].

Muller et al. performed a population survey on valid questionnaires of 43 595 individuals (39 789 controls, 2332 suspected COVID-19 cases and 1474 confirmed COVID-19 cases) in Brazil. The survey comprised demographics (sex, age, skin color, and body composition), amount of hair (head full of hair, mild alopecia, and baldness), hair color, systemic comorbidities, COVID-19 status and outcome severity. According to this review study both extensive gray hair and alopecia were associated with COVID-19 severity [144].

In the other observational study by Ghafoor et al., there was expanded frequency and severity of AGA observed in males compared with females hospitalized with COVID-19. There were 300 patients, 220 (73.33 %) men and 80 (26.67 %) women. Severe alopecia (HNS3–7) and mild to moderate Hamilton-Norwood scale (HNS3–3) were observed in 43 (20 %) and 177 (80.55 %) cases, respectively, in men. 37 (46 %) of the females had AGA while 43 (54 %) did not. Severe alopecia (Ludwig scale 2–3) and mild to moderate alopecia (Ludwig scale 2) were present in 9 (24.32 %) and 28 (75.68 %) of the 37 females with AGA, respectively. a meaningful elevation in occurrence (95 %) and severity of AGA and poor outcomes in males ($p = 0.000$), in comparison to females (46 %) ($p = 0.273$,), with remarkable adverse COVID-19 disease results in the younger age group of male and also in few females of younger age group suffering from AGA without any comorbidities was noted [145]. Results from a prospective cohort study of 77 men with AGA hospitalized due to COVID-19 showed that anti-androgens, which were used for treatment of AGA improved COVID-19 symptoms. Anti-androgens, which are commonly utilized within the treatment of AGA are finasteride, dutasteride, spironolactone, and bicalutamide. Among the anti-androgen modalities, 5α-reductase inhibitors are the fore-

most well endured due to the direct inhibition (intracellular) of DHT generation from testosterone in target tissues, not influencing testosterone levels. Dermatologists are eager to encourage their patients to preserve systemic AGA treatment with anti-androgens, especially 5α-reductase inhibitors [146].

According to an observational study, women with PCOS, who may have AGA as well as increased levels of testosterone because of the high levels of LH, are possibly at expanded chance of serious COVID-19 disease, but in this study it was shown that Cox proportional hazards regression model found no relation between androgen excess and hirsutism observed in PCOS women with increased risk of infection with COVID-19 [147].

A cross-sectional case-control analysis assessed the symptoms of COVID-19 in the following two groups: not hyperandrogenic or hyperandrogenic. A diagnosis of PCOS with two of the three Rotterdam criteria met, idiopathic hirsutism with at least eight points on the Ferriman-Gallwey scale, or androgenetic alopecia verified by trichoscopy indicate whether a condition is non-hyperandrogenic or hyperandrogenic. In this study, Cadegiani et al. found that the incidence of several common clinical symptoms of COVID-19 was significantly higher in hyperandrogenic females than in their nonhyperandrogenic counterparts [148]. A study by Stasi et al. has assessed the role of testosterone in a cohort of women with SARS-COV-2 pneumonias. The result showed that the higher total testosterone and calculated free testosterone are associated with a greater severity of the disease [149].

COVID-19 in PCa patients and efficacy of androgen deprivation therapy in these patients

The overall prevalence of cancer in patients with COVID-19 in studies was 2.0 %. In the analysis of other subgroups based on sample size, in studies with sample size < 100, the prevalence was slightly higher than 0.3 %, but in larger studies, with sample size > 100, the overall prevalence was lower than 2.0 % [150]. Cancer patients are more susceptible to infection than non-cancer patients due to the systemic state of immunosuppression caused by malignancies or anticancer therapies, such as chemotherapy or surgery [151]. Therefore, these patients may be at higher risk for COVID-19 and experience a worse prognosis [152].

The observational study was performed by Kuderer et al. on 928 COVID-19 patients (18 years older) with active or pervious malignancies [including prostate cancer (PCa)], from the United States, Canada, and Spain with mean age of 66; 50 % of patients were male. The endpoint for all mortality within 30 days of diagnosis was COVID-19. they stated that the dependent factors associated with the increase in 30-day mortality, after partial adjustment, were: increasing age, male gender, smoking, number of comorbidities and active cancer; race and ethnicity, obesity, type of cancer, type of anticancer treatment, and recent surgery were not associated with mortality [139].

Based on the study by Experton et al., which has developed a dual socio-clinical risk model for severe COVID-19 disease in the medicare population, comprised mostly of individuals aged 65 and over, PCa was more resistant to death or hospitalization by COVID-19. Among COVID-19 cases, patients with the most severe disease resulting in either hospitalization or death had higher frequencies of diabetes, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), chronic kidney disease, hypertension, ischemic heart disease, cerebrovascular disease, pulmonary fibrosis or pulmonary hypertension, chronic liver disease and asthma. Between 39 variables, prostate cancer was the third less sensitive variable to COVID-19 related death or hospitalization and overall was a protective factor [153].

