

The interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the hypothalamic and endocrinal disorders: A Mini-review

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Abstract

The worldwide medical systems are still being severely impacted by the coronavirus disease-2019 (COVID-19) pandemic, which is responsible for catastrophic mortality and morbidity. It becomes more and more obvious that this unique respiratory virus's impacts go beyond the respiratory system as time goes on and our comprehension of it deepens. The transmembrane serine protease 2 (TMPRSS2) protein is necessary for the severe acute respiratory syndrome coronavirus 2, which is the cause of COVID-19, to gain cellular entry through the angiotensin-converting enzyme 2 (ACE2) receptor. Most endocrine glands exhibit high levels of expression for ACE2 and TMPRSS2. This pays the attention to the effect of COVID-19 on the endocrine system. Besides its capability to pass to the central nervous system especially the hypothalamus inducing a lot of functional disorders in COVID-19 individuals. Although effective vaccines became widely available, and mortality declined but attention is shifting more and more to the lengthy health impacts on COVID-19 survivors. To inform suitable research and effective management, this review provides an overview of the data examining the impacts of COVID-19 on the endocrine glands besides the hypothalamus. In addition, we reported if the endocrinal and thalamic disorders could affect the incidence and progress of COVID-19.

Keywords: SARS-CoV-2; COVID-19; ACE2 receptor; hypothalamus; adrenals; pituitary; thyroid; parathyroid; pancreas; gonads

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented, positive-sense ribonucleic acid (RNA) virus. SARS-CoV-2 transmits mainly

through close contact and via oral droplets.^{1,2}

SARS-CoV-2 is a strain of coronavirus that caused the COVID-19 (coronavirus disease 2019) pandemic, which was firstly reported in China in December 2019, causing severe respiratory

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illness, and has rapidly evolved to spread as a global pandemic, resulting in an enormous burden on worldwide healthcare.³ COVID-19 pandemic represented a disastrous consequence on the world's demographics ensuing in more than 6 million deaths worldwide as of March 2022, emerging as the most consequential global health catastrophe since the era of the influenza pandemic of 1918.⁴ Data showed that the highest incidence rates have been in the United States, South America, and Europe.⁵ While most African countries have reported comparatively lower numbers of confirmed SARS-CoV-2 cases.⁶

SARS-CoV-2 patients typically endorse respiratory symptoms such as fever, cough, fatigue, dyspnea, sore throat, headache, myalgia, and arthralgia. Also, they may exhibit gastrointestinal manifestations such as diarrhea, nausea, vomiting, and abdominal pain.⁷ SARS-CoV-2 patients with comorbidities such as hypertension, diabetes mellitus, heart disease, renal disease, and cerebral stroke are at a higher risk of cytokine storm and mortality.³

Currently, there is no specific antiviral treatment recommended for the treatment of SARS-CoV-2, however, clinical trials are in progress with medications such as lopinavir/ritonavir, chloroquine, hydroxyl-chloroquine, aerosolized alpha-interferon, tocilizumab, and remdesivir.⁴

Pathogenesis

The receptor angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) on host cells act as the obligatory receptors for viral entry as seen in Figure 1. The homotrimer spike glycoprotein, composed of S1 and S2 subunits, protrudes from the virus surface and binds to ACE2. Upon binding to ACE2, the S1 subunit is dissociated with the ACE2 receptor, in a process that requires the presence of TMPRSS2.⁸ This results in a conformational change which provides the S2 subunit the increased stability necessary for membrane fusion.⁹

SARS-CoV-2 enters the lung, deposits in the lung parenchyma, and then gains access to the host cells. SARS-CoV-2 patients showed the presence of viral messenger ribonucleic acid (mRNA) in their blood, stool, and urine samples.

This suggested that SARS-CoV-2 can interact with ACE2 and TMPRSS2 expressed in other organs as well, including the cardiovascular, gastrointestinal, nervous, and endocrine systems. Endocrine glands such as the pancreas, pituitary, thyroid, adrenal glands, testes, and ovaries besides the hypothalamus have been found to express ACE2 and TMPRSS2, with the highest expression in the testes, followed by the thyroid, and the lowest is in the hypothalamus.^{1,10} There are three main mechanisms by which SARS-CoV-2 affects the endocrine glands: 1) Direct viral infection of the gland. 2) Activation of the hypothalamic-pituitary-adrenal axis (HPA) via inflammatory mediators, and 3) Immune-mediated glandular damage secondary to antibody formation or cell-mediated damage.¹¹

COVID-19-associated severe infections are mediated by a cytokine storm, known as a systemic inflammatory response with excessive activation of immune cells specifically T lymphocytes with inflammatory infiltration by macrophages and neutrophils associated with an increased number of peripheral blood cells and proinflammatory mediators such as tumor necrosis factor- α (TNF- α), tumor necrosis factor- β (TNF- β), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and chemokine ligand 2 (CCL2) that result in lung injury. Patients with a cytokine storm can present with acute respiratory failure, sepsis, disseminated intravascular coagulation (DIC), and death.³

The aim of this mini-review was to discuss the hypothalamic and endocrinal complications of SARS-CoV-2 and to highlight any mutual interaction if present focusing on the pituitary, adrenals, thyroid, parathyroid, pancreas and gonads.

