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Testosterone, COVID-19 and tadalafil
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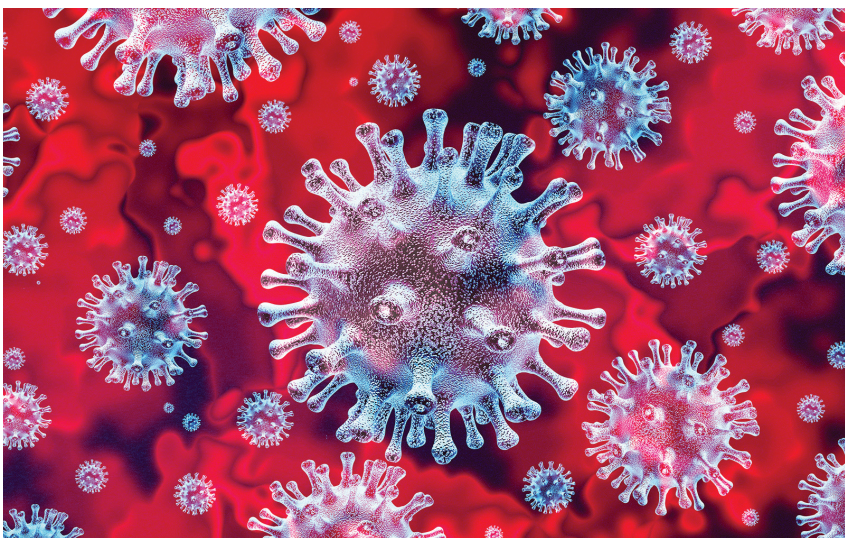
Testosterone deficiency in men infected with COVID-19

Geoffrey Hackett, Consultant in Sexual Medicine;[1] **Michael Kirby,** Editor[2]
1. University Hospitals, Birmingham NHS Foundation Trust; 2. Trends in Urology and Men's Health

As our understanding of the SARS-CoV-2 virus develops, recent research has highlighted the potential role of testosterone in the severity of illness. Here, the authors explain the role of testosterone in men infected with COVID-19.



Recently published research has highlighted the potential role of testosterone in the severity of illness in male patients infected with SARS-CoV-2. To better understand this association, testosterone levels should be investigated in all men affected by COVID-19

Regarding COVID-19 infection, several recent studies[1–5] point to an important role for hormones, particularly testosterone, during the acute phase of the illness. It is known that ACE2 is a constitutive product of adult-type Leydig cells, thus implying a role in testicular function and suggesting a possible involvement of testicles in SARS-CoV-2 infected patients, a factor that may affect testosterone secretion. Serum testosterone levels appear adversely affected and may impact on recovery. Testosterone levels therefore should be investigated in men affected by COVID-19.

Several publications[6–9] where patients have been treated with testosterone replacement therapy (TRT) to restore testosterone levels to normal have shown significant reduction in hospitalisation and all-cause mortality, and reversal and prevention of diabetes, and therefore testosterone may have a role in relevant patients with COVID-19.

It appears the SARS-CoV-2 infection facilitates the induction of endothelial dysfunction in many organs, but especially in the vascular tree. From the practical viewpoint, using drugs that improve endothelial function, such as daily PDE5 inhibitors, ACE inhibitors/Angiotensin Receptor Blockers (ARBs) and statins, could therefore be very important in these patients. Antithrombotics also have a place because of diffuse microvascular thrombi in multiple organs, mostly in pulmonary microvessels. The thrombotic risk seems to be directly related to disease severity and worsens patients' prognosis.[10]

In addition, the WHO has produced a guideline for the use of corticosteroids in patients infected with SARS-CoV-2.[11]

Male versus female deaths from COVID-19

Published mortality data consistently shows that two-thirds of nearly 45 000 UK COVID-19 deaths are in men, with rates in patients aged <85 years of 50.6/100 000 for men in the UK, versus 25.5/100 000 in women.[12] Over the age of 85 years, men only make up 30% of the population, meaning that female deaths predominate in this group.

Corresponding figures for all age groups in the USA are 43/100 000 in men and 23/100 000 in women.[13] After adjustment for age the increased risk of mortality from COVID-19 infection for Afro-Caribbean men is 1.9, and for South-Asian men is 1.8. Comorbidities such as age, obesity, type 2 diabetes (T2D), chronic kidney disease (CKD), hypertension, heart failure and COPD all increase the risk, and are more common in men.[12]

What is currently known about testosterone and mortality?

