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Male Vulnerability in COVID-19: What we Need to Know…

Arbi Pecani[1*], Silvana Bala[2]

[1] Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania
[2]Department of Pulmonology, University Hospital "Shefqet Ndroqi", Tirana, Albania

Address for correspondence: Arbi Pecani*, Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania. Email: arbipecani@gmail.com

Researchers have shown that immune response differs between genders. Females tend to develop a stronger immune response to infections and better elimination of the pathogen due to the greater expression of Toll-like receptors. Despite age, females show a greater proliferation of regulatory T cells, immunoglobulin and higher B cell number compared to males of the same age. Quantitative gene expression profiles of B cells, appears upregulated in females compared to males. Considering all above and the different effects of sex hormones that modulate the activity of immune cells we can completely explain the differential immune response between genders. Estrogen and progesterone contribute to a reduced innate immune response that can break out an acute inflammatory cytokine storm while on the other hand these hormones improve immune tolerance and antibody production as part of the adaptive immune response; testosterone leads to increased susceptibility and severity toward pathogenic infections (1).

COVID-19 is a disease caused by the new pathogen SARS-CoV2 presenting with pulmonary involvement in 30%-40% of the cases (2). Ambrosino et al. described a greater susceptibility of males to COVID-19 while other studies showed a greater clinic severity and mortality in COVID-19 for males (3). Despite comorbidities and age that play an important role in COVID, there is no doubt that gender differences influence as well. It was hypothesized that testosterone has an important role in the clinical course of the disease due to its AR receptor located on the X chromosome resulting in a polymorphism within the gene itself; patients with the "short" version of the receptor activate more testosterone and subsequently the PRSS2 gene, a co-receptor of the virus, favoring its entry through the ACE receptor (4).

Sex chromosomes contribute to genetic differences and may have an important role in the function of human systems and even on disease outcome. Females have two copies of the X chromosome that expresses several genes implicated in immune response. Beside AR gene, chromosome X contains genes that code toll –like receptors 7 and 8, genes that regulate the activity of B and T cells including FOXP3 and many other genes coding for cytokines. Although most of the alleles on the X chromosome are silenced, many escape inactivation and are over expressed in females. In this regard, it's interesting how the ACE2 gene also maps on the X chromosome but the differential levels of ACE2 expression influence the severity of COVID-19. It is known that ACE2 is expressed in heart, lungs, testicles, thus males seem to have worse outcome of COVID-19. On the other hand, reduced levels of ACE2 in lungs attributed to the effect of estrogen (estriol), results in a better outcome of COVID-19 in women (5).

In conclusion, all results of the studies point out, gender as an important risk factor for mortality and response to COVID-19. In this regard, we

should take into account gender differences when treating patients with COVID-19 toward a personalized medicine as well as in scientific research in this regard.

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