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EDITORIAL

Considerations for management of patients with diabetes mellitus and acute COVID-19

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Abstract

Diabetes mellitus (DM) is an independent risk factor for admission to intensive care unit and death in patients with coronavirus disease 2019 (COVID-19). On the other hand, medications used in the management of COVID-19 are potentially associated with increases in blood glucose levels and a higher incidence of infections. Accordingly, care of patients with DM and acute COVID-19 requires careful consideration of both diseases. Hyperglycemia and hypoglycemia are associated with adverse outcomes and therefore frequent measurement of blood glucose levels and a basal-bolus insulin regimen are required in most patients. Regarding the management of COVID-19, dexamethasone increases blood glucose levels and might also increase the risk for infections. On the other hand, limited data suggest that antiviral and immunomodulatory agents used in COVID-19 are not strongly associated with higher incidence of infections in this population. As knowledge evolves in this field, optimization of the management of both DM and COVID-19 will hopefully improve the outcome of these patients.

Key Words: Diabetes mellitus; COVID-19; Insulin; Antidiabetic agents; Dexamethasone; Tocilizumab; Remdesivir

Core Tip: Diabetes mellitus is a frequent comorbidity in patients hospitalized with coronavirus disease 2019 and is associated with adverse outcomes. Strict glycemic control using insulin is necessary in most of these patients. Dexamethasone, antiviral agents and immunomodulation are also frequently administered and require vigilance and careful monitoring for adverse effects, particularly infections.

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INTRODUCTION

Several studies showed that diabetes mellitus (DM) is an independent risk factor for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19)[1,2]. Moreover, DM is associated with longer hospitalization, increased risk for admission to an intensive care unit (ICU) and higher mortality in patients with COVID-19[1-3]. Elderly patients and those with poor glycemic control and comorbidities, including hypertension and established cardiovascular disease (CVD), are at higher risk for adverse outcomes[1-3]. In addition, patients with DM and COVID-19 appear to have higher risk for acute complications of DM, particularly diabetic ketoacidosis (DKA)[4]. On the other hand, SARS-CoV-2-induced insulin resistance and impaired insulin production, stress and dexamethasone, which is frequently used for the management of COVID-19, often cause substantial increases in blood glucose levels[5-7]. Furthermore, immunomodulatory agents, which are also part of the treatment of COVID-19, might increase the risk for infection, which is higher in patients with DM[8,9]. Therefore, the management of patients with both DM and COVID-19 requires special considerations, which are briefly summarized in the present commentary.

BLOOD GLUCOSE GOALS

In patients with DM and COVID-19, both hyperglycemia and hypoglycemia have been associated with worse outcome[10,11]. Therefore, maintaining a strict glycemic control in this population appears to be of critical importance. Blood glucose levels between 110 and 180 mg/dL have been recommended as targets in hospitalized diabetic patients with COVID-19, aiming at the higher end of range[12]. However, this target should be individualized, blood glucose levels up to 220 mg/dL are considered acceptable and glucose control should be less strict in patients at high risk for hypoglycemia, including the elderly, the underweight, and patients with severe COVID-19 and/or renal impairment[12].

MONITORING OF BLOOD GLUCOSE LEVELS

Glucose measurement should be performed at least 4 times per day, before meals and at bedtime, but in certain cases has to be done more frequently, particularly in patients who are not eating or are receiving parenteral nutrition[12]. Continuous blood glucose monitoring devices can also be used, particularly in ICU, and appear to be feasible, accurate and reduce the need for point of care glucose measurements [13]. Given the increased risk for DKA in patients with DM and COVID-19, blood ketone levels should ideally be measured in all diabetic patients at admission[12].

ANTIDIABETIC TREATMENT

Regarding antidiabetic treatment, insulin is the agent of choice in most patients. In those who are already receiving long-acting basal insulin, this should be continued[12]. If the patient is not on long-acting insulin and has ≥ 2 blood glucose measurements > 220 mg/dL within the previous day, basal insulin should be started at a total daily dose of 0.25 units/kg[12]. However, in elderly or frail patients and in those with impaired kidney function, the total daily dose of basal insulin should be lower (approximately 0.15 units/kg)[12]. In patients who are receiving glucocorticoids, the dose of basal insulin should be increased by 20%-40%, depending on blood glucose levels[8]. Basal insulin dose are then titrated once-daily according to blood glucose levels, the severity of COVID-19 and caloric intake [12]. Regarding rapid-acting insulin, corrective doses should be administered in patients with blood

glucose levels > 220 mg/dL and the dose should depend on glucose levels and either on total daily dose (in patients who were already using insulin) or on body weight (in patients naïve to insulin)[12]. In critically ill patients and in those who cannot eat, insulin should be administered intravenously[12]. Notably, sliding scale insulin and premixed insulin have been associated with higher risk for iatrogenic hypoglycemia and are not recommended[14]. Patients with type 1 DM can be treated with either subcutaneous or intravenous insulin, depending on their clinical condition. Insulin is administered intravenously at a rate between 1-5 units/h whereas in patients who cannot eat, glucose-dextrose solutions are preferred to avoid hypoglycemia[12]. Regarding patients on insulin pump therapy, this can be maintained provided that their clinical status is stable[12].

