Pharmacotherapeutic considerations for the management of diabetes mellitus among hospitalized COVID-19 patients

Abstract

Introduction: Diabetes mellitus is one of the most prevalent comorbidities identified in coronavirus disease 2019 (COVID-19) patients. This article aims to discuss pharmacotherapeutic considerations for the management of diabetes in hospitalized patients with COVID-19.

Areas covered: This paper presents a critical and comprehensive review of existing literature to present various aspects of diabetes management in hospitalized patients with COVID-19 and is divided into three sections (i) susceptibility and severity of COVID-19 among individuals with diabetes, (ii) glycaemic goals for hospitalized COVID-19 patients with diabetes, (iii) pharmacological treatment considerations for diabetes in hospitalized COVID-19 patients.

Expert opinion: The inpatient goal of therapy in both COVID-19 patients with type 1 (T1DM) and type 2 diabetes (T2DM) is to avoid disruption of stable metabolic state, tight glycaemic control, and prevent adverse glycaemic events. Patients with T1DM require insulin therapy at all times to prevent ketosis. The management strategy for T2DM includes temporary discontinuation of certain oral antidiabetic agents and consideration for insulin therapy, at least during hospitalization. Patients with T2DM who are relatively stable and able to eat regularly may continue with oral agents if glycaemic control is satisfactory. Hyperglycaemia should be anticipated in patients with systemic corticosteroid treatment and managed upon accordingly.

Keywords: Antidiabetic, Coronavirus 2019 (COVID-19), diabetes, type 1 diabetes, types 2 diabetes, therapeutics

Article highlights:

- Up to 12-18% of COVID-19 patients had concurrent diabetes and the presence of diabetes mellitus is one of the risk factors for developing severe disease in COVID-19 patients.
- Therapeutic goals in COVID-19 patients with diabetes requiring hospitalisation include minimisation of disturbances to the metabolic state, prevention of adverse glycaemic events including hypoglycaemia, and diabetic ketoacidosis/hyperosmotic hyperglycaemic state, as well as maintenance of a stable glycaemic balance.
- Type 1 diabetes patients require insulin therapy during hospitalisation for COVID-19. Moreover, insulin therapy is preferred for the management of hyperglycaemia in hospitalised COVID-19 patients with type 2 diabetes mellitus.
- Upon admission and during hospitalisation for COVID-19, type 2 diabetes patients receiving oral hypoglycaemic agents require a careful assessment of the continuation/discontinuation of these agents based on their clinical course.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently the biggest threat to the public health and an enormous challenge to the healthcare systems across the world. To date, more than 27 million people have been infected worldwide, and the death toll has exceeded 900,000 [1].

Although the exact pathophysiological mechanisms of COVID-19 are yet to be completely understood, elderly patients and patients with concurrent comorbidities, including diabetes mellitus are more likely to develop the severe form of COVID-19. About 12-18% of COVID-19 patients had concurrent diabetes as reported by early meta-analyses [2-4]. However, a recent meta-analysis based on over 23,000 COVID-19 patients from 43 studies reported that the prevalence of diabetes in COVID-19 patients was about 15% (95% confidence interval: 12%-18%), indicating earlier underestimation of the prevalence of diabetes among COVID-19 patients [5]. Furthermore, diabetes mellitus is a risk factor for a severe course of disease among COVID-19 patients. In one study, patients with diabetes constituted 11.7% of severe cases but only 4% of non-severe cases of COVID-19 [2]. Another meta-analysis reported that COVID-19 patients with diabetes had more than twice the odds of developing a severe course of illness (odds ratio: 2.47, 95% confidence interval: 1.67-3.66) [6].

The association between diabetes and COVID-19 is a serious public health concern as diabetes affects millions of people across the world. In addition, optimal glycaemic control is always of central importance in hospitalised patients with diabetes even before the existence of the COVID-19 crisis. Therefore, it is important to address the pharmacotherapeutic considerations for management of diabetes mellitus among hospitalised COVID-19 patients, regardless of those admitted in isolated medical wards or critical care units, based on currently available evidence.

2. Susceptibility and severity of COVID-19 in individuals with diabetes

Generally, individuals with diabetes (type 1 or type 2) are at increased risk of respiratory tract infections relative to the general population [7-10] that is linked to hyperglycaemia or lack of glycaemic control [11]. Hyperglycaemic state among individuals with diabetes could lead to impairment in cell-mediated immunity, phagocytosis, opsonisation, neutrophil chemotaxis, and adherence to vascular endothelium [12-14]. Diabetes and uncontrolled glycaemia have been reported to be one of the risk factors of severe illness and deaths in patients infected with novel coronaviruses, including the SARS-CoV-1 [15] and Middle East Respiratory Syndrome (MERS)-CoV [16]. A similar observation has been noticed among patients with SARS-CoV-2 infection, where a meta-analysis reported a significant association of diabetes with mortality, the occurrence of acute respiratory

distress syndrome (ARDS), and the progression of disease in patients with COVID-19 [17]. In addition, a pooled analysis of observational studies involving COVID-19 patients reported that those with diabetes had higher rates of being admitted to the intensive care unit (37.0% versus 26.7%; P = 0.028) [18]. Nevertheless, it remains unclear if diabetes *per se* leads to increased susceptibility of or adversely affects the outcomes from novel coronavirus diseases including COVID-19, or if the associated cardiovascular and renal comorbidities among patients with diabetes are the underlying factors, or it is an interplay of the both [19]. Indeed, both increased age [20] and cardiovascular comorbidities [6] are associated with increased COVID-19 severity, and both are closely related to diabetes.

