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Case Report

Euglycemic diabetic ketoacidosis development in a patient with type 2 diabetes receiving a sodium-glucose cotransporter-2 inhibitor and a carbohydrate-restricted diet

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Abstract Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become increasingly prescribed because of their proven protective effects on the heart and kidneys, and carbohydrate-restricted diets are popular therapeutic approaches for patients with obesity and diabetes. A 28-year-old obese woman with recently diagnosed diabetes developed euglycemic diabetic ketoacidosis (DKA) while on dapagliflozin, an SGLT2 inhibitor, and following a carbohydrate-restricted diet. She presented with nausea, vomiting, and epigastric pain. Hospital tests showed a blood glucose of 172 mg/dL, metabolic acidosis, and increased ketone levels, confirming euglycemic DKA. Treatment involved discontinuing dapagliflozin and administering fluids, glucose, and insulin. She recovered and was discharged on the fourth day. This is considered a case of euglycemic DKA induced by SGLT2 inhibitors and triggered by a carbohydrate-restricted diet. This case highlights the importance of physicians in confirming the symptoms and laboratory results of DKA, even in patients with normal blood glucose levels taking SGLT2 inhibitors and following carbohydrate-restricted diets. It is also crucial to advise patients to maintain an adequate carbohydrate intake.

Key words: Sodium-glucose transporter 2 inhibitors, Diet, carbohydrate-restricted, Diabetic ketoacidosis

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INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors alleviate hyperglycemia in patients with diabetes by inhibiting SGLT2 in renal proximal tubules, thereby reducing glucose reabsorption. Many clinical guidelines recommend prioritizing the prescription of SGLT2 inhibitors as first-line treatment for patients with type 2 diabetes because these drugs have cardioprotective effects in addition to glucose-lowering effects.[1] However, these drugs have several side effects, including genital and urinary tract infections, volume depletion and dehydration, need for lower extremity amputation, bone fracture, and euglycemic diabetic ketoacidosis (DKA).[2]

DKA mainly develops in patients with type 1 diabetes and is a life-threatening acute complication characterized

by hyperglycemia, increased ketone levels, and metabolic acidosis. In rare cases, euglycemic DKA has been defined as a blood glucose level lower than 250 mg/dL. The incidence of euglycemic DKA has been increasing since the introduction of SGLT2 inhibitors in 2013.[3] The risk factors for SGLT2 inhibitor-induced euglycemic DKA include type 1 diabetes, surgery, fasting, excessive alcohol intake, infections, and dehydration.[4]

Carbohydrate-restricted diets are diets in which the proportion of calories from carbohydrates is less than 45% of the total daily calorie intake. Consumption of such a diet in which the said proportion is less than 10% is known to suppress appetite and increase fat breakdown. Recently, it has become popular in Korea as a diet for weight loss.[5] Carbohydrate-restricted diets have also been recommended to improve blood glucose levels in patients with type 2 diabetes who have not reached their glycemic goals.[6]

Herein, we report a case of euglycemic DKA induced by the consumption of a carbohydrate-restricted diet in a patient with type 2 diabetes mellitus who was taking an SGLT2 inhibitor. No such case has been reported in South Korea. However, such cases are expected to increase in the future as the use of SGLT2 inhibitors and carbohydrate-restricted diets increases in the treatment of obese patients with type 2 diabetes. Therefore, we report this case to emphasize the need for physicians who prescribe SGLT2 inhibitors to be aware of this potential complication.

CASE REPORT

A 28-year-old woman presented to the emergency room with symptoms of nausea, vomiting, and epigastric pain that had developed 2-3 days before her visit. The patient had been diagnosed with diabetes 7 days before and was started on glimepiride 2 mg, dapagliflozin 10 mg, and metformin 500 mg once daily. She had also started a carbohydrate-restricted diet to lose weight 5 days ago. The patient stated that she did not consume any carbohydrate-containing foods such as rice, bread, or noodles and only ate vegetable salads and chicken breasts. She reported no history of smoking or alcohol consumption.

