Endocrine Involvement in COVID-19: Mechanisms, Clinical Features, and Implications for Care

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Abstract

Coronavirus 2019 (COVID -19) has rapidly emerged as a global pandemic with multi-system involvement. Involvement of the endocrine system is expected in COVID-19 as the interplay between severe acute respiratory syndrome corona virus-2 (SARS CoV-2) and the endocrine system occurs at multiple levels. The widespread presence of ACE-2 receptors on various tissues suggests scope for direct viral infection. The interactions via the activation of inflammatory mediators and indirect immune-mediated damage are also postulated. Evidence so far suggests that COVID-19 can cause functional hypopituitarism by direct and indirect effects on the hypothalamo-pituitary axis resulting in inappropriate adrenal response to stress. Several reports highlight possible immune-mediated damage to thyroid glands resulting in subacute thyroiditis. COVID-19 is implicated in precipitating hyperglycemia in known diabetics and uncovering insulin resistance in those previously undiagnosed. COVID-19 has also been shown to trigger Type 1 Diabetes with ketosis. Various mechanisms including direct virus-induced beta cell apoptosis and immune-mediated beta-cell damage have been demonstrated. The presence of virus in semen has unclear clinical significance at present. In this mini-review summarize the endocrine manifestations reported so far in COVID-19 disease and explore mechanisms to decipher how SARS CoV-2 may affect various endocrine organs.

Keywords: Adrenal, COVID19, diabetes, endocrine, gonads, hormone, thyroid

Search Strategy

We identified articles by searching PubMed for articles published from January 2001 to July 2020, by using the terms "COVID-19," "Coronavirus," "SARS-CoV-2," "SARS," "nCoV- 2019," "ACE-2 receptor" in combination with the words "endocrine," "hormone," pituitary", "adrenal," "hypothalamo-pituitary axis," "hypopituitarism" "pituitary insufficiency," "hypocortisolism," "hypothyroidism," "hyperthyroidism", "thyroid," "Pancreas," "islets, " "Diabetes" "hypoglycemia," "hyperglycaemia," "dysglycemia", "hypogonadism," "testis", "ovary," "luteinizing hormone", "follicular stimulating hormone", "growth hormone," "Insulin-like growth factor -1", "adrenocorticotrophic hormone", 'prolactin", "thyroxine", "insulin", "progesterone", "estrogen", "Androgen. Relevant articles were also identified through searches in the authors' files and Google Scholar. Articles resulting from these searches and related references cited in those articles were reviewed. Articles published in the English language were included.

Introduction

Coronavirus disease 2019 (COVID-19) has rapidly emerged a global pandemic needing unprecedented measures.[1] Severe acute respiratory syndrome corona virus-2 (SARS CoV-2) virus has a predilection for multi-organ involvement due to the widespread presence of angiotensin-converting enzyme-2 (ACE-2) receptors, an entry point for the virus.[2-5] Central nervous system, heart, gastrointestinal system, and coagulation cascade are affected.[6,7] Few reports of endocrine involvement exist.[6-8] Since endocrine and immunological responses are closely related, interactions are expected in

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COVID-19.[9-11] In this mini-review, we aim to summarise the endocrine manifestations reported so far in COVID-19 and explore mechanisms to decipher how SARS CoV-2 may affect various endocrine organs.

Inferences can be made from previous experiences with reports of patients with SARS infection. SARS has been known to cause hypocortisolism and central hypothyroidism in survivors.[9] Also, serum prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) have been shown to be elevated while estrogen and thyroid-stimulating hormone (TSH) are reduced in SARS CoV infection.[10] SARS CoV-2 may have similar potential for endocrine involvement.

There appear to be three main mechanisms of interaction between the endocrine system and SARS COV-2. Direct viral infection of the gland, activation of the hypothalamo-pituitary axis (HPA) via inflammatory mediators, and immune-mediated glandular damage secondary to antibody formation or cell-mediated damage. These mechanisms, their effectors, and known clinical effects are summarized in Figure 1.

