

## Mini-Review

# SARS-CoV-2 (COVID-19) and the Endocrine System

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**Abbreviations:** ACE2, angiotensin converting enzyme 2; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin A1c; HHS, hyperosmolar hyperglycemic state; IL-6, interleukin-6; LH, luteinizing hormone; MERS-CoV, Middle East respiratory syndrome coronavirus; NTIS, nonthyroidal illness syndrome; RAAS, renin-angiotensin-aldosterone system; SARS-CoV, severe acute respiratory syndrome coronavirus; SGLT-2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin (thyroid-stimulating hormone).

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## Abstract

As SARS-CoV-2 (COVID-19) overtakes the world, causing moderate to severe disease in about 15% of infected patients, COVID-19 is also found to have widespread effects throughout the body with a myriad of clinical manifestations including the endocrine system. This manuscript reviews what is known about the impact of COVID-19 on the pathophysiology and management of diabetes (both outpatient and inpatient) as well as pituitary, adrenal, thyroid, bone, and gonadal function. Findings in this area are evolving, and long-term effects of infection remain an active area of further research.

**Key Words:** COVID-19, diabetes mellitus, thyroid diseases, adrenal, gonads

With more than 28 million confirmed cases worldwide, SARS-CoV-2 (COVID-19) causes moderate to severe pulmonary disease in about 15% of infected patients. COVID-19 also has widespread effects throughout the body with lesser-known clinical manifestations. Knowledge about the impact of this virus on the endocrine system is emerging and is the focus of this review. PubMed and the Cochrane Library were searched for clinical studies and reviews concerning the effect of COVID-19 on diabetes, adrenal,

parathyroid, thyroid, and gonadal axes. Reference searches were conducted in retrieved articles.

## 1. Diabetes Mellitus

Diabetes mellitus (DM) is one of the most prevalent chronic diseases globally, estimated to affect about 9.3% of the world's population and expected to increase in the coming years [1]. Such a high prevalence of diabetes in the general

population makes it an important comorbidity to consider during the COVID-19 pandemic. Diabetes has been known to increase susceptibility to infections, particularly in the respiratory tract. This was seen in prior coronavirus outbreaks with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [2-4]. There is also evidence to suggest increased incidence of COVID-19 among patients with diabetes [5, 6]. Adequate blood glucose and blood pressure management are key to primary prevention of COVID-19 infection. Hyperglycemia has harmful effects on innate immunity, including dysfunction of phagocytosis, cell-mediated immunity, and neutrophil chemotaxis [7-9]. Elevated blood glucose levels also affect ACE2 expression, which is the COVID-19 viral binding site for host cell entry [10]. This is thought to account for the increased incidence of COVID-19 infection in patients with diabetes. To prevent infections, outpatient medical therapies should be optimized to target an outpatient plasma glucose goal of 72 to 144 mg/dL (90-144 mg/dL in the frail or elderly), and a glycated hemoglobin A1c (HbA1c) level of less than 7% [11]. For those who have continuous glucose monitors, time in range should be above 70%, and hypoglycemia less than 4% of the time. All patients are encouraged to follow advice from the government and the Centers for Disease Control and Prevention to minimize exposure by physical distancing. During the pandemic, patients may experience disruptions in their routine care, which may increase utilization of telehealth modalities or self-monitoring. Additionally, disruption to usual diet or exercise patterns may be an opportunity for physicians to promote healthy lifestyle interventions.

In the event of COVID-19 infection, patients with diabetes more often develop a severe or critical disease course compared with patients without diabetes [5]. In a recent meta-analysis of 6452 patients from 30 studies, diabetes was found to be associated with higher mortality, increased severity, and increased frequency of acute respiratory distress syndrome (ARDS) in patients with COVID-19 [12]. In a Chinese Center for Disease Control and Prevention report, the overall COVID-19 case fatality rate more than tripled from 2.3% to 7.3% in patients with diabetes when compared to their general population [13]. For these reasons, physicians should maintain a lower threshold to hospitalize a patient with COVID-19 and diabetes. Even among patients with preexisting diabetes, differences in glycemic management can affect the outcome of COVID-19 disease. In a study of 187 inpatients with COVID-19, patients with hyperglycemia (>180 mg/dL) had higher interleukin-6 and D-dimer levels, more progression of pneumonia on computed tomography scans of the chest, and overall higher mortality when compared to patients with normoglycemia (140-180 mg/dL) [14]. Another larger

