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Case Report

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The deadly combination of a keto diet and SGLT-2 inhibitors: A case of euglycemic ketoacidosis

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Abstract

Diabetic ketoacidosis is an acute and serious complication of diabetes mellitus, which usually occurs in type 1 but is not uncommon in type 2 diabetes patients. It is characterized by hyperglycemia, metabolic acidosis, and ketone bodies in the blood or urine. A subgroup of patients may present without signs of hyperglycemia with normal blood glucose levels, thus posing a diagnostic challenge. Here, we report a case of a 42-year-old gentleman who presented to the emergency room and was diagnosed with euglycemic diabetic ketoacidosis 3 days after starting Empagliflozin along with a strict low-carbohydrate diet. Extensive workup failed to demonstrate any other factor, such as infection, that may have led to this complication. This article aims to raise awareness among clinicians to be aware of this diagnosis in the differentials in patients taking SGLT-2 inhibitors who are also on a strict low-carbohydrate diet. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2025; 4 (1): 39-42]*

Keywords: Euglycemic Diabetic Ketoacidosis, Empagliflozin, SGLT-2 inhibitors, Diabetes Mellitus, Ketogenic diet, Strict low-carbohydrate diet

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Introduction

SGLT-2 inhibitors are very popular antidiabetic medications due to their cardiorenal and weight loss benefits. It reduces renal tubular glucose reabsorption, causing glycosuria, resulting in calorie loss, proteinuria, reduced blood pressure, and improved cardiac contractility.[1] However, the loss of glucose through urine reduces insulin release and switches metabolism to the burning of fatty acids, resulting in ketoacidosis. The risk is higher in those who maintain a keto diet. The ketogenic diet has become very popular in recent years as a weight management plan emphasizing eating meals high in fat and low in carbohydrates. This kind of diet results in metabolic alterations such as gluconeogenesis, the depletion of glycogen stores, and ketogenesis.[2] Despite its popularity, the diet plan is fraught with dangers like electrolyte imbalance, hypovitaminosis, nephrolithiasis, pancreatitis, osteoporosis, etc.[2] The NICE guideline specifically dictates avoiding the use of SGLT-2 inhibitors in those who are on a keto diet because of the high risk of euglycemic ketoacidosis.[3] We are doing this case report to show that despite warnings from experts, the dangerous combination of SGLT-2 inhibitors and the keto diet is frequently used, resulting in life-threatening ketoacidosis.

Case Summary

A 42-year-old Bangladeshi Muslim male patient presented to the emergency room (ER) of a private hospital with complaints of abdominal pain for 1 day, nausea and vomiting for 1 day, and generalized weakness for two days. The patient's abdominal pain was diffuse, started slowly over a few hours, dull aching in nature, mild to moderate in intensity, and had no radiation or any aggravating or relieving