The patient complained of palpitations, generalized weakness, and fatigue but not of diarrhea or constipation. The patient was 162 cm tall, weighed 85 kg, and had a body mass index of 32.4 kg/m^2. Her vital signs were as follows: blood pressure, 165/95 mmHg; heart rate, 120/min; respiratory rate, 20/min; and body temperature, 37.5℃. She appeared acutely ill, and her tongue was dry. However, her heart and respiratory sounds were normal. Jaundice or abdominal tenderness, including rebound tenderness, was not observed.

Laboratory findings were as follows: venous blood showed metabolic acidosis with a pH of 7.142, HCO_3 of 10.7, and an anion gap of 19.3. Blood β-hydroxybutyrate and urinary ketone levels increased to 4.7 mmol/L and 3+, respectively; however, the blood lactate level was normal. The blood glucose level was not very high (172 mg/dL); therefore, the patient was diagnosed with euglycemic DKA. The glycated hemoglobin level was 10.5%, indicating that glycemic control had been recently started for this patient. Her C-peptide level was 3.85 ng/mL, based on which type 1 diabetes was ruled out. Blood urea nitrogen and creatinine levels were normal, and blood sodium levels were slightly decreased. Pancreatitis was ruled out based on the absence of elevated amylase levels (Table 1). Chest radiography and electrocardiography revealed no abnormalities.

The patient was admitted to the general ward and any oral hypoglycemic agents she was taking were stopped including dapagliflozin. On the first day of the hospitalization, 3 L of fluids were administered, including normal saline, 5% dextrose water, and 5% dextrose saline. On the second day of hospitalization, 2 L of fluids were administered. Starting from the third day of hospitalization, subcutaneous insulin injections were administered for glycemic control (12 U of insulin glargine-300 once daily in the morning and 2 U of insulin glulisine three times a day before each meal). The patient's overall condition gradually improved, and nausea, vomiting, and epigastric pain disappeared. Venous blood gas analysis results and β-hydroxybutyrate levels improved over time (Table 2).

On the fourth day of hospitalization, the patient was pre-

scribed oral hypoglycemic agents (teneligliptin 20 mg and glimepiride 2 mg, once daily) and was discharged. Two weeks later, the patient visited the outpatient clinic in good health, with a fasting blood glucose level of 100 mg/dL and normal blood β-hydroxybutyrate levels (Table 2).

This case report was reviewed and approved by the institutional review board (IRB) of Jeju National University Hospital (IRB No. JEJUNUH 2023-04-029), and the

Table 1. Laboratory test findings at the time of the patient's emergency room visit

Variable	Result	Reference range
pH	7.142	7.35-7.45
pCO_2 (mmHg)	28.5	32-48
pO_2 (mmHg)	33.4	74-108
HCO_3 (mmol/L)	10.7	21-29
Anion gap (mmol/L)	19.3	12±4
Lactate (mg/dL)	10	4.5-14.4
β-hydroxybutyrate (mmol/L)	4.7	0.0-0.8
Urine ketone	3+	
Glucose (mg/dL)	172	70-110
HbA1C (%)	10.5	4.0-6.0
C-peptide (ng/mL)	3.85	0.78-5.19
WBC (×10³/μL)	22.7	4.0-10.0
Hb (g/dL)	18	12-16
Hct (%)	55.3	36-48
PLT (×10³/μL)	562	150-450
CRP (mg/dL)	1.48	0.00-0.30
AST (IU/L)	24	8-38
ALT (IU/L)	56	4-44
BUN (mg/dL)	18.3	8.0-20.0
Creatinine (mg/dL)	0.7	0.4-0.8
Na (mmol/L)	131	135-145
K (mmol/L)	4.2	3.5-5.3
Cl (mmol/L)	101	98-110
Calcium (mg/dL)	8.6	8.4-10.2
Albumin (g/dL)	5.3	3.8-5.3
Amylase (U/L)	27	43-116

HbA1c: glycated hemoglobin, WBC: white blood cell, Hb: Haemoglobin, Hct: hematocrit, PLT: platelets, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen.

