Ketoacidosis with euglycemia in a patient with type 2 diabetes mellitus taking dapagliflozin
A case report

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Abstract
Rationale: Dapagliflozin (a sodium-glucose cotransporter-2 [SGLT2] inhibitor) represents the most recently approved class of oral medications for the treatment of type 2 diabetes. Dapagliflozin lowers plasma glucose concentration by inhibiting the renal reuptake of glucose in the proximal renal tubules. In 2015, the US Food and Drug Administration released a warning concerning a potential increased risk of ketoacidosis in patients taking this medication.

Patient concerns: We present the case of a 23-year-old woman with type 2 diabetes treated with dapagliflozin (10 mg, once a day) for 2 years who presented to the emergency department with abdominal pain.

Diagnoses: We diagnosed her with severe ketoacidosis with a normal glucose level (177 mg/dL) due to dapagliflozin, accompanying acute pancreatitis due to hypertriglyceridemia. We concluded that the precipitating factor for euglycemic ketoacidosis was pseudomembranous colitis.

Interventions: She was treated with intravenous infusions of insulin, isotonic saline, and sodium bicarbonate as diabetic ketoacidosis treatment.

Outcomes: She was in shock with severe metabolic acidosis. After continuous renal replacement therapy, the uncontrolled metabolic ketoacidosis was treated, and she is currently under follow-up while receiving metformin (500 mg, once a day) and short- and long-acting insulins (8 units 3 times and 20 units once a day).

Lessons: We report an unusual case of SGLT2 inhibitor-induced euglycemic ketoacidosis recovered by continuous renal replacement therapy in a patient with type 2 diabetes and recurrent acute pancreatitis due to hypertriglyceridemia. We diagnosed a rare complication of the SGLT2 inhibitor in a patient with type 2 diabetes in whom uncontrolled metabolic ketoacidosis could be effectively managed via continuous renal replacement therapy.

Abbreviations: CKD = chronic kidney disease, CRRT = continuous renal replacement therapy, DKA = diabetic ketoacidosis, DM = diabetes mellitus, SGLT2 = sodium-glucose cotransporter-2.

Keywords: dapagliflozin, ketoacidosis, renal replacement therapy, SGLT2 inhibitor

1. Introduction
Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent the most recently approved class of oral medications for the treatment of type 2 diabetes mellitus (DM).[1] SGLT2 inhibitors lower plasma glucose levels by inhibiting the reabsorption of glucose from the glomerular filtrate into the blood through the proximal tubular epithelium.[2] The drug can be used to treat type 2 DM either as monotherapy or in combination with other oral hypoglycemic agents. It controls hyperglycemia effectively without serious complications such as hypoglycemia and is associated with reduced body weight (generally, 1–4 kg weight losses are observed) and blood pressure (decreases of 1–5 mmHg in systolic blood pressure have been found in most studies).[3,4] In addition to altering lipid parameters, decreasing arterial stiffness, and ameliorating oxidative stress through the control of serum uric acid levels,[5,6] it can reduce cardiovascular and all-cause mortality.[3–8] Safety data from pre-marketing trials emphasized that SGLT2 inhibitors are generally well tolerated, with possible side effects such as genitourinary infection.[9]

However, the US Food and Drug Administration released a warning concerning a potential increased risk of ketoacidosis in patients taking this medication in May 2015. Not long after the announcement, 5 cases of ketoacidosis occurred due to SGLT2 inhibitors, defined as ketoacidosis with serum glucose values less than 250 mg/dL,[9] and all patients were easily treated conservatively.

Herein, we present an unusual case of a patient with diabetes and euglycemic ketoacidosis due to dapagliflozin (Forxiga; AstraZeneca, Cambridge, UK). This study was approved by the institutional review boards of Keimyung University School of
Table 1
Initial and follow-up laboratory findings.

| Parameter                  | Initial | After 8 days | After CRRT |
|----------------------------|---------|--------------|------------|
| Arterial pH (7.35–7.45 mmHg) | 7.40    | 7.11         | 7.446      |
| Serum bicarbonate (21–28 mmol/L) | 24.0    | 2.2          | 27.8       |
| Anion gap (6–12 mmol/L)     | 15      | 23.8         | 6.2        |
| Serum ketone (< 0.6 mmol/L) | 1.6     | 1.1          |            |
| Serum lactate [0.5–1.8 mmol/L] | 1.6    | 0.9          |            |
| Serum sodium [135–146 mmol/L] | 130    | 127          | 136        |
| Serum chloride [95–106 mmol/L] | 95     | 101          | 102        |
| Serum glucose [74–106 mg/dL] | 177     | 148          | 150        |
| Serum osmolality [285–295 mOsm/kg] | 292 | 290          | 286        |
| BUN [9–23 mg/dL]            | 12      | 13           | 8          |
| Serum creatinine [0.7–1.3 mg/dL] | 0.58 | 0.81         | 0.46       |
| Amylase [50–118 U/L]        | 517     |              |            |
| Lipase [13.8–51.1 U/L]      | 990     | 119          |            |
| Total cholesterol [<200 mg/dL] | 797 | 334          | 220        |
| Triglyceride [< 150 mg/dL]  | 3,088   | 410          | 434        |

BUN = blood urea nitrogen, CRRT = continuous renal replacement therapy.

