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Review Article

Beyond the Fingerstick: Complications of Diabetes in the Acutely Ill Patient with Covid-19 with Lessons from Translation Biology and Therapeutics

Nashawi M[1]*, Ahmed M[1], Jarrar Y[1], Abualfoul M[2], Issa O[3] and Chilton RJ[1]

[1]Department of Medicine, Division of Internal Medicine, Texas

[2]Department of Internal Medicine, Methodist Dallas Medical Center, Texas

[3]Department of Biology, The University of Texas at Arlington, Texas

***Corresponding author:** Mouhamed Nashawi, Department of Medicine, Division of Internal Medicine, MC 7870 UT Health San Antonio 7703 Floyd Curl Dr., San Antonio, TX, 78229-3900

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Abstract

The affliction that the Coronavirus Disease 2019 (COVID-19) pandemic has placed on the infrastructure of healthcare institutions across the globe permeates to the level of the provider, hampering clinical decision-making capacity and capability. Associated with the latter has been unprecedented, sweeping changes in biomedical equipment manufacturing, triage dynamics, and implementation of medical interventions in a landscape replete with clinical literature attempting to characterize features in COVID-19 patients. Preliminary assessments into the elements of the SARS-CoV-2 virus (the strain of coronavirus responsible for COVID-19) in addition to the delineation of patient flux pertaining to COVID-19 has identified diabetes as a prevalent comorbidity with increased mortality and increased disease burden in the acutely ill. The volume of patients with COVID-19 superimposed upon complicated diabetes exemplifies that insight into this association offers an expanded perspective of diabetes mellitus. Moreover, given the extensive organ compromise seen in COVID-19 in addition to the established notion that diabetes is a systemic syndrome of metabolism, an appraisal of the literature of medical management and precursory findings serve as bearings that help render clinical principles into viable treatments. In this review we investigate the array of contemporary literature surrounding COVID-19 with a perspective centered upon the management of acute diabetes complications, namely diabetic ketoacidosis and hyperosmolar hyperglycemic state, with emphases into translational biology and pharmacotherapeutics.

Keywords: SARS-CoV-2; COVID-19; Diabetes; Diabetic; Ketoacidosis; HHS; Translational; Metabolism

Background

SARS-CoV-2 is a virus in the coronaviridae family, a grouping of positive-sense, single-stranded RNA viruses possessing an envelope that are well accounted for their propensity in causing infections of the human respiratory tract [1]. The clinical picture presenting as the cumulative manifestations of SARS-CoV-2 is called coronavirus disease 2019 (COVID-19), and this diagnosis has been associated with decreased cardiopulmonary fitness, renal compromise, neural deficits and concomitant stroke, complicated coagulopathy, and viremia among other findings being elucidated nearly daily amid active global pandemic status [2-5]. With the first reported incidence in Wuhan, China this particular coronavirus strain is notable in the sense that it expresses increased pathogenicity relative to other coronaviridae due to the expression of a novel repertoire of viral proteins as marked by genetic sequencing studies [6]. The latter is evident by SARS-CoV-2 manifesting as a global pandemic as declared by the World Health Organization (WHO) in early March of 2020, with millions of confirmed cases and hundreds of thousands of fatalities that are ever-increasing.

Some of the earliest findings regarding the distribution of COVID-19 patients recorded comorbidities in 1099 confirmed cases across multiple centers, noting that diabetes was associated with 16.2% of patients [7]. Subsequent analyses of 140 patients hospitalized with COVID-19 and confirmed SARS-CoV-2 infection revealed that 12.0% of these patients had diabetes [8]. Even larger analyses conducted by the Center for Disease Control & Prevention (CDC) in the United States using 7,162 COVID-19 patients measured the underlying prevalence of diabetes to be 11.0%, all underscoring the rife nature of hyperglycemic pathology with this virus [9]. When controlled for other comorbidities, 24 out of 174 consecutive patients analyzed by Guo et al. had a predisposition for increased risk of pneumonia, elevated inflammatory and pro-thrombotic serum markers, and mortality [10]. Given recent epidemiological studies that project the worldwide prevalence of diabetes to be over 400 million in 2019, there represents a thin line between warranted proclivity of assessment and missed opportunity for healthcare providers to scrutinize the role of diabetes and management thereof in patients with COVID-19 in the acute setting [11]. To solidify this point, one of the first case series of 138 hospitalized patients by Wang et al. comparing the distribution of comorbidities in the Intensive Care Unit (ICU) setting of COVID-19 patients found that patients receiving ICU care were more likely to have diabetes (22.2% versus 5.9%, P=0.009) [12]. However, the practice of managing acute complications of diabetes, such as Diabetic Ketoacidosis (DKA) and hyperosmolar hyperglycemic status warranting ICU care, in the setting of COVID-19 is still an