The fact that COVID-19 is associated with a fall in testosterone levels[4] may compound the risk of mortality because several age-related conditions are associated with increased rates of hypogonadism; notably, type 2 diabetes mellitus (T2DM), obesity, coronary heart disease (CHD), heart failure, CKD, COPD, HIV, and men on long-term opiates. Within these groups, secondary hypogonadism has been shown to be associated with an increased all-cause mortality

Recently, the American Urological Association (AUA) recommended that all men with low testosterone should be strongly counselled that they are at an increased cardiovascular risk.

South-Asian Men have a 2–3-fold risk of T2DM, with associated increased secondary hypogonadism.[14,15]

Afro-Caribbean men have been shown to have a steeper decline in testosterone level with age and a lower number of androgen receptor polymorphism (CAG repeats) on the androgen receptor that may also be associated with increased prostate cancer risk.[16]

Low total and free testosterone has been shown in multiple studies to increase the risk of T2DM by 3–4-fold. The association between testosterone and T2DM is considered bi-directional.[17] The American Diabetes Association, American Academy of Clinical Endocrinologists, American Urology Association, and the British Society for Sexual Medicine[18–20] all currently recommend screening for all men with T2DM, and obesity, for hypogonadism – as the current prevalence is around 40% in T2DM, (more than double the prevalence observed in the general population).

Several publications where patients have been treated with TRT to restore testosterone levels to normal have shown significant reduction in hospitalisation and all-cause mortality in men with CHD, T2DM, heart failure, CKD, COPD, and opiate use.[21–24]

Recently, a T2DM study of 1007 men with obesity and pre-diabetes treated with diet – plus either testosterone undecanoate (TU) injection or placebo – for two years, reported a 40% reduction in progression to T2DM in the TU group.[8]

The role of testosterone in the COVID-19 pandemic

Early reports have confirmed that transmembrane serine protease 2 (TMPRSS2, an androgen responsive gene) and angiotensin converting enzyme 2 (ACE2) are critical targets of SARS-CoV-2 that facilitate viral entry into host cells. TMPRSS2 and ACE2 are expressed in multiple human tissues beyond the lung, including the testes where predisposition to SARS-CoV-2 infection may exist.

Despite the link with TMPRSS2, a recent paper has cast doubt on the advisability of using ADT (androgen deprivation therapy) because it upregulates ACE2, hence the advice to avoid ADT in certain groups of prostate cancer patients.[25]

The SARS-CoV-2 virus infects lung alveolar epithelial cells using the ACE2 receptor. ACE2 plays a role in lung protection and, therefore, viral binding to this receptor may deregulate a lung protective pathway.[25] Interestingly, studies showed that ACE2 is a constitutive product of adult -type Leydig cells, thus implying a role in testicular function and suggesting a possible involvement of testicle(s) in SARS-CoV-2 infected patients, a factor that may affect testosterone secretion.[26]

Several recent studies also point to an important role for hormones, particularly testosterone, during the acute phase of the illness, and testosterone may be a key hormone in the context of COVID-19 pandemic.[26]

Studies carried out both in animals and humans have shown that hypogonadism is associated with increased pro-inflammatory cytokines and that testosterone treatment reduces IL-1β, IL-6, and TNF-α.[26]

What do recent COVID-19 studies show?

In a recent study from Germany involving 45 acute SARS-CoV-2 admissions (35 male, 10 female) 54% of male patients had TT levels below 4.9nmol/l, with 25.7% below 3nmol/l on admission. They considered 6.68 nmol/l as normal. Luteinising hormone (LH) levels were raised in 31.4%, and oestradiol was raised in 31.4% and was associated with increased inflammatory markers, especially IL-6. The authors concluded that critically ill male COVID-19 patients suffer from severe testosterone and dihydrotestosterone deficiencies.[4]

In an Italian study involving 31 male patients, those managed routinely on medical wards had a mean TT level of 8.8 nmol/l, with those on respiratory intensive care units having a mean level of 5 nmol/l, and those on intensive care units (n=4) having a mean TT level of 1.0 nmol/l, with two out of every four of these men dying. The authors concluded that low TT and calculated free testosterone (cFT) on admission predicted poor prognosis in COVID-19 infection.[5]