Regarding the use of oral antidiabetic agents, metformin should be stopped at admission but if and when the risk of lactic acidosis is considered low, it should be restarted since it appears to improve the outcome of COVID-19[12,15,16]. If used, the dose of metformin should be reduced in patients with estimated glomerular filtration rate (eGFR) between 30 and 45 mL/min and should be discontinued in patients with eGFR < 30 mL/min, liver failure, high risk for lactic acidosis and before iodine contrast imaging[17]. Sulfonylureas are not recommended because of reduced efficacy due to COVD-19-related impaired insulin production and increased insulin resistance and also due to the risk for hypoglycemia, particularly in elderly and in patients with renal impairment or poor oral intake[12]. However, emerging data suggest that these agents might also reduce mortality risk in diabetic patients with COVID-19[18]. Sodium-glucose cotransporter-2 inhibitors should also be discontinued in hospitalized patients, particularly in severely ill patients, due their association with euglycemic DKA[12]. Thiazolidinediones are also not recommended due to their association with edema and heart failure exacerbation, especially in patients with severe COVID-19 and hemodynamic instability[19]. In contrast, dipeptidyl peptidase-4 (DPP-4) inhibitors could be used alone or in combination with insulin in patients with mild hypoglycemia; however, they should be avoided in critically ill patients due to their association with increased risk for heart failure[12]. Notably, some studies suggested that continued use of DPP-4 inhibitors after hospitalization was associated with a decrease in mortality compared with discontinuation but others did not confirm this finding[18,20]. Finally, glucagon-like peptide-1 receptor agonists should also be stopped in hemodynamically unstable and severely ill patients due to risk of gastrointestinal side effects[12].

MANAGEMENT OF COVID-19

Regarding the management of COVID-19, in patients who require supplemental oxygen or ventilatory support, low-dose dexamethasone (6 mg daily for 10 d or until discharge) is recommended, according to data suggesting a clear benefit on all-cause 28-day mortality[21-23]. Indeed, in the controlled, open-label RECOVERY trial (n = 2104 patients assigned to receive dexamethasone and 4321 to receive usual care), the 28-day mortality was 36% lower in the dexamethasone group among patients on mechanical ventilation and 18% lower among those on supplemental oxygen[23]. Of note, 24% of the total study population had DM and no excess serious adverse events related to dexamethasone were recorded[23]. The incidence of death due to infections other than COVID-19 also did not differ between patients treated with dexamethasone and those assigned to usual care[23]. According to a meta-analysis by the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies Working Group, which included 7 trials in 1703 critically ill patients with COVID-19, administration of glucocorticoids was associated with 34% lower 28-d mortality with no suggestion of a higher risk of adverse effects compared with standard of care or placebo[22]. Despite these reassuring findings, patients with diabetes receiving glucocorticoids should be carefully monitored for bacterial or fungal infections, with prompt initiation of empirical antibiotic treatment if needed[8].

In patients with COVID-19 who require supplemental oxygen, but not in those on mechanical ventilation or extracorporeal membrane oxygenation, the antiviral agent remdesivir (200 mg intravenously on day 1 followed by 100 mg/d for 5 d) should be considered because it shortens recovery time and shows a trend for reduced need for mechanical ventilation and improved survival[21,24,25]. In a trial in 1062 patients hospitalized with COVID-19 pneumonia randomized to receive remdesivir or placebo (30.6% with DM), hyperglycemia was a common non-serious adverse effect, occurring in 6% of patients, but with a similar incidence in the remdesivir and the placebo group[24]. The rate of infections was also similar in the 2 groups[24]. Remdesivir can also be considered in hospitalized patients without requirement for supplemental oxygen. In a randomized, open-label trial (n = 584 patients with moderate COVID-19, defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation > 94% on room air), clinical status at day 11 was better in patients randomized to a 5-d course of remdesivir compared with standard care whereas the incidence of adverse events was similar in the 2 groups[26]. Of note, 40% of patients enrolled in this trial had DM but it was not evaluated whether the benefits and risks of remdesivir differed between this subgroup and non-diabetic patients[26].