Based on the results of a meta-analysis study conducted by Kuderer and another study by Mou et al. [140] PCa patients are not more susceptible than individuals with other types of cancer or malignancy to COVID-19 but it seems that COVID-19 and PCa have important common risk factors that can be used as therapy targets for COVID-19. TMPRSS2 is predominantly expressed in the prostate. In the lung cancer cell line and the LnCaP prostate cancer cell line, TMPRSS2 is expressed as androgen-dependent [28]. TMPRSS2 plays a pivotal role in progression of both COVID-19 and PCa, and also can be a great therapeutic target for both diseases. As TMPRSS2 has been shown to activate Protease-Activated Receptor-2 (PAR2), a G protein- coupled receptor; PAR2 activation overregulates the matrix metalloproteinase (MMP)-2 and MMP-9 in extracellular matrices, which Both are key proteases in tumor cell metastasis [154]. In addition, PCa is initiated when TMPRSS2 fuses with the ERG family of genes, which is known to induce cellular proliferation [142]. PCa is particularly similar to COVID-19 because the risk factors for both diseases are similar: male gender, old age and racial inequalities [155]. It is also proved that active AR promotes tumor growth in PCa, hence therapy approaches for PCa generally target this signaling axis, such as androgen deprivation and hormonal therapies like anti-androgens [144, 156]. According to these information, it can be concluded that, androgen-deprivation therapy (ADT) which is used for treatment of PCa and functions by decreasing the expression of TMPRSS2 [157] and also activity of AR can also be a great treatment for COVID-19 [158].

It was shown that in an observational study by Montopoli, rate of hospitalization (50 vs. 66.7 %) and occurrence of severe COVID-19 (25 vs. 27.2 %), was lower in PCa patients with COVID-19 undergoing ADT (n = 4, with ages of 94, 80, 75, and 68) compared to those not undergoing ADT (n = 114). No death was observed in ADT receiving group while 15.8 % of patients not undergoing ADT died due to COVID-19. COVID-19 infection rates were five times lower in those on ADT compared to those who did not get this treatment. It was found that cancer patients are more exposed to COVID-19 virus than non-cancer patients [159]. It should be said that it may be impossible to draw a conclusion based on this small sample of ADT patients (n = 4) and in larger samples different results from results of this study should be observed.

Patel and colleagues in a cohort study collected data from 58 PCa patients with COVID-19 receiving ADT (GnRH analog or antagonist, n = 22) or not receiving ADT (n = 36) [160]. At the baseline, individuals in the ADT group had a higher occurrence of metastatic disease (64 % versus 0 %, $p < 0.001$) and more advanced rates of pulmonary disease (27 vs. 6 %, $p < 0.02$), in comparison to the non-ADT group. After controlling for age, cardiac disease, and pulmonary disease, ADT represented lesser amounts of hospitalization ($p < 0.02$) and supplemental oxygen requirements ($p = 0.036$). ADT use was also linked with a protective effect on need for intubation ($p = 0.192$) and mortality ($p = 0.22$) (albeit non-significant) [160]. The mean age of patients was not reported.

An observational study by Lee et al., which was the largest populational study on the effects of ADT, reported that ADT was linked to a lower chance of testing positive for SARS-CoV-2 (p = 0.001, 295 of 3057). ADT patients were tested positive for COVID-19 with mean age of 73.9, in comparison to 2427 positive cases in 36 096 individuals not on ADT with other cancers and mean age of 62.9. ADT was also linked to a lower risk of severe COVID-19 outcomes [161].

Another study also failed to show the protective effects of ADT against COVID-19 in PCa patients (mean age of 75 and n = 11 for ADT, and 78.2 years for non-ADT: n = 50) [162] in which no significant difference was observed between ADT and non ADT group regarding COVID-19 mortality and severity. Overall, though, men with prostate cancer undergoing ADT are at greater risk for the consequences of COVID-19. ADT is also associated with an increased risk of type 2 diabetes and several other diseases, and severe sarcopenia. Therefore, the lack of increased risk in this population is sufficient to demonstrate a relative protection.

But after all these improving effects of ADT, in a retrospective observational study by Gedeborg et al., with collected data from 2015 to 2020 in PCa patients older than 60, findings showed that the mortality rate in 2020 increased in both ADT and non ADT groups compared to the period 2015–2019 and this increase in mortality was most likely due to COVID-19. The mortality rate in 2020 in patients not on ADT treatment was substantially lower than patients receiving ADT treatments (3.62 %, 18.87 %, 6.49 and 11.84 % for non ADT group: n = 86 644, GnRH group: n = 10 555, bicalutamid monotherapy group: n = 13 172 and any ADT group: n = 23729, respectively) [163]. As mentioned in one of the previous sections of the present study (androgens, aging, and immune system), the higher mortality rate in elder men with COVID-19 (men older than 60) than in women at the same age and also younger men was due to cytokine storm caused by androgen depletion in LOH. In two previous mentioned studies, the higher mortality rate in ADT groups compared to non ADT group and insufficiency of this treatment can be explained by the effect of ADT treatment which may further decrease androgen levels in elder men and thereby exacerbates cytokine storm as well as hyper catabolic state and subsequently leads to higher mortality rate. Even the disassociation of anticancer treatment from COVID-19 deaths (including PCa) in Kuderer study [139] is probably due to the mean age of patients (66 years old) that were observed (the mean age for PCa patients was not reported).

