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Euglycemic diabetic ketoacidosis: A case report triggered by a low larbohydrate diet and SGLT-2 inhibitor therapy

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Abstract

Introduction: Euglycemic Diabetic Ketoacidosis (euDKA) is a rare but potentially life-threatening complication associated with sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy and low carbohydrate diets. We present a case of euDKA in a 57-year-old male shortly after initiating a low carbohydrate diet.

Case presentation: A 57-year-old male presented to the emergency department with symptoms of generalized weakness, fatigue, and nausea, following the adoption of a low carbohydrate diet. Laboratory investigations revealed severe metabolic acidosis, ketonuria, and normal blood lactate levels, indicative of euDKA. Treatment was promptly initiated, resulting in resolution of the ketoacidotic state.

Discussion: This case highlights the potential risk of euDKA associated with low carbohydrate diets, particularly in individuals predisposed to insulin resistance. Clinicians should be vigilant for the development of euDKA in patients following such dietary regimens, especially when combined with medications like SGLT2 inhibitors.

Conclusion: Awareness of the association between low carbohydrate diets, SGLT2 inhibitors, and euDKA is crucial for early recognition and management of this potentially life-threatening condition. Further research is warranted to elucidate the underlying mechanisms and optimize preventive strategies in at-risk populations.

Keywords: Euglycemic diabetic ketoacidosis; Low carbohydrate diet; Sodium-glucose cotransporter-2 inhibitors; Insulin therapy; Metabolic acidosis.

Introduction

In the contemporary landscape of diabetes management, the advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors represents a significant milestone. With burgeoning research highlighting their efficacy in reducing cardiovascular events and mortality rates [1], not only among diabetic individuals but also in non-diabetic populations [2], alongside their notable renal protective effects against microvascular complications of Diabetes mellitus [3], SGLT2 inhibitors have garnered substantial attention. However, amidst these advancements, a less recognized complication, known as euglycemic Diabetic Ketoacidosis (euDKA), has emerged as a potential consequence of SGLT2 inhibitor therapy. Interestingly, recent evidence suggests that euDKA can also be triggered by dietary interventions, particularly low carbohydrate diets, thus intertwining the complexities of pharmacotherapy and dietary practices in diabetes management [4].

Case presentation

A 57-year-old man presented to the emergency department with complaints of generalized weakness, fatigue, and nausea, approximately two weeks after initiating a low carbohydrate diet. His wife noted a foul odour emanating from his mouth. The patient denied any prior episodes of similar symptoms. Laboratory investigations revealed severe metabolic acidosis, ketonuria, and normoglycemia with a plasma glucose level of 177 mg/dL (Table 1). Alcohol consumption was ruled out. Chest X-ray and electrocardiogram findings were unremarkable.

Table 1: Laboratory tests on admission.

Test	Result	Reference range
WBC'S	8 K/ul	4.50-11.00 K/ul
HB	16.2 g/dl	13.5-17.5 g/dl
HCT	48.5%	41.0-53.0%
Glucose	177 mg/dl	74-100 mg/dl
Urea	28 mg/dl	18-55 mg/dl
Creatinine	1.43 mg/dl	0.72-1.25 mg/dl
Potassium	4.1 mEq/L	3.5-5.1 mEq/L
Sodium	133 mEq/L	136-145 mEq/L
Chloride	104 mEq/L	98-107 mEq/L
Bicarbonate	12.7 mm/L	22.0-26.0 mm/L
PH	7.150	-
Lactate	1	-
PCO_2	37.2 mm/Hg	36.0-44.0 mm/Hg
Troponin I	33.2 pg/mL	10.00-34.20 pg/mL
Amylase	33 U/L	28-100 U/L
Creatinine Kinase (CPK)	665 U/L	30-200 U/L
C-Reactive protein	0.28 mg/dl	0.00-0.50 mg/dl

The patient was promptly admitted to our internal medicine department at Kaplan Medical Center, Rehovot, Israel. Treatment was initiated with an insulin drip and intravenous fluids consisting of Plasma-Lyte.

Subsequent monitoring showed improvement in ketoacidosis, and the insulin drip was discontinued approximately one hour after the administration of long half-life subcutaneous insulin (Lantus). Throughout his hospital stay, the patient's symptoms gradually resolved, and his metabolic parameters normalized. Close monitoring ensured stability before discharge, with appropriate dietary counselling and follow-up arranged to address the underlying precipitating factors of euDKA.

