Review

Sex Hormones in COVID-19 Severity: The Quest for Evidence and Influence Mechanisms

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Keywords: SARS-CoV-2; COVID-19; Hormone; Gender; Immune response

Review

Sex Hormones in COVID-19 Severity: The Quest for Evidence and Influence Mechanisms

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Abstract: Studies report variable effects of sex hormones on serious diseases. Severe disease and mortality rates in COVID-19 show marked gender differences that may be related to sex hormones. Sex hormones regulate the expression of the viral receptors ACE2 and TMPRSS2, which affect the extent of viral infection and consequently cause variable outcomes. In addition, sex hormones have complex regulatory mechanisms that affect the immune response to viruses. These hormones also affect metabolism through obesity, and severe disease can result from complications such as thrombosis. This review presents the latest research on the regulatory functions of hormones in viral receptors, immune responses, complications as well as their role in COVID-19 progression. It also discusses the therapeutical possibilities of these hormones by reviewing the recent findings of clinical and assay studies.

Keywords: SARS-CoV-2; COVID-19; hormone; gender; Immune response

1. Introduction

The coronavirus disease 2019 (COVID-19), attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 6 million fatalities. (https://coronavirus.jhu.edu/map.html). Studies have shown notable disparities in COVID-19 mortality and critical illness rates between genders. Early reports from the Chinese Center for Disease Control and Prevention (China CDC) indicated a higher mortality rate for males at 2.8% compared to 1.7% for females [1]. Subsequent large population-based studies and meta-analyses have consistently confirmed this result. Although a global meta-analysis involving 3,111,714 reporting cases found no gender disparity in the distribution of COVID-19 diagnoses, men had a significantly increased risk of intensive care unit (ICU) admission (odds ratio, OR = 2.84) and mortality (OR = 1.39) [2]. Moreover, a cohort study involving 18,647 patients revealed that both male gender (adjusted odds ratio, aOR 1.896) and age (aOR 1.065) were linked to heightened risks of ICU admission and all-cause mortality [3]. Intriguingly, observational studies have revealed that specific pregnant women, initially asymptomatic to COVID-19 and testing for SARS-CoV-2 upon admission to obstetric units, experienced worsening symptoms in the immediate postpartum period. It was consistent with the significant drop in hormones seen after giving birth [4,5]. Furthermore, a 2021 study involving 1,902 female COVID-19 patients identified menopause as a notable risk predictor associated with COVID-19 (OR = 1.91 [1.06 ~ 3.46]) [6]. Previous research suggests that gender bias in COVID-19 outcomes becomes more pronounced with age [7]. Aging, childbirth, and menopause bring about substantial alterations in sex hormones, believed to be contributing to the sex bias observed for COVID-19 severity. In line with this hypothesis, there is a relationship among SARS-CoV-2 exposed men with complications of COVID-19 with metabolic and sex hormone imbalances [8,9]. A cohort study demonstrated that testosterone (T), estradiol (E2), and insulin-like growth factor 1 (IGF-1) concentrations in the blood serum, which are regulated by sex hormone signaling, are linked to the

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disease burden in patients with COVID-19 [10]. In addition, a high proportion of T to E2 in hospitalized COVID-19 participants was associated with favorable outcomes, as shown in a subsequent cohort study of 3,005 patients from four different research centers [11]. Additionally, a study involving patients with gender anxiety disorder revealed that female-to-male patients treated with T had a 3.46 times higher rate of COVID-19 infection than did male-to-female patients treated with estrogen and anti-androgens. This result provides evidence to confirm the assumption that sex hormones might have a role to do with the development of COVID-19 [12]. Indeed, several previous studies have shown that sex hormones play an important role in the development of infectious and immune-related diseases [13–15]. Following the COVID-19 outbreak, more researchers have started to focus on the issue. An increasing evidence base has suggested that sex differences in COVID-19 may be due to gonadal hormonal influences, particularly in studies investigating the effects of oestrogen, progesterone and T on COVID-19 progression. However, the results of these studies have not been consistent.

This review presents the latest research on the regulatory functions of hormones in viral receptors, immune response, complications as well as their role in COVID-19 progression (Figure 1). It also discusses the potential therapy of such hormones based on recent findings in the clinic.

