Sex Hormones and Novel Corona Virus Infectious Disease (COVID-19)

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Abstract

Given the rapid spread of the coronavirus disease 2019 (COVID-19) pandemic and its overwhelming effect on health care systems and the global economy, innovative therapeutic strategies are urgently needed. The proposed primary culprit of COVID-19 is the intense inflammatory response—an augmented immune response and cytokine storm—severely damaging the lung tissue and rendering some patients' conditions severe enough to require assisted ventilation. Sex differences in the response to inflammation have been documented and can be attributed, at least in part, to sex steroid hormones. Moreover, age-associated decreases in sex steroid hormones, namely, estrogen and testosterone, may mediate proinflammatory increases in older adults that could increase their risk of COVID-19 adverse outcomes. Sex hormones can mitigate the inflammation response and might provide promising therapeutic potential for patients with COVID-19. In this article, we explore the possible anti-inflammatory effects of estrogen and testosterone and the anabolic effect of testosterone, with particular attention to the potential therapeutic role of hormone replacement therapy in older men and women with COVID-19.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to rapidly spread worldwide. To date, no specific therapeutic agents or vaccines for coronavirus disease 2019 (COVID-19) are available, and much information on the causative agent SARS-CoV-2 is lacking. However, descriptive reports have consistently found that older adults and men are at an increased risk of mortality from COVID-19 and that the protective effect of younger age occurs in both male and female patients.[1-3] As we search for treatment strategies for COVID-19, understanding the extent to which sex hormones underlie these differential case-fatality rates holds broad clinical and public health relevance.

For most infectious diseases, women have been consistently observed to mount a stronger immune response than do men.[4] In general, the female immune system responds more efficiently to pathogens, producing higher amounts of interferons and antibodies; however, this protective effect, mediated primarily by estrogen, is attenuated in postmenopausal women.[5] For coronaviruses in particular, women have demonstrated a consistent survival advantage over men. In the current COVID-19 pandemic, as well as in both the 2003 SARS-CoV and the 2012 Middle East respiratory syndrome epidemics, women have substantially lower case-fatality rates than do men.[6] Among the theoretical pathways through which SARS-CoV-2 is hypothesized to damage the tissues, the inflammation and cytokine storm mechanisms are the most widely accepted.[7,8] It is likely, given the pathophysiology of SARS-CoV-2, that the anti-inflammatory pathways hold particular relevance for developing therapeutic strategies against COVID-19. Moreover, the anabolic effects of testosterone may have clinical relevance for older male patients with COVID-19. In this article, we explore the effects of estrogen and testosterone and their possible therapeutic role of hormone replacement therapy in older patients with COVID-19.

Briefly, SARS-CoV-2 enters the cell via the angiotensin-converting enzyme type 2 (ACE-2) receptor, which is expressed by pneumocytes, and leads to the down-regulation of ACE-2 levels. Angiotensin-converting enzyme type 2 is normally responsible for converting angiotensin II (Ang II) into vasodilatory and less immune augmenting variants of angiotensin. Angiotensin II binds type 1 angiotensin receptors (AT1Rs) in the lung to induce vasoconstriction and inflammation via activation of the nuclear factor κB (NF-κB) pathway, which increases cytokine synthesis.[9] Low levels of ACE-2 and high levels of Ang II lead to increased pulmonary vessel permeability, which subsequently results in inflammatory damage to the lung tissue.[10] The proposed primary culprit of severe COVID-19 is the cytokine storm resulting from an unchecked inflammatory response that damages the lung tissue, rendering some patients' condition severe enough to require assisted ventilation and causing death in a substantial percentage of cases.[11] A study of patients with influenza found that high cytokine levels and low T-lymphocyte levels were predictive of high pharyngeal viral loads and increased mortality.[12] These findings are consistent with COVID-19 laboratory findings, which support the hypothesis that the augmented immune response resulting in the circulation of tissue-damaging cytokines is the primary mediator in pulmonary viral infection.[11] It is also possible that SARS-CoV-2 directly activates mast cells, which are found in the respiratory tract submucosa, with the subsequent release of proinflammatory cytokines such as interleukin (IL)-1.[13]

