**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 pul- monary 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.

# 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](#_bookmark4)]. 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 out- breaks with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [[2-4](#_bookmark6)]. There is also evidence to suggest increased incidence of COVID-19 among patients with diabetes [[5](#_bookmark7), [6](#_bookmark8)]. Adequate blood glucose and blood pressure management are key to primary prevention of COVID-19 infection. Hyperglycemia has harmful effects on innate immunity, including dysfunc- tion of phagocytosis, cell-mediated immunity, and neu- trophil chemotaxis [[7-9](#_bookmark10)]. Elevated blood glucose levels also affect ACE2 expression, which is the COVID-19 viral binding site for host cell entry [[10](#_bookmark11)]. This is thought to account for the increased incidence of COVID-19 infec- tion in patients with diabetes. To prevent infections, out- patient 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](#_bookmark12)]. 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 govern- ment and the Centers for Disease Control and Prevention to minimize exposure by physical distancing. During the pan- demic, 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.

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In the event of COVID-19 infection, patients with dia- betes more often develop a severe or critical disease course compared with patients without diabetes [[5](#_bookmark7)]. 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 dis- tress syndrome (ARDS) in patients with COVID-19 [[12](#_bookmark13)]. 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](#_bookmark14)]. 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](#_bookmark15)]. 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](#_bookmark16)]. The normoglycemic pa- tients had lower incidences of lymphopenia and leukocyt- osis, and lower levels of C-reactive protein, procalcitonin, aspartate transaminase, and D-dimer. Only 12.6% of pa- tients in the well-controlled group developed hypoxia with SpO2 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 signifi- cantly lower death rate (1.1% vs 11.0%, with an adjusted HR of 0.13, *P* < 0.001). There was also a significant differ- ence in the rates of complications, including ARDS, acute kidney injury, septic shock, and disseminated intravascular coagulation [[15](#_bookmark16)]. As more data emerges, it remains clear that diabetes and hyperglycemia have a negative effect in COVID-19 infection and that tight glycemic control re- mains crucial to prevent poor outcomes and complications. At this time, there is no evidence to change our out- patient 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 moni-

tored 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 am- bulatory setting under the right circumstances. Generally, metformin is held for patients with evidence of organ dys- function, or even for nausea, vomiting, or diarrhea, due to the risk of lactic acidosis [[12](#_bookmark13)]. 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](#_bookmark17)]. 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 in- hibitor 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 tol- erate oral intake are also candidates for inpatient manage- ment as COVID-19 is known to become more severe in this patient population.

Further medication adjustments may be necessary for pa- tients 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 dia- betes alike [[17-20](#_bookmark20)]. Prior cases have suggested a reduced in- sulin requirement of about 30% to 35% [[18](#_bookmark19), [21](#_bookmark21)].

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Of special mention, dipeptidyl peptidase-4 (DPP-4) inhibitors are attracting attention as a possible thera- peutic agent in COVID-19 [[22](#_bookmark22), [23](#_bookmark23)]. 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](#_bookmark24), [25](#_bookmark25)]. Viral modeling demonstrates the poten- tial interaction of the COVID-19 spike protein and DPP-4 receptor, but this has not been confirmed experimentally [[26](#_bookmark26)]. DPP-4 inhibitors may also indirectly affect COVID- 19 infection since they are immunosuppressive via reduced T-cell differentiation and reduced pro-inflammatory cyto- kine production. Prior to COVID-19, data had shown that patients on DPP-4 inhibitors had overall similar num- bers of upper respiratory tract infections compared with those on other antihyperglycemic agents [[27](#_bookmark27)]. In ARDS, DPP-4 inhibitor use led to reduced histological findings of lung injury [[28](#_bookmark28)]. 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 evi- dence to change prescribing patterns for DPP-4 inhibitor medications.

Patients should not self-discontinue other related medi- cations such as angiotensin-converting enzyme (ACE) in- hibitors 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 suscep- tibility to COVID-19 invasion and potentially worsen the severity of disease [[29](#_bookmark29)]. ACE inhibitor and ARB therapy may reduce lung injury by balancing the ratio of angio- tensin II and angiotensin1-7, since ACE catalyzes production

of angiotensin II and ACE2 then degrades this to angio-

tensin1-7 [[30](#_bookmark30)]. When ACE2 is downregulated, such as when COVID-19 binds, then angiotensin II levels are unopposed and lead to vasoconstriction, inflammation, and catechol- amine release [[31](#_bookmark31), [32](#_bookmark32)]. Angiotensin II levels are higher in patients infected with SARS and ARDS, and levels correlate with viral load and acute lung injury [[32](#_bookmark32), [33](#_bookmark33)]. 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](#_bookmark34), [35](#_bookmark35)].

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 infec- tion 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 hyper- tension, diabetes, kidney disease, or heart failure [[36-39](#_bookmark38)]. When compared to other patients with hypertension, there was no increase in hospital admissions, severity of dis- ease, or mortality for patients on ACE inhibitors or ARBs [[40-42](#_bookmark40)]. Some data suggests that these drugs may have a positive effect, trending toward reduced hospitalizations and mortality for patients with diabetes [[43](#_bookmark41), [44](#_bookmark42)]. 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](#_bookmark44)].

On the whole, management of diabetes and COVID- 19 in the outpatient setting should focus on tight glycemic control with medication optimization and lifestyle inter- ventions 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 ad- equate when adjusting the outpatient medication regimen. [Table 1](#_bookmark3) 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 stop- ping 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 com- plex given the severity of their illness [[9](#_bookmark10), [51](#_bookmark45)]. COVID-19 has been associated with direct *β*-cell damage in addition to immune-mediated destruction of *β*-cells due to the in- flammatory cytokines, including interleukin-1*β* and tumor necrosis factor-*α*. These patients are also prone to hypo- kalemia, due to downregulation of pulmonary ACE2 and reduced angiotensin II degradation leading to increased aldosterone secretion. Hypokalemia can lead to reduced insulin section. Also aggravating hyperglycemia is treat- ment of COVID-19 with lopinavir-ritonavir, resulting in lipodystrophy and subsequent insulin resistance [[52](#_bookmark46)].

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 indi- viduals 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 dia- betes societies have been published to help manage these 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 glu- cose 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 moni- toring of glucose levels done by fingerstick method, the use of continuous glucose monitoring (CGM) should be considered to reduce exposure time for healthcare profes- sionals, to reduce the use of personal protective equipment, and to maintain glycemic control. CGM measures and re- ports 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](#_bookmark52)]. The lag time between the capillary and interstitial compartment is approximately 4 minutes, with an accuracy of accuracy of 92.5% in adults [[59](#_bookmark52)]. 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 re- quiring vasopressors, with signs of poor perfusion, on acet- aminophen use of more than 1000 mg every 6 hours, and with significant pitting edema (3+ or greater) as seen in cir- rhosis with ascites, congestive heart failure with edema, or nephrotic syndrome.

# 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 pa- tients 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 spe- cific types of immune cells and directing them to tissues where they are needed [[60-62](#_bookmark55)]. 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](#_bookmark54), [63](#_bookmark56)].

# Conclusions

This paper explores what is presently known about COVID-19 with regard to the endocrine system, particu- larly 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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