A case of type 2 diabetes mellitus leading to euglycemic diabetic ketoacidosis in 3 days after starting sodium-glucose cotransporter 2 inhibitor while on a very-low-carbohydrate diet

Ayumi Inoue[1], Akihiro Katayama[1], Mihiro Sue[1], Momoka Hasegawa[1], Megumi Maeda[1], Masaki Matoba[1], Takahiro Ishii[1], Remi Kuribayashi[1], Masafumi Tenta[1], Yuichi Matsushita[1], Masaya Takeda[1], Izumi Iseda[1], Toshiyuki Wakatsuki[1], and Kazuyuki Hida[1]

[1]Okayama Medical Center

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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.

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.

Case report

The patient was a 57-year-old man who was diagnosed withT2DM at age 50 and treated with very-low-carbohydrate diet in (carbohydrate intake 20–40 g/day) since age 52. Because of the gradual deterioration in glycemic control and 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/m^2. 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 showed elevated white blood cell counts, slight hepatic dysfunction and elevated pancreatic exocrine enzymes. After admission, a large volume of saline was administered intravenously, followed by continuous administration of glucose and insulin. Blood glucose levels rose temporarily but gradually decreased, and acidosis improved (Figure 1). 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 ΔC-peptide immunoreactivity (6 min) of 2.04 ng/mL (2.17–4.21 ng/mL) in the glucagon stimulation test. 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 1,000 mg/day and sitagliptin 50 mg/day. In addition, the diet therapy was introduced at 1,900 kcal without carbohydrate restriction, i.e., approximately 60% carbohydrate, 15% fat, and 25% protein.

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.

DKA 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) [9]. On the contrary, EDKA was first reported by Munro et al. in 1973 as a rare DKA condition that develops in T1DM [5]. 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 [10]; since the start of using SGLT2i for the treatment of diabetes, reports of EDKA associated with SGLT2i have increased [11]. 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 [12]. 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 [13].

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 [8]. 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.

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 [14]. 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 [15]. 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. When initiating SGLT2i, healthcare providers should confirm the implementation of a low- or very-low-carbohydrate diet and provide intensive guidance on preventing the development of EDKA.

References

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-28.
2. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295-306.
3. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-46.
4. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with Empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413-24.
5. Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. Br Med J. 1973;2(5866):578-80.
6. Committee on the proper Use of SGLT2 inhibitors. Recommendations on the Proper Use of SGLT2 Inhibitors. Diabetol Int. 11(1):1-5.
7. Drug safety announcement. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. https://www.fda.gov/downloads/drugs/drugsafety/ucm446954.pdf; 2021. Accessed April 16, 2022.
8. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019;42(5):731-54.
9. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.
10. Modi A, Agrawal A, Morgan F. Euglycemic diabetic ketoacidosis: a review. Curr Diabetes Rev. 2017;13(3):315-21.
11. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73-9.
12. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of FAERS data. Diabetes Metab Res Rev. 2017;33(8): doi:10.1002/dmrr.2924
13. Somagutta MR, Agadi K, Hange N, et al. Euglycemic diabetic ketoacidosis and sodium-glucose cotransporter-2 inhibitors: a focused review of pathophysiology, risk factors, and triggers. Cureus. 2021;13(3): doi:10.7759/cureus.13665.
14. Bobart SA, Gleason B, Martinez N, Norris K, Williams SF. Euglycemic ketoacidosis caused by sodium glucose cotransporter 2 inhibitors: a Case Report. Ann Intern Med. 2016;165(7):530-2.
15. Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1

diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. Diabetes Technol Ther. 2018;20(9):571-5.

Author contribution

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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None

CONFLICT OF INTEREST

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

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. The patient provided informed consent for this manuscript.

Figure legend

Figure 1 Clinical course of the first 24 h after admission. Since the blood glucose level was not markedly elevated, we first administered large doses of saline only. Subsequently, due to insufficient improvement in pH, we administered glucose and insulin continuously, after which both blood glucose and acidosis gradually improved. PG, plasma glucose

Table1 Patient's Laboratory Data on Admission.

<CBC>	**<CBC>**	**<CBC>**	**<Biochemistry>**	**<Biochemistry>**	**<Biochemistry>**	**<Ketone Body>**
WBC	19,360	/μL	TP	8.2	g/dL	3-HBA
Seg	87.4	%	Alb	5.3	g/dL	AA
Eos	0.0	%	BUN	11.0	mg/dL	**<Arterial blood**
Baso	0.3	%	AST	49	U/L	pH
Mono	4.3	%	ALT	47	U/L	pCO_2
Lym	8.0	%	γ-GTP	37	U/L	pO_2
RBC	489 $\times 10^4$	/μL	Cre	0.93	mg/dL	Bicarbonate
Hb	16.0	g/dL	LDH	198	IU/L	Base excess
Plt	21.2 $\times 10^4$	/μL	Na	140	mmol/L	Lactate
<Urine>	**<Urine>**	**<Urine>**	K	4.9	mmol/L	**<Endocrine-rel**
Protein	+		Cl	100	mmol/L	CPR
Glucose	3+		Glucose	192	mg/dL	Anti-GAD Ab
Ketone	3+		HbA1c	7.2	%	ΔCPR (6min)

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.

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