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Case Report

Euglycemic Ketoacidosis Following Coadministration of an SGLT2 Inhibitor and Tirzepatide

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Abstract

Euglycemic ketoacidosis (EKA) is a life-threatening condition characterized by ketone production leading to systemic acidosis, dehydration, and end-organ damage. It presents similarly to diabetic ketoacidosis, except that patients have normal to slightly elevated blood glucose levels. EKA is an increasingly recognized complication of sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Recently the novel dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide was approved for treatment of diabetes and weight loss. Here, we describe a unique case in which a patient placed on both an SGLT2 inhibitor and tirzepatide to treat type 2 diabetes was admitted to the intensive care unit (ICU) for EKA. To our knowledge, this is the first case detailing a patient developing this serious condition after starting tirzepatide for diabetes. The patient required treatment and monitoring in an ICU to make a full recovery. As tirzepatide is a relatively new medication whose side effect profile has yet to be fully characterized, clinicians should be aware of this rare yet potentially fatal complication.

Key Words: tirzepatide, diabetes, euglycemic ketoacidosis, diabetic ketoacidosis

Abbreviations: AG, anion gap; BMI, body mass index; DKA, diabetic ketoacidosis; ED, emergency department; EKA, euglycemic ketoacidosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA_{1c}, hemoglobin A_{1c}; ICU, intensive care unit; SGLT2, sodium-glucose cotransporter 2; UA, urine analysis; WBC, white blood cell count.

Introduction

Diabetic ketoacidosis (DKA) is a well-known, life-threatening complication of type 1 and type 2 diabetes mellitus, classically characterized by severe hyperglycemia and ketone body production leading to systemic acidosis, dehydration, and end-organ damage. DKA often occurs in the setting of insulin deficiency, particularly with new diagnoses of type 1 diabetes and with poor compliance in patients with insulin-dependent type 2 diabetes. Euglycemic ketoacidosis (EKA) is a variant of DKA in which patients present with the symptoms of DKA yet have blood sugars less than 250 mg/dL and often less than 100 mg/dL [1, 2]. In recent decades, several new classes of hypoglycemic agents have come to market, including sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, empagliflozin, dapagliflozin) and glucagon-like peptide-1 (GLP-1) receptor agonists (eg, semaglutide, liraglutide). Although SGLT2 inhibitors appear to have a higher risk of inducing DKA than GLP-1 receptor agonists or the older dipeptidyl peptidase 4 (DPP-4) inhibitors or sulfonylureas, they all carry a theoretical risk of inducing EKA [3-5].

Tirzepatide is a novel agonist of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. It was Food and Drug Administration–approved in 2022 for treatment of type 2 diabetes and in 2023 for weight loss [6]. Similar to SGLT2 inhibitors, tirzepatide's side effects are primarily gastrointestinal, but it is unclear if tirzepatide also carries a clinically significant risk of inducing EKA. To our knowledge, as of January 2025 this is the first case detailing EKA in the setting of tirzepatide prescribed for type 2 diabetes; the other cases describe EKA/DKA in nondiabetic patients prescribed tirzepatide for weight loss [7-9]. Here, we present a case of a young patient with diabetes admitted for EKA following coadministration of empagliflozin (an SGLT2 inhibitor) and tirzepatide, the novel agonist of both GLP-1 and GIP receptors. With the recent approval of tirzepatide and increasingly common prescription of SGLT2 inhibitors [10], this case highlights a serious side effect that must be considered when prescribing diabetes and weight loss medications, particularly those with synergistic effects on metabolism.

Case Presentation

The patient was a 35-year-old man with past medical history of type 2 diabetes mellitus (not on insulin), hypertension, hyperlipidemia, and hypogonadism on testosterone therapy. His diabetes regimen initially included glipizide 5 mg twice daily and empagliflozin 25 mg daily without any apparent medication-induced side effects. Five weeks before admission, his glycated hemoglobin A_{1c} (HbA_{1c}) was 7.7% (reference range, ≤5.7%), and his glipizide was discontinued and replaced with injections of tirzepatide 2.5 mg weekly. His endocrinologist specifically noted that glipizide was changed to

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tirzepatide because it would have synergistic effects with the SGLT2 inhibitor and improve glycemic control. After this switch, the patient began to experience intermittent episodes of decreased appetite, nausea, and nonbloody emesis accompanied by poor oral intake and fewer bowel movements.