Sex differences in inflammation have been well documented and attributed to various factors. Although most of the immune regulatory genes are encoded by X chromosomes, resulting in women's generally stronger immune response, this sex difference in inflammatory response is postulated to be largely driven by sex hormones.[14] Although estrogen has a complex role in modulating the immune system, generally in a dose-dependent manner, it is reported to have an anti-inflammatory effect at normal physiological levels in premenopausal women.[5,15] Most cytokines, namely, IL-6, IL-8, and tumor necrosis factor α (TNF-α), are inhibited by periovulatory dosages of estrogen, while low levels of estradiol can augment inflammatory mediators, which could explain the proinflammatory states that most postmenopausal women suffer from (eg, atherosclerosis).[5] Postmenopausal women are reported to have higher levels of proinflammatory cytokines, such as IL-1, IL-6, and TNF-α; however, these levels are reduced with the use of hormone replacement therapy, especially estrogen-containing types, to premenopausal levels.[14] Moreover, estrogen-containing contraceptive methods have been found to enhance cellular immunity in HIV-infected patients.[16] Female mice receiving high levels of estrogen are reported to have increased survival and lower cytokine production in the lung after influenza infection.[4] Likewise, the activated estrogen receptor, specifically estrogen receptor-alpha, has been found to inhibit NF-κB—mediated inflammation response and cytokine production via immune cells, lymphocytes, macrophages, and neutrophils.[17] The finding that Ang II activates the NF-κB pathway to increase cytokine synthesis after SARS infection while estrogen can shut down the NF-κB pathway holds possible relevance for COVID-19 treatment strategies in female patients.

Estrogen's anti-inflammatory effect against coronaviruses is supported by several animal studies.[18] First, researchers who infected male and female mice with SARS-CoV reported that male mice had a worse prognosis than did female mice. Specifically, after SARS-CoV infection, male mice had higher viral titers, more pulmonary vascular permeability and/or alveolar edema, and more inflammatory monocytes and macrophages in their lungs than did age-matched female mice.[18] Second, SARS-CoV—infected female mice that were estrogen depleted by oophorectomy or estrogen receptor blocker had a worse SARS-CoV prognosis.[18] Although patients with COVID-19 suffer from lymphopenia, which might cast doubt on the estrogen anti-inflammatory effect,

these findings were independent of T- or B-lymphocyte action.[18] In view of the close genomic similarity of SARS-CoV-2 and SARS-CoV,[19] it is possible that estrogen plays a similarly protective role against SARS-CoV-2.

Although women have accounted for a lower number of COVID-19 cases than do men,[20] it is important to assess why—among men infected with SARS-CoV-2—younger age is strongly protective against adverse outcomes. It is possible that testosterone has a protective anti-inflammatory effect in younger men, analogous to the effect of estrogen in younger women. Testosterone is reported to have anti-inflammatory functions via suppression of both the cellular and humoral immune systems. In fact, testosterone was found to lower IL-6 and TNF-α levels via inhibition of the NF-κB proinflammatory pathway, analogous to estrogen.[21] Moreover, testosterone deficiency has been linked with autoimmune disease and increases in inflammatory markers, such as C-reactive protein.[22,23] In a laboratory study, removal of gonads from influenza virus—infected male mice resulted in higher death rates compared with gonadally intact male mice.[4] Low levels of testosterone, as can occur in normally aging men, have also been linked with high inflammatory markers such as IL-6 and may underlie their increased risk of lung damage after pneumonia.[24,25] Importantly, testosterone can be peripherally converted to estrogen via aromatase enzyme, which might add an anti-inflammatory effect.[26]

It is also plausible that testosterone might reduce the need for assisted ventilation through its anticatabolic effect on respiratory muscles.[27] A recent study found that hypogonadism was common in mechanically ventilated patients with acute respiratory failure and was strongly associated with longer intensive care unit stays.[28] Several small-scale clinical studies indicate that testosterone therapy may improve outcomes in hospitalized patients with chronic obstructive pulmonary disease.[29] Further research is needed on this potential effect.