A study of 81 admissions of male patients with COVID-19 infection from Wuhan, China, with a mean age of 38 years, also showed reduced TT levels and raised LH, suggestive of a compensated primary hypogonadism.[6]

In a pre-publication study,[6] the time-to-clearance of the SARS-CoV-2 virus in symptomatic patients was investigated by serial oropharyngeal/nasopharyngeal swabs followed by RT-PCR (RdRp gene) test. A total of 68 Indian subjects with median age of 37 years (the range was 3–75 years) were examined and included

48 (71%) males and 20 (29%) females. Female patients were able to achieve viral clearance significantly earlier than males, with a median difference of two days in achieving a negative PCR result (*p value* = 0.038). In order to explain this variance, the researchers studied expression patterns of the ACE2 in tissue specific repositories. The testes were one of the highest sites of ACE2 expression in three independent RNA expression databases (Human Protein Atlas, FAMTOM5 and GETx). ACE2 was also determined to be highly expressed in testicular cells at the protein levels. In contrast, very little expression of ACE2 was seen in ovarian tissue. High expression of ACE2 in testes raises the possibility that testicular viral reservoirs may play a role in viral persistence in males requiring further research.[6] Serum testosterone levels may also be adversely affected and impact on recovery.

Cayan *et al,*[27] reported their results in 232 men hospitalised with COVID-19 in Turkey. Serum hormone levels were obtained on the day of hospitalisation. Testosterone deficiency was noted in 51.1%, including severely depressed values (<100ng/dl) in 26 men, and 25 with testosterone levels of 101–199ng/dl. The probability of transfer to ICU increased with decreasing serum testosterone. Of the 11 deaths, 10 (90.9%) had serum testosterone <300ng/dl. Eight of 11 deaths (72.7%) were in men with markedly reduced serum testosterone levels (<200ng/dl). Only one death occurred in a man with normal serum testosterone level on the first day of hospitalisation.

ADT has been suggested as a treatment on the basis of a reported improved survival from COVID-19 in men with prostate cancer.[28] Five alpha reductase inhibitors (5ARIs) have also been advocated, despite evidence that both ADT[29] and 5ARIs[30] increase the risk of T2DM by up to 30%. There are also mechanisms by which 5ARIs might have adverse effects on the lungs.[31] However, both of these strategies appear illogical in the light of the recent findings from Italy and Germany of extremely low testosterone and di-hydro testosterone (DHT) levels in acutely ill patients.[4,5]

From the practical viewpoint, using drugs that improve endothelial function, such as daily PDE5 inhibitors, ACE inhibitors/ARBs and statins, could be very important in these patients, although many of the vulnerable patients will already be on these drugs because of pre-existing endothelial dysfunction and its known risk association with male sex, erectile dysfunction (ED), smoking, obesity, diabetes, hypertension, cardiovascular disease (CVD) and testosterone deficiency.[32]

What are the implications of recent COVID-19 studies?

These studies suggest that men admitted with COVID-19 have significantly lower testosterone levels than with other acute hospital admissions. Furthermore, the virus is associated with a severe primary hypogonadism, occurring in addition to the functional secondary hypogonadism that is associated with comorbid conditions. These recent studies raise the question as to whether men should be treated acutely with testosterone to boost resistance to the 'cytokine storm' associated with COVID-19 infection.[26] There seems little justification for using oestrogens in the acute phase as victims of COVID-19 already have raised oestradiol levels.[4]

So far, scant consideration has been given to the untreated hypogonadal population with comorbidities, who may have survived the current pandemic but who may be at considerable risk from second and third wave infection, or future viral pandemics. In seriously ill patients managing thrombotic risk, improving endothelial function and considering testosterone replacement in a trial setting should be considered in every male patient.

We now have firm evidence that TRT reverses progression to T2DM.[11] Current evidence- based guidelines from multiple medical disciplines already recommend screening, diagnosing, and treating men with hypogonadism in high risk groups, such as T2D, BMI >30kg/M2 and men with ED, and there have been two recent reviews underscoring the cardiovascular and prostate safety of TRT.[33,34] Ultimately, if we do not follow the evidence, T2D will still be responsible for more premature deaths in 2020 than COVID-19.[35]

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