Euglycemic diabetic ketoacidosis in a patient with type 2 diabetes mellitus 3 days after initiating sodium-glucose cotransporter 2 inhibitor while on an extremely low carbohydrate diet: A case report

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Abstract
This paper presents a case with type 2 diabetes mellitus on a very-low-carbohydrate diet who developed euglycemic diabetic ketoacidosis (EDKA) 3 days after starting sodium-glucose cotransporter 2 inhibitors (SGLT2i). When initiating SGLT2i, healthcare providers should confirm the implementation of a low-carbohydrate diet and provide intensive guidance to prevent EDKA.

KEYWORDS
euglycemic diabetes ketoacidosis, low-carbohydrate diet, sodium-glucose cotransporter 2 inhibitor, type 2 diabetes mellitus

1 | INTRODUCTION

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are expected to have multifaceted effects beyond lowering blood glucose, including renoprotective effects, reduction in cardiovascular events, and reduction in hospitalizations for heart failure.1-4 However, diabetic ketoacidosis (DKA) is a known serious adverse event of SGLT2i, and euglycemic diabetic ketoacidosis (EDKA) should receive special attention. EDKA was first reported by Munro et al. in 1973,5 and in recent years, many EDKA cases associated with the use of SGLT2i have been reported. The Japan Diabetes Society has issued a “Recommendation on the Appropriate Use of SGLT2 Inhibitors” in Japan,6 urging caution. The Food and Drug Administration has also cautioned about the risk of DKA development with SGLT2i, and because of this risk, SGLT2i is not approved for use in type 1 diabetes mellitus (T1DM) in the United States.7

We experienced a case of EDKA in a patient with type 2 diabetes mellitus (T2DM) on a very-low-carbohydrate diet who developed EDKA only 3 days after starting SGLT2i therapy. Although the American Diabetes Association (ADA) Consensus Report indicates that low- or very-low-carbohydrate diets are an effective treatment for select patients,8 the use of SGLT2i while on a low-carbohydrate diet increases ketone production due to the lack of glucose in
the body and increases the risk of ketoacidosis. Currently, SGLT2i are used not only for diabetes but also for various other diseases such as chronic kidney disease and heart failure. When initiating SGLT2i, healthcare providers should confirm the implementation of a low- or very-low-carbohydrate diet and provide intensive guidance to prevent the development of EDKA.

2 | CASE REPORT

The patient was a 57-year-old man who was diagnosed with T2DM at age 50 and treated with very-low-carbohydrate diet (carbohydrate intake 20–40g/day) since age 52. He had no other disease history other than T2DM, and his father and brother had T2DM as well. However, he was not treated with medication and only dietary therapy was performed, his glycemic control gradually deteriorated with a glycated hemoglobin >7%, his family physician started SGLT2i, dapagliflozin 5 mg/day. On Day 3 after starting dapagliflozin, he was transported by ambulance to our hospital because of vomiting, diarrhea, and abdominal pain. On admission, his body temperature, blood pressure, and heart rate were 36.4°C, 98/60 mmHg, and 78 beats/ min, respectively. He weighed 51.0 kg and stood 171 cm tall. His body mass index was 17.6 kg/m². Arterial blood gas revealed pH of 7.107, bicarbonate level of 8.1 mmol/L, and anion gap of 31.9, indicating severe metabolic acidosis. Urinary ketone bodies of 3+ suggested ketoacidosis, but blood glucose levels were not markedly elevated at 189 mg/dl. Imaging studies did not identify any other condition that could cause the acidosis, and he was admitted to our department with a diagnosis of EDKA. As shown in Table 1, laboratory findings on admission revealed elevated white blood cell counts, slight hepatic dysfunction, and elevated pancreatic exocrine enzymes. No electrolyte abnormalities were observed. Moreover, glycated hemoglobin was mildly elevated at 7.2%, and blood ketones of 3-hydroxybutyric acid and acetoacetic acid were markedly elevated at 12,994 and 3406 μmol/L, respectively. After admission, a large volume of saline was administered intravenously, followed by continuous administration of glucose and insulin, and dapagliflozin was discontinued. Blood glucose levels rose temporarily but gradually decreased, and acidosis improved (Figure 1). Abdominal symptoms also improved promptly with improvement in acidosis. Autoantibodies such as anti-glutamic acid decarboxylase antibody, islet antigen-2 antibody, and insulin autoantibody were all negative. Moreover, the insulin secretory capacity was well maintained with ∆C-peptide immunoreactivity (6 min) of 2.04 ng/ml (2.17–4.21 ng/ml) in the glucagon stimulation test. These results led to a diagnosis of EDKA complicated with T2DM. No diabetic retinopathy and nephropathy were noted. He resumed eating on Day 2 and was discharged on Day 6 after improved glycemic control was confirmed. At discharge, he was treated with metformin 1000 mg/day and sitagliptin 50 mg/day, while dapagliflozin remained discontinued. Additionally, diet therapy was reintroduced, without carbohydrate restriction at 1900 kcal, which is approximately 60% carbohydrate, 15% fat, and 25% protein. Although SGLT2i is the preferred treatment for T2DM, it was not resumed in this case because its use was considered inappropriate due to the possibility of resuming a very-low-carbohydrate diet. Since this case was a T2DM with preserved insulin secretory capacity, we selected dipeptidyl peptidase 4 inhibitor and metformin.

