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Commentary

Androgenicity—not serum testosterone—correlates best with COVID-19 outcome in European males

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Although the infection rate is no different, a plethora of epidemiological data indicate marked gender disparity in COVID-19 disease severity that is consistent across all age bands. From the very beginning of the pandemic, it was clear that men were more severely affected, having a relative fatality rate around three-fold that of age-matched women [1]. This proved a highly inconvenient truth for those undertaking risk assessments in healthcare and other workplace environments, in that placing younger women at greater risk of exposure than older men ran contrary to human instincts.

Although the media focused on lifestyle-related male vulnerabilities, with men reported to be less careful of their personal fitness, diet and hand-face hygiene, evidence nevertheless accrued that women had a more effective immune response and a lower predisposition to thromboembolism [2]. Sex differences in genetic background may contribute to this variable susceptibility. For instance, loss-of-function variants of the X-linked TLR7 gene have been associated with impaired type I and II interferon activity and inflammatory responses IFN, leading to more severe outcomes in young men [3]. However, these mutations are very rare and thus only expected to account for a small number of cases. Overall, although the host genetic background is likely to play an important role, few genetic predictors of COVID-19 outcome have been convincingly defined thus far.

Testosterone, the dominant male sex steroid, binds to the nuclear androgen receptor (AR) and thereby – especially after metabolism to dihydrotestosterone (DHT) – promotes a cascade of post-receptor processes that ultimately result in the clinical features that define androgenicity, comprising the induction and maintenance of male secondary sexual characteristics, anabolic effects on bone, muscle and haematopoiesis, and a paracrine action on Sertoli cells to support spermatogenesis.

The X-linked AR gene contains a highly polymorphic polyQ tract at its N-terminus, normally ranging from 9 to 36 polyglutamine coding CAG repeats, with the polyQ tract-length being inversely correlated to receptor functionality [4]. Although AR is expressed in both sexes, the bioavailability of its ligands (testosterone and DHT) is much higher in males. The PolyQ repeat size varies among different populations, with the shortest in Africans, medium-length in Caucasians and longest in Asians and, during the first pandemic wave, the mortality rate was notably higher in China and Italy compared to Africa [5].

Based on current evidence, androgens seem to play an ambivalent role in COVID-19 pathogenesis [6, 7]. On the one hand, they facilitate viral entry into host cells by promoting the expression of a key serine protease; on the other hand, they confer protection against SARS-CoV-2 by attenuating inflammatory immune responses. Previous studies have shown an association between hypogonadism and several chronic pulmonary diseases including severe COVID-19.

In the nested case-control study recently reported by *EBioMedicine* [8], Baldassarri and coworkers examined the genotypes of 638 males and female Italian COVID-19 patients, comparing those most severely affected versus those oligo-asymptomatic. Among males, they found an association between length of the AR polyQ tract, serum testosterone levels and disease severity, with shorter alleles ($\leq$22 triplets) appearing to protect against worse clinical outcomes.

This association was then independently confirmed in a cohort of Spanish men under 60 years of age, among whom testosterone levels were – in absolute terms – higher in subjects with longer alleles (>23 triplets), reflecting reduced negative feedback at hypothalamo-pituitary level on gonadotropin secretion. However, due to infection-related non-gonadal illness, they were nevertheless *inappropriately low* in respect of overall androgenicity, among men with >23 triplets. Moreover, men with long PolyQ repeats exhibited greater proinflammatory status (higher CRP levels) in line both with the known immunomodulatory activity of testosterone [9] and the functional importance of the AR PoyQ tract.

Notably, the authors have identified the first major genetic polymorphism that appears to predispose European male carriers to develop more severe disease, independent of age. Compared with

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respect to TLR7 gene variants, these findings involve a much larger number of subjects, as long polyQ alleles are relatively common. They could also represent an explanation for the above differences in death rate among Caucasian, Asian and African populations.

These results are also in line with previously observed associations between hypogonadism and chronic pulmonary diseases, and provide a possible underlying mechanism. Moreover, the observed infection-related failure of homeostatic feedback to compensate for weaker AR signaling leads to the conclusion that polyQ tract length is hierarchically more important than absolute serum testosterone to the clinical outcome. Hence, disease severity and subsequent need for intensive care are predicted by the overall milieu of androgenicity, resulting from the interaction between polyQ polymorphism and serum testosterone concentrations (possibly also to testosterone protein-binding in the circulation), and is closely related to the hyperinflammatory state. This concept also helps to disentangle the discrepancies arising from some early reports of better COVID-19 outcome in prostate cancer patients, who also tend to have shorter polyQ repeats, when compared to men with other cancers.

Crucially, Baldassarri and coworkers raise the prospect of deploying a cheap and simple genetic (AR polyQ-length) and biochemical (serum testosterone) test to identify those European male COVID-19 patients most likely to develop life-threatening complications, and who might potentially even benefit from testosterone therapy. This study provides, in fact, a general rationale to undertake clinical trials of testosterone in men expressing defective androgen signaling (defined as $\geq$23 PolyQ repeats) and having inappropriately low testosterone levels. One trial has already demonstrated improved peak oxygen saturation with testosterone treatment of older men with heart failure [10]. However, in future trials, patients could be randomized more precisely to testosterone versus placebo following selection based on both their serum testosterone concentration *and* polyQ repeat length. Such a study would allow us to better explore whether testosterone replacement may decrease morbidity and mortality in patients affected by the most severe forms of illness-related hypogonadism; randomization based solely on serum testosterone levels is likely to be insufficient for purpose. Moreover, these observations should also be followed by properly conducted studies aiming to delineate further X-linked variants as genetic predictors of COVID-19 outcome.

Contributors

The authors conceived and wrote this invited Commentary.

Declaration of Interests

The authors report no conflicts of interest.

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