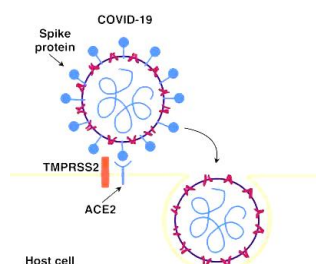


Figure 1. Entry mechanism of SARS-CoV-2.

Methods

The authors searched PubMed/Midline, Connected papers, National library for medicine, Clinical trials.gov, and Google Scholar for case reports and series, retrospective case-control or cohort studies, cross-sectional studies, and reviews. The search focused on the following topics: background of COVID-19 infection, pathogenesis, covid-19 effects on the hypothalamus, adrenals, pituitary gland, thyroid, parathyroid, pancreas, and gonads. Besides, we searched for the effect of hypothalamic and endocrinal disturbances or treatment regimens on the incidence, course, and even prognosis of Covid-19 infection. The search was for free-text words and medical subject headings' terms related to "coronavirus", "SARS-CoV-2", "COVID-19", transmembrane serine protease 2, angiotensin-converting enzyme 2, cytokines storm, hypothalamus, adrenocorticotrophic hormone, hypothalamic-pituitary-adrenal axis, blood-brain barrier, pituitary apoplexy, syndrome of inappropriate antidiuretic hormone secretion, hypophysitis, acromegaly, Cushing's syndrome, growth hormone deficiency, adrenal insufficiency, thyrotoxicosis, subacute thyroiditis, hypothyroidism, euthyroidism, corticosteroids, parathyroid gland, hypoparathyroidism, hypocalcemia, pancreas, amylase, pancreatitis, gender, estrogen, testosterone, androgen deprivation therapy, erectile dysfunction, hypogonadism, and epididymis-orchitis.

SARS-CoV-2 and Hypothalamus

It was reported that SARS-CoV-2 patients display neurological symptoms and respiratory failure in certain cases which could result from an extra-pulmonary origin. There are many hypotheses regarding the viral portal of entry into the central nervous system (CNS). The virus could enter via a hematogenous route by passing through the blood-brain barrier (BBB) or can directly reach the median eminence (ME) where the BBB is lacking or directly across the cribriform plate through the nasopharyngeal epithelium via the olfactory nerve¹² as illustrated in Figure 2.

Hypothalamic neural circuits play vital roles in hypertension, diabetes, sex differences, obesity, and aging which all present as risk factors for severe SARS-CoV-2. The hypothalamus is moreover connected to olfactory/gustative and brainstem cardiorespiratory centers. A post-mortem patient's brain showed invasion and replication of the virus in both the olfactory bulb and the hypothalamus.¹² A study by Kothandaraman et al., 2021, confirmed that SARS-CoV-2 genome sequences were associated with cytopathic effects in the neuronal cytoplasm of the hypothalamus.¹³ Also, Zhou et al., 2020, were successfully able to detect the presence of the SARS-CoV-2 genome in the cerebrospinal fluid (CSF) of a SARS-CoV-2 patient, hence confirming that the virus does indeed infiltrate into the brain, and therefore can complicate any part of the brain including the hypothalamus.¹⁴ Clinical observation of an impaired thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH) response to hypothyroidism and hypocortisolism has implied that the HPA was most probably involved either directly by SARS-CoV-2 or indirectly through autoimmunity triggered by the virus and leading to hypophysitis.^{1,13}

Though less has been documented on the hypothalamic effects of SARS-CoV-2, Chigr et al., 2020, confirmed through autopsy findings that the hypothalamus is a highly probable target of SARS-CoV-2 based on its rich expression of TMPRSS2 and ACE2, especially in the paraventricular nucleus. Magnetic resonance imaging (MRI) and computed tomography (CT) imaging have also shown evidence of SARS-CoV-2 infecting the brain and its different parts, especially via the hypothalamic fenestrated BBB capillaries with fewer tight junctions which are highly permeable to blood-borne substances including viruses.¹⁵ One of the affected regions is the ME, which is adjacent to the arcuate nucleus (AN) of the hypothalamus. The uniquely designed barriers in the hypothalamus allow the AN and ME to access the private milieu with the ME gaining access to the portal blood and the AN to the CSF. This allows the BBB at the ME/AN interface to play a major role in determining the way hypothalamic neurons are

exposed to systemic factors such as viruses.¹⁶ Also, Langlet and colleagues, 2013, found increased viral load in the brain which suggests the virus's ability to exploit this leakiness and cross the BBB.¹⁷ Such infection can result in several deficiencies involving essential growth and metabolism hormones. Therefore, it can cause long-term adverse effects on memory, growth, bone health, pituitary function, fertility, and hence the quality of life.¹⁶

Price et al., 1991, have shown strong neuronal connections between the hypothalamus and the olfactory system. Retrograde and anterograde axonal tracing studies have revealed that projections coming from the olfactory system are more prominent in the lateral hypothalamus in comparison to the thalamus.¹⁸ Moreover, four primary areas in the posterior lateral hypothalamus (olfactory tubercle, anterior olfactory nucleus, piriform cortex, and anterior cortical nucleus of amygdala) were proven to receive this input from the olfactory bulb.¹⁶ The olfactory system plays an important role in the transportation of SARS-CoV-2 into the CNS via the hypothalamus. This hypothesis was supported by recent reports which investigated the neurological manifestations associated with SARS-CoV-2 in patients already diagnosed with SARS-CoV-2. It was found that SARS-CoV-2 RNA was detected by real-time polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen but not in CSF which indicates that the neuro-invasion through the central routes is most likely via the olfactory system.¹⁶ Pascual-Goñi et al., 2020, have shown the involvement of the hypothalamus, dorsal midbrain, and mammillary bodies. This further supported the trans-neuronal spread of the virus given the presence of the neuronal connection between the hypothalamus and the other brain structures.¹⁹

