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REVIEW

The Stress of COVID-19: Playing Havoc with the Hormones-A Review

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ABSTRACT

Severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) has affected millions of people across the world engendering an unprecedented pandemic. Coronavirus disease (COVID)-19 can present asymptomatic or in the form of the acute respiratory syndrome, viral pneumonia,or sepsis. Due to the novelty of the disease, the endocrine manifestations are not fully understood. It becomes indispensable to address the underlying endocrine disruptions contributing to the severe form of illness and thereby increasing the mortality.We discuss here the SARS-CoV-2 virus and endocrine reverberations based on the research with structurally similar SARS-COV-1. SARS-CoV-2 enters the body via its attachment to the angiotensin-converting enzyme 2 (ACE2) receptors. Apart from lungs, ACE2 expression on various organs can lead to endocrine perturbations. In COVID-19 infection, pre-existing endocrine disorders warrant cautious management and may require replacement therapy. COVID-19 and its repercussions on hormones are discussed extensively in this review.

1. Introduction

The coronavirus disease (COVID)-19 pandemic caused by the novel severe acute respiratory syndrome corona virus (SARS-CoV)- 2 has led to worldwide havoc and a significant impact on psychological wellbeing. In March 2020, the World Health Organisation (WHO) declared COVID-19 a global pandemic. The existing data suggest that stress and anxiety have doubled during this pandemic. Psychological and physiological stress increases serum cortisol levels along with its bioavailability by stimulation of the hypothalamic-pituitary-adrenal axis, decreasing the number of cortisol-binding globulin, and its metabolism [1,2]. Increased cortisol level is an integral response to stress, activating adaptive changes in the immune system, metabolism, and cardiovascular function. Patients with Diabetes mellitus are considered to be under the high-risk category for having serious illness modality in case of contact with COVID-19 infection. Furthermore, other endocrine diseases such as adrenal insufficiency, mal-nutrition, and obesity can also be strongly impacted by COVID-19 [3,4].

2. Methods

It is well known that COVID 19 can produce a lot of stress; nevertheless, how much could this stress produce changes in our hormones? Keeping this research question

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in mind, we did a literature search using the key words COVID-19, SARS-CoV-2, SARS-CoV-1, endocrine, hormones, and related terms in the medical databases including Google Scholar, MedARXiv, PubMed, Cochrane and Web of Science databases. In addition to these, references were spotted through a manual search of bibliographies and via the citations in the articles. COVID-19 infection and its repercussions on hormones are discussed extensively in this review. This review tries to address the effect of the stress response on hormones and its catastrophic effect on the COVID-19 patient.

2.1 Epidemiology

The outbreak of COVID-19 in Wuhan is speculated to be associated with wild animals. According to WHO, Wuhan seafood market environmental samples were tested positive for SARS-CoV-2 and it is suggested that bats may be the origin of COVID-19 (the host of more than 30 coronaviruses) [5,6]. The bats are considered the natural reservoir of SARS-CoV and MERS-CoV, and spread to humans [7]. The short RNA-dependent RNA polymerase (RdRp) region (RaTG13) from a bat coronavirus, was nearest to SARS-CoV-2 with an identity of 96.2-98.7% in whole-genome sequence [8-11].

The mean incubation period is around 5.2 days. A research in Wuhan on 85 serious patients (median age 65yrs) concluded that most of the mortality was due to multi-organ failure such as respiratory failure(94%), acute respiratory distress syndrome (ARDS(74%) and shock (81%) [12]. In parallel to this high prevalence of multiorgan failure, a high level of D-dimer, fibrinogen, and prolonged thrombin time have also been observed in severe forms of the disease [13].

2.2 Pathogenesis

Coronaviruses are single-stranded ribonucleic acid (RNA) (30kb), positive-sense, and enveloped viruses, infecting various host species [14]. They are broadly divided into four genera based on their genomic structure; alpha, beta, gamma, and delta. Alpha and beta coronavirus causes infection in mammals only [15]. SARS-CoV-2 are classified as beta coronaviruses. The pathogenesis of COVID-19 entails the entry of inhaled SARS-CoV-2 virus and binding to the epithelial cells in the nasal cavity causing replication. After entering the respiratory system,it lodges in the lung parenchyma and interacts with angiotensin-converting enzyme(ACE)- 2 receptor to ingress into host pneumocytes. The plasma or serum of COVID-19 patients has demonstrated viral RNA showing viremia [16], this implicits that the virus is also available free to interact with ACE_2 expressed in various tissues and a number of endocrine organs including the thyroid, pituitary, pancreas, adrenal glands, testis, and ovary [17].

