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Understanding the Complex Relationship Between Androgens and SARS-CoV2

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In the United States, 54% of hospitalizations for COVID-19 are among men.[1] In Italy, men represent 70% of COVID-19-related deaths.[2] Additionally, there is a relative lack of prepubertal infection.[3] The reason for these higher rates of infection and mortality in men, and the correspondingly low rates in prepubertal children remains unknown. It is possible that an androgen-dependent process may help account for these epidemiological findings, which is a topic of intense focus currently.[4-6]

An androgen-mediated protein (transmembrane serine protease 2: TMPRSS2) plays a critical role in priming the virus' spike proteins for entry into the host cell as one of the first steps involved in infection.[7] To enter the cell, the SARS-CoV-2 virus uses primed spike proteins to bind cellular angiotensin converting enzyme receptor 2, which leads to cell entry and infection. TMPRSS2 activity is essential for spike priming, and its activation is dependent on androgens.[8] Additionally, TMPRSS2 may interact directly with angiotensin converting enzyme receptor 2 receptors allowing for augmented viral entry.[7] Because of its critical role in the process of viral infectivity, an understanding of TMPRSS2 is essential in explaining the gender disparities associated with COVID-19.

Knowledge gained from prostate cancer research revealed the androgen dependent nature of TMPRSS2: an activated androgen receptor (AR) upregulates TMPRSS2 mRNA,[9] while androgen deprivation therapy (ADT) suppresses it.[10] The androgen-dependent nature is evident outside of the prostate, as administering exogenous testosterone in vitro modestly increases expression of TMPRSS2.[9] Additional in vitro research has shown that inhibition of TMPRSS2 can prevent SARS-CoV-2 infectivity.[7]

This knowledge, in conjunction with the male predilection for infection, has led many to investigate how testosterone levels and androgen manipulation may attenuate the impact of COVID-19.[4] Given the complex relationship between androgens and the impact of COVID-19, there are 3 specific patient populations that deserve closer study to better understand the pathophysiology of androgens on SARS-CoV-2: Men receiving ADT, men with testosterone deficiency (TD), and men receiving testosterone therapy (TT).

CAN ANDROGEN DEPRIVATION THERAPY PREVENT COVID-19-RELATED MORBIDITY?

AR activity is considered a requirement for the transcription of the TMPRSS2 gene.[11] Expression of TMPRSS2 decreases when men are subjected to ADT,[10] therefore decreased transcription of the TMPRSS2 gene could lead to reduced viral entry and milder symptoms. A population based study of 4532 men sought to determine the possible role of ADT in prevention or reduction of SARS-CoV-2 infection in patients affected by prostate cancer (PCa).[12] In this cohort, men with PCa who received ADT had significantly lower rates of infection compared to men with PCa who did not receive ADT (odds ratio [OR] 4.05; 95% confidence interval [CI] 1.55-10.59). Additionally, PCa patients receiving ADT showed a decreased risk of SARS-CoV-2 infection compared to patients affected by other cancers (OR 5.17; 95% CI 2.02-13.40). This paper had several weaknesses, including its observational nature, its use of a tumor registry study as a comparison group, and most notably, the small number of PCa patients without ADT (N = 114) and with ADT (n = 4) used for their main conclusions. Despite these shortcomings, these results support the hypothesis of a protective role of androgen deprivation in the prevention of SARS-CoV-2 infection.

This possibility has led to the initiation of clinical trials to further investigate this association. A randomized controlled trial in the United States is currently underway, investigating the role of a single dose of Degarelix on SARS-CoV-2 infection in hospitalized men.[4] If an activated AR is one of the necessary steps for SARS-CoV-2 cell entry, then future trials on agents that directly antagonize the AR (such as enzalutamide) are warranted, as

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Gonadotropin-releasing hormone (GnRH) antagonists still leave small amounts of circulating androgen in the body.

The potential protective effect of ADT on COVID-19 is particularly interesting considering the use of ADT is associated with major adverse cardiac events (MACE) and venous thromboembolism (VTE).[13] Given that COVID-19 carries a worse prognosis in co-morbid men,[1] and the high rate of VTE seen in patients with COVID-19,[14] it will be important to see how these competing factors balance out in future clinical trials.

HOW DOES TD AFFECT SARS-COV-2 INFECTION?

Similar to men receiving ADT, we can posit that men with TD may experience milder effects of SARS-CoV-2 infection due to lack of TMPRSS2 transcription. However, the observational data collected thus far supports the opposite conclusion: that men with TD appear to have a worse prognosis with COVID-19.