COVID-19 study compared 282 patients with diabetes and well-controlled blood glucose to 528 patients with poorly-controlled blood glucose (mean blood glucose of 115 mg/dL vs 196 mg/dL) [15]. The normoglycemic patients had lower incidences of lymphopenia and leukocytosis, and lower levels of C-reactive protein, procalcitonin, aspartate transaminase, and D-dimer. Only 12.6% of patients in the well-controlled group developed hypoxia with SpO<sub>2</sub> below 95%, compared with 22.7% in the poorly-controlled group. The well-controlled group required less usage of antibiotics, steroids, vasopressors, intubation, and extra-corporeal membrane oxygenation and had a significantly lower death rate (1.1% vs 11.0%, with an adjusted HR of 0.13,  $P < 0.001$ ). There was also a significant difference in the rates of complications, including ARDS, acute kidney injury, septic shock, and disseminated intravascular coagulation [15]. As more data emerges, it remains clear that diabetes and hyperglycemia have a negative effect in COVID-19 infection and that tight glycemic control remains crucial to prevent poor outcomes and complications.

At this time, there is no evidence to change our outpatient glycemic targets in COVID-19 infection (plasma glucose goal remains 72-144 mg/dL, and a HbA1c goal of less than 7%). However, blood glucose should be monitored at least twice a day in the setting of infection.

All major classes of antihyperglycemic medications can be continued for patients affected by COVID-19 in the ambulatory setting under the right circumstances. Generally, metformin is held for patients with evidence of organ dysfunction, or even for nausea, vomiting, or diarrhea, due to the risk of lactic acidosis [12]. Metformin should not be arbitrarily discontinued, because recent studies suggest that metformin may have a positive influence on prognosis for type 2 diabetes mellitus (T2DM) patients with COVID-19 infection [16]. Sulfonylureas and meglitinides can cause hypoglycemia and should be held for at-risk patients with poor caloric intake. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors can worsen dehydration by increasing urinary excretion of glucose and have an increased risk of euglycemic ketoacidosis. Consider holding SGLT-2 inhibitor medications in patients at risk of dehydration, such as those who cannot maintain adequate fluid intake. Long- or intermediate- acting insulin may be started in patients who have hyperglycemia, either from held medications or COVID-19 disease. Those patients who are unable to tolerate oral intake are also candidates for inpatient management as COVID-19 is known to become more severe in this patient population.

Further medication adjustments may be necessary for patients started on hydroxychloroquine, due to the potential for hypoglycemia. Although not a dedicated antihyperglycemic agent, multiple case reports have demonstrated hypoglycemia

from hydroxychloroquine in patients with and without diabetes alike [17-20]. Prior cases have suggested a reduced insulin requirement of about 30% to 35% [18, 21].

Of special mention, dipeptidyl peptidase-4 (DPP-4) inhibitors are attracting attention as a possible therapeutic agent in COVID-19 [22, 23]. The DPP-4 protein is a known binding site for the MERS spike protein, and mice with higher DPP-4 expression had more severe MERS disease [24, 25]. Viral modeling demonstrates the potential interaction of the COVID-19 spike protein and DPP-4 receptor, but this has not been confirmed experimentally [26]. DPP-4 inhibitors may also indirectly affect COVID-19 infection since they are immunosuppressive via reduced T-cell differentiation and reduced pro-inflammatory cytokine production. Prior to COVID-19, data had shown that patients on DPP-4 inhibitors had overall similar numbers of upper respiratory tract infections compared with those on other antihyperglycemic agents [27]. In ARDS, DPP-4 inhibitor use led to reduced histological findings of lung injury [28]. Studies further looking at the role of DPP-4 inhibitors as a therapeutic agent in COVID-19 are pending (NCT04341935). For now, there is insufficient evidence to change prescribing patterns for DPP-4 inhibitor medications.

Patients should not self-discontinue other related medications such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Speculation surrounding the use of ACE inhibitors and ARBs in COVID-19 infection stems from the observation that the viral spike protein attaches to host cells through the ACE2 receptor. The renin-angiotensin-aldosterone system (RAAS) inhibitors boost the expression of ACE2, which was initially thought to increase host alveolar cell susceptibility to COVID-19 invasion and potentially worsen the severity of disease [29]. ACE inhibitor and ARB therapy may reduce lung injury by balancing the ratio of angiotensin II and angiotensin<sub>1-7</sub>, since ACE catalyzes production of angiotensin II and ACE2 then degrades this to angiotensin<sub>1-7</sub> [30]. When ACE2 is downregulated, such as when COVID-19 binds, then angiotensin II levels are unopposed and lead to vasoconstriction, inflammation, and catecholamine release [31, 32]. Angiotensin II levels are higher in patients infected with SARS and ARDS, and levels correlate with viral load and acute lung injury [32, 33]. This is the theory behind recombinant soluble ACE2 use as a potential therapy to reduce lung injury in COVID-19. ACE2 trials demonstrate a measurable effect to reduce COVID-19 lung injury in animal models and studies are ongoing in the human population (NCT04375046, NCT04382950) [34, 35].

