The role of testosterone in SARS-CoV-2 infection

The COVID-19 global pandemic was caused by infection with a coronavirus, SARS-CoV-2. Significant differences in outcomes and severity of disease have already been reported between populations, dependent on factors such as vaccination status, age, ethnicity, and pre-existing health conditions.

One study done in 2020 concluded that the number of men who died from COVID-19 was 2.4 times higher than the number of women. Data from several other countries also support this finding and have shown significant differences in the number of men admitted to hospital with COVID-19, the severity of symptoms, and the risk of mortality compared to women. A data tracker resource has shown that COVID-19 fatality risk is higher in men than women in 68 countries. However, it can be challenging to unpick this data, for example men may be more likely to smoke than women, making them more susceptible to respiratory infections. There may be other, biological reasons that men respond differently to infection from SARS-CoV-2. It is already known, for example, that men are more likely to develop some forms of non-reproductive cancers than women. One reason for such gender imbalance in disease may be the influence of sex hormones (androgens), such as testosterone. This relationship is something that Marta Camici, at The Lazzaro Spallanzani National Institute for Infectious Diseases, has set out to investigate.

TESTOSTERONE AND SARS-COV-2 INFECTION

Testosterone is thought to be a key pathogenic factor in the development of COVID-19 and may offer a biomarker (a biological molecule that can indicate a particular disease or predict outcome of treatment for severe pneumonia). Camici explains that low levels of total testosterone (TT) and calculated free testosterone (cFT) are predictive of longer hospital stays. It is thought that the link between testosterone and COVID-19 severity is likely to be due to SARS-CoV-2 directly damaging the testes and the pituitary gland, which secretes gonadotropin. Moreover, the occurrence of a hyper-inflammatory syndrome in these patients can contribute to reduce testosterone production. The immune system is activated when an individual becomes infected with SARS-CoV-2, a process which is normally kept in check by regulatory molecules. In some people, there is an enhanced immune response which can lead to hyper-inflammatory syndrome, sometimes called a ‘cytokine storm’.

PREDICTING CLINICAL OUTCOMES

This relationship can also be used to predict clinical outcomes in patients with pneumonia caused by SARS-CoV-2. Her research findings suggest that the number of men who died from COVID-19 was 2.4 times higher than the number of women. The COVID-19 global pandemic has shown gender imbalances in COVID-19 severity and risk of mortality, with worse outcomes seen in men. To explore why male gender is a major risk factor for more severe disease, Marta Camici, of The Lazzaro Spallanzani National Institute for Infectious Diseases (IRCCS), has explored the links between testosterone and COVID-19. Her research findings suggest that low testosterone levels can be used to predict disease outcomes, and offers opportunities to develop novel therapeutic approaches.

Interestingly, testosterone also has an anti-thrombotic role, meaning that it can reduce formation of blood clots, as well as helping to regulate immune responses. Both functions of testosterone could explain the link between low testosterone levels and poorer health outcomes.

TMPPRSS2 IS IMPORTANT FOR CORONAVIRUS ENTRY

It is thought that a protein called TMPRSS2 (transmembrane serine protease 2) may also have an important role in facilitating infection with coronaviruses, such as SARS-CoV and SARS-CoV-2. TMPRSS2 is important for regulating the function of the prostate, however its exact biological function remains unclear. As well as cells in the respiratory and digestive tract, cells in the prostate may also express TMPRSS2 on their surfaces. The protein may also contribute to the development of prostate cancer, and samples from prostate cancer patients show that TMPRSS2 is upregulated in response to androgens (hormones that contribute to growth and reproduction), such as testosterone.

Recent studies have suggested that, alongside other receptors on cell surfaces, TMPRSS2 is directly responsible for allowing coronaviruses to enter the human body. It is thought that TMPRSS2 activates a protein on coronaviruses called the spike protein, allowing the virus to fuse to the surface of target cells. Therefore, blocking TMPRSS2 could lead to lower infection rates in patients with COVID-19.
TMPRSS2 could offer a novel treatment option to combat COVID-19.

Interestingly, ACE2, another cell-surface protein which is important in the SARS-CoV-2 infection pathway, is also influenced by androgens, with higher activity found in men. In addition, previous research suggests that TMPRSS2 may cleave ACE2, enhancing its ability to bond to coronaviruses.

ANDROGEN SENSITIVITY

Camici also argues for the role of androgen sensitivity in COVID-19 disease severity. There is a genetic influence on androgen sensitivity that is determined by the variant of the androgen receptor that a particular individual has. The androgen receptor also regulates transcription of TMPRSS2, which may explain the link between COVID-19 severity, testosterone levels, and TMPRSS2.

Androgen sensitivity is partly determined by a gene on the X chromosome: the AR (androgen receptor) gene. It is already known that changes in this gene can predispose men to developing other androgenetic alopecia. The androgen receptor is determined by the variant of the AR gene, which may explain the link between androgen sensitivity in COVID-19 mortality rates. Clinical studies can focus on the more accurate pharmacological target to restore the healthy state.

The poorer focus on female symptoms, the underestimation of female diseases, and the consequent undertreatment of females in respect to males, are the consequence of ancient social behaviours and backward beliefs, that are reflected in medicine. It is changing as gender social equality improves.

Camici explains that low levels of total testosterone (TT) and calculated free testosterone (cFT) are predictive of longer hospital stays.