Although genetic factors can explain some of the sex differences in patients with COVID-19—women, as a result of their extra X chromosome, have stronger immune function and more efficient viral clearing—these factors might not explain the dramatic within-sex case-fatality differentials observed across age groups.[2,30] A recent study reported that comorbidities in patients with COVID-19 include hypertension, diabetes, and obesity[2]—all of which are associated with inflammation that could have put older patients at a higher risk of COVID-19 death for which estrogen and testosterone hold potential therapeutic modalities.

In evaluating sex and age case-fatality rate disparities of all 3 recent coronavirus epidemics, it is also important to consider the following potential confounders. First, men's higher mortality rate may be driven, in part, by their higher rates of smoking, which increases vulnerability of lung tissues to viral infection and other lifestyle factors, which increase their rates of underlying cardiovascular disease and diabetes.[31] Second, it is important to acknowledge that the increased mortality in older adults with COVID-19, both men and women, may be partly attributable to concurrent morbidities, especially cardiovascular diseases and diabetes. In addition, there is concern that these associations are driven by specific antihypertensive medications, angiotensin-converting enzyme inhibitors and Ang II receptor blockers drugs, both of which increase the expression of ACE-2 receptors if taken long-term, which could increase the risk of COVID-19 adverse outcomes.[32] Nevertheless, Gurwitz[10] suggested that patients chronically treated with an AT1R blocker (eg, losartan) should have a better prognosis after being infected with SARS-CoV-2. This viewpoint is supported by the finding that once SARS-CoV-2 infects the lung, ACE-2 is downregulated, increasing the availability of proinflammatory Ang II, which leads to lung damage by binding the AT1R. Thus, AT1R blockers (ie, reducing Ang II effects) could protect the patient from excess inflammation and lung damage due to the cytokine storm. Furthermore, a recent study of 5700 patients with COVID-19

treated in New York reported that the mortality rate was modestly higher for patients receiving angiotensin-converting enzyme inhibitors (32.7%) and/or Ang II receptor blockers (30.6%) than for those not taking these medications (26.7%).[2]

Exogenous estrogen and testosterone therapies have a therapeutic potential to mitigate the damaging inflammatory response to SARS-CoV-2 without hampering the immune system's response to the virus as corticosteroids do.[33] Recently, investigators have suggested the use of immune-modulating drugs to block inflammatory markers' receptors to mitigate the amplified and tissue-damaging immune response of SARS-CoV-2 (eg, anarka [an IL-1 receptor blocker] and tocilizumab and sarilumab [IL-6 receptor antagonists]).[8,33,34] However, there are concerns about these agents' possible adverse effects on patients' immune function.

In view of the well-documented role of sex hormones in immune response, specifically the anti-inflammatory effects of estrogen and testosterone and the anabolic effect of testosterone, it is important to consider their potential role in developing treatment strategies for patients with COVID-19, particularly older adults and those with hormone deficiencies. Assessing the disease progression and outcomes of such patients, with particular attention to the underlying mechanisms, may provide important clinical insight. Future research is needed to examine whether hormone replacement therapy may have a pharmacotherapeutic role in treating older adults diagnosed with COVID-19.

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Abbreviations and Acronyms: ACE2 = angiotensin-converting enzyme type 2; **Ang II** = angiotensin II; **AT1R** = type 1 angiotensin receptor; **COVID-19** = coronavirus disease 2019; **IL-1/6/8** = interleukin-1/6/8; **NF-κB** = nuclear factor κB; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **TNF-α** = tumor necrosis factor α

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