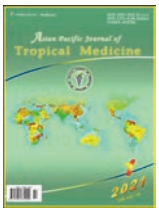

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Review Article

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Gender disparity in COVID-19: Role of sex steroid hormones

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ABSTRACT

The emerging pandemic of COVID-19 caused by the novel pathogenic human coronavirus SARS-CoV-2 has caused significant morbidity and mortality across the globe, prompting the scientific world to search for preventive measures to interrupt the disease process. Demographic data indicates gender-based differences in COVID-19 morbidity with better outcome amongst females. Disparity in sex-dependent morbidity and mortality in COVID-19 patients may be attributed to difference in levels of sex steroid hormones -androgens and estrogens. Evidence suggests that apart from the regulation of viral host factors, immunomodulatory and cardioprotective roles exerted by estrogen and progesterone may provide protection to females against COVID-19. Exploring the underlying mechanisms and beneficial effects of these hormones as an adjuvant to existing therapy may be a step towards improving the outcomes. This article aims to review studies demonstrating the role of sex steroidal hormones in modulating SARS-CoV-2 host factors and summarize plausible biological reasons for sex-based differences seen in COVID-19 mortality.

KEYWORDS: SARS-CoV-2; COVID-19; Gender differences; Steroid hormones; Estrogens; Androgens

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-Co-V2) became a global pandemic in less than 3 months since its first case reported in December 2019. Till December 2020, COVID-19 has affected 220 countries around the world with more than 70 million confirmed cases including over 1 630 521 deaths, and it is growing exponentially in most countries[1].

The current global mortality rate is estimated to be around 3.4%, however, it is dependent on age, sex and comorbidities[2]. Case fatality rate is the highest in the elderly and in people with co-mordidities or those who are immunocompromised having risk of severe illness due to COVID-19 infection. However, noticeable difference has been observed in various epidemiological studies when cases were analysed by gender, with women showing significant protection against severe disease presentations and related outcomes in response to the novel coronavirus infection[3]. COVID-19 studies worldwide have consistently observed a greater severity of the disease and a higher mortality rate in men compared to women[4]. Several national organisations of disease control and prevention have reported gender disparity in mortality (China-4.7%: 2.8%, Italy-10.4%: 6.2%, and Korea-2.99%: 1.91% in male *vs*. female, respectively)[5-7] with similar trends in Iran, Germany, France, the U.S. and the U.K.[8]. According to global health 50/50 sex-aggregated data collected from 47 countries, higher mortality rate was observed in males[9]. All these reports suggest that men are more adversely affected and have worse clinical outcomes compared to women with higher morbidity and mortality.

Reports available in India also showed males share a higher overall burden (65.7%) of COVID-19 infections than females (34.3%). A recently published analysis of crowd sourced data revealed a significantly higher case fatality rate of 3.3% in females compared to 2.9% among males with the most striking difference visible in the 40-49 age groups[10]. This contrasting trends observed in India could be due to other prevalent gender-based differences such as gender stereotypes, fear of stigmatization, poor access to healthcare, poor general health and nutrition amongst females. Trends at these points are questionable due to limited testing and reporting bias, which may change with availability of more data from accurate sources in the future. Despite these contrasting observations, presence of

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gender disparity in COVID-19 pandemic mortality appears real. Some of the underlying mechanisms have been explained below with an emphasis on the role of sex steroidal hormones in immune responses and tissue repair processes during respiratory virus infection.

2. Sex-based differences in immunity

Disparity in sex-specific disease outcomes following virus infections are most likely multifactorial and can be attributed to various social, behavioural, biological and systemic differences. Biological factors include sex-dependent production of steroid hormones, different copy numbers of immune response X-linked genes and sex-related intrinsic differences in innate immunity[11,12]. Women are functional mosaics for X-linked genes and several immune related genes are on the X-chromosome; therefore, females generally have a robust immune response and are relatively resistant to viral infections compared to men[11,13,14]. Both innate and adaptive immune response to viral infections are stronger in females compared to males. Additionally, sex hormones play an important role in immune response with estrogen acting as an immune enhancer and testosterone as an immune suppressor[15].