One study from Italy measured reproductive hormones in men on admission to a respiratory ICU. Lower testosterone on admission was associated with a higher likelihood of mortality or escalation of care.[5] Similarly, a cohort from Germany identified low testosterone and dihydrotestosterone (DHT) levels in 67% and 49% of SARS-CoV-2 infected men on admission to the ICU, respectively.[15] These studies suggest a relationship between testosterone and SARS-CoV-2 infection, however these observational data must be interpreted with caution for several reasons.

Without baseline androgen levels preinfection, it is challenging to explain the directionality of this relationship seen in the prior studies. Not only does testosterone decline with age, but the decline is also accelerated in men with co-morbidities, and in the presence of acute illness.[16] Low testosterone in the older male appears to be a robust marker of poor health, and possible mortality, rather than a causal factor.[17] Without a baseline testosterone level, it is difficult to know whether or not these prior studies simply represent a continuum of testosterone suppression that follows increasing severity of SARS-CoV-2 infection and acute illness, rather than a true cause-effect relationship.

Finally, TD may play a role in SARS-CoV-2 infection due to their shared effect on inflammation. The clinical deterioration seen with COVID-19 is in large part due to overwhelming inflammation.[18] Meanwhile, sex hormones in healthy men exert key functions on immune cell targets that express AR such as monocytes, macrophages, and neutrophils.[6] In general, this action tends to be immunosuppressive; higher levels of inflammatory cytokines are seen in men with low testosterone, and these levels normalize with testosterone replacement.[6] Because of this, some have hypothesized that men with TD are more susceptible to the inflammatory sequelae that come with COVID-19.[6] Data on baseline androgen levels in men prior to SARS-CoV-2 infection would be a useful first step to understanding this relationship.

ARE SARS-COV-2 POSITIVE MEN WHO RECEIVE TESTOSTERONE THERAPY AT HIGHER RISK OF MACE?

SARS-CoV-2 infection leads to a hypercoagulable state due to a combination of hypoxemia and a systemic inflammatory response syndrome, characterized by high fibrinogen and demonstrated by progressive D-dimer elevation.[14]

Early on, abnormal coagulation parameters were identified as a poor prognostic factor in those infected with SARS-CoV-2.[14] Further study showed that patients in the ICU with COVID-19 were found to suffer from a higher rate of thrombosis than the typical ICU patient despite anticoagulation, up to a rate of 79% in 1 study of ICU patients in France.[19] These findings have led some centers to place patients on higher prophylactic doses of anticoagulation to try and prevent sequelae of COVID-related coagulopathy, and is the subject of ongoing clinical trials.[20]

TT, particularly when resulting in supratherapeutic levels of testosterone, can induce a coagulopathic state in men, characterized by polycythemia.[21] It is not clear whether TT causes VTE, however the risk of secondary polycythemia (Hct ≥54%) is well-established, and appears to occur at higher rates in certain modalities of TT.[21] Some of the lowest rates have been seen with selective estrogen receptor modulators at 1.7%,[22] or intranasal testosterone, at 2.6%,[23] while longer-acting modalities such as injectable or implantable pellets of testosterone have published rates of polycythemia upwards of 66.7% and 35%, respectively.[24] Multiple studies support a link between polycythemia and increased rate of MACE and VTE.[21,25] Whether TT induced polycythemia causes MACE or VTE is still a matter of debate, one which may be addressed by current ongoing clinical trials.

The androgen-susceptible nature of TMPRSS2, as well as the potential for a coagulopathy with TT, may lead some practitioners to question the safety of TT during this pandemic. On the contrary, if TD is a potential poor prognostic factor for COVID-19 due to the changes in the inflammatory milieu, then TT may in fact be beneficial. Currently, there are no observational data to help guide practice on this. Based on a precautionary principle, if testosterone is being prescribed, perhaps it is prudent to use a modality with less risk of polycythemia such as short-acting preparations or off-label drugs such as clomiphene citrate or human chorionic gonadotropin until more robust data becomes available.

CONCLUSION

The association between testosterone and COVID-19 is multifactorial. Current studies using ADT to suppress activation of TMPRSS2 with the potential to prevent cellular entry of SARS-CoV-2 are underway. Whether or not testosterone deficiency worsens prognosis because of TMPRSS2 interaction, increased inflammatory state, or simply because of the associattion of poor health with low testosterone is unclear. The relationship between TT and COVID-19 remains to be elucidated, as it is not yet clear

whether TT worsens or improves outcomes. Identifying men on TT who go on to contract COVID-19, and establishing baseline androgen levels prior to infection, will be an important first step to answer this question. Prior to robust data, any changes to practice need to be made with caution, and after an informed discussion with patients.

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