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COVID-19 pandemic, endocrine disruption and insights for Endocrinologist

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The catastrophe of corona virus disease (COVID-19) pandemic continues to exert a significant impact on the health care system all over the world causing unprecedented morbidity and mortality. The understanding of this novel corona virus gradually deepening along with the passage of time and now it is clear that the effects extend far from the respiratory system.

The corona virus responsible for COVID-19 is severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which gets its cellular access through the angiotensin-converting enzyme 2 (ACE 2) receptor that requires the trans-membrane serine protease 2 (TMPRSS 2) protein. ACE 2 and TMPRSS 2, both are widely expressed in different important endocrine glands including endocrine pancreas causing disruption of pituitary, thyroid, adrenal and gonadal functions in patients with COVID-19. The involvement of endocrine system in COVID-19 has progressively acquired clinical relevance as an "endocrine phenotype" of COVID-19. The resulted disruption in endocrine function raised a significant interest regarding its long-term effect on the endocrine system in COVID-19 survivors.

SARS-CoV-2 and Endocrine System

SARS-CoV-2 gains its cellular access via the ACE 2 receptor. The spike glycoprotein constitutes S1 and S2 subunits protrude from the surface of the virus and is essential for its binding to ACE 2.[1,2] After binding to ACE 2, the S1 subunit is dissociated with the ACE 2 receptor with the help of trans-membrane serine protease 2 (TMPRSS 2) [Fig.1].[3] Subsequent conformational change provides the S2 subunit for increased stability and membrane fusion.[4] ACE 2 receptor binding is crucial for SARS-CoV-2 to gain cellular access. ACE 2 mRNA is expressed in several human endocrine glands, e.g., pituitary, pancreas, thyroid, adrenal, ovaries, and testes.[5]

The endocrine system not only possesses the necessary ACE 2 receptor but also the TMPRSS 2 protein to provide the cellular access of SARS-CoV-2 and subsequent disruption of endocrine function in a

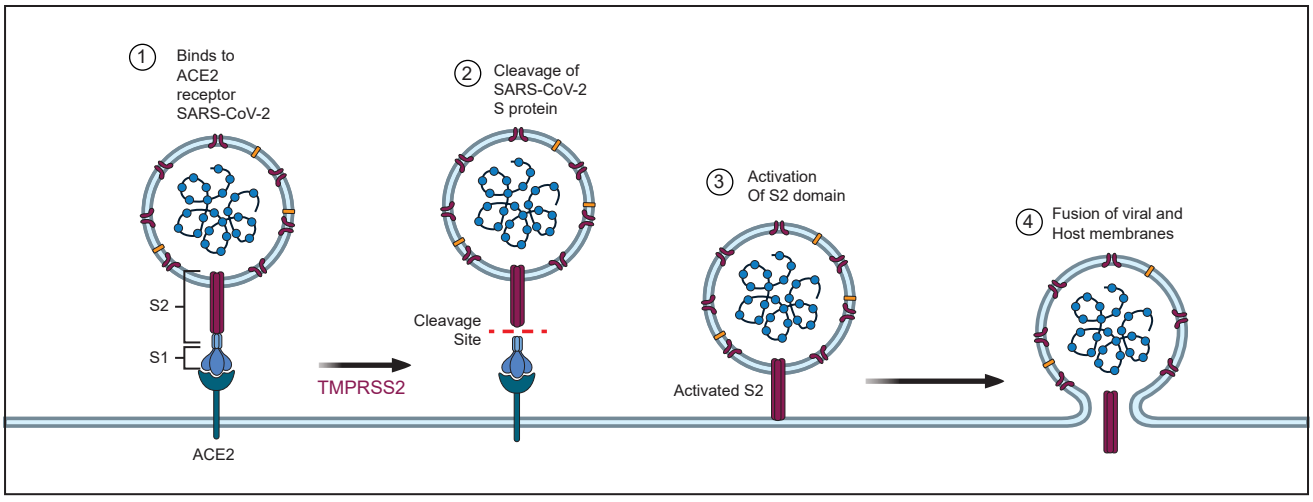

Figure 1: Binding of the SARS-CoV-2 virus to the ACE2 receptor. The SARS-CoV-2 spike protein binds to ACE2. In the presence of transmembrane serine protease receptor 2 (TMPRSS2), the S1 subunit dissociates inducing a conformational change that increases S2 subunit stability, permitting membrane fusion. Created with Biorender.com[3,4]

patient with COVID-19.

The Pituitary gland

The Pituitary gland is one of the highly vascularized organs. Vascular endothelium has abundant expression of ACE-2 receptor and is vulnerable to damage by COVID-19 infection.[6] Moreover, severe illness results in a prothrombotic and hypercoagulable state characterized by high fibrinogen, elevated D-dimer, thrombocytopenia, and increased risk of pituitary apoplexy in patients with pre-existing pituitary tumors with COVID-19 infection.[7]

Sufficient data are still lacking regarding pituitary function following COVID-19 infection.