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emerging field with a paucity of formal guidelines rooted in evidence-based medicine.

Translational Biology and Underlying Risk

While the pathways connecting increased disease burden in COVID-19 and diabetes have not been illustrated definitively, the current body of knowledge surrounding the pathophysiology of diabetes heavily implicates the inflammasome in the aforementioned outcomes in COVID-19 patients [13]. On face value, changes in the inflammasome promote pathologic airway remodeling and predispose patients with Type 1 and Type 2 diabetes mellitus to increased rates of general respiratory infections [14]. In diabetes, sustained hyperglycemia promotes an environment of increased oxygen metabolism within the aerobic processes taking place in the mitochondria during oxidative phosphorylation, and this erratic processing of oxygen results in dysfunctional oxygen metabolism and the generation of Reactive Oxygen Species (ROS) [15]. This impact of ROS on gene expression and local physiology is paramount, with an aggregate inflammatory effect that spans multiple organ systems. This damage results in an environment conducive to worsened outcomes in respiratory disease, such as infection with SARS-CoV-2 [16,17]. Evaluations of the respiratory system involving modalities such as histology and gene expression accentuate the impact of inflammation in not only describing COVID-19 but outlining shared attributes with inflammation-mediated by diabetes as a means of connecting these two diseases processes [18].

A post-mortem analysis was by Xu et al. was one of the premiere, comprehensive assessments of the lung parenchyma in a patient with COVID-19, and communicated findings suggestive of Acute Respiratory Distress Syndrome (ARDS) including pulmonary edema, alveolar exudation, inflammatory cell infiltrates and hyaline membrane formation [2,19-21]. The aggregate processes involved in hampered oxygen utility in the diabetic patient of pertinence to the COVID-19 patient is consistent with animal models of lung tissue [4.] For example, hyperglycemia-induced lung injury and subsequent ROS generation in rat models has been consistent with epithelial-to-mesenchymal transformations that accommodate lung injury with more affinity than euglycemic lungs, potentially shedding light into the pathogenesis of increased disease burden in COVID-19 patients [4]. Rabbit models of diabetic lung injury show that upon histology, glucotoxicity-mediated airway damage manifests similarly to the COVID-19 lungs, with accounts of newfound alveolar exudation, inflammatory cell infiltrates, and edema [22].

Speculation into the role that the generation of ROS has to play in mitochondrial physiology stem from the ability of ROS to expedite gene transcription regulating TGF-β and NF-κB, two central figures in systemic inflammation. For instance, TGF-β stimulates pathways that result in pathologic cellular hypertrophy, fibrosis, and the accumulation of extracellular matrix material (advanced glycation products or AGEs). The development of AGEs within vessels creates an interface that decreases the diffusion of oxygen to viable tissue [23]. From the perspective of the latter, one grave consequence that acute COVID-19 patients with concomitant respiratory infections commonly succumb to is hypoxia and subsequent Acute Respiratory Distress Syndrome (ARDS) [24]. Consistent with this is the notion that ARDS presentations in COVID-19 patients according to assessments of Italian patients show a high shunt fraction to gasless tissue ratio indicating hyperperfusion of gasless tissue [25]. Gattinoni et al. cite hypoxic vasoconstriction as a possible mechanism for this phenomenon, which gives further credence into an ROS-centric theory underlying the increased disease burden that diabetics have when facing COVID-19 [25].

