REVIEW ARTICLE

Management of Hyperglycemia in In-hospital COVID-19 Patients: A Review

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Abstract

The current coronavirus-19 (COVID-19) pandemic has diverted the world's attention to the burning problem of infectious diseases and their management. Clinicians are increasingly realizing that the management of diseases like COVID-19 requires not only antimicrobial drugs but also drugs or strategies to tackle the various comorbidities occurring or aggravating due to the disease. Hypoglycemia is one of the important adverse effects of hydroxychloroquine, used frequently in COVID-19. The known diabetics affected with COVID-19 are therefore at a greater risk of hypoglycemia. In this review article, we describe the management strategy for the known diabetics infected with COVID-19 and admitted in inpatient settings, including the dose calculations for insulin infusion and subcutaneous administration of insulin.

Keywords: COVID-19, Diabetes, Hypoglycemia, Insulin.

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Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus epidemic has drawn the attention of therapeutics toward infectious diseases from noninfectious diseases. Until recently, the momentum of medical sciences was metabolic and lifestyle disease-centric where tropical diseases and different infections were neglected. After 1987, there are no newer antibiotic classes developed. The lipopeptide class of antibiotics was introduced in that year. Thirty-three years has passed without any newer antibiotic classes. Daptomycin was approved by Food and Drug Administration (FDA) in 2003, which actually belongs to lipopeptide class of antibiotics. After 2003, there were no antibiotics approved in the US market, except for a fixed dose combination of ceftazidime and avibactam, which was approved in 2015.[1] After SARS-CoV-2 epidemic, concentrations of health-care providers are focused on preventing and managing the epidemic .

Diabetes and Covid-19: Epidemiology

A Chinese study that includes 1527 patients depicted that the most common cardiovascular metabolic comorbidities with coronavirus-19 (COVID-19) were hypertension [17.1%,{95% CI, 9.9–24.4%}] and cardio-cerebrovascular disease [16.4%, {95% CI, 6.6–26.1%}], followed by diabetes mellitus [9.7%, {95% CI, 6.9–12.5%}]. Diabetics or hypertensives had a twofold increase in the risk of developing severe disease or requiring intensive care unit (ICU) admission.[2] An Italian study had showed that in a subset of 355 patients who died of COVID-19, the mean number of preexisting underlying conditions was 2.7. Only three subjects in that subset did not have any comorbidity.[3] In another study by Chinese Centre for Disease Control and Prevention, 72,314 cases of COVID-19 showed an increased mortality in diabetics (2.3% overall and 7.3% of patients with diabetes).[4]

Covid-19 and Antidiabetic Drug

If a diabetes patient is infected with COVID-19, it is important to assess their ongoing antidiabetic medicines. If a patient needs admission, there is no alternative to switch their therapy to insulin. In case of a mild variety of COVID-19, it is important to analyze the risk versus benefit of ongoing therapy. As we know that hydroxychloroquine is widely used in COVID-19 management, its antidiabetic action needs to be considered. The patient may experience hypoglycemia, so it is essential to consider the adjustment of an anti-diabetic regimen. Therefore, the patient requires a reduction in the dose of antidiabetic drugs.

Sulfonylurea: We need to be cautious about using sulfonylurea as it can produce hypoglycemia. If a patient is mildly symptomatic and glycemic control is adequate with glimepiride or gliclazide, we can continue it but need to monitor the glucose level frequently (4–6 hourly). Patients and caregivers should be informed regarding hypoglycemia. In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, there is a chance of hemolytic anemia. Hydroxychloroquine usage can increase the chance of hemolysis with sulfonylureas. In-hospital COVID-19 patients discontinue the use of sulfonylureas and resume insulin therapy.

Metformin: Chances of acidosis are more if we use metformin in an acute care setting. It is generally not recommended to use it in the management of hyperglycemia in hospitalized patients due to its potential to produce lactic acidosis.

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Pioglitazone: Volume overload-related morbidity and mortality will be more if pioglitazone is used in hospitalized patients. So, it is better to avoid using it.