Despite hypotheses that ACE inhibitors or ARBs would affect the severity of COVID-19 infection, the data have been

inconsistent. Initial observations suggested that patients on RAAS inhibitors had worse outcomes in COVID-19 infection than patients who did not take these medications, but this was heavily confounded by the fact that patients on RAAS inhibitors have more comorbidities such as hypertension, diabetes, kidney disease, or heart failure [36-39]. When compared to other patients with hypertension, there was no increase in hospital admissions, severity of disease, or mortality for patients on ACE inhibitors or ARBs [40-42]. Some data suggests that these drugs may have a positive effect, trending toward reduced hospitalizations and mortality for patients with diabetes [43, 44]. Overall, guidelines from major hypertension societies recommend against discontinuing ACE inhibitors or ARBs due of the risk of worsening the underlying conditions these therapies were intended to treat [45-50].

On the whole, management of diabetes and COVID-19 in the outpatient setting should focus on tight glycemic control with medication optimization and lifestyle interventions to lower the risk of disease progression, morbidity, and mortality. Providers should consider how well the patient's blood glucose is controlled and if oral intake is adequate when adjusting the outpatient medication regimen. Table 1 provides a summary of common antihyperglycemic medication classes that may be continued in the outpatient setting (as well as the inpatient setting) with important considerations. Patients should be discouraged from stopping their medications without consulting their doctor, as this may lead to an exacerbation of their existing medical conditions.

In the inpatient setting, treating hospitalized COVID-19 positive patients who are hyperglycemic can be complex given the severity of their illness [9, 51]. COVID-19 has been associated with direct  $\beta$ -cell damage in addition to immune-mediated destruction of  $\beta$ -cells due to the inflammatory cytokines, including interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ . These patients are also prone to hypokalemia, due to downregulation of pulmonary ACE2 and reduced angiotensin II degradation leading to increased aldosterone secretion. Hypokalemia can lead to reduced insulin secretion. Also aggravating hyperglycemia is treatment of COVID-19 with lopinavir-ritonavir, resulting in lipodystrophy and subsequent insulin resistance [52].

One of the challenges during the COVID-19 pandemic has been the need for clinicians without diabetes expertise to provide diabetes care to COVID-19 positive patients in the hospital. In the management of the hospitalized individuals with or suspected of having COVID-19 infection, it is important to have simple and safe diabetes guidelines, which will need frequent revision as new evidence emerges. Fortunately, guidelines from the major endocrine and diabetes societies have been published to help manage these

**Table 1.** Recommendations for Antihyperglycemic Medications for the Treatment of Patients With Diabetes and COVID-19 in the Inpatient and Outpatient Settings

Medication class	Outpatient use	Inpatient use	Comments
Insulin (basal or rapid-acting)	X	X	May be added or increased to improve glycemic control
Metformin	X		Risk of lactic acidosis, particularly with organ dysfunction. Consider holding if nausea, vomiting, or diarrhea
Sulfonylureas	X	X*	Risk of hypoglycemia. Consider holding if poor dietary intake
Meglitinides	X	X*	Risk of hypoglycemia. Consider holding if poor dietary intake
DPP-4 inhibitors	X	X*	
GLP-1 agonists	X		May worsen nausea, vomiting, or diarrhea
SGLT-2 inhibitors	X		Risk of hypotension and euglycemic DKA. Consider holding if poor fluid intake

\*While sulfonylureas, meglitinides, and DPP-4 inhibitors are not contraindicated in the inpatient setting, they are often held as they may not be well tolerated and safety data on inpatient use of oral medications is limited.

Abbreviations: DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter-2.

patients [53-55]. These guidelines acknowledge the emphasis on early discharge with a need for close follow-up, especially in those newly started on insulin in whom rapid dose reduction is often required.

