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Case Report

Beyond Glucose Levels: Redefining Diabetic Ketoacidosis—A Case of Hypoglycemic Diabetic Ketoacidosis

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ABSTRACT

Background/Objective: Diabetic ketoacidosis (DKA) is a life-threatening condition typically diagnosed by the presence of hyperglycemia, acidemia, and ketonemia. A subset of patients may develop ketoacidosis without the traditionally increased glucose levels in a condition known as euglycemic DKA. This article describes an atypical presentation of DKA with concomitant hypoglycemia in a condition termed hypoglycemic DKA.
Case Report: A 74-year-old woman with a history of hypertension, type 2 diabetes mellitus (treated with empagliflozin), and hypothyroidism, presented from an outlying hospital due to concern for acute gallstone pancreatitis and choledocholithiasis. On arrival, laboratory evaluation revealed an anion gap of 16 mEq/L (reference range, 6-12 mEq/L), bicarbonate level of 11 mEq/L (reference range, 21-31 mEq/L), serum glucose level of 57 mg/dL (reference range, 70-105 mg/dL), beta-hydroxybutyrate level of 1.7 mmol/L (reference range, <0.6 mmol/L), and urinalysis demonstrating a ketone level of >80 mg/dL (reference range, <3.49 mg/dL). The patient was treated according to the institution DKA protocol, with resolution of her DKA.
Discussion: The case presented highlights a manifestation of DKA characterized by a concurrent state of hypoglycemia in a patient treated with a sodium-glucose cotransporter 2 inhibitor, an atypical and likely underreported phenomenon.
Conclusion: Clinicians should maintain a high level of suspicion for DKA in patients with metabolic acidosis and ketosis, irrespective of their glucose levels, in particular in those treated with sodium-glucose cotransporter 2 inhibitors. Additionally, redefining these cases as drug-induced ketoacidosis may assist in preventing delayed diagnosis and management.

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication primarily associated with type 1 diabetes mellitus and, to a lesser extent, type 2 diabetes mellitus. DKA is typically diagnosed by the presence of hyperglycemia noted by a plasma glucose level of >250 mg/dL (reference range, 70-105 mg/dL), acidemia, and ketonemia.[1] A subset of patients may develop ketoacidosis without the traditionally increased glucose levels, in a condition known as euglycemic DKA (EDKA). In this state, the plasma glucose level typically remains below 250 mg/dL. EDKA, first documented in 1973, was initially considered a rare phenomenon, primarily observed in insulin-dependent patients.[2] However, with the growing use of sodium-glucose cotransporter 2 (SGLT2) inhibitors, the incidence of EDKA has increased, bringing this condition into greater clinical focus.[3] Although both DKA and EDKA have been well documented, hypoglycemic DKA (HDKA)—a state in which ketosis occurs with concomitant hypoglycemia (plasma glucose level, <70 mg/dL), is atypical. This article presents a case of HDKA in a patient treated with an SGLT2 inhibitor.

Case Report

A 74-year-old woman with a history of hypertension, type 2 diabetes mellitus, and hypothyroidism presented to an outlying

Abbreviations: DKA, diabetic ketoacidosis; EDKA, euglycemic diabetic ketoacidosis; HDKA, hypoglycemic diabetic ketoacidosis; SGLT2, sodium-glucose cotransporter 2.

