

Role of estrogen in the management of COVID – 19 in females

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ABSTRACT

With the increase, the spread of COVID-19 its effect can be seen on health care systems seek innovative treatment ways as the need of the hour. The suspected leading cause of COVID-19 is due to the response to inflammations and the cytokine storm, which majorly damages the lung tissue. The difference in response to the vaccine can be seen due to different sex. Moreover, age-related decrease in sex steroid hormones like Estrogen as well as testosterone can promote pro-inflammatory raise in older individuals which in turn increases the risk of COVID-19 related adverse outcomes. Such sex hormones have the capacity of mitigating inflammatory response and can also provide promising therapeutic benefits for patients suffering from COVID-19. Moreover, over above the effects of on any ERS, these drugs showed useful ancillary properties. Most showed to highlight broader roles in mitigating viral replication by the ER-independent mechanisms as mentioned. Data simplifies ER modulation an apt pharmacological approach for restricting storm and thus prevents the inflammation due to COVID-19. Mainly the application of or tissue-selective estrogen complex can provide a pharmacological response. Such treatment options can be fruitful for both sexes in the early phase of such disease condition to prevent further progression of the disease to severe forms.



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INTRODUCTION

(SARS-CoV-2) is causing COVID-19 pandemic, which has already infected more than 8 million people and killed more than 550 000 globally [1, 2]. The search for an appropriate therapy is ongoing but is in wait to get success [3]. Thus we should look outside the box and consider the biological reasons as in why women are less effected from COVID-19 in compar-

ison to men [4].

The suspected primary cause of COVID-19 is the inflammatory response and the cytokine storm, which majorly damages the lung tissue [5]. The difference in response to the vaccine can be seen due to different sex [6]. Moreover, age-related decrease in such sex steroid hormones, mainly estrogen and testosterone can promote pro-inflammatory raise in older individuals which in turn increases the chance of COVID-19 related adverse outcomes [7]. It is found that sex hormones hold the capacity of mitigating inflammatory response and can also provide better therapeutic benefits for patients suffering from COVID-19 [2].

COVID – 19 in males Vs females

Male as well as females show prominent differences instead of several infective diseases which are caused by several viral pathogens [8].

Even though data reveals that COVID-19 has almost the same numbers of countable cases between men

and women, however significant sex differences in terms of death rate and even in terms of vulnerability to Covid-19 is being observed. Recent data reveals that more men are dying than women, potentially it can be because of sex-based immunological differences [9, 10]. One more possible explanation can be the role of estrogens. Viral infections are found to vary between men and women in terms of prevalence, intensity and various pathogenic mechanism [11, 12].

SARS-CoV2 ace/angiotensin-II receptor modulation and estrogen therapy

Virus SARS-Cov has infected and destroyed the lives of many human being starting from the end of 2019 and the beginning of 2020, which is continued [13]. Even though science and technology are most advanced, most of the countries are still struggling to overcome this pandemic [14]. Virus SARS-CoV-2 have RNA as its single-stranded genetic material [15]. Human coronavirus comes under the category of second genera corona viridae family [16]. The outer membrane of this virus is made of protein which is known as surface protein [17].

Initially, it was believed that this particular infectious disease would transmit from animal to human, but later it was clear that it spreads via human to human transmission [18, 19]. Coronavirus spread this infection by inserting its genetic material, i.e. single-stranded RNA genome into the host cell and immediately which starts its replication and thus produces ER stress in mainly three ways which are

- a) Forming double-membrane vesical (DMV),
- b) Glycosylating viral proteins
- c) Depleting ER membrane lipids.

However, estrogen hormone can lower the burden of ER stress, and it does by activating unfolded protein response (UPR) [20]. Once ER stress is experienced, then to counteract estrogen hormone binds to its receptor ER α which is present in the cytoplasm as a result of this binding, rapid activation of phospholipase C enzyme happens which cleaves its substrate PIP2 into DAG (diacylglycerol) and IP3 (inositol triphosphate) [21, 22].

Estrogen controls cytokines storm by initiating suppression of IL-1 β and IL-6 production, as a result of which it reduces the risk of any acute lungs inflammation in women. Estrogen might also play a significant role in lowering the exhaustion of T cells caused by cytokines storm. However, the protective mechanism by Estrogen in reducing ER stress is not reported and established yet as studies estrogen show it's a crucial role by reducing ER stress, caused by the infection [23].

Estrogen regulation of COVID-19 through ACE – efficient in females

SARS-CoV-2 is dependent on angiotensin-converting enzyme 2 (ACE2) for the cell entry, which in turn engages serine protease transmembrane protease serine 2 (TMPRSS2) for priming viral spike protein. Thus both ACE2 & TMPRSS2 are important for SARS-CoV-2 to cause this infection. It is found that E₂-treated NHBE cells expresses lower levels of ACE2 mRNA in comparison with treated controls. E₂-driven downregulation of ACE2 expression is helpful in this regard as the efficiency of ACE2 usage by SARS-CoV is found to be an essential determinant in terms of viral replication as well as disease severity.

Estrogen receptor modulators a possible “adjuvant drugs”

Endogenous estrogens show a protective effect, which is highlighted by drugs of the class SERMs. These drugs show agonist as well as antagonist modulatory response of the ER subtypes, which in turn shows inflammatory responses.

A preclinical study explained the need of sex hormones in a particular single-gender – highlighting the vulnerability of SARS-CoV virus where both types of mice were infected with SARS-CoV. Male mice were found to be more susceptible to SARS-CoV infection compared to female mice [24].

Moreover, over above the effects of SERMs on any ERS, these drugs showed useful ancillary properties. Most SERMs showed to highlight broader roles in mitigating viral replication by the ER-independent mechanisms as mentioned [25].

CONCLUSION

Data simplifies ER modulation an apt pharmacological approach for restricting cytokine storm and thus prevents the inflammation due to COVID-19. Mainly the application of SERMs or tissue-selective estrogen complex can provide a favourable pharmacological response. Such treatment options can be fruitful for both sexes in the early phase of such disease condition to prevent further progression of the disease to severe forms.

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Conflict of Interest

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