A significant number of COVID-19-positive patients not previously known to have diabetes present with hyperglycemia, so it is important to monitor blood glucose in all admissions. In the inpatient setting, as in the outpatient setting, medication classes may have to be changed. On admission, SGLT-2 inhibitors, metformin, and glucagon-like peptide-1 (GLP-1) receptor agonists should be discontinued, while DPP-4 inhibitors may be continued if clinically helpful (Table 1). There are many reports of unusual presentations of diabetic emergencies, including people with T2DM presenting in diabetic ketoacidosis (DKA) or mixed ketoacidosis and hyperosmolar hyperglycemic state (HHS) [5, 56]. It is important to check ketones in all patients who present with an elevated blood glucose. This is even more important if a patient is on an SGLT-2 inhibitor, which has been associated with a potential for increased incidence of euglycemic DKA. If ketones persist despite usual care and glycemic improvement, 10% to 20% glucose solutions should be utilized. Fluid requirement will be variable and may differ if DKA or HHS is present. The concern for pulmonary fluid extravasation (lung leak) or myocarditis will certainly affect fluid requirements [57]. If mild DKA is present, a subcutaneous insulin protocol using rapid-acting insulin every 2 hours should be considered to minimize need for an intravenous (IV) insulin drip with frequent glucose monitoring. Subcutaneous insulin protocols for treating mild DKA on the ward or in an observation unit are safe and effective, and demonstrate no difference in mortality, length of hospital stay, total amount of insulin administration, or number of hypoglycemic events compared with individuals treated with regular insulin drip

(or IV insulin) [58]. A reasonable glucose goal for individuals with COVID-19 in the hospital is 140 to 180 mg/dL, the same glucose target as for non-COVID hospitalized patients.

In the intensive care unit setting, severe insulin resistance may lead to a high insulin requirement of >20 units insulin/hour. Widely fluctuating insulin doses have been well-documented, often in patients on tube feeds. Hypoglycemia is also an important risk, particularly in patients whose continuous tube feeding is interrupted. Hypoglycemia should also be considered if hydroxychloroquine, sulfonylureas, or meglitinides are used, if steroids are being tapered, or if the patient's renal function is declining.

For hyperglycemia outside of the critical care area it is important to test capillary blood glucose using point of care (POC) testing before meals and at bedtime. A basal-bolus regimen based on body weight is recommended with 50% of the insulin as basal and 50% as rapid-acting to cover carbohydrates consumed with correction insulin as needed added to the dose. For individuals on only continuous tube feeding, to minimize the risk of hypoglycemia, the total insulin should be dosed as 40% basal and 60% as rapid-acting, distributed as 25% every 6 hours aligned with POC glucose testing. Blood glucose control in patients receiving only bolus tube feedings can be achieved by using rapid-acting insulin every 4 to 6 hours immediately at the start of the feeding, assuring a match of nutrition and insulin. Other dosing considerations include declining renal function and interruption of tube feedings for procedures, high residuals, or a clogged or dislodged feeding tube.

Reasonable weight-based recommendations for the total insulin dose are: 0.2 units/kg in patients with prior pancreatectomy, 0.3 units/kg in patients with acute kidney injury, chronic kidney disease, end-stage renal disease, liver failure, the malnourished or elderly, 0.4 units/kg in patients

with type 1 DM, 0.4 units/kg in insulin-naïve patients with T2DM and body mass index (BMI) <30, 0.5 units/kg in insulin-naïve patients with T2DM and BMI >30, 0.6 units/kg in patients on insulin with T2DM, and 0.6 units/kg in patients with T2DM on steroids. If steroids are instituted in patients already on insulin, a reasonable recommendation is to increase the insulin dose by 20%. If prednisone or hydrocortisone are used in the morning, the bolus dose should be increased by 20%, divided over 3 meals. If a long-acting steroid such as dexamethasone is used, the basal dose should be raised 10% and the bolus dose 10% divided by 3 for each meal.

Insulin requirements should be assessed daily. If blood glucose is greater than 100 to 140 mg/dL fasting or greater than 180 mg/dL random/nonfasting, an increase of insulin dosage by 10% to 20% is indicated. However, if blood glucose is less than 100 mg/dL, a decrease in dose by 10% to 20% should be considered. Another method can be to take half of the correctional doses over the past 24 hours and add 50% to basal insulin and 50% to short-acting insulin.

Since insulin is the main therapy to control glucose levels in admitted patients and this requires frequent monitoring of glucose levels done by fingerstick method, the use of continuous glucose monitoring (CGM) should be considered to reduce exposure time for healthcare professionals, to reduce the use of personal protective equipment, and to maintain glycemic control. CGM measures and reports the interstitial glucose levels every 5 to 15 minutes and remains accurate for the 10- to 14-day duration of the sensor life, depending on the system utilized [59]. The lag time between the capillary and interstitial compartment is approximately 4 minutes, with an accuracy of accuracy of 92.5% in adults [59]. One system has an alarm to warn users both at high and low glucose levels, along with trend arrows of the direction of the glucose change. In the United States, these devices have not been FDA-approved in the hospital setting which remains a primary barrier to further implementation. Studies are ongoing on the use of CGM in the hospital for COVID-19 and non-COVID patients alike (NCT04230694, NCT04417270, NCT04430608). When considering CGM, it is important to exclude patients on hemodialysis or peritoneal dialysis, with hypotension requiring vasopressors, with signs of poor perfusion, on acetaminophen use of more than 1000 mg every 6 hours, and with significant pitting edema (3+ or greater) as seen in cirrhosis with ascites, congestive heart failure with edema, or nephrotic syndrome.

