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ORIGINAL ARTICLE

Relation Between Sex Hormones and Covid-19

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ABSTRACT

Coronavirus is one of the major viruses that mainly attack 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 involve 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 difference in immune response between sex is consider 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 , 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 .

Keywords: sex hormones ; immunity ; Covid – 19

INTRODUCTION

COVID 19 and its relation to geneder: Outbreak of COVID-19 infection caused international risk on health in the world SARS COC-2 that cause COVID-19 infection is similar to SARS COV which responsible for occuarance of acute respiratory syndrome [1] . Data suggested that fewer women are dying from COVID-19 Pandemic than men , hospitalization rated of death admission to intensive care unit has been two – fold greater in men than women in Europe [2] . 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 [3].In Wuhan , mortality , morbidity and admission to intensive care unit are found at high rates among men than women [4] .

Differences in morbidity and mortality in patietswith COVID-19 may resulted from levels of androgens and estrogens [5] .Disparity in COVID-19 severity may be explained by differences in immune response,sex hormones, genetic factors and gender – behaviour differences [6] . Geneder related factors may affect COVID-19 severity,angiotensin converting enzyme 2(ACE2) as well as serine protease TMPRSS2 participate in viral infection ,sex hormones can affect both factors [7] .It was reported the greater rates of hospitalization and death among men than women in New York city (Fig 1).

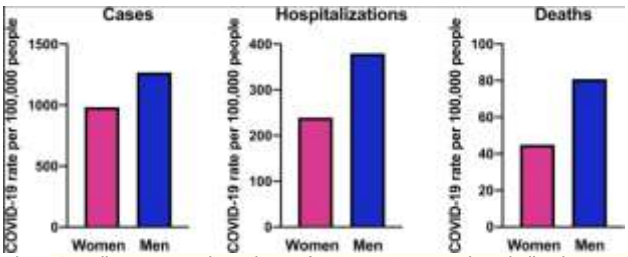

Fig 1: Sex-disaggregated numbers of COVID-19 cases, hospitalizations, and deaths per 100,000 people in New York City [8]

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 [9] . Estrogen , progesterone and testosterone have impact on antibodies production by B- cells and activity of granulocytes and natural killer cells [10] .

Estrogens have important role in immune response through stimulation the proliferation and differentiation of monocytes and lymphocytes [11] . It has shown that estrogen activate the differentiation of B- cells [12] . additionally , estrogen exert anti – inflammatory effect by activation of T- lymphocytes [13].

Estrogen exert the effect on immune cells by estrogen receptors .Estrogen Receptors activate development of immune cells and regulate innate and adaptive immune response [14] . On the other hand estrogen increase Gamma – interferone IFN levels which , in turn , regulate all cells of the immune system , this activation can explain several autoimmune disease in women [15] .

Progesterone lowered inflammatory response by interfering with NF – KB pathway which , in turn , decrease production of proinflammatory cytokines [16] . Progesterone treatment 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 migh cause inhibition of innate immune response [17] . Progesterone has immune suppressive properties by suppressing TLRs through decreasing miR – 155 in macrophage wich in turn ,suppresses TLRs induced IL-6 and IFN-β production [16] .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 [18] .In the cystol,progesterone binds to progesterone receptor .this binding interfere with NFkB 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 [19] . On the other hand , treatment with testosterone decreased pro inflammatory cytokines in old hypogonadol men [20] . Testosterone is considered as immuno – suppressive agent , which may explain higher severity and susceptibility of viral infection such as COVID-19 in men [21].

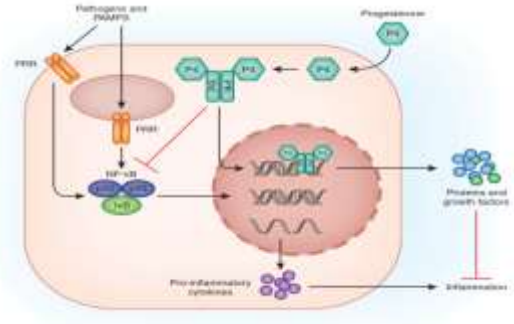

Fig 2: Progesterone reduces inflammatory response P4 :progesterone,PR:progesterone receptor .PAMPs: pathogen associated molecular patterns.PRRs:pattern recognition receptors [16]

Sex hormones and viral infection: Corona virus SARS – COV-2 use ACE2 as receptor for entery in infected cell . On the other hand, spike protein of the virus activated by transmembrane serine protease 2, TMPRSS2 [22]. 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 [24] .

Spike protein is necessary for viral entery in target cells and for virus spread . TMPRSS2 activates spike protein of virus for viral entery through cell membrane [25] . 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 [26] . 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 COVD-19 [28] .

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 receive the drug [32] . SARS . COV-2 infection downvergluted ACE2 in tissues reducing the protective role of ACE2 in lungs , heart , kidney and gut [33] .S glygoprotein of SARS-CoV-2 is activated byTMPRSS2,which stimulates virus enterance ,androgen receptor upregulates TMPRSS2 transcription (Fig 3).

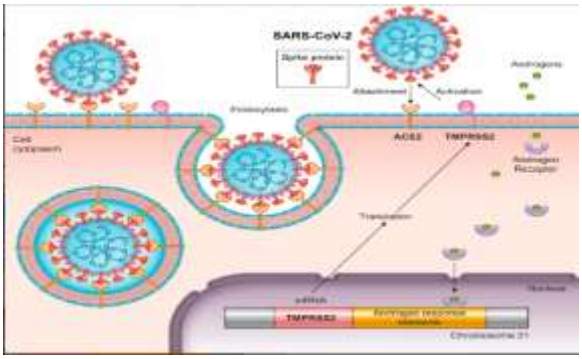

Fig 3: .Androgen receptor activates TMPRSS2 transcription which facilitates SARS-CoV-2 virus –cell membrane fusion [34] .

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 [35] . Lungs of male mice have high expression of an dragon receptors than females [36] . 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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