DPP4 inhibitors: They have a very minimal potential to cause hypoglycemia. In a study, it was seen that the treatment with DPP4 inhibitor alone or in combination with basal insulin was effective. The use of these inhibitors is associated with a lower incidence of hypoglycemia compared to a basal bolus insulin regimen in type 2 diabetic patients who are admitted in general medicine and surgical wards.[5] So physicians may consider to continue DPP4 inhibitors if patients are on them as per the glycemic status. There is one concern regarding immune reactions of this group of drugs and their effects on COVID-19-related immunogenic reactions like cytokine release syndrome. Different clinical studies suggest there is no evidence of impaired T cell-dependent immune responses with DPP4 inhibitors.[6]

GLP-1 receptor agonists: They have GI adverse effects like vomiting, which can deteriorate the hydration status of the patient. It is better not to use them for in-hospital COVID-19 patients but may consider continuing it in a stable diabetic with a mild variety of COVID-19 patient who is taking it for a long duration without any adverse effects. In a few animal studies, it was depicted that GLP-1R agonists reduced pulmonary inflammation. This group of drugs also decreases the cytokine production. In mice and rat models, GLP-1R agonists preserve the lung function after experimental lung injury.[7–9] In another mice model study, GLP-1R agonists showed a reduction in pulmonary type 2 immune cytokine responses in response to a respiratory syncytial virus isolated from a child with severe lower respiratory tract infection.[10] In one clinical study, the administration of exenatide twice daily showed safety and effectiveness in noncritically ill-hospitalized patients with type 2 diabetes mellitus treated in general medicine or surgery wards. Exenatide was used alone or in combination with basal insulin for the management of blood glucose .[11] In the short-term clinical studies with ventilated patients with critical illness, GLP-1Rr agonists reduce the blood glucose level.[12] But we have insufficient experience and clinical data on safety to prescribe GLP-1R agonists in critically ill subjects. We need to explore more data and future randomized controlled trials (RCTs) to justify therapeutic recommendations while using them in the context of coronavirus infection.[13]

SGLT2 inhibitors: They are generally contraindicated in an acute care setting for the management of hyperglycemia. Hypotension, acute kidney injury, increased chance of ketoacidosis, and associated urinary tract infection may complicate COVID-19 care. So this group of drugs is better to be avoided in the management of diabetic COVID-19 patients.

Insulin is the safest option to manage in-hospital hyperglycemia in the presence of COVID-19.

In-hospital Hyperglycemia

In-hospital hyperglycemia is defined as any blood glucose level for that particular patient is more than 140 mg/dL.[14] Hyperglycemia in hospitalized COVID-19 patients can be from three categories as follows:

1. Known diabetes,
2. Undiagnosed diabetes,
3. Iatrogenic diabetes. Especially, in a certain subset of COVID-19 patients, corticosteroids are used.

As hyperglycemia is an independent marker of ICU mortality,[15] there should be a specific protocol for the management of diabetes in COVID-19 hospitals.

Pathophysiology

COVID-19-associated hyperactivation of hypothalamic-pituitary-adrenal axis, catecholamine surge, and increased circulation of cytokines can contribute to hyperglycemia. The use of corticosteroids and vasopressor also increases the plasma glucose levels. In case of acute stressful conditions like COVID-19, there would be an increased insulin resistance along with a decreased pancreatic reserve. Increased levels of glucagon, epinephrine, cortisol, and cytokines in COVID-19 patients can elevate the plasma glucose level in two ways as follows:

1. Escalation in the production of glucose from the liver by increased glycogenolysis and decreased gluconeogenesis
2. Decreased insulin-mediated uptake

Hyperglycemia contributes to the development of endothelial dysfunction, catabolism, procoagulation, immune dysfunction, sympathetic nervous system activation, platelet activation, acid–base disturbances, proinflammatory cytokine production, mitochondrial dysfunction, electrolyte, and fluid shift.[16] These events are again responsible for developing more hyperglycemia. So this vicious cycle of hyperglycemia, oxidative stress, and subsequent events goes on without any interruption. In COVID-19, these oxidative injuries are the important risk factors for mortality, and they are even present in normoglycemic individuals. It is very important to emphasize the glycemic management to stop the extra burden from the metabolic dysfunctions. Insulin is the cat here to put these metabolic mice away. We know that when the cat is away, the mice will play. We need to bring the insulin cat quickly to stop the play of metabolic mice and break the vicious cycle.

Glycemic target: It should be between 140 mg/dL and 180 mg/dL.[17] Intravenous infusion of insulin should be started in COVID-19 ICU patients if the plasma glucose exceeds 180 mg/dL. Maintenance of plasma glucose values between 140 mg/dL and 180 mg/dL is recommended. It should not go up to 180 mg/dL and go down to 110 mg/dL.