SARS-CoV-2 is usually associated with immunosuppression and lymphopenia. The hypothalamus could contribute to this immune dysregulation in SARS-CoV-2 infection. Several cytokines are up-regulated in SARS-CoV-2 including IL-6, IL-1 β , and TNF- α which are powerful activators of the HPA. It has been found that in stroke and brain trauma, adrenergic stress which involves β -adrenergic

receptors results in massive systemic immunosuppression. The mechanisms of these effects involve activation of the HPA which leads to the release of norepinephrine (NE) and glucocorticoids. These mediators then act synergistically to induce T cell apoptosis, splenic atrophy, and natural killer (NK) cell deficiency. Tyrosine hydroxylase and NE trigger a response in mesenchymal stromal cells present inside the bone marrow most likely through β 3-adrenergic receptors, which results in a reduction of cell retention. Down-regulation of these factors results in lymphopenia and neutrophilia which are two key hematological features of SARS-CoV-2. Importantly, in SARS-CoV-2, HPA activation and glucocorticoid levels are correlated with neutrophilia and lymphopenia.²⁰

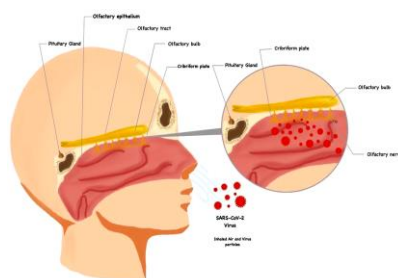


Figure 2. Portal entry of the virus into the central nervous system (CNS) via the cribriform plate into the olfactory bulb.

SARS-CoV-2 and Pituitary Gland

Pituitary Apoplexy

Since ACE2 is expressed in the cerebral vascular endothelium and due to SARS-CoV-2 neurotropism, SARS-CoV-2 invades the pituitary, thus inducing coagulopathy, thrombocytopenia, and platelet dysfunction. Therefore, SARS-CoV-2 could be a precipitating risk factor for pituitary apoplexy which is a sudden hemorrhage and blood infarction of the pituitary gland. Furthermore, several cases of pituitary apoplexy associated with SARS-CoV-2 were reported in the presence of pre-existing macroadenomas.^{21,22} The main non-specific symptoms referred by the patients were ranging from sudden onset of severe headache, nausea, and vomiting, to more serious findings of visual disturbances due to compression of the

surrounding optic structures by a pituitary macroadenoma expanding into the cavernous region.²²

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

There are diverse pathophysiological mechanisms proposed to explain hyponatremia among SARS-CoV-2 patients. The marked elevation of inflammatory cytokines in SARS-CoV-2 leads to cytokine storm which can result in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) via two mechanisms. First, inflammatory cytokines such as IL-6 can directly stimulate the release of antidiuretic hormone (ADH). Second, the cytokines storm can induce SIADH via injury of the lung tissue and alveolar cells, causing ventilation-perfusion mismatch resulting in hypoxic pulmonary vasoconstriction. Consequently, increased ADH secretion occurs due to decreased left atrial stretch,²³ as demonstrated in Figure 3.

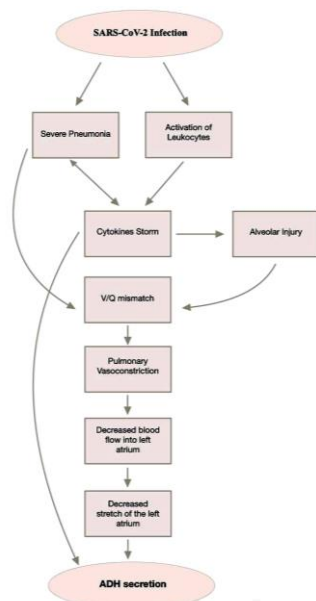


Figure 3. Pathophysiological mechanisms explaining the occurrence of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) among patients with SARS-CoV-2.

Hypophysitis

No strong data were available explaining the link between the hypophysitis occurrence and the SARS-CoV-2 infection. It has been reported that SARS-CoV-2 via an autoimmune mechanism and organ damage could induce endocrinopathies. This was evident in a study based on the severe acute respiratory syndrome (SARS) epidemic in 2003 which revealed adenohypophyseal functional damage in some patients. This damage was then validated by histological abnormalities in pituitary cells obtained from autopsies reflecting the severe course of the disease.²² Recently, Nonglait et al., 2021, reported a case of hypophysis post-SARS-CoV-2 infection. The patient's laboratory values revealed panhypopituitarism in the form of hyponatremia, hypocortisolism, hypothyroidism, low serum free thyroxine (T4), testosterone, and gonadotropins levels along with hyperprolactinemia. MRI, of the sella turcica findings, was indicative of hypophysitis as diffuse pituitary enlargement as well as a thickened stalk with homogenous post-contrast enhancement.²⁴ However, knowing that the administration of glucocorticoids typically results in the remission of hypophysitis, it is plausible that this therapy could result in a decreased incidence of SARS-CoV-2 hypophysitis.^{11,25}