According to her past medical record, her mother was also treated for acute pancreatitis due to hypertriglyceridemia. For this reason, we assumed that she had familial hypertriglyceridemia. She initially received conservative treatment for acute pancreatitis. On the 2nd day after treatment, she experienced fever and empirical antibiotics (ceftriaxone, 2.0 g once a day) were administered. On the 4th day after treatment, abdominal pain and laboratory findings had improved, and she initiated enteral feeding with oral hypoglycemic agents. However, diarrhea developed, and a stool examination showed positive test for Clostridium toxin. She fasted and received metronidazole for the treatment of pseudomembranous colitis. She suddenly developed shortness of breathing and tachycardia. Her vital signs were stable, but her laboratory findings showed a serious state: pH, 7.029; HCO₃⁻, 1.8 mmol/L; serum ketone, 2+; and urine ketone, 2+. However, her plasma glucose level showed euglycemia (148 mg/dL). She was treated conservatively for diabetic ketoacidosis (DKA) but was in shock with severe metabolic acidosis. She barely recovered through continuous renal replacement therapy (CRRT) for 2 days. After the application of CRRT, the uncontrolled metabolic ketoacidosis was treated completely, and she is currently under follow-up while receiving metformin (500 mg, once a day) and short- and long-acting insulins (8 units 3 times and 20 units once a day).

3. Discussion
Nowadays, SGLT2 inhibitors are recommended as first-line agents in patients unable to tolerate metformin or as second-line agents after metformin.[10] The major side effect of SGLT2 inhibitors is genitourinary infection. Additionally, since SGLT2 inhibitors require adequate filtration of glucose in the kidneys, the effect diminishes in patients with renal impairment. However, in the absence of renal impairment, SGLT2 inhibitors are associated with significant and sustained lowering of glycated hemoglobin and a low risk of hypoglycemia. Furthermore, they improve pancreatic beta cell function, promote weight loss, reduce blood pressure, and reduce cardiovascular and all-cause mortality.[3]

However, SGLT2 inhibitors have recently been reported to induce euglycemic ketoacidosis in patients with diabetes.[11] This was defined as ketoacidicosis with serum glucose values less than 250 mg/dL.[9] It is known that euglycemic ketoacidosis mostly develops in patients with type 1 DM; it rarely develops in patients with type 2 DM. It is known that the incidence rate of DKA is 1.34 per 1000 person-years,[12] but the incidence rate of euglycemic ketoacidosis is uncertain, and some cases have been reported until now. In general, SGLT2 inhibitors have not been shown to be safe and efficacious in patients with CKD stage 3 or greater,[13] and thus are used without dose control. Therefore, the association of dosage of SGLT2 inhibitors with euglycemic ketoacidosis was not known, and other oral hypoglycemic agents were used when the ketoacidosis improved after discontinuation of SGLT2 inhibitors.

Our case is the first report of effective treatment of euglycemic severe ketoacidosis due to dapagliflozin via dapagliflozin withdrawal and CRRT. When we applied the Naranjo Adverse Drug Reaction Probability Scale, the score was 6, which indicated a probable adverse drug reaction to SGLT2 inhibitors. Patients with DM usually experience DKA.[14,15] DKA is an extreme metabolic state caused by insulin deficiency. In this situation, the breakdown of fatty acids produces ketone bodies, and hyperglycemia leads to acute deterioration of beta-cell function.

Figure 1. Abdominal computed tomography shows diffuse pancreatic swelling with peripancreatic fluid collection.
Finally, DKA occurs due to inadequate suppression of ketogenesis. However, the mechanism of SGLT2 inhibitor-induced ketoacidosis is different from DKA because glucose levels are normal and beta-cell glucotoxicity is unlikely to be a causative factor in the absence of significant hyperglycemia. Due to the renal glucose-wasting property of this drug, ketoacidosis with only mild elevation of serum glucose levels occurs, and this makes the diagnosis difficult. In our case, the predisposing factor for euglycemic ketoacidosis might be pseudomembranous colitis based on the literature. She had developed acute pancreatitis due to recurrent hypertriglyceridemia, and her mother had the same disease. Therefore, we assessed her disease in the context of familial hypertriglyceridemia and decided it as the cause of recurrent pancreatitis. She also had a fever on the 2nd day after hospitalization. Thus, she was treated with empirical antibiotics (ceftriaxone, 2.0 g once a day), and on the 2nd day after antibiotic use, she was diagnosed with pseudomembranous colitis based on her mucoid diarrhea symptom and positive Clostridium toxin test. It can be assumed that acute pancreatitis due to familial hypertriglyceridemia can lead to an acute dysfunction of pancreatic beta-cells and insulin deficiency. Although the symptoms of acute pancreatitis were recovering, it was thought that the catabolic state such as pseudomembranous colitis and the direct effect of the SGLT2 inhibitor on pancreatic cells synergized to induce euglycemic severe ketoacidosis intractable to medical treatment with shock. In this case, patients with severe metabolic acidosis require renal replacement therapy, and we treated euglycemic ketoacidosis effectively and safely using CRRT.

The limitation of our study is that it is difficult to prove precisely the mechanism underlying the role of SGLT2 inhibitors in the development of euglycemic ketoacidosis through the reported literature until now. However, it is possible that SGLT2 inhibitors might induce euglycemic ketoacidosis though the assumptions presented in the manuscript. Also, the point being emphasized in our study is that when DKA in diabetes patients using SGLT2 inhibitors does not show typical manifestations such as dehydration and marked hyperglycemia and shows life-threatening metabolic acidosis, we should consider euglycemic ketoacidosis due to SGLT2 inhibitor stop the medication and apply aggressive treatment as soon as possible.

Herein, we report an unusual case of SGLT2 inhibitor-induced euglycemic ketoacidosis recovered by CRRT in a patient with type 2 DM and recurrent acute pancreatitis due to hypertriglyceridemia.

Author contributions

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