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Case Report

Euglycemic diabetic ketoacidosis induced by empagliflozin in the setting of helicobacter pylori and hypertriglyceridemia treatment

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Abstract

Euglycemic diabetic ketoacidosis (EDKA) is a rare complication in diabetes, with clinical triad: 1) metabolic acidosis with an increased anion gap, 2) ketonemia or/and ketonuria, and 3) normal levels of glucose in the blood (<11 mmol/L). This condition is very challenging to diagnose as euglycemia can mask the underlying diabetic acute complication of ketoacidosis. Therefore, clinical suspicion is needed in all patients at possible risk for EDKA. Here, we present a patient with type 2 diabetes, obesity, and hypertriglyceridemia. Also, with a history of cardiovascular disease, He was diagnosed with EDKA on admission and treated recently with Empagliflozin in a setting of Helicobacter pylori Eradication Therapy and Bezafibrate for hypertriglyceridemia. During admission, the patient was treated with fluids intravenously and insulin according to glucose levels in the blood until the metabolic acidosis was reversed.

Keywords: euglycemic diabetic ketoacidosis, empagliflozin, helicobacter pylori eradication therapy, hypertriglyceridemia treatment.

Introduction

Diabetes mellitus (DM) is a significant health concern in today's world [1, 2]. In 2019, the global prevalence of diabetes mellitus (DM) was 9.3%, affecting 463 million people, and it is projected to rise to 10.2% (578 million) by 2030 [1, 2]. The acute and chronic complications of DM, which have approached pandemic levels, are among the primary contributors to morbidity and mortality globally [1, 2].

Diabetic ketoacidosis (DKA) is a very serious and acute complication of diabetes. Although it primarily occurs in type 1 diabetes, it can also develop in type 2 diabetes under certain conditions. It arises when the body lacks sufficient insulin, leading to the breakdown of fat for energy. This process produces ketones, which can accumulate in the blood and result in a dangerous acidic state [3, 4].

Key triggers for DKA include illness, infections, missed insulin doses, and uncontrolled blood sugar levels. Symptoms often manifest rapidly and can include excessive thirst, frequent urination, nausea, pain in the abdomen, weakness, and fruity-smelling breath due to ketone accumulation [3, 4].

Diagnosis is typically confirmed through blood tests showing high blood glucose levels, high ketone levels, and acidosis. Immediate treatment is crucial and involves insulin therapy to lower blood glucose, fluid replacement to combat dehydration, and electrolyte management to correct imbalances [3, 4].

Euglycemic DKA (EDKA) is a very rare variant of diabetic ketoacidosis (DKA) that occurs with the glucose in normal levels or only mildly elevated, typically below 11 mmol/L but with severe acidosis of metabolic etiology (arterial pH lower than 7.3, bicarbonates in the serum lower than 18 mEq/L) and ketonemia [4–9].

The normal glucose levels in EDKA can make it difficult for both patients and doctors to quickly identify the condition. Therefore, owing to the range of possible causes and the presence of normal glucose levels in the blood, this poses a diagnostic dilemma for healthcare professionals, often leading to late diagnosis [4–9].

Recent, frequent usage of sodium-glucose cotransporter 2 (SGLT2) inhibitors was shown to be a risk for this complication in certain conditions in diabetic patients [7–15]. SGLT2 inhibitors are shown to be a very good treatment choice in type 2 diabetes as they provide cardiorenal protection and advantages unrelated to glycemic management [4, 7, 10–19].

The risk of developing EDKA can be increased when it occurs alongside factors such as surgery, trauma, severe illness, infection, low food intake, ongoing vomiting, gastroparesis, dehydration, or the sudden discontinuation of insulin [2, 4–9].

Our goal is to report a case of Euglycemic Diabetic Ketoacidosis induced by Empagliflozin in a setting of Bezafibrate and Helicobacter pylori Eradication Therapy for a type 2 diabetic patient with obesity, hypertriglyceridemia (metabolic syndrome) and four years post-myocardial infarction state.