2.3 COVID-19 and its effects on Different on Endocrine Organs

2.3.1 Pituitary gland

Alteration in the function of the pituitary in severe acute respiratory syndrome (SARS) was first documented by Leow et al. [18] An evaluation of 61 patients who survived the SARS outbreak found evidence of central mild hypocortisolism (40%) and hypothyroidism (5%) [18]. Hypothalamic and pituitary tissues both express ACE2 and could be the vital target in the case of COVID-19 [19]. COVID-19 patients with pituitary-hypothalamic disorders usually have diabetes insipidus (DI) that can cause insensible water loss due to fever eventually resulting in hypernatremia [20], requiring extra precautions. Dopamine synthetic pathways alteration has also been implicated in the pathophysiology of COVID-19 [21].

Anterior pituitary cells have illustrated changes in biopsy of SARS-CoV patients [22]. The number of corticotrophs,thyrotrophs,and somatotrophs was decreased and vice-versa was seen in the number of gonadotrophs and lactotrophs. These results correspond with biochemical abnormalities of an increased level of luteinising, follicle stimulating hormone, and prolactin as reported in Chinese literature earlier [23].

Postviral cataclysm:

Postviral syndrome manifests as low moods, low energy level, and dizziness. It is associated with hypocortisolism (postviral) and it enormously improves with cortisol replacement [24]. Furthermore, the interaction of ACE receptors with the neurotransmitter pathways could lead to idiopathic chronic fatigue syndrome and chronic fatigue [24,25]. This effect has been suggested to be mediated by deletion/insertion polymorphisms in the ACE gene coding for its receptor [25]. Disruption of the ACE2 receptors expressed in the hypothalamus, may play a pivotal role in hypocortisolism and post-viral fatigue [26,27].

It has been observed that the entry of the SARS-CoV in the brain is via the ACE2 receptors seated in the olfactory bulb causing ageusia and anosmia [28]. It is attributed to a central or local pathway leading to hormonal deficiencies due to the damage to the hypothalamus [29].

2.3.2 Prolactin

Hyperprolactinemia is considered as a repercussion in response to sepsis or infection [30]. Increased prolactin levels have been demonstrated in severe respiratory infection

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in infants and severe sepsis [31,32]. As of now, no data are available in patients with hyperprolactinemia on having susceptibility to infection.

2.3.3 Thyroid

A research conducted on SARS-CoVsurvivors for any hormonal derangements three months after recovery found that 6.7% of the patients had developed biochemical hypothyroidism [24], out of which 75% had a central etiology and 25% had positive antibodies with primary hypothyroidism. Also, thyroid hormone replacement was continued at the end of the study. Alterations in the thyroid profile on the follow-up of central hypothyroidism were found to be normalised. The authors suggested monitoring of thyroid function tests during active and convalescence period of SARS-CoV-2 disease, also suggesting replacement therapy if needed [24].

A research conducted on forty-eight SARS-CoV1 infected patients demonstrated decreased triiodothyronine(T3) (94%), thyroxine (T4) (46%) along with reduced serum thyroid stimulating hormone (TSH), considering the possibility of either the sick euthyroid syndrome or central hypothyroidism [33]. A follow-up study of sixty-one SARS patients inspecting endocrine disorders, found 2 cases of subclinical thyrotoxicosis, 3 cases with central hypothyroidism, and 1 patient with primary hypothyroidism with positive thyroid autoantibodies [24]. Significantly low levels of TSH and free T3 were found in deceased patients when compared to recovered patients in a report of 274 patients [34].

Different effects of acute illness have been observed on the thyroid axis (Figure1) along with down-regulation of the hypothalamo-pituitary axis [35].

