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CHALLENGES IN SEVERE DIABETIC KETOACIDOSIS: CASE REPORT AND LITERATURE REVIEW

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Abstract: Diabetic ketoacidosis (DKA) is a serious acute complication of diabetes mellitus (DM), especially type 1 diabetes mellitus (DM1), which can occur as the first manifestation of the disease. Diagnosis requires blood glucose above 250mg/dL, metabolic acidosis with serum bicarbonate <18mEq/L and/or blood pH < 7.4, as well as ketone bodies in the blood or urine. The main etiologies are infections and poor adherence to insulin treatment. In management, it is essential to check serum potassium levels before insulin therapy. Serum bicarbonate replacement can also be useful, although this is controversial in the literature. The case in question refers to a patient who sought emergency care for dyspnea, fatigue and abdominal pain, evolving with worsening general condition, due to a cutaneous lumbar abscess. The rarity of the condition is due to a serum bicarbonate level of less than 1 mmol/L, with few reports found in the medical literature, as it is mostly incompatible with life.
Keywords: Diabetes mellitus; insulin therapy; ketosis; hyperglycemia.

INTRODUCTION

DKA is characterized by the triad of hyperglycemia, increased anion gap metabolic acidosis and ketosis. Although it is more common in DM1, it can also occur in type 2 diabetes mellitus (DM2). In most cases, if DKA is the first presentation of DM, the underlying diagnosis is likely to be DM1, especially if the patient has a short history of symptoms, a young age and a normal body mass index (BMI). The main etiologies are infection, voluntary discontinuation of insulin and malfunctioning electronic devices, as well as trauma, medication and alcohol and drug abuse. DKA is caused by absolute or relative insulin deficiency, which results in low cellular glucose uptake despite high blood glucose levels. In this scenario, an increase in hormones such as glucagon, catecholamines and cortisol are also responsible for hyperglycemia. The result of this is an attempt to use other sources to produce ATP, with lipolysis and the formation of ketone bodies being the answer to meeting the energy demand.

At the same time, there is an increase in diuresis due to hyperglycemia, through an increase in urine osmolarity, since, in this condition, glycemia exceeds tubular reabsorption capacity. As a result of these metabolic alterations, a state of dehydration sets in with hydroelectrolytic alterations, especially those relating to potassium, which are exacerbated by attempts to compensate, forming a state of metabolic acidosis. In management, potassium and serum bicarbonate levels are measured and, if necessary, replaced, in addition to hydration and insulin therapy. CAD is still one of the main causes of morbidity and mortality in diabetic patients, despite the great advances in diagnosis and treatment in contemporary medicine. The aim of this paper is to report a case of severe CAD with unusual features in the natural history of the disease, in which a favorable outcome was possible despite the severity of the clinical presentation.

CASE PRESENTATION

A 45-year-old female patient from Porto Alegre in the south of Brazil came to the emergency department with dyspnea, fatigue and abdominal pain. She developed worsening general condition, increased ventilatory effort (Kussmaul's breathing), vomiting, polydipsia and polyuria, without sensory impairment. There was no family predisposition to type 1 or type 2 diabetes mellitus. She was taking combined oral contraceptives and had a medical history of skin abscesses in the lumbar region since childhood, which resolved spontaneously, requiring drainage only once. In the month prior to the condition, she had undergone body-caudal pancreatectomy and

splenectomy by videolaparoscopy due to a simple mucinous cyst in the tail of the pancreas. Diabetic ketoacidosis was diagnosed, according to: arterial pH 6.8, glycemia 656 mg/dL and ketonuria 3+. Other markers were also altered, such as glycated hemoglobin 12.3%, bicarbonate 0.2 mmol/L, total CO2 10 mmol/L, amylase 231 U/L and lipase 371 U/L. As inflammatory markers, C-reactive protein and leukocyte count were significantly increased. Initial serum potassium, other electrolytes and renal function were within normal limits.

