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REVIEW ARTICLE

Dissecting the interaction between COVID-19 and diabetes mellitus

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a global pandemic that is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus-2. Data from several countries have shown higher morbidity and mortality among individuals with chronic metabolic diseases, such as diabetes mellitus. In this review, we explore the contributing factors for poorer prognosis in these individuals. As a significant proportion of patients with COVID-19 also have diabetes mellitus, this adds another layer of complexity to their management. We explore potential interactions between antidiabetic medications and renin–angiotensin–aldosterone system inhibitors with COVID-19. Suggested recommendations for the use of antidiabetic medications for COVID-19 patients with diabetes mellitus are provided. We also review pertinent clinical considerations in the management of diabetic ketoacidosis in COVID-19 patients. In addition, we aim to increase clinicians' awareness of the metabolic effects of promising drug therapies for COVID-19. Finally, we highlight the importance of timely vaccinations for patients with diabetes mellitus.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, was first reported in Wuhan, China, in December 2019[1]. Similar to its counterparts, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, SARS-CoV-2 is highly pathogenic, and can cause severe pneumonia, acute respiratory distress syndrome and multiorgan failure. Furthermore, the rapid transmission of SARS-CoV-2 has caused a worldwide pandemic with >6 million cases and 360,000 deaths since June 2020[2].

Diabetes mellitus affects approximately 463 million people worldwide[3], while obesity inflicts nearly one-third of the world's population[4]. The co-existence of obesity and diabetes mellitus, also known as "diabesity," is yet another major pandemic that the world currently faces. Patients with diabesity are at significantly increased risk of developing severe infections and impaired pulmonary function[5]. Furthermore, there are also unique and complex interactions between antidiabetic medications and other commonly used agents for diabetes mellitus-related comorbidities with COVID-19 infection. To further complicate this interplay, some of the promising drug therapies are also associated with metabolic effects.

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DIABETES MELLITUS AND OBESITY ARE RISK FACTORS FOR SEVERITY OF COVID-19 INFECTION

Diabetes mellitus is a well-established risk factor for infections, and the risk increases with poor glycemic control[6]. In general, glycated hemoglobin (HbA1c) >9% has been shown to be associated with 60% increased risk of severe bacterial pneumonia[7]. Although current evidence does not suggest that patients with diabetes mellitus are at higher risk of contracting SARS-CoV-2[8], diabetes mellitus has been listed as the third most prevalent comorbidity, behind cardio-cerebrovascular disease and hypertension[9], and is also associated with a two- to threefold increase in adverse outcomes[9]. Similarly, obese individuals with body mass index >35 kg/m^2 are at nearly sevenfold higher risk of requiring mechanical ventilation[10]. A recent study suggested a lower body mass index threshold of 25 kg/m^2 for disease severity stratification in the Asian population[11]. In addition, patients with microvascular and macrovascular complications of diabetes mellitus, as well as obstructive sleep apnea, were found to be at significantly higher risk of severe disease and mortality[12]. Figure 1 summarizes the diverse interactions between these two conditions.

PATHOGENIC LINK BETWEEN DIABETES MELLITUS, OBESITY AND INCREASED SEVERITY OF COVID-19

There are several mechanisms that predispose patients with diabetes mellitus to increased disease severity. Diabetes mellitus is

