# Let's talk about sex in the context of COVID-19

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**Abstract**

In recent months, the coronavirus disease 2019 (COVID-19) pandemic has sent many countries into crisis. Studies have shown that this virus causes worse outcomes and a higher mortality in men than in women. It has been recognized that sex can affect the immune response to a pathogenic agent, as well as the susceptibility for some respiratory diseases. These different responses in males and females may be related to the actions of sex hormones. Angiotensin converting enzyme 2 (ACE2) acts as the receptor for severe acute respiratory syndrome coronavirus (SARS-CoV), which causes COVID-19. The expression of ACE2 is influenced by sex hormones; therefore, we discuss in this article that this could be one of the reasons why COVID-19 is more prevalent in men than in women.

Recently, we wrote a review about sex differences in breathing control (13). More than ever, we recognize that there is a higher prevalence in men to respiratory diseases than in women. In the last months, COVID-19 showed us this fact very clearly. As of April 30th, 2020, only 35 countries have reported official data regarding sex prevalence in confirmed cases of COVID-19. Of the 35 countries reporting, 14 reported having a higher number of cases in men, 2 reported having a similar incidence in both men and women, and 19 reported having a higher number of cases in women. This shows that for contamination, it seems that both sexes can be affected (14) (https://figshare.com/s/1545eece1ed31deb0c99). That sex differences in contamination can involve many factors, such as sociocultural gender factors and behaviors (3). In fact, a recent study also pointed out that ethnic/racial minority groups are being disproportionately affected by COVID-19 (3). Therefore, in addition to sex, other factors such as age, gender, and socioeconomic status need to be examined and disclosed to have a clearer picture of this pandemic.

However, 33 of those countries reported that the number of deaths was higher in men compared to women, that might indicate a clear sex difference. The highest proportion of men/women was seen in Dominican Republic (men represented 78% of all deaths) (14) (Figure 1). In China, where the disease is thought to have begun, the COVID-19 mortality in men was reported to be 4.7%, whereas in mortality women was 2.8% (number of deaths / number of cases), showing that men died 68% more often than women (14).

But why this “preference” in males?

One putative answer to this question is sex hormones. The main sex hormones are testosterone (T), progesterone (P), and estrogen (E2), produced by males and females during their adult lives in different concentrations. Males produce more T compared to females, who, in turn, produce E2 and P in higher concentrations (13). Sex hormones exert their actions via nuclear and membrane receptors (36) and are capable of changing membrane fluidity and the expression of mitochondrial proteins and genes that mediate many cellular mechanisms (22).

Sex hormones are very important for the development and activity of the immune system (36), contributing to the sexual dimorphism observed in immunological responses to viral infections (see (35), for review). In general, E2 has immunostimulatory roles, while P and T are immunosuppressive and counteract the pathways affected by E2 (36) . Therefore, males produce less robust immune responses and are more susceptible to a variety of infectious agents (21). Specifically, regarding the severe acute respiratory syndrome coronavirus (SARS-CoV), a mouse model was developed to mimic SARS-CoV in humans (41). They performed 15 passages of the virus in the respiratory tract of young BALB/c mice, which resulted in a lethal mouse-adapted SARS-CoV virus (MA15). These mice died from a very strong viral infection, with extensive destruction of pneumocytes and ciliated epithelial cells of the respiratory tract (41). Using this MA15 mouse model, Channappanavar et al. (7) evaluated whether SARS-CoV infection is sex or age dependent. First, the authors demonstrated that sexually immature, 2-month-old male and female mice were completely resistant to developing SARS. They then used different doses of MA15 and evaluated the survival rate in sexually mature 8- to 10-month-old male and female C57BL/6 mice. When the mice were infected with 5000 PFU (plaque-forming units, which indicates the number of viral particles capable of lysing host cells and forming a plaque), the mortality rate was ~90% in males and ~20% in females. Upon increasing the MA15 dose to 10000 PFU, all males died during the $5^{th}$ day, while 50% of females died. Interestingly, when they gonadectomized the animals, the mortality rate increased in females, but did not change in males, suggesting a protective effect of E2 in female mice infected with SARS-CoV. The authors also observed that the degree of sex bias to viral infections increased with advancing age such that middle-aged mice (8-9 months old) showed much more pronounced differences compared to young mice (2 months old). All of these sex and age biases of SARS-CoV were also observed in humans (20).

