SARS-CoV-2: the endocrinological protective clinical model derived from patients with prostate cancer

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Dear Editor,

As researchers clinically and scientifically engaged in the management of male hypogonadism, we read with interest a recent article entitled 'Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study ($n=4532$)'[1], published in the *Annals of Oncology*, that suggests a possible role for androgen-deprivation therapy (ADT) in male patients with Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection.

In a cross-sectional, population-based study performed on 4532 male patients with SARS-CoV-2 infection from Veneto (Italy), the authors reported an impressively low frequency of SARS-CoV-2 infection (4/5273) in patients with prostate cancer on ADT, with no deaths. Also, among all infected patients, those receiving ADT for prostate cancer had around a four-fold lower risk of SARS-CoV-2 infection compared with those not on ADT, thus suggesting prognostic implications of the androgenic status in these patients. As an explanatory mechanism, the authors focused on the androgen-modulated expression of the TMPRSS2 protein, which is involved in SARS-CoV-2 cellular infection by promoting the fusion of viral and cellular membranes. In particular, since androgens trigger the expression of TMPRSS2, ADT might interfere with SARS-CoV-2 entry into the host cells by enhancing its downregulation.[1]

This study confirms clinically the 'androgen hypothesis' that we recently advanced by analyzing the *in vitro* evidence on SARS-CoV-2 infection.[2] Beyond TMPRSS2, the ACE2 protein is also very likely involved in the modulation of sex-specific SARS-CoV-2 mortality. ACE2 is the ligand of the viral spike protein that plays a relevant role in the mechanisms by which SARS-CoV-2 penetrates cells.[3] ACE2 is expressed in several tissues, such as the alveolar cells, myocardium, or Leydig cells. A low ACE2 expression could hypothetically deter SARS-CoV-2 penetration into the host cells. Also, ACE2 is highly expressed in the myocardium of spontaneously hypertensive male mice compared with female mice.[4] Interestingly, its expression decreases significantly after orchiectomy, thus suggesting that androgens sustain ACE2 protein expression.[2] This additional mechanism may explain the lower severity of SARS-CoV-2 infection in patients with prostate cancer under ADT[1] and leads to a possible beneficial consideration for the management of SARS-CoV-2 infection.

First, testosterone (T) [or luteinizing hormone (LH)/human chorionic gonadotropin] discontinuation should be considered in hypogonadal patients with SARS-CoV-2 infection,[2] and ADT could be temporarily counseled to male patients at high risk (e.g. patients with high venous thromboembolic risk).[2] Second, it would be appropriate to assess the gonadal function upon ADT discontinuation. Recent findings point to the possible risk that male patients infected with SARS-CoV-2 may develop hypogonadism. In 81 infected male patients of reproductive age, SARS-CoV-2 led to a significant increase in serum LH levels and LH/T ratio, indicating an early stage Leydig cell dysfunction.[5] Third, male hypogonadism occurs in 2–15% of elderly patients (40–79 years).[6] The evaluation of SARS-CoV-2 infection in male untreated hypogonadal patients would be relevant in further confirming the androgen influence on this disease. Finally, hypogonadism, ADT, and T replacement

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need fine management by endocrinologists with andrological expertise to minimize the risk of over- or under-treatment in these delicate patients.

Although no clinical evidence is currently available on the prognosis of COVID-19 in hyperandrogenic women or in those treated with weak androgens (e.g. dehydroepiandrosterone (DHEA)), it might be speculated that hyperandrogenism or androgen therapy may promote SARS-CoV2 infection in women. Epidemiological data on this topic should be collected to confirm clinically this hypothesis.

Author contributions

Sandro La Vignera: Conceptualization; Writing–review & editing.

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Conflict of interest statement

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