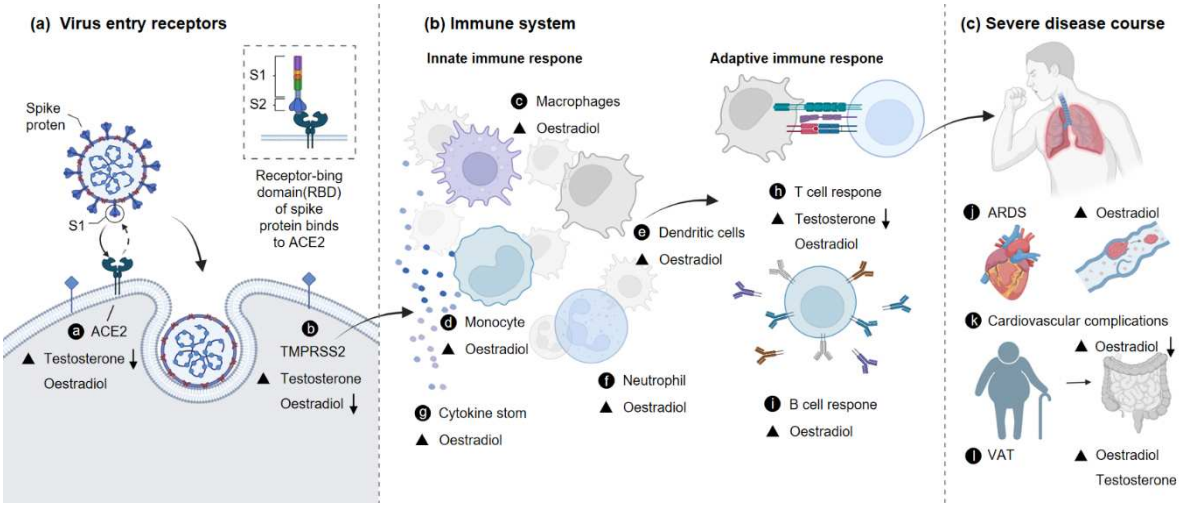

Figure 1. Effects of sex hormones on the course of severe COVID-19. (**a**) Mechanism of viral invasion (**b**) Immune system re-sponse. (**c**) Regulation and direction of severe disease course a-l by sex hormones. TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; VAT, visceral adiposity.

2. Sex Hormones and COVID-19

2.1. Androgens and COVID-19 Severity

Current research has demonstrated that baseline androgen values are linked to adverse outcomes in COVID-19. In addition, low levels of T in patients are connected with organ damage and poor prognosis. However, attempts to test antiandrogenic treatments in clinical trials have not yielded positive results. In a prospective study, it was found that severe COVID-19 patients had lower baseline T levels than those with milder symptoms (53ng/dL vs. 151ng/dL) [10]. In addition, a significant positive association between total circulating T levels assessed in several cohorts prior to contact with SARS-CoV-2 infection and the risk of death from COVID-19 was found in an observational study that controlled for covariates such as lifestyle, underlying diseases, and other variables [10]. It provides added support for the hypothesis of an androgen involvement in COVID-19. Early studies during the COVID-19 outbreak suggested a potential connection between male-pattern baldness, driven by increased androgen activity (androgenetic alopecia), and disease severity [16,17]. It implies a potential link between androgen sensitivity and hospitalization and severe symptoms in persons exposed to SARS-CoV-2. Subsequent observational studies found reduced

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readmission and mortality rates in prostate cancer patients receiving second-generation androgen deprivation therapies (ADTs) and in men with COVID-19 on long-term use of 5-alpha reductase inhibitors (5ARIs) to treat benign prostatic hyperplasia (BPH) [18,19]. However, clinical trial data provide limited evidence to suggest the benefit of anti-androgen therapy for serious disease associated with COVID-19. A clinical trial investigating the androgen receptor blocker enzalutamide in a limited group was prematurely terminated due to a greater rate of hospitalization among the treatment group than among the placebo control group [20]. Additionally, one clinical study of 96 COVID-19 inpatients found no evidence of reduced COVID-19 severity with the use of the antiandrogenic compound degarelix [21]. Furthermore, similar results were demonstrated in an epidemiologic study of 7,894 prostate cancer patients, where ADT had no preventive effect on outcomes among those patients with COVID-19 [20]. Multiple recent observational trials have refuted the link between elevated androgen activity and T replacement therapy and adverse COVID-19 outcomes [22,23]. In fact, several studies have suggested that low serum T levels may indicate organ damage and prognosis in patients infected with SARS-CoV-2 and may characterize the hormonal milieu of critically ill patients [10,24–26]. It may be attributed to the significant reduction in T levels caused by contracting SARS-CoV-2 [27]. One potential coherent trial found a significant reduction in T levels in critically ill men compared to mildly ill men. Upon admission, there was a 64.9% decrease in T levels, followed by an 84.1% decrease on three days [10]. In a cohort study published last year, levels of T were lower among severely symptomatic patients with COVID-19 than among mild to moderately symptomatic hospitalized patients (85.1 ng/dl vs. 315 ng/dl), and lower among those requiring ICU care than among non-ICU patients (64 ng/dl vs. 286 ng/dl) [24]. In summary, circulating androgen levels suggest a complex relationship with COVID-19 severity that has not been completely elucidated. More research is needed to elucidate potential effects of androgen on disease outcome [28].

