Androgen-deprivation therapy and SARS-Cov-2 infection: the potential double-face role of testosterone

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Dear Editor,

We read with great interest the recent articles published in *Therapeutic Advances in Endocrinology and Metabolism* on the role of androgen-deprivation therapy (ADT) in patients with prostate cancer (PC) and SARS-Cov-2 infection.[1]

The 'endocrinological protective model' proposed by La Vignera *et al.* is very interesting and intriguing but we believe the topic is still being debated on the basis of available clinical evidence.

In a first study by Montopoli *et al.*, the authors analyzed the role of ADT in a large and unselected series of patients with PC obtained from the cancer database of Veneto (Italy). They observed that patients under ADT had lower rates of SARS-Cov-2 infection, suggesting that ADT could also be a therapeutic opportunity for patients with complications from coronavirus disease (COVID-19).[2] In contrast, Caffo *et al.*[3] reported that patients with metastatic hormone-sensitive PC and metastatic castration-resistant PC (mCRPC) on ADT displayed a higher lethality from SARS-CoV 2. More recently Klein *et al.*, in a cohort of 1779 men with PC, did not observe a protective role of ADT from SARS-Cov-2 infection [odds ratio (OR) 0.93, 95% confidence interval (CI) 0.54–1.61; $p = 0.8$].[4] In the study by Montopoli *et al.*[2] the pathophysiologic basis explaining the protective role of ADT was hypothesized to act through the androgen receptor-mediated regulation of TMPRSS2, a type II transmembrane serine protease that is relevant for SARS-CoV-2 introduction into host cells.[5]

On the basis of the conflicting results from these studies, some conjectures can be made. First, the differences in the results could be in part explained by the different populations included in the studies; potentially a more frail population susceptible to infection and adverse clinical outcomes in the study of Caffo *et al.*[3], where a more advanced oncologic situation was present. Moreover, in the study of Caffo *et al.*[3] mCRPC cases are often on additional therapies in addition to ADT such as new generation androgen-target therapies or taxane treatments. The second and probably more important consideration is that none of these studies tracks the role of total testosterone (TT) on the immune response and other mechanisms of the male organism, particularly in the setting of infectious disease involving the lung. Clinical manifestations of COVID-19 infection vary from asymptomatic or paucisymptomatic cases to complicated cases that develop severe pneumonia with acute respiratory distress syndrome (ARDS).[6] ARDS represents the final stage for many critically ill patients and evidence suggests a specific role for a cytokine storm.[7] In this context, Pozzilli and Lenzi[8] hypothesized a role for TT in the clinical course of SARS-CoV-2 infection: low testosterone levels can cause a reduction in respiratory muscle activity and overall strength and exercise capacity,[9] whilst normal circulating testosterone levels show a protective effect on several respiratory outcomes.[10] Moreover, evidence from unrelated studies points to a possible immunosuppressive role of TT on different components of the immune system and in different phases of the immune response.[11] Based on the role of androgens in the immune response and on the variation in androgen levels throughout life,[12]

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testosterone could play a double-edged role in the natural history of COVID-19 infection. In the early phase, the immunosuppressive action of testosterone could explain mens' greater susceptibility to infection and also leads to speculation about a protective role for ADT. On the contrary, when the infection occurred in elderly men who frequently develop ARDS, lower testosterone levels related to age could result in a lower immunosuppressive effect on the cytokine storm. Moreover in aging men the role of lower testosterone levels in the development of illnesses such as hypertension, diabetes, and cardiovascular disease is well established as well as their action on pro-inflammatory cytokines.[13] Therefore, hypogonadism may have a protective role on the initial induction of COVID-19 infection, while on the contrary, it could configure a patient with comorbidities and high basal levels of pro-inflammatory cytokines able to induce a higher risk for a critical clinical course, when infection is progressing. Preliminary clinical data support this hypothesis: Rastrelli *et al.*[14], in a series of 31 male patients affected by SARS-CoV-2 pneumonia and recovering in the respiratory intensive care unit, showed that lower baseline TT levels predict poor prognosis and mortality in men infected SARS-CoV-2. In a similar COVID-19 population, our research group observed that TT levels were significantly lower in the patients with ARDS compared with patients without ARDS ($p=0.003$), and higher serum TT levels (ng/ml) were found independently associated with lower odds of invasive oxygenation (OR 0.43, 95% CI 0.23–0.85; $p=0.016$). In addition, low TT levels were associated with a worse clinical COVID-19 phenotype and TT levels were also inversely correlated with IL-6 levels ($p=0.002$).[15]

We believe that the results of these preliminary studies are crucial for providing answers on the topic of ADT and SARS-Cov2 and they lead to major questions: (a) are we ready to treat patients with COVID-19 with ADT?; (b) is it safe to continue ADT in patients with PC and SARS-Cov2 infection?; (c) can we use TT levels as predictors of COVID-19 courses?

In our opinion, the study by Montopoli *et al.*[2] represents a main stepping stone but does not allow us to say that ADT can be a suitable treatment for patients with SARS-Cov2 and ARDS. Moreover, in the study of Montopoli *et al.*[2], the lethality rate of SARS-Cov2 infection was not reported. On the contrary, Caffo *et al.*[3], with patients aged <70 years, reported a lethality rate (25%) that was higher than that expected in the whole population of infected Italian men of the same age (<13.0%). On the basis of Caffo *et al.*[3] results, we may speculate that ADT could be contraindicated in patients with ARDS since it could exacerbate or activate the cytokine storm.

Based on these considerations, we suggest that the role of TT and consequently of ADT should be better pathophysiologically defined before considering the compassionate use of ADT in SARS-Cov2 infection. Testosterone levels and their effects on the immune response can explain some of the differences between men and women in COVID-19 incidence and mortality. However it is crucial to underline that testosterone and therapies used in PC against it may have a double-sided role in the different phases of COVID-19 infection: low testosterone levels may be protective against initial susceptibility, whereas they may stimulate a worse course in advanced COVID-19 infection.

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