

Case Report

Euglycemic diabetic ketoacidosis due to a strict low-carbohydrate diet during treatment with sodium-glucose cotransporter 2 inhibitors

Yuita Fukuyama,¹ Kenji Numata,¹ Kaede Yoshino,² Takushi Santanda,¹ and Hiraku Funakoshi¹

¹Department of Emergency and Critical Care Medicine, and ²Department of General Internal Medicine, Tokyo Bay Urayasu Ichikawa Medical Center, Chiba, Japan

Background: Euglycemic diabetic ketoacidosis is a critical clinical presentation that can occur during treatment with sodium-glucose cotransporter 2 inhibitors. However, little is known regarding how a low-carbohydrate diet in combination with this treatment can increase the risk for this condition. Here, we report a case of euglycemic diabetic ketoacidosis in a patient treated with sodium-glucose cotransporter 2 inhibitors after initiation of a low-carbohydrate diet.

Case Presentation: A 54-year-old woman who was taking canagliflozin was transferred to our hospital with severe dyspnea. She had been started on a strict low-carbohydrate diet for 6 days before admission. Laboratory evaluation revealed severe ketoacidosis and a blood glucose level of 196 mg/dL. After her symptoms improved, she was diagnosed with type 1 diabetes mellitus.

Conclusion: Although low-carbohydrate diets are recommended for patients with diabetes mellitus, physicians should exercise great caution in recommending low-carbohydrate diets to patients undergoing treatment with sodium-glucose cotransporter 2 inhibitors.

Key words: Carbohydrate-restricted diet, diabetic ketoacidosis, endocrinology and metabolism, ER, sodium-glucose cotransporter 2 inhibitor

INTRODUCTION

EUGLYCEMIC DIABETIC KETOACIDOSIS (euDKA) is a critical clinical presentation that can occur during treatment with sodium-glucose cotransporter 2 (SGLT2) inhibitors. However, little is known about the increase in risk for euDKA when this treatment is combined with a low-carbohydrate diet.¹ Here, we describe the development of euDKA after the initiation of a strict low-carbohydrate diet in a patient with type 1 diabetes mellitus (DM) treated with SGLT2 inhibitors.

Corresponding: Yuita Fukuyama, MD, Department of Emergency and Critical Care Medicine, Tokyo Bay Urayasu Ichikawa Medical Center, 3-4-32 Todaijima, Urayasu City, Chiba 279-0001, Japan. E-mail: yuita0530@yahoo.co.jp.

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CASE DESCRIPTION

A 54-year-old woman was transferred to our hospital with severe dyspnea. Approximately 5 months before admission, she had experienced persistent thirst. One month before admission, her symptom had worsened, so she visited a nearby clinic. She was prescribed the SGLT2 inhibitor canagliflozin (100 mg/day) because her blood glucose level was 638 mg/dL (reference range, 70–100 mg/dL) and hemoglobin A1c level was 12.5% (reference range, 4.4–5.8%). Because her symptoms did not improve, she visited another clinic. The clinician informed her that the symptoms were due to DM and recommended a carbohydrate-restricted diet for the treatment, 6 days before admission to our hospital. She assumed that carbohydrates should be avoided and ate only zero-calorie gelatin, chicken tenders, and salad, with an estimated intake of only 500 kcal per day, but her thirst worsened and she also experienced dyspnea. She initially presented at another hospital with a 2-day history of dyspnea and was transported to our emergency department for further evaluation.

Her height was 163 cm and her body weight was 63 kg (body mass index 25.7 kg/m²). On examination, she had severe dyspnea with a respiratory rate of 45 breaths/min and an altered mental status. Laboratory evaluation revealed metabolic acidosis (pH 7.0, bicarbonate 2.7 mmol/L, lactate 27.20 mg/dL, and pCO₂ 11.0 mmHg, anion gap 24 mmol/L; Table 1). Her blood ketone levels were elevated at 4.0 mmol/L (reference range, <0.12 mmol/L), and her blood glucose level was 196 mg/dL. There were no signs of sepsis or toxicosis. On the basis of her medical history and laboratory findings, euDKA was suspected. Canagliflozin was discontinued, and she was started on i.v. fluids, continuous venous insulin, glucose infusion, and potassium replacement. Her dyspnea required emergency intubation and mechanical ventilation; therefore, she was admitted to the medical intensive care unit. She was extubated on day 2 after the acidemia improved and dyspnea disappeared. She was diagnosed with type 1 DM on the basis of anti-glutamic acid decarboxylase antibody (176.7 U/mL; reference range, <5.0 U/mL) and anti-islet antigen-2 antibody (anti-IA-2 Ab, 16.8 U/mL; reference range, <0.4 U/mL) positivity. The patient's low-carbohydrate diet was discontinued. After

complete recovery from her symptoms, she was discharged on day 15 and treated with insulin degludec (24 units/day) and insulin lispro (40 units/day). At her last follow-up visit 6 months later, she did not show any complications.

DISCUSSION

OUR CASE REVEALS the potential of low-carbohydrate diets to increase the risk of euDKA in patients treated with SGLT2 inhibitors.