## 2. Pituitary-Adrenal Axis

Numerous studies have shown that adrenal hormones play a crucial role in the immune response. The effect of adrenal

hormones cortisol, epinephrine, and norepinephrine on the immune system is complex; this raises the concern that patients with adrenal insufficiency may be at a disadvantage in fighting COVID-19. Investigators have found that while norepinephrine and epinephrine mobilize immune cells into the bloodstream, epinephrine and cortisol are responsible for “trafficking” or directing the cells to become more specific types of immune cells and directing them to tissues where they are needed [60-62]. It is recognized that a short-term increase in blood leukocytes indicates mobilization of cells, whereas a decrease represents a trafficking of the cells to target organs such as the lung or skin [61, 63].

Scientists have studied the extent to which the lack of cortisol in patients with adrenal insufficiency may affect how the immune system responds to stress. Healthy individuals and patients with chronic adrenal insufficiency were exposed to a psychosocial stress test in one study [64]. Both groups showed similar norepinephrine response; however, epinephrine and cortisol levels were lower in chronic adrenal insufficiency patients and only the healthy individuals demonstrated the expected stress-related rise in lymphocytes with a subsequent decrease. The patients with chronic adrenal insufficiency only exhibited the normal post-stress migration of lymphocytes if they were given additional steroids to mimic a stress response. There is currently no direct evidence that this altered response worsens the course of patients who contract COVID-19 and have underlying adrenal insufficiency; however, it certainly raises that concern.

Retrospective studies have shown variable degrees of increased mortality in patients with adrenal insufficiency compared with the general population [65]. Infections, cancer, and cardiovascular disease account for the increase in mortality. Furthermore, a retrospective, observational study in patients with Addison disease found a 5-fold higher mortality from infection, with pneumonia as the major cause [66, 67]. Investigators studied the immune cell make-up of patients with primary adrenal insufficiency due to autoimmune adrenalitis or bilateral adrenalectomy and compared them with healthy subjects [68]. They found natural killer cells were significantly lower in the patients with adrenal insufficiency, which, they concluded, has the potential to render patients with adrenal insufficiency more susceptible to invading pathogens. Studies have also suggested that, due to underlying depletion of the innate immune system of patients with adrenal insufficiency, steroid replacement regimens that aim to restore a more physiological circadian glucocorticoid rhythm result in reduced susceptibility to infections [69].

Treatment of patients with adrenal insufficiency under major stress to avoid adrenal crisis has been studied and should be considered when treating critically ill patients with COVID-19. Prete et al recently conducted an

investigation of steroid administration regimens during major stress and found that continuous intravenous hydrocortisone infusion was the only administration mode that achieved expected stress level median cortisol levels in patients with primary adrenal insufficiency [70]. Continuous intravenous infusion of 200 mg hydrocortisone over 24 hours, preceded by a bolus of 50 to 100 mg of hydrocortisone, is recommended when treating critically ill COVID-19 patients who have known adrenal insufficiency.

Expert consensus to date notes that patients with adrenal insufficiency can be assumed to have an increased risk of COVID-19 and have a higher risk of complications due to potential for adrenal crisis [71]. To date we do not have data or studies reporting the risk of COVID-19 in adrenal insufficiency and recommendations are based on expert consensus. As recent reviews and society guidelines have recommended, patients with known adrenal insufficiency should be counseled on using sick-day rules immediately at the onset of symptoms suspicious for COVID-19 and should continue these doses until symptoms resolve [72, 73]. Expert consensus has recommended oral stress dose coverage of 20 mg hydrocortisone every 6 hours to maintain a more continuous level of steroid support in a patient with known adrenal insufficiency, given the known associated persistent inflammation and stress associated with a suspected or confirmed acute COVID-19 infection [71].