Coronavirus is formed by type 1 transmembrane spike (S) glycoproteins, which contain two functional domains (S1 and S2) that associate with cellular receptors to promote infection of their host cells (17). The angiotensin-converting enzyme 2 (ACE2) is considered the functional receptor for SARS-CoV. The receptor binding domain of the S1 spike protein enters cells by binding to ACE2 (28). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus identified as the cause of coronavirus disease (COVID-19), uses ACE2 as its receptor for cellular entry, similarly to the SARS-CoV (17). Additionally, viral S glycoproteins are activated by the transmembrane serine protease 2 (TMPRSS2), which facilitates virus-cell membrane fusion (17) (Figure 2). In fact, an *in vivo* study using ACE2-knockout mice demonstrated that ACE2 is essential for the viral infection (24). These data provide the first genetic proof that ACE2 is indeed a crucial *in vivo* SARS receptor required for effective replication of infectious SARS-CoV. For instance, lung injury was reduced in ACE2-knockout mice compared to wild-type mice.

ACE2 mRNA and protein have been identified in several tissues (27) . Recently, mRNA expression patterns of ACE2 were analyzed in 31 normal, human tissues using two databases (27). The highest ACE2 expression was observed in the small intestine, testis, kidneys, heart, thyroid, and adipose tissue. The lungs, colon, liver, bladder, and adrenal gland showed moderate levels of ACE2 expression, while blood, spleen, bone marrow, brain, blood vessels, and muscle presented the lowest expression. Despite other tissues having higher ACE2 expression than the lungs, pneumonia is one of the main symptoms of patients infected with SARS-CoV-2. This might be attributed to the fact that the respiratory tract is the most readily available route of transmission for the virus (27). Besides ACE2, TMPRSS2 is also widely expressed in multiple tissues in the gastrointestinal system, lung and kidney (46). Accordingly, multi-organ expression of these enzymes may explain the multi-organ dysfunction observed in patients with COVID-19 (48).

Recently, Sommerstein and Gräni (44) suggested that the use of angiotensin-converting enzyme inhibitors (ACE-Is) by patients with cardiovascular diseases could represent a lethal danger for COVID-19 by up-regulating ACE2 and increasing the infection. However, this is not a consensus. Some authors believe the use of ACE-Is might be protective against COVID-19, since there is overwhelming evidence of mortality reduction in cardiovascular disease with this drug (25).

ACE converts angiotensin (Ang)-[1-10] into Ang-[1-8], which can promote vasoconstriction by acting on the angiotensin type 1 receptor ($AT_1$) or vasodilation via the angiotensin type 2 receptor ($AT_2$). ACE2 is a monocarboxypeptidase that catabolizes the conversion of Ang-[1-8] to the heptapeptide Ang-[1-7], which is described to have vasodilatory effects by binding MAS or MAS-related G protein-coupled receptors. ACE2 also converts Ang-[1-10] into the nonopeptide Ang-[1-9], also described to have vasodilatory proprieties by binding to $AT_2$ (15). ACE2 has been identified as an important renin–angiotensin system (RAS) regulator, which is a peptidergic system that regulates extracellular fluid volume and controls homeostasis of the cardiovascular and renal systems (10, 15, 31). The gene that codes for ACE2 is located on the X chromosome (23), which raises the possibility that females, having two X chromosomes, could have differences in ACE2 expression compared to males with only one X chromosome. However, the expression of ACE2 appears to be more influenced by sex hormones, such as E2, than the presence of a second X chromosome, as demonstrated by Liu et al. (30). Using the four core genotype mouse model which enables separation of sex-chromosome effects from gonadal hormone effects, this study showed that E2-mediated down-regulation of ACE2 expression in the kidney is sex-chromosome independent.

