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LETTER TO THE EDITOR

Androgenic hormones and the excess male mortality observed in COVID-19 patients: new convergent data

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Dear Editor,

According different studies and reports by live gender data tracker, more infected men than women seem to be dying from the new coronavirus, in different countries hit by the pandemic [1, 2]. In France, during March 2020 we observed a more pronounced excess mortality in men than in women (+ 13%) compare to March 2019 and 2018. The excess mortality was even higher in region registering high rate of COVID-19 in North and East France [3].

Men can be more susceptible to viruses than women. Women generally tend to have stronger immune responses to viruses, though the reason for that is still up for debate. Genetic and hormonal differences may play a role, while environmental factors could also contribute to susceptibility to different viruses. During previous epidemics of coronaviruses, male sex was associated with worse clinical outcomes due to severe acute respiratory syndrome (SARS) in Hong Kong [4], and a higher risk of dying from Middle East respiratory syndrome (MERS) [5].

As specialists of prostate cancer, we were particularly interested to learn SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. SARS-CoV-2 may even require the combined presence of ACE-2 and TMPRSS2 to enter cells [6]. TMPRSS2 is a transmembrane serine protease. Its expression is regulated by the androgen receptor and is abundantly expressed in the prostate. TMPRSS2 is overexpressed in advanced and metastatic prostate cancers. It has been shown that blockage of AR activity by androgen deprivation therapy reduces significantly the TMPRSS2 transcripts [7].

Considering this interplay, we hypothesize that androgens could upregulate TMPRSS2 expression in pneumocytes and consequently facilitates the viral entry into target cells. Augmented TMPRSS2 expression was also found to be associated with increased risk of severe influenza upon infection with the 2009 H1N1 pandemic virus and with increased susceptibility to H7N9 FLUAV infection [8]. TMPRSS2 expressed in lung tissues may be a determinant of viral tropism and pathogenicity at the initial site of SARS-CoV2 infection as it was demonstrated with SARS-CoV [9]. It could be also related with severity and mortality of the disease. TMPRSS2 knockout mice have less viral replication in the lungs than wild-type mice, and less severe immunopathology, resulting in milder lung pathology [10]. Patients with lung cancer showed also higher susceptibility to SARS-CoV2 possibly related with high expression of TMPRSS2 in normal lung tissue [11].

A putative androgen dependence for virus cell entry relative to high expression of TMPRSS2 in men could explain the male mortality displacement. To our knowledge, there is few comparisons between men and women on TMPRSS2 respiratory tract expression. Recently, in a study comparing patients with severe asthma and healthy people, gene expression of ACE2 and TMPRRS2 were similar in the both groups. However, among asthma patients, male gender, African Americans race, and history of diabetes mellitus, was associated with higher expression of ACE2 and TMPRSS2 [12]. All those correlations are consistent with Covid-19 risk factors previously described. In another study, TMPRRS2 is slightly increased in the lung in men [13]. The authors

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underline that if TMPRSS2 is also promoted by estrogen, in the group at risk of fatal disease, above 60 years, all women will be postmenopausal giving to androgens a major role in TMPRRS2 regulation.

Hoffmann et al. [6] suggested a serine protease inhibitor camostat mesylate, which blocks TMPRSS2 activity, might constitute a treatment option. Another option to regulate TMPRSS2 expression could be androgen receptor antagonists commonly used in metastatic prostate cancer treatment. Those molecules are well-know with side-effects that could be managed easily, especially for a short-term administration. Enzalutamide has been shown to down-regulate TMPRRS2 on cell lines. In the same way, long time exposure to estradiol led to down-regulation of TMPRSS2 [14]. Two Italian studies on patients with laboratory confirmed COVID-19 treated by anti-androgenic therapies suggest that reduced androgen stimulation might represent a protective factor [15, 16].

