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Letter to the Editor

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Androgen-driven COVID-19 infection – is testosterone an enemy or a friend?

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Dear Editor,

There are raising theories about the COVID-19 pathogenesis and ongoing discussions regarding the possible antiviral strategies of how to inhibit or decrease entering of COVID-19 into the epithelial lung cells. It seems these mechanisms are promising for the future therapy [1, 2] but on the other hand they open many controversies, which severely need to be discussed [1].

Beside the angiotensin-converting enzyme 2 (ACE-2), other main way which is introduced to be responsible for the entering of SARS-CoV-2 into the epithelial lung cell is a type II transmembrane serine protease (*TMPRSS2*), an enzyme that in humans is encoded by the androgen responsive gene *TMPRSS2*, located on human chromosome 21 [3, 4].

A significant feature of the TMPRSS2 gene is that several androgen receptor elements (AREs) are located upstream of the transcription start site and the first intron. A stimulation of androgen receptor with testosterone and his active form dihydrotestosterone allows the transcription of the TMPRSS2, which than serves as an entrance for the SARS-CoV-2 [5].

A pre-press Research Gate theory titled "Androgen-driven COVID-19 pandemic theory" from Carlos Gustavo Wambier and coworkers [1], introduced the plausible role of androgen receptor for SARS-CoV-2 infection and proposed a theory why males seem to be more vulnerable to the disease and have higher mortality [6], which is very convincing.

The physiological roles of TMPRSS2 are currently unknown, but its connection with the androgen receptor gains suspicions about the possible involvement in less good outcome of COVID-19 infection in men. Recently, a great deal of evidence has already suggested that a TMPRSS2 plays a critical role in SARS and MERS coronavirus and in 2013 Asian H7N9 influenza virus and several H1N1 subtype influenza A viruses infections, indicating that targeting TMPRSS2 could be a novel antiviral strategy to treat not only COVID-19, then other coronaviruses and some low pathogenic influenza virus infections [5].

The concerns are directed toward the belief that the therapeutic and prophylactic potential of medications that target androgen activity, such as androgen receptor inhibitors, steroidogenesis inhibitors, five-alpha reductase inhibitors, and chemical castration with GnRH analogues could mitigate the clinical course and reduce mortality in SARS-CoV-2 infected subjects [7], but on the other hand could compromise the health status of men having low levels of serum testosterone or those taking testosterone replacement therapy (TRT). The question that arises from this, are these men in equal risk as the men having normal serum testosterone level and taking no TRT therapy, or should they stop taking TRT because they will be less vulnerable in case of COVID-19 infection?

Another additional fact, which needs to be considered in men receiving TRT, is the recent knowledge that COVID-19 may predispose patients to arterial and venous thrombotic disease [8]. Namely, although there are reports in recent studies (Baillargeon et al. 2015 and Sharma et al. 2016) that TRT was not associated with an increased risk of venous thromboembolism (VTE) [9, 10], another controversy is detected in recent study from Walker and coworkers, 2019 [11].

However, testosterone is men's vitality hormone, which allows not only the normal quality of life, then prevents diabetic state that is one of the major risk factors in case of COVID-19 infection [12, 13]. Furthermore, previous studies have suggested that testosterone replacement therapy may have a positive effect on lung function in in middle-aged and older men with chronic obstructive pulmonary disease (COPD), and that testosterone replacement therapy may slow the progression of disease and decrease the respiratory hospitalizations compared to non-users [14]. As we know, people with COPD are more likely to be at higher risk having worse COVID-19 infection outcome, this

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could be a big controversy to the opinion how anti-androgenic therapy can be good therapy choice to improve the clinical picture of COVID-19 infection, especially in patients with diabetes, obesity, CODP or other low serum testosterone level comorbidities. Furthermore, it is well established that plasma testosterone concentration is reduced by age and comorbidities like obesity, diabetes and obstructive sleep apnea, all comorbidities highly prevalent in COVID-19 patients [15].

These findings suggest that caution should be used when prescribing both, anti-androgenic therapy or testosterone replacement therapy. Just following these few contradictory facts about testosterone, we come to the conclusion that these therapies should be understood individually and take into account all the positive and negative consequences, and approach patients more carefully with additional analyzes and tests to help make the right decision.

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