While available studies are yet to explicitly analyse the pathophysiology behind the poor prognosis of in COVID-19 patients with diabetes, it has been suggested that increased vascular permeability in patients with diabetes may play a role. Patients with diabetes may have enhanced vasculature permeability associated with vasculitis where in fact, endothelial dysfunction is not uncommon among patients with diabetes [21,22]. Since many of the clinical phenomenon observed in COVID-19 patients are also associated with endothelial dysfunction, this may explain the increased incidence of ARDS among COVID-19 patients with diabetes, a major complication of COVID-19, and potentially responsible for increased death [23,24].

3. Glycemic goals for hospitalized COVID-19 patients with diabetes

Reasonable goals in COVID-19 patients with diabetes requiring hospitalisation include minimisation of disturbances to the metabolic state, prevention of adverse glycaemic events including hypoglycaemia, and returning/maintenance of a stable glycaemic balance. These goals may be difficult to achieve clinically: on one hand, the acute stressors from COVID-19 tend to increase blood glucose levels; and on the other hand, the anorexia that may accompany the severe course of COVID-19 [25] would do the opposite. To illustrate, a retrospective analysis of capillary blood glucose tests among 29 hospitalised patients with type-2 diabetes mellitus (T2DM) with positive COVID-19 status revealed that 56.6% (499/881) of the tests had elevated glucose levels, including 29.4% (58/197) pre-prandial blood glucose (>7.8 mmol/L) tests and 64.5% (441/684) postprandial blood glucose (>10.0 mmol/L) tests [26].

Hyperglycaemia can cause volume and electrolyte disturbances mediated by osmotic diuresis, and thus a predilection towards acute kidney injury or septic shock in COVID-19 patients [27]. Therefore, it shall not be far from the truth that to expect a poor prognosis among COVID-19 patients with hyperglycemia. Indeed, a multicenter observational study [28] among 1,122 COVID-19 patients found that COVID-19 patients with hyperglycaemia (defined as blood glucose readings persistently above 10 mmol/L during any 24 hours throughout their hospitalisation) had an increased risk for inpatient

mortality than their counterparts who were without diabetes or hyperglycaemia (41.7% versus 6.2%). Furthermore, COVID-19 patients with hyperglycaemia were found to have a significantly longer median length of hospital stays than those without diabetes or hyperglycaemia (6.8 days versus 4.3 days) [28]. Besides, there is some evidence to suggest that patients with hyperglycaemia may not receive the same benefits from anti-inflammatory therapies for COVID-19 compared to their counterparts without hyperglycaemia. A retrospective study reported that the administration of tocilizumab in hyperglycaemic patients did not reduce the risk of severe outcomes from COVID-19 as opposed to normoglycemic patients who demonstrated significant risk reduction [29].

On the other hand, the hypoglycaemia is also harmful, since the secretion of counterregulatory hormones upon the development of hypoglycaemia, especially catecholamines, may induce arrhythmias and other cardiac events [30]. This is especially a concern in COVID-19 patients since COVID-19 *per se* has been associated with the development of myocardial injury [31-33]. Furthermore, many COVID-19 patients have pre-existing coronary heart disease as underlying comorbidity and they may not tolerate as much insult on the cardiovascular system [2-4]. If blood glucose falls to 2.8 mmol/L or below, transient cognitive deficits may also develop, which may increase the risk of falls as well as aspiration potentially leading to secondary aspiration pneumonia in COVID-19 patients [34]. In a retrospective cohort study of over 2,500 hospitalised patients with diabetes (non-COVID-19), patients who experienced one or more hypoglycaemic events (blood glucose level of ≤2.8 mmol/L) [35] were associated with significantly higher inpatient mortality.

For most hospitalised COVID-19 patients with diabetes, it is reasonable to maintain a pre-prandial blood glucose target of <7.8 mmol/L, with all random blood glucose levels <10 mmol/L, which are extrapolated from hospitalised diabetic patients without COVID-19. These targets are consistent with the consensus statement by the American Diabetes Association (ADA) [36] and the clinical practice guideline of the Endocrine Society [37] for hospitalized patients, formulated before the COVID-19 crisis. The ADA [35] has not stipulated any differences in target glucose values based on the timing of the measurements (preprandial versus postprandial) while the Endocrine Society [37] recommends premeal targets of <7.8 mmol/L and "random" glucose levels of <10 mmol/L. Nevertheless, tighter targets may be appropriate for stable COVID-19 patients with previously good glycaemic control, and the goal may be relaxed for elderly patients and those with a severe course of COVID-19 where the increased risk of hypoglycaemia may negate any potential benefit. Although the aforementioned glucose targets are not specific to COVID-19 patients, an observational study [38] suggested that such a target can be extrapolated to this population. The authors reported that COVID-19 patients with controlled blood glucose levels within 3.9 to 10.0 mmol/L were associated with a significant reduction

in the mortality risk compared to those with blood glucose levels of >10.0 mmol/L (adjusted hazard ratio 0.14, 95% confidence interval: 0.03-0.60).