The Thyroid gland

Thyroid follicular cells have ACE 2 mRNA and potential for cellular access by SARS-CoV-2.[8] Autopsy finding revealed both follicular and para-follicular cells of the thyroid gland were extensively damaged in patients who died of SARS.[9]

COVID-19 infection may cause sub-acute thyroiditis.[10] Among patients infected with COVID-19 requiring intensive care unit support were more likely to develop thyrotoxicosis.[11] Patients requiring intensive care unit admission, 10.8% developed overt thyrotoxicosis and 0.7% had hypothyroidism. Patients having higher IL-6 levels with greater inflammatory response were more prone to develop thyrotoxicosis.[12] SARS-CoV-2 infection may trigger autoimmune thyroid diseases like sub-acute thyroiditis and Graves' thyrotoxicosis.[13]

Primary hypothyroidism was noticed in 4.9% of patients after three to six months of SARS, the majority of the patients revert to a euthyroid state after nine months of SARS.[14] Thyroid function tests may be acutely altered with COVID-19 infection and returned to baseline within three to six months following recovery.[15] Features of "long COVID'' like fatigue, malaise, myalgia, and brain fog may simulate with thyroid dysfunction and have clinical significance.

The Adrenal Gland

ACE 2 receptors are abundantly present in the inner two layers of the adrenal cortex, zona fasciculata (producing glucocorticoid) and zona reticularis (producing androgen). TMPRSS 2 is widely expressed in all three layers of the adrenal cortex. Patients who died of COVID-19, adrenal ischemic necrosis, focal inflammation, and hemorrhage were found at autopsy.[16] Hypocortisolism was found in 39.4% of patients at ≥3 months after acute COVID -19 infection.[14]

Hyponatremia is a common accompaniment in patients suffering from COVID-19, may be up to 30% of patients have serum sodium <135 mmol/L[17] and it indicates a worse outcome.[18] In most of the patients with acute COVID-19, adrenal functions were preserved. An elevated level of cortisol within 48 hours of admission was associated with higher mortality. Long COVID symptoms like fatigue, postural drop, and cognitive impairment mimicking adrenal insufficiency are not actually due to cortisol deficiency. The use of exogenous steroids in many patients of acute COVID-19 may impair adrenal function by suppressing the hypothalamo-pituitary-adrenal axis.

The Gonads

ACE 2 receptors are present in testicular germ cells, Leydig cells, and Sertoli cells.[19] Expression of ACE 2 and TMPRSS 2 mRNA are up-regulated in patients with COVID-19.[20] Evidence suggests that the morphology of the testes may be altered and also damaged by SARS-CoV-2. The testicular function is impaired leading to reduced sperm count, mobility, and morphology. Also, there is a chance of development of epididymo-orchitis.[21] There may be also reduced concentration of total testosterone, LH, and FSH and immune-mediated hypogonadism.[22]

ACE 2 and TMPRSS 2 receptors are present in the female reproductive system, though to a lesser extent than the male reproductive system. In one study, 46% of women had experienced a new onset of dysmenorrhoea, menorrhagia, or variability of duration of menstrual cycle[23] and post-menopausal bleeding.[24] Serum anti-Mullerian hormone was found to be lower in patients with COVID-19.[25]

The Endocrine Pancreas

ACE 2 receptors are abundantly expressed in pancreatic β-cells. Human endocrine pancreatic cells are vulnerable to infection by SARS-CoV-2[26] and viral RNA has been detected in the β-cells of patients with COVID-19.[27]

Patients with diabetes are the worst sufferer of COVID-19 with a 50% higher risk of fatal outcomes than patients without diabetes. Depending on the global region, 20-50% of patients with COVID-19 had diabetes with a higher rate of hospitalization, ICU support, morbidity, and mortality. There is a bidirectional relationship between diabetes and COVID-19, worsening of glycemic homeostasis in pre-existing diabetes, often complicated by

ketoacidosis and hyper-osmolarity. There is new onset of diabetes due to β-cell dysfunction and damage.[28] Patients with diabetes with COVID-19 need special attention.

Conclusion

At the end of the second year of the COVID-19 pandemic, it is clear that the impact of COVID-19 is beyond the respiratory system and that impairs the health and quality of life. The endocrine system is particularly vulnerable to COVID-19 infection. Apart from the significant effect on the endocrine pancreas and serious consequences on glycemic homeostasis; pituitary, thyroid, adrenal and gonadal functions are also affected. COVID-19 become an emerging challenge to the healthcare system, its long-term effect on the endocrine system is an area of future priority research.

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