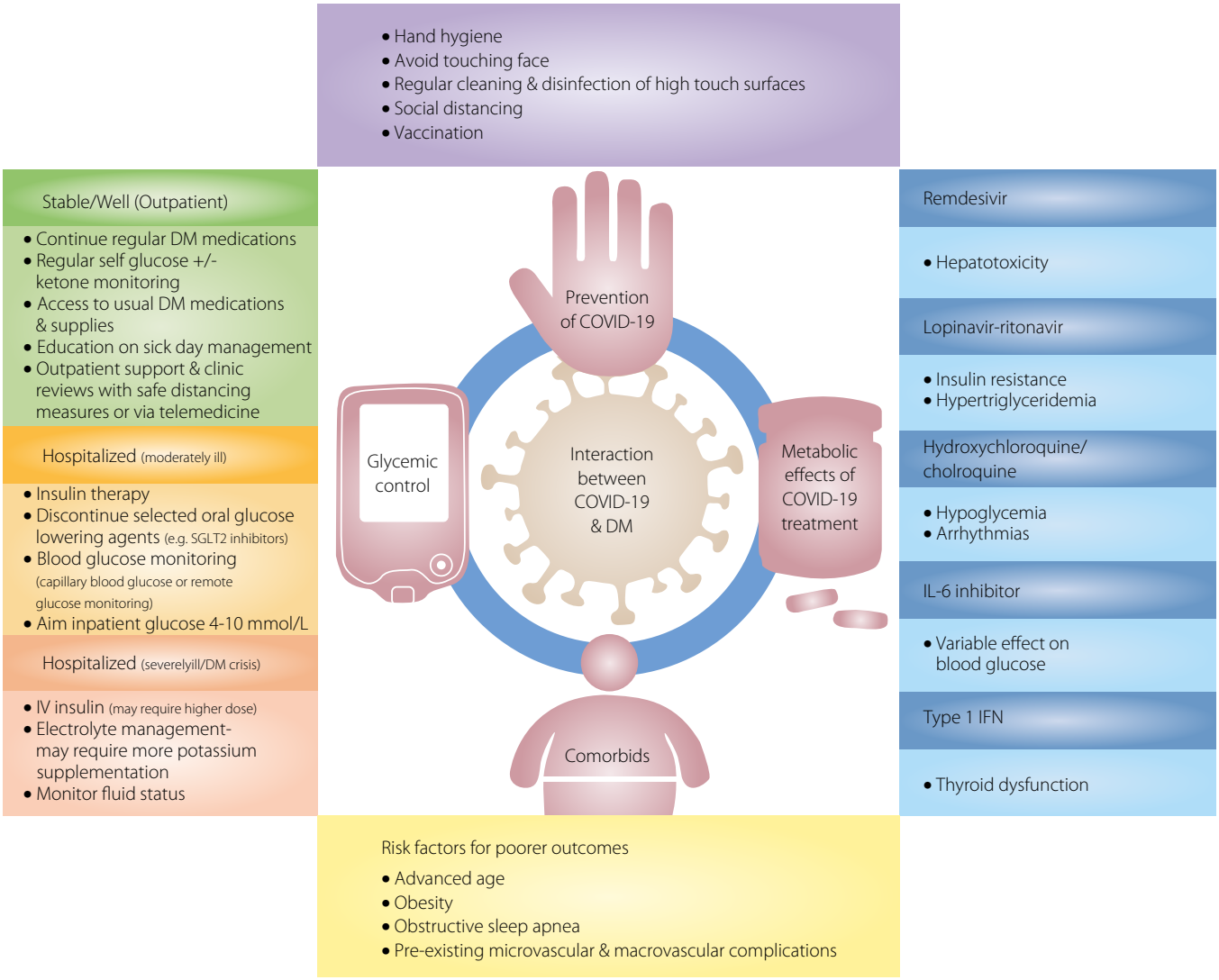

Figure 1 | Interaction between coronavirus disease 2019 (COVID-19) and diabetes mellitus (DM). IFN, interferon; IL-6, interleukin-6; SGLT2, sodium–glucose cotransporter 2.

associated with immune dysfunction[13], increased susceptibility to inflammation[14] and reduced viral clearance[15]. Furthermore, a possible association between SARS-CoV-2 and the renin–angiotensin–aldosterone system (RAAS) might increase adherence of SARS-CoV-2 to target cells and might worsen the severity of COVID-19[16], generating controversies about the use of RAAS blockers, which will be discussed further.

Diabetes mellitus is associated with immune dysfunction and increased inflammation

The immune system is dysregulated in hyperglycemia. The humoral system, which mediates immediate defense responses by polymorphs, macrophages and dendritic antigen presenting cells to pathogens, is attenuated in diabetes mellitus[17]. Defects in adaptive immunity are associated with impaired type 1 interferon production[18]. Furthermore, increased generation of advanced glycation end-products could also inhibit the generation of interferon gamma by T lymphocytes[19]. These could reduce antiviral activity and increase the severity of infection. The low T lymphocyte counts in diabetes mellitus patients might blunt antiviral interferon responses[20]. Furthermore, the co-existence of diabetes and obesity or "diabesity" is characterized by a pro-inflammatory state, driven by cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha[21,22]. These patients are at increased risk of uncontrolled inflammation, which could induce a cytokine storm and contribute to an overall poor prognosis.

