REUE | Review Article

Diabetic ketoacidosis and sodium glucose cotransporter-2 inhibitors: What do we need to know?

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Diabetic ketoacidosis related to sodium glucose cotransporter-2 (SGLT2) inhibitors is a rare but potentially serious complication. Outside of a clinical context that leads to suspicion of diabetic ketoacidosis a priori, the diagnosis is challenging. Treatment requires insulin given at an injection rate able to inhibit the production of ketone bodies, the process causing the problem; glucose must be concomitantly administered in many cases. Diabetic ketoacidosis can be avoided by knowing which patients are at greatest risk for this complication before prescribing SGLT2 inhibitors and by refraining from reducing the patient's usual insulin dose regimen or carbohydrate intake. It is also essential to equip the patient with information, such as possible precipitating factors and how to detect and treat ketosis in its early stages. Emergency departments should test for high ketone body concentrations in blood during the initial evaluation of patients who are on SGLT2 inhibitors.

Keywords: Sodium glucose cotransporter-2 (SGLT2) inhibitors. Diabetic ketoacidosis. Euglycemic ketoacidosis. Acidosis.

Cetoacidosis diabética e inhibidores del cotransportador de sodio y glucosa 2: ¿qué debemos saber?

La cetoacidosis diabética relacionada con los inhibidores del cotransportador de sodio y glucosa 2 (SGLT2) es una complicación muy poco frecuente, pero potencialmente grave. Su diagnóstico no es fácil si no existe una sospecha previa y en su tratamiento es fundamental la administración de insulina a una velocidad de infusión suficiente para inhibir la cetogénesis causante del proceso, junto a la administración concomitante de glucosa en muchos de los casos. Podemos evitar su aparición conociendo qué paciente está en mayor riesgo de desarrollarla antes de prescribir estos fármacos y evitando disminuir las dosis habituales de insulina o la ingesta de hidratos de carbono. Es fundamental además facilitar al paciente la información necesaria sobre posibles factores precipitantes, o cómo detectar y tratar la cetosis en fases tempranas. Una estrategia para su detección precoz en los servicios de urgencias podría ser la realización de cetonemias en el triaje a pacientes en tratamiento con SGLT2.

Palabras clave: Inhibidores del cotransportador de sodio y glucosa 2 (SGLT2). Cetoacidosis diabética. Cetoacidosis diabética euglucémica. Acidosis.

Introduction

In recent years, there has been a notable increase in the prescription of sodium–glucose cotransporter 2 (SGLT2) inhibitors. This rise is likely related to their proven prognostic benefit in patients with heart failure (HF), rather than their original indication as antidiabetic agents.[1] In Spain, dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin are commercially available.

Published evidence positions these agents as the first drugs to reduce mortality across the entire spectrum of HF, regardless of ejection fraction, in both diabetic and non-diabetic (DM) patients.[2-5]

However, as indications expand and prescriptions of SGLT2 inhibitors increase, it is reasonable to expect a rise in emergency department (ED) visits due to potential adverse effects or complications, as occurs with any medication. Among these is diabetic ketoacidosis (DKA), whose true incidence rate is difficult to determine but is estimated between 0.6 and 2.2 per 1,000 patient-years in those treated with SGLT2 inhibitors.[6-8] Canagliflozin carries the highest risk, with a hazard ratio (HR) of 3.58 vs empagliflozin (HR, 2.52) or dapagliflozin (HR, 1.86).[8]

Although very uncommon, the potential severity of this complication raises important questions for emergency physicians: What factors predispose to its development? Is it preventable? How should it be diagnosed? And, above all, does its treatment differ in any meaningful way from that of classic type 1 diabetes–related DKA?

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Pathophysiology of ketoacidosis

The risk of developing DKA after initiating SGLT2 therapy is higher than with other antidiabetic agents, with an HR of 1.91 (95% CI, 1.91–4.11), vs an HR of 1.13 (95% CI, 0.43–3) for other treatments.[9]

DKA develops when there is an absolute insulin deficiency or impaired insulin activity—meaning reduced use of carbohydrates together with a parallel rise in counter-regulatory hormones. Hypoinsulinemia promotes lipolysis and ketogenesis as alternative energy pathways when glucose–insulin signaling is deficient.

Diagnostic criteria for typical DKA include blood glucose > 250 mg/dL, ketones > 3 mmol/L, pH < 7.30, and bicarbonate < 15 mEq/L.[10] However, a small proportion (estimated at 1–7%) present with only mildly elevated glucose levels.[11] These are exceptional in type 1 diabetes and have been associated with concurrent factors such as pregnancy, alcoholism, or caloric deficit due to urinary glucose loss driven by elevated counter-regulatory hormones.