Immunomodulatory agents can also be considered in diabetic patients who are hospitalized due to COVID-19. Tocilizumab, an interleukin-6 inhibitor (8 mg/kg as a single intravenous dose), may be used

Table 1 Principles of the management of patients with diabetes mellitus and acute coronavirus disease 2019

	Principles of the management
Blood glucose goals	Between 110 and 180 mg/dL in most patients. Less strict goals in patients at high risk for hypoglycemia
Monitoring of blood glucose levels	At least 4 times daily. More frequently in selected patients (*e.g.*, in the intensive care unit)
Antidiabetic treatment	Insulin in most patients. Metformin and dipeptidyl peptidase-4 inhibitors might be considered. Other antidiabetic agents should be avoided
Management of COVID-19 in hospitalized patients	Similar to non-diabetic patients. Patients receiving glucocorticoids or immunomodulatory agents should be carefully monitored for infections
Management of COVID-19 in the outpatient setting	Patients with symptomatic COVID-19 are eligible for treatment with monoclonal antibodies, remdesivir, nirmatrelvir-ritonavir or molnupiravir

COVID-19: Coronavirus disease 2019.

in patients who require high-flow oxygen or mechanical ventilation and it may also be an option for selected patients on low-flow oxygen with significantly elevated inflammatory markers (C-reactive protein levels ≥ 75 mg/L) or with a rapid increase in oxygen requirements despite dexamethasone therapy, within 96 h of hospitalization[25]. In a meta-analysis of 10930 patients hospitalized for COVID-19, administration of tocilizumab was associated with a 17% lower all-cause 28-d mortality with no increased risk of infection compared with standard of care or placebo[27]. Sarilumab may be an alternative interleukin-6 inhibitor option if tocilizumab is not available, but with limited trial data[27]. Another treatment option is baricitinib (4 mg/day orally for 14 d), a Janus Kinase inhibitor with immunomodulatory properties, that may be used with the same indications as tocilizumab, with the exception of patients on mechanical ventilation due to limited trial data in this subgroup of patients[25]. In a randomized, placebo-controlled trial in 1525 patients (30% had DM), baricitinib reduced 28-d and 60-d mortality by 38% without an increased risk for infection or other adverse events[28]. Notably, it has not been evaluated whether these immunomodulatory agents have different safety or efficacy in patients with DM[27,28].

Notably, patients with acute COVID-19 are at higher risk for thrombosis than the general inpatient population and the presence of DM further increases this risk[29]. Accordingly, this population should be carefully monitored for the occurrence of thrombotic events and should receive prophylactic dose of heparin[21,25]. In patients who are already receiving antiplatelet agents for DM or for established CVD, these should be continued and low-dose heparin should be added[21,25].

Regarding the outpatient management of COVID-19, even in the absence of symptoms of severe disease, both patients with type 1 and 2 DM are considered at high risk for evolution to severe disease, especially if they are ≥ 65 years-old or have obesity, chronic kidney disease or established CVD[30]. Therefore, patients with DM and symptomatic COVID-19 are eligible for treatment with monoclonal antibodies, remdesivir, nirmatrelvir-ritonavir or molnupiravir, to reduce the risk of hospitalization[21,25]. The choice between these agents depends mainly on availability and should start as soon as possible after symptom onset[21,25]. There is no specific agent that is contraindicated in patients with DM, however nirmatrelvir-ritonavir cannot be used if eGFR is < 30 mL/min[21,25]. Moreover, before prescription of ritonavir-boosted nirmatrelvir, a careful review of concomitant medications is required, because it has significant drug-drug interactions with commonly prescribed medications in patients with DM and CVD, including rosuvastatin, clopidogrel and rivaroxaban[21,25].

Patients with DM also appear to be at higher risk for persistence of COVID-19-related symptoms (*i.e.*, long COVID)[31]. It has also been reported that an aggravation of insulin resistance persists for up to 2 mo after recovery from COVID-19[32]. Accordingly, patients with DM should be followed up closely after the resolution of COVID-19.

CONCLUSION

Diabetic patients with acute COVID-19 are a particularly vulnerable population at a high risk for complications. Close monitoring of blood glucose levels and careful administration of insulin with appropriate titration are needed to achieve glycemic control without complications. On the other hand, management of COVID-19 in these patients requires individualization and heightened attention for the occurrence of adverse events, particularly hyperglycemia and infections (Table 1). There are currently limited data regarding the safety and efficacy of both antidiabetic and antiviral treatments in diabetic patients with acute COVID-19. As knowledge evolves in this field, optimization of the management of both DM and COVID-19 will hopefully improve the outcome of these patients.

FOOTNOTES

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