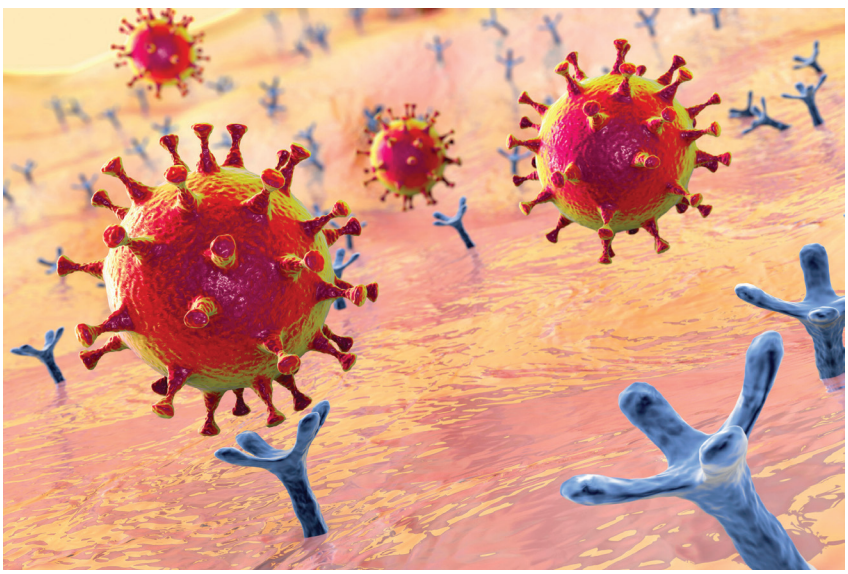
Webinar
COVID-19: biological factors in male risk
Join the discussion:
www.trendsinmenshealth.com

COVID-19: biological factors in men's vulnerability

Alan White, Emeritus Professor of Men's Health;[1] **Mike Kirby,** Editor[2]
1. Leeds Beckett University; 2.Trends in Urology and Men's Health

The reasons behind the disproportionately higher number of deaths among men compared with women as a result of the COVID-19 pandemic may not be clear for some time. Here the authors discuss some of the potential biological explanations for why men seem to succumb more readily to the deadly effects of the virus.



COVID-19 binding to an angiotensin converting enzyme 2 (ACE2) receptor

As COVID-19 wreaks havoc across the globe, the UK has been particularly hard hit. The death toll on 19 June 2020 was 49 369 across England and Wales, of which 27 183 were male and 22 186 were female (see Figure 1). This disparity in male mortality has been noted elsewhere,[1–4] and was also recognised during the two previous significant outbreaks of coronavirus: the 2003 severe acute respiratory syndrome (SARS-CoV),[5,6] and the 2012 Middle East respiratory syndrome (MERS).[7] In particular, during the SARS-CoV outbreak men had a higher case fatality rate of 21.9% as compared with 13.2% for females, and twice as many male-to-female deaths in the 0–44 year age range.[5]

It is too soon for certainty as to why men are more at risk, but our knowledge of the biological, behavioural and sociocultural factors involved is growing and the picture is becoming clearer. This paper will focus onto what is currently understood about the biological implications of being male for the course of the disease. However, this requires an early warning about many of the scientific papers that have emerged about the outbreak, as the majority have still not gone through formal peer review and may therefore be amended or not accepted.

As well as gender, age is seen to be one of the most important risk factors for developing severe disease and a higher mortality,[8] with the median age of those admitted to hospital being 72 years.[9] The most common recorded comorbidities for admission to hospital across the UK are chronic cardiac disease (29%), diabetes (19%), chronic pulmonary disease excluding asthma (19%), and asthma (14%). Just under half (47%) of patients had no documented comorbidity.[9]

