DOI: 10.7860/JCDR/2022/50986.15927

Review Article

Internal Medicine Section

Association of COVID-19 and Endocrine Disorders

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by the coronavirus, since its start in Wuhan a city in China has spread like a wild fire and created havoc all over the globe. Initially, the disease was thought to be causing only respiratory complications, but gradually it was found to be causing multiorgan complications. Due to the hypercoagulable property of coronavirus, it has shown neurological, cardiological and endocrine complications. Recently, the effect of the virus on endocrine system has also been noted. Evidence has shown that COVID-19 can hamper the hypothalamo-pituitary axis resulting in altered adrenal response to stress. The immune-mediated damage to the endocrine glands results in subacute thyroiditis. The presence of Angiotensin Converting Enzyme 2 (ACE 2) receptors on various tissues could be the cause of this immune mediated damage. The COVID-19 has also precipitated hyperglycaemia and in few cases, uncovered the insulin resistance in previously undiagnosed cases. It is crucial to have knowledge about the impact of endocrine system, as it is the powerhouse of the body.

Keywords: Angiotensin converting enzyme 2 receptors, Coronavirus disease 2019, Cytokine storm, Endocrine system, Hypothalamo-pituitary axis

INTRODUCTION

Severe Acute Respiratory Syndrome–Coronavirus-2 (SARS-CoV -2), A novel Coronavirus (nCoV), that resulted in the recent outbreak of COVID-19, was first discovered in province of Wuhan of China in December 2019 [1]. COVID-19 which in the initial few days is asymptomatic can gradually deteriorate in few days complicated by pneumonia and Acute Respiratory Distress Syndrome (ARDS) [2]. The pathogenesis of COVID-19 has been related to entry of virus via the respiratory tract and its interaction with ACE 2 receptors that leads to entry into host pneumocytes. Moreover, the Ribonucleic Acid (RNA) of COVID-19 virus has been detected in the sera of patients thus implying free interaction of virus with any tissue containing ACE 2 receptors [3]. Various endocrine organs like pancreas, thyroid, adrenals, pituitary and gonads express ACE 2 receptors, thus, opening up the possibility of their involvement during the course of disease [2]. The present article aimed to provide a narrative review of the involvement of endocrine system with COVID-19.

COVID-19 and Thyroid Gland

The nCoV causes "cytokine storm" which is linked to immune response hyperactivity involving Th1/Th17 lymphocytes resulting in release of various pro-inflammatory cytokines like Tumour Necrosis Factor-Alpha (TNFα) and Interleukin-6 (IL-6) [4]. This may lead to thyrotoxicosis, disruption of de-iodinases and thyroid hormone transport proteins, and impaired pituitary Thyroid Stimulating Hormone (TSH) secretion. Another unique thyroid gland dysfunction is known as 'low Triiodothyronine (T3) syndrome' or 'sick euthyroid syndrome' which is characterised by low T3 levels, normal to moderately decreased Tetraiodothyronine (T4) levels and normal to low TSH. These thyroid gland abnormalities are transient and do not require any treatment [5].

Autopsies done in patients with SARS-CoV-2 infection have shown destruction of thyroid follicular cells. Histological examination of thyroid gland has revealed absence of lymphocytic infiltrate but presence of apoptosis suggestive of thyroiditis [6]. A recent study done on patients with COVID-19 pneumonia showed low levels of T3 and TSH as compared to non COVID-19 pneumonia. A significant association was found between low T3 and severe form of COVID-19 resulting in more death than SARS-CoV-2 survivors [7].

In another follow-up study done by Muller I et al., on eight patients having findings of atypical subacute thyroiditis, two developed hypothyroidism while six had suppressed TSH suggesting long term effects of SARS-CoV-2 on thyroid gland [8].

