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Paolo Pozzilli, Andrea Lenzi

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Testosterone, a key hormone in the context of COVID-19 pandemic

Paolo Pozzilli MD(1) and Andrea Lenzi MD(2)

(1)Unit of Endocrinology and Diabetes, Dept. of Medicine, Campus Bio-Medico, University of Rome and

(2) Dept. of Experimental Medicine, Sapienza University of Rome, Italy

Daily data show that entire population with SARS-CoV2 is 58% made of males [1–3]. The difference in the number of cases reported by gender increases progressively in favor of male subjects up to the age group ≥60-69 (66.6%) and ≥70-79 (66.1%), with the exception of the 20-29 years and 30-39 years group in which the number of female subjects it is slightly higher. Furthermore, higher lethality is in favor of male subjects in all age groups. Deaths among 30-39ys are 82.4% males; among 40-49ys are 73.1 % males; among 50-59ys are 78.5% males; among 60-69ys are 79.7% males; among 70-79ys are 79.6% males; among 80-89ys are 66.9% males [4]

The initial clinical manifestation of the COVID-19 is pneumonia, though are described gastrointestinal symptoms and asymptomatic infections, the last not yet been definitely assessed [5]. The infection can progress to severe disease with dyspnoea and chest symptoms corresponding to pneumonia in the second or third week of a symptomatic infection. Clinical data show decreased oxygen saturation, changes visible through chest X-rays and other imaging techniques. Furthermore, lymphopenia appears to be common, and an increase of inflammatory markers (C-reactive protein and pro-inflammatory cytokines) has been reported [6].

<u>Is low testosterone</u> a promoter of COVID-19 infection?

It is well established that plasma testosterone concentration is reduced by age and comorbidities like obesity, diabetes and obstructive sleep apnea (OSA) [7], all comorbidities highly prevalent in COVID-19 patients [8] Several studies have shown that in men with chronic obstructive pulmonary disease (COPD) hypogonadism is associated with a prevalence ranging between 22% and 69% [9]. In this context low testosterone levels can cause a reduction of respiratory muscles activity and overall strength and exercise capacity [10], whilst normal circulating testosterone levels show a protective effect on several respiratory outcomes (i.e. forced expiratory volume in one second- FEV1, and forced vital capacity - FVC) [11]. A randomized controlled trial reported an improvement in peak oxygen consumption in men receiving testosterone replacement therapy [12]. SARS-CoV2 infects lung alveolar epithelial cells using as an entry receptor the angiotensin-converting enzyme II (ACE2) [13]. ACE2 plays a role in lung protection and therefore viral binding to this receptor may deregulate a lung protective pathway [14]. Interestingly, studies showed that ACE2 is a constitutive product of adult-type Leydig cells [15], thus implying a role in testicular function and suggesting a possible involvement of testicle in COVID-19 infected patients, a factor which may affect testosterone secretion.

Pro-inflammatory cytokines have a central role in the progression of COVID-19 infection. Reduction of cytokine activity and/or their receptors (anti-cytokine therapy), can be useful for treatment. In this context testosterone may downregulate inflammation. As a matter of fact, several studies carried out both in animals and humans showed that hypogonadism is associated with increased pro-inflammatory cytokines and that testosterone treatment reduces IL-1β, IL-6, and TNF-α [16]. Furthermore, the association between an increase

of pro-inflammatory state and decline in testosterone is often observed in aging men [17] and in men with stable coronary artery disease [18]. Based on the above considerations, the hypothesis arises that testosterone may have a role in the cascade of events leading to progression of COVID-19 infection due to the cytokine storm. Suppression of ACE2 expression by inflammatory cytokines accompanied by the decrease of androgens and estrogens of the elderly, may establish a negative correlation between ACE2 expression and COVID-19 mortality [19].

Measuring testosterone levels may be recommended at the time of an identified COVID-19 positive patient.

At present data on testosterone can be collected systematically at one or more institutions. If values are low, use of testosterone may be considered to reduce the associated pulmonary syndrome, thus preventing progression to severe COVID-19 disease where pro-inflammatory cytokines play a major role. In a further selection of patients for testosterone treatment, avoidance of enrolling patients in whom therapy with the hormone is contraindicated, should be taken into account. A proper randomized trial with testosterone should be then designed.

Is high testosterone a promoter of COVID-19 infection?

As opposed to what mentioned earlier, stands the testosterone-driven COVID-19 theory [20]. This is based on the androgen receptor activation of the transcription of a transmembrane protease, serine 2 (TMPRSS2), exploring possible implications in risk stratification and transmissibility of COVID-19 infection [21]. Although other proteases were described to activate the COVID-19 spikes in vitro, only TMPRSS2 activity is regarded as essential for viral spread and pathogenesis in the infected hosts [22]. TMPRSS2 may also cleave ACE2 for augmented viral entry [23]. Androgen receptor activity has been considered a requirement for the transcription of TMPRSS2 gene as no other known TMPRSS2 gene promoter has been reported to exert the same action in humans [24,25]. The modulation of TMPRSS2 expression by testosterone has been suggested to contribute to male predominance of COVID-19 infection [26]. Finally, TMPRSS2 is both the most frequently altered gene in primary prostate cancer and a critical factor enabling cellular infection by SARS-CoV-2 [24]**.** The hyper adrogenic phenotype could explain the COVID-19 positivity in those few young males with severe COVID-19 infection [27], possibly with shorter AR CAG lengths, who are at greater risk of developing prostate cancer because higher receptor transcription activity [28].

A role for TMPRSS2 variants and its expression levels in modulating COVID-19 severity has been suggested, leading to foster a rapid experimental validation on large cohorts of patients with different clinical manifestations of COVID-19 infection [29]. Since TMPRSS2 are expressed also at pulmonary level, the use of TMPRSS2 inhibitors, currently used for prostate cancer, represent an appealing target for prevention or treatment of COVID-19 pneumonia [21,22]. Studies are required to validate this hypothesis and to evaluate the therapeutic and prophylactic potential of drugs that temporarily target androgen activity, such as androgen receptor inhibitors, steroidogenesis inhibitors and 5-alpha reductase inhibitors [20].

The elucidation of the role of testosterone in the battle towards COVID-19 infection turns out to be an urgent need.

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