HYPOTHALAMO-PITUITARY AXIS

The hypothalamo-pituitary axis is central in inflammatory or stress responses during viral infections. The effect on HPA function can be a result of direct or indirect injury. Direct injury may relate to the ACE-2 receptor-mediated SARS CoV-2 infection of neuronal cells causing cell edema and necrosis.[11] The indirect effects on HPA are mediated by cytokines: interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) activate the HPA axis and subsequently raise serum cortisol levels.[12] Also, inflammation may result in damage to the pituitary and hypothalamus; causing hypophysitis in SARS CoV.[9]

In 2010, the hormonal profile of SARS patients revealed elevated prolactin, FSH, and LH, while estradiol (E2), progesterone (P), and TSH were lower than controls.[10] This study had also demonstrated reduced expression of growth hormone (GH), TSH, adrenocorticotrophic hormone (ACTH) but increased PRL, FSH, and LH on pituitary autopsy samples of SARS CoV infected patients.[10] Leow *et al.* reported hypocortisolism and central hypothyroidism as long term effects on SARS survivors.[9]

While the role of GH and insulin-like growth factor-1 (IGF1) is currently unknown in COVID-19, it has been known to modulate influenza A mediated lung injury in rats.[13] Inflammatory cytokine storm syndrome reported in COVID-19 mediated by IL-6 is also known to suppress IGF-1.[14] Though reduced IGF-1 has not been demonstrated, it has been speculated as a possible risk factor for autism in infants of pregnant mothers with COVID-19.[15] An interesting cross-talk between the IGF-1 system and ACE-2 receptor for SARS CoV-2 is the common second messenger involving signal transducer and activator of transcription (STAT) pathway. Activation of ACE2 receptors by cytokines through pan JAK-STAT enhancers was demonstrated in a recent mRNA expression study.[16] The clinical relevance of this is unknown.

In COVID-19, two studies have shown low normal TSH, tri-iodothyronine (T3), thyroxine (T4) suggesting a possible central mechanism related to cytokines.[8,17] In another report, levels of LH were found to be elevated in patients with SARS CoV-2 infections.[18,19] Long term follow-up of patients recovering from COVID-19 is needed to estimate any long-term morbidity.
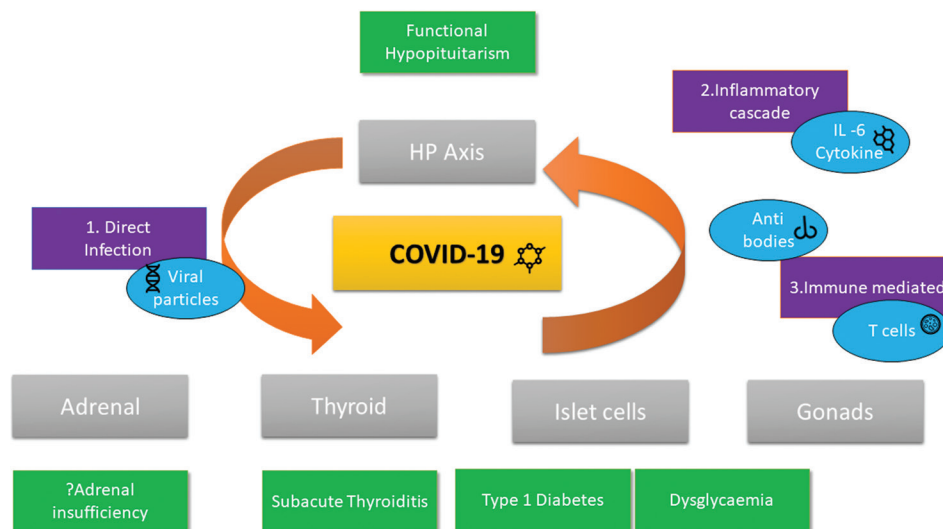
Figure 1: The multi-level interaction between SARS-CoV-2 and the endocrine system. Viral particles may directly infect the endocrine tissues via ACE-2 receptors and cause cytopathology or apoptosis as in the pancreas. Other mechanisms are immune cell/antibody-mediated damage as in subacute thyroiditis. A final mechanism is inflammatory cytokine-mediated dysregulation of the endocrine axis to cause functional hypopituitarism and relative adrenal insufficiency. Clinical features reported so far are marked in green

ADRENALS

Viral causes of direct adrenal insufficiency are well known.