A reasonable glycaemic control to avoid hypoglycaemia is to achieve fasting blood glucose levels of no lower than 5.0 mmol/L, which will usually provide a comfortable cushion in case the blood glucose level falls further as the clinical condition improves. In general, all random blood glucose levels should be kept below 10.0 mmol/L range to avoid further elevation, which may be associated with dehydration, glycosuria, and ketoacidosis.

3.1 Continuous glucose monitoring (CGM)

CGM devices measure the glucose content of the interstitial fluid, which correlates to the plasma glucose, albeit a 10- to 15-minute lag-time if blood glucose is changing rapidly. CGM, depending on the type of the device, measures glucose levels every 5 to 15 minutes and therefore offers a solution to staff shortages in conducting point-of-care blood glucose testing for hospitalised COVID-19 patients amid the COVID-19 pandemic. A randomised controlled trial comparing nursing workload between the use of subcutaneous CGM and frequent point of care blood glucose testing reported a 19-minute reduction in nursing workload within 24 hours [39].

Furthermore, the use of CGM in intensive care is also linked to better glycaemic control. A randomised controlled trial among 124 mechanically ventilated patients in the intensive care units found significantly lower rates of severe hypoglycaemia in patients randomised to real-time CGM group compared to those randomised to the control group (1.6 vs 11.5%, P = 0.031) despite attainment of similar mean glucose levels [40]. Besides, a reduction of 9.9% in the absolute risk of hypoglycaemia was also observed (95% confidence interval 1.2-18.6). Similar reports of better control with CGM have also been reported with surgical [41] and other non-intensive care units (ICU) settings [42].

Unlike subcutaneous CGM, the intravascular CGMs carry risks of thrombosis, which may not be desirable considering the hypercoagulable state in COVID-19 [43,44]. Besides, acetaminophen (paracetamol) which is commonly used for febrile COVID-19 patients interferes with the glucose biosensors in the device and may cause a false overestimation of glucose [45]. Moreover, the use of CGM devices in a hospital setting may be hindered by barriers including the cost and the training required for the nursing staff. Therefore, while CGM use in COVID-19 patients within a hospital setting can help with the nursing workload, consideration should also be given to the availability of local expertise and resources in the hospital to operate CGM devices along with due consideration to the factors that may disrupt the accuracy of blood glucose readings. It is recommended that the clinicians who wish to consider using CGM for the management of COVID-19 diabetic patients should consult

their local diabetes team for localised support and recommendations on the feasibility of CGM use in a particular setting. There was only one case report thus far which demonstrated the safety of remote CGM in a COVID-19 patient with diabetes [46].

In the United States, Food and Drug Administration (FDA) has issued guidance permitting two CGM devices—the Dexcom G6 and Abbott FreeStyle Libre — to be used in hospitals during the COVID-19 pandemic, despite neither being officially approved for the hospital use [47]. A reasonable target for hospitalised COVID-19 diabetic patients with CGM in place would be >70% of time glucose readings in the range of 3.9–10.0 mmol/L, <4% of time glucose readings <3.9mmol/L, <1% of time glucose readings <3.0 mmol/L, and <25% of time glucose readings >10mmol/L, in a 24-hour period [48].

4. Pharmacologic treatment considerations for diabetes in hospitalized COVID-19 patients

The presence of COVID-19 in patients with or without previously diagnosed diabetes portends the risk for the development of emergency states of hyperglycemia including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Therefore, all newly admitted patients with COVID-19 should be evaluated for the presence of diabetes (and state of ketosis) and an assessment of the type of diabetes which will determine a suitable therapeutic approach. In fact, approaches to glycaemic control should be instituted early (within 24 hours of admission) to mitigate the progression of disease in hospitalised COVID-19 patients with diabetes and acute hyperglycaemia. A preliminary study has reported a lower rate of progression to severe COVID-19 disease and death at 20 days among patients who achieved a reduction in blood glucose levels between baseline and 24 hours of hospital admission compared to their counterparts without a reduction in blood glucose levels [49].

4.1 COVID-19 patients with type 1 diabetes mellitus

Patients with type 1 diabetes mellitus (T1DM) would require insulin therapy during hospitalisation for COVID-19. However, fluctuation in blood glucose levels should be expected. Insulin can be administered either subcutaneously or intravenously, although the latter is generally preferred only in those who are critically ill or those who have marked hyperglycemia [36].

