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EXPERT OPINION

Testosterone's Role in COVID-19

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ABSTRACT

COVID-19 consistently displays a higher mortality in males. This sex-specific difference in outcomes is seen not only in the current COVID-19 pandemic, but also in prior viral epidemics and pandemics. Sex hormones, such as testosterone, play a clear role in modulating the immune response, providing a clue that may illuminate the underpinnings of these outcomes. Developing a deeper understanding of these epidemiological findings permits a more effective response to the disease. This article summarizes the sex-specific COVID-19 outcomes, the role of androgens in generating these outcomes, and the potential role of modifying testosterone levels as a form of treatment of COVID-19. **Auerbach JM, Khera M. Testosterone's Role in COVID-19. J Sex Med 2021;18:843–848.**

Key Words: Coronavirus; Hypogonadism; Androgens; Immune System; Cytokines

INTRODUCTION

COVID-19, a novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide. Many countries affected by the COVID-19 pandemic are seeing worse clinical outcomes in males than in females.[1] This pattern of outcomes was also seen in prior coronavirus epidemics, including the severe acute respiratory distress (SARS) and Middle East respiratory syndrome (MERS) coronavirus epidemics.[2,3] These sex-specific outcomes of viral pandemics are not limited to the 21st century, with the 1918 influenza pandemic resulting in higher mortality in males than in females in the United States.[4] Sex hormones, such as testosterone and estrogen, are a defining driver of the physiologic distinctions between males and females and likely play a role in the observed pattern of outcomes in COVID-19. Testosterone has complex effects on the immune system, introducing an essential question of how varied levels of testosterone might influence COVID-19 in males. Developing a better understanding of testosterone's influence on COVID-19 will provide more clarity in the broader public health approach to the disease. This review explores the sex differences in COVID-19 outcomes, the potential role of testosterone in driving such differences, and the implied utility of modulating testosterone levels in the treatment of COVID-19.

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SEX OUTCOME DIFFERENCES IN COVID-19

Levels of testosterone typically decline as men age, with studies estimating a 2% per year decline in testosterone production in men after age 30, resulting in a higher prevalence of hypogonadism (HG) in elderly men.[5,6] However, age alone is not a significant cause of declining testosterone levels. As we age, it is the acquisition of comorbid conditions, such as obesity, type II diabetes, and metabolic syndrome that contribute to declining testosterone levels. HG has been consistently linked with obesity, type II diabetes, and worse health outcomes in men.[7] Given the routine finding that COVID-19 displays especially high mortality in elderly men,[8-10] one hypothesis is that declining levels of testosterone as men age confer higher mortality. Worldwide case fatality rates appear to be nearly three times higher in men, with men representing 73% of deceased patients in China,[11] 59% in South Korea,[12] and 70% in Italy.[13] Although elderly adults have a higher mortality with COVID-19, it should be noted that men exhibit higher mortality than women regardless of age.[14] The hypothesis that COVID-19 mortality rates increase with declining testosterone levels in men would not explain why women, who have lower natural levels of testosterone, display better outcomes than men across all ages. Potential explanations for this finding will be discussed in later sections.

Prior studies have shown that low levels of testosterone are associated with increased all-cause mortality in male intensive care unit (ICU) patients.[15] Recent studies have highlighted the early data regarding the relationship between HG and COVID-19 outcomes in men admitted to the ICU. Rastrelli et al analyzed outcomes in a small cohort of 31 men affected by SARS-CoV-2 that received care in a single respiratory intensive care unit (RICU).[16] First, lower baseline levels of testosterone were associated with more severe acute respiratory distress

syndrome at RICU admission. Additionally, progressively lower levels of total testosterone (TT) and calculated free testosterone (cFT) were associated with progressively worse clinical outcomes, including transfer to the intensive care unit (ICU) or death. Importantly, TT and cFT were not significantly associated with age, implying an independent role of low testosterone in driving worse outcomes. Finally, low testosterone was correlated with worse biochemical markers of disease severity, with TT and cFT displaying a negative significant correlation with neutrophil count, lactate dehydrogenase, procalcitonin, and C-reactive protein.

In a larger prospective cohort study, Çayan et al investigated the clinical course of 221 men affected by SARS-CoV-2 and tracked their outcomes.[17] Men admitted to the ICU displayed significantly lower average testosterone levels. Of the 46 patients admitted to the ICU, 76% had serum TT levels less than 300 ng/dL, while nearly half had serum TT levels less than 200 ng/dL. While the mean TT level in men admitted to the ICU was 241 ng/dL, the mean TT level in the asymptomatic group and those admitted to the internal medicine unit were 346 ng/dL and 318 ng/dL, respectively. As serum TT declined, the probability of ICU admission and mortality both significantly increased. Of the 11 patient deaths, all had baseline serum TT levels of less than 300 ng/dL and 8 of 11 had serum TT levels below 200 ng/dL. It should be noted that these findings do not distinguish the temporal relationship of COVID-19 disease and lower testosterone levels — it remains possible that testosterone levels decline as a result of infection rather than being present prior to the development of disease.