Epidemiological data from SARS and Middle East respiratory syndrome (MERS) outbreaks in the recent decades, caused by similar pathological coronaviruses, also showed sex specific differences in infection and case fatality rates[16,17]. Experimental proof was further obtained in animal studies, where male mice were more susceptible to viral infection than female mice, with a lower immune response and was slower in virus clearance when age-matched male and female mice were infected[18,19]. Male mice were found to have elevated virus titres, enhanced vascular leakage, alveolar edema, suffered more lung damage and had higher rate of death. Interestingly, while ovariectomy blocking estrogen or intervention with estrogen receptor antagonists increased the mortality of female mice, gonadectomy or anti-androgen treatment in male mice did not affect the disease outcome, suggesting a possible "estrogen-protective effect" against respiratory coronaviruses[19]. Additional evidences for such protective effects have been documented in previous studies which showed estrogen and selective estrogen receptor modulator have antiviral properties against coronaviruses, MER-CoV, SARS-CoV, HIV and other RNA viruses, and also against Ebola and hepatitis virus[20,21].

Estrogen has been shown to have immunomodulatory effects as it is involved in both early immune and secondary repair responses. This hormone exhibits bipotential effects; stimulation with estrogen at its physiological level enhances proinflammatory cytokine responses while sustained high doses of estrogen inhibit the production of proinflammatory cytokines and chemokines[11,13]. In the initial phase of type 1 immune response to a viral infection, there is an increased production and activation of innate immune cells, monocytes, macrophages and neutrophils, which are elevated in the presence of estrogen. It acts through estrogen receptor (ER) in the immune cells, inducing the production of proinflammatory cytokines/chemokines which results in type Ⅰ and Ⅲ interferon production. These increase aromatase expression, further inducing conversion of androgens to estrogens[22]. Increased concentration of estrogen upregulates ER signalling, which in turn suppresses the escalation phase of immune response that may otherwise lead to cytokine release syndrome or cytokine storm syndrome with acute respiratory distress syndrome, as it is seen in severe cases of COVID-19[23]. In the secondary or repair phase, ER signalling promotes type 2 immune response required for viral clearance and repair of injured tissues. Thus, estrogen may play a protective role in COVID-19 patients by regulating inflammatory cytokines and chemokines that may otherwise aggravate tissue injury, leading to poor outcome in COVID-19 patients.

Another female hormone, progesterone is also known to have immunomodulatory properties. A recent study showed the impact of progesterone against viral diseases outside of the reproductive tract in animals, in which progesterone administration protected female mice against influenza A virus infection by altering inflammation, improved pulmonary function and induced pulmonary tissue repair by upregulating epithelial repair pathways[24]. *In-vitro* studies have demonstrated that exposure to progesterone may alter the immune environment of various tissues, by inhibiting production of pro-inflammatory cytokines and increasing production of anti-inflammatory cytokines, thereby altering the outcome of infections at diverse mucosal sites[25]. Though the protective role of progesterone against coronaviruses has not been explored previously, it's anti-viral and anti-inflammatory properties at mucosal sites; especially lungs pose an interesting opportunity for testing its role in COVID-19.