Preparation of Insulin Infusion Pump in Critical Care Unit[18]

Fifty units of the short-acting human regular insulin needs to be dissolved in 50 mL of normal saline (NS) in a 50-mL disposable syringe, and an intravenous infusion pump would help to deliver the required unit of insulin. Different units of insulin have different pharmacokinetic properties. They are different due to their absorption kinetics. But in case of IV insulin, all of them are equal in terms of pharmacokinetic features. So it is important to choose the most economic insulin that is regular human insulin. Monitoring is necessary for those who are on an insulin infusion. Either by CBG or from the venous site/central line, every 1-hour interval needs to assess the glycemic status until there is a stability in the blood glucose value. We need to be vigilant against serum potassium levels as insulin infusion may produce hypokalemia. The patient may need a potassium replacement. Checking regularly for blockage, disconnection, and infusion pump malfunctioning is extremely important as it carries the dangerous consequences.

Initiation of Insulin Therapy

Insulin infusion should be initiated to control hyperglycemia in critical care unit. If the blood glucose value is greater than 180 mg/dL, we have to trigger an insulin initiation. Injection of a priming bolus of regular insulin at 0.1 U/kg body weight is needed if the initial blood glucose value is more than 300 mg/dL. The initial rate of insulin infusion should be determined by the current blood glucose value divided by 100.

Maintenance of Insulin Infusion

Need to check CBG at the one-hour interval, and as per the CBG value, the insulin infusion rate would be changed. This is a published[19] and validated algorithm to change the insulin infusion rate

Check BG q at 30-minute interval till BG >90 mg/dL and then check BG q at 1-hour interval. Restart infusion at 50% of the previous rate when BG increases >140 mg/dL

Example: BG = 40 mg/dL, give (100 – 40) × 0.8 = 60 × 0.8 = 48 mL of 25% dextrose IV and check BG after 15 min

In Case of Hypoglycemia

We should suspend the insulin infusion as early as possible in case of hypoglycemia. And we need to be cautious especially as patients were also on hydroxychloroquine tablet. Initiate 25% dextrose infusion and dose is calculated as follows:

Dose (in mL) = (100-documented blood glucose value) × 0.8

We should monitor CBG values at 15-minute interval, and if it is less than 70 mg/dL, we need to repeat the same and restart the insulin infusion at the rate of 50% of the prior infusion rate when the CBG value crosses 140 mg/dL.

Transition from Insulin Infusion to SC Insulin

An abrupt discontinuation of IV insulin infusion may result in rebound hyperglycemia. The plasma half-life of insulin is around 2 to 6 minutes while injecting intravenously. We need to assess a few safety indicators before the transition from IV to SC insulin:

1. Stable blood glucose levels <180 mg/dL for at least 4–6 hours.
2. Resolution of acidosis in the presence of diabetic ketoacidosis.
3. Patients are hemodynamically stable without the use of vasopressors.
4. Patients can follow a stable nutrition plan.
5. They are on stable IV drip rates (low variability). Transition is more likely to be successful if the blood glucose levels are between 140 mg/dL and 180 mg/dL with an insulin drip rate of <2 units/hour and that persists for at least 4 hours.

The first dose of SC insulin should be overlapped with the IV drip to prevent rebound hyperglycemia during the transition. Short-acting or rapid-acting insulin should be given for 1–2 hours before discontinuing IV insulin drip. Long-acting insulin should be administered for 2–3 hours before discontinuing the IV drip if the patient is not expected to eat. The stabilized insulin drip rate in 4 hours prior to drip discontinuation is used to calculate the patient's total daily insulin (TDI) requirement. A 20% reduction in TDI was made in the anticipation of a rapidly improving clinical status. We should also consider the concurrent use of hydroxychloroquine and be watchful for hypoglycemia. Then, 50% of this calculated dose is given in the form of basal insulin, and the rest 50% of the dose needs to be divided into three parts, injected as bolus dose of the short-acting insulin.

There should be a correctional bolus dose and that dose would depend on premeal blood glucose value. It is essential to consider the following formula for premeal bolus dose calculation:

Correction factor (CF) (of regular/rapid-acting insulin)

CF = 1500/TDD (regular insulin)

Or

CF = 1800/TDD (insulin analogue)

(Premeal CBG-100)/CF = Dose to be Added with Predefined Bolus Dose before Meal

Estimating the Total Daily Dose (TDD) for Noncritical Patients

For patients already treated with insulin, we have to consider preadmission subcutaneous regimen and glycemic control on that regimen. Weight-based estimation of the total daily dose is simple to adhere.

TDD = 0.4 units × Wt (kg) [in general type 2 diabetics]

TDD = 0.3 units × Wt (kg) [in kidney failure, type 1 diabetes (especially if lean), frail/low body weight/malnourished elderly, or insulin-naïve patients]

TDD = 0.5–0.6 units × Wt (kg) [in obesity and high-dose glucocorticoid treatment]

The dose needs to be divided as discussed before in basal bolus regimen. By using the same formula as already mentioned and the correction factor calculation, we should adjust the premeal bolus dose of insulin as per the premeal blood glucose value.

