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Empagliflozin-Induced Euglycemic Diabetic Ketoacidosis: A Case Report

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Abstract This study reports a case of a 63-year-old female patient who developed euglycemic diabetic ketoacidosis (euDKA) within 24 h adding Empagliflozin. Upon admission, the patient's fasting blood glucose was 14.7 mmol/L and glycated hemoglobin (HbA1c) was 7.9%. She had been using insulin combined with repaglinide for long-term blood glucose control. On the next day after initiating Empagliflozin, persistent positive urine ketones were detected, with blood glucose fluctuating between 7.8 - 14.7 mmol/L. Serum bicarbonate was normal (32.0 mmol/L), and there were no typical symptoms of acidosis. After discontinuing Empagliflozin, receiving intravenous fluid rehydration, and low-dose insulin therapy, urine ketones gradually turned negative. This case suggests that in clinical practice, it is necessary to achieve a precise balance between cardiovascular benefits and metabolic risks, adhering to the principle of individualized medication.

Key words Empagliflozin, Euglycemic diabetic ketoacidosis (euDKA), Cardiovascular diseases

1 Introduction

SGLT-2i is a novel class of glucose-lowering drugs, possessing advantages in improving lipid metabolism, lowering blood pressure, protecting cardiovascular function, and inhibiting inflammation and fibrosis, with close interconnections among these beneficial factors. By inhibiting renal glucose reabsorption, it significantly reduces glycated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus (T2DM) and demonstrates breakthrough progress in the fields of cardiovascular and renal protection. Empagliflozin is one type of SGLT-2i. Multiple large-scale randomized controlled trials (RCTs) have confirmed that Empagliflozin, dapagliflozin, and others can reduce the risk of major adverse cardiovascular events (MACE) and heart failure (HF) hospitalization in T2DM patients with atherosclerotic cardiovascular disease (ASCVD). The ADA Guidelines (2023) recommend it as a first-line medication for patients with ASCVD or high-risk factors. Furthermore, SGLT-2i shows significant efficacy for both heart failure (HFrEF and HFpEF) and chronic kidney disease (CKD), reducing the risk of heart failure worsening and the incidence of end-stage kidney disease (ESKD). Diabetic ketoacidosis is a rare but serious adverse reaction, especially euglycemic DKA, which is easily missed; this case focuses on a situation of diabetic ketoacidosis triggered by the use of Empagliflozin, conducting a comprehensive review and analysis, aiming to broaden clinicians' diagnostic and therapeutic approaches for such conditions and assist them in accurately identifying such cases.

2 Clinical data and examination

Patient: Female, 63 years old, with comorbid type 2 diabetes mellitus and peripheral neuropathy.

Chief complaints: Recurrent chest tightness for over 4 years, recurrence accompanied by dizziness for 1 week.

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Presenting symptoms: Chest tightness, intermittent episodes lasting approximately several minutes each, relieved after rest; accompanied by dizziness. Headache, chest pain, and palpitations are noticeable upon waking and positional changes. No orthopnea, cough, sputum production, or nocturnal dyspnea. Normal mental status, appetite, and sleep. Normal bowel and bladder function. No significant weight change since illness onset.

Pre-onset medication: Repaglinide Tablets 2 mg orally once daily, combined with Glargine Insulin Injection 8U subcutaneously at bedtime for blood glucose control.

Past history and personal history: History of "chronic bronchitis" for over 10 years. Denies history of "hypertension, kidney disease," *etc.* Elder brother has history of hypertension. Denies other family genetic disease history.

Physical examination: T 36.6 ℃, P 77 bpm, R 20 bpm, BP 123/65 mmHg. Clear breath sounds in both lungs, no significant dry or moist rales detected. Cardiac borders not enlarged. Heart rate 77 bpm, rhythm regular. No significant murmurs heard over cardiac valve auscultation areas.

Neurological examination: Bilateral Achilles tendon and patellar reflexes diminished. Slight reduction in temperature, pain, and touch sensation. Other physiological reflexes present. No pathological reflexes elicited.