Acromegaly

Acromegaly is a chronic disease caused by a growth hormone (GH) secreting pituitary adenoma eliciting excessive production of insulin-like growth factor-I (IGF-I).^{22,26} Acromegaly patients have several characteristics that may worsen their condition if they contract SARS-CoV-2.²⁷ Numerous comorbidities, including cardiovascular diseases, diabetes mellitus and pulmonary illness with sleep apnea are associated with a higher mortality rate. Thus, if acromegaly is not well-controlled especially in the setting of the SARS-CoV-2 pandemic, it will disturb the life quality and survival because of the multi-system affection as mentioned earlier. Patient's comorbidities and treatment regimen may be altered because of drug-drug interactions with medications used for SARS-CoV-2 treatment.

Long-acting somatostatin receptor ligands (SRLs) such as Lanreotide, Octreotide, and Pasireotide are the main class of drugs used to treat acromegaly. SRLs medications may cause an increase in QTc interval and arrhythmias as a side effect. Despite being unsuccessful in treating and preventing SARS-CoV-2, azithromycin and chloroquine are still prescribed and have been associated with QTc interval prolongation as well. Since acromegaly itself causes arrhythmia, the administration of the medications described above should be restricted or monitored closely. As a result, patients and healthcare professionals must adapt to these changes to keep the disease and comorbidities under control and to prevent acute infections like SARS-CoV-2.^{26,27}

Cushing's Syndrome

Some pituitary patients with Cushing's disease, have certain risk factors that include hypertension, and susceptibility to bacterial, viral, and fungal infections, particularly pneumonia, which is associated with an increased mortality rate. Patients receiving supraphysiologic doses of steroids have an increased risk of contracting SARS-CoV-2 due to steroids' immunosuppressive potential. According to the increased cardiovascular risk profile that this condition involves, cardiovascular diseases (including strokes and heart attacks) are the leading cause of mortality. Not only but also, patients with Cushing's disease have been shown to have an increased venous thromboembolism risk, as frequently reported with SARS-CoV-2, particularly in cases of immobilization, surgery, cardiovascular events, and severe infections. In patients with significant hypercortisolism, intensive surveillance and early intervention is advised when SARS-CoV-2 infection is suspected.^{22,28}

Growth Hormone Deficiency

There are multiple possible pathophysiologic mechanisms that link changes in the GH/IGF-I axis to the severity of SARS-CoV-2. Lubrano et al. 2020, suggested that lower GH levels, seen with older age and males, were significant contributing factors to SARS-CoV-2 infection susceptibility which is hypothesized to be age

and gender-dependent. Poorer SARS-CoV-2 outcomes have been linked to several characteristics of the adult GH deficient syndrome, including immune system dysregulation, hyperglycemia, and obesity. A major factor in defining the severity of SARS-CoV-2 is immune system dysregulation, along with its association with adult-onset GH Deficiency (AoGHD). Since GH is physiologically involved in the growth and maintenance of the immune system, therefore, its pharmacological replacement appears to significantly affect GH-deficient patients' inflammatory status. Another factor in GH Deficiency (GHD) patients that is associated with GH/IGF-I axis impairment and the severity of SARS-CoV-2 is impaired fibrinolysis. GH deficient patients have elevated TNF- α and IL-6 levels, as well as impaired fibrinolysis, which is suggested to increase the cardiovascular risk. Hence, after GH replacement, these parameters improve, indicating that GH may have an inhibitory effect on inflammatory cytokines and normalize the fibrinolytic system.^{29,30}

SARS-CoV-2 and Adrenal Glands

The adrenal glands play an important physiological role in the stress response which is very crucial in the course of SARS-CoV2 infection, such as in the regulation of fluid homeostasis, the regulation of immune response, the control of blood pressure, and the production of sex hormones, which might be responsible for the gender-associated difference in disease progress and survival as observed in SARS-CoV-2 infected patients.³¹

The primary immuno-invasive mechanism used by SARS-CoV-2 is to knock down the host's cortisol stress response. There is a hypothesis indicating that the virus can decrease the host's cortisol stress response by releasing certain amino acids by the SARS-CoV that mimic the host ACTH molecularly. Thus, the generated antibodies against the virus particles will destroy the ACTH in the circulatory system leading to a decrease in cortisol which results in secondary adrenal insufficiency (AI).²¹ There are various mechanisms that can induce AI in patients with SARS-CoV-2 such as vascular damage, viral reproduction, and inflammatory factors.⁸ Critically sick patients frequently have

AI. The storm of cytokine caused by SARS-CoV-2 leads to negative feedback toward the HPA. Also, SARS-CoV-2 can cause adrenalitis and hypophysitis which can lead to either primary or secondary AI.³² SARS-CoV-2 takes the same strategy of molecular mimicry why the SARS-CoV-2 may put patients at risk for reversible adrenal dysfunction which is known as critical illness-related corticosteroid insufficiency (CIRCI). Controlling cellular inflammation with glucocorticoids is ineffective in the case of CIRCI. There are a lot of causes to develop CIRCI in a patient infected with SARS-CoV-2, including dysregulation of the HPA, decreased cortisol metabolism, or glucocorticoid receptor alpha tissue resistance.⁸

