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Case Report

A Novel Presentation of Euglycemic Diabetic Ketoacidosis Associated with SGLT2 Inhibitor and Weekly GLP-1 Agonist: Case Report

Young Sang Lyu

Department of Endocrinology and Metabolism, Chosun University Hospital, Chosun University School of Medicine, Gwangju, Republic of Korea; lyu0923@naver.com

Abstract

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are widely used in managing type 2 diabetes mellitus (T2DM) due to their glucose-lowering and cardioprotective effects. However, euglycemic diabetic ketoacidosis (euDKA) is an uncommon but serious adverse event. EuDKA is characterized by metabolic acidosis and ketosis with only mild to moderate hyperglycemia, making diagnosis challenging. Risk may be elevated with concurrent use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), especially during reduced caloric intake or gastrointestinal symptoms. **Case:** A 38-year-old woman with newly diagnosed T2DM presented with five days of fatigue, poor oral intake, nausea, and vomiting. She had recently initiated semaglutide (GLP-1RA) for weight loss and was practicing prolonged intermittent fasting. One week prior, she was started on metformin and enavogliflozin, a selective SGLT2 inhibitor. Laboratory results showed glucose 137 mg/dL, urine ketones (+++), lactate 4.87 mg/dL, HbA1c 9.3%, C-peptide 0.88 ng/mL, and high anion gap metabolic acidosis. She was diagnosed with euDKA and treated with IV fluids, insulin infusion, dextrose, and potassium supplementation. Her symptoms resolved, and she was discharged in stable condition. **Conclusion:** This case emphasizes the importance of recognizing euDKA in patients using SGLT2 inhibitors and GLP-1RAs, particularly with fasting or gastrointestinal symptoms. Clinicians should suspect euDKA even without significant hyperglycemia, enabling prompt diagnosis and appropriate management to prevent complications.

Keywords: euglycemic diabetic ketoacidosis; SGLT2 inhibitor; GLP-1 receptor agonist

1. Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a cornerstone in the management of type 2 diabetes mellitus (T2DM), offering significant benefits beyond glycemic control, including reductions in body weight and improvements in cardiovascular and renal outcomes [1–4]. Consequently, their use has expanded rapidly in clinical practice, not only for glycemic control but also for cardiometabolic risk mitigation. Despite these advantages, SGLT2 inhibitors have been associated with a unique spectrum of adverse metabolic effects, among which euglycemic diabetic ketoacidosis (euDKA) is of particular concern[5–7].

EuDKA is a rare but serious complication of diabetes characterized by the triad of high anion gap metabolic acidosis, ketonemia, and only mild to moderate hyperglycemia, often defined as a serum glucose level <250 mg/dL[8]. This atypical biochemical presentation can delay diagnosis and treatment, especially in patients with non-specific symptoms such as nausea, vomiting, or fatigue. The pathogenesis of SGLT2 inhibitor-associated DKA involves multiple mechanisms, including reduced insulin secretion due to glycosuria-induced normoglycemia, elevated glucagon levels, enhanced lipolysis, and increased hepatic ketogenesis[7,9–11]. In contrast to classic DKA, euDKA lacks the pronounced hyperglycemia that often prompts urgent evaluation and treatment, making clinical suspicion critical.

Further complicating the clinical picture is the increasing use of combination therapies, particularly with glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide. These agents, while beneficial for weight loss and glycemic control, frequently cause gastrointestinal side effects such as anorexia, nausea, and vomiting, which can lead to reduced caloric intake, dehydration, and catabolic stress—all recognized precipitating factors for DKA[12,13]. Additionally, GLP-1RAs delay gastric emptying and can suppress insulin secretion, further enhancing the ketotic milieu in susceptible individuals.

Recent reports have highlighted an increased risk of euDKA with concurrent use of SGLT2 inhibitors and GLP-1RAs, especially in patients engaging in low-calorie diets, intermittent fasting, or undergoing periods of physiological stress[14]. However, awareness of this risk remains limited, and early symptoms of DKA may be misattributed to known side effects of GLP-1RA therapy, potentially resulting in diagnostic delays.

