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Euglycemic Diabetic Ketoacidosis Associated With SGLT2 Inhibitor Therapy: A Case Report

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ABSTRACT

Sodium-glucose cotransporter-2 inhibitors are now considered second-line treatment agents for type 2 diabetes and offer a unique treatment approach with added cardiorenal benefits. Drugs in this class increase the risk of euglycemic diabetic ketoacidosis, which may be difficult to diagnose if clinicians are not aware of the risk factors and subtle symptoms. This article describes a case of euglycemic diabetic ketoacidosis in a patient with coronary artery disease who was taking a sodium-glucose cotransporter-2 inhibitor and experienced acute mental status changes immediately after heart catheterization.
Key words: diabetes mellitus, euglycemic diabetic ketoacidosis, sodium-glucose cotransporter-2 inhibitor

Diabetic ketoacidosis is a life-threatening condition characterized by hyperglycemia, ketosis, and metabolic acidosis.[1,2] In this article, we present the case of a patient with a unique variation of diabetic ketoacidosis characterized by normoglycemia, ketosis, and metabolic acidosis. This condition, known as euglycemic diabetic ketoacidosis (euDKA), has been associated with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors.[3] Agents belonging to this relatively new drug class, introduced in 2014, are being prescribed with increasing frequency because of evidence showing that they are associated with reduced cardiovascular and kidney risk for those with and without a history of diabetes.[4,5]

Case Presentation

A man in his seventies with coronary artery disease and a history significant for type 2 diabetes, stroke, and hypertension was scheduled for heart catheterization because of fatigue, weakness, dyspnea on exertion, and an abnormal stress test result. His outpatient diabetes medication regimen included glipizide 10 mg twice daily, metformin 1000 mg twice daily, and dapagliflozin 10 mg daily. He was also taking lisinopril 30 mg daily for hypertension and diabetic nephropathy. The patient had been told not to take dapagliflozin for 3 days before the procedure. The catheterization went as planned, although the patient was hypertensive throughout the procedure. After the heart catheterization, the patient had acute mental status changes including aphasia and severe agitation, which prompted initiation of a stroke code and admission to the cardiac intensive care unit.

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Table 1: Patient Laboratory Values After Heart Catheterization

	Reference Range	Results at 12 h	Results at 24 h	Results at 48 h
Sodium, mmol/L	136-145	140	143	141
Potassium, mmol/L	3.5-5.1	4.3	3.4	3.9
Chloride, mmol/L	98-107	106	110	109
Carbon dioxide, mmol/L	22-29	17	24	23
Anion gap, mmol/L	7-14	20	9	9
β-**Hydroxybutyrate**, mmol/L	0.02-0.27	3.38		<0.05
POC glucose, mg/dL	70-99	117	146	165
Urine glucose, mg/dL	Negative	>1000		
Urine ketones, mg/dL	Negative	60		

Abbreviation: POC, point of care.

Diagnostic Assessment

The stroke work-up included a computed tomographic scan of the head, which showed no acute intracranial hemorrhage, mass, or parenchymal changes. An electroencephalogram showed evidence of encephalopathy secondary to hypertension. Capillary (point-of-care) blood glucose monitoring showed a blood glucose level of 85 mg/dL before the procedure and 117 mg/dL after the procedure. The patient continued to exhibit confusion overnight. Laboratory test results 12 hours after the procedure revealed an anion gap metabolic acidosis with an elevated ß-hydroxybutyrate level of 3.38 mmol/L (reference range, 0.02-0.27 mmol/L) (Table 1). Tests for urine glucose and ketones were positive. Given these results and the patient's use of an SGLT2 inhibitor (ie, dapagliflozin) before the admission, his mental status changes were attributed to euDKA.

Therapeutic Intervention

An intravenous insulin infusion was initiated at 2 units per hour after consultation with the inpatient diabetes management service using the same institutional protocol as that used for classic DKA. The patient's capillary glucose level was 183 mg/dL at the start of the infusion. Dextrose-containing fluids were also started to avoid iatrogenic hypoglycemia given the patient's near-normoglycemic values. Laboratory testing was repeated 4 hours after insulin infusion initiation and indicated a normalized anion gap, which persisted with subsequent testing. Laboratory results at 24 and 48 hours after the procedure are shown in Table 1.