2.2. Estradiol and COVID-19 Severity

E2 has been linked to reduced levels of inflammation in the context of acute infectious disease and play a major rule in modulating both innate and adaptive immunity [13]. Post-menopausal females are at increased hospitalization risk relative to nonmenopausal females, according to a prospective analysis of medical records from 1,902 COVID-19 patients (OR=1.91) [6]. Moreover, anti-Müllerian hormone (AMH) and E2 might be considered possible preventive agents against the severity of COVID-19, showing a negative correlation [6]. Multiple studies have provided evidence that supplemental estrogen confers a preventive effect on COVID-19 in postmenopausal females, with particular emphasis on the effectiveness of E2 [7,29]. A significant population-based study further supports the hypothesis of a preventive effect of estrogen in COVID-19. This study discovered that antiestrogen therapies (AETs) decreased the occurrence of serious illness in patients suffering from hormone-driven cancers (HDCs) [30]. However, it's worth noting that sex hormone values among severely affected women with COVID-19 did not show statistically significant differences compared to female patients with mild disease [9]. This phenomenon can be attributed in part to the complexity of estrogen and COVID-19 interactions, reflecting the interplay among different subtypes of estrogen, age, and reproductive status [31].

2.3. Progesterone and COVID-19 Severity

Progesterone, in addition, serves as a vital humoral steroid hormone with a significant role in maintaining pregnancies in female mammals [32]. Notably, it is also produced and has functions in males. Progesterone possesses the capability to reduce leukocyte activation, mitigate pro-inflammatory mediator production, regulate T-cell differentiation, contribute to neurodevelopment, and yield a wide array of anti-inflammatory effects [33–36]. Progesterone has been identified as a crucial factor in facilitating rapid recovery from influenza A virus infection, prompting discussions about its potential advantages during instances of immune dysregulation in SARS-CoV-2 infection [37]. Furthermore, regarding progesterone's potential benefits associated with the infection, clinical trial data from 2021 offered additional support for the hypothesis. These trials revealed that

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subcutaneous delivery of progesterone improved the condition in 20 severely affected male patients diagnosed with SARS-CoV-2 [38]. Moreover, the results suggested that progesterone might have the capacity to modulate Immune dysfunction., mitigate Strong signs, and reduce the likelihood of critical illnesses. However, it's essential to note that the significance of the findings was constrained by the marginally significant p-value and a limited number of samples, which made it difficult to draw conclusions [38]. This hypothesis received added support from experimental studies showing that progesterone, when administered in a dose-dependent manner, could reverse weight loss and ameliorate severe pneumonia in SARS-CoV-2-infected hamsters [39]. Furthermore, current data from China indicates that women who are becoming pregnant are expected to suffer the most serious instances from COVID-19 after childbirth, which coincides with a rapid decline in progesterone levels [40]. According to the U.S. Centers on Disease Control and Prevention (CDC) monitoring database, among 8,207 female pregnancies in early stages of an outbreak, there was an increased chance of serious disease among the pregnant patients, although the risk of death was similar to that of non-pregnant women [41]. However, it's important to note that some small-scale independent reports among female pregnancies exposed to SARS-CoV-2 did not indicate any adverse pregnancy and/or COVID-19 outcomes [42,43]. In summary, the evidence for a direct association of progesterone with adverse outcomes in COVID-19 remains inconclusive at this time.