Hyperglycemia and obesity are associated with alterations in pulmonary function and reduced viral clearance

Studies have shown that hyperglycemia can directly increase glucose concentrations in the airways and affect pulmonary

function, as well as alter pulmonary vascular permeability and alveolar epithelial function[23]. These factors might contribute to increased severity of respiratory infections. Furthermore, a recent study has also shown delayed clearance of SARS-CoV-2 in patients with diabetes mellitus[15].

With regard to obesity, pulmonary function studies have shown a restrictive pattern and reduced lung volumes in obese individuals[10]. The reduced cardiorespiratory reserve, coupled with difficulty in ventilation, could account for the significant increased disease severity in these patients[5,10,11].

Increased adherence of SARS-CoV-2 to target cells

SARS-CoV-2 has glycoprotein spikes on its surface, which attach to angiotensin-converting enzyme 2 (ACE2) receptors on target cells. On binding to ACE2, the virus is processed by proteases, such as the transmembrane serine protease 2 and furin, resulting in the internalization of the virion complex[20]. ACE2 and furin expression are increased in diabetes mellitus, which might facilitate viral entry and replication[20,24].

POTENTIAL EFFECTS OF SARS-COV-2 ON PANCREATIC FUNCTION

The binding of SARS-CoV to the ACE2 receptors on pancreatic islets could potentially cause acute diabetes[25]. In a study by Yang *et al.*[25], just two of 39 patients with SARS-CoV and labeled to have diabetes mellitus during admission continued to have diabetes mellitus after 3 years. Further characterization showed significant immunostaining for ACE2 in the pancreatic islets, but this was weak in the exocrine tissues. In addition, SARS-CoV-2 might be associated with elevated amylase, lipase and focal changes to the pancreas, raising the possibility of pancreatic injury[26]. Other viruses, such as enteroviruses, Coxsackie B virus and cytomegalovirus, had previously been found to be associated with the development of type 1 diabetes mellitus[27]. We recently reported a case of diabetic ketoacidosis (DKA) precipitated by COVID-19 in a patient with newly diagnosed diabetes mellitus[28]. Similar to other acute illnesses that necessitate hospitalization among patients with diabetes mellitus, inpatient glycemic management and being alert to the potential risk of DKA are crucial. However, the long-term effects of SARS-CoV-2 are unclear, and long-term follow up will be required to determine the magnitude of its impact on pancreatic function and the consequent risk of developing diabetes mellitus.

MANAGEMENT OF DIABETES MELLITUS IN A PATIENT WITH COVID-19

Glycemic control is important for all patients. Previous experiences with SARS-CoV and current data with COVID-19 have shown that hyperglycemia and diabetes mellitus are significant risk factors for complications and mortality[29].

One of the main challenges in the management of acutely unwell COVID-19 patients with diabetes mellitus is the reduced oral intake. As such, the dosage of usual oral antidiabetic agents and/or insulin might have to be reduced and adjusted accordingly to avoid hypoglycemia.

In the next section, we review the different classes of oral antidiabetic agents, and their effects on infection and inflammation, and provide recommendations on their use during acute illness.

Metformin

In stable patients with normal oral intake and who do not have nausea and vomiting, metformin can be continued. Interestingly, metformin has gained recent interest given its potential role in immunomodulation. Animal studies have shown reduced expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha and IL-6, associated with continued metformin use in sepsis[30]. Metformin has also been shown to improve survival in mice infected with *Legionella pneumophila*[31]. However, in the critically ill patient with acute renal, hepatic injury or hemodynamic instability, metformin should be avoided due to the risk of lactic acidosis.

Dipeptidyl peptidase-4 inhibitors

Concerns regarding the slight increased risk of nasopharyngeal[32] and urinary tract infections[33] have arisen from the use of dipeptidyl peptidase-4 (DPP4) inhibitors. However, a meta-analysis by Cai *et al.*[34] did not report significant differences in DPP4 inhibitor use with increased risk of upper respiratory tract infections. Another cohort study also did not show an association between DPP4 inhibitor and risk of pneumonia[35].