Kanczkowski et al., 2022, found that SARS-CoV-2 can replicate in the adrenocortical cells and not only target them. They found SARS-CoV-2 RNA and protein in the adrenal gland in 45% of patients who died from SARS-CoV-2. In addition to that, they found SARS-CoV-2 in the adrenal endothelial cells. Also, the infection of SARS-CoV-2 can enhance the inflammation and activation of apoptosis of adrenocortical cells. The histological findings revealed lymphocytic infiltration and marked inflammation of adrenal vessels in 90% of patients. Moreover, they reported focal necrosis in the glands and vasculitis. In postmortem samples of patients with SARS-CoV-2, they found adrenal lesions that showed adrenal hemorrhage and infarction in mild to severe cases.⁸ Furthermore, Clarke et al., 2021, found fibrin and microthrombi deposited in the adrenal capillaries.⁹

SARS-CoV-2 and Thyroid Gland

SARS-CoV-2-related thyroid dysfunctions include thyrotoxicosis, subacute thyroiditis, hypothyroidism, and non-thyroidal illness syndrome (euthyroid sick syndrome). As ACE2 and TMPRSS2 are expressed in high levels in the thyroid gland so it could infect the host cells directly.^{10,33} ACE2 binds to integrin and modulates the signal transduction, T4 regulates the genes of monomeric proteins that make up integrins, and the thyroid hormones promote the internalizing of integrins, therefore it can influence the SARS-CoV-2 uptake involving integrins, and SARS-CoV-2 could lead to thyroid

dysfunction.^{33,34} Also, thyroid damage and thyrotoxicosis can occur indirectly with SARS-CoV-2 by the “cytokines storm” immune mechanism¹⁰ where the concentration of IL-6 is elevated.³⁵ Hanley et al., 2020 and Yao et al., 2020, reported lymphocytic infiltration in the interstitium,^{36,37} and follicular epithelial disruption.^{21,33,38} Therefore, systemic inflammation and high levels of IL-6 suppress the production of triiodothyronine (T3) and T4.³⁴

The serum levels in thyroid dysfunction with SARS-CoV-2 patients revealed that the patients will mainly have low T3 levels, followed by a decrease in T4 levels, and slightly lower TSH.³³ The reduced TSH levels cannot be explained by the destruction of the follicular epithelium, and it may be related to pituitary gland dysfunction. The levels of T3, T4, and TSH will be lower with increasing the severity of the disease, especially in intensive care unit (ICU) patients.^{10,33}

Furthermore, patients with thyroid autoimmune disease will have worse SARS-CoV-2 clinical course because of the higher levels of IL-6 and TNF- α in comparison with healthy individuals, and as for the predisposed patients, it may break the immunotolerance leading to the onset of immune-mediated thyroiditis or worsen the previous thyroid disease or inducing recurrence.³⁴

Moreover, patients with preexisting hypothyroidism were found not to affect the prognosis of SARS-CoV-2, unlike hyperthyroidism which was found to have a strict relationship with the severity of the systemic inflammation mainly IL-6, it may induce hyperthyroidism onset or relapse of grave's disease. Some SARS-CoV-2 patients with hyperthyroidism and thyrotoxicosis showed poor prognosis and more extended hospital stay in comparison with euthyroidism, and hypothyroidism patients. It was reported that uncontrolled hyperthyroidism could lead to adverse cardiac effects, such as arrhythmias, myocardial ischemia, hemodynamic instability, hypercoagulative-hypofibrinolytic imbalance, and the promotion of oxidative stress.^{34,39} The severity of SARS-CoV-2 infection will determine the injury to the thyroid gland, the levels of T3,

T4, and TSH will be lower as the severity of SARS-CoV-2 infection increases.^{33,34}

Patients with subacute thyroiditis (SAT) may show three consecutive phases: Thyrotoxicosis for the first few months,^{33,35} followed by hypothyroidism for three months then euthyroidism.^{21,33} In the United Kingdom (UK), a study included 334 patients without a history of thyroid gland disease and confirmed with SARS-CoV-2.⁴⁰ Most of the patients were presented with non-thyroidal illness syndrome "euthyroidism" when hospitalized in the ICU, with mild TSH and reduced T4 levels or at normal levels. This is because of the indirect effect on thyroid cells due to systemic immune-mediated post-viral inflammatory response.^{16,39}

In addition, the evaluation of thyroid dysfunction in SARS-CoV-2 patients could be influenced by some medication that the patients receive to prevent the infection or to improve the prognosis of SARS-CoV-2 and reduce the hospital stay. Thyroid glands got affected in some patients that used heparin in the management of SARS-CoV-2 for thromboembolism prevention, as it interfered with the free thyroid hormones assays. Heparin liberates the lipoprotein lipase from the vascular endothelium and the blood samples of the patients showed increased lipoprotein lipase activity, generating non-esterified fatty acids (NEFA). The elevated serum NEFA causes displacement of T4 from the thyroid binding protein, therefore increasing the free T4 (FT4).^{34,38}

In addition, corticosteroids could also influence the thyroid assays, by acting on the hypothalamic-pituitary control of the thyroid reducing the TSH levels and the FT4 and inhibiting the activation of thyroid hormone. Finally, some SARS-CoV-2 patients had been exposed to multiple chest iodinated contrast-enhanced CT which led to transient thyrotoxicosis.³⁸

