Euglycemic Diabetic Ketoacidosis after the Initiation of Treatment in a Patient with New-Onset Type 2 Diabetes Mellitus

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Abstract

Keywords

► SGLT2 inhibitors
► new-onset type 2 diabetes
► hyperglycemia
► euglycemic
► DKA
► ketoacidosis

We report the onset of euglycemic diabetic ketoacidosis (EDKA) in a 20-year-old male patient with new-onset type 2 diabetes mellitus (T2DM) 5 days after the initiation of diet restriction and the combination of SGLT2 (sodium–glucose co-transporter 2) inhibitors, glucagon-like peptide 1 receptor agonists, and metformin. The use of SGLT2 inhibitors in symptomatic patients with new-onset T2DM along with the extreme reduction in carbohydrate intake might trigger the onset of EDKA. Judicious, stepwise use of available diabetes therapies and strict monitoring can reduce the risk of this complication.

Introduction

Euglycemic diabetic ketoacidosis (EDKA) is an acute, life-threatening complication of both type 1 and type 2 diabetes mellitus (T2DM). EDKA is diagnosed with confirming the coexistence of metabolic acidosis (pH less than 7.3), serum bicarbonate of less than 18 mEq/L, elevated serum, and urine ketones in the presence of capillary blood glucose (BG) of less than 250 mg/dL.[1]

Potential causes of EDKA include starvation, fasting, pancreatitis, sepsis, toxic alcohol ingestion, pregnancy, and alcoholic ketoacidosis.[2–4]

The reports of EDKAs in patients with T2DM have been more frequent since the introduction of the SGLT2 (sodium–glucose co-transporter 2) inhibitors. These relatively new agents have the following effects: increasing the excretion and blocking reabsorption of glucose at the kidney level, stimulating the release of glucagon, suppressing the removal ketones by the kidneys, and increasing ketone reabsorption. The net effect of these changes would lead to a state of carbohydrate starvation, worsening volume depletion, increasing glucagon/insulin ratio, increased lipolysis, and ketosis.[1,5–10]

Case Presentation

A 20-year-old law student, obese male with new-onset T2DM presented to a diabetes specialty clinic with a 2-week history of polyuria, polydipsia, and weight loss. According to the mother, he was drinking too many sugary beverages lately. BG checked at home and was 27.8 mmol/L (500 mg/dL). Laboratory testing revealed fasting BG of 14.7 mmol/L (265 mg/dL), C peptide of 0.79 nmol/L (0.37–1.47), and A1C of
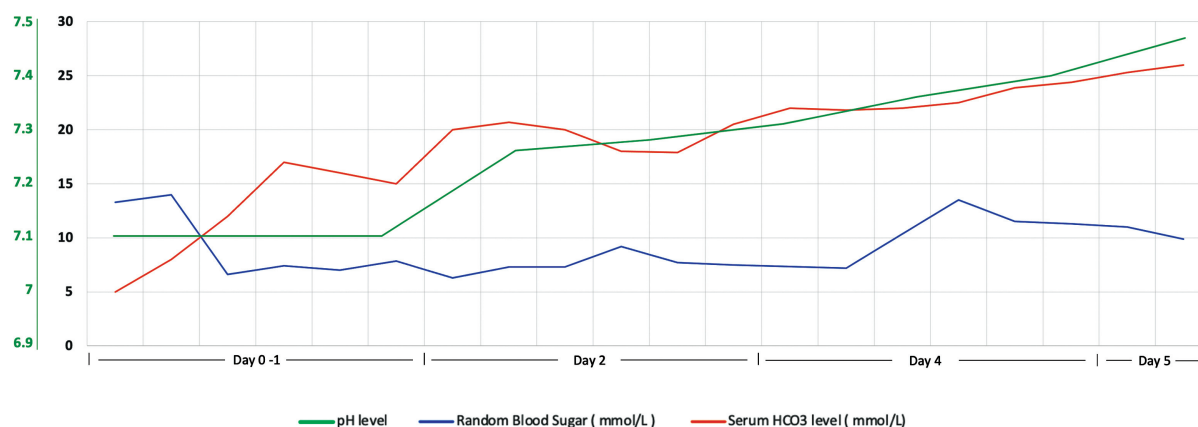
Fig. 1 Serum pH, random blood glucose, serum HCO_3 levels.

10.5%, along with negative GAD and anti-IA2 autoantibodies. The patient was advised on lifestyle modifications and started on dapagliflozin (an SGLT2 inhibitor) 10 mg once daily, semaglutide (a glucagon-like peptide 1 [GLP-1] receptor agonist) 0.25 mg daily subcutaneous injections, and metformin 1,000 mg twice daily.