Several trusted organizations have given us guidance on recommendations for patients with adrenal insufficiency during this pandemic. The American Association of Clinical Endocrinologists (AACE) Position Statement urges physicians to ensure that patients with adrenal insufficiency and uncontrolled Cushing syndrome strictly adhere to physical distancing and hand-washing guidelines, have sufficient medication supply (ideally a 90-day supply), and are well-educated on when they need to seek emergency medical treatment [74]. A statement from the European Society of Endocrinology indicates that although we lack direct evidence and data on outcomes of COVID-19 in adrenal insufficiency patients, historical data on impaired immune function may suggest higher risk of complications and mortality [75]. The Italian Society of Endocrinology Expert opinion recommends a more graded approach, with the doubling of usual steroid dose in suspected COVID-19 with mild symptoms and increasing further to 100 mg (parenteral preferred) if condition progresses to what is defined as moderate COVID-19, and finally high-dose 200 mg/24 hour continuous infusion in the setting of severe disease [76]. This group of experts also recommends introducing heparin early in adrenal insufficiency patients, due to the known coagulation abnormalities associated with glucocorticoid use and coagulopathies observed with severe COVID-19 [77, 78].

There is good evidence that hypercortisolism due to both adrenal and pituitary Cushing syndrome is associated with increase in mortality and risks for acute myocardial infarction, venous thromboembolism, stroke, and infections [79]. Guidance set forth by expert consensus are recommending patients with Cushing syndrome be informed they are at a higher risk of infection from COVID-19 due to an immunocompromised state and therefore should adhere to strict social distancing guidelines and precautions [80]. To date, this is based on expert group consensus and not on stronger data or statistics of COVID-19 infections in patients with Cushing syndrome. Comorbidities associated with Cushing disease, such as diabetes and hypertension, should be aggressively managed, since data suggest they adversely affect outcomes in COVID-19 infections [37, 81]. Medical therapy for treatment of Cushing syndrome is recommended as first-line therapy during the pandemic. Transsphenoidal surgery is not recommended unless urgently required during the peak of the pandemic, due to the high risk of aerosol formation and risk to health care providers; however, this is an evolving area and neurosurgical expertise should be requested to weigh risks and benefits [82].

At this time, there is no evidence of direct pituitary or hypothalamic effect from COVID-19 infection; however, authors have described evidence of hypothalamic-pituitary involvement by SARS in a study of 61 survivors. Forty percent of survivors had biochemical evidence of central adrenal insufficiency and most resolved within a year [83]. The proposed mechanism was reversible hypophysitis or direct hypothalamic damage by the virus. Data from SARS experience demonstrate that antibodies produced against the virus inadvertently destroyed adrenocorticotropic hormone and led to blunting of cortisol stress response [84]. Authors Pal and Banerjee point out that, as endocrinologists, we can assume COVID-19 may affect the hypothalamus-pituitary based on prior SARS experience and genomic similarities of the coronaviruses, and therefore we should have a low threshold for suspicion of central adrenal insufficiency in a patient with current or prior COVID-19 infection and concerning signs or symptoms [52, 85].

### 3. Pituitary-Thyroid Axis

There is currently inadequate data regarding COVID-19's impact on the thyroid. ACE2 receptors, the entry site for COVID-19, have been located in the thyroid [86]. Several case reports have described the onset of subacute thyroiditis in patients diagnosed with COVID-19 infection during the pandemic [87-89]. Given that the etiology of subacute thyroiditis has been attributed to viral infections, it is not surprising that COVID-19 could be an etiology.

It is important to note that although infections have been implicated in the genesis of thyroid autoimmunity, having an autoimmune thyroid disease has not been shown to predispose patients to increased infections.

In general, thyroid function should not be assessed during severe clinical illness unless thyroid dysfunction is deemed to be a contributing factor to the underlying clinical picture; in critical illness such as in some cases of COVID-19 infection, there is an increased risk of nonthyroidal illness syndrome (NTIS) evidenced by decreased free triiodothyronine (T3), increased reverse T3, with low-normal or decreased free thyroxine (T4) and low-normal thyrotropin (thyroid-stimulating hormone; TSH) [90]. In severe illness, the degree of change in thyroid hormones is related to the severity of illness. A retrospective analysis of thyroid function tests in hospitalized patients with moderate to critical COVID-19 symptoms found decreased TSH and total T3 compared with similarly ill patients who had non-COVID pneumonia. The degree of TSH and total T3 suppression correlated with the disease severity; total T4 was not significantly different from the control group and thyroid function tests normalized after recovery [91]. A report on 274 patients showed TSH and free T3 were significantly lower in deceased patients compared with recovered patients [92]. NTIS is thought to be adaptive but might be associated with poor clinical outcomes in certain cases. Current data is inconclusive as to the benefit of treating NTIS, and it has been shown on occasion to be detrimental when thyroid hormone levels have been supplemented in patients with NTIS [90].