It is important to acknowledge the various confounding factors that have been suggested as potential influences of these outcomes. First, some suggest that women are generally more aware of disease risk and are more adherent to treatment regimens.[18,19] Others suggest that the higher tobacco exposure in men could influence the sex differences in SARS-CoV-2 outcomes.[20] However, studies suggest that sex differences in smoking do not account for worse outcomes of COVID-19 in men.[21] Finally, a reasonable suspicion may be that cardiovascular disease and diabetes, which are more common in men and in the elderly, influence the morbidity and mortality of COVID-19.[22]

MECHANISMS OF ANDROGEN MODULATION IN COVID-19

There is convincing data that men affected by COVID-19 have worse prognoses than women and that HG predicts worse outcomes. However, the physiological mechanisms by which testosterone may influence outcomes remains unclear. There are two aspects of androgen-driven physiology that have emerged as potential explanations for outcome differences between the sexes. First, the influence of testosterone on viral entry of SARS-CoV-2 into human cells has gained much attention. Second, the effect of testosterone on immune regulation more broadly has also been proposed as a primary explanation.

Regulation of Viral Entry and Fusion

SARS-CoV-2 relies on specific cellular receptors for successful infection and replication. SARS-CoV-2 enters cells via angiotensin-converting enzyme type 2 (ACE-2), an enzyme expressed by pneumocytes that is responsible for converting angiotensin II into variants of angiotensin that have a milder role in the immune response.[23] Angiotensin II, in its unconverted state, strongly induces vasoconstriction and inflammation. SARS-CoV-2 entry into pneumocytes via ACE-2 leads to downregulation of ACE-2 levels. Consequently, lower levels of ACE-2 and the resulting higher levels of the more immunologically active angiotensin II lead to an enhanced inflammatory state in the lung.[24] Low levels of ACE-2 are also seen in other pulmonary diseases.[25]

Sex-specific differences in ACE-2 expression may provide insight as to why the lower mortality rates seen in women are not limited to the elderly. Female sex hormones likely influence the expression of ACE-2,[26] and serum ACE/ACE-2 activity ratios are higher in males than in females. One potential explanation for this finding is through a direct stimulatory effect of estrogen on ACE-2 activity.[27] Additionally, the X chromosome is specifically responsible for the expression of ACE-2 and the *ACE2* gene escapes X inactivation.[28] As a result, a second copy of the *ACE2* gene may preserve expression of ACE-2 and protect females from deleterious polymorphisms that may hinder expression in males. Overall, higher levels of ACE-2 may lead to a natural baseline suppression of immune inflammation in females, which may partially explain why women have lower mortality rates in COVID-19 regardless of age.

While ACE-2 is considered essential for SARS-CoV-2 entry, evidence suggests that transmembrane protease serine 2 (TMPRSS2) cleaves the SARS-CoV-2 spike antigen, contributing to fusion with the host cell membrane.[29] Androgens enhance the expression of TMPRSS2 and provide a further potential explanation for the higher susceptibility of men compared to women.[30] One clue that provides insight into the androgen-driven nature of this protein is its recognized role in prostate cancer. TMPRSS2 is conventionally recognized as a contributor to prostate cancer development, with nearly half of all prostate cancers containing a translocation that places the TMPRSS2 regulatory element directly upstream from an oncogene.[31] Since TMPRSS2 is regulated by androgens, this context allows the expression of androgens to drive oncogene expression.[32] Although there is no evidence that TMPRSS2 is modulated by androgens in the lungs in a similar manner, a cell line model derived from lung tissue demonstrated an androgen-dependent regulation of TMPRSS2.[33] If TMPRSS2 is indeed regulated by androgens in the lung, testosterone could help drive the higher SARS-CoV-2 infection rates by upregulating TMPRSS2. Overall, it appears that testosterone may enhance the expression of key cellular receptors that allow SARS-CoV-2 entry and fusion.