Although, both androgen related mechanisms (relationships between androgens, aging and immune system, and also correlation between androgens and TMPRSS2 expression) have been shown to have fundamental roles in COVID-19 deaths in men but all of the results obtained from above studies in PCa patients cannot be justified just by these 2 mechanisms and other mechanisms are likely to be involved.

The difference observed in results of mentioned studies could be due to the behavioral pattern of the participants in this study and their different exposures with infection; the individuals in the study were not also all in the same condition in terms of disease stage, the drugs they received and immune system status.

The absolute role of androgens in preventing or promoting COVID-19 infections, especially in men aged more than 60, seems to be highly controversial. According to previous studies, both high and low testosterone levels can predispose person to severe COVID-19 [164, 165]. In theory it seems that androgens, including testosterone, suppress cytokine storm, and that they can reduce the severity of disease; it also seems that use of ADT can causes worsening of symptoms, but this condition was not observed in Montopoli et al. and Patel et al. studies, and contradictory results was reported. Therefore, further studies with suitable design are needed to elucidate other involved mechanisms and relationships.

Conclusion

The review of literature on role of androgens in severity and mortality of COVID-19 symptoms proved fundamental roles for androgens in developing COVID-19 symptoms and also in causing COVID-19 associated deaths. As it was shown that the development of COVID-19 symptoms and its associated deaths were substantially higher in males, especially elderly males than young females and also in patients with androgenic alopecia than patients without it. Since men have substantially higher level of androgens, expression of TMPRSS2, which is required for SARS-COV-2 cell entry is higher in men, especially in their testis which cause higher virus entry and thereby infection. In addition, drop in androgen levels including testosterone, in men due to infection of Leydig cells by SARS-COV-2 in testis leads to cytokine storm, hypercatabolic states and thereby worse outcomes in disease. More severity and mortality in aged males than young ones are due to hypogonadism associated with aging, which leads to metabolic disease and comorbidities that worsens COVID-19 outcomes along with testosterone depletion following viral infection of Leydig cells. Still further studies are needed to define the exact role of androgens as well as effect of ratio between male sex hormones and female sex hormones and their associated mechanisms in severity and mortality of COVID-19.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Li L-q, Huang T, Wang Y-q et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020; 92: 577–583

[2] Li X, Xu S, Yu M et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146: 110–118

[3] Robinson DP, Lorenzo ME, Jian W et al. Elevated 17β-estradiol protects females from influenza A virus pathogenesis by suppressing inflammatory responses. PLoS Pathog 2011; 7: e1002149

[4] Ortona E, Pierdominici M, Maselli A et al. Sex-based differences in autoimmune diseases. Ann Istitut Sup Sanita 2016; 52: 205–212

[5] Iaccarino G, Grassi G, Borghi C et al. Gender differences in predictors of intensive care units admission among COVID-19 patients: the results of the SARS-RAS study of the Italian society of hypertension. PLoS One 2020; 15: e0237297

[6] 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

[7] Mauvais-Jarvis F. Do anti-androgens have potential as therapeutics for COVID-19? Endocrinology 2021; 162: bqab114. doi:10.1210/endocr/bqab114

[8] Manning JT, Fink B. Understanding COVID-19: digit ratio (2D: 4D) and sex differences in national case fatality rates. Early Hum Develop 2020; 146: 105074

[9] Vahedian-Azimi A, Pourhoseingholi MA, Saberi M et al. 23 Gender susceptibility to COVID-19 mortality: androgens as the usual suspects? Adv Exp Med Biol 2021; 1321: 261–264

[10] Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected? J Am Coll Cardiol Case Rep 2020; 2: 1407–1410

[11] Ghandehari S, Matusov Y, Pepkowitz S et al. Progesterone in addition to standard of care vs standard of care alone in the treatment of men hospitalized with moderate to severe COVID-19: a randomized, controlled pilot trial. Chest 2021; 160: 74–84

[12] Breithaupt-Faloppa AC, Correia CDJ, Prado CM et al. 17β-Estradiol, a potential ally to alleviate SARS-CoV-2 infection. Clinics (Sao Paulo) 2020; 75: e1980. doi:10.6061/clinics/2020/e1980

[13] Dambha-Miller H, Hinton W, Joy M et al. Mortality in COVID-19 amongst women on hormone replacement therapy or combined oral contraception: a cohort study. Fam Pract 2022 cmac041. doi:10.1093/fampra/cmac041

[14] Salonia A, Pontillo M, Capogrosso P et al. Severely low testosterone in males with COVID-19: A case-control study. Andrology 2021; 9: 1043–1052