The regulation of vascular compliance is of interest to the diabetic and the COVID-19 patient experiencing hypoxia. This can be appreciated through the appraisal of Nitric Oxide (NO) metabolism which is mediated through endothelial NO Synthase (eNOS). An increase in TNF-α expression, another inflammatory biomarker that is prevalent in chronic hyperglycemia, is a central mediator of this pathway [26]. TNF-α modulates arginase, which competes against eNOS for the substrate of L-arginine (the physiologic precursor of NO) in addition to inhibiting the expression of eNOS promotor genes, thereby reducing the aptitude of the endothelium to generate viable NO in the local vascular environment [27-29]. This scarcity of active eNOS and NO compromises the capacity of the endothelium to respond to neuronal innervation that modifies vascular tone. Moreover, the aforementioned nerves themselves rely heavily on oxygen as marked by their mitochondrial density, owing to their metabolic requirements that make them susceptible to the autonomic demise in diabetic patients [30]. A loss of autonomic oversight within the endothelium leads to a net contractile state in the patient with chronic inflammatory disease secondary to COVID-19 and diabetes, narrowing the scope of vessel caliber fluctuations needed for proper oxygen delivery. Further advancing the tenets of hypoxia in COVID-19 and diabetes are scanning electron studies that demonstrate Red Blood Cell (RBC) hemoglobin undergoes glycosylation as a result of hyperglycemia mediated inflammation, resulting in diminished oxygenation capacity limited by pathologic changes in the molecular configuration of such RBCs [31].

Solidifying the role of the inflammasome in COVID-19 patients with pertinence to diabetes is the phenomenon of increased expression of TNF-α in COVID-19 patients as part of a cytokine-storm profile observed in the clinical setting [32]. Among the array of cytokines manifesting in COVID-19 include IL-2, IL-6, and IL-7, and these inflammatory cytokines discussed induce iron sequestration, a phenomenon found in diabetics at baseline which hinders hemoglobin synthesis mutually exclusive from glycosylation mediated derangement [33-38]. Findings summarizing the implications of this cytokine flux in COVID-19 patients with diabetes. Some authors hypothesize that low-grade inflammation seen in the background inflammasome in diabetics raises the threshold for cytokine storm presentations in COVID-19 [39,40]. The cytokine profile that arises from COVID-19 results in impaired RBC function independently of hyperglycemia, with compounding insult to the RBC function in diabetics with unique oxygen demands as a result of chronic disease status [12,32,41,42]. These ideas show that diabetic patients with COVID-19 do not experience disease burden attributed to discrete sequelae, but rather the role of hypoxia and complicated diabetes in the story of COVID-19 is bidirectional. Hypoxia mediated by diabetes mellitus should not be underestimated, as comparisons of uncomplicated COVID-19 cases relative to complicated cases have revealed diabetes and saO_2 to be prominent risk factors for disease exacerbation that would warrant more tailored therapy [43].

Clinical Manifestations of Diabetes Pertinent to the Covid-19 Patient

Familiarity with salient end-organ damage signs of pertinence to the COVID-19 patient receiving acute care offers indispensable tools to gauge the clinical progression of patients. An audit of renal function in all diabetic patients is prudent, as Diabetic Kidney Disease (DKD) develops in approximately 40% of patients with diabetes [44]. There is also increased attention in the role of assessing nephropathy in hospitalized patients with COVID-19. A retrospective analysis of 193 COVID-19 patients conducted by Li et al. exemplifies the latter point, as it was noted upon analysis that roughly 60% of patients presenting with COVID-19 experienced renal compromise in the form of proteinuria upon admission, implying renal injury that preceded advanced care45. Throughout hospitalization, patients experienced elevations of renal function tests in the form of serum creatinine (SCr, defined as a threshold of >1.18mg/dL in men and >0.95 mg/dL in women, seen in 22% of patients) and blood urea nitrogen (BUN, defined as >22.5mg/dL in all participants, seen in 31% of patients) [45]. Over one-fourth of patients experienced progression to Acute Kidney Injury (AKI), with an increased prevalence of mortality 5.3 times higher than patients with normal renal function parameters [45]. Increases in Blood Urea Nitrogen (BUN) and Serum Creatinine (SCr) were noted in patients with more acute cases of COVID-19 in addition to a control sample of 28 patients with various forms of pneumonia ($p<0.001$ for both variables). It was noted that SCr was elevated throughout hospitalization, a concept that has been established as a prognostic factor in monitoring renal function in patients with acute kidney injury associated with other well-studied members of the coronaviridae family [46].

