

Extreme Insulin Resistance in Critically Ill Patient With Sepsis

Vidhya D.S. Illuri,¹ Brian T. Layden,^{1,2} and Grazia Aleppo¹

Patients who are critically ill can develop acute insulin resistance manifesting as hyperglycemia and hyperinsulinemia. Rarely, patients can develop extreme insulin resistance, defined as having an insulin requirement of >3 units/kg/day (1). We report here a case of a septic patient who developed acute extreme insulin resistance in the critical care setting that was difficult to treat, and after 4 days, reversed rapidly, necessitating rapid down-titration of the intravenous insulin infusion and close blood glucose monitoring to avoid hypoglycemia. This case illustrates a general lack of understanding of 1) why severe insulin resistance occurs, 2) how to treat this clinical dilemma safely and effectively, and 3) what the treatment goals should be to achieve the best medical outcomes.

Presentation

A 64-year-old Hispanic woman with type 2 diabetes, hypertension, hyperlipidemia, and hypothyroidism was initially admitted with a right humeral head and neck fracture, right malleolar fracture, and navicular fracture. One day after admission, she developed acute hypoxemic respiratory failure requiring continuous positive airway pressure and transfer to the medical intensive care unit (MICU). Before hospitalization, her diabetes regimen included sitagliptin 50 mg daily, metformin 1,000 mg daily, and human insulin 70/30 combination (70% human insulin isophane suspension and 30% human insulin)

at a dose of 40–50 units twice daily. Her A1C was 8.5%, and her weight on admission was 110 kg, with a BMI of 44.4 kg/m². Physical exam was notable for central obesity. She denied any complications of diabetes.

The primary team had started the patient on 40 units of subcutaneous insulin glargine daily and a high-dose supplemental corrective scale with insulin lispro to be given every 6 hours. Shortly after transfer to the MICU, the patient developed severe hyperglycemia. When her blood glucose level reached 430 mg/dL, 15 units of subcutaneous lispro were given and her glargine dose was increased to 50 units daily. Six hours later, her blood glucose level was 358 mg/dL, and she was given an additional 39 units of lispro over the next 7 hours (13 units immediately, 13 units at 2 hours, and 13 units at 7 hours). Despite the administration of 102 units of subcutaneous insulin on that day, her blood glucose remained elevated consistently >400 mg/dL.

Because of her continuing hyperglycemia, the critical care team started an intravenous insulin infusion protocol with regular insulin (human recombinant insulin). During this time, the patient's respiratory status became compromised, and she eventually required mechanical intubation. Additionally, she developed septic shock and was started on vasopressor infusion (norepinephrine, vasopressin, phenylephrine, and epinephrine) and stress-dose steroids (intravenous hydrocortisone 100

¹Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

²Jesse Brown Veterans Affairs Medical Center, Chicago, IL

Corresponding author: Grazia Aleppo, aleppo@northwestern.edu

DOI: 10.2337/diaclin.34.3.158

©2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0> for details.

mg every 8 hours). Despite increasing doses of the intravenous insulin infusion according to the protocol titration, her blood glucose levels remained persistently in the mid-300 mg/dL range.

On day 2, the patient developed acute kidney injury and continuous veno-venous hemofiltration was initiated urgently. She was also placed on wide-spectrum antibiotics (linezolid, cefepime, and amikacin) for a possible infectious cause. On day 3, bronchoalveolar lavage was positive for influenza B, and oseltamivir was added. The patient reached a peak intravenous insulin infusion rate of 142 units/hour on day 4. With this insulin infusion rate, her blood glucose levels stabilized in the 180 to 230 mg/dL range.

In the latter portion of day 4, the patient's glucose levels started to decrease to the 120 to 160 mg/dL range. The insulin infusion was quickly reduced from 142 to 22 units/hour over the next 16 hours (day 4 to day 5). Her blood glucose levels were measured every 30–60 minutes; the insulin infusion was reduced by 20–30 units every 60 minutes with a goal of maintaining a blood glucose level between 180 and 200 mg/dL. In the next 24 hours, her intravenous insulin infusion rate was reduced to 8.5 units/hour.

The patient never developed hypoglycemia, and her lowest blood glucose level was 130 mg/dL. On day 6, her family decided to withdraw care, and the patient died shortly thereafter.

Questions

1. What is the mechanism of transient extreme insulin resistance?
2. What is the best approach to treat extreme insulin resistance in critically ill patients?
3. How can we avoid hypoglycemia in patients receiving high-dose intravenous insulin who develop transient extreme insulin resistance?

Commentary

Critically ill patients often develop dysregulated glucose homeostasis, which manifests as hyperglycemia and hyperinsulinemia, both of which indicate insulin resistance (2). Intravenous insulin infusion is the preferred method of treating hyperglycemia in critically ill patients because it has been shown to reduce morbidity and mortality (3,4). As defined elsewhere, severe insulin resistance is suspected when an individual receives ≥ 2 units/kg/day of insulin, and extreme insulin resistance is a condition in which an individual requires >3 units/kg/day (1). The mechanism of extreme insulin resistance that is transient, as in this case, is largely undefined.

