



Insulin Resistance in a Hospitalized COVID-19 Patient: A Case Review

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Case Presentation

C.R., a 59-year-old White man presented to the emergency room with fever, cough, shortness of breath, and diaphoresis for 4 days. His medical history was significant for hypertension treated with bisoprolol-hydrochlorothiazide 10 mg/6.25 mg daily and type 2 diabetes treated with metformin 1,000 mg nightly. He reported recent travel to Florida for 1 month before returning to Colorado 1 week before admission. His vital signs on admission (day 1), which took place 7 days after social distancing was instituted statewide, included blood pressure of 135/73 mmHg, pulse of 98 bpm, BMI of 38.46 kg/m² (weight 126 kg, height 181 cm), oxygen saturation of 65% on room air, 76% on 3 L/min high-flow nasal cannula, and 85% on 15 L/min high-flow nasal cannula. His presenting blood glucose was 324 mg/dL, with an A1C of 9% on admission.

C.R. was admitted to the intensive care unit (ICU) after intubation. On hospital day 3, continuous renal replacement therapy (CRRT) was initiated because of worsening acute kidney injury (glomerular filtration rate on admission was >60 mL/min/1.73 m² and decreased to a nadir of 14 mL/min/1.73 m²). He was also placed on veno-venous extracorporeal membrane oxygenation (VV ECMO) for worsening hypoxia despite proning, high positive end-expiratory pressure, and 100% fraction of inspired oxygen. C.R. remained on VV ECMO from day 3 to day 11 and on CRRT from day 3 to day 23. He intermittently required pressor therapy after discontinuation of ECMO from day 12 to day 19. In addition, nutritional therapy with enteral nutrition (EN), parenteral nutrition (PN), or a combination was started on day 3. There was an

interruption of EN between day 9 and day 10 for ~24 hours due to high volume residuals. C.R. did not receive corticosteroid therapy during his hospital stay. He was extubated successfully on day 22 and transferred to the floor on day 26.

C.R.'s insulin needs varied substantially during his ICU stay (Figure 1). He was placed on insulin via intravenous (IV) infusion at admission and continued this therapy through day 9. That day, biphasic human insulin 70/30 was added. From day 1 to day 9, C.R.'s total daily dose (TDD) of insulin ranged from 0.74 to 2.51 units/kg. On days 10 and 11, he did not require any insulin to maintain glycemic control. Insulin lispro correctional doses were started on day 12 when PN and trickle EN were started. By day 13, C.R.'s blood glucose started to rise to >250 mg/dL, so IV insulin infusion was reinitiated. His insulin infusion rate rose steadily to a maximum of 16 units/hour by day 15. At this time, biphasic human insulin 70/30 was restarted with the goal of reducing the insulin infusion rate and eventually discontinuing the insulin infusion to minimize staff exposure. Between days 15 and 18, C.R. had his highest insulin needs, with his TDD ranging from 338 to 353.6 units (2.7–2.8 units/kg) coinciding with a peak in his white blood cell (WBC) count (22.3–28.2 $10^9/L$). His blood glucose values stayed within the range of 120–180 mg/dL during most of his ICU stay. Occasional readings >180 mg/dL were associated with changes in nutritional therapy and were corrected with insulin adjustments. C.R. did not experience any hypoglycemia with close glucose monitoring and insulin adjustments while his severe insulin resistance improved.

C.R. was transferred to the coronavirus 2019 (COVID-19) medical floor on day 26 of his hospital stay. Despite remaining on EN for a number of days, he did not require supplemental insulin to maintain glycemic control. C.R. was transferred to our acute rehabilitation unit for treatment of deconditioning from his prolonged hospital stay. He was discharged home 44 days after his initial presentation with COVID-19 and resumed metformin, with a dose change to 500 mg twice daily.

