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Case Report

Postoperatory Euglycemic Diabetic Ketoacidosis: A Not So Rare Complication of Sglt2 Inhibitors

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ABSTRACT

Diabetic ketoacidosis is one of the most well-known complications of diabetes mellitus and is potentially fatal. It is characterized by a state of hyperglycemia (glycemic levels >300mg/dL), associated with metabolic ketoacidosis. It has been described that up to 3% of diabetic ketoacidosis can occur with blood glucose levels below 250 mg/dL, an incidence that has been increased since the introduction of SGLT2-i. We report the case of a female patient in her seventies, with a history of hypertension, dyslipidemia, ischemic heart disease and type 2 diabetes mellitus treated with insulin, metformin and canagliflozin. During the post-operative period of an elective surgery, she presented a decreased level of consciousness associated to metabolic acidosis. She was admitted to the ICU and required invasive mechanical ventilation and vasopressors. Euglycemic diabetic ketoacidosis was diagnosed and after treatment, she was discharged with no sequelae.

Background

Diabetic ketoacidosis (DKA) is a very well-known clinical and potential life-threatening complication of diabetes mellitus (DM), occurring mainly in type 1 DM patients (T1DM), rather than in type 2 DM (T2DM) [1, 2]. Typical DKA is characterized by hyperglycemia, metabolic acidosis and ketosis; however, Munro *et al.*, first described in 1973, euglycemic DKA (EDKA) [3]. It consists of euglycemia, defined by blood glucose levels less than 250 mg/dL, associated with metabolic ketoacidosis, which includes an arterial pH less than 7.3, a serum bicarbonate minor than 18 mmol/L and ketonemia [4].

It is described that approximately 3% of DKA admissions to the ER present normal glucose blood levels, but the incidence has recently grown with the introduction of sodium-glucose cotransporter 2 inhibitors (SGLT2-i), such as canagliflozin, as a step in the T2DM treatment [1, 5, 6]. Moreover, some studies report that ketone-associated effects in T1DM using SGLT2 inhibitors can be not only higher than 3%, but reaching almost 10%.

As far as SGLT2 inhibitors are concerned, they were first approved by the FDA in 2013 [7]. They are a type of diabetes drugs that work by avoiding the reuptake of the glucose in the convoluted segment of proximal tubule, increasing the glucosuria and promoting weight loss and cardiovascular protection in selected patients. Although SGLT2-i are found to be safe, they are not exempted of complications, such as the one discussed in this article [3, 6].

Case Presentation

We report the case of a female patient in her seventies, with a medical history of hypertension, dyslipidemia, ischaemic cardiomyopathy without myocardial dysfunction and poorly controlled T2DM, in treatment with insulin, metformin and canagliflozin.

She was admitted to the critical care unit after developing an acute-onset altered mental state two days after undergoing an elective total knee replacement, with intradural anaesthesia and without immediate complications. Her postoperative course initially followed the expected

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evolution, but after 48 hours she was disoriented, had an unintelligible speech and a glasgow coma scale of 12 points.

She was transferred to the emergency room where a blood test and arterial blood gases were completed. She was diagnosed with severe metabolic acidosis with pH < 6.8 and an elevated anion gap, undetectable serum bicarbonate, glycemia of 238 mg/dL and ketonuria. Lactate was 1.7 mmol/dL, PCR 33 g/dL and procalcitonine 1. Renal and liver function were within the normal range, and chest X-ray showed no abnormalities. She also underwent a cranial CT which was normal.

Treatment with bicarbonate, fluid resuscitation, insulin infusion and empiric antibiotic therapy was established. As her low level of consciousness didn't improve, she was intubated and admitted to the intensive care unit to continue therapy.

Outcome and Follow Up

During her stay in the ICU she was diagnosed with an euglycemic ketoacidosis. Intensive fluid resuscitation and insulin perfusion were continued and gradually the metabolic acidosis improved, as well as the overall condition of the patient; she was removed from mechanical ventilation 48 hours after the admission and transferred to the surgery ward after 4 days in the ICU. At that moment, she presented a normal glucose level with a pH normalized to 7.47. Lactic acid was also normal in 5 mg/dL and the PCR was still decreasing in 8.5mg/dL. She was discharged from the hospital 16 days after the surgery, without further complications or sequelae.

Differential Diagnosis

Using acidosis as the guide clinical sign, it is suggested to discard any kind of respiratory depression that could develop hypercapnia or hypoxemia that can cause a decrease in the level of consciousness. For this reason, it is recommended to take a blood gases to differentiate a respiratory acidosis from a metabolic one [6].

Once metabolic acidosis is determined in patients with an acute-onset mental status change, a variety of diagnoses should be considered. Infections should be dismissed, as they could lead not only to other neurologic syndromes, but also to septic shock if not treated promptly. Evaluation of lactic acid and ketonuria are recommended, as well as a complete electrolyte panel in order to calculate the anion gap. These results could lead the suspected diagnosis to an alcoholic or other-drug intoxication. In this case, it can be easily dismissed with blood and urine tests [3].