In other studies, cardiovascular disease (especially hypertension and heart failure), obesity, diabetes mellitus, respiratory disease, renal and liver disease were found to be the biggest factors in patients developing the more serious form of the disease, along with a higher mortality.[10–12] Patients who are immunosuppressed or having had recent surgery are also recognised as being at risk, but this may be due to contact within the hospital setting.[11] In a New York analysis of patients with severe disease, hypertension, obesity and diabetes were found to be the most common factors for admission to hospital.[12] For all these chronic diseases there are a higher proportion of affected men, with a greater number affected at an earlier age.[13]

Angiotensin converting enzyme 2

The angiotensin converting enzyme 2 (ACE2) is the main route the virus

takes to enter cells,[14] and the enzyme is more highly expressed in males.[15] ACE2 is present in the lungs, blood vessels, renal tubular cells, the stomach and intestines, endothelial and smooth muscle cells in the human brain, and the Leydig and Sertoli cells in the seminiferous ducts in the testis. It is more highly expressed in smokers and in obese patients.

The ACE2 receptor is part of the renin angiotensin aldosterone system (RAAS), converting angiotensin II into angiotensin (1–7) via its binding to the Mas receptor. Angiotensin II is vasoconstrictive, pro-inflammatory and pro-coagulation – as well having a role in increasing blood pressure. Angiotensin (1–7), on the other hand, is vasodilatory, anti-inflammatory and has a role in glucose homeostasis, lipid metabolism, and energy balance; it is cardioprotective and neuroprotective, and has a positive effect in reducing lung injury and kidney pathology.[16–18]

The interaction between the virus and ACE2 leaves it depleted through receptor endocytosis and, therefore, leaves the damaging angiotensin II unopposed, meaning that the body loses the positive effects of angiotensin (1–7).[14] Losing the metabolic effect of angiotensin (1–7) may also explain why both obese patients and those with diabetes are at greater risk. A link has also been made with metabolic syndrome, which is more common in males, and severity of the disease.[19]

ACE2 is produced by the X-chromosome, and as females have two X-chromosomes they have twice the capacity to form the enzyme and tend to create two types of ACE2. As males have only one X-chromosome, they also have only one form of ACE2. This means that if the virus can unlock the single form of male ACE2 it has access to every cell in which the enzyme is present, while in women the virus has to unlock both of the two forms of ACE2 (one from each X-chromosome) to have the same impact. The effect of this on males is twofold: it means that the higher ACE2 levels in males may make it easier to get the infection; and, once they are infected, they may have less ACE2 and therefore angiotensin (1–7) available to help counter the damaging effects of angiotensin II. For females there may be less virus entry into the cells, and also more remaining unaffected cells and angiotensin (1–7) to tackle subsequent lung injury.

Patient age group	Male	Female
Under 1 year	2	0
1 to 14 years	2	2
15 to 44 years	325	206
45 to 64 years	3104	1634
65 to 74 years	4740	2542
75 to 84 years	9446	6516
85 years and over	9566	11286

Figure 1. Deaths attributed to COVID-19 infection in England and Wales, distributed by age and sex, 19 June 2020.©statista.com

The availability of the ACE2 is also affected by age, with the highest levels found in younger age patients, which would appear counterintuitive in relation to infection rates and severity of the disease in older age patients. However, as the young are less likely to have other risk factors (such as chronic diseases and comorbidities) they may be more able to use its protective function to fight the disease. In older age patients, a reduced ACE2 may mean the enzyme is more quickly exhausted, leading the risk of more severe disease.

The ACE2 is also highly expressed within the testis and prostate,[15] with orchitis, infertility and testicular tumour identified in the earlier SARS-CoV outbreak.[6] The longer term impact of this ACE2 prevalence in male-specific organs should be assessed through the current outbreak.[22,23] It has also been postulated that the virus may be transmissible in seminal fluid.[22]

Endothelial dysfunction

Endothelial dysfunction is an important risk factor for cardiovascular disease (CVD), and is frequently present in men with erectile dysfunction and type 2 diabetes.[20] It appears the SARS-CoV-2 infection facilitates the induction of endotheliitis in multiple organs, and the induction of apoptosis might play an important role in endothelial cell injury in these patients. From the practical viewpoint, using drugs that improve endothelial function – such as PDE5 inhibitors, ACE inhibitors and statins – could be important in these patients,[24,25] although many vulnerable patients will already be on these drugs because of pre-existing endothelial dysfunction and its known association with male sex and vascular risk factors.