Ancillary examination: Fasting blood glucose: 14.7 mmol/L. Electrocardiogram: Sinus rhythm (mean ventricular rate 77 bpm), left axis deviation. Cardiac markers show no significant abnormalities. Lipid profile: Total cholesterol 7.53 mmol/L, Triglycerides 3.24 mmol/L, LDL-cholesterol 4.38 mmol/L. Serum bicarbonate 32.0 mmol/L. Glycated hemoglobin (HbA1c) on January 9, 2025: 7.90% ↑. Thyroid function and coagulation tests show no significant abnormalities. Cardiac ultrasound on January 9, 2025: Mild mitral and tricuspid valve regurgitation.

Admission diagnosis: Chest tightness (etiology to be determined); type 2 diabetes mellitus with peripheral neuropathy; chronic bronchitis in clinical remission; hyperlipidemia; right subclavian artery plaque.

Clinical course and outcome: The patient was admitted primarily with chest tightness and has a history of diabetes. Given the current presence of dyslipidemia and a high risk of cardiovascular diseases such as coronary heart disease, atorvastatin calcium tablets were added orally to regulate lipids and stabilize plaques, aluminum magnesium aspirin tablets were administered orally for antiplatelet aggregation as primary prevention for coronary heart disease, and hyzetimibe tablets were given orally to lower blood lipids. Coronary angiography was planned. Since fasting blood glucose and glycated hemoglobin (HbA1c) were both elevated, Empagliflozin tablets were added for oral blood glucose control. Treatment with repaglinide tablets orally combined with subcutaneous injection of insulin glargine (8 units) at bedtime was continued for glycemic control.

On January 10, 2025, at 09:29, the patient's urinalysis showed: Ketones 4 +, Glucose 4 + mmol/L; Fingerstick blood glucose was 7.8 mmol/L. Considering possible laboratory error, the test was repeated. At 15 : 52 on January 10, urinalysis showed: Ketones 3 +, Glucose 4 + mmol/L. Fluid replacement and a low-dose insulin intravenous drip were administered to correct ketosis. By 22 : 50 on January 10, ketones had decreased to weakly positive. Repeat urinalysis on January 11 showed: Ketones 2 +, Glucose 4 + mmol/L. Ketones had increased again, so fluid replacement and low-dose insulin intravenous drip therapy were continued, after which ketones returned to weakly positive. Repeat urinalysis on January 12 showed: Ketones 3 +, Glucose 4 + mmol/L. This was considered likely Empagliflozin-associated diabetic ketosis. The patient was instructed to discontinue Empagliflozin. With continued fluid replacement and ketosis correction therapy, the patient's ketosis did not recur. Follow-up urinalysis in the outpatient clinic on January 21, 2025, remained negative.

Table 1 Changes of urine ketone in patients

Examination date	Examination time	Urine ketone
2025 -01 -10	9 : 29	4
	15 : 52	3
	22 : 50	0.5
2025 -01 -11	14 : 53	2
	18 : 57	0.5
2025 -01 -12	12 : 51	3
	21 : 21	3
2025 -01 -13	9 : 14	3
2025 -01 -15	8 : 54	0

3 Clinical risk and mechanism of DKA and SGLT2 inhibitor

3.1 Clinical features and diagnostic challenges of DKA Diabetic ketoacidosis (DKA) is a serious acute complication of diabetes, but its early manifestations (such as gastrointestinal symptoms like nausea, vomiting, and abdominal pain) are easily misdiagnosed or overlooked. Without timely intervention, patients can rapidly progress to impaired consciousness, shock, or even death. Notably, the use of SGLT2 inhibitors (such as Empagliflozin) may trigger euglycemic diabetic ketoacidosis (euDKA), where ketosis occurs with normal or only mildly elevated blood glucose levels, leading to difficulties in clinical recognition. The patient described in this article represents such a case, DKA developed just one day after adding Empagliflozin to the existing regimen of insulin combined with repaglinide for suboptimal glycemic control. Due to limited testing capabilities, ketosis in this case was only indirectly assessed through qualitative urine ketone testing (which is susceptible to interference by renal function, specimen transit time, and sulfhydryl-containing drugs), while the more accurate blood ketone (β-hydroxybutyrate) test could not be performed, potentially affecting the assessment of the condition.