Table 1 Patient’s laboratory data on admission

| CBC          | Biochemistry | Ketone body          |
|--------------|--------------|----------------------|
| WBC 19,360   | TP 8.2 g/dl  | 3-HBA 12,994 μmol/L |
| Seg 87.4%    | Alb 5.3 g/dl | AA 3406 μmol/L       |
| Eos 0.0%     | BUN 11.0 mg/dl | Arterial blood gas analysis |
| Baso 0.3%    | AST 49 U/L   | pH 7.107             |
| Mono 4.3%    | ALT 47 U/L   | pCO₂ 25.7 mmHg       |
| Lym 8.0%     | γ-GTP 37 U/L | pO₂ 118.0 mmHg       |
| RBC 489×10⁶ | Cre 0.93 mg/dl | Bicarbonate 8.1 mmol/L |
| Hb 16.0 g/dl | LDH 198 IU/L | Base excess −19.9 mmol/L |
| Plt 21.2×10⁴| Na 140 mmol/L | Lactate 24 mg/dl     |
| Urine K 4.9 |            |                      |
| Protein 0+   | Cl 100 mmol/L | Endocrine-related tests |
| Glucose     | Glucose 192 mg/dl | CPR 0.92 ng/ml     |
| Ketone 3+    | HbA1c 7.2%   | Anti-GAD Ab <5.0 U/ml |

Abbreviations: CPR, C-peptide immunoreactivity, GAD, glutamic acid decarboxylase, HbA1c, glycated hemoglobin, pCO₂, partial pressure of carbon dioxide, pO₂, partial pressure of oxygen, 3-HBA, 3-Hydroxybutyric acid, AA, acetoacetic acid.
DISCUSSION

Herein, we described a case of EDKA induced by SGLT2i while on a very-low-carbohydrate diet. Since islet-associated autoantibodies were negative and insulin secretory capacity was preserved, this case was diagnosed as T2DM with EDKA.

