Euglycemic Diabetic Ketoacidosis in a Type II Diabetic Patient Treated with Empagliflozin

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Abstract
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of oral drugs used to treat type 2 diabetes (T2DM). EuGlycemic Diabetic Ketoacidosis (EuDKA) is associated with an almost normal level of blood glucose, causing a delay in its diagnosis and treatment. The diagnosis of EuDKA is a challenge for doctors due to its unusual manifestations. EuDKA is one of the rare complications associated with the use of SGLT-2 inhibitors, but it is serious and dangerous. Early diagnosis and treatment of EuDKA require the knowledge and precision of doctors so that they can quickly and safely restore the acid-base balance. EuDKA appears with a slight increase in blood glucose (less than the level defined in the diagnostic criteria for DKA), metabolic acidosis, and increase in the anion gap. Its manifestations are somewhat different from typical DKA. Patients with type 1 or 2 diabetes who present weakness, nausea and vomiting, and metabolic acidosis and are taking SGLT-2 inhibitors should be evaluated for the presence of urine and/or serum ketones. In this report, we reported a case of euglycemic DKA following the use of SGLT2 inhibitor and its treatment.

Keywords: SGLT2 inhibitors, Diabetic ketoacidosis, Euglycemia

Introduction
Blood glucose levels in EuGlycemic DKA (EuDKA) increase moderately to mildly, and diagnosis and treatment are usually delayed due to this glucose level. One of the causes of EuGlycemic DKA is the use of SGLT2 inhibitor (SGLT2i) drugs, and it is an acute, life-threatening side effect of these drugs (1). SGLT2 inhibitor drugs have an effect on the renal proximal tubule and inhibit glucose reabsorption and increase renal excretion of glucose (2).

The mechanisms by which SGLT2i causes EuDKA include decreased blood glucose levels and insulin secretion by pancreatic b-cells, stimulation of pancreatic a-cells, and increased glucagon. SGLT2i also promotes hepatic ketogenesis, increasing ketones in the blood and urine by increasing the production and reabsorption of a ketone substance called acetoacetate in the renal tubules (3,4).

Case Presentation
A 54-year-old male was admitted to the ICU of Shahid Beheshti Hospital, Kashan, Iran, due to a car accident and a head injury, with a diagnosis of intraventricular hemorrhage. His medical history included diabetes from 13 years ago; he was under treatment with Empagliflozin daily and Sitagliptin/Metformin BID for eight months with no hypertension or hyperlipidemia.

And the treatment continued with empagliflozin and sitagliptin/metformin.
The patient was diagnosed with euglycemic DKA and was treated. Five percent dextrose solution, 0.45% normal saline, regular insulin infusion, and intravenous potassium were started for the patient. The patient’s oral medications (SGLT2 inhibitor and sitagliptin/metformin) were discontinued. He was transferred to the intensive care unit. After starting the treatment, the patient’s test results were as follows: anion gap 22 mEq/L, pH 7.07, pCO2 15 mm Hg, and bicarbonate 4.6 mEq/L. The patient stayed in the ICU for two days. Intravenous fluids, regular insulin infusion, and potassium continued and the patient’s condition gradually improved. After the patient’s partial recovery, he was transferred to the internal ward, and his regular insulin regimen was changed to subcutaneous basal-bolus insulin (the patient’s laboratory tests included: bicarbonate 22.3 mEq/L, pCO2 30 mm Hg, and bicarbonate 4.6 mEq/L). The patient was discharged after the stabilization of the clinical and laboratory conditions, and he was treated with insulin at home. For follow-up, the patient was referred to a diabetes specialist. The results of the patient’s blood glucose monitoring during hospitalization are shown in Figure 1.

Discussion

Diabetic ketoacidosis (DKA) is an acute, life-threatening complication in people with type 2 diabetes or uncontrolled type 1 diabetes caused by the absence or severe deficiency of insulin in the body. People with type 2 diabetes develop DKA when exposed to external stressors such as infection, injury, or surgery. The diagnostic criteria of DKA are hyperglycemia, ketosis, and acidosis. DKA is usually characterized by elevated blood glucose but is sometimes associated with moderate or normal blood glucose concentrations. The latter form of DKA (euglycemic or normoglycemic DKA) was defined as a blood glucose level of less than 300 or 200 mg/dL. Euglycemic DKA occurs most often in people with type 1 diabetes, rarely in people with type 2 diabetes, and occasionally in pregnant women with DM, possibly due to alterations in glucose metabolism during pregnancy (5). Sodium-glucose cotransporter 2 (SGLT2) inhibitors help control glucose in patients with type 2 diabetes. Doctors use SGLT2 inhibitors in type 2 diabetes patients and patients with stage 2 or 3A chronic kidney disease to control blood glucose and reduce glycosylated hemoglobin. The function of these drugs is to reduce the reabsorption of glucose in the kidney and urinary glucose excretion (6). SGLT2 inhibitors are used alone or in combination with other drugs.