In addition, DPP4 has been shown to be a receptor for cellular entry of Middle East respiratory syndrome coronavirus[36]. Whether this translates into increased susceptibility to certain coronavirus infections or increases the severity of coronavirus infections is currently unclear. At present, the use of DPP4 inhibitors did not show any difference in lymphocyte function or production of inflammatory cytokines in human studies[37]. Further studies are required to elicit potential therapeutic benefits of DPP4 inhibitors in SARS-CoV-2 infection. In stable patients with satisfactory oral intake, clinicians might elect to continue DPP4 inhibitors.

Glucagon-like peptide-1 receptor agonists

There is emerging evidence of the potential anti-inflammatory properties arising from glucagon-like peptide-1 (GLP-1) receptor signaling[38]. GLP-1 receptor agonist treatment in mice infected with respiratory syncytial virus is associated with a significant reduction in inflammatory cytokine production and attenuation of inflammation in the respiratory epithelium[39]. Furthermore, GLP-1 receptor agonist therapy in the intensive care unit setting is associated with a reduction of hypoglycemia, glucose variability and catabolism by suppressing glucagon[40], all of which can be protective in these critically ill patients. However, delayed gastric emptying, which is common in the critically ill, might affect the extent of the benefits of glycemic control. Its use is also relatively contraindicated in patients with

renal impairment. Currently, there is insufficient evidence to support for or against the use of GLP-1 receptor agonists in the context of the coronavirus infection.

Thiazolidinedione, sulphonylurea, meglitinide and sodium–glucose cotransporter 2 inhibitors

Studies have suggested increased ACE2 expression associated with thiazolidinedione use, raising concerns about possible increased susceptibility to SARS-CoV-2 infection[41]. However, in view of the adverse effects, such as fluid retention, which is commonly associated with thiazolidinedione, it should be discontinued in acutely ill patients. Similarly, sulphonylureas and sodium- glucose cotransporter 2 inhibitors are generally unfavorable in the setting of acute illness. Sulphonylurea and meglitinide increase the risk of hypoglycemia in the presence of poor oral intake.

Sodium–glucose cotransporter 2 inhibitors are associated with increased risks of dehydration and euglycemic DKA, particularly in the setting of an acute illness.

Insulin

Insulin has been the treatment of choice for optimization of glycemic control in acutely ill patients. Several landmark studies have shown mortality and morbidity benefits associated with the use of intensive insulin therapy. Intravenous insulin can be administered as a continuous infusion that allows rapid titration. Furthermore, insulin has been shown to downregulate ACE2 receptors[42], but more research is required to identify direct clinical benefits of insulin in the context of COVID-19. In addition, observational studies have reported significantly higher insulin requirements among COVID-19 patients[43], supporting the postulation that β-cell dysfunction might be induced by SARS-CoV-2.

The classes of antidiabetic medications, their effects in the context of COVID-19 and the recommendations during acute illness are summarized in Table 1.

PRACTICAL CONSIDERATIONS FOR INPATIENT GLYCEMIC CONTROL IN PATIENTS WITH COVID-19

Maintaining good glycemic control is important for these patients. In a retrospective study by Bode *et al.*[44] examining the outcomes of inpatient glycemic control of 1,122 patients with COVID-19, uncontrolled hyperglycemia (defined as ≥2 episodes of blood glucose >10 mmol/L) was associated with a nearly fivefold increase in mortality and increased length of hospitalization. Zhu *et al.*[45] showed that inpatients whose blood glucose was maintained between 3.9 and 10 mmol/L had significantly lower rates of complications and all-cause mortality. Frequent monitoring of blood glucose is essential with the aim of maintaining blood glucose levels within the recommended target of 4–10 mmol/L[43]. Furthermore, it is important to emphasize that inpatient diabetes management is highly dynamic. The titration of antidiabetic medications needs to be guided by ongoing glucose measurements and trends, illness severity, route of nutrition and concomitant medications that might affect glucose levels, such as glucocorticoids. The need for frequent inpatient blood glucose monitoring increases exposure of healthcare workers to SARS-CoV-2. Besides donning personal protective equipment and strict adherence to recommendations from the Centers for Disease Control and Prevention in preventing transmission of pathogens during glucose monitoring[46], additional care needs to be taken to reduce the spread of COVID-