Single-cell transcriptome analyses of kidney cells have identified ACE-2 receptors in glomerular endothelial cells and cells lining the renal proximal tubule, highlighting the potential for these cells to be the source of AKI [47]. However, explication of which types of cells in the kidney are susceptible to damage in COVID-19 is not absolute. Post-mortem analyses of 26 kidneys in patients with COVID-19 endorsed the notion of ischemic glomerular damage as marked by retracting and kinking of the capillaries lining the glomerulus in addition to proximal tubule damage as marked by loss of brush borders [48,49]. While this supports the notion of proximal tubule damage, assays measuring the presence of a nuclear protein of SARS-CoV-2 found the presence of the protein in tubular epithelium implying that renal parenchyma is a target of COVID-19, most likely through viremia [49].

While nephropathy represents microvascular consequences of diabetes, macrovascular consequences in the form of Major Adverse Cardiovascular Events (MACE) represent a significant proportion of morbidity and mortality in diabetes secondary to vascular damage, thrombotic effects, and associated hypertension with nephropathy [50,51]. The previously mentioned study by Wang et al. that noted 138 hospitalized patients with COVID-19 in was able to record cardiac injury (defined as elevated Troponin I or newfound morphologies on echocardiographic or electrocardiogram imaging modalities) in 7.2% of all 138 patients, and 22% of patients that required elevation to ICU care12. A communications release from the National Health Commission of China studied a cohort of patients with COVID-19, reporting that approximately 12% of patients without a previous history of Cardiovascular Disease (CVD) experienced troponemia or cardiac whilst hospitalization, highlighting the vigilance needed for patients with diabetes and COVID-1952. Whether or not viremia in COVID-19 can present with direct seeding of the myocardium in a manner similar to the purported seeding of the tubular epithelium in the kidney has not been established, and evidence for this phenomenon or lack thereof is highly anticipated.

Complicated Type 1 Diabetes in Covid-19

Given the established epidemiological and pathophysiological principles that intertwine COVID-19 and diabetes, an appraisal of the diabetic status in these patients is vindicated if receiving critical care attention for COVID-19 as perturbations in the metabolic status of these patients has ramifications of acute mortality. Moreover, an understanding of the principles guiding this tandem presentation helps establish a framework for treatment and understanding the rationale between management. Precluding glycemic control are the public health challenges that COVID-19 poses, with restrictions on mobility, food security, and health-care secondary to jurisdictional regulations aimed at mitigating contact and exposure of the virus en masse to an open population [53].

One of the most acute complications patients with Type 1 Diabetes Mellitus (T1DM) pose is the risk of DKA given lapses in insulin access or acute exacerbation of disease processes. A survey of 238 patients admitted for DKA in the United Kingdom revealed infection as the principal etiology of DKA, highlighting the increased risk in COVID-19 infection in patients with T1DM [54]. The hallmarks of DKA involve elevated blood glucose, elevated serum ketones, and metabolic acidosis. Components of SARS-CoV-2 infection may aggravate these etiologies. Yang et al. established that previous strands of coronaviridae may damage pancreatic islet cells, the principle insulin-producing cell in the body, and of significant dearth in T1DM secondary to autoimmune damage or improper functionality [55]. In the patient with T1DM, this may potentially increase relative insulin deficiency within the body, spurring glucagon production and hyperglycemia as demonstrated by previous viral models of diabetes involving the pancreas [56]. Such hyperglycemia spills over into ketone production, the hallmark of DKA. Moreover, infection with SARS-CoV-2 produces a node of vulnerability in ketone regulation in patients with T1DM given the construct of viral dynamics. SARS-CoV-2 relies upon the Angiotensin-converting enzyme 2, an enzyme heavily expressed in renal, cardiovascular, and lung tissue, as a conduit for endocytosis [57,58]. The receptor is downregulated as a result of viral entry, leading to decreased ACE-2 expression during active viral infection [59]. A decrease in ACE-2 may preclude angiotensin-II negative feedback, which has been shown to promote further induce islet cell inflammation that precludes insulin secretion [60]. Further inquiries into the unique array of viral proteins in this novel coronavirus strain are needed to confirm this association. Supporting these worries, a retrospective analysis of 658 hospitalized patients with COVID-19 found that patients with ketosis had a higher inclination towards having a diagnosis of diabetes (35.7% *versus* 18.5%, $P=0.007$) [61].

