

# Severe Hypertriglyceridemia Causing High Anion Gap Metabolic Acidosis in a Patient With Severe Insulin Resistance

Parul Tandon, HBSc, Faizul Hussain, DO, Shakeela Shakoor, MD, and Mohammad A. Hammoude, MD

## PRESENTATION

J.D., a 27-year-old white man, presented to the emergency department with a 4-day history of nausea, 10–15 episodes of nonbilious vomiting, and complaints of polyuria and polydipsia. The patient had been drinking 8–11 l/day of water before admission. He also reported mild epigastric and retrosternal pain. He had no significant medical history and denied the use of any medications because he does not have a primary care physician. The patient denied smoking or a history of significant alcohol use. His family history was significant for paternal hypercholesterolemia.

J.D.'s weight was 150 kg, his height was 71 inches, and his BMI was 46 kg/m<sup>2</sup>. His presenting vital signs included blood pressure of 214/110 mmHg, pulse of 110 bpm, respiratory rate of 20 bpm, temperature of 97.7° F, and oxygen saturation of 97% on room air. Physical examination identified dry mucous membranes and an extensive acanthosis nigricans rash at the cervicothoracic junction, bilateral axillae, bilateral distal extremities, and posterior thoracic wall. Otherwise, the physical examination revealed a soft, nontender abdominal examination and absence of Kussmaul's respiration. There were no findings of eruptive xanthomas.

Initial laboratory findings included an arterial blood gas (pH 7.250, carbon dioxide partial pressure 31.3 mmHg, oxygen

partial pressure 89.1 mmHg, and bicarbonate [HCO<sub>3</sub><sup>-</sup>] 13.4 mEq/l), and a random glucose of 567 mg/dl. Additional routine chemistry values included creatinine 1.43 mg/dl, sodium 110 mmol/l, potassium 4.5 mmol/l, chloride 76 mmol/l, CO<sub>2</sub> 8 mmol/l, and anion gap 26 mmol/l. A lipid panel included total cholesterol 1,249 mg/dl, HDL cholesterol 71 mg/dl, direct LDL cholesterol 50 mg/dl, triglycerides > 5,500 mg/dl, and a serum turbidity of 4+. Serum osmolality was determined to be 332 mOsm/kg. The complete blood count included white blood count 14.8, hemoglobin 15.0, hematocrit 43.4, and platelets 410,000. The patient's A1C was 10.1%. Liver function testing included total bilirubin 0.4 mg/dl, alkaline phosphate 111 units/l, and aspartate aminotransferase 60 units/l. The level of serum lipase was 31 units/l. Urinalysis showed a specific gravity of 1.015, a yellow and clear appearance, 30+ mg/dl protein, 1,000+ mg glucose, 150+ mg ketones, and trace amounts of blood.

J.D. was treated for diabetic ketoacidosis (DKA) with rigorous normal saline infusion, potassium supplementation, and an intravenous insulin drip. His severe hyponatremia was secondary to both hyperglycemia and hypertriglyceridemia and was corrected with continuous normal saline infusion. During the next 24 hours, his sodium level returned to 130 mmol/l. He was also started on fenofibrate 200 mg/

day, omega-3-acid ethyl esters 2,000 mg every 12 hours, and atorvastatin 40 mg/day for his lipid abnormalities. The patient continued to experience high anion gap metabolic acidosis despite normalization of his blood glucose levels and adequate fluid resuscitation.

On day 2 of hospitalization, 80 units of insulin glargine every 12 hours was added to the insulin management regimen. However, there continued to be minimal, if any, improvement in the anion gap measurements (17–21 mmol/l), serum glucose concentrations (163–226 mg/dl), and serum CO<sub>2</sub> concentrations (19–23 mmol/l). Furthermore, the patient's nothing-by-mouth nutrition, insulin management, and statin and fibrate treatment slightly improved his triglyceride levels to 4,642 mg/dl.