Case presentation

A 40-year-old male with type 2 diabetes (T2DM), obesity class III, and DKA was admitted to the Endocrinology Clinic, University Clinical Center of Kosovo. For the last ten days, he has been undergoing Eradication Therapy for Helicobacter pylori with Amoxicillin, Clarithromycin, Pantoprazole, and Bezafibrate for hypertriglyceridemia. Due to poor glycemic control, Empagliflozin was added to his treatment three days before admission, with Metformin and Vildagliptin being administered seven days before Empagliflozin. All the medications were stopped at admission, including Empagliflozin, three days after starting because he was unable to eat or drink due to nausea and vomiting. He had a history of coronary heart disease after suffering myocardial infarction and undergoing stenting four years ago. He also had a history of normal values of glycemia, polyuria, and constipation for the last three days since adding Empagliflozin to the treatment. According to the physical examination at admission, the patient was dehydrated, showing loss of skin turgor, dry mucous membranes, generalized malaise, lethargy, abdominal pain, and a fruity odor to the breath.

Investigation

The patient's BMI was 43.6 Kg/m^2, and his blood pressure was 110/70 mmHg, SPO_2 99%. According to the blood glucose level measurements, he was normoglycemic on admission and during the first 24 hours (Figure 1).

Blood gas analysis showed the presence of metabolic acidosis. Afterward, a complete blood workup was done, which included a hemogram, electrolytes, HbA1c, lipid profile, C-reactive protein, thyroid hormone levels, and renal function tests. The values and normal reference ranges, are presented in Table 1.

Ketone bodies were present in urine, which was negative for bacteriuria or leukocytes. The blood gas analysis revealed an increased anion gap metabolic acidosis. Therefore, EDKA was established as a diagnosis.

Treatment

He was treated with a 6 L bolus of IV liquids (in the first 24 hours), normal saline, 5% glucose, and insulin according to his glucose levels. Intravenous potassium was administered according to the blood level. The gas analysis was performed every four hours, while serum glucose levels were monitored every two hours. He started oral nutrition at a pH level of 7.37 and was placed on a basal-bolus insulin regimen.

Outcome and follow-up

The patient was discharged with normal gas analysis results, in good condition, on premixed 30/70 insulin and advised to diet and continue oral antidiabetics before the next appointment with his endocrinologist.

Discussion

DKA is characterized by a triad: high levels of glucose in the blood (serum glucose >14 mmol/L), low pH (pH <7.3 and bicarbonate <15 mEq/L), and ketosis (high