Major sex differences have been identified in the expression levels of components of the RAS (45). For instance, ACE2 protein and mRNA expression, as well as ACE2 activity, are higher in the kidney in male mice than in female mice under basal conditions (30), which would imply

that SARS-CoV would find ACE2 to be more readily available in males. Remarkably, this sex difference in ACE2 activity was not observed in the heart or lung in the same animals. Likewise, supplementation with E2 caused a down-regulation of ACE2 mRNA expression in the mouse kidney, but not in the lung, showing that sex hormones can also regulate ACE2 in a tissue-specific manner (30). However, under pathological conditions, several studies have found that Ang-[1-7] levels are higher in women than in men, particularly in those with hypertension (45), indicating a higher ACE2 activity. Thus, increased levels of this vasodilator could also contribute to female protection from Ang-[1-8]-induced hypertension (45). In this regard, a recent study in mice showed that ACE2 plays a larger role in protecting females than males from Ang-[1-8]-induced hypertension by increasing catabolism of Ang-[1-8] and by downregulating $AT_1$ (19). Hypertension is a recognized major risk factor for COVID-19 morbidity and mortality (26). Women are more protected from hypertension due to higher Ang-[1-7] expression (45), which may play a role in their protection from COVID mortality, despite potential elevations in ACE2 levels. Regarding COVID-19, there are no clear data about sex hormone levels and their association with ACE2 activity in different organs, including the lungs. As previously mentioned, ACE2 is widely distributed in many tissues, and its activity appears to be differentially regulated in different organs. Thus, further studies are urgent to provide new insights into the role of ACE2 in the SARS-CoV-2 pandemic and for understanding the associations of SARS-CoV-2 symptoms and sex differences.

To date, there are no data in the literature regarding the effects of T on the concentration of ACE2 receptors in the lungs. Nevertheless, TMPRSS2 is highly expressed in epithelial cells in adult human lungs, small intestine, heart, liver, thymus and prostate (46), and its transcription is upregulated by the androgen receptor (Figure 2) (32). This protease may also cleave ACE2 for augmented viral entry (16). This could also explain the higher susceptibility of males to SARS-CoV-2 infection compared to females. However, Channappanavar and Perlman (8) observed that

SARS-CoV infection significantly reduced serum T levels in mice, which was also recently demonstrated in humans infected with COVID-19 (47). Interestingly, low levels of T appear to be linked to increased susceptibility of respiratory diseases, such as asthma and COPD (37), as well as cardiovascular disease, diabetes and others (1) that represent risk factors for the severity of COVID-19 (33, 49). Additionally, animal studies and human studies showed that T deficiency is associated with an increase in pro-inflammatory cytokines (4, 37), independent of other risk factors (2, 38). In illness with COVID-19, an important mediating factor in mortality appears to be excessive release of pro-inflammatory cytokines ("cytokine storm"). As mentioned before, deaths from COVID-19 are higher in men, affecting mostly elderly men (49), who, in turn, have naturally low levels of T compared to young men. In some cases, the hypogonadism promoted by COVID-19 can cause severe complications in the infected. Therefore, measuring T levels in these patients would be helpful, since androgen suppression would reduce host vulnerability when infection risk is high, but can worsen the systemic inflammatory response during the course of the disease.

The transcriptional regulation of ACE2 is not completely elucidated; however, Clarke et al. (9) demonstrated that ACE2 is up-regulated by interleukin (IL)-1β treatment and in response to hypoxic conditions by activation of transcriptional mediators, such as the silent information regulator T1 (SIRT1), which binds to the promoter region and facilitates ACE2 mRNA expression. Although hypoxia, IL-1β and angiotensin peptides regulate ACE2 expression, steroid hormones appear to be a modulator of its expression (4, 6). Moreover, sex hormones also regulate the hypoxic ventilatory response (13) and the concentrations of pro-inflammatory cytokines, such as IL-1β (34, 40, 43). Further, E2 signaling via hormone receptors can augment SIRT1 levels (11, 42). Therefore, sex hormones can act directly or indirectly to control ACE2 (Figure 3).