[15] Kumar N, Zuo Y, Yalavarthi S et al. SARS-CoV-2 spike protein S1-mediated endothelial injury and pro-inflammatory state is amplified by dihydrotestosterone and prevented by mineralocorticoid antagonism. Viruses 2021; 13: 2209

[16] Peng Z, Shu B. Zhang Yet al. Endothelial response to pathophysiological stress. Arterioscler Throm Vasc Biol 2019; 39: e233–e243

[17] Karkin K, En Alma. Erectile dysfunction and testosterone levels prior to COVID-19 disease: what is the relationship? Arch Ital Urol Androl 2021; 93: 460–464

[18] Gheblawi M, Wang K, Viveiros A et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020; 126: 1456–1474

[19] Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. Shock 2016; 46: 239–248

[20] Kalidhindi RSR, Borkar NA, Ambhore NS et al. Sex steroids skew ACE2 expression in human airway: a contributing factor to sex differences in COVID-19? Am J Physiol Lung Cell Mol Physiol 2020; 319: L843–L847

[21] Guy J, Lambert D, Warner F et al. Membrane-associated zinc peptidase families: comparing ACE and ACE2. Biochim Biophys Acta 2005; 1751: 2–8

[22] 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: 271–80, e8

[23] Douglas GC, O'Bryan MK, Hedger MP et al. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. Endocrinology 2004; 145: 4703–4711

[24] Li L, Li Y, Sottas C et al. Directing differentiation of human induced pluripotent stem cells toward androgen-producing Leydig cells rather than adrenal cells. Proc Natl Acad Sci U S A 2019; 116: 23274–23283

[25] Walls AC, Park Y-J, Tortorici MA et al. Function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020; 181: 281–292

[26] Millet JK, Whittaker GR. Host cell proteases: critical determinants of coronavirus tropism and pathogenesis. Virus Res 2015; 202: 120–134

[27] Walls AC, Tortorici MA, Snijder J et al. Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. Proc Natl Acad Sci U S A 2017; 114: 11157–11162

[28] Lin B, Ferguson C, White JT et al. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. Cancer Res 1999; 59: 4180–4184

[29] Jacquinet E, Rao NV, Rao GV et al. Cloning and characterization of the cDNA and gene for human epitheliasin. Eur J Biochem 2001; 268: 2687–2699

[30] Ambrosino I, Barbagelata E, Ortona E et al. Gender differences in patients with COVID-19: a narrative review. Monaldi Arch Chest Dis 2020; 90. doi:10.4081/monaldi.2020.1389

[31] Mehra MR, Desai SS, Kuy S et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Eng. J Med 2020; 382: e102

[32] Kuba K, Imai Y, Rao S et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus – induced lung injury. Nat Med 2005; 11: 875–879

[33] Dai M, Liu D, Liu M et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov 2020; 10: 783–791

[34] Kim TS, Heinlein C, Hackman RC et al. Phenotypic analysis of mice lacking the Tmprss2-encoded protease. Mol Cell Biol 2006; 26: 965–975

[35] Iwata-Yoshikawa N, Okamura T, Shimizu Y et al. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J Virol 2019; 93: e01815–e01818

[36] Li F, Han M, Dai P et al. Distinct mechanisms for TMPRSS2 expression explain organ-specific inhibition of SARS-CoV-2 infection by enzalutamide. Nat Commun 2021; 12: 1–14

[37] Zhao H, Lu L, Peng Z et al. SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with Delta variant in TMPRSS2-expressed cells. Emerg. Microb Infect 2022; 11: 277–283

[38] Meng B, Abdullahi A, Ferreira IA. Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity. Nature 2022; 603: 706–714

[39] Yeap BB, Marriott RJ, Manning L et al. Higher premorbid serum testosterone predicts COVID-19-related mortality risk in men. Eur J Endocrinol 2022; 187: 159–170

[40] Cadegiani F, Lin EM, Goren A et al. Expression of concern: potential risk for developing severe COVID-19 disease among anabolic steroid users. BMJ Case Rep CP 2021; 14: e241572

[41] Brooke G, Bevan C. The role of androgen receptor mutations in prostate cancer progression. Curr Genom 2009; 10: 18–25

[42] Tan ME, Li J, Xu HE et al. Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacol Sinica 2015; 36: 3–23

[43] Clinckemalie L, Spans L, Dubois V et al. Androgen regulation of the TMPRSS2 gene and the effect of a SNP in an androgen response element. Mol Endocrinol 2013; 27: 2028–2040

[44] Cano LQ, Lavery DN, Sin S et al. The co-chaperone p23 promotes prostate cancer motility and metastasis. Mol Oncol 2015; 9: 295–308

[45] Mikkonen L, Pihlajamaa P, Sahu B et al. Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol 2010; 317: 14–24

[46] Yoon G, Kim JY, Choi YK et al. Direct activation of TGF-β1 transcription by androgen and androgen receptor complex in Huh7 human hepatoma cells and its tumor in nude mice. J Cell Biochem 2006; 97: 393–411