Questions

1. What comorbidities can adversely affect the outcomes of patients with COVID-19?

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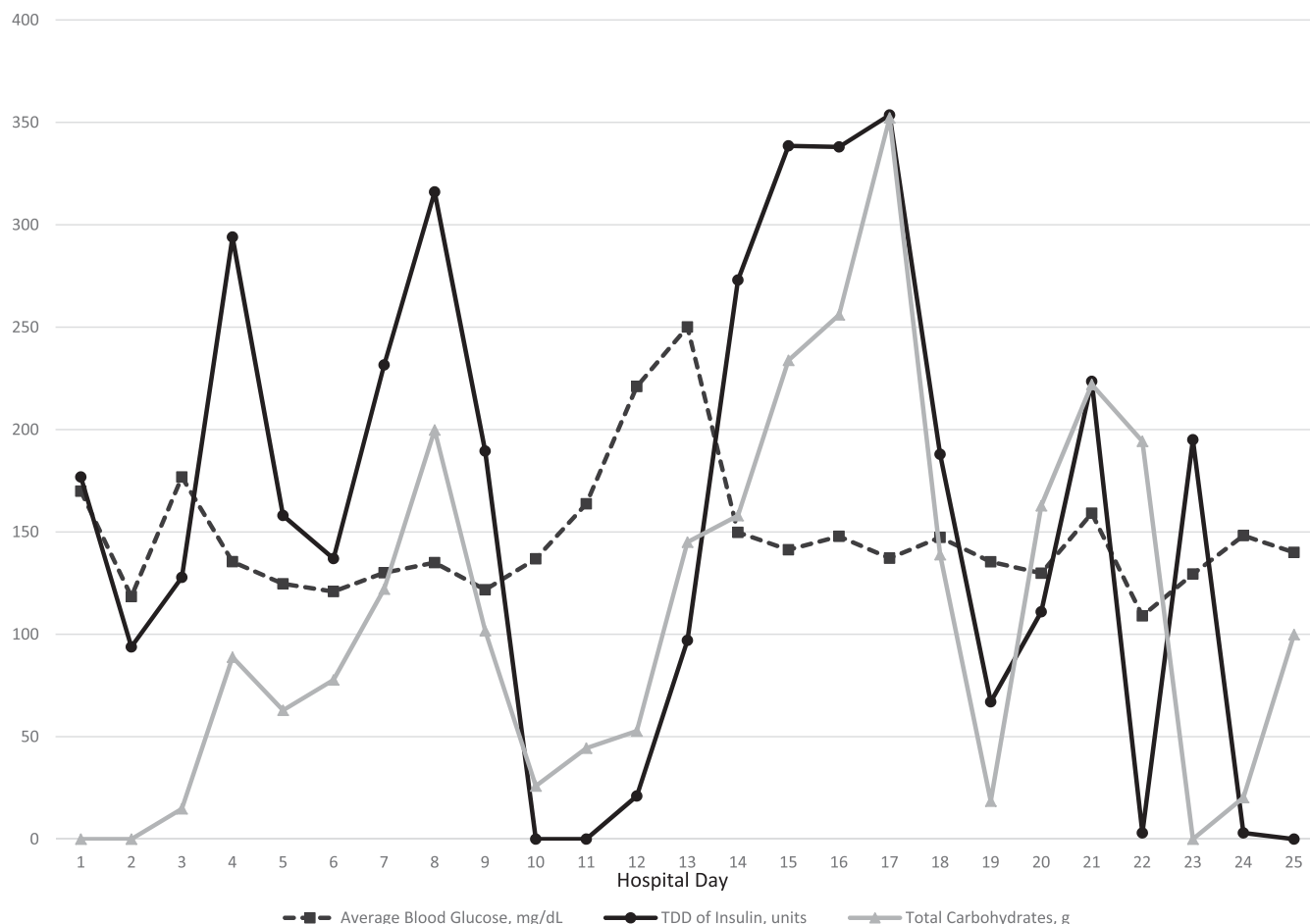


FIGURE 1 Daily comparisons of average blood glucose, insulin, and total carbohydrates.

2. What factors may contribute to insulin resistance and hyperglycemia observed in patients with COVID-19?
3. What insulin regimen may be used for optimization of glycemic control in patients with COVID-19?

Commentary

Anecdotal findings of extreme insulin resistance in patients with COVID-19, the infection caused by the SARS-CoV-2 virus, have been reported (1–3). C.R. had diabetes, obesity, and hypertension, which are conditions associated with hospitalization for COVID-19 and have been correlated with a more severe disease course (4–7). Chronic inflammation from these conditions, combined with severe acute inflammation in response to COVID-19 infection, can lead to extreme insulin resistance (4–7). Guan et al. (4) noted elevated C-reactive protein (CRP), creatinine kinase (CPK), lactate dehydrogenase (LDH), and WBC count in patients with COVID-19.

Our patient demonstrated elevated CRP, CPK, LDH, and WBC count on admission (Table 1). Of note, on days

15–18, when C.R.'s insulin needs were the highest, there was a corresponding peak in WBC count (Table 2). C.R.'s admission CRP level was highest at 455.7 mg/dL and then trended down, except for a slight increase during days 15 to 18. While C.R.'s CPK was elevated on admission, it trended down during his ICU stay and was within normal limits on days 15–18. Unfortunately, interleukin-6 drawn close to admission could not be interpreted because of interfering substances and was not redrawn.