Out of 287 patients hospitalized with COVID-19 in Italy, at least 20% had thyrotoxicosis with negative thyroid receptor antibodies and a majority of that subgroup subsequently normalized their thyroid function with resolution of the illness [93]. Of the autopsy data currently available in English, there is only one that reported thyroid findings (normal thyroid and multinodular goiter in 2 patients) [94]. For hyperthyroid patients who are being treated with antithyroid drugs, the possibility of agranulocytosis should be kept on the forefront. Although a rare side effect, with 0.2% to 0.5% prevalence, agranulocytosis could present with symptoms such as sore throat or fever, also seen in patients with COVID-19, and can occur at any point during treatment. If this occurs, it is imperative to check a complete blood count as soon as possible to ascertain the presence of agranulocytosis (absolute neutrophil count <500). Once confirmed, immediate cessation of the antithyroid drug is warranted, as is initiation of treatment with antibiotics [95].

The new onset of thyroid dysfunction should prompt a referral to an endocrinologist if there are any management concerns during the pandemic. Overall, with regards

to thyroid disease management, the American Thyroid Association, the Endocrine Society, and the American College of Clinical Endocrinologists have included information on their various websites to provide guidance in the management of thyroid disease during this outbreak of COVID-19 disease.

#### 4. Bone and Parathyroid

With the exception of interest in the possible role of vitamin D in mitigating COVID-19 disease, there is a lack of data on the impact of COVID-19 on the parathyroid gland and bone. Most of the focus has been on access to therapy during the pandemic. There is a valid concern over difficulties in accessing hospital or clinic administered osteoporotic drugs, particularly denosumab (Prolia), which has detrimental effects with delays of more than 6 months between dose administration. To avoid delays in management, expert consensus suggests either setting up low-risk COVID-19 environments and administering denosumab when it is due or switching to bisphosphonates where appropriate [96]. Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL) that inhibits osteoclast formation, decreases bone resorption, increases bone mineral density, and reduces the risk of fracture. There are currently no data to suggest an increased risk of viral infections when denosumab is used for the treatment of osteoporosis [97]. However, hypocalcemia is known to be associated with infections; a recent report of COVID-19 patients showed that lower calcium levels were correlated with worse clinical outcomes [98].

The interest in vitamin D as a possible tool in the armamentarium of COVID-19 treatment stems from the widespread distribution of the vitamin D receptor in most tissues throughout the body. Vitamin D has been implicated in innate and adaptive immune responses. It helps to maintain cell physical barrier integrity through tight junctions, gap junctions, and adherens junctions. Vitamin D has also been found to enhance cellular innate immunity partly through the induction of antimicrobial peptides. It also preferentially increases the expression of anti-inflammatory cytokines while reducing the expression of pro-inflammatory cytokines, which are all beneficial in COVID-19 [99, 100].

Prior to the COVID-19 pandemic, there had been interest in investigating the impact of vitamin D supplementation on the risk of respiratory infections. Although the data around use of vitamin D and infection prevention is inconclusive, a recent meta-analysis using individual data points concludes that oral vitamin D<sub>3</sub> supplementation reduced the risk of acute respiratory tract infections (OR 0.88%). The effects were more pronounced when

baseline 25-hydroxyvitamin D levels were less than 25 ng/mL. Subgroup analysis showed the protective effects were mainly in individuals receiving daily or weekly vitamin D without additional bolus doses [101].

In the current COVID-19 pandemic, there are some data suggesting that European countries with lower mean vitamin D levels had higher rates of infection and mortality related to COVID-19 [102]. In a similar vein, a number of reports have looked at the geographic location of countries or states and compared their COVID-19 related mortality rate. Generally, northern latitude locations with higher rates of vitamin D deficiency, be it in Europe or the United States, have had higher rates of related mortality [103, 104]. Thus, although the data are inconclusive, it would be prudent to ensure patients have sufficient levels of vitamin D and initiate supplementation where needed, especially in inpatient groups such as the elderly who have a higher risk of vitamin D deficiency. The Endocrine Society recommends supplementation with 1000 to 4000 IU/d of vitamin D and a serum 25(OH)D concentration of 30 ng/mL or higher.

## 5. Pituitary-Female Gonadal Axis

Data on COVID-19 and the female gonadal and reproductive function are not available or are limited. Authors recently speculated on possible ways COVID-19 might attack ovarian tissue and endometrial epithelial cells due to the expression of ACE2 in these tissues [86, 105, 106]. Jing et al also provide an insightful review on potential COVID-19 targets that may influence reproductive health, also noting ACE2 expression in oocytes, ovary, uterus and vagina [107].

Men with COVID-19 are at higher risk for worse outcomes and death compared with women despite same prevalence of infection [108]. Sex differences in immune response in general (not specific to COVID-19) have long been studied. Although the process is complex, experts point out that adult females mount a stronger innate and adaptive immune response than males, which subsequently results in faster clearance of pathogens but contributes to their increased susceptibility to inflammatory and autoimmune disease [109].