The increased expression of ACE-2 receptors in patients with COVID-19 highlights the possible concern of patients taking

Angiotensin Converting Enzyme Inhibitors (ACEI) and increased morbidity and mortality [62]. Patients with diabetic nephropathy rely on these medications to decrease the progression of diabetic glomerulopathy in T1DM and T2DM. One purported mechanism for the ACEI therapy is through the reduction of glomerular pressure therapy *via* downregulation of Angiotensin 2 (ATII) mediated vasoconstriction of renal efferent arterioles. Despite these concerns, there is no conclusive evidence that suggests that providers should stray away from continuing ACEI medications in patients with diabetes and COVID-19 [63].

A deficiency in insulin is responsible for the pathophysiology of DKA and points to the management of the disease process. A lack of insulin promotes lipolysis in adipose tissue, causing the liberation of Free Fatty Acids (FFA) that eventually get metabolized to ketone bodies, which render a metabolic acidosis. Coupled with hyperglycemia that does not transit intracellularly due to a lack of insulin, osmotic diuresis occurs and draws multiple electrolytes in the urine, resulting in serum osmolality abnormalities. Within the context of the previous discussion, however, it is important to note that DKA may result in T2DM if insulin secretion is transiently compromised in the context of hyperglycemia, such as in the case of islet cell inflammation that may occur as a result of downstream coronavirus infection [60].

Complicated Type 2 Diabetes in Covid-19

One of the more well-accounted complications in T2DM is Hyperglycemic Hyperosmolar Syndrome (HHS), which is marked by marked hyperglycemia and hyperosmolarity in the absence of ketosis. Similarly, to DKA being seen in T2DM, HHS may present in T1DM patients who have enough insulin activity to preclude ketosis but still experience deficits in insulin dynamics manifesting as hyperglycemia. Criteria for hyperglycemia in HHS include a serum glucose concentration greater than 600mg/dL, osmolality cutoff of >330 mOsm/kg, and a metabolic component requiring serum bicarbonate >5mmol/L in the context of a serum pH>7.3 [64]. In addition to the rampant hyperglycemia triggering inflammatory pathways mentioned previously related to vasoconstriction, the hyperglycemia in HHS creates an osmotic gradient that promotes a net diuresis. This net diuresis is presumed to play a role in hemoconcentration, increasing the risk for thrombosis [65-67]. Given the elevated troponins previously discussed in tandem with COVID-19, a thrombosis that manifests as angina secondary to arterial clots in the coronary vessels compounded with the loss of consciousness and perfusion seen in HHS may mimic a myocardial infarction, and therefore workup of the latter should be pursued with a higher index of suspicion in COVID-19 with diabetes receiving critical care. Moreover, there are interesting reports of coagulopathies associated with COVID-19, showing acute hemodynamic decompensation in cases with findings suggestive of vascular embolization with fatal thrombotic complications [68,69]. Refractory hypoxemia, shortcomings in ARDS therapeutics, and observations of coagulopathy as measured by hematologic serum markers are the clinical signs pointing to these observations [25].

Pharmacotherapy, Management, and Diabetic Comorbidities

Insights from pharmacotherapeutic drugs targeting diabetes and its sequelae must be considered for in COVID-19 given its novelty as an infectious agent. Namely, the mechanisms by which these agents act intersect with pathways relevant to COVID-19 and the propagation of disease. Therefore, commentaries on these medications and their effects must be introduced. Antidiabetic agents are predicated upon modulating physiological pathways within the diabetic patient, and failure to exercise prudence in this domain may have consequences in COVID-19 patients with diabetes.