Five days later, he presented to the emergency room with loss of appetite, abdominal pain, nausea, and vomiting. Body mass index (BMI) was 41 kg/m^2 and vital signs were all within normal. Physical examinations of the lungs, the heart, abdomen, and extremities were normal. Point-of-care BG was 13.5 mmol/L (246 mg/dL) and amylase was normal. Arterial blood gas analysis showed a pH of 7.10 and HCO_3^- of 5 mmol/L, along with a positive serum and urine ketones. Rapid COVID-19 polymerase chain reaction was negative. The diagnosis of EDKA was confirmed. Treatment with hydration and small-dose intravenous insulin infusion was initiated, along with 5% dextrose. Acidosis completely resolved by the third day of admission (►**Fig. 1**). The patient was discharged on a basal bolus insulin regimen. Two weeks postdischarge, metformin 500 mg twice daily and semaglutide 0.25 mg daily subcutaneous injections were introduced and insulin was tapered off. Two months later, the patient was totally off insulin, and flash glucose monitoring revealed normal BG readings. BMI was 37 kg/m^2, HCO_3^- level was 24 mmol/L, and HbA1c was 6.5%.

Since this case report does not disclose any identifiable patient information, written informed consent was deemed unnecessary.

Discussion

To the best of our knowledge, we here report the earliest onset of EDKA, only 5 days after the initiation of treatment in a symptomatic patient with new-onset T2DM. The patient presented with a BMI of 41 kg/m^2 and had a strong family history of T2DM and negative autoantibodies. He was started simultaneously on diet with the combination of SGLT2 inhibitor, GLP-1 receptor agonists, and high-dose metformin.

The principles of hyperglycemia management in patients with new-onset T2DM include rehydration, diet adjustment, healthy lifestyle adaptations, and pharmacotherapy. The restriction of carbohydrate consumption and increased water intake can reduce glucose levels significantly in a few days. Pharmacotherapy selection is classically based on the presence of symptoms, the level of random BG, HbA1c, and presence of ketone bodies. In symptomatic patients presenting with random glucose of >300 mg/dL (16.7 mmol/L) and A1C >10% (86 mmol/mol), insulin or a high-dose oral sulfonylurea agent is considered as the preferred initial treatment.[11–13] Metformin can be considered as a part of the initial treatment regimen, but it should be started at a small dose and increased slowly over few weeks. According to the American Diabetes Association, GLP-1 receptor agonists may be added early or later, at the lowest dose, particularly when weight loss is a priority.[14] Conversely, SGLT2 inhibitors have not been recommended in the initial treatment protocols for symptomatic hyperglycemic patients.

EDKA might occur in T2DM and can be triggered by reduced food intake, dehydration, persistent vomiting, and acute illness. SGLT2 inhibitors are reported to increase the risk of EDKA irrespective of the duration of exposure.[6] Additionally, the risk of EDKA may be higher in patients with β-cell insufficiency, where hyperglycemia reduces pancreatic β-cell's ability to secrete insulin leading to worsening hyperglycemia.[15,16] The essential mechanisms of EDKA with the use of SGLT2 inhibitors are related to a carbohydrate depletion, generalized decreased serum insulin levels, and increased counter-regulatory hormones like glucagon, epinephrine, growth hormone, and cortisol. The increased level of glucagon relative to insulin level leads to increased lipolysis, increased free fatty acids, and hence, ketoacidosis.[5,6,9]

In our young patient who presented with symptomatic hyperglycemia due to islet cell dysfunction, there was a strong indication for treatments that address the relative insulin deficiency and glucagon dysfunction, namely, insulin, sulfonylureas, and possibly GLP-1 receptor agonists.[11] Starting GLP-1 receptor agonists and high-dose metformin might have caused adverse gastrointestinal symptoms. Additionally, the

drastic reduction in carbohydrates intake and the initiation of an SGLT2-I might have led to a state of increase catabolism with relative hypoglycemia, insulin deficiency, and increased glucagon levels leading to EDKA in a few days.

The incidence of EDKA is increasing exponentially with the extensive use of SGLT2 inhibitors in patients with T2DM.[17] While many cases of EDKA have been reported to develop within 180 days after the initiation of an SGLT2 inhibitor,[18] our patient had a full-blown incident within 5 days of such treatment. The diagnosis is very challenging specifically in patients with confirmed T2DM. Early diagnosis and initiation of treatment can significantly improve morbidity and mortality. Therefore, physicians must identify the potential triggers of this potentially fatal condition and should not be misled by the normal glucose levels.

Finally, this is a single retrospective case report and therefore, a cause–effect relationship cannot be proven.

Conclusions

The use of SGLT2 inhibitors in symptomatic patients with new-onset T2DM along with the extreme reduction in carbohydrate intake might trigger the onset of EDKA. Judicious, stepwise use of available diabetes therapies and strict monitoring can reduce the risk of this complication.

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