The British Thyroid Association and the Society for Endocrinology have passed a consensus statement regarding thyroid dysfunction during COVID-19 pandemic [36]. Patients with underlying hyperthyroidism and hypothyroidism are guided to pursue their medications as prescribed. In hyperthyroid patients on antithyroid drugs, agranulocytosis should be kept in mind, although the prevalence is rare (0.2%-0.5%) [36]. Agranulocytosis symptoms such as sore throat, fever are congruent with those of COVID-19 and it is imperative to get a complete blood count to ascertain the possibility of agranulocytosis.

A histopathological study of the thyroid gland on the effects of SARS infection found immense injury to the follicular and parafollicular cells. Parafollicular cells are responsible for the production of calcitonin. Osteonecrosis of the femoral head in SARS recovered patients was attributed to it as a possible mechanism [37].

2.3.4 Adrenal Gland

A primary immunological strategy employed by the SARS-CoV is to blow down the cortisol stress response

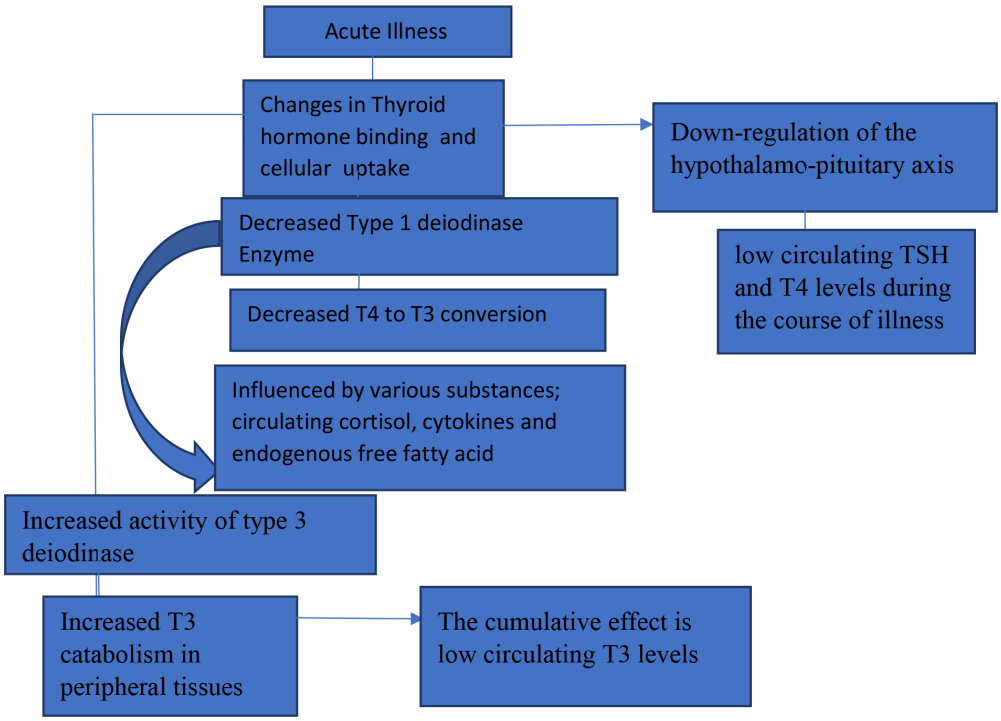

Figure 1. Acute phase effects on the thyroid axis [35]

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in the host. It has been suggested that there is a possibility that the expression of few amino acid sequences by the SARS-CoV that are a molecular imitation of the host adrenocorticotropic hormone (ACTH) can obtund the stress induced rise in cortisol level and the antibodies produced against the virus can inadvertently demolish the circulating ACTH [38].

Ding et al. demonstrated the histological changes in the adrenal gland from the post-mortem biopsies of patients dying from SARS-CoV. The author found mainly lymphocytes and monocytes infiltrating the adrenal medulla [39].

Homogeneity of the SARS-CoV2 proteins with the SARS-CoV might mimic the same molecular strategy, thus making severe COVID-19 patients vulnerable to develop critical illness- correlating corticosteroid insufficiency [40]. Furthermore, clinicians must be cautious regarding the underlying relative cortisol deficiency in COVID-19 patients. Primary adrenal insufficiency (PAI) patients are at high risk of respiratory tract infections. There is a need for glucocorticoid support in PAI with COVID-19; nevertheless,hypokalaemia has been reported in these patients [41].