Stimulation of HPA axis by cytokines has several effects. It results in increased perfusion of adrenals, in turn, increases risk of hemorrhage.[20] Second, increased steroidogenesis results in immunomodulation towards Th-2 helper T cell response. Though useful in the acute phase, in protracted phase, this dysregulated response results in a delay in viral clearing.[20]

SARS-CoV produces viral peptides that are structurally similar to ACTH. The host immune response produces antibodies against these viral proteins which also collaterally destroy host ACTH resulting in adrenal insufficiency.[21] There are reports of hypocortisolism in SARS survivors who had never received steroids.[9] Similar mechanism of molecular mimicry resulting in Anti-ACTH antibody has been proposed in SARS CoV-2. The propensity of SARS CoV-2 virus to cause adrenal insufficiency has also been supported by the presence of ACE-2 receptors on the adrenal gland.[22]

The benefits of glucocorticoids in COVID-19 were hypothesized from the ability of SARS Cov-2 virus to cause dysregulated stress response and consequent adrenal insufficiency. Apart from this steroids may prove beneficial in the cytokine storm syndrome by limiting unregulated inflammation.[14,23] Also, steroids may have some local action on the pulmonary alveolar membrane either due to their membrane-stabilizing effects or other unknown mechanisms to prevent hyaline membrane formation in the lungs.[24]

Early systematic reviews showed that steroids did not reduce deaths in COVID-19 but resulted in increased hospitalization and delayed viral clearing.[25] Other studies suggested that the use of low dose glucocorticoids did not delay viral clearing.[26] Based on these, WHO had recommended against the use of corticosteroids in patients with COVID-19 except in refractory shock.[27]

Recent results from the RECOVERY trial suggest significant benefits with steroid use in critically ill COVID-19 patients.[28] The trial demonstrated that dexamethasone reduced the risk of mortality by 17% in ventilated patients. Other clinical trials are underway.[29] This practice-changing result is expected to benefit patients. Endocrine implications include risk for long term adrenal suppression, infections, and dysglycemia due to exogenous steroids.[30]

Till date, there is no report of adrenal insufficiency in SARS-Cov-2, while suppressed cortisol levels have been reported with SARS infection.[9] A recent report by Tan *et al.* has shown that severe COVID-19 patients mount a robust adrenal response and that baseline serum cortisol was a reliable predictor of mortality in COVID-19. The authors have suggested a cut off of 27 mcg/dL (744 nmol/L) as a predictor of 15-day mortality.[7] These results suggest that the beneficial effects of steroids in critically-ill COVID-19 patients are unlikely to be due to adrenal insufficiency and may possibly relate to local lung effects of steroids. It remains to be explored if the timing is critical to the beneficial effects of glucocorticoid therapy and what other mechanisms may explain this beneficial effect of steroids.