For subcutaneous administration, intermediate-acting insulin, such as neutral protamine hagedorn (human NPH), or a long-acting (basal) insulin analog (glargine, detemir, or degludec) can be combined with a pre-meal rapid-acting insulin analogue (lispro, aspart, glulisine) in patients who are eating regular meals (i.e., a basal-bolus regimen) [36]. The short-acting (human regular) insulin has fallen out of favour for meal-time dosing in the hospital, although there are no good studies comparing its efficacy and safety to the costlier rapid-acting analogues. Variable doses of rapid-acting insulin can be added to usual pre-meal rapid-acting insulin in patients on basal-bolus regimens to correct premeal

glucose excursions [36]. The dose of correction insulin should be individualised based upon relevant patient characteristics, such as the historical glucose control, past insulin requirements, and, if possible, the carbohydrate content of meals.

For patients treated with a continuous subcutaneous insulin infusion via an insulin pump, the basal insulin can be continued at the usual rate, with insulin boluses administered before mealtimes [50]. Since nursing staff is not always familiar or comfortable with the use of insulin pumps, they may need further support to manage patients using these devices whilst in hospital, for example from diabetes teams, when patients are uncomfortable with or become incapable to manage their insulin pump whilst in hospital. Also, vigilance regarding pump catheter placement is necessary since catheters may inadvertently be dislodged while patients are in bed. If the patient is not alert enough to provide self-care or the continued use of an insulin pump is deemed not feasible, a change to conventional injection therapy should be considered during hospitalisation.

Most COVID-19 patients with T1DM in the general medical wards can be managed with subcutaneous administration of insulin. However, many practitioners choose to initiate a variable rate of intravenous insulin infusion (VRIII) (human regular insulin in solution) in certain circumstances, such as those with marked hyperglycemia (blood glucose >16.7 to 19.4 mmol/L) and those in the critical care setting. Nevertheless, there is little evidence to suggest that intravenous insulin is superior to subcutaneous insulin. Also, it is of paramount importance that the subcutaneous basal insulin is continued alongside VRIII due to the short half-life of intravenously administered insulin. This way, individuals have at least a small amount of insulin circulating at all times, which will significantly increase the likelihood of controlling blood glucose levels during hospitalisation for COVID-19.

The safe implementation of insulin infusion protocols requires frequent blood glucose monitoring, which is not typically the case in an isolated medical ward for COVID-19. Other practical considerations include the skill of the nursing staff working in the frontline for COVID-19 which may not be adequately trained for diabetes and the complexity of intravenous regimens. A complicated regimen may introduce risk where diabetes nurses are short-staffed amid the COVID-19 pandemic. Thus, it is best to reserve insulin infusions for critically ill COVID-19 patients in the ICU, in which it is the most effective method for glycemic management in this patient population.

VRIII should be administered based on validated protocols (either written or computerized) that detail predefined adjustments in the infusion rate, taken into account the blood glucose fluctuations and the current rate of infusion [36]. Several safe and effective insulin infusion protocols [51-53] have been published, with low rates of hypoglycemic events, although most have been validated only for patients in the ICU, where the nurse-to-patient ratio may be higher than that during COVID-19. The protocol

validated by Smiley et al. [53] in non-critical care settings may be suitable when the nurse-to-patient ratio is non-optimal.

A reasonable regimen usually involves a continuous insulin infusion at a rate of 1 to 5 units of regular insulin per hour; within this range, the dose of insulin is increased or decreased according to the patient's usual insulin dose. In patients who are not eating, concomitant but separate glucose infusion is necessary to provide some calories, reduce protein loss, and decrease the risk of hypoglycemia [54]. A prospective study of 59 COVID-19 patients reported that patients with hyperglycemia upon admission and treated with insulin infusion had better outcomes, such as a lower risk of developing composite endpoint of severe disease, admission to an intensive care unit, use of mechanical ventilation, or death, than the patients without insulin infusion [55].

When the clinical condition of COVID-19 patients receiving intravenous insulin is deemed stable, the prior insulin regimen can be resumed, provided that it was effective in achieving glycemic goals. Because of the short half-life of intravenous regular insulin, the first dose of subcutaneous short- or rapid-acting insulin must be given 1 to 2 hours before discontinuation of VRIII [36].

4.2 COVID-19 patients with type 2 diabetes mellitus previously treated with insulin

Insulin therapy should be continued in all COVID-19 patients with T2DM already receiving insulin before hospitalization to maintain a reasonably constant basal level of circulating insulin. Failing this, severe hyperglycemia or even hyperglycemic crises may occur. Noteworthy, the insulin requirement may be greater than the usual due to acute stressors from COVID-19. A basal-bolus regimen similar to the one recommended above for patients with T1DM can be used when the patient is eating regularly in an isolated medical ward. However, different basal-bolus regimens are similarly effective in reducing HbA1c concentrations when insulin doses are titrated to achieve glycemic goals. For instance, a trial comparing detemir/aspart versus NPH/regular in 130 hospitalized patients found no difference in glycemic control or frequency of hypoglycemia between the two regimens [56].

COVID-19 patients treated with more concentrated insulins (such as U-500 regular insulin with 500 units/ml) at home may continue U-500 insulin if available in the hospital. Since the high concentration of insulin delays absorption, the pharmacological profile of U-500 regular insulin is highly similar to that of NPH [57]. Thus, if U-500 insulin is not available, U-100 NPH insulin can be substituted. We would caution that errors are common with U-500 administration, and clear communication among patients, clinicians, nursing staff, and pharmacy is imperative to ensure proper dosing, especially amid the COVID-19 pandemic where there may be staffing shortage.