3. Sex-based differences in ACE2 and TMPRSS2 regulation

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors for entry into the cells through its surface spike (S) protein, which is then proteolytically cleaved by the serine protease TMPRSS2 (transmembrane protease/serine subfamily member 2), resulting into the fusion of viral and cellular membranes[26]. Differential regulation of the activity or expression of these two SARS-CoV-2 host factors in men and women may result in gender disparity in COVID-19 related severity and outcome. ACE2 also has an important role in renin-angiotensin-aldosterone system (RAAS) which is crucial for the homeostasis of both cardiovascular and respiratory systems. ACE2 opposes the vasoconstrictor action of angiotensin Ⅱ by catalysing its conversion to angiotensin (1-7), which exerts vasodilatory anti-oxidative and anti-inflammatory properties through an efficient binding with the G protein-coupled receptor Mas and angiotensin Ⅱ type 2 receptors (AT2 receptors)[27]. Angiotensin Ⅱ exerts its vasoconstrictor effects by stimulating AT1 receptors

through ACE and critical balance between ACE2→angiotensin1-7→Mas/AT2 receptor axis with ACE→angiotensin Ⅱ→AT1 essential for proper functioning of the hemodynamic system.

ACE2 is predominantly expressed on type Ⅱ alveolar epithelial cells of normal human lungs and facilitates entry of SARS-CoV-2, thereby serving as a reservoir for viral invasion[28]. Previous studies have shown that the over-expression of ACE2 in mouse SARS-CoV models resulted in enhanced viral entry and antibodies and inhibitors of ACE2 were able to block SARS-CoV invasion. Administration of female sex steroid 17β-estradiol (E2) has shown to downregulate the mRNA expression of ACE2 in human bronchial epithelial cells, thereby restricting the viral entry[29].

After the initial entry of SARS-CoV-2 mediated by ACE2, there is subsequent downregulation of ACE2, resulting in angiotensin Ⅱ accumulation and activation, which causes lung injury and risk of acute respiratory distress syndrome[30]. Additionally, in preclinical studies, it has been observed that ACE2 knockout mice are characterized by severe cardiac defects, which was reversed in mouse models with overexpressed ACE2 by prevention of cardiovascular events and strokes[31,32]. In view of the current COVID-19 pandemic, it is noteworthy that angiotensin Ⅱ also modulates adaptive immunity by activating macrophages and other immune cells, resulting in increased production of inflammatory cytokines, which may ultimately result in acute respiratory distress syndrome. Therefore, ACE2 regulation is essential for both virus cell entry and local tissue homeostasis.

Several previous studies have shown that female sex hormones, especially estrogen provides protective effects by directly modulating the RAAS[33,34] and others have demonstrated that the ACE2 expression is upregulated by estrogen, thereby preventing hyperactivation of the RAAS pathway[35]. While estrogen may provide protection against cardiovascular and pulmonary injury by modulating RAAS, it could possibly lead to increased viral infectivity due to upregulated ACE2 expression. Most of the currently available epidemiological data does not favour this argument with almost equal rate of infection between males and females indicating additional factors are operable for SARS-CoV2 entry in addition to over expression of ACE2. Moreover, as the viral entry into the cells leads to destruction of ACE2, we hypothesize that lower levels of ACE2 could in turn activate the estradiol regulatory feedback loop, leading to increased production ACE2 to maintain the balance in its levels. Therefore, it is important to understand when during the course of infection, estrogen levels can determine the outcome. Mortality is higher in males perhaps due to the lack of stimulatory effects by estrogen to increase the production of ACE2 when its level goes down after SARS-CoV2 infection. Clinical data related to the role of ACE2 regulation in the setting of SARS-CoV-2 remains limited, therefore, it is imperative to elucidate the mechanisms of RAAS modulation by estrogen and how it would impact the pathophysiology of COVID-19.

Though SARS-CoV-2 was initially considered to affect the alveolar tissue in the lung, it has now been shown to affect non-pulmonary tissues as well, particularly the cardiovascular system leading to myocarditis and damage, microvascular dysfunction, plaque instability and myocardial infarction along with endothelial dysfunction[36]. Moreover, pre-existing comorbidities, especially related to cardiovascular diseases, results in severe outcome to SARS-CoV-2 infection. Beneficial and protective roles of estrogens on cardiovascular health is well documented in females[33,34]. Estrogen is known to influence endothelial function mainly by nitric oxide mediated dilation that are hallmarks of a healthy endothelium and beneficial modulation of the RAAS in the atrial myocardium[37]. Estrogen mediated cardio-protection in females could explain lower mortality rate and less severe complications associated with SARS-CoV-2 infection and better disease outcome seen in them compared to males.