The patient was seen twice in the emergency department (ED) before his admission to the intensive care unit (ICU). The night before his initial presentation, he began to experience vomiting episodes every 30 to 60 minutes with associated chills and reflux, partially improved with over-the-counter antacids. His symptoms persisted through the night, and early the next morning he presented to the ED with stable vitals and normal blood glucose levels. His urine analysis (UA) demonstrated glucosuria and ketonuria, but he was treated with 2-L normal saline and ondansetron, then discharged home with a reported diagnosis of dehydration secondary to nausea and vomiting. His vomiting worsened throughout the day, and he returned to the ED with tachycardia, hypoxia, and severe malaise. On physical examination, the patient was uncomfortable-appearing, fatigued, tachycardic, mildly dyspneic, and had epigastric tenderness; the remaining physical examination was unremarkable.

Diagnostic Assessment

Laboratory results from initial presentation, admission, hospital stay, and follow-up appointment are shown in Table 1. The patient initially presented with a body mass index (BMI) of 20.7 kg/m^2. Notable laboratory studies included white blood cell count (WBC) 8800 cells/μL (reference range, 4500-11 000 cells/μL), serum bicarbonate 17.8 mmol/L (17.8 mEq/L) (reference range, 22.0-32.0 mmol/L; 22.0-32.0 mEq/L), anion gap (AG) 21 mmol/L (21 mEq/L) (reference range, 4-12 mmol/L; 4-12 mEq/L), and blood glucose 89 mg/dL (4.9 mmol/L) (reference range, 70-106 mg/dL; 3.9-5.9 mmol/L). UA showed glucose greater than 1000 mg/dL (>55.5 mmol/L) (reference range, ≤15 mg/dL; ≤0.8 mmol/L) and acetoacetate (ketone) levels greater than 160 mg/dL (>15.7 mmol/L) (reference range, absent). Complete blood count, serum sodium, serum calcium, serum potassium, and lipase levels were within normal limits. Except for weight loss, our patient displayed no other clinical signs or laboratory values suggesting adrenal insufficiency, which may have masked hyperglycemia.

Our patient returned to the ED 8 hours after initial discharge with heart rate 130 beats per minute (reference range, 60-100 beats per minute), oxygen saturation 90% (reference range, ≥95%), WBC 11 200 cells/μL, serum bicarbonate 12.3 mmol/L (12.3 mEq/L), AG 24 mmol/L (24 mEq/L), blood glucose 72 mg/dL (4.0 mmol/L), and HbA_{1c} 6.9%. UA showed glucose concentration 500 mg/dL (27.8 mmol/L) and acetoacetate greater than 160 mg/dL (>15.7 mmol/L). A venous blood gas demonstrated acidosis with a pH 7.17, and repeat laboratory tests several hours later showed severe metabolic acidosis with serum bicarbonate 8.2 mmol/L (8.2 mEq/L).

Treatment

The patient was admitted to the ICU for standard treatment of ketoacidosis. For fluid resuscitation, in total the patient received 2000-mL normal saline, 1000-mL dextrose 5% in water (D5W) with 150-mEq sodium bicarbonate, and 4000-mL D5W with 20-mEq potassium chloride. An additional 40-mEq potassium chloride was given intravenously.

Outcome and Follow-up

Our patient's AG closed within 24 hours of treatment (see Table 1). He had 1 blood glucose reading of 186 mg/dL after starting D5W, but all other readings were less than 135 mg/dL. He was discharged home 2 days after admission on a regimen of metformin 500 mg daily and extended-release glipizide 5 mg daily; both tirzepatide and empagliflozin were discontinued. At a follow-up appointment 2 days later with his primary care provider, the patient's most concerning abnormalities had resolved.

Discussion

Here we present a unique case of EKA following coadministration of an SLGT2 inhibitor and tirzepatide. We suspect these agents had synergistic effects in our patient, leading to adequate control of his blood sugars yet a state of starvation, ketone production, and resultant systemic acidification. The development of SGLT2 inhibitors, GLP-1 receptor agonists, and the dual GLP-1/GIP receptor agonist, tirzepatide, has radically changed the fields of diabetes management and weight loss. GLP-1 and GIP are incretins, gut-derived hormones released in response to ingestion of carbohydrates and fats that aid in the release of and response to insulin. Activation of their receptors may increase insulin sensitivity, improve satiety, and reduce triglyceride levels [11]. In a growing number of randomized, controlled phase 3 trials, tirzepatide has shown great promise in diabetes treatment, with substantial reductions in HbA_{1c} and fasting serum glucose levels [12-17], as well as for weight loss as monotherapy or combined with other agents [16-18]. In these large-scale trials, tirzepatide demonstrated a favorable side-effect profile, with primarily gastrointestinal effects. However, we present the first detailed case of EKA after starting tirzepatide to treat type 2 diabetes.