factors. His vomiting was associated with nausea; the vomitus contained little digested food, which was non-bilious and non-bloody. He also mentioned that he has been feeling weak and tired for the last few months, but the situation worsened in the last 2 days. On a further query about past illness and recent treatment history, he mentions that he was diagnosed with diabetes mellitus with an HbA_{1C} level of 12.3% two days back. He was started on a strict low carbohydrate diet since diagnosis, along with the tablet Empagliflozin 25 mg per day. He was very much compliant with the treatment. He gave no history of taking alcohol ever. After 2 days of starting a strict low-carbohydrate diet coupled with Empagliflozin, he developed the aforementioned symptoms and came to the ER. In the ER, he was conscious, well-oriented but ill-looking, in mild distress with mild tachypnea. His blood pressure was 100/80 mmHg, pulse was 102 beats per minute, temperature was 99°F, respiratory rate was 20 breaths per minute, $Sp0_2$: 96% in room air, dehydration: (++) present. His systemic examination, including the respiratory system and abdomen, was unremarkable. His investigations in the ER revealed random plasma glucose: 5.4 mmol/L, urine routine examination: ketone: (+++), complete blood count: hemoglobin: 16.7 g/dL, hematocrit: 49.6%, leucocyte: 14620 /uL, neutrophil: 90%, platelet: 203000/uL, s. creatinine: 0.9 mg/dL, s. electrolytes: sodium: 136 mmol/L, potassium: 4.29 mmol/L, chloride: 107 mmol/L, TCO_2: 9 mmol/L, s. amylase: 62 U/L, s. lipase: 67 U/L. His initial arterial blood gas revealed pH: 7.2, pCO_2: 28 mmHg, HCO_3-: 8mmol/L with an anion gap of 21 meq/L (high anion gap metabolic acidosis). His chest X-ray and ultrasonography of the abdomen were unremarkable. The patient was diagnosed with euglycemic diabetic ketoacidosis and managed accordingly. He was given aggressive IV fluid (Inf. Normal Saline), Insulin Lispro in a syringe pump, and Inj. Potassium chloride mixed in 5% Dextrose in Aqua (10 mmol in 1L). All the previous oral medications, including Empagliflozin, were stopped. However, initially, the patient's blood sugar was barely rising despite giving Inf. 5% Dextrose, which made it difficult to continue insulin infusion. So, Inf. 5% Dextrose in aqua was switched to 10% Dextrose in aqua, and an insulin syringe pump was given according to variable rate infusion. Surprisingly, the patient's blood sugar was still in the lower normal range. So, normal saline was switched to 5% Dextrose in normal saline (DNS), after which the patient's blood sugar began to rise, and insulin infusion could be given without causing hypoglycemia. The patient was also started on an empirical broad-spectrum antibiotic (Injection of Ceftriaxone 1 gram intravenously every 12 hours) and prophylactic low molecular weight heparin (40 mg subcutaneously once daily). His blood sugar was monitored every hour and serum electrolytes, venous blood gas, and urinary ketone body were monitored every 4 hours until satisfactory improvement was observed (Table-I and II). Once blood sugar was above 14 mmol/L, DNS was switched to normal saline. With the aforementioned treatment, his venous blood gas showed gradual improvement in pH and HCO_3-. The patient also improved clinically. Basal insulin (Inj. Glargine: 20 units subcutaneously) was started the next morning (day 2), and bolus insulin (Inj. Lispro 10 units) was started in the evening. The insulin syringe pump was stopped 1 hour after bolus insulin was given. By that time, the patient's venous pH and HCO_3- were within normal range, and the urinary ketone body was no longer positive. The patient was monitored for 24 hours after the Basal-bolus regimen was started. Once his blood sugar control was satisfactory, he was discharged with medical advice and close follow-up. The patient and the patient's attendants were counselled in detail about the necessity of insulin for the patient's management as well as to avoid a strict calorie-restricted diet.

Table-I: Serial venous blood gas report in the first 12-hour

Tests	Day 1 at 10 PM	Day 2 at 2 AM	Day 2 at 6 PM
pH	7.18	7.24	7.29
HCO_3-	13.4 mmol/L	18 mmol/L	19.2 mmol/L
pCO_2	36 mm Hg	42 mm Hg	40 mmHg
Base Excess (ecf)	15 mmol/L	-9.4 mmol/L	-7.4 mmol/L

Table-II: Serum electrolytes on admission and discharge

Tests	Day 1	Day 4
Sodium (Na^+)	136 mmol/L	145 mmol/L
Potassium (K^+)	4.29 mmol/L	3.44 mmol/L
Chloride (Cl^-)	107 mmol/L	110 mmol/L
Carbon dioxide (TCO_2)	9 mmol/L	26 mmol/L