There were two important learning points from this case. First, this patient was prescribed an SGLT2 inhibitor without being diagnosed with type 1 DM. Sodium-glucose cotransporter 2 inhibitors are the newest oral anti-hyperglycemic medication for the treatment of DM. They are now widely used but have been known to cause euDKA, particularly in patients with type 1 DM.² These drugs work by inhibiting SGLT2 in the proximal convoluted tubule, thus preventing reabsorption of glucose and facilitating its excretion in urine.³ They stimulate the release of glucagon, thus increasing the production of ketone bodies. Furthermore, the inhibition of SGLT2 stimulates ketone reabsorption in the

Table 1. Laboratory findings in a 54-year-old woman with euglycemic diabetic ketoacidosis following treatment with sodium-glucose cotransporter 2 inhibitors and a low-carbohydrate diet

Complete blood count		Blood gases		Urinalysis	
WBC	11,100/ μ L	pH	7.0	pH	5.5
RBC	531 \times 104/ μ L	pCO ₂	11.0 mmHg	Glucose	4+
Hgb	13.1 g/dL	HCO ₃ ⁻	2.7 mmol/L	Ketones	4+
Hct	41.10%	Anion gap	24 mmol/L		
Platelets	34.5 \times 104/ μ L	Lactate	27.20 mg/dL		
Blood chemistry					
TP	7.5 g/dL	Na	137 mEq/L	Anti-GAD Ab	176.7 U/mL
Albumin	3.8 g/dL	K	4.3 mEq/L	Anti-IA-2 Ab	16.8 U/mL
UN	13.3 mg/dL	Cl	106 mEq/L		
Cre	0.62 mg/dL	Ca	8.8 mg/dL		
AST	14 U/L	iP	2.4 mg/dL		
ALT	11 U/L	Mg	2.4 mg/dL		
ALP	459 U/L	CRP	0.28 mg/dL		
LD	214 U/L	TSH	3.840 μ U/mL		
CK	49 U/L	FT3	1.21 pg/mL		
GGT	19 U/L	FT4	0.69 ng/dL		
T-Bil	0.41 mg/dL	BNP	41.3 pg/mL		
Glucose	219 mg/dL	Troponin	0.009 ng/mL		
Lipase	264 U/L				

Ab, antibodies; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CK, creatine kinase; Cre, creatinine; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; GAD, glutamic acid decarboxylase; GGT, γ -glutamyl transferase; Hct, hematocrit; Hgb, hemoglobin; IA-2, islet antigen-2; iP, inorganic phosphorus; LD, lactate dehydrogenase; RBC, red blood cell count; T-Bil, total bilirubin; TP, total protein; TSH, thyroid-stimulating hormone; UN, urea nitrogen; WBC, white blood cell count.

renal tubule.⁴ Finally, when a patient develops diabetic ketoacidosis (DKA), SGLT2 inhibitors maintain relative euglycemia, as they lead to secretion of glucose in the urine. Diabetic ketoacidosis is classically defined as presence of the triad of hyperglycemia (>250 mg/dL), ketosis, and anion gap acidosis. Euglycemic DKA is then DKA without marked hyperglycemia (\leq 250 mg/dL).⁵ We diagnosed euDKA in our patient on the basis of her high blood ketone level, relatively low blood glucose level (196 mg/dL), and history of taking canagliflozin. Her condition was deemed serious on the basis of her bicarbonate levels (<10 mmol/L) and altered mental status.⁵ We presume that her first clinician diagnosed type 2 DM on the basis of her age and weight. However, when we detected anti-IA-2 Ab positivity, we diagnosed type 1 DM. Atkinson *et al.* reported that approximately 5–15% of adults diagnosed with type 2 DM might actually have type 1 diabetes with the presence of islet autoantibodies.⁶ Therefore, when patients diagnosed with type 2 DM are prescribed SGLT2 inhibitors, we should be mindful of the possibility of misdiagnosing the type of DM and thereby risking euDKA.

Second, there is potential that a low-carbohydrate diet causes euDKA. To our knowledge, there are no other case reports on euDKA caused by the initiation of a low-carbohydrate diet in patients undergoing treatment with SGLT2 inhibitors. Our patient, despite having type 1 DM, did not show any signs or symptoms suggestive of euDKA for nearly 1 month after starting treatment with SGLT2 inhibitors. However, a few days after the initiation of the strict low-carbohydrate diet, she developed severe dyspnea. This was presumed to be caused by metabolic acidosis; thus, euDKA in this patient might have been due to the strict low-carbohydrate diet. A low-carbohydrate diet is known to improve glycemic control and blood lipid levels and lead to greater weight loss compared with conventional control diets.⁷ Although avoidance of excessive carbohydrate intake is recommended for the treatment of DM,⁸ low carbohydrate levels can increase the risk of ketoacidosis.⁹ Low-carbohydrate diets are formulated to replace glucose as the body's main source of fuel and cause ketosis as a result of fatty acid metabolism. Our patient was on a strict low-carbohydrate diet, estimated at only 500 kcal per day. We suggest that the combination of SGLT2 inhibitors and the low-carbohydrate diet caused euDKA.

In conclusion, this study reports a serious case of euDKA that developed after the initiation of a strict low-carbohydrate diet in an undiagnosed type 1 DM patient treated with an SGLT2 inhibitor. A low-carbohydrate diet is not contraindicated for patients treated with SGLT2 inhibitors. However, both a low-carbohydrate diet and SGLT2

inhibitors carry a risk of ketoacidosis. Therefore, physicians should exercise a high degree of caution in recommending a low-carbohydrate diet to patients undergoing treatment with SGLT2 inhibitors.

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DISCLOSURE

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Animal studies: N/A.

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