On day 4 of hospitalization, a catheter was placed in the internal jugular vein, and therapeutic plasma exchange (TPE) was conducted to treat the severe triglyceride levels to resolve the anion gap and prevent acute pancreatitis. After 12 hours of completing the first TPE treatment, his triglyceride levels were reduced by > 50% to 2,508 mg/dl, the anion gap resolved to 11, and serum CO<sub>2</sub> returned to a normal level of 24 mmol/l (Figure 1).

After receiving three additional TPE treatments during the next 4 days, triglyceride levels were reduced to 343 mg/dl, the anion gap remained

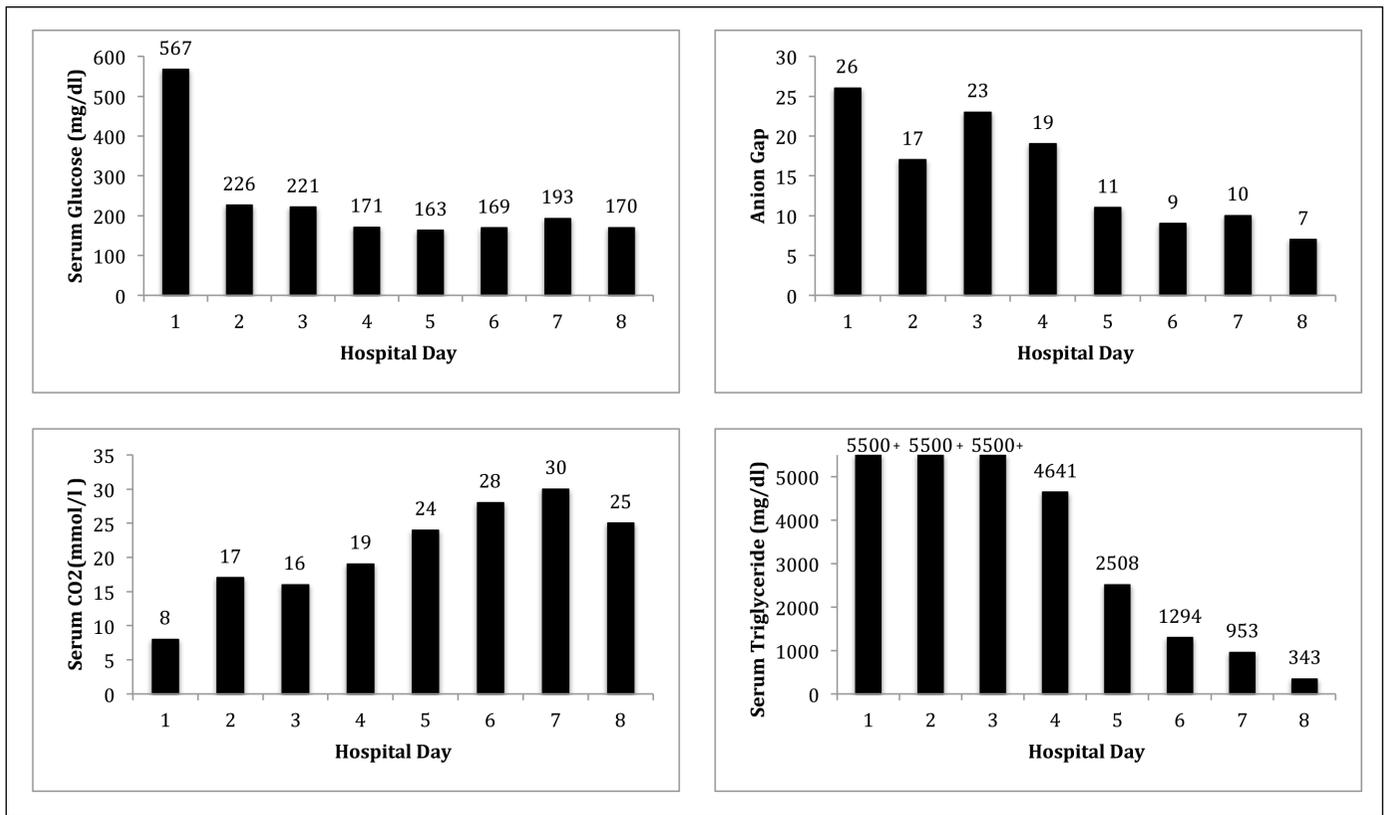


Figure 1. Serial measurements of serum glucose, anion gap, serum carbon dioxide, and serum triglycerides throughout the patient's hospital stay. Normal serum glucose levels are < 126 mg/dl. Normal carbon dioxide levels are 23–34 mmol/l. A normal anion gap is between 4 and 14. Normal triglyceride levels are < 150 mg/dl. The first TPE treatment was performed between day 4 and day 5.

< 11, and serum CO<sub>2</sub> remained between 24 and 30 mmol/l (Figure 1). J.D. did not have further episodes of metabolic acidosis and had no episode of acute pancreatitis.

**QUESTIONS**

1. What is the possible etiology of J.D.'s severe hypertriglyceridemia?
2. How can severe hypertriglyceridemia contribute to high anion gap metabolic acidosis in an insulin-resistant patient?
3. How can a high anion gap metabolic acidosis in a patient with type 2 diabetes and severe hypertriglyceridemia be treated?

**COMMENTARY**

Severe hypertriglyceridemia is defined as a triglyceride level > 500 mg/dl. One well-known life-threatening

complication of severe hypertriglyceridemia is the development of acute pancreatitis; hypertriglyceridemia is the third leading etiology of this condition after alcohol and gallstones.<sup>1</sup> Hypertriglyceridemia may result from primary or secondary causes. In particular, research has demonstrated a correlation between type 2 diabetes and hypertriglyceridemia.<sup>2</sup>

