Abstract

As SARSCoV2 (COVID19) overtakes the world, causing moderate to severe disease in about 15% of infected patients, COVID19 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 COVID19 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 longterm effects of infection remain an active area of further research.

Key Words: COVID19, diabetes mellitus, thyroid diseases, adrenal, gonads

With more than 28 million confirmed cases worldwide, SARSCoV2 (COVID19) causes moderate to severe pul monary disease in about 15% of infected patients. COVID 19 also has widespread effects throughout the body with lesserknown 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 COVID19 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 worlds 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 COVID19 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 (SARSCoV) and Middle East respiratory syndrome (MERSCoV) [24]. There is also evidence to suggest increased incidence of COVID19 among patients with diabetes [5, 6]. Adequate blood glucose and blood pressure management are key to primary prevention of COVID19 infection. Hyperglycemia has harmful effects on innate immunity, including dysfunc tion of phagocytosis, cellmediated immunity, and neu trophil chemotaxis [79]. Elevated blood glucose levels also affect ACE2 expression, which is the COVID19 viral binding site for host cell entry [10]. This is thought to account for the increased incidence of COVID19 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]. 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 selfmonitoring. Additionally, disruption to usual diet or exercise patterns may be an opportunity for physicians to promote healthy lifestyle interventions.

In the event of COVID19 infection, patients with dia betes more often develop a severe or critical disease course compared with patients without diabetes [5]. In a recent metaanalysis 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 COVID19 [12]. In a Chinese Center for Disease Control and Prevention report, the overall COVID19 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 COVID19 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 COVID19, patients with hyperglycemia (>180 mg/dL) had higher interleukin6 and Ddimer levels, more progression of pneumonia on computed tomography scans of the chest, and overall higher mortality when compared to patients with normoglycemia (140180 mg/dL) [14]. Another larger COVID19 study compared 282 patients with diabetes and wellcontrolled blood glucose to 528 patients with poorlycontrolled blood glucose (mean blood glucose of 115 mg/dL vs 196 mg/dL) [15]. The normoglycemic pa tients had lower incidences of lymphopenia and leukocyt osis, and lower levels of Creactive protein, procalcitonin, aspartate transaminase, and Ddimer. Only 12.6% of pa tients in the wellcontrolled group developed hypoxia with SpO2 below 95%, compared with 22.7% in the poorly controlled group. The wellcontrolled group required less usage of antibiotics, steroids, vasopressors, intubation, and extracorporeal 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]. As more data emerges, it remains clear that diabetes and hyperglycemia have a negative effect in COVID19 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 COVID19 infection (plasma glucose goal remains 72144 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 COVID19 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]. 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 COVID19 infection [16]. Sulfonylureas and meglitinides can cause hypoglycemia and should be held for atrisk patients with poor caloric intake. Sodium glucose cotransporter2 (SGLT2) inhibitors can worsen dehydration by increasing urinary excretion of glucose and have an increased risk of euglycemic ketoacidosis. Consider holding SGLT2 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 COVID19 disease. Those patients who are unable to tol erate oral intake are also candidates for inpatient manage ment as COVID19 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 [1720]. Prior cases have suggested a reduced in sulin requirement of about 30% to 35% [18, 21].

Of special mention, dipeptidyl peptidase4 (DPP4) inhibitors are attracting attention as a possible thera peutic agent in COVID19 [22, 23]. The DPP4 protein is a known binding site for the MERS spike protein, and mice with higher DPP4 expression had more severe MERS disease [24, 25]. Viral modeling demonstrates the poten tial interaction of the COVID19 spike protein and DPP4 receptor, but this has not been confirmed experimentally [26]. DPP4 inhibitors may also indirectly affect COVID 19 infection since they are immunosuppressive via reduced Tcell differentiation and reduced proinflammatory cyto kine production. Prior to COVID19, data had shown that patients on DPP4 inhibitors had overall similar num bers of upper respiratory tract infections compared with those on other antihyperglycemic agents [27]. In ARDS, DPP4 inhibitor use led to reduced histological findings of lung injury [28]. Studies further looking at the role of DPP4 inhibitors as a therapeutic agent in COVID19 are pending (NCT04341935). For now, there is insufficient evi dence to change prescribing patterns for DPP4 inhibitor medications.

Patients should not selfdiscontinue other related medi cations such as angiotensinconverting enzyme (ACE) in hibitors and angiotensin II receptor blockers (ARBs). Speculation surrounding the use of ACE inhibitors and ARBs in COVID19 infection stems from the observation that the viral spike protein attaches to host cells through the ACE2 receptor. The reninangiotensinaldosterone system (RAAS) inhibitors boost the expression of ACE2, which was initially thought to increase host alveolar cell suscep tibility to COVID19 invasion and potentially worsen the severity of disease [29]. ACE inhibitor and ARB therapy may reduce lung injury by balancing the ratio of angio tensin II and angiotensin17, since ACE catalyzes production

of angiotensin II and ACE2 then degrades this to angio

tensin17 [30]. When ACE2 is downregulated, such as when COVID19 binds, then angiotensin II levels are unopposed and lead to vasoconstriction, inflammation, and catechol amine 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 COVID19. ACE2 trials demonstrate a measurable effect to reduce COVID19 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 COVID19 infection, the data have been inconsistent. Initial observations suggested that patients on RAAS inhibitors had worse outcomes in COVID19 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 [3639]. 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 [4042]. 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 [4550].

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 patients blood glucose is controlled and if oral intake is ad equate 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 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, 51]. COVID19 has been associated with direct cell damage in addition to immunemediated destruction of cells due to the in flammatory cytokines, including interleukin1 and tumor necrosis factora. 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 COVID19 with lopinavirritonavir, resulting in lipodystrophy and subsequent insulin resistance [52].

One of the challenges during the COVID19 pandemic has been the need for clinicians without diabetes expertise to provide diabetes care to COVID19 positive patients in the hospital. In the management of the hospitalized indi viduals with or suspected of having COVID19 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 greate