In this report, we present a case of euDKA in a previously healthy woman with newly diagnosed T2DM, who developed severe metabolic acidosis shortly after initiating semaglutide and enavogliflozin, in the setting of prolonged intermittent fasting. This case underscores the need for heightened clinical awareness, early recognition of atypical DKA presentations, and careful patient education when prescribing these agents in combination.

2. Case Presentation

A 38-year-old woman (height 165 cm, weight 70 kg, BMI 25.7 kg/m²) presented to our tertiary hospital with a 5-day history of progressive fatigue and decreased appetite. Apart from a recent diagnosis of diabetes, she had no significant past medical history. Three weeks prior to presentation, she had initiated subcutaneous semaglutide (0.25 mg weekly) for weight loss. One week before admission, she was diagnosed with type 2 diabetes mellitus at a local clinic and was prescribed metformin 1000 mg/day and enavogliflozin 0.3 mg/day.

The patient had also been practicing intermittent fasting from the time she started semaglutide, following a 20:4 dietary pattern (20 hours fasting and a 4-hour eating window) to enhance weight loss. Since starting antidiabetic medications, she reported persistent nausea and intermittent vomiting, which she attributed to common side effects of semaglutide and therefore did not seek immediate medical care. As her symptoms worsened, she was admitted to a local hospital four days prior to transfer for suspected euDKA. Despite treatment, her acidosis did not improve, and she was referred to our institution.

Variable	0 Hours	+24 Hours	+48 Hours	+72 Hours	Normal Reference Range
Glucose	131 mg/dL	134 mg/dL	137 mg/dL	139 mg/dL	70–100 mg/dL (3.9–5.5 mmol/L)
Creatinine	0.71 mg/dL	0.70 mg/dL	0.57 mg/dL	0.50 mg/dL	0.4–1.30 mg/dL
Sodium	131 mEq/L	134 mEq/L	137 mEq/L	139 mEq/L	136–144 mEq/L
Potassium	4.0 mEq/L	3.4 mEq/L	3.5 mEq/L	3.9 mEq	3.3–5.5 mEq/L
Chloride	101 mEq/L	102 mEq/L	104 mEq/L	102 mEq/L	99–111 mEq/L
Bicarbonate	11 mEq/L	16 mEq/L	9 mEq/L	27 mEq/L	17–29 mEq/L
Anion gap	19 mEq/L	16 mEq/L	15 mEq/L	10 mEq/L	7–17 mEq/L
Total bilirubin	1.4 mg/dL	1.0 mg/dL	1.2 mg/dL	1.2 mg/dL	≤1.2 mg/dL
AST	34 U/L	30 U/L	20 U/L	24 U/L	10–35 U/L
ALT	28 U/L	26 U/L	18 U/L	18 U/L	10–35 U/L
Lipase	90 U/L	40 U/L	35 U/L	38 U/L	12–53 U/L
Lactic acid	16 mg/dL	10 mg/dL	8 mg/dL	6 mg/dL	4.5–19.8 mg/dL

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Initial laboratory evaluation at the local clinic revealed fasting glucose 137, strongly positive urine ketones (+++), normal serum lactate (4.87 mg/dL; reference range: 4.5–19.8), an HbA1c of 9.3%, and a C-peptide level of 0.88 ng/mL (Table 1). Arterial blood gas analysis at our hospital demonstrated high anion gap metabolic acidosis (pH 7.269, pCO₂ 25.3, pO₂ 106, HCO₃ 11.6, Anion gap 17), consistent with diabetic ketoacidosis. Given the relatively low serum glucose level and biochemical findings, she was diagnosed with euglycemic diabetic ketoacidosis (euDKA).