Straub goes in depth into potential causes for the immuno-supportive role of estrogens and complex criteria such as the type of immune stimulus which determine if estrogens play an anti-inflammatory or pro-inflammatory role [110]. A study of male and female mice infected with SARS revealed that male mice were more susceptible to infection compared to female mice [111]. They highlight the protective effect of estrogen signaling in females by noting the increase in mortality of mice after removing

this signaling pathway with ovariectomy or treating with estrogen receptor antagonist. A different study in mice infected with influenza A virus found that ovariectomized female mice treated with estradiol had reduced severity of illness with less morbidity compared to placebo-treated mice despite having the same virus titers [112]. This is an area of future research in trying to understand the differences in severity between men and women with COVID-19.

## 6. Pituitary-Male Gonadal Axis

The mRNA for ACE2, the receptor for COVID-19, is expressed in human testes, primarily in spermatogonia, Leydig cells, and Sertoli cells [113]. The expression level there is perhaps the highest in the body [114]. In addition, the cellular transmembrane serine protease TMPRSS2, also important for viral cellular entry, is also present in the testes [115].

Leydig cells produce testosterone and Sertoli cells interact with spermatogenic cells to control sperm cell differentiation. COVID-19 shares a 76% amino acid sequence identity with SARS, which caused orchitis and widespread germ cell destruction in human testes more than a decade ago [116]. Therefore, there is potential for COVID-19 to invade the testes via ACE2 and interfere with testosterone release and sperm production, especially since the blood-testicular barrier may be disrupted in the presence of systemic or local inflammation. There are several reports of scrotal discomfort, even severe scrotal pain in people with COVID-19 and one report of a case of orchiepididymitis [114, 117-119].

Testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin levels were measured in 81 hospitalized confirmed COVID-19 patients, aged 20 to 54 with a median age of 38 years [120]. Controls were age-matched males who had previously received reproductive function evaluation and were healthy with normal fertility. It is important to remember that any acute illness may lower testosterone levels. Testosterone was nominally but not significantly reduced in the COVID-19 patients compared with controls, but LH was significantly higher. The testosterone-to-LH ratio was significantly lower in the infected individuals. This pattern of elevated LH with statistically unchanged testosterone is what might be seen in early gonadal failure and speaks against a direct COVID-19 effect at the hypothalamus or pituitary and likely on gonadal Leydig cells. FSH was unchanged. This testicular defect could be caused by direct testicular damage by the virus or by an indirect inflammatory/immune response in the testicles [121].

Semen was examined for COVID-19 mRNA in 12 affected men aged 22 to 38 years and in testes samples of



a 67-year-old man who died [122]. Of the 12 survivors, 11 had mild clinical disease and 1 was asymptomatic. None of the semen samples was positive for COVID-19 mRNA. In another study, no COVID-19 mRNA was found in the semen of 34 men collected between 8 and 75 days (median 31 days) after COVID-19 diagnosis [117]. A third group reported on a population of 18 men who had recovered from COVID-19 infection and a control group of 14 unaffected men [123]. No COVID-19 mRNA could be detected in any of the semen samples. Patients with moderately severe infection had a statistically significant impairment of sperm quality (sperm concentration, total number of sperm per ejaculate, total number of progressive motility, total number of complete motility) compared with men who had recovered from a mild infection and the control group. Subdividing people who had a fever from those who had not (regardless of the severity of infection) showed that there were significant differences in sperm volume, motility, and immotile sperm, although all values were still in the normal range. In contrast, in another study of 38 men providing semen samples, 23 had clinically recovered, while 15 were in the acute stage of the infection. Semen was COVID-19 positive in 6 patients including 4 of 15 patients who were in the acute stage of infection [124]. Therefore, it appears that COVID-19 mRNA can be seen in some men who had infection, although the numbers reported are still small. It also appears that COVID-19 may alter sperm quality, although again the numbers are small. We lack data on those with severe acute infection and the possible effects of drugs used to treat the disease.

The American Society for Reproductive Medicine (ASRM) has regular updates on its website. At this point, acknowledging that much remains to be learned about COVID-19, ASRM calls “for gradually and judiciously resuming the delivery of reproductive care” [125].

## 7. Conclusions

This paper explores what is presently known about COVID-19 with regard to the endocrine system, particularly as it pertains to diabetes, thyroid and parathyroid disease, adrenal disease, and the gonadal axes. COVID-19 and the systemic short- and long-term effects of infection remain an active area of further research.

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## Additional Information

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