The insulin infusion continued for 20 hours, with infusion rates ranging from 0.5 to 9 units per hour and glucose values ranging from 102 to 202 mg/dL. Laboratory values before discontinuation of the insulin drip showed a ß-hydroxybutyrate level of less than 0.05 mmol/L and a normalized anion gap. Potassium supplementation was required because of hypokalemia. The patient's mental status improved significantly as his acidosis resolved, returning to his baseline mental status within 24 hours of the procedure.

Discussion

Euglycemic diabetic ketoacidosis has been reported as a complication of SGLT2 inhibitor therapy.[1,3,6] The mechanism of action is complex (see Figure),[7] contributing to the risk of delayed DKA diagnosis. Sodium-glucose cotransporter receptors are located in the gastrointestinal tract and kidneys. Sodium-glucose cotransporter-2 inhibitors block the reabsorption of glucose in the proximal renal tubule.[3,8,9] This process results in urinary excretion of glucose and reduced plasma glucose levels. Sodium-glucose cotransporter-2 inhibitors reduce insulin levels and increase glucagon levels, causing a shift to fat metabolism, lipolysis, and ketone production.[3,8-10] Sodium reabsorption is also blocked, which causes diuresis and subsequent reduction in plasma volume and blood pressure.[8,10] Examples of available SGLT2 inhibitor medications, with initial and maximum daily dosing based on indications for treatment, are listed in Table 2[7,11]; other options are available in combination with metformin and other oral agents.

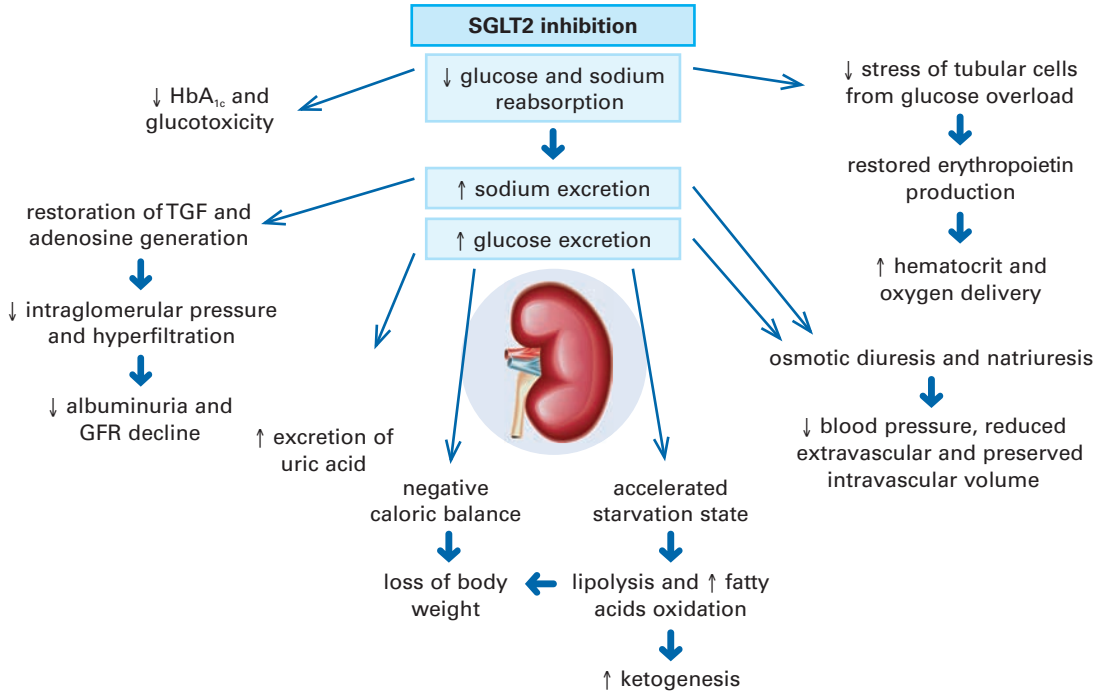

Figure: Cardiorenal effects of sodium-glucose cotransporter-2 (SGLT2) inhibition.[7] Reproduced under Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0). GFR indicates glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; TGF, tubuloglomerular feedback.