COVID-19 and Pancreas

The ACE 2 receptors are also present in the pancreas with m-RNA levels being higher in the pancreas than in lungs. This expression involves both the exocrine and endocrine functions of pancreas [9]. Hyperglycaemia has been frequently reported in COVID-19 [10]. A recent study which explored physiological model for SARS-CoV-2 using organoid derivatives from human pluripotent stem cells, demonstrated alpha and beta-cell death due to viral cytotoxic effects. Islet cell injury by SARS-CoV-2 may result in hyperglycaemia and acute diabetes [11]. Immunohistochemistry and in-situ hybridisation done on pancreas of patients who died due to COVID-19 showed evidence of SARS-CoV-2 [12]. Worsening of insulin resistance has been reported in patients with pre-existing diabetes with SARS-CoV-2. Increased levels of glycoprotein called serum fetuin has been reported in SARS-CoV-2 which is associated with impaired insulin sensitivity [13]. Anti-retroviral drugs like Lopinavir–ritonavir which has been suggested as possible treatment for COVID-19 can lead to lipodystrophy and subsequent development of insulin resistance [14].

Treatment with chloroquine/hydroxylchloroquine can lead to hypoglycaemia, especially, if the patient is on insulin or sulfonylureas with possible mechanisms being interaction with insulin release, degradation and action [15]. Diabetic patients with COVID-19 are at increased risk of developing severe pneumonia, ARDS and mortality as compared to non diabetics; with possible explanation in such patients being suppressed immunity and down-regulation of ACE 2 levels [16]. Recent survey done in United Kingdom (UK) on 23,804 patients who died due to COVID-19 showed that about 32% had type 2 Diabetes Mellitus (DM) while 1.5% had type 1 DM with odds ratio of 2.03 and 3.5 respectively of dying from large number of COVID-19 patients have been reported to develop diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome during the course of illness. In one study, ketosis was reported in 6.4% in COVID-19 patients, with incidence rising to 11.6% in patients with diabetes and was associated with higher mortality rate (33%) [17,18].

Obese patients are more likely to develop severe pneumonia and ARDS and are more likely to die from COVID-19 as compared to non obese individuals [19]. Adipose tissue also expresses ACE 2 receptor and obese persons have higher adipose tissue, leading to increased ACE 2 receptors for binding of SARS-CoV-2 [20]. Various mechanisms have been proposed for higher mortality in obese individuals. Obesity often co-exists with diabetes and both are pro-inflammatory states leading to increase levels of pro-inflammatory markers like leptin and decreased levels of anti-inflammatory markers like adiponectin [17]. Also, obesity is associated with lower vitamin D levels, which might impair the immune response [21]. In a study, the requirement of invasive mechanical ventilation in individuals admitted in Invasive Care Unit (ICU) with Body Mass Index (BMI) more than 35 kg/m^2 was seven times more than persons with BMI of less than 25 kg/m^2 [22]. Another study concluded that individuals with BMI more than 25 kg/m^2 and non alcoholic fatty liver disease were six times more likely to develop severe infection as compared to non obese individuals [23]. It has been hypothesised that the vaccines that are being developed to control the COVID-19 pandemic, will be less effective in obese individuals due to poor immune response due to altered immunity pathway [24].

COVID-19 and Adrenal Gland

The ACE 2 receptor is also expressed in adrenal glands. In a study done by Freire Santana M et al., autopsy findings of adrenal glands of 28 patients who died of severe COVID-19 infection, microscopic lesions were identified in the adrenal glands in 13/28 patients (46%) [25]. Seven cases showed necrosis, generally ischaemic; four showed cortical lipid degeneration; two showed haemorrhage; and one unspecific focal adrenalitis [25].

The primary mechanism adopted by SARS-CoV virus is to blunt the host cortisol stress response. A very interesting mechanism has been proposed to explain this finding- "molecular mimicry" i.e., sharing of certain amino acid sequence by SARS-CoV with the host Adrenocorticotropic Hormone (ACTH) sequence [26]. Since proteins of SARS-CoV-2 share similarity (95-100%) with original SARS-CoV, similar mechanism of molecular mimicry has been proposed for blunted adrenal response [2]. The benefits of glucocorticoid therapy in COVID-19 could be because of propensity of SARS-CoV-2 to cause impaired host stress cortisol response and subsequent adrenal insufficiency. Another mechanism of benefit could be the tackling of the phenomenon of 'cytokine storm' by reducing inflammation [27].