Table 1 | Summary of antidiabetic medications, effects on coronavirus disease 2019 and recommendations on their use during acute illness

Antidiabetic medication	Effects on infection	Recommendations during acute illness
Metformin	Reduces inflammatory cytokines May reduce viral replication	Avoid in the setting of renal, hepatic failure or critically ill due to risk of lactic acidosis
DPP4-inhibitor	May be associated with disease severity in MERS-CoV, but effect on SARS-CoV-2 not defined	More data needed for the acutely ill patient. May consider continuing in patients who are well with satisfactory oral intake
GLP-1 receptor agonist	Significant reduction in inflammatory responses in animal models	More data needed for the acutely ill patient. May consider continuing in patients who are well with satisfactory oral intake
Thiazolidinediones	May be associated with increased ACE2 expression, but clinical implication is unclear	Discontinue in acutely ill patients due to risk of fluid retention
Sulphonylurea/meglitinides	No apparent direct effect in SARS-CoV-2	Discontinue in patients with poor oral intake due to hypoglycemia risk
SGLT-2 inhibitors	No apparent direct effect in SARS-CoV-2	Discontinue in acute illness due to risk of euglycemic DKA and further dehydration
Insulin	May downregulate ACE2 receptors	Treatment of choice in acutely ill patients to achieve glycemic targets with dose titration based on glucose levels

ACE2, angiotensin-converting enzyme 2; DKA, diabetic ketoacidosis; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SGLT-2, sodium–glucose cotransporter 2.

19 during capillary glucose monitoring, as viable SARS-CoV-2 might be present on contact surfaces. It is therefore important to clean and disinfect the glucometer after each and every use, and to use disposable safety lancets. Where possible, the responsibility for routine cleaning and disinfection should be assigned to appropriately-trained personnel[47].

If resources permit, the use of remote glucose monitoring might prove beneficial. Real-time continuous glucose monitoring has been reported as a useful alternative for COVID-19 patients with diabetes mellitus, allowing rapid titration of insulin doses, while minimizing the risk of staff exposure.

MANAGEMENT OF DIABETIC EMERGENCIES IN COVID-19

Patients who are acutely ill are at risk of diabetic emergencies. In a study involving a cohort of 174 Chinese patients with COVID-19, 37 had diabetes mellitus, of which two developed DKA[49].

DKA occurs as a result of insulin deficiency and increased counterregulatory responses, which favor the production of ketones. The unique interactions between SARS-CoV-2 and the RAAS might provide yet another mechanism in the pathophysiology of DKA. First, as alluded to earlier, direct entry of SARS-CoV-2 into pancreatic islet cells might worsen β-cell injury[25]. Second, downregulation of ACE2 after viral entry can lead to unopposed angiotensin II, which might impede insulin secretion[50].

In addition, the relationship between SARS-CoV-2 and the RAAS can complicate DKA management. As angiotensin II increases pulmonary vascular permeability and worsens damage to lung parenchyma[16], fluid replacement needs to be administered judiciously to avoid aggravating pulmonary injury. This also raises the importance of careful assessment of fluid status through objective hemodynamic parameters to determine the amount of fluid replacement.

Another important aspect in DKA management is that of monitoring and correcting electrolyte abnormalities. As angiotensin II stimulates aldosterone secretion and increases renal potassium loss, this can potentiate the risk of hypokalemia, which might necessitate additional potassium supplementation in order to continue intravenous insulin to suppress ketogenesis[28].

USE OF RAAS INHIBITORS IN COVID-19

Many patients with diabetes mellitus have other comorbidities and are taking RAAS inhibitors. The complex relationship between the RAAS and SARS-CoV-2 has led to controversies surrounding the use of these agents.

As ACE2 is the key receptor that facilitates entry of SARS-CoV-2, it is postulated that ACE inhibition could lead to a compensatory increase in the ACE2 expression with concerns that this might provide increased binding sites for viral entry into pneumocytes[16].