3. Sex Hormones and Expression of Viral Receptors

3.1. ACE2 and TMPRSS

The COVID-19 pathogen, SARS-CoV-2, forms a viral envelope with spike glycoproteins (S-proteins) and is a sensory RNA virus [44]. For entry, SARS-CoV-2 relies on surface proteins on the human respiratory tract epithelial cells, particularly transmembrane serine protease 2 (TMPRSS2) as well as angiotensin-converting enzyme 2 (ACE2) [45–47] (Figure 1). TMPRSS2 triggers cleavage and activation of the S proteins, resulting in viral-host cell membrane fusing [48]. Intracellular entry is facilitated through ACE2, a type I transmembrane glycoprotein acting as a terminal carboxypeptidase. The two types of proteins differ in their expression levels across several tissues, with the highest expression levels in lung type 1 and type 2 alveolar epithelial cells (AT1 and AT2) [49,50]. TMPRSS2 expression was identified in various lung and bronchial cells, demonstrating higher levels in AT2 cells compared to AT1 cells. ACE2 is normally expressed in the lungs [49], oral mucosa [51], cardiovascular system [52], testes [53], and immune cells [54].

During the course of SARS-CoV-2 disease, excessive levels of ACE2 could facilitate the entry of the virus into the body, potentially leading to organ damage. Experimental studies demonstrate that the removal of respiratory TMPRSS2 affects the primary infection site and the spread of the virus in the airways, ultimately reducing the degree of lung pathology following SARS-CoV and MERS-CoV infection [55]. Various types of TMPRSS2 blockers were found to prevent SARS-CoV-2 entry into the virus in culture [56–58]. Research indicates upper airway SARS-CoV-2 transmission involves TMPRSS2 along with closely related proteases, while transmission in human lung may be inhibited by camostat mesylate as well as the metabolite GBPA [59]. During the clinical trial, COVID-19 patients receiving camostat mesylate, a serine protease inhibitor, experienced symptom relief and faster recovery of taste and smell sensation compared to other groups [60]. However, a randomized trial found that adding a hemostat to the usual care regimen did not reduce treatment time, and only a narrow percentage of COVID-19 risk patients who required O_2 therapy showed accelerated recovery [61]. Indeed, TMPRSS2 depends on ACE2 for its functional activity in viral fusion. A case-control study determined that the TMPRSS2/ACE2 ratio proved more effective than ACE2 alone in predicting COVID-19 severity [62].

3.2. Sex-Specific Expression of TMPRSS2 and ACE2

ACE2 expression has been found to be increased in men compared to women, both overall and within the lung [50,63]. There are two main causes: sex chromosomes and sex hormones. In females, both X chromosomes are switched off at the end of blastocyst stage to prevent imbalances in genetic

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expression, but certain genes on the X chromosome, including those encoding ACE2 and angiotensin II receptor 2, escape this silencing [64,65]. Additionally, studies have shown that the SRY family of genes found in the Y sex chromosome of males increases the activation of RAAS components, thereby decreasing the promoter activation of ACE2 [66]. However, studies and experimental models evaluating ACE2 expression across various tissues have yielded conflicting results. Some studies report comparable ACE2 expression levels in various tissues in both women and men [67,68]. In the lung, there is a debate regarding if the levels of TMPRSS2 expression in males are higher than in females, although some research has shown a small significant difference [69,70]. Conversely, other studies have reported a lack of significance in pulmonary phenotypes among the sexes, while indicating a higher level of ACE2 locus in pulmonary and bronchial muscle cells in males [71,72].

However, hormonal factors may also influence gender specific differences in TMPRSS2 and ACE2 expression and activity. Estrogen, a regulator of these factors, notably affects various tissue types [73,74]. Moreover, the ACE and angiotensin pathways govern mineralocorticoid receptor (MR)[75].

3.3. Regulation of TMPRSS2 and ACE2 by Sex Hormones

The intricate interplay between estrogen and ACE2 appears to vary across specific organs or environments (Table 1). Analysis of publicly available genomic data reveals that estrogen amplifies ACE2 expression in thymus cells from mice and adenocarcinoma cells from human lung epithelium [76]. MR antagonists suppress proinflammatory genes while concurrently boosting ACE2 mRNA expression and activity [77]. Elevated concentrations of E2 lead to reduced lung ACE2 expression, whereas lower levels result in an increase [78]. Experimental evidence suggests that estrogen interferes with the glycoprotein and glycol can junctions within ACE2 and SARS-CoV-2, preventing virus insertion peak proteins within alveoli [79]. Conversely, Epithelial cells of the bronchus and smooth muscular tissue cells of respiratory tract cells show a modest downregulation of ACE2 in response to 17β-estradiol [72,73]. Moreover, estrogen appears to diminish ACE2 expression in the myocardium and kidneys in vivo [80]. In comparison, progesterone demonstrates greater efficacy in reducing ACE2 expression in uterine tissue compared to estrogen treatment [81]. Previous animal model studies have reported decreased ACE2 expression and activity with estrogen and estrogen modulators.