It is also important to rule out any type of vascular cerebral pathology, such as ischaemic stroke or intracerebral hemorrhage. Finally, if all these causes are ruled out, ketoacidosis should be considered as a possible diagnose, keeping in mind alcoholic and diabetic ketoacidosis as possibilities.

Discussion

Most DKA appear in T1DM and are associated to hyperglycemia, usually with glucose blood levels over 400 mg/dL; for this reason, a diagnosis of EDKA in patients with T2DM is an unexpected syndrome. The mechanism by which hyperglycemia develops in DKA is based on three backbones [4]. An increase in gluconeogenesis and also in glycogenolysis as well as a decrease in the peripheral uptake of glucose because of a decrease in insulin levels. The physiopathology behind this is that glucose is not able to get inside the cells so it is not used as metabolic fuel. For this reason, there is an increase in lipolysis and in fatty acids used in the liver in order to produce energy and, consequently, an increase of the ketone bodies [3, 6].

Many factors are known to trigger the EDKA in diabetic patients, all of them causing a carbohydrate deficit and a resultant decreased serum insulin associated with an excess of counter-regulatory hormones. This hormone dysregulation leads to ketosis by increasing lipolysis and free fatty acids, resulting in metabolic acidosis with elevated anion gap which triggers respiratory compensation [1].

However, the underlying mechanism of EDKA development is quite unknown. The most accepted one is the glycosuria caused by blocked glucose reabsorption on the proximal convoluted tubule by SGLT2 inhibitors. This situation leads to a glucagon release that causes an elevation of the glucagon to insulin ratio, increasing the gluconeogenesis, lipolysis and ketogenesis [3]. This mechanism can be exacerbated because of the dehydration caused by the natriuretic and osmotic effect on glucose and sodium cotransporter that SGLT2 has, which leads to a secondary osmotic effect on reabsorption of water [8].

Apart from conditions like starvation, pancreatitis, surgery, infections and other disorders assisting a high malnutrition risk in our patients, it is also known that SGLT-2 can also facilitate EDKA, unrelated to the duration of the exposure [4, 9]. The process by which can produce EDKA is not other than the main mechanism of action of the drug: to enhance excretion and block reabsorption of glucose in the proximal convoluted tubule, leading to a loss of urinary glucose which develops a state of carbohydrate starvation and boosting a glucagon/insulin ratio disbalance. Additionally, it has been found that SGLT2 inhibitors can also stimulate the release of glucagon from the pancreas, worsening the dysregulation above mentioned by maintaining euglycemia [8].

The signs and symptoms can be variable between patients, and it is usually not recognized because serum glucose levels are not elevated. However, when described, it is as similar as in hyperglycemic DKA, presenting with severe mental status changes but in less cases with polyuria or polydipsia, since serum glucose is normal (less than 250-300 mg/dL) [6]. Regarding serum levels of beta-hydroxybutyrate, they should be greater than 3 mmol/L to agree with EDKA diagnosis, close attention should also be paid to a metabolic acidosis and a serum bicarbonate less than 18 mEq/L.

The management recommended by the American Diabetes Association is in first place to stop the inciting agents. In case of EDKA induced by SGLT2i it is recommended to discontinue them immediately [6]. In second place, intensive fluid resuscitation with isotonic serum therapy is recommended, and it should be the main pillar of medical management [3]. It is justified by the important fluid loss caused by EDKA, which can reach from 6 to 9 L, so an important rehydration could avoid the tissular hypoperfusion and the consequently metabolic alterations. In this

context, monitoring ketones and electrolytes is recommended until the patient is stable [9].

Fluid replacement should be followed by a continuous insulin infusion, monitoring serum potassium levels and adding dextrose 5% from beginning of treatment, as glucose levels are already normal. Sodium bicarbonate infusions are controversial, and most of the guidelines do not recommend using it. Most patients recover well with an early diagnosis which can also allow an early treatment. A delay in any of them, can lead to a persistent acidosis and all the complications derived from a prolonged hospitalization.

Learning Points/Take Home Messages

- Acute-onset mental status change has a wide variety of possible causes, including intoxication, severe infection, metabolic alteration or brain structural alteration.
- The EDKA diagnosis is challenging, and health care professionals should keep it in mind once other causes of increased anion gap metabolic acidosis are excluded.
- SGLT2 inhibitors are often used in diabetes treatment, clinicians should be aware of their possible complications.
- The recommended treatment of EDKA includes: intensive rehydration and continuous insulin infusion. It is important to monitor the serum potassium levels to avoid hypokalemia.

Conflicts of Interest

None.

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None.

Consent

Written informed consent was obtained from the patient to publish this case report. On request, a copy of the written consent is available for review by the Editor-in-Chief of this journal.

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