A Real-life Covid-19-Positive Case and His Hyperglycemia Management

Mr. AG aged 60 with diabetic hypertensive COVID-19-positive male patient was admitted in a critical care unit in a tertiary care hospital at 12.30 am. He was drowsy, and had high-grade fever and shortness of breath. His pulse was 124/min, BP 96/60 mm Hg, SpO_2 90%, RR 28/min, and GCS 13. His body weight was 80 kg. Emergency capillary blood glucose (CBG) level was 456 mg/dL. He was on lispro mix 25 (16 U BBF and 10 U BD), telmisartan 40 mg, rosuvastatin 20 mg, and clopidogrel 75 mg. He was not taking lispro mix 25 for the last 5 days as he felt anorexia. Here, we are going to discuss the management offered for hyperglycemia for this particular patient.

As his body weight = 80 kg

The dose of IV bolus dose of insulin was calculated as 80 × 0.1 = 8 Unit IV stat. As CBG was 456 mg/dL, we had started insulin infusion at the rate of 456/100 = 4.56 → 4 unit/hour → 4 mL/hour at 1 am. The instruction was given to check CBG hourly, and the infusion rate was adjusted as per the chart mentioned below.

Time	*CBG (mg/dL)*	*Infusion rate (unit/hour)*
1.00 am	456	4
2.00 am	430	7
3.00 am	355	7
4.00 am	304	7
5.00 am	268	7
6.00 am	222	7
7.00 am	218	9
8.00 am	243	12
9.00 am	176	6
10.00 am	143	6
11.00 am	110	3
12.00 noon	154	4
1.00 pm	106	Suspend
2.00 pm	156	2
3.00 pm	176	2
4.00 pm	161	2
5.00 pm	144	2
6.00 pm	139	2
7.00 pm	156	2

Visiting physician had planned to shift him to the ward next morning, and needed to off insulin infusion and start SC insulin.

From 2 pm to 7 pm, the patient had stable CBG values between 140 mg/dL and 80 mg/dL, and his infusion rate is also stable, i.e., 2 units/hour. Insulin required per hour = 2 units/hour

Insulin required per day = $2 \times 24 = 48$

A 20% reduction in TDI is required, so it is = $48 \times 0.2 = 9.6 \rightarrow 9$

$48 - 9 = 39$

So for this particular patient, the total dose of insulin selected = 38 unit for the ease of calculation. We should also consider the potential to produce hypoglycemia by HCQ.

Basal insulin = $38 \times 0.5 = 19$ unit; injection glargine (U 100) 20 units was selected as the basal dose. Basal dose of insulin was given 3 hours before switching off the insulin pump.

Bolus insulin = $38 \times 0.5 = 19$ units → 1/3rd before breakfast, 1/3rd before lunch, and 1/3rd before dinner. Six units of SC human regular insulin before each meal was selected as a bolus dose.

Mr. AG had a prebreakfast CBG of 200 mg/dL. By the following way, we had adjusted his bolus dose. The patient is on glargine (U 100) 20 units SC at night and human regular insulin 6 units SC before breakfast, lunch, and dinner

(Premeal CBG-100) → (200 − 100) = 100

Correction factor = 1500/TDI = 1500/38 = 39.47

(Premeal CBG-100)/CF = 100/40 = 2.5

2 units to be added with 6 units

Prebreakfast human regular insulin dose − (6 + 2) = 8 units SC

After 14 days, we had a plan to discharge the patient. The patient was stable with glargine (U 100) 20 units and 6–8–6 units human regular insulin dose. He was discharged with this basal-bolus regimen and asked to do self-monitoring of blood glucose. The patient was given education for hypoglycemic alertness.

Epilogue

"I" is an important word in hyperglycemia management in hospitalized patients. Critical care patients treated in the intensive coronary care unit (ICCU) should be treated with insulin. Even in general ward, for COVID-19 diabetic patients insulin is the safest evidence-based option. Generally, during the initiation of insulin therapy in outpatient department (OPD) patients, we had faced inertia to insulin. But during in-hospital hyperglycemia management, we are in an advantageous position for not having this issue. The sliding scale concept needs to be slide away and needs to emphasize on basal bolus insulin therapy with the incorporation of adding of correctional bolus doses as per the premeal blood glucose values. Integration of medical sciences with easy mathematics can bridge the gap between optimum glycemic management and SARS-CoV-2-infected patients. Along with researches on anti-COVID-19 therapeutics, we have to emphasize on achieving a good glycemic control in SARS-CoV-2-infected individuals.

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