Medical nutrition therapy (MNT) is a contributing factor to hyperglycemia in the hospital setting. C.R. was receiving both EN and PN when he exhibited higher insulin needs. During his hospital course, we accounted for these forms of nutrition by calculating total nutritional carbohydrates administered daily, including the carbohydrate content of specific tube feed formulas and dextrose from his PN (Figure 1). On days 10–12, when there was a notable decrease in insulin requirement, there was an associated decrease in carbohydrate intake, since the EN was being infused at a trickle rate of only 10 mL/hour (an 80% decrease in carbohydrate content).

TABLE 2 C.R.'s Data, Day 13 Through Day 24

	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24
Average blood glucose, mg/dL	250.1	149.8	141.3	147.8	137.1	147.3	135.4	129.8	159.1	109.0	129.4	148.2
Insulin TDD, units	97.0	273.0	338.5	338.0	353.6	187.9	67.0	111.0	223.5	3.0	195.0	3.0
Insulin drip, gtt rate range/day	3-9	9-11	11-45	8-15	0-19	1.3-12.5	0.5-5	3.5-7	0-10.5	—	—	—
Biphasic 70/30 insulin TDD, units	—	—	5	35	60	—	—	—	130	—	195	—
Rapid-acting correctional insulin TDD, units	27	—	—	—	—	—	—	—	—	3	—	3
Regular insulin in PN daily total, units	14	26	26	29	29	29	—	—	—	—	—	—
GFR, mL/min/1.73 m ²	12	10	15	21	21	24	24	15	23	38	47	51
CRP, mg/L	22.1	20.4	29.6	66.7	44.5	27.0	19.1	—	—	46.8	—	23.6
CPK, units/L	235	148	88	—	—	—	—	—	—	—	—	—
LDH, units/L	459	453	463	—	—	—	—	—	—	—	—	—
WBC, 10 ⁹ /L	—	18.5	22.3	25.1	28.2	20.3	19.5	10.7	9.3	9.1	10.4	10.3
Platelet count, 10 ⁹ /L	126	64	57	66	46	53	97	74	103	136	262	324
Prothrombin time, seconds	—	—	—	13.8	—	15.3	—	15.4	14.3	14.8	—	—
Partial thromboplastin time, seconds	35.0	49.4	74.0	38.9	37.3	34.6	—	31.2	30.7	31.4	32.8	43.3
D-dimer, FEU	—	35,210	—	—	—	—	—	—	—	—	—	—
Fibrinogen, mg/dL	—	—	—	—	—	289	—	—	—	—	—	—
Intubation	X	X	X	X	X	X	X	X	X	X	—	—
ECMO	—	—	—	—	—	—	—	—	—	—	—	—
CRRT	X	X	X	X	X	X	X	X	X	X	X	—
Pressor therapy	X	X	X	X	X	X	X	X	X	X	X	—
EN, hours/24 hours	—	4	24	24	24	—	10	24	24	20	—	8
EN, carbohydrates/24 hours	—	13.0	88.8	111.0	207.2	—	18.5	162.8	222.0	194.3	—	20.3
PN, hours/24 hours	24	24	24	24	24	23	—	—	—	—	—	—
PN, dextrose/24 hours	145	145	145	145	145	138.9	—	—	—	—	—	—

Boldface type indicates laboratory values that were significantly out of range. FEU, fibrinogen equivalent units; gtt, drops.

Basal-bolus insulin or biphasic human insulin can also be used. However, the use of a nonpeaking basal insulin can increase the risk of hypoglycemia with quickly changing insulin needs in critical illness. On day 9, C.R. required a TDD of 189.5 units of insulin in contrast to day 10, when he required no insulin. The approach used for C.R. was dosing of biphasic human insulin 70/30 three times daily to cover EN.

The standard of care for patients receiving MNT in our institution is the use of either an insulin infusion if critically ill or biphasic human insulin 70/30 dosed three

times a day with a rapid-acting insulin correctional scale for blood glucose levels >180 mg/dL dosed as needed every 4 hours. This approach may reduce the risk of hypoglycemia in patients compared with long-acting basal insulin (14). However, to avoid hypoglycemia, it is crucial that a dextrose-containing IV infusion such as D10 W be started if the EN is interrupted for any reason.

Finally, an additional method for management of PN-associated hyperglycemia is the addition of regular insulin to the PN solution (13). Insulin was added to C.R.'s PN infusion using a ratio of 1 unit of regular insulin for every