Although thyroid disorders are common in SARS-CoV-2 patients, it seems that these dysfunctions do not affect the SARS-CoV-2 progression in most cases and are not considered risk factors for the infection. It is worth noting that the majority of the critically ill SARS-CoV-2 patients who have been admitted to the ICU and had chronic illnesses were

diabetes mellitus and chronic kidney disease patients.⁴¹ But the data on the need for monitoring the thyroid patients who were infected are still unclear and the need for follow-up is not supported.³⁴ However, patients who had a thyroid disorder before the infection, still require adequate management during the pandemic.^{38,39,41}

SARS-CoV-2 and Parathyroid Gland

Hypoparathyroidism and hypocalcemia were reported in SARS-CoV-2 patients. There are various ways which can explain the hypocalcemia in COVID-19: low oxygen reaching the tissues damages them with an impaired response of parathyroid gland and inadequate parathyroid hormone (PTH) secretion in response to calcium disturbance as well as increased levels of inflammatory cytokines.⁴²⁻⁴⁴ SARS-CoV-2 affects the parathyroid function by either of two mechanisms. First, by directly invading the parathyroid glands in which they bind to the acidophilic cells' ACE2 receptors which is referred to as true hypoparathyroidism. Secondly, and indirectly through respiratory alkalosis associated with SARS-CoV-2 infection that affects the activation of parathyroid hormone in renal tissue which is named relative hypoparathyroidism. In addition, chronic respiratory alkalosis will lead to an increase in the resistance of renal PTH receptors to PTH which will lead to hypocalcemia and hyperphosphatemia,⁴⁵ as shown in Figure 4.

Hypocalcemia is a common biochemical characteristic that sets SARS-CoV-2 apart from other acute respiratory distress syndromes.⁴⁶ Additionally, it seems to be a predictor of the emergence of a serious SARS-CoV-2 infection. However, these findings seem to be mostly related to a lack of vitamin D, which is why hypocalcemia is understood to be related to infections, a report by Sun et al., 2020, demonstrated that lower calcium levels were associated with poor clinical outcomes.⁴⁷ Serum calcium levels below 1.9 mmol/L and/or symptoms at any level below the reference range indicate severe hypocalcemia.⁴⁸

Moreover, decompensation of primary hypoparathyroidism, which was previously well-tolerated, has also been linked to SARS-CoV-2 illness as reported by Bossoni et al., 2020, who

noticed acute perioral paresthesia, dysarthria, low levels of serum calcium, phosphorus, and PTH, in addition to a minor SARS-CoV-2 infection in an elderly female patient with a history of thyroidectomy. This pointed to the possibility that the SARS-CoV-2 infection precipitated severe hypocalcemia in the setting of subclinical post-surgical hypoparathyroidism.⁴⁹

On the other side, according to the available data, there is no evidence that people with hypoparathyroidism are more likely to have the SARS-CoV-2 virus or even worse outcomes. Patients with hyperparathyroidism should be reminded that hypercalcemia can cause symptoms like nausea, vomiting, and abdominal pain, and should also be aware of the value of remaining hydrated because dehydration can cause hypercalcemia.⁵⁰ Fever, diarrhea, and vomiting which are all signs of SARS-CoV-2 infection can all lead to dehydration. Therefore, it is crucial that patients stay hydrated if these symptoms start to manifest. Failure to hydrate properly could result in progressive hypercalcemia and a worsening of their health, which might necessitate emergency admission.⁵¹

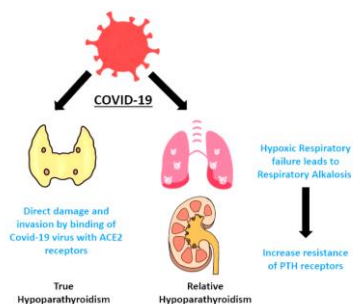


Figure 4. Pathogenesis of hypoparathyroidism in SARS-CoV-2 infection.

SARS-CoV-2 and Pancreas

ACE2 receptors are highly expressed in both the exocrine and the endocrine (islet cells) parts of the pancreas, even higher than in the lung alveolar epithelial cells.⁵² Infection of the pancreas is plausible as the virus could spread from the duodenal epithelium to the pancreatic duct and then to the acinar and islet cells.⁵³

Moreover, SARS-CoV-2 infects and replicates in islets cells, inducing morphological, transcriptional, and functional changes with subsequent reduction in insulin secretory granules and impairment of glucose-dependent insulin secretion of β -cells.¹⁰ There are several underlying mechanisms that explain the damage of the pancreatic islets by SARS-CoV-2 these include direct virus-mediated injury, systemic inflammatory response, circulating proinflammatory interleukins and cytokines, drug-induced injury, and virus-induced lipotoxicity.⁵⁴ Moreover, pancreatic injury can be induced by several indirect events such as cytokine storm and endothelial dysfunction, leading to a process called “viral sepsis”.⁵⁵ In addition, the immune response against the virus can impair the ability of the liver, muscles, and other peripheral organs to uptake glucose. Then the impaired muscles and liver insulin-mediated glucose uptake and gluconeogenesis induced by the inflammation result in hyperinsulinemia and hyperglycemia. Therefore, SARS-CoV-2 can cause acute transient skeletal muscle insulin resistance by increasing interferon- γ production.¹⁰ Moreover, the pancreatic islets damage during the infection was indicated by elevated levels of circulating pancreatic enzymes (amylase and lipase).⁵⁶