[47] Jeong Y, Xie Y, Lee W et al. Research resource: diagnostic and therapeutic potential of nuclear receptor expression in lung cancer. Mol Endocrinol 2012; 26: 1443–1454

[48] Leach D, Mohr A, Giotis E et al. The antiandrogen enzalutamide downregulates TMPRSS2 and reduces cellular entry of SARS-CoV-2 in human lung cells. Nat Commun 2021; 12: 1–12

[49] Wang X-M, Mannan R, Xiao L et al. Characterization of SARS-CoV-2 and host entry factors distribution in a COVID-19 autopsy series. Commun Med 2021; 1: 1–10

[50] 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: e15–e17

[51] Velavan TP, Pallerla SR, Rüter J et al. Host genetic factors determining COVID-19 susceptibility and severity. EBioMed 2021; 72: 103629

[52] Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 2005; 26: 833–876

[53] Wu FC, Tajar A, Pye SR et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study. J Clin Endocrinol Metab 2008; 93: 2737–2745

[54] Tajar A, Forti G, O'Neill TW et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European male ageing study. J Clin Endocrinol Metab 2010; 95: 1810–1818

[55] Travison TG, Araujo AB, O'Donnell AB et al. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab 2007; 92: 196–202

[56] Harman SM, Metter EJ, Tobin JD et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab 2001; 86: 724–731

[57] Carcaillon L, Blanco C, Alonso-Bouzon C et al. Sex differences in the association between serum levels of testosterone and frailty in an elderly population: the Toledo study for healthy aging. PLoS One 2012; 7: e32401

[58] Saad F, Gooren LJ. The role of testosterone in the etiology and treatment of obesity, the metabolic syndrome, and diabetes mellitus type 2. J Obes 2011; 471584. doi:10.1155/2011/471584. Epub 2010 Aug 10

[59] Laouali N, Brailly-Tabard S, Helmer C et al. Testosterone and all-cause mortality in older men: the role of metabolic syndrome. J Endocr Soc 2018; 2: 322–335

[60] Corona G, Rastrelli G, Monami M et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 2013; 168: 829–843

[61] Basaria S, Muller DC, Carducci MA et al. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer 2006; 106: 581–588

[62] Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology 2004; 63: 742–745

[63] Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006; 91: 1305–1308

[64] Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. Therap Adv Endocrinol Metab 2010; 1: 207–223

[65] Yandi H, Dong Y, Huafen Z et al. Lower testosterone levels predict increasing severity and worse outcomes of hepatitis B virus-related acute-on-chronic liver failure in males. BMC Gastroenterol (Web) 2021; 21: 1–11

[66] Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. Therap Adv Endocrinol Metab 2010; 1: 207–223

[67] Burger HG. Androgen production in women. Fertil Steril 2002; 77: 3–5

[68] Davison SL, Bell R, Donath S, Montalto J, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005; 90: 3847–3853

[69] Morley JE, Perry HM III. Androgens and women at the menopause and beyond. J Gerontol Ser A 2003; 58: M409–M416

[70] Zumoff B, Strain GW, Miller LK et al. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab 1995; 80: 1429–1430

[71] Kim C, Harlow SD, Zheng H et al. Changes in androstenedione, dehydroepiandrosterone, testosterone, estradiol, and estrone over the menopausal transition. Women Midlife Health 2017; 3: 1–9

[72] Shifren JL, Gass ML.Group NRfCCoMWW The north American menopause society recommendations for clinical care of midlife women. Menopause 2014; 21: 1038–1062

[73] Papadopoulos V, Li L, Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone? Andrology 2021; 9: 65–72

[74] Potluri T, Fink AL, Sylvia KE et al. Age-associated changes in the impact of sex steroids on influenza vaccine responses in males and females. NPJ Vacc 2019; 4: 1–12

[75] vom Steeg LG, Klein SL. SeXX matters in infectious disease pathogenesis. PLoS Pathogens 2016; 12: e1005374

[76] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Ann Rev Med 2000; 51: 245–270

[77] Wikby A, Nilsson B-O, Forsey R et al. The immune risk phenotype is associated with IL-6 in the terminal decline stage: findings from the Swedish NONA immune longitudinal study of very late life functioning. Mech Ageing Develop 2006; 127: 695–704

[78] Thompson WW, Shay DK, Weintraub E et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289: 179–186

[79] Reed C, Chaves SS, Daily Kirley P et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One 2015; 10: e0118369

[80] Wong KC, Luscombe GM, Hawke C. Influenza infections in Australia 2009–2015: is there a combined effect of age and sex on susceptibility to virus subtypes? BMC Infect Dis 2019; 19: 1–10

[81] Eshima N, Tokumaru O, Hara S et al. Sex-and age-related differences in morbidity rates of 2009 pandemic influenza A H1N1 virus of swine origin in Japan. PLoS One 2011; 6: e19409

[82] Moncada I. Testosterone and men's quality of life. Aging Male 2006; 9: 189–193

[83] Muehlenbein MP, Bribiescas RG. Testosterone-mediated immune functions and male life histories. Am J Hum Biol 2005; 17: 527–558