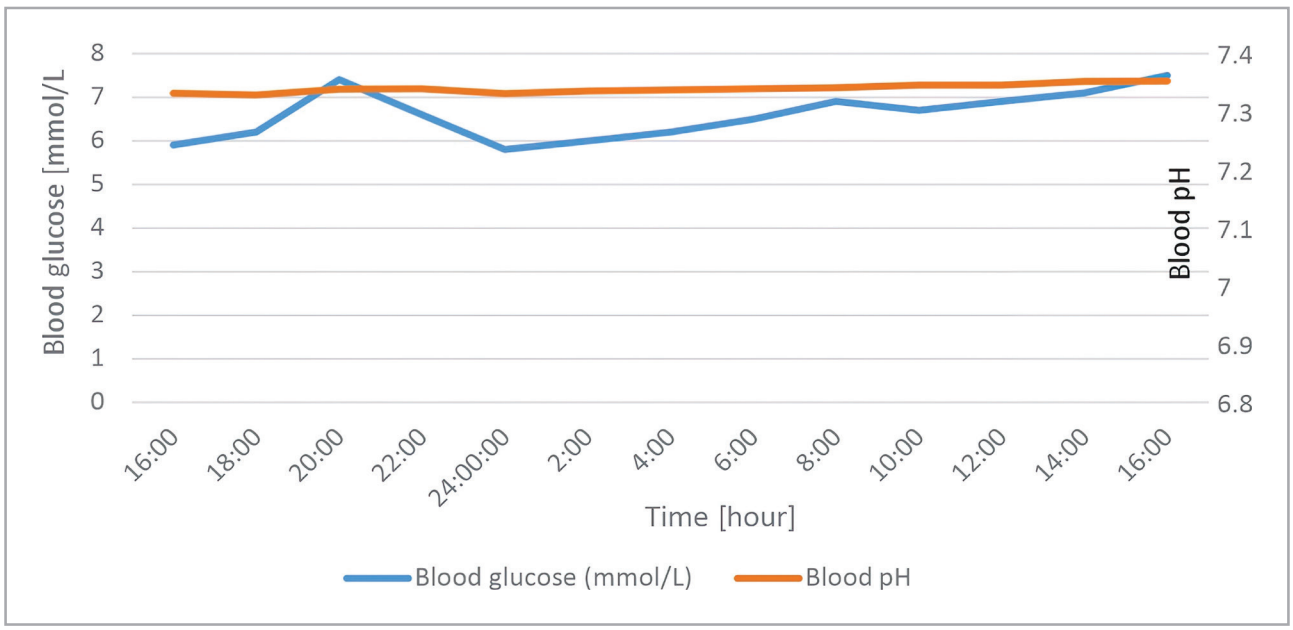

Figure 1: The glucose and pH levels in the blood of the case during the first 24 hours of hospitalization.

Table 1: Laboratory tests of the patient upon admission.

Lab. tests (units)	Patient's values	Normal reference range
Random blood sugar (mmol/L)	5.9	3.9–6.1
pH	7.09	7.35–7.45
Cholesterol (mmol/L)	5.5	3.6–5.7
Triglycerid (mmol/L)	5.7	0.45–1.81
Hemoglobin (g/dL)	12.7	12–15
White blood cells (10^3/mm^3)	9.8	3.5–10.0
Platelets (10^3/mm^3)	287	150–390
Red blood cells (10^6/mm^3)	4.61	3.80–5.80
Blood hemotocrit (%)	40.2	35.0–50.0
HbA1c (glycosylated hemoglobin) (%)	11.6	4.0–6.0
Na+ (mmol/L)	130	135–145
K+ (mmol/L)	2.5	3.5–5.0
Cl- (mmol/L)	100	98–109
HCO3- (mmo/L)	6.8	22–26
Anion gap	23	1–10
Blood urea nitrogen (mmol/L)	6.43	1.7–8.3
Creatinine (umol/L)	106.7	53–115
TSH (uIU/ml)	1.1	12.0–22.0
FT4 (pmol/L	13.4	0.27–4.2
FT3 (pmol/L)		3.1–6.8
Glucose in urine	1+	0
Ketones in urine	3+	0
WBC in urine (cells/hpf)	0	0
Urine nitrites	0	Negative

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ketones in urine and/or blood) [2–9]. The body's glycemic balance is maintained through the coordinated action of insulin and counter-regulatory hormones, where we have to mention glucagon, glucocorticoids, growth hormone, and epinephrine [2–11]. DKA occurs when there is either a lack of insulin or an excess of counter-regulatory hormones, both leading to hyperglycemia. Despite high blood glucose, the body's organs cannot utilize it effectively due to insufficient insulin, resulting in lipolysis and excessive ketone production [2–9]. In this case, however, DKA occurred without the presence of hyperglycemia.

Food and Drug Administration approved SGLT2 inhibitors in 2013 to treat T2DM. SGLT2 inhibitors work by blocking the SGLT2 protein, which is the protein responsible for the reabsorption of glucose in the proximal portion of the renal tubule [2, 4, 7, 9]. This mechanism promotes increased renal glucose excretion, thereby lowering blood glucose levels. Strong evidence suggests that SGLT2 inhibitors have beneficial effects in reducing mortality from cardiovascular events, including a decreased incidence of myocardial infarction and strokes [2, 4, 16–19]. These drugs also contribute to weight loss and carry no risk of hypoglycemia. Given these positive outcomes, SGLT2 inhibitors are highly recommended for treating type 2 diabetes mellitus (T2DM) [2, 4, 7, 16–19]. However, there is a growing body of literature highlighting the incidence of Euglycemic Diabetic Ketoacidosis (EDKA) associated with SGLT2 inhibitors [2, 4, 7, 12–15].

In EDKA, the fundamental mechanism for developing this complication may be either due to decreased hepatic glucose production in a fasting state or increased urinary glucose excretion caused by a higher level of counter-regulatory hormones [6, 9]. Therefore, in a diabetic patient, if it has any risk factor that could trigger DKA and is in a prolonged fasting state, the liver's glycogen stores will be depleted, resulting in reduced glucose production [3–9]. Simultaneously, lipolysis will occur, leading to increased fatty acid production, ultimately producing excessive ketone bodies [3–9].