Table 2: Sodium-Glucose Cotransporter-2 Inhibitor Agents

Generic Name	Daily Starting Dose, mg	Maximum Daily Dose, mg	Half-life,[7] h
Canagliflozin	100	300	11-13
Dapagliflozin	5	10	13
Empagliflozin	10	25	13
Ertugliflozin	5	15	17

This case report briefly highlights one of the risks of SGLT2 inhibitor therapy that may be unfamiliar to inpatient care providers—euglycemic diabetic ketoacidosis. Hyperglycemia is one of the first identifiable indicators of classic DKA and prompts further testing to confirm metabolic acidosis and presence of ketones.[2,12] In this case, the patient's history of stroke prompted providers to appropriately consider stroke as a cause of his postprocedure acute mental status changes. Confirmation of hypertensive encephalopathy and normoglycemia delayed additional laboratory investigation, which ultimately revealed anion gap metabolic acidosis 12 hours after the procedure.

In addition to constituting another treatment option for diabetes mellitus, SGLT2 inhibitor therapy is also indicated for patients with heart failure with or without diabetes[5,13] because of its reduction of plasma volume and blood pressure. Several large trials have shown cardiovascular and renal benefits including reductions in all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, progression of nephropathy and kidney disease, and hospital readmission for those with heart failure.[4,5,14-17] Given these outcomes, the American Diabetes Association Standards of Medical Care in Diabetes include recommendations to consider prescribing agents in this drug class as second-line therapy after metformin but to consider using SGLT2 inhibitors as first-line treatment with or without metformin for those at high risk for atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[4,5] The use of SGLT2 inhibitors for type 1 diabetes is off label and not approved by the US Food and Drug Administration.[6,8]

Risk factors for euDKA are similar to those of classic DKA.[2,8] Conditions that induce metabolic stress with an excess of counterregulatory hormones (eg, catecholamines, cortisol, glucagon, and growth hormone) can increase the risk of euDKA.[3,8] These conditions include infection, acute illness, trauma, stroke, myocardial infarction, and surgery. Dehydration, periods of fasting, strenuous exercise, and alcohol use are additional risk factors.[3] Use of exogenous glucocorticoids may mimic a counterregulatory state, which would increase the risk of euDKA.[10] Other precipitating factors in SGLT2 inhibitor–associated euDKA are listed in Table 3.[3,8,10]

Diagnosis of euDKA is based on laboratory findings reflective of anion gap metabolic acidosis with pH of less than 7.3 or a serum bicarbonate level of less than 18 mgEq/L; presence of ketones, ideally confirmed with direct measurement of serum ß-hydroxybutyrate level; and a near-normal blood glucose level.[8,10,18]

Table 3: Precipitating Factors for Sodium-Glucose Cotransporter-2 Inhibitor–Associated Euglycemic Diabetic Ketoacidosis

Precipitating Factors
Infection
Illness
Surgery
Trauma
Stroke
Myocardial infarction
Exogenous glucocorticoids
Dehydration/hypovolemia
Absolute or relative insulin deficiency
Very low–carbohydrate/ketogenic diets or prolonged fasting
Extreme physical activity
Alcohol or other drug use
Pregnancy

Clinical Interventions

Treatment of euDKA is similar to that of classic DKA, involving correction of dehydration and ketosis.[1,8] Because euDKA is characterized by blood glucose levels less than 250 mg/dL,[18] dextrose-containing fluids are used with intravenous insulin to prevent hypoglycemia. Insulin is necessary to suppress ketogenesis and correct the metabolic acidosis. The SGLT2 inhibitor should be discontinued, electrolytes monitored and repleted as needed, and dehydration corrected.[10] Because ketonuria is expected with the use of SGLT2 inhibitor therapy, direct measurement of ß-hydroxybutyrate in the blood is recommended.[2,3,10] Additionally, the long half-life of SGLT2 inhibitor medications, reported to be 11 to 17 hours,[7,10] may prolong the need for intravenous insulin. Some case reports indicate that the glycosuric effects of SGLT2 inhibitors can persist for 3 to 12 days after their discontinuation, which increases the risk of DKA relapse if insulin is stopped too soon.[19,20]

Clinicians should consider multiple factors when determining whether to prescribe or continue SGLT2 inhibitors. An appealing reason for prescribing agents in this drug class beyond their cardiorenal benefits is the low risk of hypoglycemia and the simplicity of once-daily dosing.[5,9] Given the reduction in serum glucose levels with use of SGLT2 inhibitors, dose reductions of other antihyperglycemic agents may be necessary, although reductions of insulin may increase euDKA risk.[3,6,7,10,21] Dose adjustments may also be warranted for any prescribed diuretics or antihypertensive medications given the osmotic diuresis caused by SGLT2 inhibitors.[11,21] Given the glycosuric effect, patients may have an increased risk of genital yeast infections, with less clear evidence of an increased risk of urinary tract infections.[22] Discontinuation of an SGLT2 inhibitor is indicated during times of infection, when use of high-dose steroids is required, 3 to 4 days before surgery or periods of fasting, and during acute management of euDKA.[3,6,10]