Coagulopathy

The vascular immunopathology associated with COVID-19 presents as a diffuse pulmonary intravascular coagulopathy, which in its early stages is distinct from disseminated intravascular coagulation. Increased circulating D-dimer concentrations caused by pulmonary vascular bed thrombosis with resultant fibrinolysis and elevated cardiac enzyme concentrations in the face of normal fibrinogen and platelet levels are key early features of severe pulmonary intravascular coagulopathy related to COVID-19.

Extensive immunothrombosis over a wide pulmonary vascular territory before the confirmation of early COVID-19 viraemia possibly explains the adverse impact of male sex,

hypertension, diabetes, and obesity on the prognosis of COVID-19 patients. The combination of immunomodulatory and anticoagulant strategies in patients with high D-dimer concentrations and evidence of myocardial stress requires urgent research.[21]

Cytokine proteins

The immune system is also supported by the cytokine proteins, which act as a communicator between cells. They are involved in the pro-inflammatory process, with some (CCL2, CCL3, CCL4 and CCL16) having a protective effect and being found more often in women. Men tend to have more of the interleukin cytokines (IL6ST, IL-7, IL-16 and IL-18) that provoke more of an inflammatory response and, with excess stimulation, can lead to the cytokine release syndrome (or cytokine storm) that can rapidly overtake the body's immune system and result in a catastrophic shock. Men also tend to have more highly expressed TNFSF13b (BAFF), which is associated with an increased risk of inflammation and is associated with the progression of chronic obstructive pulmonary disease (COPD).[15]

For the virus to enter the cells they also need two spike proteins – FURIN and TMRPSS2. FURIN is more highly expressed in the lungs of smokers (with men being more prevalent smokers), and TMPRSS2 is an androgen-responsive gene that is more responsive to testosterone and dihydrotestosterone.[26]

Wider immunity factors

Females also have higher expression of TLR7 and TLR8, both of which are important in immune responses and are found (and remain active) on both X-chromosomes, whereas in men there is just a single copy. As such, females are more likely to activate a successful immune response and have been suggested to be more active with single strand viruses such as SARS-CoV-2.[27]

A hormonal component is also important, with oestrogen having an immunoprotective function by the regulation of myeloid cells and innate lymphocytes, and in dampening the proinflammatory cytokines. It may also have a more direct effect on the metabolic function of the cell limiting viral replication. Oestrogen also promotes type 2 repair responses of alveolar macrophages and resolution of the immune response to the virus.

Testosterone has been suggested to be immuno-suppressive, by promoting the proinflammatory cytokines and suppressing inflammation;[6,28] however, there is now *in-vivo* evidence that although testosterone does have an immunomodulatory effect there may be less negative effects on immunity than previously thought.[29] Age may still have an effect on the viral infection, with oestrogen levels falling in women quickly in the perimenopause whereas testosterone levels remain stable in 75% of men into old age, but this does leave a significant number of men testosterone and oestrogen deficient.[30]

Risk factors for a low testosterone include type 2 diabetes, obesity, erectile dysfunction, sleep apnoea, comorbidity and others.[31] Female patients are able to achieve viral clearance significantly earlier than males, and this might be because the testis was shown to be one of the sites with the highest expression of ACE2 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.[32]

Serum testosterone levels may be adversely affected by the testicular involvement and have a significant impact on recovery.[33] Testosterone may also be helpful by downregulating inflammation. Testosterone deficiency (TD) is associated with increased pro-inflammatory cytokines, and testosterone treatment reduces IL-1β, IL-6, and TNF-α.[34] A pro-inflammatory state and decline in testosterone has been demonstrated in ageing men[35] and those with vascular disease.[36]