SGLT2 inhibitors act primarily by blocking glucose reabsorption in the proximal tubule. In diabetic patients receiving SGLT2 therapy, drug-induced glucosuria combined with hypoinsulinemia may rarely trigger ketogenesis, leading to DKA. One-third of these cases present with normal or slightly elevated glucose levels.[12] SGLT2 inhibitors increase urinary glucose loss, thus reducing glucose availability and thereby diminishing the stimulus for insulin secretion—resulting in "less glucose and less insulin." Diabetic patients at greatest risk are those with underlying insulin deficiency, that is, individuals with type 1 diabetes who reduce their insulin dose, or type 2 diabetes with limited pancreatic reserve and/or depleted glycogen stores. That is the reason why some countries restrict SGLT2 inhibitor use in type 1 diabetes.

Of note, many reported cases of SGLT2-related DKA have been associated with reduced caloric intake or insulin dose, both of which act synergistically to promote ketogenesis.[11,12]

Precipitating factors

Although patients with type 1 diabetes have the highest risk of SGLT2-related DKA, other intrinsic conditions may further increase susceptibility, including pregnancy, alcohol or drug use, low-carbohydrate intake or "ketogenic" diets, lack of diabetes education, previous DKA, use of continuous subcutaneous insulin infusion pumps, inappropriate insulin dose reductions, high SGLT2 doses, or latent autoimmune diabetes in adults (LADA).[11]

On the other hand, common precipitating events include intercurrent illness or infection, vomiting, volume depletion, strenuous exercise, surgery, failure of insulin infusion pumps, reduced insulin dosing, or changes in dietary carbohydrate intake.

Because some SGLT2-related DKA cases present with nearly normal glucose levels and nonspecific symptoms, such as nausea, vomiting, abdominal pain, dyspnea with tachypnea, diagnosis in the ED may be challenging. This raises the question of whether routine ketone testing should be implemented—possibly beginning at triage—for patients on SGLT2 inhibitors. Although not yet included in published protocols, such an approach may expedite diagnosis and benefit patients.

Prevention of SGLT2-related DKA

Although this is a very uncommon complication, strategies must be implemented to prevent the development of DKA (Table 1). First, when prescribing an SGLT2 inhibitor, it is essential to identify patients who, due to their clinical characteristics, are at higher risk—such as insulin-dependent diabetics, those with limited pancreatic reserve and/or depleted glycogen stores, or those with any of the previously mentioned precipitating conditions (Table 2). Type 2 diabetics who are not treated with insulin and who have no precipitating factors are at very low risk of developing DKA.[14]

Patients prescribed an SGLT2 inhibitor who are considered "at risk" should receive diabetes education that includes recognition of symptoms and early self-detection of ketogenesis. Furthermore, it is recommended to start at lower SGLT2 doses[11] and perform ketone testing within the first weeks—even in the absence of symptoms—because most cases of DKA occur within the first 2 months after starting therapy.[15]

Protocols have been developed for patients with type 1 diabetes to help them recognize ketosis and prevent the development of DKA.[16] The measures in these protocols are likewise applicable to type 2 diabetics. Depending on the degree of ketonemia, and in addition to temporarily discontinuing the SGLT2 inhibitor until reassessment, patients should ingest 15–30 g of rapidly absorbed carbohydrates and administer an insulin bolus.[12]

Once SGLT2 therapy has been initiated, its withdrawal is recommended prior to scheduled surgery or during intercurrent acute illness requiring hospitalization. More data are still needed, since SGLT2 inhibitors may have the potential to reduce oxidative stress, endothelial dysfunction, and sympathetic activity, which could be beneficial in some acute conditions.[17,18] In fact, continuation may be considered in certain hospitalizations for HF under specific stability criteria, given their proven benefit in this condition.[19]

Table 1. Recommendations to prevent the development of diabetic ketoacidosis related to sodium–glucose cotransporter 2 inhibitors

Careful selection of the patient to whom SGLT2 inhibitors will be prescribed, assessing risk factors for developing DKA.
Initiation of treatment at low doses in high-risk patients.
In insulin-dependent patients, appropriate adjustment of insulin dose to avoid insulinopenia.
Provide diabetes education that includes: • Identification of DKA symptoms and detection of ketone bodies, especially if insulin doses are modified. • Steps to follow if ketone bodies appear. • Comprehensive information on predisposing situations. • Emphasis on maintaining a diet with an appropriate amount of carbohydrates, avoiding prolonged fasting.

DKA: diabetic ketoacidosis; SGLT2: sodium–glucose cotransporter 2 inhibitors.

Table 2. Conditions associated with a higher risk of developing ketoacidosis
Type 1 diabetes.
Suspected LADA (onset in early adulthood, BMI < 25 kg/m^2, and early need for insulin).
Type 2 diabetes treated with insulin.
Long-standing type 2 diabetes with poor usual control and poor treatment adherence.
Type 2 diabetes with precipitating factors such as prolonged fasting, low-carbohydrate diets, alcohol misuse, or reduction of insulin doses.

DM: diabetes mellitus; BMI: body mass index.