Both HHS and DKA are rooted in aberrant insulin availability, and therefore insulin therapy is vital. However, there is an assortment of different insulin types with different dynamics, pharmacokinetics, and indications. Infused insulin that requires frequent dosage changing may pose risks in the acute care setting as each dosing change is essentially a high risk encounter that increases total exposure of COVID-19 to hospital staff, who then thereby interact with other workers. Moreover, there are considerations of resource allocation regarding Personal Protective Equipment (PPE) to be made if workers are frequently adjusting the insulin of dosage within an ICU room. Options such as single-dose insulin, or insulin that can be adjusted remotely, such as insulin-pumps would prove paramount for modulation of insulin while minimizing COVID-19 exposure70. To exemplify the point of technology introduction, a multicenter study involving 2, 665 patients with DKA treated with a computer-directed approach to management of insulin needs (n=1750) relative to paper calculation in institutional protocols (n=915) resulted in decreased hypoglycemia during the duration of insulin exposure (12.9% *vs* 35%, p=0.001), quicker time to euglycemia (9.7±8.9 *vs* 10.97±10.2 hours, p=0.0001), and mediation of metabolic acidosis (13.6±11.8 *vs* 17.3±19.6 hours, p=0.0001), and decreased hospital stay time (3.2±2.9 *vs* 4.5±4.8 days, p=0.01). These results are promising and are of potential value in institutions needing to modulate insulin in uncharted territories while simultaneously needing to minimize exposure for non-acute disease exacerbation [71].

Insulin needs in the context of DKA requires scrupulous calculation of electrolyte needs, given the ability of insulin to produce hypokalemia. There is also a baseline hypokalemia superimposed in untreated DKA, as hyperglycemia induces a diuresis that causes aldosterone production and subsequent potassium as a consequence of pressure preservation. Reports in the literature are scant regarding the management of DKA, but a case report by Chee et al. note that a COVID-19 patient was treated using aggressive fluid resuscitation and intravenous insulin to remediate hypoinsulinemia, with a transition to subcutaneous insulin [61]. However, this is only one report of a patient with DKA, and challenges regarding repletion with insulin considerations are complicated with concomitant COVID-19 infection. Hypokalemia presumably secondary to a lack of negative-feedback induced RAAS regulation, was found in virtually all of 175 COVID-19 patients presenting to a hospital in China [72]. There is a lack of current studies addressing optimal potassium repletion in COVID-19 patients, especially in the context of DKA. Current guidelines across multiple institutions recommend holding insulin until patients receive an adequate potassium threshold, usually around K+<3.3mmol/L, to mitigate hypokalemia and potential cardiovascular sequelae, especially in these patients who are pre-disposed to worse cardiovascular outcomes [73,74]. However, an audit of appropriate potassium repletion should be conducted in

similar fashion as hypokalemia complicated by other etiologies in conjunction with hypokalemia induced by DKA in order to elucidate whether or not insulin treatment modalities should differ in diabetic patients with COVID-19 receiving ICU care [75-77].

Insulin considerations in patients with COVID-19 and HHS are treated differently from DKA. Because there is no need for counterregulatory suppression of free-fatty acids to blunt ketosis in most cases, fluid resuscitation alone has been shown to be enough to resolve most cases with insulin therapy reserved for hyperglycemia refractory to therapy [64]. One potential pitfall in the management of patients with HHS and COVID-19 is rapid fluid correction resulting in heart failure or pulmonary edema in the diabetic COVID-19 patient with baseline elevations in HEART score risk factors and compromised airway, both principal symptoms of angina and may potentially contribute to the masking of symptoms in patients at risk for myocardial infarction or myocardial injury in COVID-19. Unfortunately, there does not exist a randomized control trial with an endpoint of mortality, times of hospitalization, or other indexes of disease burden in HHS to evaluate optimal management practices [78]. A lack of a reference point makes the advent of tailored treatment of HHS in COVID-19 bleak, representing a major node of needed inquiry.

Previous studies of coronaviridae have established DPP-4 as a potential receptor for viral entry [79]. This raises interest in the potential utilization of DPP-4 inhibitors as both an antidiabetic agent in patients with COVID-19, as well as an agent that may confer amelioration in patients with COVID-19 and diabetes the ICU through attenuation of the viral replication cycle. Moreover, there is potential for this drug to express benefit in patients through mitigation of cardiovascular sequelae as DPP-4 is expressed within the myocardium and endothelial vessels, highlighting the importance of these pathways is not only the diabetic patient, but COVID-19 cases as well as previously demonstrated [80,81]. Moreover, there is hope that these drugs may help inhibit DPP-4 itself, which is known to initiative immunological and inflammatory responses [82]. However, there have been no formal trials illustrating this involvement, highlighting the lack of differential mortality profiles for patients with COVID-19 and the retrospective analyses of their outpatient antidiabetic medications.