[84] Vom Steeg LG, Attreed SE, Zirkin B et al. Testosterone treatment of aged male mice improves some but not all aspects of age-associated increases in influenza severity. Cell Immunol 2019; 345: 103988

[85] Bereshchenko O, Bruscoli S, Riccardi C. Glucocorticoids, sex hormones, and immunity. Front Immunol 2018; 9: 1332

[86] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016; 16: 626–638

[87] Traish A, Bolanos J, Nair S et al. Do androgens modulate the pathophysiological pathways of inflammation? Appraising the contemporary evidence. J Clin Med 2018; 7: 549

[88] Nakashima A, Ohkido I, Yokoyama K et al. Associations between low serum testosterone and all-cause mortality and infection-related hospitalization in male hemodialysis patients: a prospective cohort study. Kidney Int Rep 2017; 2: 1160–1168

[89] Vom Steeg LG, Vermillion MS, Hall OJ et al. Age and testosterone mediate influenza pathogenesis in male mice. Am J Physiol Lung Cell Mol Physiol 2016; 311: L1234–L1244

[90] Furman D, Hejblum BP, Simon N et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc Natl Acad Sci 2014; 111: 869–874

[91] Bobjer J, Katrinaki M, Tsatsanis C et al. Negative association between testosterone concentration and inflammatory markers in young men: a nested cross-sectional study. PLoS One 2013; 8: e61466

[92] Maggio M, Basaria S, Ble A et al. Correlation between testosterone and the inflammatory marker soluble interleukin-6 receptor in older men. J Clin Endocrinol Metab 2006; 91: 345–347

[93] Tsigos C, Papanicolaou DA, Kyrou I et al. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997; 82: 4167–4170

[94] Malkin CJ, Pugh PJ, Jones RD et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004; 89: 3313–3138

[95] Corrales J, Almeida M, Burgo R et al. Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men with partial androgen deficiency. J Endocrinol 2006; 189: 595–604

[96] Bianchi VE. The anti-inflammatory effects of testosterone. J Endocr Soc 2019; 3: 91–107

[97] Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033–1034

[98] Ansariniya H, Seifati SM, Zaker E et al. Comparison of immune response between SARS, MERS, and COVID-19 infection, perspective on vaccine design and development. BioMed Res Int 2021; 8870425. doi:10.1155/2021/8870425

[99] Michot J-M, Albiges L, Chaput N et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure. A case report. Ann Oncol 2020; 31: 961–964

[100] Chi Z, Zhao W, Jia-Wen L et al.The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab man be the key to reduce the mortality https://www ncbi nlm nih gov/pmc/articles/PMC7118634/pdf/main pdf 2020;

[101] Fox WJU, Brahmer JR, Chen DS et al. Correction: Insights from immuno-oncology: the society for immunotherapy of cancer statement on access to IL-6-targeting therapies for COVID-19. J Immunother 2020; 13: e000878corr1

[102] Liu Y, Sun W, Li J et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. MedRxiv 2020. doi:org/10.1101/2020.02.17.20024166

[103] Akbaş T, Deyneli O, Sönmez FT et al. The pituitary-gonadal-thyroid and lactotroph axes in critically ill patients. Endokrynol Polska 2016; 67: 305–312

[104] Vanhorebeek I, Langouche L, Van den Berghe G. Endocrine aspects of acute and prolonged critical illness. Nat Clin Pract Endocrinol Metab 2006; 2: 20–31

[105] Nierman DM, Mechanick JI. Hypotestosteronemia in chronically critically ill men. Crit Care Med 1999; 27: 2418–2421

[106] Van den Berghe G, Weekers F, Baxter RC et al. Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. J Clin Endocrinol Metab 2001; 86: 3217–3226

[107] Iglesias P, Prado F, Macias MC et al. Hypogonadism in aged hospitalized male patients: prevalence and clinical outcome. J Endocrinol Invest 2014; 37: 135–141

[108] Iglesias P, Prado F, Ridruejo E et al. Hypogonadism and mortality in aged hospitalized male patients: a 5-year prospective observational study. Exp Clin Endocrinol Diabetes 2015; 123: 589–593

[109] Nasir N, Jamil B, Siddiqui S et al. Mortality in sepsis and its relationship with gender. Pakistan J Med Sci 2015; 31: 1201

[110] Bech A, Van Leeuwen H, De Boer H. Etiology of low testosterone levels in male patients with severe sepsis requiring mechanical ventilation. Crit Care 2013; 17: 1–200

[111] Christeff N, Benassayag C, Carli-Vielle C et al. Elevated oestrogen and reduced testosterone levels in the serum of male septic shock patients. J Steroid Biochem 1988; 29: 435–440

[112] Stanojcic M, Finnerty CC, Jeschke MG. Anabolic and anticatabolic agents in critical care. Curr Opin Crit Care 2016; 22: 325

[113] Heffernan DS, Dossett LA, Lightfoot MA et al. Gender and ARDS in critically injured adults: a prospective study. J Trauma 2011; 71: 878