In theory testosterone may have a role in the events leading to progression of COVID-19 infection and preventing the cytokine storm. Suppression of ACE2 expression by inflammatory cytokines accompanied by the decrease of androgen and oestrogen in some ageing men may establish a negative correlation between ACE2 expression and COVID-19 mortality.[37] Testosterone levels should be investigated in these men affected by COVID-19 because of the known adverse impact of TD on cardiovascular mortality and heart failure, and men with low testosterone may be at high risk if they get infected.[38]

Conclusion

We are not at the end of the pandemic, and there will be many more theories emerging as to the biological causes and consequences of the disease as our understanding develops. As the search for a vaccination continues apace there are many avenues being followed that may lead to a breakthrough, but this is proving to be a very tricky infection with many twists and turns in the experiences of patients. We fear we are just at the beginning…

Declaration of interests

Mike Kirby has received funding from the pharmaceutical industry for research, travel and educational initiatives; however, no funding was directly related to the writing of this article.

References

1. Márquez EJ, Trowbridge J, Kuchel GA, *et al*. The lethal sex gap: COVID-19. *Immun Ageing* 2020;17(1):13.
2. Jin J-M, Bai P, He W, *et al*. Higher severity and mortality in male patients with COVID-19 independent of age and susceptibility. *Front Public Health* 2020 (https://doi.org/10.3389/fpubh.2020.00152; accessed 11 June 2020).
3. Wenham C, Smith J, Morgan R. COVID-19: the gendered impacts of the outbreak. *Lancet* 2020;395(10227):846–8.