4.3 COVID-19 patients with type 2 diabetes mellitus treated with oral antidiabetic agents

In general, insulin therapy is preferred for the management of hyperglycemia in hospitalized COVID-19 patients with type 2 diabetes mellitus. However, in certain circumstances where patients have been well controlled on their outpatient regimen, are relatively stable, and eating regularly, may continue their oral hypoglycemic agents. Even when there is decreased food intake, hyperglycemia is still likely, and we anticipate that most hospitalized diabetic patients with COVID-19 may eventually need insulin during hospitalisation. Also, there may be specific contraindications to the oral hypoglycemic agents in hospitalized COVID-19 patients (refer next section). In this connection, oral agents should, therefore, be discontinued temporarily. Overt hyperglycemia (>10.0 mmol/L) in patients previously treated with oral hypoglycemic agents (or diet-treated) can be treated briefly with intermittent, subcutaneous doses of regular (every six hours) or rapid-acting (every four to six hours) insulin as a dose-finding approach, provided the blood glucose is not severely elevated and the patient responds well to the insulin [36]. However, a more formal and comprehensive insulin regimen as detailed above for patients with T1DM, including some form of basal insulin, is usually preferred in patients with persistent hyperglycemia.

4.4 Medicines management of oral antidiabetic agents in the context of COVID-19

Most patients with T2DM are treated with one or the other oral hypoglycemic agent. However, there are issues related to the use of oral hypoglycemic agents in patients with COVID-19 especially among hospitalized patients who are critically ill (**Table 1**).

4.4.1 Biguanides (Metformin)

The lactic acidosis related to metformin remains a cause for concern owing to the associated high case-fatality rate [58,59]. Lactic acid accumulation with metformin may occur in patients with COVID-19 due to associated hypoperfusion and hypoxemia. For instance, ARDS which is the major cause of morbidity and mortality among patients who develop critical illness from COVID-19, and is largely due to acute viral pneumonitis that evolves to acute hypoxemic respiratory failure, represents a compromised hemodynamics state which could lead to lactic acidosis in COVID-19 patients taking metformin [23, 60-67]. Also, hypoperfused state such as shock and multi-organ failure does occur in patients with COVID-19, with 13% of patients requiring vasoactive agents as reported in a prospective study [60]. A significant proportion of COVID-19 patients also require vasopressor support due to hypotension associated with sedative medications or cardiac dysfunction [57]. On the other hand, cardiac dysfunction such as acute decompensated heart failure which may be precipitated by COVID-19 in patients with pre-existing or undiagnosed heart disease (e.g., coronary artery disease or

hypertensive heart disease) or incident acute myocardial injury (e.g., acute myocardial infarction, stress cardiomyopathy, cytokine storm) could increase the risk of lactic acidosis with continued metformin use [68]. Therefore, metformin should be discontinued at least temporarily in hospitalized patients with COVID-19 who have developed or are likely to develop haemodynamic decompensation (severely or critically ill) due to an increased risk of lactic acidosis [58].

Otherwise, it may be safe to continue metformin in haemodynamically stable patients. In fact, a retrospective cohort study of 283 diabetic patients with COVID-19 in China reported a significantly lower rate of inpatient mortality among patients receiving metformin compared to their counterparts not receiving metformin (2.9% versus 12.3%; P=0.01) [69]. Another large retrospective database review involving more than 6,000 COVID-19 patients in the United States though reported no difference in mortality with regards to metformin use in the overall study population, subgroup analyses found metformin use was significantly associated with decreased mortality upon propensity matching among female patients (odds ratio: 0.759, 95% confidence interval: 0.601-0.960) [70].

4.4.2 Thiazolidinediones (glitazones)

The thiazolidinediones (e.g., pioglitazone, rosiglitazone) are associated with peripheral edema and should be avoided in patients with COVID-19 in whom acute heart failure may be precipitated by the current illness [71]. Such fluid retention may also lead to an increased risk of heart failure. In meta-analyses of randomized trials of thiazolidinediones for the treatment or prevention of type 2 diabetes, the estimated relative risk of developing heart failure in patients receiving thiazolidinediones compared to placebo ranged from 1.5 to 2.1 (95% confidence interval 1.2-2.4 and 1.1-4.1, respectively) [72-74]. Given, the antihyperglycemic effect of thiazolidinediones extends for several weeks after discontinuation (as does the fluid-retaining effect), the temporary interruption of therapy should have little effect on glycemic control [75].

Pioglitazone has been recently suggested as a potential treatment option for COVID-19 [76]. In-vitro evidence indicates that various immune cells, including T cells, dendritic cells, and macrophages express peroxisome proliferator-activated receptor gamma (PPAR-γ). It has been observed that the activation of PPAR-γ by its high-affinity synthetic ligand such as pioglitazone could inhibit the inflammatory nuclear factor (NF)-κB pathway and mitogen-activated protein kinase signalling for the production of cytokines, and could, therefore, mitigate cytokine storm syndrome associated with COVID-19 [77,78]. However, the beneficial effect of pioglitazone seen in human dendritic cells *in-vitro* requires preclinical and clinical validations before any firm conclusion on its use in COVID-19. Temporary discontinuation of glitazones should still be considered in hospitalized diabetic patients with COVID-19 due to potential risks of peripheral edema.