In human primary bronchial epithelial cells, estrogen inhibits ACE2 expression without affecting TMPRSS2 expression [73]. In non-pituitary cells, for example, prostate, breast or kidney cells, estrogen may inhibit TMPRSS2 expression [75,82]. Prostate carcinoma containing the TMPRSS2:ERG fusion gene may respond to estrogen signalling[82]. Application of 17β-estradiol treatment on VERO E6 cells results in reduced intracellular SARS-CoV-2 viral load, leading to a decrease in TMPRSS2 mRNA. However, ACE2 mRNA remains unchanged in the same VERO E6 cells [75].

Modulating ACE2 expression is a mechanism through which androgens control viral entry. Androgens raise markers of ACE2 activation, blood plasma renin activation and the expression of angiotensinogen [83]. A recent comprehensive screen of nearly 1,500 drugs approved by the FDA was designed to find compounds that reduce ACE2 in normal cell cultures. The results highlight the androgen signaling pathway as a major regulator of ACE2 levels [8]. Multiple studies have affirmed that T amplifies ACE2 expression. In aging men, declining androgen levels lead to reduced ACE2 expression, while T markedly boosts ACE2 levels in normal male primary airway smooth muscle cells [76]. Treatment with antiandrogen drugs decreases ACE2 expression in cardiomyocytes generated by stem cell-derived cells and protects pulmonary organs from SARS-CoV-2 infection [8]. Androgens and antiandrogens can also regulate ACE2 expression in prostate cancer cell lines [67], corroborated by research on mouse lung tissue [84]. In addition, androgen receptor stimulation enhances ACE2 levels in mouse airway epithelium cells. Exposure to T for 24 hours elevates ACE2 levels on exposed human airway epithelium from both sexes [67,72]. Consequently, a slight downregulation of ACE2 gene levels is found in the lungs of mice treated with the potent anti-androgen enzalutamide [85]. Further, androgen deprivation through antiandrogen treatments,

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administered via depot or in vitro methods, causes decreased expression of transcripts and proteins of both TMPRSS2 and ACE2 [84].

Androgens influence viral entry by regulating TMPRSS2. Androgens, including T, can enhance TMPRSS2 gene expression, potentially resulting in higher levels in men than in women [69]. Consequently, SARS-CoV-2 can more readily enter target host cells in males than in females [86]. Androgen ligands and androgen receptor promoter binding elements control TMPRSS2 promoter activity in the prostate. TMPRSS2 is high in the prostate tissue and levels increase in response to androgens through targeted androgen receptor expression [87]. Androgen deprivation therapy (ADT) is believed to offer protective effects through preventing the entrance of pseudotyped and live SARS-CoV-2 viruses in prostate cancer cells [67]. In contrast, TMPRSS2 regulation by androgens in lung tissue remains uncertain, unlike in the prostate. Human lung adenocarcinoma cells treated with androgen lines resulted in increased TMPRSS2 expression [88]. Similarly, androgens and anti-androgens regulate TMPRSS2 in various human lung cell lines and mouse lung epithelial cells [70]. Nevertheless, following enzalutamide treatment, TMPRSS2 expression remained unchanged across cancer cell lines, mouse lung and human pulmonary organs [85,89].

Table 1. Regulation of TMPRSS2 and ACE2 by sex hormones.