2.3.5 Endocrine Pancreas

Coronavirus enters the pancreas by interacting with the ACE2 receptors. ACE2 receptors are expressed more in the endocrine pancreas in comparison to pancreatic exocrine tissues [42]. 51% of SARS-CoV patients have been found to have developed new-onset diabetes with no history of diabetes or receival of any steroid treatment during the illness [42]. Pancreatic exocrine injury is manifested as an increased level of biochemical markers, raised amylase (1-2%) and lipase (17%) in severe or non-severe COVID-19 [17]. SARS-CoV facilitated injury of the pancreas (beta cells) was suggested as the feasible theory behind acute diabetes in this subset of patients [43].

Pro-inflammatory mileu, as explicit by increased interleukin, inducible protein-10, interleukin-1β, monocyte chemo-attractant protein-1 (MCP-1), even in mild COVID-19 may play a pivotal role in the foreground process [44]. Poor glycaemic control is an independent marker of increased mortality and morbidity in SARS-CoV patients with or without history of diabetes mellitus [45].

Insulin resistance can be accentuated in COVID-19 patients with pre-existing Type2 DM. This is further accentuated due to COVID-19 treatment drugs. Ritonavir/ Lopinavir produce further insulin resistance and lipodystrophy. Down-regulation of ACE2 levels and decreased innate immunity could be the possible mechanisms responsible for severe disease and acute respiratory distress syndrome (ARDS) in DM with COVID-19 patients [46]. Hypokalaemia produces downregulation of pulmonary ACE2 receptors, subsequent increase in aldosterone secretion and this can further deteriorate the glucose control in pre-existing Type 1and 2 DM patients [46] (Figure 2).

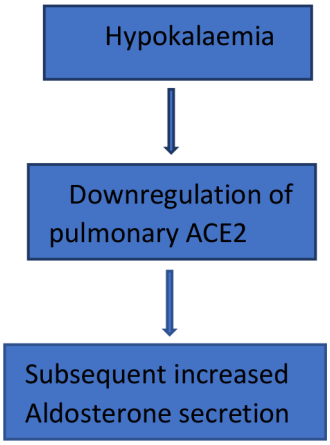

Figure 2. Hypokalaemia in COVID-19

The susceptibility of cytokine storm is exacerbated in patients with diabetes leading to rapid deterioration, as evidenced by the high level of biomarkers,interleukin-6(IL-6), C-reactive protein, serum ferritin, and D-dimer [17]. In a few post-mortem reports, hydropic degeneration, interstitial proliferation, and fatty degeneration have been found to be indicators of pancreatic injury [47].

2.3.6 Androgens

A high level of ACE2 expression in the human testis has been analysed, demonstrating testis to be a high-risk organ susceptible to SARS-CoV2 infection [48,49]. In a neo- study, ACE2 has been found to be expressed in somatic (Sertoli and Leydig) and spermatogonia cells in the testis [50]. Transmembrane protease serine 2 (TMPRSS2)expressed in spermatogonia and spermatids is also expressed in the pulmonary level. Furthermore, TMPRSS2 inhibitors used for prostate cancer, may present an effective target for the prevention or treatment of COVID-19 pneumonia [51]. Also, poor outcomes of COVID-19 in males might be due to a high level of co-morbidities, hypertension, lung disease, and cardiovascular comorbidity. Serum testosterone levels require cautious interpretation in COVID-19 patients, as acute critical illness can cause suppression of the hypothalamic-pituitary-testicular axis, manifesting biochemically as decreased luteinizing hormones (LH), follicle -stimulating hormone (FSH) and testosterone(T). Serum T:LH ratio was found lower in COVID-19 patients and was negatively associated with the severity of the disease[52]. In a study, 81 COVID-19 males exhibited lower total serum testosterone and higher serum LH, when compared to healthy males [52]. In an au-

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topsy-based study on males who died of SARS-CoV-1, orchitis was demonstrated in all the patients with markedly thickened basement membrane, germ cell destruction and leukocyte infiltration thus suggesting immune-mediated damage rather than viral entry and direct damage [53].