A better understanding of the mechanisms behind extreme insulin resistance is needed to improve treatment in these cases. Currently, no guidelines have been published for the treatment of acute transient extreme insulin resistance in the inpatient setting.

Although many patients develop acute insulin resistance in the critical care setting, they rarely require intravenous insulin infusion at rates as high as described here. Oo et al. (5) described a patient requiring up to 120 units/hour of intravenous insulin. This patient had a history of type 2 diabetes treated with 20 units of glargine subcutaneously and repaglinide 1 mg orally three times daily and was subsequently admitted to the hospital with acute myocardial infarction and diabetic ketoacidosis. That patient required variable rates of intravenous insulin infusion ranging from 1 to 120 units/hour in 1 day. After undergoing emergency coronary artery bypass graft surgery during the same hospitalization, the patient's insulin resistance improved, and the patient was discharged on liraglutide 1.2 mg daily and premeal insulin aspart 15 units three times daily. Gupta et al. (6) described a patient requiring intravenous insulin infusion at a rate of 64 units/hour after receiving a heart transplant

along with high-dose steroids. This patient was also receiving multiple anti-hypotensive agents. After 10 hours, the insulin resistance “broke,” and glucose levels decreased gradually. The insulin dose was reduced by 50% every hour until the infusion was stopped after ~5 hours. Despite this aggressive and rapid down-titration of insulin, the patient's blood glucose level fell to 69 mg/dL. In the case presented here, the patient developed acute extreme insulin resistance requiring intravenous insulin infusion at a rate of up to 142 units/hour, her acute insulin resistance “broke” at day 4, and the infusion rate was rapidly reduced, avoiding hypoglycemia.

In all three cases described (ours and the two noted above), an intravenous insulin infusion was used to treat extreme insulin resistance. From our experience, it is important to monitor blood glucose levels with increased frequency when insulin resistance “breaks” because an acute rapid reversal of insulin resistance often occurs. It is unclear whether aggressive glycemic control is beneficial in this subset of patients; less strict glycemic control is warranted given the possibility of severe hypoglycemia. Therefore, we recommend being less aggressive with the insulin infusion, targeting a slightly higher glucose goal (3).

Clinical Pearls

- Critically ill patients can acutely develop extreme insulin resistance, and intravenous insulin infusion is the treatment of choice.
- There are no published guidelines for the treatment of transient extreme insulin resistance in critically ill patients, and after the insulin resistance “breaks,” patients are prone to quick reversal of insulin resistance and development of acute hypoglycemia.
- Strategies for treating extreme insulin resistance in critically ill patients include:
 - Treating underlying conditions that could be causing extreme

- insulin resistance (e.g., sepsis or myocardial infarction)
- Using intravenous insulin infusion as treatment for hyperglycemia because this type of insulin administration can be titrated up and down rapidly. If subcutaneous insulin is used, there may be a higher risk of hypoglycemia because of the longer half-life of the insulin used
 - Checking glucose levels at bedside frequently (every 30–60 minutes) to monitor blood glucose trends and avoid hypoglycemia
 - Reducing the intravenous insulin infusion rapidly when hyperglycemia begins to improve, which may reflect rapid reversal of insulin resis-

tance. Rapid reduction of the infusion rate and increased frequency of bedside glucose monitoring (every 30 minutes) are necessary to avoid hypoglycemia

- Setting higher blood glucose targets than normally recommended (180–200 mg/dL, as opposed to the usual 140–180 mg/dL) to help avoid hypoglycemia

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Ovalle F. Clinical approach to patient with diabetes mellitus and very high insulin requirements. *Diabetes Res Clin Pract* 2010;90:231–241

2. Hillenbrand A, Weiss M, Stromeyer HG, Henne-Bruns D, Huber-Lang M, Wolf AM. Association of adiponectin levels and insulin demand in critically ill patients. *Diabetes Metab Syndr Obes* 2011;4:45–51
3. American Diabetes Association. Diabetes care in the hospital, nursing home, and skilled nursing facility. Sec. 13 in *Standards of Medical Care in Diabetes—2015*. *Diabetes Care* 2015;38:S80–S85
4. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
5. Oo YH, Karam JG, Resta CA. Extreme insulin resistance in a patient with diabetes ketoacidosis and acute myocardial infarction. *Case Rep Endocrinol* 2013;2013:520904
6. Gupta S, Johnson Oakes D, Therasse A, Wallia A, Molitch ME. Extreme insulin resistance following heart transplant. In *Diabetes Case Studies: Real Problems, Practical Solutions*. Draznin B, Ed. Alexandria, Va., American Diabetes Association, 2015, p. 214–217