Viral Receptor	Sex Hormone /Study Drug	Species	Primary Findings	Sample	Refs.
ACE2	Antiandrogen enzalutamide	Human	Decreases ACE2 expression	Heart cells and pulmonary tissue derived from human embryonic stem cells (hESC)	[8]
	Testosterone	Human	Upregulation of ACE2 gene in men and women	Airway smooth muscle cells	[62]
	Estrogen	Human	Reduces ACE2, but not substantially	Airway smooth muscle cells	
	Antiandrogen enzalutamide	Human	Reducing TMPRSS2 expression	Human lung cells	[84]
	Estrogen	Mouse	Increases ACE2 expression	Thymus	[76]
	Testosterone	Mouse	Increase ACE2 expression	Kidney	
TMPRSS2	Antagonist enzalutamide	Mouse	Moderately suppressible	Lung	[85]
	Antagonist enzalutamide	Mouse	Did not decrease pulmonary TMPRSS2	Lung	
	Antiandrogen enzalutamide	Mouse	Reduced TMPRSS2 levels	Airway epithelial cells	[70]
	Leuprolide or Estradiol	Human	In males treated with leuprolide or estradiol, TMPRSS2 levels were markedly lower.	Epithelial cells	[87]
ACE2 and TMPRSS2	Androgen	Mouse	Decreased Tmprss2 and Ace2 expression in lung epithelial cells.	Lung epithelial cells	[67,72]
	Castration	Mouse	Reduced levels of ACE2 and TMPRSS2 in lung, seminal vesicles and small intestine; ACE2 upregulated in kidney tissue, but not TMPRSS2	Systemic	[84]

4. Sex Hormones and Immune Responses

4.1. Cytokine Storm

SARS-CoV-2 infection triggers the development of innate and adaptive immune responses, often leading to dysregulated innate inflammation and compromised adaptive immunity in critically ill

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patients. This dysregulation may result in cytokine storm, as demonstrated by a significant increase of pro-inflammatory cytokines in patient serum, including IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, CCL3 and TNF [90,91] (Figure 1). The cytokine storm, in turn, may induce shock, organ damage, respiratory failure, and, in severe cases, multiple organ failure. It is also associated with significant neutrophil and monocyte infiltrates and results in extensive damage to the alveoli, characterized by the formation of hyalinization and alveolar wall thickness. Ultimately, this immune-mediated damage extends to include conditions like splenic atrophy and lymph node necrosis, which have been observed in deceased patients [92].

4.2. Gender Differences in Immune Responses

There are significant sex differences in innate and adaptive immune responses. Typically, immune responses to pathogens are stronger in females compared to males, including female animals. This sexual dimorphism is attributed to various factors. First, females possess a greater abundance of internal defense macrophages, including monocytes, macrophages and dendritic cells [93,94]. Moreover, females exhibit enhanced cytotoxic T-cell activity [95], elevated immunoglobulin levels [96], and increased $CD3^+$ and $CD4^+$ cell counts [97]. Conversely, male COVID-19 patients often have lower lymphocyte counts, elevated neutrophil to leukocyte ratios, and elevated levels of C-reactive plasma protein in serum than women [98]. Additionally, while females typically demonstrate viral infections with stronger cytokine responses, male SARS-CoV-2-infected individuals tend to have elevated proinflammatory cytokines like IL-8, contributing to the poorer prognosis in COVID-19 cases. Furthermore, T-cell activation is generally weaker in males, which correlates with worse outcomes in COVID-19 patients.

4.3. Sex Hormones and the Immune Response

Discrepancies in circulating sex hormone levels may underlie gender-related responses to infections. Progesterone is critical for the release of vital immune response cytokines, including IL-6, TNF-α, and IFN-γ. The hormone also orchestrates immune cell activities and induces potent anti-inflammatory effects [99]. Besides, estrogen upregulates various genes associated with B cell activation and survival, such as CD22, SHP-1, and Bcl-2.119, thus enhancing immune system responses, particularly in B cells [100]. In contrast, T appears to inhibit the recruitment of both eosinophils and neutrophils, interfere with T helper 2 (TH2) $CD4^+$ recruitment and suppress IgE generation [101]. Additionally, T inhibits TH2 and TH17 cell function [102,103] and alters the production of cytokines, including IFNγ [104] resulting in immunosuppressive effects. In summary, these gender-related differences extend from innate to adaptive immunity and are influenced by the interplay of intrinsic and adaptive immune factors, often linked to sex hormone levels.