Early studies failed to show benefit of glucocorticoid therapy in reducing mortality and was instead associated with increased hospital stay and delayed viral clearing [27]. On the basis of these studies, World Health Organisation (WHO) recommended against the use of glucocorticoids in COVID-19 except in refractory shock [28]. However, the 'RECOVERY' trial was a landmark study which showed that use of dexamethasone is associated with 17% reduction in mortality of ill-ventilated ventilated patients [29]. Accordingly, dexamethasone has been recommended for use in moderate and severe COVID-19 patients. In a recent study by Tan T et al., patients with severe COVID-19 infections were found to have blunted adrenal response and baseline serum cortisol level was a reliable indicator of mortality in COVID-19 [30].

COVID-19 and Pituitary Gland

Leow MK-S et al., first reported disruption of pituitary gland function during SARS-CoV-2 outbreak. A total of 61 patients were followed up at three months after recovery, of which 40% had mild central hypocortisolism. Among this 62.5% resolved within a year, while 5% developed central hypothyroidism. Autopsy findings showed evidence of oedema and neuronal degeneration of hypothalamus along with SARS-CoV genome. The authors had proposed the possibility of reversible hypophysitis or direct involvement of hypothalamus leading to disruption of hypothalamic-pituitary axis [31]. ACE 2 receptors are involved in the SARS- CoV-2 infection. These same, ACE 2 receptors are present in hypothalamus and pituitary gland which leads to its affect in COVID-19 infection. However, at present ample data of pituitary involvement in COVID-19 is not available. It is thought that due to higher incidence of neurological symptoms in SARS-CoV-2, involvement of hypothalamus and pituitary gland can occur either directly or due to immune mediated hypophysitis. Thus, an eagles eye should be kept on hypothyroidism in cases with unexplained symptoms like fatigue, lassitude, malaise, orthostatic dizziness, anorexia and apathy [2].

COVID-19 and Lipid Profile

Four cases of hypertriglyceridemia have been reported till date, possibly, as a side effect of drugs used in the treatment of COVID-19. Two cases were due to use of combination of lopinavir/ritonavir [32] while remaining two were due to simultaneous use of the above combination along with tocilizumab [33].

Due to immunomodulatory actions, statins have been proposed as a possible add-on drug therapy in patients with COVID-19 [34]. Statins exert pleiotropic effects on inflammation and oxidative stress and modulate the immune response at different levels, including immune cell adhesion and migration, antigen presentation, and cytokine production [34]. Studies in the past have reported efficiency of statins in treatment of various influenza virus by reducing hospital stay and mortality [35]. Moreover, statins are economical, extensively studied and widely available and can be explored as a possible adjunctive treatment option.

COVID-19 and Andrgens

Males are more prone to develop infection on exposure to the virus and have higher mortality than females [36]. The viral entry requires two host proteins- ACE 2 receptor and transmembrane protease, serine 2 (TMPRSS2). Transcription of TMPRSS2 requires androgen receptor activity. This modulation of TMPRSS2 by testosterone has been considered as major reason for male predominance of worse outcomes. Since, TMPPRSS2 is expressed in lungs and its inhibitor has been widely used in treatment of prostate cancer, it can emerge as a target specific treatment for prevention or treatment of COVID-19 pneumonia [37].

CONCLUSION(S)

There appears to be widespread involvement of endocrine organs in patient with COVID-19. Considering the ongoing COVID-19 pandemic, future prospective studies are needed to increase epidemiological and clinical knowledge and optimise the management of endocrine disorders in COVID-19 patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 24, 2021
- Manual Googling: Sep 27, 2021
- iThenticate Software: Nov 09, 2021 (21%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jun 22, 2021**
Date of Peer Review: **Jul 30, 2021**
Date of Acceptance: **Sep 29, 2021**
Date of Publishing: **Feb 01, 2022**