

# Review of: "[Hypothesis] The protective role of Testosterone in COVID-19"

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**Potential competing interests:** No potential competing interests to declare.

Although numerous studies have shed light on the importance of testosterone (and sex hormones in general) in the pathogenesis of SARS-Cov-2 infection, I think the topic still has many open questions.

Therefore, I agree with the purpose of the article.

The protective role of testosterone in SARS-Cov-2 infection seems to me a certainty rather than a hypothesis.

The complexity lies in understanding:

1. Which is the specific weight of transient hypogonadism in COVID-19. Does it only represents a proxy of ageing or does it have an additional action in determining the onset of a severe SARS-CoV-2 infection?
2. How is it possible that a disease, which recognize the male gender (androgen sensitivity) as risk factor, could recognize testosterone as a protective factor? Camici M, Zuppi P, Lorenzini P, et al. Role of testosterone in SARS-CoV-2 infection: A key pathogenic factor and a biomarker for severe pneumonia. *Int J Infect Dis.* 2021 Jul;108:244-251. doi: 10.1016/j.ijid.2021.05.042. Epub 2021 May 20. PMID: 34023492; PMCID: PMC8135187.

Interestingly, also in myocardial infarction pathogenesis, considered as an inflammatory disease, it has been underlined the important role of testosterone in regulating endothelial homeostasis. Pugh PJ, Channer KS, Parry H, Downes T, Jone TH. Bio-available testosterone levels fall acutely following myocardial infarction in men: association with fibrinolytic factors. *Endocr Res* 2002;28:161–73

So, I suggest to integrate the article with others example of "inflammatory diseases" worsened by testosterone depletion (e.g. myocardial infarction). Secondly, I would explain more in detail how the depletion of the SIRT1 pathway can increase inflammation and thrombogenesis, loss of cellular energy, can impair metabolism, proliferation, and cell survival (biochemical mechanisms). Curry AM, White DS, Donu D, Cen Y. Human Sirtuin Regulators: The "Success" Stories. *Front Physiol.* 2021 Oct 21;12:752117. doi: 10.3389/fphys.2021.752117. PMID: 34744791; PMCID: PMC8568457.

Third I would better explain the concept of androgen sensitivity.