The pathophysiology of Euglycemic Diabetic Ketoacidosis (EDKA) with SGLT2 inhibitors involves insulin production lowering and a higher glucagon secretion that shifts metabolism from glucose to fat and stimulates ketogenesis [2, 4, 7, 11–15]. SGLT2 inhibitors reduce glucose levels in the blood by increasing urinary glucose excretion, which subsequently decreases insulin secretion from pancreatic β-cells. The decrease in circulating insulin levels diminishes its anti-lipolytic effects, thereby promoting the production of free fatty acids, which are converted into ketone bodies via β-oxidation in the liver [2, 4, 7, 11–15].

The use of SGLT2 inhibitors leads to increased glucagon secretion, either due to the reduced insulin levels or through a direct effect on the α-cells of the pancreas [2, 4, 7, 11–15]. Another proposed mechanism for EDKA is related to the effects of SGLT2 inhibitors on kidneys. During prolonged fasting, renal reabsorption of ketones is enhanced, leading to higher ketone levels in the serum without a clear excretion threshold, while renal utilization of ketones is reduced [2, 4, 7]. By lowering the renal glucose excretion threshold, SGLT2 inhibitors can mimic a state of starvation, boosting ketone production and renal reabsorption [2, 4, 7, 11–15]. As a result, SGLT2 inhibitors make the body more prone to acidemia due to increased ketogenesis while continuing to eliminate glucose through urine, leading to normal or near-normal glucose levels, in contrast to the elevated glucose levels typically seen in DKA [2, 4, 7, 11–15].

Some of the common causes reported in the literature triggering EDKA in SGLT2 use include surgery interventions, vigorous physical activity, acute infections, acute myocardial infarction, dehydration, starvation, beta cell failure, type 1 diabetes, rapid reduction or discontinuation of insulin, rapid weight loss, and alcohol use [4, 7–15, 17].

There is also a report of a case of EDKA after the usage of an SGLT2 inhibitor in the setting of non-treated hypertriglyceridemia [4, 7]. Extreme hyperlipidemia has been reported to cause lipemic serum, which can lead to falsely low blood glucose levels (pseudo normoglycemia) and falsely low blood sodium levels (pseudo hyponatremia) [2, 4, 7, 11–15]. Blood glucose levels can appear decreased due to volume displacement caused by elevated lipid levels in the circulating blood [2, 4, 7, 11–15]. SGLT2 inhibitors are reported to increase low-density lipoprotein cholesterol levels as they decree its catabolism [4–7]; however, there is no evidence that SGLT2 inhibitors can cause high levels of triglycerides [4, 7], which in our case was present even before the use of SGLT2.

Both agencies, the European Medicines Agency and the US Food and Drug Administration (FDA) have released warnings about SGLT-2 inhibitors, stating that they may elevate the risk of DKA in certain conditions [2, 19–22]. It has been found that 71% of reported cases of DKA associated with SGLT-2 inhibitors were classified as Euglycemic Diabetic Ketoacidosis (EDKA). Compared to other drugs, SGLT2 inhibitors had up to 7-fold increased risk when used in type 2 diabetes [2, 23].

Our patient had none of the conditions so far reported in the literature that could cause the use of Empagliflozin to put the patient at risk of EDKA. Therefore, to the best of our knowledge, we report the first case of the setting of the eradication treatment of Helicobacter pylori gastritis (Amoxicillin, Clarithromycin, and Pantoprazole) with Bezafibrate as a condition where adding Empagliflozin for the better management of Type 2 Diabetes, has caused EDKA.

Conclusions

EDKA is a serious condition that requires prompt recognition and treatment. Awareness of its distinct features and triggers is essential for effective management, especially in patients using certain diabetes medications, such as SGLT2 inhibitors. While SGLT2 inhibitors are an excellent choice for managing type 2 diabetes due to their significant cardiovascular benefits, including prevention of cardiovascular outcomes in patients with or without cardiovascular comorbidities, they have been rarely associated with EDKA, a unique form of diabetic ketoacidosis.

In EDKA, normal blood glucose levels can delay diagnosis, underscoring the importance of clinical vigilance. The risk of EDKA should be carefully considered in type 2 diabetes patients initiating SGLT2 inhibitors, particularly in the presence of other conditions such as gastritis, Helicobacter pylori eradication therapy, or hypertriglyceridemia treatment.

Conflict of interest

The authors declare no conflict of interest.

Consent to participate

Informed consent was given in written form by the patient to publish their clinical details.

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