Empagliflozin is one of the SGLT2 inhibitor drugs which reduces the patient’s weight and blood pressure; this function occurs without changing the heart rate (7). SGLT2 inhibitors affect renal proximal tubule function, inhibit glucose reabsorption in the blood, and reduce blood glucose levels and urinary glucose excretion. Because the half-life of SGLT2 inhibitors is long (11 to 13 hours), the effects of the drug on blood sugar continue even after discontinuation (8,9). When SGLT2 inhibitors are added to other medications in diabetic patients, the amount of insulin needed to control diabetes decreases, and the person becomes more susceptible to DKA (4,5). In a systematic review conducted by Burke et al., 34 diabetic patients were evaluated to determine the association between SGLT2i and DKA (10). The results of this review were: common symptoms in two-thirds (25 cases) of type 2 diabetes cases were nausea, vomiting, and abdominal pain; the average blood glucose at the beginning of the diagnosis of DKA caused by SGLT2i was 265.6 ± 140.7 mg/dL (11). They studied patients with EuDKA caused by the use of SGLT2 inhibitors, nine patients did not have an aggravating factor, and these patients were adults with autoimmune diabetes (11). The factors predisposing

### Table 1. Laboratory results upon admission and follow-up

<table>
<thead>
<tr>
<th>Index</th>
<th>Upon admission</th>
<th>Intensive care unit</th>
<th>Upon discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>280 mg/dL</td>
<td>200 mg/dL</td>
<td>274 mg/dL</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>17 mg/dL</td>
<td>14 mg/dL</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 mg/dL</td>
<td>0.7 mg/dl</td>
<td>0.7 mg/dl</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>139 mEq/L</td>
<td>136 mEq/L</td>
<td>139 mEq/L</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.3 mEq/L</td>
<td>4 mEq/L</td>
<td>3.9 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>6 mEq/L</td>
<td>11.9 mEq/L</td>
<td>18.3 mEq/L</td>
</tr>
<tr>
<td>pH (7.35–7.42)</td>
<td>7.17</td>
<td>7.34</td>
<td>7.44</td>
</tr>
<tr>
<td>Base excess (mEq/L) − 2–2</td>
<td>18.7 mEq/L</td>
<td>11 mEq/L</td>
<td>4.8 mEq/L</td>
</tr>
<tr>
<td>WBC count (neutrophil) differential</td>
<td>12.24 × 10³ μL (75.9%)</td>
<td>13.34 × 10³ μL (91.8%)</td>
<td>9.8 × 10³ μL (64.4%)</td>
</tr>
</tbody>
</table>

![Figure 1. Plot of changes in the patient’s glucose level after receiving insulin](image-url)
a diabetic person to EuDKA and DKA appear to be the same. Administration of SGLT2 inhibitors should be done with caution and after careful consultation with patients (11). To minimize the risk of DKA and achieve multiple benefits, the “STOP DKA protocol” (an available tool and a risk reduction strategy to reduce DKA in patients with diabetes treated with SGLT inhibitors) was developed (12). Causes of euglycemic DKA with an SGLT2 inhibitor can be caused by a variety of reasons including withdrawal or reduction of insulin dose, severe acute illness, dehydration, excessive exercise, surgery, low carbohydrate diets, and alcohol consumption. To prevent SGLT2 inhibitors-caused DKA, SGLT2 inhibitors should be discontinued and insulin discontinuation or inappropriate reduction of insulin dose should be avoided. SGLT2 inhibitors should be discontinued when DKA is diagnosed (8). While searching for articles similar to this one, several studies on the relationship between EuDKA and SGLT2 inhibitor therapy were found in the database (10,13-16).

Conclusion
Diagnosing EuDKA is difficult for physicians due to normal blood glucose levels, often leading to delayed diagnosis. There are many causes for EuDKA in diabetic patients. However, with the increasing incidence of EuDKA in the use of SGLT2 inhibitors, the diagnosis of this complication requires the awareness and caution of medical doctors. When symptoms such as nausea, vomiting, weakness, or development of metabolic acidosis occur during SGLT-2 inhibitor therapy, urine and/or serum ketones should be checked immediately.

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Authors’ Contribution
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Writing—review & editing: Reza Mohamad Hosein Zade Davatgari, Mahsa Soti khiabani, Parviz Shahmirzalou, Maryam Habibi.

Competing Interests
The authors declare that there is no conflict of interest.

Consent for Publication
Informed consent was obtained from the patient for publication of this report.

Data Availability Statement
All data generated or analyzed during this study are included in this published case report.

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