[114] Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. Curr Allergy Asthma Rep 2017; 17: 1–9

[115] Dhindsa S, Champion C, Deol E et al. Association of male hypogonadism with risk of hospitalization for COVID-19. JAMA Network Open 2022; 5: e2229747-e

[116] Marinelli L, Beccuti G, Zavattaro M et al. Testosterone as a biomarker of adverse clinical outcomes in SARS-CoV-2 pneumonia. Biomedicines 2022; 10: 820

[117] Lanser L, Burkert FR, Thommes L et al. Testosterone deficiency is a risk factor for severe COVID-19. Front Endocrinol 2021; 12: 694083

[118] Salonia A, Pontillo M, Capogrosso P et al. Severely low testosterone in males with COVID-19: A case-control study. Andrology 2021; 9: 1043–1052

[119] Toscano-Guerra E, Gallo MM, Arrese-Muñoz I et al. Recovery of serum testosterone levels is an accurate predictor of survival from COVID-19 in male patients. BMC Med 2022; 20: 1–18

[120] Ruan Y, Hu B, Liu Z et al. No detection of SARS-CoV-2 from urine, expressed prostatic secretions, and semen in 74 recovered COVID-19 male patients: a perspective and urogenital evaluation. Andrology 2021; 9: 99–106

[121] Leach DA, Mohr A, Giotis ES et al. The antiandrogen enzalutamide downregulates TMPRSS2 and reduces cellular entry of SARS-CoV-2 in human lung cells. Nat Commun 2021; 12: 4068

[122] Baratchian M, McManus JM, Berk M et al. Sex, androgens and regulation of pulmonary AR, TMPRSS2 and ACE2. bioRxiv 2020. doi:10.1101/2020.04.21.051201

[123] Baratchian M, McManus JM, Berk MP et al. Androgen regulation of pulmonary AR, TMPRSS2 and ACE2 with implications for sex-discordant COVID-19 outcomes. Sci Rep 2021; 11: 11130

[124] Deng Q, Rasool RU, Russell RM et al. Targeting androgen regulation of TMPRSS2 and ACE2 as a therapeutic strategy to combat COVID-19. iScience 2021; 24: 102254

[125] Wang SC, Chen Y, Wang YC et al. Tannic acid suppresses SARS-CoV-2 as a dual inhibitor of the viral main protease and the cellular TMPRSS2 protease. Am J Cancer Res 2020; 10: 4538–4546

[126] 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 2021; 35: e243–e246

[127] Cadegiani FA, Zimerman RA, Fonseca DN et al. Final results of a randomized, placebo-controlled, two-arm, parallel clinical trial of proxalutamide for hospitalized COVID-19 patients: a multiregional, joint analysis of the proxa-rescue androCoV trial. Cureus 2021; 13: e 20691. doi:10.7759/cureus.20691

[128] McCoy J, Goren A, Cadegiani FA et al. Proxalutamide reduces the rate of hospitalization for COVID-19 male outpatients: a randomized double-blinded placebo-controlled trial. Front Med (Lausanne) 2021; 8: 668698

[129] Cadegiani FA, Goren A, Wambier CG et al. Proxalutamide improves inflammatory, immunologic, and thrombogenic markers in mild-to-moderate COVID-19 males and females: an exploratory analysis of a randomized, double-blinded, placebo-controlled trial early antiandrogen therapy (EAT) with proxalutamide (The EAT-Proxa Biochemical AndroCoV-Trial). medRxiv 2021. doi:10.1101/2021.07.24.21261047

[130] Cadegiani FA, Fonseca DN, Correia MN et al. Proxalutamide (GT0918) improves lung injury in hospitalized COVID-19 patients – an analysis of the radiological findings of the proxa-rescue androCoVtrial. medRxiv 2021. doi:10.1101/2021.07.01.21259656

[131] Cadegiani FA, McCoy J, Gustavo Wambier C et al. Proxalutamide significantly accelerates viral clearance and reduces time to clinical remission in patients with mild to moderate COVID-19: results from a randomized, double-blinded, placebo-controlled trial. Cureus 2021; 13: e13492

[132] Zimerman RA, Fonseca DN, Correia MN et al. Proxalutamide (GT0918) reduction of mortality rate in hospitalized COVID-19 patients depends on treatment duration – an exploratory analysis of the proxa-rescue androCoV trial. . medRxiv 2021. doi:10.1101/2021.06.28.21259661

[133] Barnette KG, Gordon MS, Rodriguez D et al. Oral sabizabulin for high-risk, hospitalized adults with Covid-19: interim analysis. N Engl J Med Evidence 2022; 1: EVIDoa2200145

[134] Markowski MC, Tutrone RF, Eisenberger MA et al. VERU-111, an oral cytoskeleton disruptor, to treat men with metastatic castration-resistant prostate cancer (mCRPC) who failed an androgen receptor targeting agent. J Clin Oncol 2021; 39: 5056

[135] Cadegiani FA, McCoy J, Wambier CG et al. Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to-remission in males with COVID-19: a randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV trial–biochemical). Cureus 2021; 13: e13047