Influence on the Immune Response

Testosterone potentially increases susceptibility to SARS-CoV-2 infection, which may explain a higher infection rate in men. However, a higher susceptibility to infection does not necessarily imply a higher risk of death once infected. The primary cause of death from COVID-19 is often the resulting cytokine storm.[28] In other words, infection is more likely to result in death primarily in the context of an overactive immune response. Consequently, much attention has been given to a potential role of testosterone in modulating the sex-specific immune response. Testosterone has been shown to suppress the activity of IL-6 and TNF-α through inhibition of NF-κB, a protein complex that is essential for cytokine production.[34] Testosterone also enhances the anti-inflammatory response via androgen receptor signaling by increasing expression of IL-10 and transforming growth factor-β (TGFβ).[35,36] On a cellular level, Rastrelli et al observed higher neutrophil-to-lymphocyte ratios among hypogonadal men infected with SARS-CoV-2.[16] Neutrophilia is generally implicated in cytokine storms,[37] potentially explaining why this cellular profile is associated with worse outcomes in these men. Furthermore, the androgen receptor is expressed on the majority of white blood cells, leaving the possibility for direct modulation by testosterone.[36]

Given testosterone's role in immune regulation, a logical progression would be the consideration of hypogonadism in predisposing to an overactive immune response. Indeed, numerous studies corroborate this notion. Men with low levels of androgens have higher levels of proinflammatory cytokines, including IL-1, IL-2, and TNF-α.[38-40] Hypogonadism is also associated with autoimmune disease and increased levels of C-reactive protein.[41] Younger men consistently display better outcomes than elderly men in the context of COVID-19. Given the gradual decline in testosterone as men age, the pro-inflammatory state that accompanies hypogonadism may be a key contributor to poor outcomes in elderly men. It is important to consider the evidence regarding regulation of viral entry together with the evidence regarding adverse inflammatory states.

Taken together, the evidence suggests that baseline, normal levels of testosterone may increase viral entry while paradoxically providing a relative protection from the hyperreactive immune state that drives mortality from COVID-19. While the evidence suggests that low levels of testosterone predispose to worse inflammatory disease, it must be noted that women still do not have worse outcomes in any age group despite having lower biological levels of testosterone. This raises the question as to whether estrogen has any similarities to testosterone in subduing the immune response. Indeed, estrogen appears to play a similar role in subduing the immune response. Major cytokines, including IL-6, IL-8, and TNF-α are inhibited by estrogen,[42] and estrogen receptor-alpha suppresses NF-κB-driven inflammatory processes.[43] In addition, numerous antiviral-related genes, which exhibit 10-fold higher expression levels in female immune cells,[44] contain estrogen response elements in their promotors.[45] In general, women display a stronger T cell response but a lower baseline level of proinflammatory cytokines than men,[46] providing a clear potential explanation for worse inflammatory processes in men than in women.

THE POTENTIAL ROLE OF EXOGENOUS TESTOSTERONE

The role of testosterone in mitigating the inflammatory response has spurred interest in testosterone therapy in SARS-CoV-2 infections.[47] Several studies show that the proinflammatory state that arises due to low testosterone can be suppressed with the provision of exogenous testosterone.[48-50] More specifically, testosterone therapy suppresses typical inflammatory factors such as IL-1, IL-6, and TNF-α.[50] Evidence also suggests that testosterone therapy may confer a certain advantage over corticosteroids by blunting the inflammatory response to SARS-CoV-2, but without hindering the cellular immune response to the virus, as might be the case with steroid use.[51] The use of testosterone in patients with chronic obstructive pulmonary disease (COPD) provides a useful analog in which to investigate it's potential therapeutic role. Importantly, men with COPD have worse outcomes when infected with SARS-CoV-2.[52] Studies indicate that testosterone replacement enhances lung function in middle-aged and elderly men with COPD, slowing disease progression and reducing hospitalizations compared to men with COPD not treated with testosterone replacement therapy.[53] Low testosterone levels reduce respiratory muscle activity and exercise capacity,[54] while normal testosterone levels show a protective effect on various respiratory parameters, such as forced expiratory volume and forced vital capacity.[55] Given these findings, Caminiti et al conducted a randomized controlled trial and found that testosterone replacement therapy improved peak oxygen consumption and respiratory function,[56] indicating a potential role for testosterone replacement therapy in protecting lung function in men with SARS-CoV-2. Further research on the specific use of testosterone replacement therapy in SARS-CoV-2 patients is needed to accurately assess its efficacy in this context, including age-stratified studies as well as investigations to illuminate the ideal timing and dosage of testosterone provision.

CONCLUSION

As SARS-CoV-2 continues to spread, it remains unclear why men disproportionately display higher rates of infection and mortality. While there is no direct evidence that testosterone is directly responsible for the increased susceptibility in men, there is a potential role of testosterone driving ACE-2 and TMPRSS2 to permit viral entry and fusion. The body's inflammatory response is the recognized culprit in those with adverse outcomes. While testosterone may enhance SARS-CoV-2 viral entry and fusion, it appears that testosterone is protective against immune dysregulation. Accordingly, men with low testosterone may be more likely to

respond with a dangerous inflammatory response to the virus and may therefore benefit from testosterone replacement therapy. Further studies are needed to illuminate the applicability of testosterone replacement therapy in men with SARS-CoV-2.

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