We are also aware that gender is associated with social norm and behaviors than can also induce different bias. The reasons for a true gender difference in the COVID-19 fatality rate could be hormonal, be also related to a non-uniform case definition of the COVID-19, a different treatment regimen, work-environment factors, gender-specific immune-defense factors. Another important bias could be smoking history that is according different countries more pronounced in men. However, daily smokers' rate in patients with symptomatic COVID-19 could be lower as compared to the general population [17]. Some data also suggest that smoking history is more likely associated with the negative progression and adverse outcomes of COVID-19 [18]. Genetic variants could also support COVID-19 outcome variations between genders. *ACE2* is a gene located on chromosome X with different regulation between men and women [19] and *TMPRSS2* genetics variants have been proposed to explain lethality diversity among different populations as well as sex differences [13].

Considering the mortality displacement in men infected by SARS-CoV2, there is an urgent need for large studies including comprehensive data stratified by gender. Hormonal impregnation, particularly androgen dependent TMPRRS2 expression could be one cause of male mortality displacement and deserve a specific study.

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Compliance with ethical standards

Conflict of interest None.

References

1. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 323:1239–1242
2. https://globalhealth5050.org/covid19/
3. https://www.insee.fr/fr/information/4470857
4. Karlberg J, Chong DSY, Lai WYY (2004) Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? Am J Epidemiol 159:229–231
5. Chen X, Chughtai AA, Dyda A, MacIntyre CR (2017) Comparative epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia and South Korea. Emerg Micro Infect 6:1–6
6. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. https://doi.org/10.1016/j.cell.2020.02.052
7. Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, Morrissey C, Corey E, Montgomery B, Mostaghel E, Clegg N, Coleman I, Brown CM, Schneider EL, Craik C, Simon JA, Bedalov A, Nelson PS (2014) The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 4:1310–1325
8. Chen Z, Song X, Li Q, Xie L, Guo T, Su T, Tang C, Chang X, Liang B, Huang D (2019) Androgen receptor-activated enhancers simultaneously regulate oncogene TMPRSS2 and lncRNA PRCAT38 in prostate cancer. Cells. https://doi.org/10.3390/cells8080864
9. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F (2010) Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol 84:12658–12664
10. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N (2019) TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J Virol. https://doi.org/10.1128/JVI.01815-18
11. Kong Q, Xiang Z, Wu Y, Gu Y, Guo J, Geng F (2020) Analysis of the susceptibility of lung cancer patients to SARS-CoV-2 infection. Mol Cancer 19:80
12. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, Woodruff PG, Mauger DT, Erzurum SC, Johansson MW, Denlinger LC, Jarjour NN, Castro M, Hastie AT, Moore W, Ortega VE, Bleecker ER, Wenzel SE, Israel E, Levy BD, Seibold MA, Fahy JV (2020) COVID-19 Related genes in sputum cells in asthma: relationship to demographic features and corticosteroids. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.202003-0821OC
13. Asselta R, Paraboschi EM, Mantovani A, Duga S (2020) ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *medRxiv* 2020.2003.2030.20047878
14. Wang XDR, Povysil G, Zoghbi A, Motelow J, Hostyk J, Goldstein D (2020) Transcriptional inhibition of host viral entry proteins as a therapeutic strategy for SARS-CoV-2. Preprints 2020030360
15. Duga S, Asselta R, Lazzeri M, Guazzoni G, Azzolini E, Buffi N, Fasulo V, Persico F, Saita A, Hurle R, Lughezzani G, Casale P (2020) Impact of anti-androgenic therapies on COVID-19: an observational study in male population from a COVID-19 regional centre of Lombardy (Italy). *medRxiv* 2020.2004.2020.20068056

16. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, Carbone GM, Cavalli A, Pagano F, Ragazzi E, Prayer-Galetti T, Alimonti A (2020) Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532). Ann Oncol. https://doi.org/10.1016/j.annonc.2020.04.479
17. Miyara M, Tubach F, Pourcher V, Morelot-Panzini C, Pernet J, Haroche J (2020) Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. Qeios. https://doi.org/10.32388/WPP19W.3
18. Vardavas CI, Nikitara K (2020) COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 18:20
19. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W (2020) Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 6:11