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hospital with epigastric pain and vomiting. Home medications for glycemic control included empagliflozin 25 mg daily, glipizide 5 mg twice daily, and linagliptin-metformin 2.5 to 1000 mg twice daily. She was diagnosed with acute pancreatitis, evidenced by computed tomography of the abdomen, increased serum lipase level, and supporting symptomatology. Right upper quadrant ultrasound revealed gallstones, and due to concerns of acute gallstone pancreatitis as well as choledocholithiasis, she was transferred to our institution for further management that included an evaluation for endoscopic retrograde cholangiopancreatography. Upon arrival, the patient's laboratory values revealed an anion gap of 16 mEq/L (reference range. 6-12 mEq/L), bicarbonate level of 11 mEq/L (reference range, 21-31 mEq/L), serum glucose level of 57 mg/dL, and beta-hydroxybutyrate level of 1.7 mmol/L (reference range, <0.6 mmol/L). Urinalysis demonstrated a ketone level of >80 mg/dL (reference range, <3.49 mg/dL). The patient received 250 mL of 10% dextrose with repeat laboratory examinations demonstrating an anion gap of 17 mEq/L, bicarbonate level of 11 mEq/L, beta-hydroxybutyrate level increasing to 5.7 mmol/L, and plasma glucose level increasing to 211 mg/dL. A venous blood gas test was performed and showed a pH of 7.15 (reference range, 7.35-7.45) (Table). Due to concern for DKA, the patient was transferred to the intensive care unit and treated with an insulin infusion according to the institution DKA protocol, accompanied by concomitant dextrose infusion to maintain normoglycemia. Subsequently, the patient's DKA resolved, and she was transitioned from the insulin infusion to a basal and short-acting insulin regimen. The patient later underwent a cholecystectomy for gallstones and endoscopic retrograde cholangiopancreatography with biliary sphincterotomy and balloon extraction due to confirmed choledocholithiasis. The Endocrinology Consult Service was consulted for long-term treatment recommendations and assisted with inpatient guidance and glucose management. Upon discharge, antidiabetic regimen included metformin 1000 mg twice daily, glipizide 10 mg daily, and 8 units of insulin glargine daily. Both empagliflozin and linagliptin were discontinued indefinitely due to the occurrence of DKA as well as pancreatitis.

Discussion

The case presented highlights a manifestation of DKA characterized by concurrent hypoglycemia. Traditionally, DKA has been defined by the classic triad of hyperglycemia (plasma glucose level, 250 mg/dL), metabolic acidosis (blood pH level of <7.3 or serum bicarbonate level of <18 mEq/L), and ketonemia. It was thought to result from either absolute or relative insulin deficiency leading to decreased glucose uptake in insulin-dependent tissues, increase in the counterregulatory hormone levels, lipolysis, and, in turn, increase in free fatty acid levels.[4]

Highlights

- Hypoglycemic diabetic ketoacidosis (HDKA) is a condition characterized by metabolic acidosis and ketosis with concomitant hypoglycemia
- The use of sodium-glucose cotransporter 2 inhibitors is likely to increase the prevalence of diabetic ketoacidosis (DKA), euglycemic DKA, and HDKA
- Clinicians should maintain a high level of suspicion for DKA in patients with metabolic acidosis and ketosis, irrespective of their glucose levels
- Shifting away from the current terminology of DKA and toward a more inclusive drug-induced ketoacidosis may assist in preventing delayed diagnosis and management

Clinical Relevance

A 74-year-old woman with a history of type 2 diabetes mellitus treated with a sodium-glucose cotransporter 2 (SGLT2) inhibitor presented with laboratory-evidenced diabetic ketoacidosis (DKA) and concomitant hypoglycemia. A need for a shift in DKA terminology and definition, especially in those treated with SGLT2 inhibitors is discussed.

In 1973, Munro et al[2] identified a subset of DKA in which the plasma glucose levels, previously thought required to be increased, were reduced to normal or near-normal ranges. This condition was termed EDKA. Although EDKA was initially regarded as a rare occurrence among insulin-dependent diabetics, the widespread use of SGLT2 inhibitors has led to a notable increase in its prevalence. This increase in EDKA prevalence could potentially be attributed to a pathophysiologic difference in those treated with SGLT2 inhibitors. In these cases, SGLT2 inhibition leads to excretion of glucose in the urine, reducing the plasma glucose level, and therefore, a reduced plasma glucose level is expected. Additionally, SGLT2 inhibitors have been shown to result in increased plasma glucagon levels thought to be due to pancreatic alpha cell SGLT2 expression.[5] The increase in glucagon levels compared with those of insulin may result in lipolysis due to a decrease in antiloplytic effects of insulin and increase in lipase stimulation as well as hepatic beta-oxidation of free fatty acids by glucagon.[6] Furthermore, SGLT2 inhibitors may reduce renal clearance of ketones, resulting in a further increase in circulating ketonemia (Fig.)—each contributing to a state of ketosis in the setting of a reduced plasma glucose level.

Although both DKA and EDKA have been well documented in the literature, this article demonstrates a unique presentation of

Table
Laboratory Data on Presentation and Post–Dextrose Administration

	Admission	After dextrose administration	Reference range
Venous blood glucose	57 mg/dL	211 mg/dL	70-105 mg/dL
β-Hydroxybutyrate	17.7 mg/dL	59.7 mg/dL	<6.25 mg/dL
Anion gap	16 mEq/L	17 mEq/L	6-12 mEq/L
HCO_3	11 mEq/L	11 mEq/L	21-31 mEq/L
Potassium	4.5 mEq/L	4.7 mEq/L	3.5-5 mEq/L
Lactate	9.01 mg/dL	Not obtained	4.5-19.8 mg/dL
Urinary glucose	>500 mg/dL	Not obtained	<15 mg/dL
Urinary ketones	>80 mg/dL	Not obtained	<3.49 mg/dL
HbA_{1c} (%)	7.6%	Not obtained	<5.9%

Abbreviations: HbA_{1c} = hemoglobin A1c; HCO_3 = bicarbonate.