Diabetes mellitus (DM) is the highest comorbidity in hospitalized patients with SARS-CoV-2. Elderly patients with DM are at greater risk to develop severe SARS-CoV-2 disease with its subsequent complications and increased mortality.¹⁰ Diabetic microvascular and macrovascular complications may lead to these outcomes. In addition, decreased exercise capacity, stress, cachexia, and muscle weakness in patients during severe infection and long-term hospitalization decrease insulin sensitivity, especially in survivors of acute respiratory distress syndrome (ARDS) and sepsis. Moreover, rhabdomyolysis can arise during infection, which might contribute further to glucose dysregulation. In DM patients, SARS-CoV-2 reduces the ACE2 expression, resulting in decreased degradation of angiotensin II, increased secretion of aldosterone, and hypokalemia. Renal potassium loss can lead to a further decrease in insulin secretion.¹⁰

Dipeptidyl peptidase-4 (DPP-4) is another coronavirus receptor that has a vital role in glucose homeostasis. DPP-4 can bind to SARS-CoV-2 and affect glucose homeostasis; however, it is not yet confirmed.¹⁰ Glucocorticoids used for patients with severe SARS-CoV-2 may also result in hyperglycemia.¹¹

Acute pancreatitis (AP) is not specifically caused by SARS-CoV-2, it is a common disease with many causes, and the etiology remains unknown. Several viruses have been implicated in the etiology of AP including cytomegalovirus, Epstein-Barr virus, hepatitis A/E viruses, herpes simplex virus, varicella-zoster virus, mumps, measles, and coxsackie virus. The mechanism by which these viruses cause pancreatitis is unknown and each virus might cause pancreatitis by a different mechanism. These mechanisms include viral replication in pancreatic acinar cells, and impaired zymogen secretion resulting in protease leakage and activation, in addition to cholangiopathy and ampullary edema,⁵⁷ as seen in Figure 5.

According to the Atlanta classification,⁵² the diagnosis of the AP requires at least two of three of the following features: (a) Acute severe abdominal pain suggestive of pancreatitis. (b) Serum lipase or amylase level greater than three times of upper normal limit. (c) Imaging findings of AP. Severe cases of AP and SARS-CoV-2 are characterized by a cytokine storm, which leads to multiorgan failure and increased mortality.⁵⁴

The SARS-CoV-2 infection has been reported to trigger Type 1 DM with diabetic ketoacidosis and hyperosmolarity suggesting either direct β -cell cytotoxicity or an immune reaction.¹¹ The cytopathic effect of SARS-CoV-2 on the pancreas is still unclear since the virus isolation on pancreatic tissue has not been reported.⁵⁶

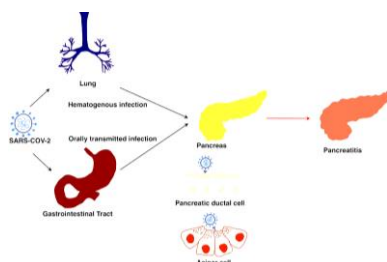


Figure 5. SARS-CoV-2 induced pancreatitis.

SARS-CoV-2 and Gonads

The SARS-CoV-2 pandemic can be called a sexually dimorphic disease, as the females are less susceptible to getting infected by SARS-CoV-2 and exhibit a significantly low mortality rate in comparison to males.⁵⁸ The reason behind this, is estrogen, the main sex hormone in females. Estradiol (E2) receptors regulate the strength of both innate and adaptive immunity. The estrogen, estrone and estriol, interact with estrogen receptor 1/2 (ESR1/2), inhibiting SARS-CoV-2 that causes inflammation and immune response signaling in the host cells and regulating the expression of ACE2 in differentiated airway epithelial cells.⁵⁸ In support of this, high levels of E2 protect young females in SARS-CoV-2 patients, and in females, > 55 of age the estrogen drops to extremely low levels that cause an increase in the mortality rate among them.⁵⁹ Recent studies show that estrogen can be used as a treatment in SARS-CoV-2 patients, as high concentrations of E2 treatment may reduce ACE2 mRNA expression.^{34,59} However, ACE2 receptors have been detected in the ovaries and oocytes of both reproductive and postmenopausal women.³⁴ Positive vaginal fluid has been detected in a few cases only, while others failed to detect the virus in vaginal fluid.¹⁰ Researchers hypothesized that SARS-CoV-2 infects the ovarian tissue and thus hampers ovarian function, and oocyte viability causing infertility, and miscarriage. In addition, it mutilates the endometrial cells and distresses the early embryo implantation.⁶⁰

On the other hand, the main risk factors for mortality from SARS-CoV-2 are old age, male gender, and comorbidity. The evidence points to the immunosuppressive role of testosterone on a different aspect of the immune system, and it appeared to suppress the antibody response to infection as well as vaccination, and the inflammatory cells such as dendritic cells and macrophages. Also, testosterone dampens the development and function of T and B cells. Thus, testosterone affects the immune response to viral infection negatively, and that explains the higher morbidity and mortality among males.^{61,62}