The patient was treated according to the usual guidelines for CAD, with intravenous hydration, subcutaneous and intravenous insulin, bicarbonate replacement and empirical broad-spectrum antibiotic therapy, as well as monitoring the response through arterial blood gases. However, during management, potassium decreased considerably, reaching 2.4 mEq/L. Due to the severity of the condition, she was referred to the ICU, where potassium replacement was carried out several times until adequate levels were reached. An investigation into the cause of the DKA was then launched. Physical examination revealed the presence of a cutaneous lumbar abscess, which had not been mentioned by the patient. An ultrasound was carried out with local drainage, which revealed the presence of oxacillin-sensitive *staphylococcus aureus* according to the antibiogram. The patient was treated with cephalexin and subsequently discharged.

DISCUSSION

The overall prevalence of CAD is between 50 and 100 events per thousand adult individuals with DM1, decreasing with increasing age. Other characteristics have also been associated as risk factors, such as lower economic status, inadequate glycemic control, female gender and psychiatric disorders [1]. In individuals with DM1, CAD can be the initial presentation of the disease in up to 40%. Similarly, in patients with DM2, CAD can also occur in 20 to 30% of patients [2,3]. Despite this, mortality from CAD has fallen to less than 1% in the last 20 years [4]. Regarding the etiology of the case, the performance of a body-caudal pancreatectomy and the existence of a lumbar abscess were the two components responsible, showing the importance of clinical follow-up of pancreatectomized patients. The initial symptoms of the disease are polyuria, polydipsia, polyphagia, weight loss, vomiting, abdominal pain and fatigue. Dehydration, tachycardia, tachypnea with Kussmaul's pattern and ketone breath can also occur, as in the case under discussion. Laboratory investigation for diagnostic confirmation is essential for proper management and better outcomes. All the diagnostic criteria of the American Diabetes Association (ADA) were present: glycemia > 250mg/dL, pH measurement < 7.3, serum bicarbonate < 18 mEq/L, ketonuria ≥ 2+ or ketonemia, assessed by beta-hydroxybutyrate ≥ 3 mmol/L.

The main tests to be ordered are gasometry, glycemia, ketonemia or ketonuria, electrolytes (sodium, potassium and phosphate), renal function, complete blood count and electrocardiogram. The severity of the case was evidenced by the pH of 6.8, with a bicarbonate below 1 mEq/L. With regard to bicarbonate replacement, there is little evidence in the literature to support the conduct with a pH and bicarbonate at such extreme levels.

In adults, the AAD classified the severity of DKA according to the degree of acidosis, being mild between pH 7.2 and 7.3, moderate between pH 7.10 and 7.20 and severe pH less than 7.10. Other indicators of severe conditions would be a bicarbonate of less than 5 mmol/L, hypokalemia of less than 3.5 mmol/L at the time of admission and decreased sensory function, with a Glasgow < 12. Treatment includes fluid and electrolyte therapy, insulin application, treatment of the triggering cause, monitoring of therapy and resulting complications [5].

A crucial point in the management of DKA is the management in the first hour, which aims to provide hemodynamic and respiratory stabilization of patients. In this scenario, the ABCDE sequence is followed, with emphasis on replacing saline solution with 10 to 20mL/kg in 20 or 30 minutes. In this first hour, it is not recommended to start insulin due to the risk of cerebral edema, although there are no studies evaluating the risk of cerebral edema in adults with CAD, only a few conducted in the pediatric population [6]. Once initial hydration has been carried out, it is very important to calculate the estimated water deficit in order to replace it within 24 to 48 hours with 0.9% or 0.45% NaCl saline solution.

