Euglycemic Diabetic Ketoacidosis Accompanied by Severe Hypophosphatemia During Recovery in a Patient With Type 2 Diabetes Being Treated With Canagliflozin/ Metformin Combination Therapy

Sonia Shoukat, Nida Arshad Usmani, Oluwakemi Soetan, and Faisal Qureshi

Introduction

Euglycemic diabetic ketoacidosis (DKA) is defined as acidosis with a blood glucose level <300 mg/dL and bicarbonate level <10 mEq/L and is associated with ketonemia/ketonuria (1). It is usually caused by starvation in conjunction with intercurrent illness in patients with diabetes. This is a relatively uncommon presentation that can go unrecognized.

Canagliflozin belongs to the class of sodium–glucose cotransporter 2 (SGLT2) inhibitors and is used for the management of type 2 diabetes. These agents lower blood glucose levels by selectively inhibiting SGLT2 cotransporters expressed in the proximal convoluted tubule of the kidney. Adverse effects include urinary tract infections, genital fungal infections (2), electrolyte abnormality, and DKA (3).

During the recovery phase of DKA, hypophosphatemia can develop as a life-threatening condition. However, it is uncommon to have a phosphate level as low as <1 mg/dL (normal range 2.5–5 mg/dL).

Herein, we describe the case of a patient with type 2 diabetes who presented with euglycemic DKA within 2 months of starting canagliflozin/ metformin therapy. She had severe hypophosphatemia with phosphate levels <1 mg/dL during the recovery phase, requiring repletion of phosphate.

Case Presentation

A 32-year-old woman with a history of type 2 diabetes presented to the emergency room with a 1-week history of nausea and intractable emesis. Two months earlier, she had started on combination therapy with canagliflozin and metformin. On admission, her laboratory test results were as follows: blood glucose level of 277 mg/dL, anion gap of 19 mmol/L, bicarbonate of 8 mmol/L, serum pH of 7.22, creatinine of 0.81 mg/dL, potassium of 4.4 mEq/L, corrected serum sodium of 129 mmol/L, and positive serum and urine ketones.

A diagnosis of euglycemic DKA was made. For treatment of DKA, the patient was started on intravenous (IV) normal saline (NS) at 1 L/h for the first hour. NS infusion was continued at the rate of 500 mL/h. Potassium was replaced. She was started on IV regular insulin with a 0.1 unit/kg bolus, which was continued at 0.1 unit/kg/h.

At a blood glucose level of 200 mg/dL, fluids were switched to dextrose 5% in water and 0.45% NS at 250 mL/h. At that time, that patient's serum phosphate level was <1 mg/dL. However, she was asymptomatic. Phosphate was replaced with potassium phosphate 30 mmol in 250 mL of sodium chloride 0.9%.

After a few hours of treatment, that patient's basic metabolic profile (BMP) showed a sodium level of 134 mmol/L, potassium level of 3.3 mmol/L, bicarbonate level of 11 mmol/L, anion gap of 11 mmol/L, and phosphate level of 1.6 mg/dL. She was started on a potassium, sodium, and phosphate 280-160-

Presence Saint Joseph Hospital, Chicago, IL

Corresponding author: Faisal Qureshi, faisal.qureshi@presencehealth.org

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250 mg packet four times daily. Her symptoms improved (Figure 1). Subsequent BMP and arterial blood gas measurements showed normal anion gap, normal serum pH, and a potassium level of 4.2 mmol/L. At this point, IV insulin and IV fluids were stopped. The patient started tolerating food, and her appetite improved. She was eventually discharged on insulin lispro three times daily along with insulin NPH every morning.

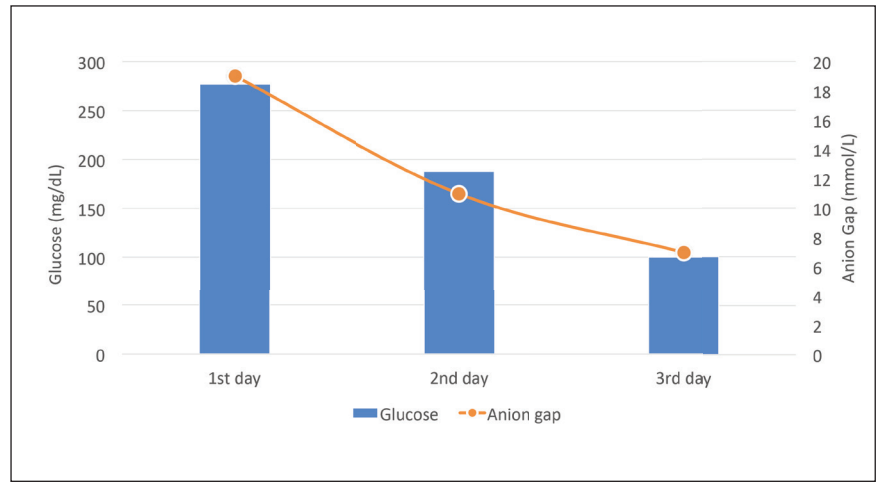

FIGURE 1. Glucose and anion gap trends during the patient's 3 days of hospitalization.