Low testosterone levels in both pre-puberty and advanced age exhibit less susceptibility to infection than older adult males. However, despite the high testosterone levels in neonates, the infection rate was low in babies at the 6th to 8th week after delivery, which indicates that age and comorbidity are much more important factors than testosterone levels.⁵⁸ Furthermore, it had been reported that most of the male patients who transferred to ICU had low testosterone levels.^{34,61}

Two mechanisms can be used for androgen deprivation therapy (ADT): (1) Blocking TMPRSS2 by interfering with infection at the lung level, and (2) Stimulating the immune system by reducing testosterone's immunosuppressive properties. Therefore, ADT for prostate cancer may reduce susceptibility to SARS-CoV-2 infection but worsen the course in an advanced stage.⁶³ In prostate and testis, ACE2 and TMPRSS2 receptors are highly expressed, specifically in seminiferous duct cells, spermatogonia, Leydig and Sertoli cells increasing the vulnerability of the male reproductive organs to SARS-CoV-2 damage.^{60,62}

In convalescent SARS-CoV-2 patients, erectile dysfunction (ED) has been reported and viral particles have been detected in penile tissue for up to 7 months after infection.⁶³ Several causes associated with illness recovery can affect erectile function, such as subclinical hypogonadism, psychological distress, or impaired pulmonary hemodynamics. However, the majority of studies are based on a relatively small sample size, and there is no confirmation that SARS-CoV-2 severity is associated with ED.⁶⁴

Epididymo-orchitis as well has been reported in almost a quarter of infected males. This raises concerns about the ability of SARS-CoV-2 to enter the testis and break down the testis-blood barrier and affect spermatogenesis, and potentially be spread through sexual contact.⁶⁴ Spermatogenesis is a temperature-sensitive process; subsequently, it might be affected by high temperature due to fever.¹⁰ Testicular inflammation due to SARS-CoV-2 infection could be attributable to direct viral invasion in addition to the seminiferous injuries, reduction in Leydig cells, mild inflammation, impaired

spermatogenesis, and delay in sperm maturation.⁶⁴

It is worth mentioning that the rate of ACE2 is much higher in infertile men than in normal fertile men means those with reproductive disorders are more susceptible to getting infected by SARS-CoV-2. Nevertheless, hypogonadism may have a protective effect on the initial SARS-CoV-2 infection but may lead the patient towards a more severe clinical course as well.⁶⁰

In conclusion, it is crucial to highlight that ACE2 and TMPRSS2 receptors represent an entry point for SARS-COV-2. Possible endocrine derangements and hormonal imbalances can occur as new-onset symptoms or as a recurrence of previous endocrine diseases. Reviewing the aspects of the effects of SARS-COV-2 on the endocrine glands draws attention to the importance of establishing a focused research effort to identify the exact mechanisms for glandular pathogenesis and impairment that may be involved in the development of these glandular disorders associated with SARS-COV-2 infection.

Abbreviations

ACE: Angiotensin Converting Enzyme; ACE2: Angiotensin Converting Enzyme 2; ACTH: Adrenocorticotrophic Hormone; ADH: Antidiuretic Hormone; ADT: Androgen Deprivation Therapy; AI: Adrenal insufficiency; AoGHD: Adult-Onset GH Deficiency; AP: Acute pancreatitis; ARDS: Acute Respiratory Distress Syndrome; BBB: Blood Brain Barrier; CCL2: Chemokine ligand2; CIRCI: Critical Illness-related corticosteroid insufficiency; CNS: Central Nervous System; COVID-19: Corona Virus Disease-2019; CSF: Cerebrospinal fluid; CT: Computed Tomography; DM: Diabetes mellitus; DPP4: Dipeptidyl Peptidase 4; E2: Estradiol; ED: Erectile Dysfunction; ESR1/2: Estrogen receptor ½; FT4: Free thyroxine; GH: Growth Hormone; GHD: Growth Hormone Deficiency; HPA: Hypothalamus-pituitary-adrenal axis; ICU: Intensive Care Unit; IFNγ: interferon gamma; IGF-I: Insulin-like growth factor-I; IL-1β: Interleukin-1β; IL-6: Interleukin-6; ME: Median Eminence; MRI: Magnetic resonance imaging; mRNA: Messenger ribonucleic acid; NE: Norepinephrine; NEFA: Non-esterified fatty acids; NF-KB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NK: Natural killer; PAI: Primary adrenal insufficiency; PCR: Polymerase chain reaction; PTH:

Parathyroid hormone; RBD: Receptor Binding Domain; RNA: Ribonucleic acid; RT-PCR: Reverse transcription-polymerase chain reaction; SARS: Severe Acute Respiratory Syndrome; SARS-CoV-2: Severe Acute Respiratory Syndrome-Corona Virus-2; SAT: Subacute thyroiditis; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; SRLs: Somatostatin Receptor Ligands; T3: Triiodothyronine; T4: Thyroxine; TMPRSS2: Transmembrane Protease Serine 2; TNF- α : Tumor necrosis factor- α ; TNF- β : Tumor necrosis factor- β ; TSH: Thyroid stimulating hormone; UK: United Kingdom.

Author Contributions

AMK, EMA, HYN, JAA, MMA, RAA and SKF equally contributed to conceptualization, data collection and writing of the manuscript draft. FEH contributed to the conceptualization, supervision, reviewing, and editing of the final manuscript.

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