Table 2. Changes in the findings of venous blood gas analysis, anion gap and β-hydroxybutyrate levels according to treatment

Variable	D1	D2	D3	D4	D15	Reference range
pH	7.142	7.221	7.377	7.399		7.35-7.45
pCO_2 (mmHg)	28.5	30.1	40.6	46.9		32-48
pO_2 (mmHg)	33.4	53.5	65.3	52.8		74-108
HCO_3 (mmol/L)	10.7	13.6	23.3	27.1		21-29
Anion gap (mmol/L)	19.3	14.4	10.7	9.9		12±4
β-hydroxybutyrate (mmol/L)	4.9	3.6	2.1	1.2	0.2	0.0-0.8

D: days since hospitalization.

requirement of obtaining the patient's informed consent was waived.

DISCUSSION

We report a case of a patient with type 2 diabetes in whom euglycemic DKA developed 7 days after the use of dapagliflozin, an SGLT2 inhibitor, and 5 days after starting a carbohydrate-restricted diet. Because the patient had a slightly high blood glucose level at the time of her hospital visit and showed improvement after discontinuing dapagliflozin and receiving standard DKA treatment, which included the use of intravenous fluids, glucose, and insulin, the patient was diagnosed with euglycemic DKA caused by an SGLT2 inhibitor. The symptoms of euglycemic DKA began to manifest 2-3 days after starting the carbohydrate-restricted diet, which increases ketone production in the body. The patient's condition was diagnosed 5 days after she started the carbohydrate-restricted diet. Because there were no other precipitating factors such as surgery or fasting, it can be concluded that the carbohydrate-restricted diet triggered the SGLT2 inhibitor-induced euglycemic DKA.

The mechanism by which SGLT2 inhibitors induce euglycemic DKA is as follows: SGLT2 inhibitors lower blood glucose levels by leading to glucose excretion in the urine, leading to a decrease in blood insulin levels and an increase in glucagon levels. With the decrease in carbohydrates in the body because of a carbohydrate-restricted diet, lipolysis and lipid oxidation increase when fat is used as an energy source. In addition, a decrease in the insulin-to-glucagon ratio in the blood activates hydroxymethylglutaryl-CoA. Finally, the production of ketone bodies, a byproduct of fatty acid beta-oxidation, increases.[7] SGLT2 inhibitors have been shown to have cardioprotective and renal protective effects in large-scale clinical trials. Moreover, in Korea, the prescription of SGLT2 inhibitors is expected to continue to increase because the reimbursement standards for combined therapy with SGLT2 inhibitors have recently been relaxed.[8] Therefore, attention should be paid to the side effects of SGLT2 inhibitors, such as euglycemic DKA.

A very low-carbohydrate diet, with a carbohydrate content of less than 10% of the total daily calorie intake, promotes the production of ketone bodies owing to the lack of carbohydrates in the body. This diet is called a ketogenic diet.[9] Therefore, individuals taking SGLT2 inhibitors who follow carbohydrate-restricted diets are at an increased risk of ketoacidosis.[4] We assumed that the patient consumed a very low amount of carbohydrates, which could have led to an increase in ketone production. However, given that the determination of the components of the patient's diet was based solely on the patient's statement, the exact quantity of carbohydrates consumed could not be determined. Carbohydrate-restricted diets have long been used for the treatment of obesity[9] and have recently gained much attention and popularity.[5] In addition, a meta-analysis showed that carbohydrate-restricted diets have a blood glucose-lowering effect and are recommended as appropriate diets for patients with type 2 diabetes and poor glycemic control.[6,10]

We evaluated euglycemic DKA in an obese patient with type 2 diabetes who was taking an SGLT2 inhibitor and following a carbohydrate-restricted diet. Euglycemic DKA is a side effect of SGLT2 inhibitors, and severe carbohydrate-restricted diets promote ketone production in the body. Therefore, it can be concluded that the euglycemic DKA in the case of our patient was caused by SGLT2 inhibitor use and triggered by a carbohydrate-restricted diet. Recently, the prescription of SGLT2 inhibitors has rapidly increased, and carbohydrate-restricted diets have become popular as weight-loss diets. Therefore, there may be an increase in the development of euglycemic DKA in obese patients with type 2 diabetes in the future. To prevent this, doctors who prescribe SGLT2 inhibitors should carefully examine patients' dietary habits and advise them to ensure that they do not have insufficient carbohydrate intake. Even in the absence of hyperglycemia, efforts should be made to confirm the symptoms and laboratory test results indicative of DKA.

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