As mentioned in the introduction, the other cases of patients developing EKA after initiation of tirzepatide were all patients who were female, with a BMI greater than 25, and prescribed tirzepatide specifically for weight loss [7-9]. Comparing cases, our patient was notably of the male sex and had a BMI within normal limits, 18.5 to 24.9 kg/m^2. Additional cases are needed to determine if the variables of sex and BMI play clinically significant roles. In our case, the authors find it important to again emphasize that tirzepatide was prescribed alongside an SGLT2 inhibitor with the intention of tighter glycemic control rather than weight loss.

In the international SURPASS-3 trial, participants were treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months, then treated with injections of weekly tirzepatide (of various doses) or daily insulin degludec [14]. Of the 1444 participants assigned to treatment groups, 342 were on a combination of tirzepatide, metformin, and an SGLT2 inhibitor, like our patient who was on an SGLT2 inhibitor and tirzepatide. However, in this greater than 52-week-long trial there were no reported cases of ketoacidosis [14]. In the SURPASS J-combo trial in Japan, tirzepatide was studied as an add-on medication for patients taking a single antihyperglycemic medication, including SGLT2 inhibitors [17]. Of the 443 participants in the SURPASS J-combo trial who received tirzepatide, there were no reported cases

Table 1. Diagnostics at initial presentation to emergency department, admission (evening of day 0), hospital days 1 and 2, and follow-up clinic appointment (day 4)

Variable	Day 0, morning (initial presentation)	Day 0, evening (admission)	Day 1, morning (hospital ICU)	Day 2, morning (hospital discharge)	Day 4 (follow-up)	Reference range
Anion gap	**21 mmol/L (21 mEq/L)**	**24 mmol/L (24 mEq/L)**	**19 mmol/L (19 mEq/L)**	11 mmol/L (11 mEq/L)	9 mmol/L (9 mEq/L)	4-12 mmol/L (4-12 mEq/L)
Blood glucose	89 mg/dL (4.9 mmol/L)	72 mg/dL (4.0 mmol/L)	104 mg/dL (5.8 mmol/L)	**113 mg/dL (6.3 mmol/L)**	**113 mg/dL (6.3 mmol/L)**	74-106 mg/dL (3.9-5.9 mmol/L)
Serum bicarbonate	**17.8 mmol/L (17.8 mEq/L)**	**12.3 mmol/L (12.3 mEq/L); on repeat 8.2 mmol/L (8.2 mEq/L)**	**15.3 mmol/L (15.3 mEq/L)**	22.7 mmol/L (22.7 mEq/L)	30.9 mmol/L (30.9 mEq/L)	21.0-32.0 mmol/L (21.0-32.0 mEq/L)
pH	N/A	**7.17** (venous)	**7.27** (arterial)	N/A	N/A	7.35-7.45
BMI	20.7 kg/m^2	20.8 kg/m^2	N/A	N/A	21.0 kg/m^2	18.5-25 kg/m^2
Urine acetoacetate	**>160 mg/dL (>15.7 mmol/L)**	**>160 mg/dL (>15.7 mmol/L)**	N/A	N/A	N/A	0 mg/dL (0 mmol/L)
HbA_{1c}	**6.9%**	N/A	N/A	N/A	**6.9%**	<5.7%
WBC	8.8 cells/μL	**11.2 cells/μL**	**12.1 cells/μL**	5.4 cells/μL	5.8 cells/μL	4500-10 500 cells/μL

Abnormal values are shown in bold.
Abbreviations: BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; ICU, intensive care unit; N/A, not available; WBC, white blood cell count.

of ketoacidosis, including in the 63 who were on tirzepatide and an SGLT2 inhibitor. Collectively, these studies demonstrate that EKA is a rare side effect, but with a combined 405 patients taking both tirzepatide and an SGLT2 inhibitor, they do not provide a large enough sample size to rule out synergistic combination as a contributing factor to EKA in our patient [14, 17]. Further studies examining EKA in patients taking tirzepatide as monotherapy or in combination with other diabetes agents are needed to determine absolute risks.

In conclusion, mounting data demonstrate high efficacy and a favorable side-effect profile for tirzepatide both in diabetes treatment and weight loss. However, rare yet serious side effects must be considered. This case demonstrates one such side effect, EKA, which may have fatal consequences if unrecognized and untreated. As prescriptions for tirzepatide increase, the absolute risks for EKA and its potential risk factors, such as combinations with other medications, will be established.

Learning Points

- SGLT2 inhibitors, GLP-1 agonists, and the novel GLP-1/GIP dual-agonist tirzepatide carry a rare but serious risk of inducing EKA.
- Combining these agents may have a synergistic effect that increases the risk for EKA.
- Patient comorbidities, weight/body composition, sex, and other medications may have considerable effects on the side-effect profile of tirzepatide.

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Contributors

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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