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[Hypothesis] The protective role of Testosterone in COVID-19

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Abstract

In this manuscript, we hypothesize that testosterone may play a protective role against the severity of SARS-CoV-2 infection through immunomodulatory mechanisms with anti-inflammatory effects supported by the action of testosterone.

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Main Text

Testosterone, the primary male sex hormone, affects reproductive tissue development, secondary characteristics such as

increased muscle mass, and the immune system. Sex differences in various aspects of the immune response and the role of sex hormones are well established both in animal models and in practice in humans. These differences involve both innate and acquired immunity, biochemical mechanisms such as the REDOX signaling pathway, and even behavioral aspects. Evidence and models range from autoimmunity to allergy and infectious diseases. [1] The hormones interfere with the regulation of immune cell activity and can cause damage to target organs. [2] Androgens play an important immunomodulatory role supported by their ability to suppress proinflammatory cytokines and stimulate anti-inflammatory factors such as interleukins IL -4, IL -10 and the synthesis of nitric oxide by the enzyme endothelial nitric oxide synthase (eNOS). [3] In the face of an inflammatory process, there is an increase in circulating proinflammatory interleukins in the serum, such as IL -1 and IL -6, which favors the inhibition of eNOS and thus the initiation of prothrombotic events. [4] In these situations of oxidative stress, with the suppression of eNOS, there is an impairment of signaling in the sirtuin 1 (SIRT1) pathway, a nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylase responsible for modulating the activity of eNOS. [5] Once the sirtuins pathway is suppressed, there is an impairment of physiological activity, such as regulation of energy metabolism, proliferation, and cell survival. [5] Since December 2019, with the establishment of a pandemic by the new coronavirus, SARS-CoV-2, several pathophysiological mechanisms have been investigated to understand its mechanism of action and individual selection for inflammatory exacerbations and adverse developments in some infected individuals. [6] Cellular entry of the SARS-CoV-2 virus occurs via the angiotensin-converting enzyme 2 (ACE2) receptor with subsequent fusion in the TMPRSS2 gene. [7] After cell entry, the virus causes depletion of the SIRT1 pathway, leading to an exacerbation of proinflammatory cytokines, such as IL -1 and IL -6, which favors cytokine storm, and the aggravation of Covid-19, mainly by increasing interleukins 2 and 6, in addition to other thrombogenic patterns such as fibrinogen activation. [8] Testosterone is able to reduce the pro-thrombotic state by reducing fibrinogen and not altering plasminogen activator, causing the clot to have less basis for formation and more substrate for breakdown.[9] The cross-sectional study Bobjer 2013, found a relationship of high levels of pro-inflammatory markers in young men with subnormal testosterone concentrations in the absence of concurrent metabolic disease. [10] Those are just a few points in the very complex pathways that regulate inflammation, and once can point to equally as important mechanisms of enhanced inflammation by estrogen and progesterone such as those seen in several autoimmune diseases like as systemic lupus erythematous. [11] In May 2021, Sandeep Dhindsa et al[12] published a paper in JAMA Network Open, hypothesizing that low serum testosterone levels in men are associated with the more severe forms of Covid-19, as evidenced by a prospective cohort study.

Conclusion

Therefore, in this manuscript, we address the hypothesis that testosterone is established as a protective factor for COVID-19 severity because it physiologically exerts an immunomodulatory pathway with anti-inflammatory activity that contrasts with the conditions leading to the cytokine storm seen in severely ill patients infected with COVID-19. The specific role of a single hormone is hard to determine in COVID-19 and the gender differences are likely multifactorial. A role for a sex hormone like testosterone cannot be disregarded, although it is hard to separate it from the lack of its counterpart estrogen. Although an important protease involved in viral entry, TMPRSS2, is regulated by androgen and Toll-like

receptor 4 and the inflammasome are which regulate most types of tissue inflammation are increased by testosterone.

List of Abbreviations

- Interleukins (IL)
- Endothelial nitric oxide synthase (eNOS)
- Nicotinamide adenine dinucleotide (NAD +)
- Sirtuin 1 (SIRT1)
- Angiotensin-converting enzyme 2 (ACE2)

Declarations

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