However, after SARS-CoV-2 entry, the expression of ACE2 was found to be significantly downregulated, which could be associated with significant lung injury[20]. This can be attributable to the physiological action of ACE2, which catalyzes the breakdown of angiotensin II to angiotensin (1-7), the latter having anti-inflammatory and anti-oxidant properties that protects the lungs against acute respiratory distress syndrome[51]. With regard to the effects of RAAS inhibitors on ACE2 expression in humans, studies have shown conflicting results. Although Ferrario *et al.*[52] previously reported that lisinopril and losartan are associated with a significant increase in ACE2 levels, others did not report an effect on ACE2 among patients treated with RAAS inhibitors[16,53]. At this point, there is insufficient evidence to conclude whether RAAS inhibition is beneficial or harmful in COVID-19.

Despite these uncertainties, abrupt cessation of RAAS inhibitors might be associated with more harm. Many diabetes mellitus patients have concomitant cardiovascular diseases and are at risk of decompensation if these medications are stopped. At present, professional societies worldwide have therefore recommended continuation of RAAS inhibitors[54].

METABOLIC COMPLICATIONS OF TREATMENTS OF COVID-19

Moving forward, there are currently numerous trials underway in search of effective treatments for this infection. We aim to provide a summary of the current treatments, mechanisms of actions, and highlight some of these agents that are associated with the effects on glucose and/or lipid metabolism.

In brief, the SARS-CoV-2 replication cycle starts by gaining host entry through the S protein, facilitated by host transmembrane serine protease 2[20]. Viral polyproteins are synthesized by ribonucleic acid polymerase, followed by assembly of structural proteins and release of new viral particles. There are several drug targets that might interfere with the replication cycle of SARS-CoV-2, including chloroquine and hydroxychloroquine, which reduce viral entry; lopinavir–ritonavir, which inhibit proteolysis; and tocilizumab, which disrupts IL-6 signaling. Other potential candidates include the transmembrane serine protease 2 inhibitor, camostat mesylate, which has been shown to prevent viral cell entry, as well as remdesivir, which inhibits ribonucleic acid polymerase[55]. Type 1 interferon might interfere with viral replication and minimize systemic inflammation[56]. As the use of these medications is likely to increase with the growing number of COVID-19 cases, we highlight three agents with accompanying metabolic effects, which might be beneficial or detrimental by exacerbating the underlying metabolic comorbidities already established in some of these patients.

Chloroquine and hydroxychloroquine

These two agents inhibit SARS-CoV-2 entry, proteolytic processing and might also have immunomodulatory effects by reducing cytokine production[55].

Hydroxychloroquine has been shown to improve insulin and glucose metabolism. Studies have shown a significant reduction in HbA1c and reduction in insulin doses[57]. Although the exact mechanisms remain to be elucidated, the improvements in glycemic control are likely associated with reduced insulin degradation[58], increased insulin binding to its receptor with an increase in the half-life of the insulin receptor complex[59,60] and increases insulin secretion[61]. Given the potential benefits of hydroxychloroquine/chloroquine on glucose metabolism, close glycemic monitoring in diabetes mellitus patients, timely reduction of the dosages of antidiabetic medications and insulin in patients who receive these treatments is essential to avoid hypoglycemia.

Although *in vitro* studies have shown antiviral activity of hydroxychloroquine/chloroquine against SARS-CoV-2[62,63], observational studies did not show a significant reduction in the need for intubation or mortality[64,65]. Furthermore, there is concern about the cardiovascular safety associated with this class of medication[66]. Electrophysiological studies suggest that hydroxychloroquine/chloroquine use might interfere with cardiac channels, lead to prolongation of action potential and cause life-threatening arrhythmias[67]. Thus, the efficacy and safety of hydroxychloroquine/chloroquine in the treatment of COVID-19 are currently inconclusive and await further confirmation with randomized controlled trials.

Lopinavir–ritonavir

Lopinavir–ritonavir are protease inhibitors used in the treatment of human immunodeficiency virus. The mechanism of action is thought to inhibit 3-chymotrypsin-like protease in viral ribonucleic acid processing[55].