Polycystic ovarian syndrome (PCOS) is the most frequent endocrine disorder among the reproductive age group women[54]. Although the median age affecting the female suffering from PCOS is considered at low risk of COVID-19, the patients with associated comorbid conditions including obesity and metabolic disorders are prone to develop severe symptoms of COVID-19. Overlap of symptoms commonly associated with PCOS and risk factors identified for severe COVID-19, seem to enhance the severity of the SARS-CoV2 symptoms. Albeit, further research is necessary to elicit the direct potential relation between the factors increasing metabolic-cardiac risk in PCOS e.g hyper-androgenemia, hyper-cytogenemia, vitamin- D deficiency and COVID-19 related adverse outcome [54].

2.4 COVID-19 and Renin -Angiotensin Aldosterone System (RAAS)

RAAS plays a pivotal role in the regulation of blood pressure and fluid balance [55]. The final product, angiotensin II of the RAAS,is a main vasoactive hormone, binding angiotensin II receptors type I (AT-1) located in the heart,blood vessels, kidney and adrenal gland. It thereby, plays a vital role in the inflammation, myocardial hypertrophy, fibrosis,and vascular remodelling.

Few researchers have suggested that down-regulation of ACE_2 receptors due to SARS-CoV-2 infection can conduce secondary damage to the cardiac, lung,and other tissue injuries because of the presence of ACE_2 in these organs. ACE_2 convert angiotensin II causing vasodilatation and acting as counter-regulation of the blood pressure elevation [56]. Hypertension seems to magnify the inflammation silhouette in the inflammatory silhouette in SARS-C0V-2 infection, deducing that hypertension may intensify the risk for a severe illness. Furthermore, these patients already have an increased level of inflammatory biomarkers such as TNF-, IL-6. Nonetheless, more research is needed to elucidate the pathophysiology and eventually associated risk in patients having resistant hypertension and COVID-19 [57].

The interplay between ACE deletion and insertion polymorphism can be correlated with the severity of ARDS [58,59]. ACE-2 alleviates inflammation, fibrosis and pulmonary hypertension in the lungs, in addition to the inhibition of tumor angiogenesis and cancer cell growth [60,61].

2.4.1 ACE-2 Expression in the Blood Vessels

ACE-2 expression in the small and large blood vessels produces angiotensin (1-7) [62,63] thereby causing vasodilatation, thrombotic and anti-inflammatory effects [62]. Disseminated intravascular coagulation (DIC) and elevation of D-dimer (plasma) are observed with severely infected COVID-19 infections [64,65]. Furthermore, organ injury in COVID-19 can be attributed to increased permeability, microcirculation disruption, activation of coagulation cascade, and damage of the vascular endothelium integrity due to viral infection and inflammatory response.

2.4.2 Hypocalcemia and COVID-19

Intracellular calcium signalling plays a crucial part in the replication and cellular outcome of certain viruses [66]. Although in the milieu of COVID-19, the role of intracellular calcium signaling is still to be explicated and requires further research, Past research suggests that hypocalcemia is common in SARS infection [67]. Moreover, COVID-19 infection has been associated as a precipitating cause of hypoparathyroidism post-surgically with severe hypocalcemia [68]. In a retrospective study of 531 COVID-19 patients,hypocalcemia was suggested in 80% cases on initial evaluation in hospital. Albeit, no data on ACE-2 expression, inflammation, or alteration in parathyroid function or calcium homeostasis have been reported during COVID-19 infection and hence require further research. The role of Vitamin-D as a tool in the armamentarium of COVID-19 has been shown to enhance innate immunity (cellular) partially through antimicrobial peptide induction and help in reducing the pro-inflammatory cytokine expression which can be indeed beneficial in COVID-19 [69,70].

3. Conclusion

The endocrine system can be severely affected by the SARS-CoV infection in a multitude of ways and data on this is still evolving. Amidst the ongoing pandemic, a high index of suspicion for endocrinal involvement and an endeavour to detect and manage newly emerging endocrine entities and alterations in the pattern of pre-existing endocrine diseases is of utmost importance.

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