Indeed, Brosnihan et al. (4) investigated the role of E2 in the regulation of ACE/ACE2, and in the angiotensin receptor subtypes $AT_1$/$AT_2$, using mRNA measurements in the lung and kidney

of female mice. They found that non-pregnant mice treated with E2 without alpha E2 receptors presented a reduction in gene expression of ACE2 in the lungs, suggesting that E2 might be involved in the regulation of the ACE2 gene in the lung. Notably, renal ACE2 activity has been shown to be upregulated during pregnancy in Sprague Dawley rats (5). A recent study suggested that during pregnancy, women may be more susceptible to COVID-19, since pregnant women, in general, are vulnerable to respiratory infection (29). However, a systematic recent review suggests that COVID-19 during pregnancy has a similar clinical presentation and infection severity to non-pregnant adults and may not be associated with poor maternal or perinatal outcomes (12). In fact, COVID-19 is less severe in pregnancy than the two SARS-CoV and Middle East Respiratory Syndrome-related coronavirus (MERS) (12). According to the authors, the concept that during pregnancy occurs an immune suppression increasing the risk for infection is incorrect. During pregnancy, human chorionic gonadotropin and P inhibit the proinflammatory cytokines, which could be protective for the cytokine storm (12).

At the moment, no vaccine is available to control the spread of COVID-19, and many potential therapeutic drugs have been suggested for treatment of this disease. Here, we point out the potential of sex hormones as therapeutics, which have not yet been explored. We believe that consideration of sex as a factor can increase the efficacy and safety of medicine use and can also help to design effective translational interventions for sexually dimorphic disorders. One good example of how sex can be a determinant in disease treatments is the study of Huded et al (18) where consideration of sex in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) resulted in a 50% reduction in mortality of women (following 30 days of STEMI, mortality rate was initially 6.1%, and after considering sex, in treatment, was reduced to 3.1%).

Notably, there is an on-going study, led by Dr. Sharon Nachman from Stony Brook University, which aims to evaluate whether E2 delivery to COVID-19-positive or presumed-

positive patients via a transdermal patch for 7 days can reduce the severity of COVID-19 symptoms compared to standard care (39). They hypothesized that E2 would reduce symptom severity in adult men and older women if given prior to intubation.

In summary, from our understanding, patients who are currently receiving oral contraceptives or hormone replacement therapies need to be studied for their potential disparities related to COVID-19 outcomes.

**Figure Legends:**

Fig 1. Graphs of data from 35 countries who provided information on the number of COVID-19-related deaths by sex. Death rate expressed in % of data using only number of confirmed deaths. Represented are the data acquired on or before April 30, 2020.

Fig 2. Schematic illustration showing SARS-CoV-2 binding of the spike protein with ACE2, which acts as a receptor for the virus. Viral S glycoproteins are activated by TMPRSS2, which facilitates virus-cell membrane fusion. TMPRSS2 transcription is upregulated by the androgen receptor. This leads to viral entry into the cell by endocytosis.

Fig 3. Schematic illustration showing the classic renin-angiotensin system (RAS) and the sequential cleavage of protein substrates by specific proteases. The primary substrate for the RAS is angiotensinogen, which is converted by renin into angiotensin (Ang)-[1-10]. In a sequential reaction, the dicarboxyl-peptidase angiotensin converting enzyme (ACE) cleaves Ang-[1-10] to form Ang-[1-8]. Angiotensin-[1-8] could bind to angiotensin $AT_1$ and $AT_2$ receptors, each with distinct functions, or could be degraded by angiotensin converting enzyme 2 (ACE2) into a heptapeptide, Ang-[1-7]. ACE2 also can degrade Ang-[1-10] into a nonapeptide, Ang-[1-9]. ACE2 expression is regulated by hypoxia, IL-1β and estradiol (E2) via histone deacetylasesirtuin 1 (SIRT1), which binds to the promoter region and facilitates ACE2 mRNA expression. Hypoxia and IL-1β can also be modulated by E2.

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