SGLT2 inhibitors (-flozin drugs, SLGT2i) have received a bevy of interest in the medical community due to their positive outcomes across multiple cardiorenal outcome trials, showing statistically positive benefits in MACE rates, time to End-Stage Renal Disease (ESRD), and HgbA1C [83-85]. SGLT2i works *via* inhibition of the SGLT2 protein in the renal proximal tubule, which is responsible for the bulk of glucose reabsorption in the nephron. Inhibition of SGLT2 results in a marked glucosuria as well as associated natriuresis that results in an osmotic diuresis that ameliorates hyperglycemia and hypertension86. Of relevance to COVID-19, it is hypothesized that dapagliflozin, one agent within the family of SGLT2i, has a positive effect on lactate secretion and production [87]. Mechanisms include mitigation of oxygen consumption and ROS production and increasing urinary lactate excretion [87]. Of pertinence to augmentation as an antidiabetic agent in the scope of COVID-19, is preliminary evidence for increased Lactic Dehydrogenase (LDH) and lactic acidosis involved in COVID-19 [88]. If true, a reprieve of lactic acidosis as well as attenuation of comorbidities in the diabetic COVID-19 patient receiving ICU care may be a beneficial agent. A Stage III clinical trial investigating this association, DARE-19 (Dapagliflozin in Respiratory Failure in Patients With COVID-19) is currently underway [89]. However, there is concern for this trial as SGLT2i have been associated with euglycemic diabetic ketoacidosis [90,91]. The proposed mechanism for this is that glucosuria may induce transient causes a transient decrease in blood glucose, which invites counterregulatory hormones to promote lipolysis in adipose tissue and resultant ketone formation from free fatty acids [92]. With respect to HHS, there have been reports have the osmotic diuresis seen may precipitate kidney injury [93,94]. There have been reports in the literature that have delineated osmotic nephrosis seen with canagliflozin, an SGLT2 inhibitor and with the speculation that COVID-19 may seed directly into renal parenchyma, caution may need to be exercised prior to initiation of SGLT2i in patients with complicated diabetes and COVID-19 in the ICU [95].

Conclusion

COVID-19 presents challenges across multiple domains within the clinical setting. Namely, its physiological ramifications represent uncharted territory and given its status as a global pandemic with a significant mortality count, the axioms that guide patient care become uncertain once we consider SARS-CoV-2. Diabetes, a comorbidity commonly associated with COVID-19 patients (especially in the intensive care unit setting) has acute complications that share many pathways with the natural course of SARS-CoV-2 infection and is associated with worse outcomes in patients. The formal establishment of COVID-19 and DKA or HHS prevalence and outcomes in hospitalized patients has not been extensively delineated with multiple studies, but there is an abundance of overlapping points of compromise that exacerbate the course of COVID-19 in diabetic patients. Bidirectionality is established when we assess the role of COVID-19 in triggering diabetic complications such as DKA and HHS, hence emphasizing the role for the management of both disease process in the acutely ill patient. Amelioration of diabetes *via* pharmacotherapy therefore has a role in mitigating COVID-19 symptoms. Prompt usage of established drugs for compassionate use or expedited clinical trial status allocation for experimental treatments are reflections of our urge to find evidence-based treatments. Considerations into treatment options for grave complications of diabetes such as diabetic ketoacidosis and hyperosmolar hyperglycemic state may soon follow, or are already following, suite. Provident appraisal of the sequelae of these complications and synthesizing findings from the current literature with our current understanding of the translational biology and therapeutic management of diabetes give providers parameters to base their clinical decision making off of. It can be seen with a commentary on the latter that careful monitoring for COVID-19 sequelae that overlaps with diabetic sequelae, in addition to cautious use of antidiabetic agents that deviate may avoid peril in the ICU. Further investigations are needed to assess these agents role in direct COVID-19 treatment, or amelioration of complicated diabetes in COVID-19. Moreover, residual benefit may be salvageable from COVID-19 in the sense that this pandemic has recalibrated our current understanding of diabetology with the prospect of allowing us to develop more efficacious clinical-decision making tools to reduce the burden of diabetes in the future.

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