It is thought that hypertriglyceridemia is the most common lipid abnormality in type 2 diabetes. It is theorized that insulin resistance accelerates the rate of adipose tissue lipolysis, causing a transient increase in the serum free fatty acid concentration. This subsequently induces hepatic very-low-density lipoprotein (VLDL) production and an increase in the serum triglyceride concentration. Additionally, insulin resistance

can concomitantly decrease activation of peripheral lipoprotein lipase and decreased degradation of VLDL, which also increases the serum triglyceride concentration.

In our patient, the etiology of the severe hypertriglyceridemia was a combination of severe insulin resistance, presence of morbid obesity (BMI 46 kg/m<sup>2</sup>), consumption of an inappropriate diet, and a genetic disorder of lipid metabolism. His severe insulin resistance was indicated by his requirement of 200 units/day of insulin to maintain optimal glucose concentrations. Additionally, familial hypertriglyceridemia may also have contributed to the severe hypertriglyceridemia as indicated by the incidental finding of hypercholesterolemia. Further work-up at a future time is warranted.

We believe J.D.'s severe hypertriglyceridemia may have contributed to his high anion gap metabolic acidosis. Lipolysis of triglycerides produces 3 palmitate, 3 hydrogen ions (H<sup>+</sup>), and glycerol.<sup>3</sup> The H<sup>+</sup> may titrate out HCO<sub>3</sub><sup>-</sup>, leading to a subsequent decrease in pH and metabolic acidosis. J.D.'s severe hypertriglyceridemia may cause excessive lipolysis, leading to increased titration of HCO<sub>3</sub><sup>-</sup>, adding to the metabolic acidosis that was originally present with the episode of DKA. Furthermore, excessive triglyceride levels could result in increased hydrolysis and increased free fatty acid production. In the plasma, coenzyme A could then react with excessive free fatty acids to form acyl-coenzyme A, which can undergo increased ketogenesis in the mitochondria. This could further account for J.D.'s persistent high anion gap metabolic acidosis.