Treatment and Progress

Upon admission, the patient was noted to be moderately to severely dehydrated. Intravenous fluid resuscitation was promptly initiated using a balanced crystalloid solution at a rate of 160 mL/hr. Simultaneously, a standard treatment protocol for diabetic ketoacidosis (DKA) was implemented. To suppress ketogenesis and gradually lower circulating ketone levels, a continuous intravenous insulin infusion was initiated at a rate of 1–2 units/hr. Given the patient's relatively low serum glucose level of 137 mg/dL, an 18% dextrose solution was co-administered at 40 mL/hr to prevent hypoglycemia. Electrolyte correction was performed carefully, with potassium chloride (KCl) administered at a concentration of 40 mEq/L and an infusion rate of 80 mL/hr to prevent hypokalemia during insulin therapy. Electrolytes were closely monitored and adjusted as needed throughout treatment.

Within the first 48 hours, both the patient's clinical condition and laboratory findings began to improve. Nausea and vomiting subsided, and she was able to tolerate oral fluid intake. By hospital day 3, the anion gap had decreased significantly, and serum bicarbonate levels had begun to rise, suggesting resolution of metabolic acidosis. Consequently, the insulin infusion rate was gradually tapered. Once the anion gap had normalized, intravenous insulin was transitioned to subcutaneous insulin. A once-daily basal insulin regimen was initiated to maintain glycemic control and prevent recurrence of ketogenesis. Both the SGLT2 inhibitor and the GLP-1 receptor agonist, suspected as contributing factors to the development of euDKA, were discontinued.

Throughout hospitalization, blood glucose levels and arterial blood gas analyses were closely monitored to assess the response to therapy. Dextrose infusion rates were adjusted to maintain blood glucose levels in the target range of 140–180 mg/dL, ensuring continuous insulin activity against ketone production. The patient's mental status, dietary intake, and hemodynamic stability improved steadily. By hospital day 5, her appetite had returned, she was able to tolerate a regular diet without nausea, and her serum chemistry values had stabilized. On day 6, her high anion gap metabolic acidosis had fully resolved, urinary ketones had cleared, and she was discharged in stable condition.

Prior to discharge, comprehensive education was provided on the prevention of DKA recurrence. Topics included sick-day management strategies, medication adherence, and the importance of maintaining adequate nutrition. The SGLT2 inhibitor, considered a precipitating factor in this case of euDKA, was permanently discontinued. The GLP-1RA (semaglutide) was also held, as its gastrointestinal side effects and the patient's associated fasting behavior were suspected to have contributed to the condition. At discharge, a conservative diabetes management regimen consisting of basal insulin, metformin, and a DPP-4 inhibitor was initiated. The patient was discharged in a clinically stable condition on hospital day 6.

Outpatient Follow-up

At the two-week follow-up visit, the patient remained clinically stable, with no recurrence of ketosis. She had adapted well to the basal insulin regimen, and self-monitored blood glucose readings were within the target range. Intermittent fasting had been discontinued, and she had resumed a regular diet. No gastrointestinal symptoms or abdominal discomfort were reported, and overall health status had improved. The current plan is to maintain the regimen of basal insulin, metformin, and a DPP-4 inhibitor, with the possibility of cautiously introducing other antihyperglycemic agents if needed, under close monitoring. She continues to be followed regularly in the outpatient clinic and has maintained good glycemic control without further episodes of acidosis.

3. Discussion

This case presents a clinically significant episode of euglycemic diabetic ketoacidosis (euDKA) in a patient with newly diagnosed type 2 diabetes mellitus (T2DM) who was initiated on combination therapy with a glucagon-like peptide-1 receptor agonist (GLP-1RA) and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. While these agents are widely prescribed due to their favorable effects on glycemic control, weight loss, and cardiometabolic outcomes, clinicians should be aware that they may increase the risk of ketone accumulation and ketoacidosis, particularly under physiological stress.

SGLT2 inhibitors have revolutionized the management of T2DM by promoting urinary glucose excretion and lowering plasma glucose levels independently of insulin. In addition to improving glycemic control, they have demonstrated cardiovascular and renal protective effects, leading to their widespread adoption in clinical practice[2,15,16]. However, their mechanism of action is closely linked to increased ketone production. By inducing glycosuria, SGLT2 inhibitors can reduce circulating insulin levels, thereby creating a relative insulin-deficient state. Simultaneously, they stimulate glucagon secretion and enhance free fatty acid mobilization through lipolysis, ultimately facilitating hepatic ketogenesis[6,7]. When additional precipitating factors such as decreased oral intake, dehydration, infection, or acute illness are present, this metabolic shift can be amplified, potentially leading to DKA even in the absence of significant hyperglycemia[7,17,18].