4.4. Regulation of Disease by sex Hormones Through Immunization

Gender-related disparities in sex hormone-induced immune responses appear to be important for the outcome of COVID-19 therapy (Table 2). Recent research shows that acute respiratory distress syndrome (ARDS) leading to respiratory failure is the leading cause of death in COVID-19 patients [105]. In a 2021 study, males who had reduced T and lymphocyte plasma concentrations on admission to hospital with COVID-19 were more likely to have more severe ARDS and worse condition after admission [106]. Even before the 2020 epidemic, studies had pointed out that low total testosterone (TT) levels, as well as circulating free testosterone (cFT), were related to the emergence of the hyperinflammatory syndrome leading to prolonged hospitalisation after COVID-19 infection [107,108]. Additionally, a retrospective study involving symptomatic men, conducted independently, established a correlation between low serum TT levels and higher estrogen/T ratios, often indicative of systemic inflammation, and a heightened risk of in-hospital mortality [108,109]. Furthermore, two clinical trials, one involving the anti-androgen drug of choice dutasteride, a 5-alpha reductase blocker used to reduce prostate hyperplasia and male baldness in 87 patients, and the other involving, an androgen receptor antagonist, in 236 patients, showed faster viral clear-up, less viral spill-over and

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lower C-reactive product scores [110,111]. In a clinical evaluation performed in 2022, raloxifene, which is a specific estrogen receptor modulator, increased white blood count and accelerated viral clearance among patients infected with SARS-CoV-2 [112]. Furthermore, there's evidence that progesterone can modulate the sexual dimorphism in SARS-CoV-2 transmission and disease progression, suggesting a therapeutic value of COVID-19. They demonstrated that progesterone can inhibit excessive pro-inflammatory cytokine release and inhibit replication of the virus in the pulmonary tissues of hamsters infected with SARS-CoV-2 [39]. Within pulmonary epithelia, progesterone receptors (PRs) control the production of several proinflammatory cytokines, which also regulate the activation of immune cell s[113,114]. A 2022 animal study Another study, published in the same year, delved deeper into this topic. The authors found that viral infection can induce somatic progesterone through the HPA axis and that progesterone, in turn, can enhance intrinsic antiviral responses in cells and mice through downstream antiviral genes [115].

Table 2. Regulation of COVID-19 by sex hormones through immunization.

Research	STUDY DRUG	Species	Primary Findings	Refs.
Observational Research	Testosterone	Male	Men with lower plasma levels of Testosterone were more likely to have more severe ARDS and to experience a worsening of their status after hospitalization.	[106]
Exploratory retrospective study	Testosterone	Male	Plasma angiotensin 1-7 levels and neutrophil count were predictors of ARDS outcome only in women, while plasma Testosterone levels and lymphocyte count were only indicative in men.	[108]
Exploratory retrospective study	Estradiol	Female	Estrogen plasma concentrations were positively correlated with pulmonary function in COVID-19 women and negative correlated with pulmonary function in COVID-19 men.	
Exploratory retrospective study	Estradiol/Testosterone ratio	Male/Female	The non-survivors had a significantly higher median value for the Estradiol/Testosterone ratio.	[104]
Randomized controlled trial	Raloxifene	Male/Female	Increased white blood cell counts and accelerated viral clearing.	[112]
Experimental research	Progesterone	Hamsters	Inhibit proinflammatory cytokine overproduction and viral replication in lung.	[39]
Experimental research	Progesterone	Mice	Triggers downstream antiviral genes, stimulating cellular as well as mouse innate antiviral response.	[115]

5. Complications of COVID-19

5.1. Tissue Damage

Severe illness and death from progression of acute viral pneumonia to ARDS are common in COVID-19 patients [116]. These phases encompass exudative and proliferative stages characterized by hyaline membrane changes and microvascular thrombosis, culminating in diffuse alveolar injury [117] (Figure 1). Effective management during these stages is vital for improving patient outcomes and preventing mortality. Specifically, in a lipopolysaccharide model of acute lung damage, males exhibit increased airway hyperreactivity and increased airway obstruction relative to females. Administration of T therapy enhances the inflammatory response in females to levels similar to those observed in males. However, gonadectomy attenuates lung injury in the men rather than the women, indicating androgens maintain inflammatory effects in lipopolysaccharide-induced pulmonary injury [118]. Furthermore, estrogen replacement therapy effectively alleviates the features of pulmonary damage by inhibiting cellular adhesion and inflammatory cytokines, thereby reducing the inflammatory consequences of the disease.