Discharge Planning

When developing discharge plans for inpatients who need improved glycemic management, SGLT2 inhibitors may be a good choice for patients at risk of heart failure, cardiovascular disease, and renal impairment. However, it is important to assess their hydration status, oral intake, and other risk factors that may increase risk for euDKA and hypovolemia. It is important to monitor their blood pressure, because SGLT2 inhibitors may decrease blood pressure further and cause orthostatic hypotension.[11,21] It is recommended to consider dose reductions of medications with a diuretic effect for patients at risk of hypovolemia and hypotension.[11,21] Gradual dose reduction of insulin, insulin secretagogues, or both may be necessary to avoid hypoglycemia and risk for euDKA, which has been reported with insulin

dose reductions of more than 20%.[7,10,21] Baseline glomerular filtration rate (GFR) and electrolyte levels should be measured before initiating SGLT2 inhibitors. The GFR must be greater than or equal to 20 mL/min per 1.73 m^2 to initiate SGLT2 inhibitor therapy, with US Food and Drug Administration–approved thresholds varying slightly based on the specific SGLT2 inhibitor agent and treatment indication.[11] An acute decline in estimated GFR may occur after initiation, but continuation of the SGLT2 inhibitor is recommended if tolerated because of the cardiorenal benefits; SGLT2 inhibitors should be discontinued if kidney replacement therapy or kidney transplant is needed.[11,21] After the SGLT2 inhibitor is initiated, follow-up is needed within 4 weeks to assess for hypovolemia, hypotension, acute kidney injury, and glucose-lowering effects.[11,21]

Patients who are prescribed an SGLT2 inhibitor need education about the medication's action, dose, and side effects. It is important that patients monitor for and report signs and symptoms of genital yeast infections and urinary tract infections, as well as signs and symptoms of euDKA such as nausea, vomiting, fatigue, and weakness without hyperglycemia.[3,8,21] Patients should also monitor for and report signs and symptoms of hypovolemia and hypotension such as dizziness, weight loss, and low blood pressure.[8,21] Patients should be advised to suspend any SGLT2 inhibitors 3 to 4 days before fasting for procedures or surgeries.[6,10] Patients must discuss with their clinician intentions to begin a low-carbohydrate or ketogenic diet, which could increase the risk of euDKA.[3,8]

Case Resolution

The patient returned to baseline cognitive status with the resolution of euDKA. Despite the patient stopping his SGLT2 inhibitor for the recommended 3 days before his procedure, he still developed euDKA, which was effectively treated with intravenous insulin with avoidance of hypoglycemia or DKA relapse. At discharge the dapagliflozin was discontinued, and the patient resumed glipizide 10 mg twice daily and metformin 1000 mg twice daily. In place of dapagliflozin he was started on dulaglutide 0.75 mg weekly, which also has cardiorenal benefits but requires subcutaneous injection.[5]

Conclusion

Sodium glucose cotransporter-2 inhibitors constitute an additional valuable treatment option for patients with diabetes mellitus as well as those with or at high risk for atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. However, a potential adverse effect of SGLT2 inhibitor use is risk of developing euDKA, a condition that can present with subtle symptoms and can be challenging for clinicians to recognize and diagnose.

Strategies to mitigate risk of euDKA and related complications include stopping SGLT2 inhibitor therapy at least 3 to 4 days before procedures or surgery, discontinuing an SGLT2 inhibitor if diabetic ketoacidosis is suspected, suspending these agents when patients are fasting or at risk for dehydration, and considering discontinuing them if high-dose steroids are prescribed.

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CE Evaluation Instructions

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Identify at least 3 precipitating factors for euglycemic diabetic ketoacidosis.
2. Discuss clinical effects of sodium-glucose cotransporter-2 inhibitors and expected assessments needed after prescribing.
3. Describe 2-3 strategies to mitigate risk of euglycemic diabetic ketoacidosis.

Contact hour: **1.0**
Pharmacology contact hour: **1.0**
Synergy CERP Category: **A**

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