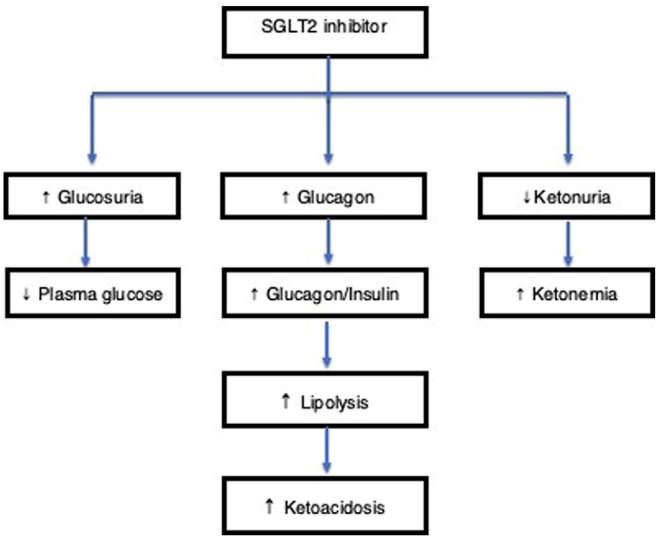

Fig. Hypothesis of sodium-glucose cotransporter 2 (SGLT2) inhibitor–induced hypoglycemic diabetic ketoacidosis.

ketosis and metabolic acidosis despite a decreased blood glucose level to a hypoglycemic range. Given the hypothesis behind the pathophysiology leading to DKA in patients treated with SGLT2 inhibitors and the well-documented EDKA in this population, cases of HDKA are a reasonable sequela and potentially a manifested continuation of the EDKA timeline.

Furthermore, DKA has also been reported in nondiabetic patients.[7] Notably, in a case described by Hayes et al,[7] a nondiabetic patient treated with an SGLT2 inhibitor initially presented with hypoglycemia, evidenced by a plasma glucose level of 41 mg/dL. It is plausible that these cases are more prevalent than thought yet underreported or underrecognized due to their nontraditional presentation.

This case of HDKA prompts a reconsideration of the diagnostic criteria and terminology of DKA, traditionally tied to hyperglycemia, later expanding to euglycemic states and now to hypoglycemia. Given the aforementioned, ketosis and acidosis should prompt suspicion regardless of glucose level especially in those treated with SGLT2 inhibitors. Additionally, with SGLT2 inhibitor use prevalence expanding to patients beyond those necessitating glycemic control, in conditions such as heart failure, an increase in the prevalence of DKA is expected. In these cases of nondiabetic patients, if DKA were to occur, EDKA or HDKA would be the more likely presentation. Therefore, moving away from the current terminology of DKA and toward drug-induced ketoacidosis may assist in preventing delayed diagnosis and management of this population.

It is important to acknowledge that in the presented case, the patient's home medications included a sulfonylurea, which could have contributed to the observed hypoglycemia at presentation, yet the timing of the last dose administration was unknown. It is also reasonable to consider that hypoglycemia could have been exacerbated by prolonged starvation associated with the patient's gallstone pancreatitis. Finally, although the timeline of empagliflozin administration is also unclear, the high urinary glucose level observed despite the low plasma glucose level is consistent with the action of SGLT2 inhibitor and support its activity.

In conclusion, this case underscores the importance of vigilance in recognizing atypical presentations of DKA, such as HDKA in clinical practice. With the increasing use of SGLT2 inhibitors, expanding to nondiabetic patients, clinicians should be alert to the possibility of DKA in individuals presenting with metabolic acidosis and ketosis, regardless of their glucose levels. To better reflect these increasing presentations, it may be time to reconsider our terminology. Shifting from a diabetic-centric definition of ketoacidosis to one that incorporates drug-induced ketoacidosis could provide greater clarity and potentially improve patient care.

Disclosure

The author has no conflicts of interest to disclose.

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