3.2 Potential mechanism of DKA induced by SGLT2 inhibitor

3.2.1 Metabolic pathway imbalance. Empagliflozin, while lowering blood glucose, induces a series of metabolic changes. As blood glucose gradually decreases, the body initiates corresponding feedback regulation, causing insulin secretion to progressively diminish. Insulin is a crucial hormone regulating body metabolism; a reduction in its secretion disrupts metabolic balance. The ratio of glucagon to insulin increases, and elevated glucagon activates gluconeogenesis. The liver converts non-carbohydrate substances (such as amino acids and glycerol) into glucose to maintain blood glucose levels. Additionally, it promotes the oxidation of fatty acids. Fatty acids undergo oxidation in the liver to generate acetyl-CoA. When the production of acetyl-CoA exceeds the metabolic capacity of the tricarboxylic acid (TCA) cycle, it is extensively converted into ketone bodies, including acetoacetate, β-hydroxybutyrate, and acetone. This ultimately leads to ketonemia and ketonuria, thereby progressing to diabetic ketoacidosis.

3.2.2 Transformation of energy metabolism pattern. Under normal circumstance, glucose is preferentially used by the body as an energy source. After the use of Empagliflozin, because a large amount of glucose is excreted from the urine, the body's available glucose decreases, which promotes the increase of fat mobilization, and fat decomposition produces fatty acids for energy supply. This shift in the pattern of energy metabolism enhances fat metabolism and increases ketone body production. In addition, it has been suggested that SGLT2 inhibitors may interfere with the normal regulation of intracellular energy metabolism by affecting mitochondrial function, further promoting ketone body production.

3.3 Clinical risk factors and management strategies In clinical practice, multiple factors may increase the risk of Empagliflozin-induced euDKA. If the patient has relative insulin deficiency, or is in a state of stress, such as infection, surgery, trauma, *etc.*, these conditions will increase the body's demand for insulin, while Empagliflozin reduces blood sugar while inhibiting insulin secretion, exacerbating the state of relative insulin deficiency, thus inducing ketosis. In addition, changes in dietary struc-

ture, such as excessive restriction of carbohydrate intake, can also make the body more dependent on fat metabolism for energy, increasing the risk of ketosis.

3.4 Case inspiration This case resolved with timely intervention, but it underscores the need for clinicians to remain vigilant regarding the risk of SGLT2 inhibitor-associated euDKA, particularly in patients receiving concomitant insulin therapy or with metabolic instability. Optimizing monitoring methods (*e.g.*, dynamic blood ketone testing) and implementing individualized medication strategies are crucial for mitigating this risk.

4 Conclusions

This case report details the clinical presentation and management process of Empagliflozin-induced euglycemic diabetic ketosis. Analysis reveals that although Empagliflozin effectively controls blood glucose, the mechanism by which it triggers euglycemic DKA is complex. It primarily involves metabolic imbalance caused by reduced insulin secretion, as well as a shift in energy metabolism patterns that enhances fat metabolism and increases ketone body production. In clinical practice, multiple factors increase the risk of this adverse reaction. For clinicians, when using Empagliflozin to treat diabetic patients, high vigilance for the occurrence of euglycemic DKA is necessary. A detailed patient history should be obtained, and insulin secretion status and potential stress factors should be assessed. For patients with relative insulin deficiency or those in a stressed state, medication should be used with caution and close monitoring is required. Simultaneously, patient health education should be strengthened, informing them of the importance of a reasonable diet and advising against excessive restriction of carbohydrate intake. During treatment, patient indicators such as blood glucose, blood ketones, urine ketones, and blood gas analysis should be closely monitored. Once signs of ketosis are detected, prompt measures should be taken, such as adjusting medication dosage, supplementing insulin, correcting fluid and electrolyte imbalances, *etc.*, to reduce the risk of severe complications and ensure safe and effective medication use for the patient.

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