PANCREAS

The expression of ACE-2 receptors on the exocrine pancreas and islets cells suggest that the pancreas is susceptible SARS- CoV-2.[31] Autopsy findings of patients with SARS demonstrated the presence of SARS CoV virus in the pancreas with a stronger predilection for islet cells.[32] Yang *et al.* found that 20 out of 39 patients developed diabetes on follow up with no history of corticosteroids use.[32]

COVID-19 has been reported to cause exocrine pancreatic injury in varying severity. Wang *et al.* reported pancreatic injury in 17% of 52 COVID-19 patients with elevated serum amylase or lipase levels and two-third had abnormal blood glucose levels.[33] Baltar *et al.* also found isolated elevated lipase in COVID-19.[34] Hadi *et al.* reported two cases of severe acute pancreatitis in three family members with COVID-19 infection.[35] Further, drugs being explored for COVID-19 can result in acute pancreatitis.[36]

Hyperglycaemia is frequently reported in COVD-19.[37] 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.[38] Islet cell injury by SARS CoV-2 results in hyperglycemia and acute diabetes. Glucocorticoids used for patients with severe COVID-19 disease may also result in hyperglycemia.[39] Finally, hyperglycemia may result from alteration in glucose metabolism due to stress response.[40]

SARS CoV-2 infection has been reported to trigger Type 1 diabetes mellitus with diabetic ketoacidosis and hyperosmolarity suggesting either direct beta-cell cytotoxicity or an immune reaction.[41,42] A report by Li *et al.* found that 6.4% of 658 patients presented with ketosis on admission with no obvious cause.[43] A global database (CoviDIAB Project) has been established to collect information on patients with COVID-19 and high blood sugar.[44] Diabetes also remains an important risk factor for severe COVID-19 disease and a predictor of morbidity and mortality.[44,45] Lacobellis *et al.* reported that admission hyperglycemia was the best predictor of SARS CoV-2 radiological findings.[37] Inflammatory milieu and elevated levels of cytokines in diabetes may contribute to severe disease and ARDS. The bidirectional relationship between diabetes and COVID-19 needs further exploration.[44]

Clinical care in COVID-19 patients must consider these factors and close monitoring of blood glucose levels is required in diabetics. Given the frequency of dysglycaemia in COVID-19, it may be prudent to employ blood glucose screening of all admitted COVID-19 patients to check for new-onset dysglycaemia.

THYROID GLAND

There have been reports of thyroid dysfunction with both low T3 and T4 in SARS-CoV.[46] A study exploring organ distribution to detect SARS-CoV genetic material in tissues from SARS patients did not detect viral genome in thyroid tissues.[47] ACE-2 receptor expression on thyroid tissue suggests the potential for direct SARS-CoV-2 infection.[48] Huang *et al.* reported low normal T3, T4, and TSH in COVID-19 without clinically apparent hypothyroidism.[49] Another study reported low T3 and TSH in COVID-19 patients compared to controls.[8] Post COVID-19 subacute thyroiditis was first reported from Italy.[50] Another report described thyrotoxicosis in a patient during the hospital stay.[51] A recent report by Muller *et al.* has highlighted the prevalence of atypical subacute thyroiditis in COVID-19 patients receiving high-intensity care. Of 8 who were followed, two developed hypothyroidism and 6 had suppressed TSH suggesting long-term effects of COVID-19 on thyroid functions. They were negative for thyroid antibodies. A cell-mediated immune mechanism was proposed by the authors to explain these findings.[6] Larger follow-up studies are required to explore the long term effects of SARS-CoV-2 on thyroid functions.

GONADS

Severity and case fatality of COVID-19 has been observed more in males as compared to females.[49] This disparity was also seen in infections with similar viruses- SARS CoV and MERS CoV.[52,53] Multiple mechanisms have been postulated to explain this gender disparity. SARS-CoV-2 virus enters the human cells via ACE-2 receptors and cellular serine protease—TMPRSS2. These are abundant in testes with ACE-2 abundant on spermatogonia, Sertoli, and Leydig cells while TMPRSS-2 on spermatogonia and spermatids.[54,55] This has led to the hypothesis that testes may act as a viral reservoir.