4.4.3 Sulfonylureas

Sulfonylureas (e.g., glyburide, glipizide, glimepiride) with their associated risk of hypoglycemia can be severe and prolonged [79]. However, continued use of sulfonylureas (especially of short-acting such as gliclazide) in stable hospitalized COVID-19 patients can still be justified if patients can take regular normal diets, albeit, unexpected alterations in meal intake, particularly in ICU settings, may increase the risk for severe hypoglycemia.

There are contrasting reports on the safety of sulfonylureas in patients with myocardial infarction (MI). Some studies suggest that treatment with sulfonylureas may be associated with poorer outcomes in patients who had an MI [80]. Conversely, some refute any association of sulfonylurea with the deaths due to MI [81,82]. Since COVID-19 can lead to cardiac injury *per se* [30-32], caution is advised if sulfonylureas are used in patients with severe COVID-19 patients during hospitalization. The adverse outcomes in patients with MI are attributed to the non-selective binding of sulfonylureas to pancreatic and cardiac receptors. In this context, it may be argued that the newer drugs (gliclazide and glimepiride) that selectively bind to the pancreatic receptors may be safer than the older non-selective drugs. Although there are no randomized controlled trials to confirm this as yet, preliminary findings from a nationwide French registry of MI has shown improved in-hospital outcomes for patients receiving gliclazide/glimepiride compared with those on glibenclamide [83]. For the time being, due to cardiovascular safety and the risk of severe hypoglycemia, sulfonylureas should be avoided in diabetic patients hospitalized due to COVID-19.

4.4.4 Meglitinides (glinides)

Meglitinides (e.g., repaglinide, nateglinide) work similarly to the sulfonylureas but have a shorter duration of action [84] and exhibit a better prandial glucose regulation and therefore may be preferred in hospitalized COVID-19 patients with diabetes who are eating regularly. However, they should still be used with caution, particularly in patients with COVID-19-associated cardiac injury, due to their similarity in their mode of action to that of sulfonylureas, and hence probably pose a similar cardiovascular risk. In a retrospective cohort study of patients with T2DM taking gliclazide, glyburide, or repaglinide prior to hospitalisation for coronary heart disease, there was no difference in adverse cardiovascular outcomes at 30 days among the three antidiabetic agents [85].

4.4.5 Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (e.g., acarbose, miglitol) are generally used infrequently and typically are not on hospital formularies. Moreover, these inhibitors of intestinal carbohydrate absorption are only

effective in patients who are eating and therefore may have a limited role in COVID-19 patients, especially in ICU settings.

4.4.6 Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

DPP-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin, alogliptin) inhibit the degradation of glucagon-like peptide-1 which stimulates insulin secretion in response to food. Unlike sulfonylurea, they mainly affect the postprandial glucose level and therefore may be of little use for patients with COVID-19 who may not be eating properly during hospitalization. In addition, DPP-4 inhibitors have not been tested extensively in the acute care setting [86]. Two studies suggested that they may be reasonably effective in mildly hyperglycemic patients with T2DM who are eating normally [87,88].

There has been a debate on the potential role of DPP-4 inhibition in COVID-19 patients [88]. In addition to its involvement in glucose and insulin metabolism, DPP-4 plays also a vital role in the regulation of the immune system via activation of T cells and upregulation of CD86 expression through the nuclear factor-κB pathway and thus the inhibition of DPP-4 may adversely affect the immune response to viral infection [89]. However, activation of the nuclear factor-κB pathway may also lead to the production of various pro-inflammatory cytokines which could contribute to lung inflammation [90]. In an animal study, upon being infected with MERS-CoV, human virus replication was observed in the lungs of DPP-4 knock-in mice but they developed no illness [91]. In another experimental model of ARDS, DPP-4 inhibition through sitagliptin mitigated histological lung injury through the inhibition of proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor α, and IL-6 [92]. Therefore, much left to be understood on the effect of DPP-4 inhibition and a clinical trial is ongoing to determine the outcomes of DPP-4 inhibition in COVID-19 [93]. Nevertheless, several case reports of vildagliptin-induced interstitial pneumonia have been reported, which laid doubts on the safety of vildagliptin and other DPP-4 inhibitors in patients with pulmonary infection [94,95]. In addition, sitagliptin has been associated with increased risk of venous thromboembolism according to a recent pharmacovigilance study, which may make sitagliptin, undesirable in hospitalized COVID-19 patients due to increased recognition of thrombo-inflammation [96]. Recently, a retrospective case-control study that evaluated the effect of exposure to DPP-4 inhibitors in hospitalized COVID-19 patients noted no significant difference with regards to admittance into ICU and deaths between those on DPP-4 inhibitors versus their matched counterparts without DPP-4 inhibitors [97].

