A Case of Euglycemic Diabetic Ketoacidosis due to Empagliflozin Use in a Patient with Type 1 Diabetes Mellitus

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ABSTRACT

Euglycemic diabetic ketoacidosis is characterised by serum blood glucose <250 mg/dl, arterial blood pH <7.35, and the presence of ketones in urine or blood. Here, we present a 36-year female with type-1 diabetes mellitus, a case of euglycemic diabetic ketoacidosis, who was admitted to the emergency unit with nausea, vomiting, and confusion after using empagliflozin, which was added to her treatment one month ago. She was followed up in the intensive care unit for four days. Empagliflozin was discontinued. Intravenous fluids and insulin infusions were given. The patient, whose metabolic acidosis regressed, was discharged with the necessary recommendations and training. Euglycemic diabetic ketoacidosis should be kept in mind as a differential diagnosis in patients with type-1 diabetes and type-2 diabetes presenting with acidosis. Attention should be paid to the patients' medications and whether there are SGLT-2 inhibitors among these drugs.

Key Words: *Diabetes mellitus, Sodium-glucose co-transporter-2 inhibitors, Euglycemic diabetic ketoacidosis, Empagliflozin.*

INTRODUCTION

Diabetes Mellitus (DM) is characterised by chronic hyperglycemia caused by insulin deficiency or resistance to its effects. Type-1 diabetes mellitus (T1DM) may present with various complications in the following years after the diagnosis.[1] Diabetic ketoacidosis (DKA) may occur in patients with T1DM and in some patients with type-2 diabetes mellitus (T2DM).[2]

Sodium-Glucose Co-Transporter-2 inhibitors (SGLT-2i) exert an insulin-dependent effect on blood sugar and decrease the blood sugar by reducing the reabsorption of glucose in the kidney. This mechanism helps to regulate the patients' blood sugar while protecting them from concurrent hypoglycemia. Moreover, a reduction in HbA1c and weight could be achieved with this treatment. However, it has various side effects such as urinary tract and genital infections, acute kidney injury, and euglycemic DKA (EDKA).[3]

EDKA is characterised by serum blood glucose <250 mg/dl, arterial blood pH <7.35, and the presence of ketones in urine or blood. The incidence of DKA associated with SGLT-2i was less than 1/1,000 in controlled trials.[3]

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In this report, we aimed to present a case admitted to the emergency clinic with nausea, vomiting, confusion, and was diagnosed with EDKA due to empagliflozin after evaluation.

CASE REPORT

A 36-year female patient was admitted to the emergency unit (EU) with nausea, vomiting, and confusion for 2 days. She did not have diarrhea or constipation. She has never had such complaints before.

She had a history of T1DM for 25 years and used insulin 4 times a day until 1 month ago, when her diabetes treatment was switched to vildagliptin 50 mg, 2×1, empagliflozin 25 mg, 1×1 and pioglitazone 15 mg, 1×1 along with basal insulin.

She had nausea for the last 2 days and abdominal pain for one day when brought to the EU with confusion. She was drowsy and appeared ill. Her systolic and diastolic blood pressures were 100 and 55 mmHg, respectively. The heart rate was 96 per minute. Her body temperature was 36.7°C and her respiratory rate was 18 breaths per minute. Finger blood glucose checked in the EU was 220 mg/dL. The laboratory tests revealed 2+ ketones, and 3+ glucose in urine. Arterial blood gas analysis revealed pH: 6.8, PCO_2: 28.3 mmHg, HCO_3: 5 mmHg, and Lactate: 1.62 mmol/L. Serum urea was 24 mg/dL, creatinine: 0.9 mg/dL, serum sodium: 140 mEq/L and serum potassium: 4.4 mEq/L and glycated hemoglobin (HbA1c) was 9%. Other electrolytes and biochemical tests were in the normal range. Meanwhile, plasma glucose was 225 mg/dL. A diagnosis of EDKA due to empagliflozin was established.

Initial follow-up was done in the intensive care unit (ICU) due to severe acidosis and reduced conscious level. Oral antidiabetics were discontinued. Intravenous (IV) saline solutions and insulin infusion were initiated with a dose of 0.1/IU/kg/hour. 5% dextrose infusion was added to the IV treatment after blood glucose-insulin infusion was initiated to keep blood sugar level between 150-250 mg/dL.

When the patient's DKA improved, subcutaneous basal-bolus insulin therapy (basal long-acting insulin and pre-prandial short-acting insulin before meals) was initiated instead of insulin infusion. On 4th day, she was moved to the general ward. She was discharged from the hospital with full recovery with the basal-bolus insulin treatment. She was given a detailed diabetes education in order to acknowledge the importance of the insulin treatment.

DISCUSSION

The main aspect of the present case report was that EDKA could complicate the course of DM treatment in subjects receiving empagliflozin.

The incidence of DKA associated with SGLT-2i was less than 1/1,000 in controlled trials. In cohort studies, it was determined as 1.6/1,000 person-years.[4] Peters et al. recently reported 13 episodes of DKA associated with mild hyperglycemia or normoglycemia in nine patients treated with SGLT-2i.[5]

A systematic review reveals that there are many cases of EDKA in endocrinology, critical care, anesthesia, and surgery literature. However, the number of EDKA cases in the nephrology literature is very low.[6] In another systemic review, EDKA due to SGLT-2i use was detected in 25 patients with T2DM. When the cases were evaluated in terms of the reasons for DKA, it was observed that some of them had autoimmune latent diabetes in adulthood, a history of recent surgery, decrease of insulin dose, or discontinuation of insulin.[7]

Hine et al. reported two cases of EDKA in persons diagnosed with T2DM and treated with dapagliflozin. One in two subjects had undergone distal pancreatectomy for mucinous cystadenoma and was treated with insulin after surgery, but was switched to SGLT-2i during the ICU stay.[8] However, there is no recommendation for the use of SGLT-2i in patients with T1DM.

In a retrospective study, data of 50 patients with T1DM, who used SGLT-2i together with insulin treatment, were examined and none of the patients had EDKA.[9]

In the literature, a patient diagnosed with EDKA and coronavirus disease 2019 (COVID-19) at hospital admission with muscle pain, fever, and diarrhea after empagliflozin was added to the treatment of T1DM for 23 years, is mentioned. In the same case, it was also mentioned that EDKA worsened the severity of COVID-19.[10]

In the present case, the patient developed EDKA within the first month of starting empagliflozin. After treatment in ICU for 4 days, the patient was discharged in stable condition.

In conclusion, EDKA should be kept in mind as a differential diagnosis in patients with type-1 diabetes and type-2 diabetes. Attention should be paid to the patients' medications, particularly to SGLT-2i among these drugs.

PATIENT'S CONSENT:
The patient's informed consent was obtained for publication of the case data.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SB: Collected medical data, wrote the first draft, and approved the final version of the manuscript.
TTD: Performed literature research and approved the final version of the manuscript.
OK: Performed literature research and approved the final version of the manuscript.
FY: Collected medical data and approved the final version of the manuscript.
GA: Collected medical data, wrote the first draft, and approved the final version of the manuscript.

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