4. Global Health 5050. Sex, gender and COVID-19: overview and resources (https://globalhealth5050.org/covid19; accessed 11 June 2020).
5. Karlberg J, Chong DSY, Lai WYY. Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do? *Am J Epidemiol* 2004;159(3):229–31.
6. Channappanavar R, Fett C, Mack M, *et al*. Sex-based differences in susceptibility severe acute respiratory syndrome coronavirus infection. *J Immunol* 2017;198(10):4046–53.
7. Ahmadzadeh J, Mobaraki K, Mousavi SJ, *et al*. The risk factors associated with MERS-CoV patient fatality: A global survey. *Diagn Microbiol Infect Dis* 2020;96(3):114876.
8. Ho FK, Celis-Morales CA, Gray SR, *et al*. Modifiable and non-modifiable risk factors for COVID-19: results from UK Biobank. medRxiv (preprint) 2020 (https://doi.org/10.1101/2020.04.28.20083295; accessed 11 June 2020).
9. Docherty AB, Harrison EM, Green CA, *et al*. Features of 16 749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv (preprint) 2020 (https://doi.org/10.1101/2020.04.23.20076042; accessed 11 June 2020).
10. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality – preliminary results. medRxiv (preprint) 2020 (https://doi.org/10.1101/2020.02.24.20027268; accessed 11 June 2020).
11. Beeching NJ, Fletcher TE, Fowler R. Coronavirus disease 2019 (COVID-19). *BMJ Best Practice* (https://bestpractice.bmj.com/topics/en-us/3000168; accessed 11 June 2020).
12. Petrilli CM, Jones SA, Yang J, *et al*. Factors associated with hospitalization and critical illness among 4103 patients with Covid-19 disease in New York City. *BMJ* 2020;369:m1966.
13. World Health Organization (WHO). *World Health Statistics 2019: Monitoring health for the SDGs, sustainable development goals*. Geneva: WHO, 2019.
14. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020;76:14–20.
15. Wei X, Xiao Y-T, Wang J, *et al*. Sex Differences in Severity and Mortality Among Patients With COVID-19: Evidence from Pooled Literature Analysis and Insights from Integrated Bioinformatic Analysis. arXiv (preprint) 2020 (http://arxiv.org/abs/2003.13547; accessed 11 June 2020).
16. Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related Stroke. *Transl Stroke Res* 2020;11:322–5.
17. Imai Y, Kuba K, Rao S, *et al*. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436(7047):112–6.
18. Komukai K, Mochizuki S, Yoshimura M. Gender and the renin-angiotensin-aldosterone system. *Fundam Clin Pharmacol* 2010;24(6):687–98.
19. Marhl M, Grubelnik V, Magdic M, Markovic R. Diabetes and metabolic syndrome as risk factors for COVID-19. *Diabetes Metab Syndr* 2020;14:671–7.
20. Hackett G, Kirby M, Wylie K, *et al*. British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction in Men – 2017. *J Sex Med* 2018;15(4):430–57.
21. McGonagle D, O'Donnell JS, Sharif K, *et al*. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020 (https://doi.org/10.1016/S2665-9913(20)30121-1; accessed 11 June 2020).
22. Zhang J, Wu Y, Wang R, *et al*. Bioinformatic analysis reveals that the reproductive system is potentially at risk from SARS-CoV-2. OSFPreprints 2020 (https://osf.io/j2uyw; accessed 11 June 2020).
23. Shen Q, Xiao X, Aierken A, Liao M, Hua J. The ACE2 Expression in Sertoli cells and Germ cells may cause male reproductive disorder after SARS-CoV-2 Infection. OSFPreprints 2020 (https://osf.io/fs5hd; accessed 11 June 2020).
24. Zhang XJ, Qin JJ, Cheng X, *et al*. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell Metabolism* (2020); https://doi.org/10.1016/j.cmet.2020.06.015.
25. Spiegeleer A, Bronselaer A, Teo JT, *et al*. The effects of ARBs, ACEIs and statins 1 on clinical outcomes of 2 COVID-19 infection among nursing home residents. *medRxiv* (preprint); doi: https://doi.org/10.1101/2020.05.11.20096347.
26. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med* 2020;201(12):1557–9 (www.atsjournals.org/doi/abs/10.1164/rccm.202003-0693LE; accessed 11 June 2020).
27. De Groot NG, Bontrop RE. COVID-19 pandemic: is a gender-defined dosage effect responsible for the high mortality rate among males? *Immunogenetics* 2020. doi: 10.1007/s00251-020-01165-7 [Epub ahead of print].
28. Kadel S, Kovats S. Sex hormones regulate innate immune cells and promote sex differences in respiratory virus infection. *Front Immunol* 2018;9:1653.
29. Nowak J, Pawłowski B, Borkowska B, *et al*. No evidence for the immunocompetence handicap hypothesis in male humans. *Sci Rep* 2018;8(1):1–11.
30. Wu FCW, Tajar A, Beynon JM, *et al*. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363(2):123–35.
31. Hackett G, Kirby M, Edwards D, *et al*. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. *J Sex Med* 2017;14(12):1504–23.
32. Shastri A, Wheat J, Agrawal S, *et al*. Delayed clearance of SARS-CoV2 in male compared to female patients: High ACE2 expression in testes suggests possible existence of gender-specific viral reservoirs. medRxiv (preprint) 2020 (https://doi.org/10.1101/2020.04.16.20060566; accessed 12 June 2020).
33. Pozzilli P, Lenzi A. Commentary: Testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism* 2020. doi.org/10.1016/j.metabol.2020.154252 [Epub ahead of print].
34. Mohamad NV, Wong SK, Wan Hasan WN, *et al*. The relationship between circulating testosterone and inflammatory cytokines in men. *The Aging Male* 2019;22:129–40.
35. Maggio M, Basaria S, Ceda G, *et al*. The Relationship Between Testosterone and Molecular Markers of Inflammation in Older Men. *J Endocrinol Invest* 2005;28(11 Suppl Proceedings):116–9.
36. Nettleship JE, Pugh PJ, Channer KS, *et al*. Inverse relationship between serum levels of interleukin-1β and testosterone in men with stable coronary artery disease. *Horm Metab Res* 2007;39(5):366–71.
37. Chen J, Jiang Q, Xia X, *et al*. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. Preprints 2020. 202003.0191.v1 (www.preprints.org/manuscript/202003.0191/v1; accessed 12 June 2020).
38. Kirby M, Hackett G, Ramachandran S. Testosterone and the Heart. *Eur Cardiol* 2019;14(2):103–10.