[136] Zarehoseinzade E, Allami A, Ahmadi M et al. Finasteride in hospitalized adult males with COVID-19: a risk factor for severity of the disease or an adjunct treatment: a randomized controlled clinical trial. Med J Islam Rep Iran 2021; 35: 30

[137] Cadegiani FA, Goren A, Wambier CG et al. An open-label prospective observational study of antiandrogen and non-antiandrogen early pharmacological approaches in females with mild-to-moderate COVID-19. The pre-androCoV female trial. medRxiv 2020. doi:10.1101/2020.10.05.20206870

[138] Nickols NG, Mi Z, DeMatt E et al. Effect of Androgen suppression on clinical outcomes in hospitalized men with COVID-19: the HITCH randomized clinical trial. JAMA Network Open 2022; 5: e227852-e

[139] Kuderer NM, Choueiri TK, Shah DP et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020; 395: 1907–1918

[140] Mou R, Jin X, Li W et al. Prostate cancer: a risk factor for COVID-19 in males?: a protocol for systematic review and meta analysis. Medicine (Baltimore) 2020; 99: e22591

[141] Lucas JM, Heinlein C, Kim T et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. TMPRSS2 influences prostate cancer metastasis. Cancer Discov 2014; 4: 1310–1325

[142] Perner S, Mosquera J-M, Demichelis F et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. Am J Surg Pathol 2007; 31: 882–888

[143] Kizilkan Y, Senel S, Ozercan AY et al. Evaluating the anxiety and depression status of prostate cancer patients whose operations were postponed because of the COVID-19 pandemic. Int J Clin Pract 2021; 75: e14278

[144] Crawford ED, Heidenreich A, Lawrentschuk N et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prost Dis. 2019; 22: 24–38

[145] Ghafoor R, Ali SM, Patil A et al. Association of androgenetic alopecia and severity of coronavirus disease 2019. J Cosmet Dermatol 2022; 21: 874–879

[146] 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: e13–e15

[147] Subramanian A, Anand A, Adderley NJ et al. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. Eur J Endocrinol 2021; 184: 637–645

[148] Cadegiani F, Lim R, Goren A et al. Clinical symptoms of hyperandrogenic women diagnosed with COVID-19. J Eur Acad Dermatol Venereol 2021; 35: e101–e104

[149] Di Stasi V, Rastrelli G, Inglese F et al. Higher testosterone is associated with increased inflammatory markers in women with SARS-CoV-2 pneumonia: preliminary results from an observational study. J Endocrinol Invest 2022; 45: 639–648

[150] Desai A, Sachdeva S, Parekh T et al. COVID-19 and cancer: lessons from a pooled meta-analysis. JCO Global Oncol 2020; 6: 557–559

[151] Sica A, Massarotti M. Myeloid suppressor cells in cancer and autoimmunity. J Autoimmun 2017; 85: 117–125

[152] Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335–337

[153] Experton B, Tetteh HA, Lurie N et al. A predictive model for severe COVID-19 in the medicare population: a tool for prioritizing primary and booster COVID-19 vaccination. Biology 2021; 10: 1185

[154] Lucas JM, Heinlein C, Kim T et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 2014; 4: 1310–1325

[155] Kizilkan Y, Senel S, Ozercan AY et al. Evaluating the anxiety and depression status of prostate cancer patients whose operations were postponed because of the COVID-19 pandemic. Int J Clin Pract 2021; e14278:

[156] Nuhn P, De Bono JS, Fizazi K et al. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol 2019; 75: 88–99

[157] Bennani NN, Bennani-Baiti IM. Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy. Ann Oncol 2020; 31: 1585–1586

[158] Bahmad HF, Abou-Kheir W. Crosstalk between COVID-19 and prostate cancer. Prostate Cancer Prostat Dis 2020; 23: 561–563

[159] 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

[160] Patel VG, Zhong X, Liaw B et al. Does androgen deprivation therapy protect against severe complications from COVID-19? Ann Oncol 2020; 31: 1419–1420

[161] Lee K, Heberer K, Gao A et al. A population-level analysis of the protective effects of androgen deprivation therapy against COVID-19 disease incidence and severity. Front Med (Lausanne) 2022; 9: 774773

[162] Jiménez-Alcaide E, García-Fuentes C, Hernández V et al. Influence of androgen deprivation therapy on the severity of COVID-19 in prostate cancer patients. Prostate 2021; 81: 1349–1354

[163] Gedeborg R, Styrke J, Loeb S et al. Androgen deprivation therapy and excess mortality in men with prostate cancer during the initial phase of the COVID-19 pandemic. PLoS One 2021; 16: e0255966

[164] Pozzilli P, Lenzi A. Testosterone, a key hormone in the context of COVID-19 pandemic [Commentary]. Metabolism 2020; 108: 154252

[165] Cattrini C, Bersanelli M, Latocca MM et al. Sex hormones and hormone therapy during COVID-19 pandemic: implications for patients with cancer. Cancers 2020; 12: 2325