In this case, the patient was started on semaglutide for weight reduction and subsequently developed progressive gastrointestinal symptoms, including nausea and reduced appetite, which resulted in prolonged fasting. GLP-1RAs are known to delay gastric emptying and suppress appetite, which may contribute to caloric restriction and increase ketone production[12]. In this ketotic-prone state, the addition of an SGLT2 inhibitor may exacerbate ketogenesis and overwhelm the patient's compensatory metabolic capacity. Several reports have documented cases of euDKA in the setting of GLP-1RA use combined with prolonged fastin[14,19]. Moreover, nausea and vomiting—common side effects of GLP-1RAs—may mimic early symptoms of DKA, potentially delaying diagnosis.

The patient presented with severe fatigue, vomiting, and anorexia. Although blood glucose was only 137 mg/dL, laboratory[20] findings revealed high anion gap metabolic acidosis and strong ketonuria, confirming the diagnosis of euDKA. As severe hyperglycemia is absent in such cases, euDKA can often be overlooked. Therefore, a high index of suspicion is warranted in patients receiving GLP-1RA or SGLT2i therapy who present with unexplained acidosis. Notably, recent studies suggest that euDKA may be associated with worse clinical outcomes compared to classic DKA, underscoring the importance of early recognition and management[8].

The treatment of euDKA generally follows the standard protocols established for classical DKA, which include prompt intravenous fluid resuscitation, continuous insulin infusion, and correction of electrolyte imbalances—most notably potassium. In this case, application of these standard measures led to rapid resolution of metabolic acidosis and a favorable clinical outcome[20,21]. In this case, application of these standard measures led to rapid resolution of metabolic acidosis and a favorable clinical outcome. However, euDKA presents several unique therapeutic challenges compared to hyperglycemic DKA, with notable differences in insulin administration strategies[22]. Because blood glucose levels in euDKA typically remain near normal or only mildly elevated (usually <250 mg/dL), a major clinical concern is how to administer insulin effectively without inducing hypoglycemia. Insulin remains essential to suppress lipolysis, inhibit hepatic ketogenesis, and facilitate the clearance of circulating ketone bodies.

However, in the absence of significant hyperglycemia, insulin therapy alone may precipitate profound hypoglycemia. To prevent this, it is necessary to co-administer dextrose-containing fluids—commonly 5% to 10% dextrose in normal saline or half-normal saline—alongside insulin infusion. This approach allows for continuous insulin activity while maintaining appropriate blood glucose levels. This dual-therapy strategy (insulin-dextrose combination therapy) requires frequent monitoring of blood glucose, ketone levels (or anion gap), and serum electrolytes—particularly potassium—to enable careful titration of both insulin and dextrose infusion rates. Since insulin drives

potassium intracellularly and promotes renal excretion, hypokalemia is a common and potentially life-threatening complication during treatment. As such, aggressive potassium supplementation is required to maintain serum potassium within the target range of 4.0–5.0 mEq/L and to prevent cardiac arrhythmias or neuromuscular complications.

4. Conclusions

SGLT2 inhibitors are beneficial for type 2 diabetes treatment but can induce euglycemic DKA. This case report presents a severe DKA episode following SGLT2 inhibitor use. Early recognition and aggressive management are crucial. Before initiating SGLT2 inhibitors, it is essential to assess for catabolic symptoms related to hyperglycemia and to avoid triggering factors such as fasting, dehydration, and infection. Patients should be advised to seek immediate medical attention if symptoms occur.

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Data Availability Statement: All data supporting the findings of this case are available from the corresponding author upon reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body Mass Index
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
euDKA	Euglycemic Diabetic Ketoacidosis
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
SGLT2	Sodium-Glucose Cotransporter-2

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