Protease inhibitors have been shown to inhibit glucose uptake[68]. Euglycemic, hyperinsulinemia clamp studies showed a reduction in glucose disposal with lopinavir–ritonavir use[69]. The increase in peripheral insulin resistance might be secondary to dysregulation in insulin signaling, by causing inhibition of glucose uptake[70] and phosphorylation of the insulin receptor[71].

With regard to lipid metabolism, among HIV patients taking lopinavir–ritonavir, triglyceride levels nearly doubled within 3 months of initiation[72]. Another study showed that hypertriglyceridemia can occur within 2 weeks of therapy[73].

Protease inhibitors stimulate hepatic triglyceride synthesis[74], and inhibit chylomicron uptake and triglyceride clearance[75]. As severe hypertriglyceridemia is a risk factor for acute pancreatitis, it is important to monitor the lipid levels of patients initiated on this treatment, especially for diabetes mellitus patients, who are at higher risk of developing severe hypertriglyceridemia.

The efficacy of lopinavir–ritonavir is currently inconclusive. Its use was previously reported to be associated with reduced mortality at 28 days, and shortened intensive care unit admissions and duration of viral shedding[76]. However, a more recent randomized controlled trial involving 199 patients with COVID-19 infection treated with lopinavir–ritonavir did not show a mortality benefit[77].

IL-6 receptor antagonist

Tocilizumab is a biological agent that binds to the IL-6 receptor, interferes with IL-6 signaling and attenuates the "cytokine storm" in severe COVID-19 infection[55]. More commonly used in rheumatic conditions, tocilizumab has been shown to be associated with contrasting effects on glucose metabolism in different tissues. IL-6 has been shown to have an unfavorable effect on glucose metabolism by increasing hepatic insulin resistance[78,79]. The use of tocilizumab is associated with a small, but significant, improvement in HbA1c at 1 and 3 months of initiation of tocilizumab in patients with rheumatoid arthritis, reflecting improved insulin sensitivity from IL-6 inhibition[80]. However, IL-6 has a complex role in modulating insulin sensitivity, being both an enhancer and inhibitor of insulin action on different tissues, and having differential roles in regulating metabolism in individuals with diabetes, as compared with individuals with normal glucose tolerance. It has been postulated that the higher circulating levels of IL-6 in patients with diabetes mellitus serves as a compensatory mechanism to promote glucose uptake in skeletal muscle, and thus, the use of IL-6 inhibitors might adversely impact glucose homeostasis in skeletal muscles[81]. Nevertheless, the impact of short-term use of IL-6 receptor antagonist for treatment of COVID-19 on glucose metabolism is currently unclear and needs to be corroborated by further research.

Type 1 interferon

Thyroid dysfunction is a common side-effect of interferon therapy, and its prevalence has been reported to be up to 35%[82]. The development of thyroid dysfunction does not appear to be related to the dose of interferon therapy[83]. However, among those who develop thyroid dysfunction and with positive thyroid autoantibodies, 50% continue to carry the antibodies after interferon therapy is stopped, necessitating the need for long-term follow up[84].

Interferon-induced type 1 diabetes mellitus has been reported, but its occurrence is rare. Most of these cases occur in patients who test positive for the glutamic acid decarboxylase antibody[85,86]. Checking for glutamic acid decarboxylase positivity might be worthwhile before initiation of interferon therapy.

Remdesivir

Remdesivir use is associated with clinical improvement in >50% of patients with COVID-19 and shortens the time to recovery[87,88]. Remdesivir attenuates hepatic lipid deposition and insulin resistance in mice[89]. Paradoxically, hepatotoxicity is one of its major adverse effects in humans, and needs to be used with caution in patients with underlying liver disease or receiving statin therapy[87].

The mechanism of action and metabolic effects of the medications used to treat COVID-19 are summarized in Table 2.