The patient had a medical history significant for hypertension and diabetes mellitus. He was diagnosed with hypertension at the age of 18 and underwent investigations for secondary hypertension, which yielded negative results. His blood pressure was controlled with Amlodipine/Valsartan 10/160 mg and Bisoprolol 5 mg once daily. Additionally, he was diagnosed with diabetes mellitus at the age of 40, without any microvascular or macrovascular complications. Due to inadequate glycemic control on oral medications, he underwent further evaluation, which revealed positivity for Glutamic Acid Decarboxylase Autoantibodies (GAD), indicating latent autoimmune diabetes of adults (LADA) [5]. Basal insulin therapy via an insulin pump was initiated, but poor control persisted, prompting the addition of empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor [6], and a recommendation from his endocrinologist to adopt a low carbohydrate diet. This case underscores the complex interplay between dietary modifications, pharmacotherapy, and metabolic complications in patients with diabetes mellitus, highlighting the need for vigilant monitoring and individualized management strategies in such individuals.

Discussion

This case highlights the intricate relationship between dietary interventions, pharmacotherapy, and metabolic complications, particularly in individuals with diabetes mellitus. Our patient's development of euglycemic diabetic ketoacidosis (euDKA) following initiation of a low carbohydrate diet and concurrent treatment with an SGLT-2 inhibitor underscores the importance of recognizing potential risks associated with these interventions. The concept of euDKA, characterized by the triad of metabolic acidosis, ketosis, and normoglycemia, challenges traditional diagnostic criteria for Diabetic Ketoacidosis (DKA), which typically include hyperglycemia. In our patient, despite a plasma glucose level within the normal range, severe metabolic acidosis and ketonuria were evident, indicative of euDKA. This phenomenon has been increasingly recognized in association with SGLT-2 inhibitor therapy, attributed to the glucose-lowering effect of these agents leading to decreased insulin secretion and subsequent ketogenesis. Additionally, the adoption of a low carbohydrate diet further exacerbates the risk of ketosis, predisposing individuals to euDKA, as observed in our case. The management of euDKA involves prompt recognition and aggressive intervention, including fluid resuscitation, insulin therapy, and correction of electrolyte imbalances. In our patient, initiation of insulin infusion and intravenous fluids led to rapid improvement in ketoacidosis, highlighting the effectiveness of early intervention in mitigating potentially life-threatening complications.

Emerging evidence suggests that both low carbohydrate diets and Sodium-Glucose Cotransporter-2 inhibitor (SGLT2i) therapy independently elevate triglyceride levels [7]. Furthermore, the combination of these therapies exacerbates this effect. Additionally, studies in animal models, such as Akita mice, have demonstrated a significant increase in free fatty acid levels with SGLT2i treatment, contributing to enhanced ketone production. Interestingly, while SGLT2i therapy potentiates ketone production approximately four-fold in these models, low carbohydrate diets alone do not significantly alter 3-Hydroxybutyric Acid (3-OHBA) levels compared to non-treated controls. These findings underscore the intricate metabolic effects of both dietary interventions and pharmacotherapy in individuals with diabetes mellitus [8].

Our patient's medical history is notable for Latent Autoimmune Diabetes of Adults (LADA), a subtype of diabetes characterized by autoimmune destruction of pancreatic beta cells. The presence of GAD autoantibodies in our patient underscores the autoimmune etiology of his diabetes, contributing to the challenges in glycemic management. Despite initiation of basal insulin therapy via an insulin pump, inadequate glycemic control persisted, necessitating the addition of empagliflozin, an SGLT-2 inhibitor, and a recommendation to adopt a low carbohydrate diet. While these interventions aim to improve glycemic control and reduce cardiovascular risk, our case serves as a cautionary

reminder of the potential metabolic consequences associated with their use, particularly in individuals with autoimmune diabetes.

Clinicians should use caution when prescribing SGLT2 inhibitors to patients at greater risk for euDKA, such as those with an infection. Sick-day strategies during acute illness for those taking SGLT2 inhibitors should be discussed with patients, such as temporarily discontinuing SGLT2 inhibitors, staying well hydrated, and contacting their provider [9,10]. Patients should also avoid excess alcohol consumption and very low carbohydrate/ ketogenic diets [11]. This is particularly important, as carbohydrate-restrictive diets, a popular approach to weight loss, with SGLT2 inhibitors can lead to euDKA [12-14]. A randomized, open-label study investigating the safety and efficacy of a SGLT2 inhibitor in individuals with differing carbohydrate intakes found that ketone bodies were significantly higher in the low carbohydrate group compared to the high carbohydrate group and concluded that a strict low carbohydrate diet while on SGLT2 inhibitor therapy should be avoided to prevent DKA [15].

Conclusion

Our case underscores the importance of individualized management strategies in patients with diabetes mellitus, considering the complex interplay between dietary modifications, pharmacotherapy, and metabolic complications. Clinicians should maintain a high index of suspicion for euDKA in patients following low carbohydrate diets, especially in the presence of SGLT-2 inhibitor therapy and remain vigilant for early signs of metabolic decompensation. Further research is warranted to elucidate the underlying mechanisms and optimize therapeutic approaches to mitigate the risk of euDKA in susceptible individuals.

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