The presence of orchitis was reported in SARS infection and autopsy findings revealed germ cell destruction with lymphocytic infiltrates in testes.[56] Semen analysis of men with COVID-19 has shown the presence of SARS-CoV-2 but its clinical implication or relation to infertility is unknown.[57] Studies have shown low serum testosterone in COVID-19 patients compared to controls. Low testosterone levels may serve as a marker of COVID-19 disease and severity, at least in older males.[18] In these patients, serum LH was elevated suggesting local destruction.[18]

The gene for ACE-2 receptors is on the X chromosome, which raises the possibility of different gender-specific activity

Table 1: Clinical features of endocrine involvement in SARS and COVID-19 with possible mechanism

Gland involved	Possible Pathogenetic Mechanism	Clinical Implications
Severe Acute Respiratory Syndrome (SARS)		
Hypothalamo-pituitary axis	Direct injury to the hypothalamus and anterior pituitary cells	Hypocortisolism and central hypothyroidism requiring long term hormone replacement.
	Indirect injury due to cytokine storm and inflammatory cascade induced injury to hypothalamus resulting in hypophysitis	
Gonads	Orchitis and lymphocytic infiltration in testes on autopsy	Uncertain.
	Direct Cytopathic effects of virus on testicular cells	? Infertility in males
COVID-19		
Hypothalamo-pituitary axis	Intact HPA Axis	Robust adrenal response in critically ill.
	Direct injury to hypothalamus and anterior pituitary cells	Basal Serum cortisol may serve as severity and mortality marker.
	Indirect injury due to cytokine storm and inflammatory mediators	Central Hypothyroidism with Low TSH, low T3 and low normal T4
	Anti ACTH antibodies	Possible adrenal insufficiency
Pancreas and islet cells	Direct cytopathic injury caused by virus in islet cells leading to altered functioning and hyperglycaemia	Development of new onset Diabetes in SARS CoV-2 infection
	Stress response of the body	Elevated serum amylase and lipase
	? Drug induced hyperglycaemia	Ketosis in the presence and absence of diabetes
	Direct viral injury to pancreatic cells due to presence of ACE-2 receptors	
	Possible autoimmune mechanism	
Thyroid Gland	Direct injury by virus to thyroid gland	Atypical subacute thyroiditis
	Immune-mediated injury to thyroid gland	
Gonads	Injury to testicular cells resulting in low testosterone and activation of Hypothalamo-pituitary-gonadal (HPG) axis	Elevated levels of LH and low serum testosterone levels.
	Presence of ACE-2 receptors on testes resulting in virus entry and presence in semen	Low serum testosterone may serve as a severity marker in elderly males.
		Semen analysis of COVID-19 patients showed the presence of SARS CoV-2.
		Possible sexual transmission.
		Long term implications unknown

due to X chromosome inactivation and parental imprinting. But animal studies have shown that the differential ACE-2 activity in females is the result of female hormones and is independent of gonadal sex. Also, this sexual dimorphism in ACE-2 activity is organ-specific and is not found in the lungs and myocardium.[58]

Estrogen and 17-β-estradiol can act on cellular subsets of the immune system by epigenetic mechanisms resulting in modulation of lymphocyte activity and number. This may explain why females were able to clear SARS CoV-2 virus earlier than males. Several clinical trials for the use of estrogen and androgen deprivation therapies in reducing the severity of COVID-19 are ongoing.[59-62]

A case report of a patient with autoimmune polyendocrine syndrome type 1 with COVID-19 was reported wherein the patient experienced prolonged hospital stay and the authors recount issues in endocrine management.[63]

Table 1 summarises all endocrine clinical features reported till date and possible mechanisms for the same.

CONCLUSION

Thus, the relationship between COVID-19 disease and the endocrine system appears to be bidirectional and occurs at multiple levels.

As on date, frequent dysglycaemia and the use of steroids for critically ill patients are likely to have immediate and widespread clinical implications for the management of COVID-19 patients. Further studies are urgently needed to establish the extent and mechanisms of how COVID-19 affects endocrine systems. There are concerns for long term metabolic and endocrine complications after SARS-CoV-2 infection which need further exploration.[64]

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Conflicts of interest
There are no conflicts of interest.

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