Though there may be limitations with case-control study design until we have strong clinical evidence in the forms of randomized controlled trials to suggest otherwise, it is recommended to discontinue DPP-4 inhibitors (at least temporarily) in all but stable COVID-19 hospitalized patients who are expected to eat regularly.

4.4.7 Glucagon-like peptide-1 (GLP-1) agonists (incretin mimetics)

Like DPP-4 inhibitors, the GLP-1 agonists (e.g., exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide) also mainly effective for postprandial glucose control. Besides, they may result in nausea and pose a possible risk of dehydration, which could lead to acute renal injury or worsen septic shock in critically ill COVID-19 patients [98]. As a result, their use should probably be avoided in the acute care setting among COVID-19 patients. However, there has been discussion to repurpose GLP-1 agonists for the treatment of COVID-19 due to its potential in modulating the pulmonary renin-angiotensin system [99]. Attachment of coronavirus with angiotensin-converting enzyme 2 (ACE2) leads to the downregulation of ACE2 and the subsequent reduced low angiotensin(1-7) levels [100]. Such an effect of novel coronavirus on the renin-angiotensin system can be counter-regulated by the GLP-1 agonists. In a rat model, the GLP-1 agonist, liraglutide has been found to provoke a strong increase in angiotensin-converting enzyme 2 expressions in the lungs, and in the circulating angiotensin(1–7) level [101]. Furthermore, a study among patients with type 1 diabetes reported the potential for liraglutide to reduce the pro-inflammatory IL-6 level [102]. The effect of GLP-1 agonists in COVID-19 patients was limited to a mere case report [103] reporting the safety of liraglutide in a COVID-19 patient with severe illness, more data is needed to establish its efficacy and safety in COVID-19.

4.4.8 Sodium-glucose co-transporter 2 (SGLT2) inhibitors (gliflozins)

SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin) promote renal excretion of glucose. They increase calorie losses, risk of dehydration, and volume contraction, as well as genitourinary tract infections [104]. Also, euglycemic diabetic ketoacidosis has been documented in patients with both T1DM (during off-label use) and T2DM who were taking SGLT2 inhibitors [104,105]. Since COVID-19 *per se* could precipitate atypical presentations of hyperglycemic emergencies (e.g., hyperosmolar states), these drugs should, therefore, be discontinued temporarily in inpatients with COVID-19 upon admission to reduce the risk of metabolic decompensation [106].

Table 1: A summary of oral antidiabetic agents and concerns regarding their use with recommended actions among inpatients with COVID-19

Class	Concern	Practical options
Biguanides (Metformin)	Risk of lactic acidosis due to the likelihood of hemodynamic compromise among hospitalized patients with COVID-19	Discontinue (at least temporarily) upon admission with COVID-19
Thiazolidinediones (glitazones)	May precipitate peripheral oedema and/or heart failure	Discontinue in COVID-19 in-patients with the risk of acute heart failure by current illness

Sulfonylureas	- Risk of hypoglycemia - Potential adverse cardiovascular effect	Discontinue (at least temporarily) in COVID-19 hospitalized patients who are not eating regularly or when cardiac injury is likely
Meglitinides (glinides)	Potential adverse cardiovascular effect	Discontinue (at least temporarily) in COVID-19 hospitalized patients who are not eating regularly or when cardiac injury is likely
Alpha-glucosidase inhibitors	Effect mainly on postprandial blood glucose level	Discontinue (at least temporarily) in all but stable COVID-19 hospitalized patients who are expected to eat regularly
DPP-4 inhibitors (gliptins)	- Effect mainly on postprandial blood glucose level - Vildagliptin is associated with interstitial lung injury - Sitagliptin is associated with increased risk of venous thromboembolism	Discontinue (at least temporarily) in all but stable COVID-19 hospitalized patients who are expected to eat regularly
GLP-1 agonists (incretin mimetics)	- May cause intense nausea and worsen gastrointestinal symptoms of COVID-19 - Possible risk of dehydration - Effect mainly on postprandial blood glucose level	- Discontinue (at least temporarily) in all but stable COVID-19 hospitalized patients who are expected to eat regularly and without associated gastrointestinal symptoms - Ensure adequate fluid intake if no contraindication
SGLT2 inhibitors (gliflozins)	- Increased risk of dehydration - May precipitate diabetic ketoacidosis - Increased risk of UTIs	Discontinue (at least temporarily) upon admission with COVID-19

COVID-19: novel coronavirus disease 2019; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose co-transporter 2

4.5 Management of corticosteroid-related in-hospital hyperglycemia

More widespread use of corticosteroid, particularly, dexamethasone in CoViD-19 patients is expected following recent updates from the World Health Organization (WHO) in its treatment guidance [107] among patients with a severe and critical course of COVID-19 due to its mortality benefits in a meta-analysis [108] performed by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. As discussed beforehand, hyperglycemia may be an independent predictor of poor prognosis in hospitalized patients with COVID-19 with diabetes. Since the administration of systemic corticosteroids could lead to or may worsen the hyperglycemic state, the possibility of hyperglycemia to compromise the mortality benefits from systemic corticosteroids cannot be ruled out.