The second protein of importance mediating the entry of SARS-CoV2 into cells is a serine protease TMPRSS2, which has been implicated as a critical host factor for the spread of several clinically relevant viruses including SARS-CoV-2 as stated before[38,39]. TMPRSS2 which is androgen responsive, is predominantly expressed in prostrate epithelium, and also expressed in airway epithelia, cardiac endothelium, kidney and digestive tract which are important target organs of SARS-CoV-2[40]. Due to its presence on microvascular endothelial cells, SARS-CoV-2 infection may cause endothelial dysfunction, which in turn lead to thrombosis and associated complications[41]. Experimental animal models have shown that TMPRSS2-knockout mice were protected against SARS-CoV infection and showed lower cytokines and chemokines levels[42], which in excess may result in cytokine storm as seen in severe COVID-19 patients.

In vitro and *in vivo* experimental studies have shown that androgen administration enhances TMPRSS2 expression in human lung epithelial cells and its deprivation in murine lung resulted in its re-expression[43]. Higher circulating levels of androgens and their regulation of TMPRSS2 is considered one of the contributing factors to severe outcomes noted in COVID-19 male patients[41]. Besides TMPRRS2 regulation, androgens are also known to increase the number of circulating neutrophils and decrease the body's antibody response to viral infection, thereby enhancing the severity of disease in men[11,44]. A recent study also showed that estrogen and ER modulators significantly downregulated the expression of TMPRRS2[45]. Another recent study reported that expression of the TMPRSS2/ERG fusion gene seen in prostate cancer is decreased by ERβ agonist but increased by ERα agonist, however the effect of estrogen on TMPRSS2 in non-prostatic tissue and whether it plays a role in COVID-19 is still unknown[46].

Though all the data above explains the gender disparity in COVID-19 mortality to favourable roles of female sex steroids, it is fascinating to understand reasons for similar persistent favourable trends even amongst postmenopausal women where physiological circulating levels of these steroids show significant decrease. While

17β-estradiol (E2) is the most potent estrogen in premenopausal women, estrone (E1) is produced by ovaries in high quantities in postmenopausal women[47]. In addition, estrogen produced by several extragonadal sites such as the peripheral adipose tissue collectively may contribute enough quantity and distribution to provide similar protection against COVID-19 mortality in this age group.

4. Conclusions

Epidemiological data from around the globe confirms the gender-based differences in susceptibility and mortality in COVID-19 pandemic though sex-aggregated data is unavailable from all the regions at present. While it is important to gather sex-specific information in COVID-19 infected patients from many other large nations for adequate representation, established trends thus far are unlikely to change. Female sex hormones, estrogen/or progesterone may have a protective role against SARS-CoV-2 by acting as an immune booster and by providing protection from lung and myocardial injury. Emerging evidences suggest that the expression of two important viral host factors, ACE2 and TMPRSS2 can be modulated by sex hormones, estrogens and androgens. Regulating the expression of these host factors through steroid hormone modulators may act as novel therapeutic agents for patients with severe symptoms of SARS-CoV-2 in improving the outcome. Several clinical studies are underway to investigate the effect of modulators of sex-hormones and inhibitors of ACE2/TMPRSS2 in COVID-19 patients, however, further studies are needed to determine their circulating levels over the course of disease and to exploit the potential of sex steroid hormones as an adjuvant therapy in COVID-19 patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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Authors' contributions

Jyothi S Prabhu and Anuja Lipsa participated in study design. Anuja Lipsa did literature mining and data acquisition. Anuja Lipsa drafted the manuscript. Review and editing of the manuscript were done by Jyothi S Prabhu. Both authors approved the final draft for publication

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