Treatment should also be stopped during fasting or before intense physical exercise.[20]

It is important to ensure that insulin doses are not reduced unless clearly indicated, and to inform patients about the need for ketone monitoring whenever their treatment changes or during intercurrent illness.[14]

The occurrence of SGLT2-related DKA does not necessarily contraindicate re-initiation of the drug later on particularly if the precipitating factor has been clearly identified and the patient can receive specific education regarding prevention and management of ketosis.[21]

Treatment of SGLT2-related DKA

The management of SGLT2-related DKA is essentially similar to that of type 1 diabetes–associated DKA. Both require the administration of fluids, insulin, and glucose, in addition to treatment of the precipitating cause. In both conditions, close monitoring of volume status and serum potassium (and other electrolytes) is mandatory.

The distinctive feature of SGLT2-related DKA is that, at the time of diagnosis, blood glucose levels may be normal or not exceed 250 mg/dL. Insulin administration is vital to inhibit ketogenesis and must be initiated as early as possible. However, euglycemic DKA requires early glucose supplementation to avoid hypoglycemia during IV insulin infusion. This point is critical, as insufficient insulin administration—regardless of glucose level—prevents resolution of ketonemia and acidosis.[11]

Three phases can be distinguished in the treatment of DKA: 1) stabilization phase, with correction of acidosis and dehydration; 2) maintenance phase, during which treatment continues until ketogenesis resolves; and 3) resolution phase, involving gradual discontinuation of IV therapy and transition to subcutaneous (SC) insulin and oral carbohydrate intake. During the stabilization phase, aggressive rehydration should begin at 250–500 mL/h, unless contraindicated, such as in patients with cardiac disease, in whom strict volume monitoring is required. If initial hyperglycemia is absent, dehydration tends to be less severe because osmotic diuresis is reduced.

Simultaneously with fluid therapy—and in the absence of hypokalemia—IV insulin infusion should be started promptly at 0.1 U/kg/h (typically 6–8 U/h). Many protocols recommend adjusting the insulin infusion rate based on reductions in glucose of 50–100 mg/dL per hour.[10,22] However, in euglycemic DKA requiring concurrent IV glucose infusion, glucose decline is not a reliable guide. Instead, insulin adjustments should be based on decreases in serum ketone levels. The primary therapeutic goal is inhibition of ketogenesis, not normalization of glucose levels. If ketone levels do not fall, the insulin infusion rate must be increased[23]—and glucose administration increased as needed to maintain adequate insulin dosing. Ketone measurement should preferably be performed in blood, where β-hydroxybutyrate (β-OHB) predominates, rather than in urine, where acetoacetate is measured. Urine acetoacetate may paradoxically rise during treatment as β-OHB is converted and excreted.[9] In patients with normal potassium levels, potassium supplementation is required during insulin therapy to prevent hypokalemia.

Of note, adequate insulin dosing is essential in SGLT2-related DKA. Although if serum glucose exceeds 200 mg/dL the insulin infusion rate may be reduced, it must remain sufficient to suppress ketogenesis and reduce serum ketone concentrations. In these cases, IV dextrose must be provided at a rate that allows continuation of at least 0.05 U/kg/h of insulin without causing hypoglycemia. Insulin administration is the intervention that resolves DKA by inhibiting ketogenesis; thus maintaining an adequate infusion rate is essential.

Insulin infusion (along with glucose, fluids, and potassium) must be continued until ketogenesis has stopped and metabolic acidosis has resolved (maintenance phase). As in classic DKA, IV insulin should not be discontinued until 2 hours after administering SC insulin and after the patient has begun oral carbohydrate intake (resolution phase).[10]

A controversial aspect is the need for bicarbonate. Its use is not recommended in DKA because no clear clinical benefit has been demonstrated, and adverse effects have been reported—such as impaired renal ketone clearance leading to paradoxical worsening of acidosis, hypokalemia, and risk of cerebral edema.[24]

The perception that SGLT2-related DKA requires a longer resolution time and large amounts of bicarbonate likely reflects insufficient insulin and glucose administration, which fails to halt ketogenesis and correct acidosis. More data are needed to confirm this hypothesis.

Conclusions

The widespread use of SGLT2 inhibitors requires clinicians to be prepared to recognize their potential adverse effects. Although SGLT2-related DKA may seem increasingly common, it remains a rare and preventable complication.

The possibility of DKA occurring with normal glucose levels raises the question of whether ketone testing should be protocolized in triage for patients taking SGLT2 inhibitors who present with compatible symptoms—or even performed routinely. Recognizing precipitating factors helps guide prevention strategies, and patients must be engaged in identifying these risks and in early detection and management of ketosis.

The main aim of treatment is inhibition of ketogenesis, achieved through insulin administration. Hypoglycemia must be avoided with concurrent glucose infusion. Potassi-

um supplementation is essential to prevent hypokalemia, and aggressive fluid resuscitation is a key component of therapy. Bicarbonate administration does not appear to provide benefit.

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