Therefore, it is of utmost importance for clinicians who decide to use systemic corticosteroids in their COVID-19 patients to pre-empt hyperglycemia in the management plan fo the patients. Within the limited literature focusing on the management of corticosteroid-related in-hospital hyperglycemia, there is a randomized, open-labeled, parallel-arm trial [109] which included 67 patients with or without diabetes comparing the efficacy of two protocols for the management of hyperglycemia related to systemic corticosteroids. The first was the standard basal-bolus insulin protocol and the second was the correctional insulin protocol which aimed to match the glycemic profile of the particular systemic corticosteroids administered with or without usual basal-bolus insulin. Relative to patients who were randomized to standard basal-bolus insulin protocol, those who received the correctional insulin protocol reported significantly lower mean blood glucose and glycemic variability.

Hence, the core to the management of corticosteroid-related in-hospital hyperglycemia involves the use of insulin therapy with a glucose-lowering profile coinciding with the glycemic profile of the systemic corticosteroids. The glycemic profile of systemic corticosteroids is closely related to its duration of action; the glycemic effect of dexamethasone which is a long-acting systemic corticosteroid may last as long as 48 hours. Considering its glycemic profile, coverage with insulin glargine or insulin degludec as the correctional insulin having a glucose-lowering effect lasting more than 24 hours may be suitable in patients who are insulin naïve and may develop persistent hyperglycemia [110,111]. Twice-daily human NPH insulin or insulin detemir may be considered if more flexibility with dose adjustment is required [112]. Correctional insulin should be administered along with the systemic corticosteroid and should be tittered according to the dose of dexamethasone administered [109]. Considering a recommendation of 6 mg dexamethasone once daily in severely ill COVID-19 patients, a recommended dose of correctional insulin will be 0.3 units/kg [112]. Nevertheless, in patients who are already receiving basal insulin or basal-bolus insulin, the current amount of basal insulin may be increased by 20-40% depending on the response if persistent hyperglycemia is detected [112]. On the other hand, patients on twice-daily premixed insulin with persistent hyperglycemia may have their morning dose increased by 20-40%, though there should also be a low threshold to switch to a basal-bolus insulin regimen to allow for more flexibility with dose adjustment [112].

Expert opinion

Over 463 million people worldwide are living with diabetes and this large group of population is currently at increased risk of developing a severe course of illness upon contracting COVID-19. Therefore, clinicians caring for patients with COVID-19 may encounter the need for managing diabetes concurrently. The altered glucose homeostasis in patients with diabetes may be the cause of shifting

for most cases form moderate to severe form of the illness, ICU admissions, and deaths in COVID-19 since hyperglycemia could contribute to over-inflammation enhanced oxidative stress, and refractoriness of anti-inflammatory therapies. It is, therefore, of utmost importance to discuss the optimal glycemic goals and the pharmaceutical considerations for the management of diabetes in hospitalized COVID-19 patients. COVID-19 patients with diabetes constitute a significant risk group for emergency states of hyperglycemia, which highlights the need to maintain optimal glycemic state, where pre-prandial blood glucose level should be <7.8 mmol/L, and all random blood glucose levels should be <10 mmol/L. This would require frequent testing of blood glucose (every 4-6 hours) in hospitalized COVID-19 patients with diabetes. The use of CGM in this patient population may obviate the need for frequent blood glucose testing if local expertise and resources in the hospital to operate CGM devices are available.

Patients with T1DM should continue to receive their insulin whilst treated in hospital, and local guidelines concerning the use of VRIII should be followed. The insulin pump for patients with T1DM may be continued provided patients are capable to self-manage their pump or there is competent nursing staff for monitoring. Therapeutic management of T2DM needs careful consideration in individual patients where the potentially adverse consequence in COVID-19 is confounded by other risk factors that may impact the appropriateness of oral antidiabetic agents. These oral antidiabetic agents used to maintain outpatient glycemic control in patients with T2DM require careful review upon hospitalization for COVID-19 considering individualized risk assessment and glycemic status. The oral hypoglycemic agents in COVID-19 patients with diabetes may, therefore, require temporary adjustments, the recommendations in **Table 1** should provide a useful guide for the treatment optimisation. In general, insulin therapy, similar to those for T1DM, is preferred for managing hyperglycemia in hospitalized T2DM patients with COVID-19. Furthermore, clinicians who opt for the systemic corticosteroid treatment in their patients with COVID-19, especially those with underlying diabetes, should pre-empt hyperglycemia in their management plan. The core to the management of corticosteroid-related in-hospital hyperglycemia involves the use of insulin therapy with a glucose-lowering profile to match the glycemic profile of the systemic corticosteroids.

As our understanding of COVID-19 improves with more evidence, we may soon, better understand the relationship between COVID-19 and diabetes. This way, the diabetes-associated risk for the development of severe COVID-19 during hospitalization can be mitigated. Also, oral hypoglycemic agents such as thiazolidinediones and DPP-4 inhibitors that hold promise for some benefit in COVID-19 based on their mechanism of action should be investigated further for potential inclusion into the armamentarium against COVID-19. However, until their efficacy amid COVID-19 is proven in the clinic,

the recommendations on use of DPP-4 inhibitors in this article with regards to glycemic control should be followed.

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