Diabetic ketoacidosis is an acute life-threatening complication in patients with T1DM and T2DM, with diagnostic criteria including a high anion gap metabolic acidosis (pH <7.3 and serum bicarbonate <15 mmol/L), ketone bodies in the blood and/or urine, and hyperglycemia (>250 mg/dl). On the contrary, EDKA was first reported by Munro et al. in 1973 as a rare DKA condition that develops in T1DM. Despite the lack of unified diagnostic criteria, EDKA is a subgroup of DKA without a concurrent rise in blood glucose levels (<200–250 mg/dl); since the start of using SGLT2i for the treatment of diabetes, reports of EDKA associated with SGLT2i have increased. A recent meta-analysis also reported a 2.2-fold higher risk of developing EDKA in patients with T2DM treated with SGLT2i compared with patients not treated with SGLT2i. An analysis of the Food and Drug Administration’s adverse event reporting system described a sevenfold increased risk of developing DKA due to SGLT2i, and around two-thirds of the reported DKA cases were in euglycemia. Multiple factors are assumed to be involved in the association between SGLT2i and EDKA. SGLT2i decreases blood glucose levels via increased urinary glucose excretion, which is considered to result in a relative reduction in insulin secretion, leading to a lower insulin/glucagon ratio, which enhances lipolysis, and free fatty acids are metabolized in the liver to produce ketone bodies. SGLT2i is also supposed to decrease ketone excretion by the kidneys, and a combination of these factors is responsible for the elevated blood ketones and ketoacidosis. Other factors that have been implicated in the development of EDKA include starvation, acute infection, pregnancy, low-carbohydrate diet, dehydration, insulin depletion, and vigorous exercise. In a review of 72 cases of T2DM treated with SGLT2i who developed EDKA, the duration from the start of SGLT2i to the onset of EDKA varied from 1 day to 2690 days. Moreover, the most frequent risk factor for EDKA was fasting, followed by surgery, infection, and reduction or stopping insulin administration. Only three cases had an onset of EDKA within 5 days from the initiation of SGLT2i, and the risk factors were acute infection, prolonged fasting, and insulin discontinuation, respectively, with few cases of early-onset of EDKA being due to dietary changes.
The consensus report issued by the ADA defines a very-low-carbohydrate diet as reducing carbohydrate intake to <26% of the total calories, and a carbohydrate intake of 20–50 g/day. This report indicates that low- and very-low-carbohydrate diets are viable approaches for select patients with T2DM who are not meeting glycemic targets or in whom reducing antiglycemic medications is a priority. However, a very-low-carbohydrate diet may cause nutritional ketosis; thus, further studies are needed to determine its effectiveness in preventing long-term complications. The patient had been on a very-low-carbohydrate diet with a carbohydrate intake of 20–40 g/day for approximately 5 years, which likely led to a chronic increase in ketone bodies in the blood. The addition of an SGLT2i in such a chronic hyperketonic state may lead to EDKA in a very short period of 3 days. This patient had no previous liver function abnormalities and no history of heavy alcohol consumption. He also had no vigorous exercise habits, indicating that the addition of SGLT2i was the primary cause of his EDKA onset.

The treatment of EDKA generally follows the usual form of DKA treatment, which requires intravenous administration of rapid-acting insulin and large volumes of infusions. However, early glucose replacement may be also necessary to prevent hypoglycemia. On the contrary, there was a case report of a patient with SGLT2i-induced EDKA who required insulin administration only for the first 3 h of treatment and could be treated only with a glucose-containing infusion. Since EDKA is primarily due to an absolute lack of available glucose and increased urinary glucose excretion by SGLT2i, whereas DKA is primarily due to significant insulin deficiency, cases of EDKA with preserved insulin secretory capacity may not require continuous insulin administration and may be treatable only by the cessation of SGLT2i and appropriate glucose replacement. However, even though the patient had preserved insulin secretory capacity, glucose administration markedly elevated the blood glucose level, requiring continuous administration of high-dose insulin; further case studies are needed to determine the treatment strategy for EDKA. The STICH protocol has been proposed for the treatment of DKA complicated by T1DM on SGLT2i, which consists of (1) the discontinuation of SGLT2i, (2) bolus insulin administration, (3) 30-g carbohydrate intake, and (4) fluid intake. A treatment strategy comparable to this protocol may be appropriate for EDKA in T2DM, but this is also an issue for future consideration.

**CONCLUSION**

We experienced a case of EDKA in a patient with T2DM on a very-low-carbohydrate diet who developed EDKA within 3 days of receiving SGLT2i. At present, SGLT2i are used not only for diabetes but also for various diseases such as chronic kidney disease and heart failure. SGLT2i will be used increasingly. Even with the use of SGLT2i for T2DM and other conditions in which insulin secretion capacity is preserved, EDKA may occur depending on the diet and prolonged fasting. Therefore, when initiating SGLT2i, healthcare providers should keep this possibility in mind, and confirm the implementation of a low- or very-low-carbohydrate diet and provide intensive guidance on preventing the development of EDKA.

**AUTHOR CONTRIBUTIONS**

All authors contributed significantly. Ayumi Inoue, Akihiro Katayama, Mihiro Sue, Momoka Hasegawa, Takahiro Ishii, Masafumi Tenta, Yuichi Matsushita, Masaya Takeda, and Toshiyuki Wakatsuki treated the patient. Ayumi Inoue, Akihiro Katayama, Megumi Maeda, Masaki Matoba, and Remi Kuribayashi contributed the design of the work. Ayumi Inoue and Akihiro Katayama wrote the manuscript in consultation with Izumi Iseda and Kazuyuki Hida.

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**CONFLICT OF INTEREST**

None of the authors have any potential conflicts of interest associated with this research.

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

**ETHICAL APPROVAL**

This article does not contain any studies with human or animal subjects performed by any of the authors. The identity of the patient has been protected.

**CONSENT**

Written informed consent was obtained to publish this report in accordance with the journal’s consent policy.

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