Table 2 | Mechanism of action and metabolic effects of medications used to treat coronavirus disease 2019

Name of medication	Mechanism of action	Metabolic effects
Chloroquine/hydroxychloroquine	Inhibit SARS-CoV-2 entry and viral replication	Improves glycemic control and may even cause hypoglycemia May be associated with increased risk of arrhythmias
Lopinavir–ritonavir	Inhibit 3-chymotrypsin-like protease in viral RNA processing with antiviral activity against SARS-CoV-2	Increases triglyceride synthesis leading to hypertriglyceridemia Inhibits glucose uptake, which may result in hyperglycemia
IL-6 receptor antagonist	Interferes with IL-6 signaling and attenuates "cytokine storm"	Improves hepatic insulin sensitivity May worsen skeletal muscle insulin resistance
Type 1 interferon	Interferes with viral replication Minimizes inflammation	Thyroid dysfunction Rarely associated with type 1 diabetes mellitus
Remdesivir	Inhibits viral RNA polymerase	May cause hepatotoxicity

IL-6, interleukin-6; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

PREVENTION OF COVID-19 IN DIABETES MELLITUS PATIENTS

General recommendations

The prevention of COVID-19 includes maintaining good hand hygiene, abiding by social distancing measures and avoiding close contact with people who are unwell. Diabetes mellitus patients should be encouraged to continue regular self-monitoring of blood glucose, maintain healthy nutrition, keep physically active with home-based exercises, and have an adequate supply of and access to diabetes mellitus medications and supplies. Diabetes mellitus patients should also be educated on sick day rules by their healthcare team.

The use of remote consultation has also enabled care to be delivered to diabetes mellitus patients while minimizing their exposure to SARS-CoV-2. The use of telemedicine has recently been shown to be effective in the management of even high-risk diabetes mellitus patients, such as those with newly diagnosed type 1 diabetes mellitus[90]. Before the COVID-19 pandemic, a Cochrane review by Flodgren *et al.*[91] showed that interactive telemedicine can effectively assist physicians in the management of diabetes mellitus. Patients allocated to telemedicine consultations had a lower HbA1c compared with usual care at a median of 9 months' follow up. The COVID-19 pandemic is expected to accelerate the transformation of healthcare delivery and increase the use of telemedicine in the management of chronic diseases.

Vaccinations in diabetes mellitus patients

Vaccinations have major public health benefits by providing direct protection to those who are vaccinated, as well as indirect protection to the unvaccinated, but susceptible, individuals[92].

In patients with diabetes mellitus, their innate cellular immune response is decreased, which increases their risk of developing infections. Despite this, influenza vaccination is effective in diabetes patients and it is important to vaccinate this group of vulnerable individuals[93]. McElhaney *et al.*[94] showed that antibody titers did not differ between elderly patients with and without diabetes mellitus who were vaccinated against influenza. Long-term antibody titers and antibody persistence were also similar in patients with and without diabetes mellitus for at least up to 6 months[95]. In clinical practice, Wang *et al.*[96] showed reductions in hospitalizations, respiratory failure and mortality among elderly patients with diabetes mellitus who were vaccinated against influenza. Similar results were also shown in a meta-analysis involving 170,924 participants, although there were multiple confounders that weakened the evidence[97]. With regard to pneumococcal infections, vaccinations have also shown mortality benefit in bacteremic pneumococcal infection[98].

The efficacy of vaccinations might be of concern among patients with type 1 diabetes mellitus, as it has been speculated that they might not be able to mount sufficient immunological response[99]. Nevertheless, the overall response to vaccination exceeds 70% among patients with diabetes mellitus, with type 2 diabetes mellitus patients showing similar immune responses to controls[98]. As of 30 May 2020, there were 10 candidate vaccines for COVID-19 under investigation[100].

CONCLUSIONS

With the exponential increase in the number of new COVID-19 cases, it has been postulated that this pandemic might persist for the next few months and could even recur seasonally. The coexistence of two global pandemics – COVID-19 and diabetes mellitus – has significant clinical implications, and impacts on morbidity and mortality. It is therefore crucial for clinicians caring for people with diabetes mellitus and COVID-19 to be aware of the metabolic risk factors associated with disease severity, and keep abreast of the latest developments emerging on the metabolic interactions between antidiabetic agents, RAAS inhibitors and potential drug treatments for

COVID-19 (Figure 1). Last, but not least, we highlight the importance of timely vaccinations for individuals with diabetes mellitus, with a view of including the COVID-19 vaccine, when available, so as to offer early protection against this life-threatening infection. The evidence on COVID-19 is evolving rapidly, and further metabolic interactions, both acute and long-term outcomes, will surface with increasing data made available.

DISCLOSURE

The authors declare no conflict of interest.

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