Questions

1. What is the association between canagliflozin and euglycemic DKA?
2. What is the association between canagliflozin and severe hypophosphatemia during the recovery phase of euglycemic DKA?
3. What is the importance of early diagnosis and management of euglycemic DKA?
4. What is the importance of immediate repletion of phosphate for severe hypophosphatemia during the recovery phase of DKA?
5. What is the mechanism of euglycemic DKA and hypophosphatemia during the recovery phase of DKA due to canagliflozin?

Commentary

The SGLT2 inhibitor canagliflozin is associated with euglycemia. Hence, the pancreas senses normal blood glucose levels and does not secrete insulin. Lower levels of insulin, along with increased secretion of cortisol, glucagon, catecholamines, and growth hormone, stimulate glycogenolysis, gluconeogenesis, and lipolysis (4). Increased lipolysis leads to excessive production of free fatty acids, which are then used as fuel in the form of ketone bodies and cause DKA.

In May 2015, the U.S. Food and Drug Administration issued a drug safety communication indicating that SGLT2 inhibitors may lead to ketoacidosis (5). In our case, a patient diagnosed with type 2 diabetes who was recently started on canagliflozin/metformin combination therapy experienced severe hypophosphatemia with a phosphate level <1 mg/dL during the recovery phase of DKA.

Hypophosphatemia during the recovery phase of DKA is attributed to different mechanisms. It is believed that phosphorylations proceed intracellularly concomitant with glucose uptake by insulin-sensitive tissues, induced by effective insulin action. This increased cellular uptake of phosphate is partly responsible for hypophosphatemia during the recovery phase of DKA. Excessive hyperphosphaturia during the development of DKA also results in hypophosphatemia (6).

Phosphate repletion is usually not recommended as an adjuvant in the treatment of DKA. However, severe hypophosphatemia <1 mg/dL is recognized as a cause of morbidity and mortality in DKA that does require immediate repletion (6).

When severe hypophosphatemia occurs as a complication in the treatment of DKA, there is often a secondary reason such as chronic alcoholism, severe hypovitaminosis D, primary hyperparathyroidism, or malabsorption. Unfortunately, in this case, we lacked measurements of vitamin D metabolites, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23). Our patient did not have known secondary reasons for hypophosphatemia other than the intake of canagliflozin for 2 months. Therefore, we speculate that the antecedent use of canagliflozin may have contributed to severe hypophosphatemia during her recovery from DKA.

The mechanism by which canagliflozin therapy causes hypophosphatemia is not yet confirmed. Inhibitors of renal tubular reabsorption of glucose decrease phosphate excretion and promote a slight elevation in serum phosphate (7). In relation to bone loss, it has been speculated that the use of SGLT2 inhibitors may set up a counterregulatory response involving elevations of PTH and FGF-23 (8). Against a background of such counterregulation, a patient experiencing DKA may be predisposed to hypophosphatemia during recovery. To our knowledge, the time course of the effect on phosphate handling that results from single doses and from chronic use of SGLT2 inhibitors, along with the impact on total body intracellular phosphate stores that might result from chronic use, are unknown.

We need clear data about renal tubular reabsorption of phosphate during treatment with SGLT2 inhibitors, which may require a study of 24-h urine clearances of creatinine

and phosphate. We also need to understand whether a treated patient experiences escape from phosphate retention between daily doses. At present, there is a lack of certainty regarding whether that relationship exists between hypophosphatemia and SGLT2 inhibition. Further studies are needed.

In our case, alcoholic ketoacidosis, metabolic acidosis due to salicylate, lactic acidosis due to metformin, and DKA due to type 1 diabetes were all excluded because the patient had no history of alcohol and salicylate use, a normal lactic acid level, and negative anti–glutamic acid decarboxylase and anti–islet cell antibodies. The patient had no signs of infection. Her only medication was ondansetron (Zofran), which does not carry any risk of hypophosphatemia.

The short time frame between the commencement of SGLT2 inhibitor therapy and the development of DKA, which necessitated hospitalization, accompanied by severe hypophosphatemia during DKA recovery, raised the concern that DKA and severe hypophosphatemia during its recovery phase were potentially a serious adverse effect of the SGLT2 inhibitor therapy.

Clinical Pearls

- SGLT2 inhibitors can cause euglycemic DKA as a direct effect of their mechanisms of action, noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion.
- The recovery phase of DKA may be associated with severe hypophosphatemia requiring timely and appropriate repletion of phosphate (9,10).
- Euglycemic DKA may be overlooked in the setting of moderately elevated blood glucose, which can lead to misdiagnosis, delayed treatment, and worsening metabolic derangements.
- Patients started on SGLT2 inhibitors should be counseled extensively about DKA. They should be promptly evaluated for ketonemia, ketonuria, and severe hypophosphatemia. We suggest that the monitoring of phosphate levels should be considered during ongoing treatment with SGLT2 inhibitors, as well as during the treatment of any episode of DKA.

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Duality of Interest

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

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