Discussion

Diabetic Ketoacidosis is defined by hyperglycemia (>250 mg/dl), Ketoacidosis, and anion gap acidosis.[4] Euglycemic diabetic ketoacidosis (EDKA) is characterized by severe metabolic acidosis (pH <7.3, HCO_3-<18 mEq/l), ketonemia, and blood glucose <250 mg/dl.[5] EDKA and DKA have significant overlaps in their clinical features. Symptoms of EDKA include nausea, vomiting, malaise, fatigue, anorexia, shortness of breath, tachycardia, and abdominal pain.[4,6,7] However, the onset of symptoms in EDKA may be more gradual than in DKA.[8] One notable difference is that due to the absence of pronounced hyperglycemia, patients may not experience the characteristic osmotic symptoms of polyuria, polydipsia, or severe mental status changes. This masking of polyuria and polydipsia is more pronounced in individuals taking sodium-glucose cotransporter 2 (SGLT-2) inhibitors due to renal excretion of glucose.[9]

Typically, the onset of EDKA is triggered by factors such as strict dieting or starvation, pregnancy, alcohol intake, and the use of SGLT-2 inhibitors.[10] The incidence of EDKA in type 2 diabetes patients using SGLT2 inhibitors is approximately 0.1%.11 SGLT-2 inhibition induces a rapid increase in urinary glucose excretion, which leads to low plasma insulin levels, resulting in reduced glucose utilization and enhanced lipolysis to promote free fatty acid (FFA) oxidation and production of ketone bodies.[11] Furthermore, reduced insulin production from pancreatic β-cells stimulates α-cells to increase plasma glucagon concentrations.[12] These changes result in a decreased insulin-to-glucagon ratio, further stimulating lipolysis, augmenting the production of FFAs, and inducing ketogenesis.[13]

The keto diet is a strict low-carbohydrate, high-fat, and adequate-protein diet. It has been previously used for the treatment of seizure disorders and neurodegenerative disorders and has more recently become mainstream as a method for weight loss.[14,15] The aim of this diet is to enter a state of nutritional ketosis, deriving energy from fat burn-down in the form of ketones. Short-term benefits have been postulated by faster weight loss, improved cognitive functioning, appetite suppression, and improved eating behaviour and metabolic profile.16 However, the long-term benefits have been largely unexplored.[17] Our case demonstrates an example where the use of an SGLT-2 inhibitor coupled with a strict low carbohydrate diet (Keto diet) led to the development of euglycemic DKA within just 3 days. Our patient had non-specific features of DKA but the blood sugar level was within normal range (5.4mmol/L), yet there was clear evidence of high anion gap metabolic acidosis with significant ketonuria. This unique presentation of DKA with normal blood sugar makes the diagnosis very challenging. Arterial or venous blood gas is not a widely available test in our country, and normal blood sugar on presentation makes the diagnosis harder. In addition, there is an ongoing trend nowadays among some healthcare professionals to vilify insulin and advocate for dietary and lifestyle modification for the control of diabetes, disregarding the patient's clinical situation or comorbidities. So, there is a rising popularity of a strict low carbohydrate diet (keto diet) among patients who are not suitable candidates for dietary restriction and are prone to develop ketoacidosis. Therefore, doctors must take a dietary history of diabetic patients and determine whether they are on any particular diet before prescribing SGLT-2 inhibitors. Patients should also be educated about the possible complications of particular diets and medications and warning signs to watch out.

Conclusions

Both the Ketogenic diet and SGLT-2 inhibitors are risk factors for ketogenesis and ketonemia. Together, they are a potentially dangerous combination that can lead to EDKA. This is particularly concerning because DKA has a significant mortality, and when it presents without typical features of hyperglycemia, diagnosis is often missed or delayed. So, detailed dietary history and drug history are invaluable. Clinicians should take detailed dietary history before prescribing SGLT-2 inhibitors. Patients who are being prescribed SGLT-2 inhibitors must be discouraged from trying any specific diet (especially a strict low-carbohydrate diet) without proper consultation.

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Disclosure

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Data Availability

Any inquiries regarding supporting data availability of this study

should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient. All methods were performed in accordance with the relevant guidelines and regulations.

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