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5.2. Cardiovascular System

In the context of COVID-19, patients can experience various extrapulmonary symptoms, making it crucial to promptly diagnose and manage these complications to enhance patient outcomes. Among these complications, over one-third of COVID-19 hospitalized patients encounter cardiovascular issues such as myocardial dysfunction, arrhythmias, acute coronary syndromes, and thrombosis. These complications are highly correlated with mortality and result in direct cardiomyocyte damage, viral-mediated endothelial injury, systemic inflammation and hypoxia [119]. Estrogens exhibit a vasculoprotective effect, which might partly account for the gender disparities in COVID-19 fatalities [120]. Research suggests that 17β-estradiol is protective for ischemic myocardium and reduces infarct size [121]. Through direct membrane signaling, estrogen leads to vasodilation by releasing nitric oxide. Similarly, estrogen receptor signaling preserves the structure and function of endothelial cells by inhibiting the activation of the apoptotic pathway [122]. These findings highlight the cardioprotective effects of estrogen, which could reduce susceptibility to COVID-19-related cardiac injury, endothelial inflammation, and consequent cardiovascular complications [123].

5.3. Visceral Adiposity

Research consistently demonstrates a heightened potential for serious illness and increased mortality among persons with an elevated body mass index (BMI) [124–126]. Importantly, adipose tissue expresses ACE2 receptors, and in obese patients with larger fat stores, these receptors are more abundant, intensifying the systemic response to SARS-CoV-2[127]. Conversely, visceral obesity contributes to elevated levels of prothrombotic circulating factors, increasing susceptibility to thrombosis [128]. Fat distribution is also influenced by sex hormones. Knocking down estrogen receptors and reducing estrogen signaling leads to Male and female mouse obesity [129]. In addition, a randomized controlled trial showed the effects of androgen replacement therapy on overall body composition in overweight post-menopausal women, with separate effects on abdominal and visceral fat deposition. It suggests a link between treatments involving anabolic steroids with androgenic properties and an increased accumulation of visceral fat [130]. Notably, the typical distribution of body fat in females has been associated with reduced cardiometabolic risk, reduced systemic activation, and reduced COVID-19 severity. Research suggests a robust correlation between the intensity of COVID-19 and the fat distribution in the abdomen, which is characterized by elevated visceral adiposity (VAT) levels combined with reduced total subcutaneous adiposity (SAT). SAT levels are more likely to increase in females than males and are inversely related to the incidence of severe disease. For each 1-mm increment of SAT thickness, there was a 16% increase in the chance of serious disease [131]. VAT plays a crucial role in the body's defense system, contributing to the production of pro-inflammatory factors such as TNF-α, IL-6 and IL-1β.

It's worth noting that approximately a third of IL-6 is generated by the adipose cells and stroma in adipose tissue [132]. Interestingly, SARS-CoV-2 infection may exacerbate inflammation in VAT. The mesenteric visceral adipose tissue, which surrounds the small intestine, acts as a primary defense against pathogen migration from the intestines to the circulatory system [133]. It's noteworthy that over half of COVID-19 participants with positive fecal SARS-CoV-2 test results have experienced gastroenterological discomfort, reflecting the impact of SARS-CoV-2 in intestinal cells [134]. Single-cell analysis of RNA sequencing data reveals high levels of ACE2 and TMPRSS2 SARS-CoV-2 infectious proteins in intestinal cells [135], suggesting the intestines could potentially serve as an entry point for the virus. When the virus is detected by the intestinal defense mechanism, it can trigger an immune-inflammatory response that spreads to the mesenteric VAT, exacerbating local inflammation. These intricate interactions among sex hormones, immune responses, and immunometabolic factors create an environment that influences COVID-19 progression on multiple levels.

6. Conclusions

In summary, sex hormone level differences contribute in part to the gender variations in SARS-CoV-2 outcomes. Nonetheless, the existing evidence lacks consensus, and the intricate interplay between viruses and sex hormones makes it challenging to determine the precise effect of sexual steroids on neo-coronary remission. The clinical evidence evaluating the impact of sexual hormones on regression of COVID-19 does not support the use of E2 or discontinuation of these agents in patients suffering from COVID-19. Therefore, more prospective trials are required to obtain a full picture of the long-term impact sex hormones have on COVID-19 outcomes. Several pertinent trials have explored the effects of COVID-19 results from sex hormones, including their influence on ACE2 and TMPRSS2 expression, immune responses and complications such as cardiovascular disease. However, these reports yield inconsistent findings, and a thorough exploration of the underlying mechanisms and hypotheses is required, utilizing advanced analytical methods such as multi-omics. Lastly, the impact of sociocultural gender on an individual's life experiences, immunization awareness, and medical conditions indirectly affects COVID-19 outcomes [136–138]. Therefore, it is crucial to study both gender-related biological and sociocultural differences to enhance our understanding and management of the pandemic.

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