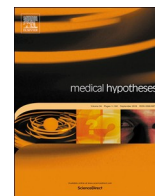




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Role of testosterone in COVID-19 patients – A double-edged sword?

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ABSTRACT

COVID-19 affects males twice as frequently as females with significantly increased severity and mortality. Current data suggest a direct correlation between the lower level of serum testosterone, inflammatory cytokines, disease severity, and poor clinical outcomes among male patients with COVID-19. The gradual decline in total and free testosterone levels has a direct correlation with serious pulmonary complications requiring advanced care (ICU, ventilators, ECMO, etc.). SARS-CoV-2 utilizes Angiotensin-Converting Enzyme II (ACE2) for entry in the host cell, and Transmembrane Protease, Serine 2 (TMPRSS2) to prime spike protein of SARS-CoV-2. Testosterone induces ACE-2 expression, a critical pulmonary protective enzyme. Low testosterone levels in males have a direct correlation with the high probability of ICU admission and the worse disease outcome (ARDS, duration of ICU stay, mortality). On the contrary, however, high testosterone levels can lead to thrombosis which is also one of the fatal manifestations in COVID-19 patients. A critical evaluation of the serum testosterone and its relevance to COVID-19 is warranted to re-evaluate strategies to effectively triage, prioritize, and manage high-risk patients for ICU admission, survival outcomes, targeted solutions, and operational algorithms.

Introduction

Coronavirus disease 2019 (COVID-19) affects men significantly more than women [1,2]. Male patients with COVID-19 are reported to die at twice the rate of females when they contract the virus [3]. Lower levels of testosterone result in the upregulation of ACE2 and TMPRSS2 receptors, facilitating SARS-CoV-1 entry into the alveolar cells, and deregulating a lung-protective pathway [4]. Decreased testosterone levels in critically ill males negatively affect endothelial cell functioning, promote defective immune response, impair the ability to clear the virus, and promote systemic inflammation. Obesity among males also generates more pro-inflammatory cytokines important in cell signaling, emanating in increased vulnerability, severe disease, and worst outcome. Lower serum testosterone level is a poor prognostic indicator for patients with COVID-19 by deregulating pulmonary protective pathways [5,6]. Thereby we hypothesize that low testosterone levels in males have a direct correlation with the severity of disease and a worse outcome in COVID-19.

Evaluation of hypothesis

COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and was declared a global pandemic by

the World Health Organization (WHO) on March 11th, 2020 [7,8]. As of July 10, 2020, there have been more than 12,588,223 confirmed cases of COVID-19 and 561,402 deaths, worldwide [9]. COVID-19 presentation can range from mild to life-threatening pneumonia, acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure, and death [10–14]. Males typically have 7–8 times higher levels of circulating testosterone compared to females [15].

The route of entry of COVID-19 is typically through the mucosal membranes, where it enters the lung alveolar epithelial cells using Angiotensin-Converting Enzyme II (ACE-2) receptors and TMPRSS2 for S protein priming [16–18]. ACE-2 has a pivotal role in pulmonary protection and the lung-protective pathway is deregulated as a result of viral binding to these receptors. Additionally, ACE-2 is also expressed by the Leydig cells of testis as a constitutive product [19] and affects the testosterone secretion in COVID-19 patients. TMPRSS2 is a known target of androgen receptor, the ligand-activated transcription factor; activation of androgen receptor increases TMPRSS2 levels in various tissues. TMPRSS2 expression is significantly higher in the male lungs compared to females. Testosterone modulates the immune response, and the low serum testosterone is known to impact both of these biological markers negatively [20,21]. Patients with low testosterone have reportedly developed severe manifestations requiring assisted ventilation because of the upregulation of ACE-2 receptors in lower respiratory

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cells, increased risk of lung damage, and respiratory muscle catabolism.

Lower testosterone levels also inhibit endothelial cell functions as SARS-CoV-2 reduces ACE-2 level by binding, increasing the Angiotensin-II (AT-II), and lowering Angiotensin 1–7 (AT 1–7). This process increases superoxide species, leading to endothelial cell dysfunction because of oxidative stress and inflammation [22,23]. This leads to increased vWF and development of thrombosis in the alveolar capillaries, a precursor of ARDS [24–26]. Moreover, hypothyroidism also plays a role in lowering male testosterone levels and thyroiditis has reported to be a manifestation of the COVID-19 [27].

Consequences of the hypothesis

Male COVID-19 patients are at increased risk for ICU admission and worse outcomes compared to females. Therapeutic modalities and vaccine development can be targeted to transcriptionally inhibit lung ACE-2 and TMPRSS2 expression. Down-regulation of TMPRSS2 will result in attenuated spike protein priming, reducing SARS-CoV-2 interaction with ACE-2, and blocking viral entry. It could potentiate the anti-inflammatory effect of tocilizumab in COVID-19 ARDS or cytokine release syndrome (CRS). The role of testosterone screening, optimal pharmacotherapeutic administration of DHEA, and hormone replacement therapy needs to be considered to minimize the pulmonary syndrome and severity of COVID-19. However, exogenous administration of testosterone needs to be carefully monitored as it can exacerbate the benign prostatic hyperplasia (BPH) and prostate cancer. Moreover, there is already an increased risk of thrombosis in COVID-19 patients therefore testosterone use should be contraindicated in COVID-19 patients with known thrombosis [28,29]. The optimal dose of testosterone replacement therapy (TRT) needs to be determined to strike the fine balance in varied indications, especially COVID-19. Careful dose titration and monitoring can help alleviate undesirable side effects (erythrocytosis, thromboembolism, etc.) [30]. Baseline hemoglobin and hematocrit levels and periodic monitoring for dose adjustment and risk assessment is pivotal for optimal outcome [31]. Thyroid axis also must be corrected if testosterone replacement is sought. If TRT is undertaken in COVID-19 patients, at least monthly monitoring of hemoglobin should be undertaken given the heightened risk of thrombosis in this population due to erythrocytosis. Further longitudinal studies are required to determine the effect of gender and low testosterone levels on the cellular and molecular pathways associated with COVID-19 by facilitating a personalized medical approach to risk stratification, prevention, and treatment.

Introline

This article describes the direct correlation between serum testosterone levels, inflammatory cytokines, disease progression and worse clinical outcomes among male COVID-19 patients.

Authorship contributions

AH, SKH & FH wrote the first draft and contributed equally to the manuscript. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data for the work and approved the final approval of the version to be published.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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