



#### LETTER TO THE EDITOR

### Testosterone and COVID-19 – a stone in the way

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This letter highlights the relevance of investigating the potential connection between testosterone and SARS-CoV-2 infection to support the comprehension of the COVID-19 pathophysiological outcome. The relationship converges since SARS-CoV-2 has a virulence mechanism, the Spike glycoprotein, that mediates viral entry by binding to ACE2 on the epithelial cell surface, a process supported by transmembrane protease serine 2 (TMPRSS2) (Osuchowski et al. 2021). Therefore, the co-expression of TMPRSS2 and ACE2 is required to ensure viral infection.

Interestingly, the TMPRSS2 transmembrane protease gene transcription is stimulated by the nuclear androgenic receptor and the Prostatic Specific Antigen (PSA) (Afar et al. 2001). This receptor plays a function in several tissues, being expressed in the adult heart, lung, brain, and fetus liver, in addition to a tangible expression in the prostate (Vaarala 2001). TMPRSS2 has a well-established role in some viral infections, such as H7N9 Influenza, some *Coronaviridae* family viruses, furthermore neoplasms, for example, in prostate cancer and metastases (Lucas et al. 2014).

In animal studies, the *TMPRSS2* expression occurs substantially in type II pneumocytes, a cell that presents a strong tropism for SARS-CoV-2 infection (Matsuyama et al. 2010). Besides, there is a strong relationship between ACE2 expression and sex hormones observed in animal models (La Vignera et al. 2020).

Given the facts, it is rational to consider the hypothesis of an interaction between biological genera through hormonal production such as testosterone and how this could interfere with infectious processes and their outcome (Burström & Tao 2020). In the current COVID-19 overview, several studies have reported an increase in complications and even more deaths in men (The OpenSAFELY Collaborative 2020). Although the possibility that the difference between the COVID-19 outcome and the patient's gender may be related to the immune system function or social parameters, economic and cultural circumstances (Torcia et al. 2012), the hormonal expression role is imperative. Therefore, we emphasize the necessity of investigating the biological elements behind this discrepancy.

Analyzing *TMPRSS2* function during the SARS-CoV-2 infection, the testosterone inhibition could severely affect the secondary characteristics connected to the hormone since the low testosterone

levels are a tight linkage to pathologies and expression of pro-inflammatory cytokines (Mohamad et al. 2019).

Eventually, this letter is an invitation to consider the role of testosterone in the COVID-19 clinical evolution. The reflection might open to new therapeutic possibilities. In the current context, considering the SARS-CoV-2 infection epidemiological relationship and pieces of evidence discussed here, it is necessary to ponder about biological aspects concerning the sex hormones' role to lead to a broader pathophysiology comprehension and the linkage with gender.

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Pedro Ricardo Gonçalves Azevedo and Natália Lopes de Freitas contributed equally to data acquisition, writing, and discussion. Fabiana Brandão contributed to the conception, data acquisition and interpretation, discussion, and critically revised the manuscript. All authors gave their final approval and agreed with all aspects of the work.

