Relation between Sex Hormones and COVID-19

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ABSTRACT

Coronavirus is one of the major viruses that mainly attack the human respiratory system. There are similarities in symptoms between COVID-19 and earlier Coronavirus infections such as fever, dry cough, however, COVID-19 showed unique clinical feature, that involves the targeting of the lower airways as evident by upper respiratory tract symptoms such as rhinorrhea, sneezing and sore throat.

The severity of COVID-19 as indicated by hospitalization, admission to intensive care unit, has been greater in men than women. Many hypotheses have been found to explain this difference in susceptibility and severity of the disease. The severity of COVID-19 is considered the main factor in outcomes of viral infection. Estrogen has immunoenhancing effect on the immune system, while testosterone has immunosuppressive role, also progesterone inhibits inflammatory innate immune response. In this review, it was concluded that sex hormones have a role in COVID-19 severity. It was concluded that estrogen and progesterone reduce disease severity in contrast, testosterone increase the severity and susceptibility for COVID-19.

Keywords: sex hormones; immunity; Covid – 19

INTRODUCTION

COVID-19 and its relation to gender: Outbreak of COVID-19 infection caused international risk on health in the world SARS-COV-2 that cause COVID-19 infection is similar to SARS COV which responsible for occurrence of acute respiratory syndrome. Data suggested that fewer women are dying from COVID-19 Pandemic than men, hospitalization rates of death admission to intensive care unit has been two – fold greater in men than women in Europe. In addition, most countries recorded high range of death in men compared with women. Sex – bias factor has important role in immunological response to viral infection. In Wuhan, mortality, morbidity and admission to intensive care unit are found at high rates among men than women.

Differences in morbidity and mortality in patients with COVID-19 may result from levels of androgens and estrogens. Disparity in COVID-19 severity may be explained by differences in immune response, sex hormones, genetic factors and gender – behaviour differences. Gender related factors may affect COVID-19 severity.

ABSTRACT

Sex hormones and immunity: Sex based difference in immune response can be mainly attributed to sex hormones. Sex hormones have receptors on immune cells such as B- cells, T-cells and monocytes which, in turn, affect innate and adaptive immune response. Estrogen, progesterone and testosterone have impact on antibodies production by B-cells and activity of granulocytes and natural killer cells. Estrogens have important role in immune response through stimulation the proliferation and differentiation of monocytes and lymphocytes. It has shown that estrogen activate the differentiation of B-cells. Additionally, estrogen exert anti-inflammatory effect by activation of T-lymphocytes.

Estrogen exert the effect on immune cells by estrogen receptors. Estrogen Receptors activate development of immune cells and regulate innate and adaptive immune response. On the other hand estrogen increase Gamma – interferon IFN – levels which, in turn, regulate all cells of the immune system, this activation can explain several autoimmune disease in women. Progesterone lowered inflammatory response by interfering with NF – KB pathway which, in turn, decrease production of proinflammatory cytokines. In mice infected with influenza A virus, declined pulmonary inflammation, in addition progesterone can inhibit TLRs and NF-KB production in macrophage, supporting the concept, that progesterone might cause inhibition of innate immune response. Progesterone has immune suppressive properties by suppressing TLRs through decreasing miR – 155 in macrophage which in turn, suppresses TLRs induced IL-6 and IFN-β production. Progesterone has anti-inflammatory effect, it’s showed that progesterone inhibit gene expression of IL – 1B, IL – 6, IL – 8 and TNF – α induced by E. coli. In the cystol, progesterone binds to progesterone receptor, this binding interfere with NFκB resulting in reduction in the inflammatory response (Fig 2). Testosterone suppressed inflammation in patients with diabetes, prostate cancer and coronary artery disease through the decrease in pro inflammatory cytokines IL 1B, IL – 6 and TNF – α and increase IL – 10 as anti-inflammatory cytokines. On the other hand, treatment with testosterone decreased pro inflammatory cytokines in old hypogonadal men. Testosterone is considered as immune – suppressive agent, which may explain higher severity and susceptibility of viral infection such as COVID-19 in men.

Fig 1: Sex-disaggregated numbers of COVID-19 cases, hospitalizations, and deaths per 100,000 people in New York City.

Fig 2: Progesterone reduces inflammatory response P4: progesterone, PR: progesterone receptor, PAMPS: pathogen associated molecular patterns, PRRs: pattern recognition receptors.
Sex hormones and viral infection: Corona virus SARS -- COV-2 use ACE2 as receptor for entry in infected cell . On the other hand, spike protein of the virus activated by transmembrane serine protease 2, TMPRSS2 25. ACE2 expression has important role in susceptibility of epithelial cells in airways to the infection with SARS -- COV 23. Expression of ACE2 and TMPRSS2 can be influence by sex hormones . ACE2 protein are highly expressed in male mice than female , while estrogen downregulate expression of ACE2 . So this may explain that SARS - COV is more available in males than females .

Spike protein is necessary for viral entry in target cells and for virus spread . TMPRSS2 activates spike protein of virus for viral entry through cell membrane 26. Androgens activate upregulation of TMPRSS2 expression and this may explain the male predominance in COVID-19 infection ,while Estrogen lowered ACE2 expression in mice . It's reported that androgens upregulated TMPRSS2 expression in prostrate cancer cell lines 28. Some researchers concluded that TMPRSS2 inhibition may prevent viral entry . It's revealed in one study that use of TMPRSS2 in combination with hydroxyl chloroquine has effective role against SARS-COV-2 27. Androgen receptor mediated TMPRSS2 transcription , elevation of TMPRSS2 in men may explain sex based disparities in the severity of COVID-19. In a recent study found that plasma concentrations of ACE2 were higher in men than women 29. also high activity of ACE2 was found in male rats compared to females 30. Androgen receptor elements are located on transcription site of TMPRSS2 31. Androgens can affect TMPRSS2 in prostate, as well as in the lung . It was shown that patients with prostate cancer receiving androgen inhibitors have lower risk of COVID-19 compared to those who didn't received the drug 32. SARS - COV-2 infection downregulated ACE2 in tissues reducing the protective role of ACE2 in lungs , heart , kidney and gut 33. Glycoprotein of SARS-CoV-2 is activated by TMPRSS2,which stimulates virus entrance ,androgen receptor upregulates TMPRSS2 transcription (Fig 3).

Recent study recorded that ACE2 expression is elevated in Lung and trachea in obese male mice in comparison with obese females , also TMPRSS2 expression was higher in trachea of obese male mice compared with females 34. Lungs of male mice have high expression of an dragon receptors than females 35. On the other hand , ACE2 was highly expressed by synthetic androgen and downregulated by androgen receptor blocker 37.

CONCLUSION
its concluded that sex hormones have relation with COVID-19 severity . It was concluded that estrogen and progesterone reduce disease severity in contrast , testosterone increase the severity and susceptibility for COVID-19 .

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