Clinical experience has shown that insulin treatment can reduce triglyceride levels by activating lipoprotein lipase and chylomicron breakdown.<sup>4,5</sup> Medications such as fenofibrate are considered first-line treatments to lower triglyceride levels, but they have a slow onset of action. Their mechanism of action includes increasing lipoprotein lipase levels and free fatty acid oxidation. Omega-3 fatty acids are also used to reduce triglyceride levels because they decrease hepatic triglyceride synthesis and increase lipoprotein lipase expression. However, these traditional methods and the routine DKA treatment failed to substantially lower J.D.'s severe triglyceride

levels and the anion gap metabolic acidosis.

TPE is clinically known to have a rapid onset of action because it uses a filtration membrane to remove large macromolecules from the patient's plasma.<sup>4,5</sup> The blood is then supplemented with colloid solution and returned to the patient. TPE adequately reduced triglyceride levels by > 50% (from 5,500+ to 2,508 mg/dl) and the anion gap metabolic acidosis resolved almost immediately after the first of four treatments. By the fourth treatment, we had adequately reduced J.D.'s triglyceride levels to 343 mg/dl and prevented any recurrence of his anion gap metabolic acidosis and onset of acute pancreatitis.

We believe that resolution of the anion gap metabolic acidosis may have been secondary to a decreased amount of triglyceride ionization, decreased ketogenesis, and therefore increased levels of bicarbonate available in the serum. It is also possible that the reduction in triglyceride levels may have allowed for more accurate laboratory measurements and a precise measurement of the anion gap. Further research is necessary to delineate the mechanism.

#### CLINICAL PEARLS

- Severe insulin resistance, inappropriate diet, morbid obesity, and genetic abnormalities can increase triglyceride levels and augment anion gap metabolic acidosis in a patient with type 2 diabetes.
- Reducing severe triglyceride levels using immediate TPE can treat high anion gap metabolic acidosis and

prevent the onset of acute pancreatitis in a patient with DKA.

- In a patient with severe hypertriglyceridemia, insulin resistance, and anion gap metabolic acidosis, it is important to follow the patient clinically and monitor blood glucose and bicarbonate levels to prevent acute pancreatitis.

#### REFERENCES

- <sup>1</sup>Stefanutti C, Labbadia G, Morozzi C: Severe hypertriglyceridemia-related acute pancreatitis. *Ther Apher Dial* 2:130–137, 2013
- <sup>2</sup>Ginsberg HN, Zhang YL, Hernandez-Ono A: Regulation of plasma triglycerides in insulin resistance and diabetes. *Arch Med Res* 36:232–240, 2005
- <sup>3</sup>Cuthbert C, Alberti KGMM: The hydrogen ion in normal metabolism. In *Ciba Foundation Symposium 87: Metabolic Acidosis*. Porter R, Lawrenson G, Eds. London, Pitman Books, 1982, p.1–16
- <sup>4</sup>Poonuru S, Pathak SR, Pathak RD: Rapid reduction of severely elevated serum triglycerides with insulin infusion, gemfibrozil and niacin. *Clin Med Res* 9:38–41, 2011
- <sup>5</sup>Ewald N, Kloer HU: Treatment options for severe hypertriglyceridemia (SHTG): the role of apheresis. *Clin Res Cardiol Suppl* 7:31–35, 2012

#### SUGGESTED READING

- Miccoli R, Bianchi C, Penno G, del Prato S: Insulin resistance and lipid disorders. *Future Lipidol* 3:651–664, 2008

*All of the authors are based in Warren, Mich. Parul Tandon, HBSc, is a third-year osteopathic medical student at the St. John Providence Health System St. John Macomb-Oakland Hospital and Michigan State University College of Osteopathic Medicine. Faizul Hussain, DO, is an internal medicine resident; Shakeela Shakoore, MD, is an internal medicine physician; and Mohammad A. Hammoude, MD, is an endocrinologist at St. John Macomb-Oakland Hospital.*