After the first hour, the mainstay of treatment for DKA is the use of insulin, with special attention to kalaemia [7]. Reducing acidosis results in potassium returning to the intracellular medium and hypokalemia, the manifestations of which can be fatal arrhythmias and weakness of the respiratory muscles. Therefore, if the patient has serum potassium levels < 3.3 mEq/L, the start of insulin should be postponed until this electrolyte has been replaced with an infusion of 20 to 30 mEq/hour, with the goal of serum potassium > 3.3 mEq/L. When it is possible to start insulin, it can be given by intravenous (IV) infusion, without a bolus, at a dose of 0.14 IU/kg/hour, with the goal of reducing blood glucose by up to 10% in the first hour. If this reduction is not achieved, the recommendation is to add a bolus dose of insulin 0.14 IU/kg to the previous infusion. In the event of a drop in blood glucose of more than 100 mg/dL/hour, the insulin dosage should be reduced and/or associated with the administration of 5 to 12% glucose solution in order to avoid hypoglycemia.

In order to assess the response to treatment, it is important to monitor gasometry [8], serum electrolytes, blood glucose, creatinine and urea levels for 2 to 4 hours. One of the goals of CAD treatment is the transition from IV to subcutaneous insulin administration, as well as changing hydration to the oral route. In this scenario, regarding insulin administration and serum potassium correction, a controversial topic in the medical literature is the role of sodium bicarbonate administration in cases of severe CAD, i.e. with pH < 6.9. One of the justifications for correcting acidosis with sodium bicarbonate would be the risk of reduced cardiac contractility and the possibility of potentially lethal arrhythmias [9,10]. However, despite the biological plausibility of this approach [11], this benefit is not clear in the medical literature [12,13].

In 2013, Duhon et al [14] conducted a single-center retrospective cohort study. They assessed 86 patients with DKA and initial pH < 7, and separated them into 2 groups, in which one received sodium bicarbonate (44 patients) and the other did not (42 patients), in which the primary outcome was the time to resolution of acidosis. Secondary outcomes consisted of length of hospital stay, length of continuous insulin infusion, amount of intravenous fluid, potassium levels and need for insulin in the first 24 hours of hospitalization. The outcomes with statistically significant results were the amount of insulin in 24 hours and the need for intravenous fluids, which was higher in the groups that received bicarbonate. The other outcomes showed no difference between the two groups. Thus, the authors' conclusion is that in this study there was no evidence of benefit from bicarbonate replacement for CAD patients with a pH < 7.

In 2011, Chua et al [15] published a systematic review comparing bicarbonate administration and non-administration in the context of emergency care in adult and pediatric patients. As a limitation of the studies, there was great heterogeneity in the definition of the cut-off value to determine the need for

bicarbonate treatment, which weakens the comparison between the studies. In addition, of the 22 studies evaluated, only three were randomized clinical trials whose main limitations were: low number of patients; 2 studies excluded patients with acidosis pH 6.9; variability in the form of bicarbonate administration. The conclusion of the study was that there is a lack of evidence of clinical benefit from correcting acidosis in cases of CAD with bicarbonate, which does not justify the routine use of this drug [15].

According to the AAD guidelines, the resolution criteria are glycemia less than 200 mg/dL and two of the following criteria: venous pH greater than 7.3, anion gap less than or equal to 12 mEq/L and serum bicarbonate level greater than or equal to 15 mEq/L. In high-risk cases, some populations require a personalized approach to treatment, such as pediatric patients, obstetrics, those with chronic kidney disease, COVID-19 and euglycemic DKA, in which the blood glucose level is lower than 250 mmol/L, despite metabolic acidosis and ketosis. The incidence of euglycemic DKA has increased in recent years, specifically with the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with insulin deficiency in DM2, DM1 or latent autoimmune DM.

CONCLUSION

Ketoacidosis is a serious medical emergency that requires proper medical management because it has a high mortality rate. The disease is characterized by symptoms of hyperglycemia, metabolic acidosis and ketonuria/ketonemia. Despite the controversies regarding serum bicarbonate replacement, the correct management, with hydration, insulin therapy and potassium assessment, is very well established in the medical literature. Therefore, the aim of this study is to show that critically ill patients, such as the case described, can have favorable outcomes and thus stimulate quality clinical studies specific to this population with severe CAD.

NOTES

The authors have declared that there are no conflicts of interest.

HUMAN ETHICS

Consent was obtained from all participants.

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