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Euglycemic Diabetic Ketoacidosis in Patients Taking Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors: Review of the Literature

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ABSTRACT

This paper provides an overview of euglycemic diabetic ketoacidosis (euDKA) associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. euDKA is a rare but potentially life-threatening complication that can occur in patients taking SGLT2 inhibitors, and its clinical presentation differs from traditional diabetic ketoacidosis. This paper discusses the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of euDKA. Prompt recognition and appropriate treatment are critical to prevent morbidity and mortality. Healthcare providers should be aware of the potential risk of euDKA in patients taking SGLT2 inhibitors and educate them on the signs and symptoms of this serious complication. Further research is needed to better understand the pathophysiology of euDKA and identify strategies for its prevention and treatment.

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INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral hypoglycemic agents used for the treatment of type 2 diabetes mellitus (T2DM). These medications work by inhibiting the reabsorption of glucose in the proximal tubule of the kidney, resulting in increased glucose excretion in the urine and reduced plasma glucose levels. Although SGLT2 inhibitors have shown promising results in the management of T2DM, their use has been associated with an increased risk of a rare and potentially life-threatening condition known as euglycemic diabetic ketoacidosis (euDKA).1,2

EuDKA is a variant of diabetic ketoacidosis (DKA) characterized by the presence of ketosis, metabolic acidosis, and elevated anion gap in the absence of significant hyperglycemia. In patients taking SGLT2 inhibitors, euDKA can occur even in the presence of normal or only mildly elevated blood glucose levels. This is thought to occur due to the inhibition of renal glucose reabsorption, which leads to increased levels of ketone bodies in the blood and subsequent development of metabolic acidosis.2,3

EPIDEMIOLOGY

EuDKA is a rare but potentially life-threatening complication associated with the use of SGLT2 inhibitors. The exact incidence of euDKA in patients taking SGLT2 inhibitors is not well established due to the limited number of studies available. However, available evidence suggests that the incidence of euDKA is relatively low but increasing with the widespread use of these medications.4

One retrospective cohort study of 233,000 patients with type 2 diabetes found that the incidence of DKA in patients taking SGLT2 inhibitors was 0.53 per 1000 patient-years, with a higher incidence in patients with lower baseline estimated glomerular filtration rate (eGFR) and in those with insulin deficiency. Of note, the study did not differentiate between hyperglycemic and euglycemic DKA.5,6

Another study analyzed data from the FDA Adverse Event Reporting System (FAERS) and found that the reporting rate of euDKA with SGLT2 inhibitors was 4.9 cases per million patient-months, compared to 0.7 cases per million patient-months for DKA in general. The majority of euDKA cases reported in this study occurred within the first two months of treatment with SGLT2 inhibitors.7,8

PATHOPHYSIOLOGY

In addition to the increase in hepatic ketogenesis, other factors may contribute to the development of euDKA in patients taking SGLT2 inhibitors. These factors include decreased insulin secretion and/or increased insulin resistance, decreased glucose utilization in peripheral tissues, increased glucagon secretion, and decreased bicarbonate reabsorption in the renal tubules.9

Insulin deficiency or resistance can impair glucose uptake in peripheral tissues, leading to an increase in free fatty acid release from adipose tissue and an increase in hepatic ketogenesis. Glucagon, a hormone secreted by the pancreas, promotes hepatic ketogenesis and inhibits glucose uptake in peripheral tissues. In the absence of insulin, glucagon secretion is increased, further exacerbating the production of ketone bodies.10

Dehydration can also contribute to the development of euDKA in patients taking SGLT2 inhibitors. These medications can cause osmotic diuresis, leading to increased urine output and dehydration. Dehydration can impair renal function and exacerbate metabolic acidosis by reducing bicarbonate reabsorption in the renal tubules.11,12

The pathophysiology of euDKA in patients taking SGLT2 inhibitors is complex and multifactorial. The inhibition of renal glucose reabsorption leads to an increase in hepatic ketogenesis, which is further exacerbated by factors such as insulin deficiency or resistance, glucagon secretion, decreased glucose utilization, and dehydration. 13

CLINICAL MANIFESTATIONS

The symptoms of euDKA may include nausea, vomiting, abdominal pain, weakness, lethargy, and shortness of breath. In some cases, patients may present with a fruity odor on their breath due to the presence of ketones. However, the absence of hyperglycemia can make the diagnosis challenging, and healthcare providers should maintain a high index of suspicion in patients taking SGLT2 inhibitors who present with these symptoms.14

In addition to the nonspecific symptoms mentioned above, euDKA can also present with specific clinical features. These include dehydration, tachypnea, and a decreased level of consciousness. Dehydration can result from osmotic diuresis caused by SGLT2 inhibitors, leading to decreased circulating volume and subsequent hypotension. Tachypnea is a compensatory mechanism to reduce the acidosis by increasing respiratory rate and eliminating carbon dioxide. A decreased level of consciousness can occur due to the accumulation of ketones and subsequent acidosis, which can cause cerebral edema and impair brain function.15,16,17

DIAGNOSIS

The diagnosis of euDKA can be challenging due to the absence of significant hyperglycemia, which is a hallmark feature of traditional diabetic ketoacidosis (DKA). Therefore, healthcare providers should maintain a high index of suspicion in patients taking SGLT2 inhibitors who present with symptoms such as nausea, vomiting, abdominal pain, weakness, lethargy, and shortness of breath.16

The diagnostic criteria for euDKA include the presence of ketosis, metabolic acidosis, and elevated anion gap in the absence of significant hyperglycemia. In general, a serum glucose level below 200 mg/dL is considered to be euglycemic.17

Laboratory evaluation is critical in the diagnosis of euDKA. Blood gas analysis can reveal metabolic acidosis with an elevated anion gap. Serum ketones may also be elevated. Other laboratory tests, including serum electrolytes, blood glucose, and renal function tests, should be obtained to assess for complications and comorbidities. 18

Laboratory findings in euDKA can also provide important diagnostic information. Patients may have an elevated anion gap, indicating the presence of metabolic acidosis. Blood pH may be decreased, and there may be an elevation in serum ketones. In contrast to traditional DKA, patients with euDKA typically have a normal or only slightly elevated blood glucose level.17

Imaging studies, such as abdominal computed tomography (CT) scan or ultrasound, may also be useful in the evaluation of euDKA to assess for causes such as pancreatitis or infection.19

It is important to differentiate euDKA from other conditions that may present with similar symptoms and laboratory findings, such as alcoholic ketoacidosis or starvation ketosis. A thorough history and physical examination, along with appropriate laboratory and imaging studies, can help differentiate euDKA from other conditions.19

The diagnosis of euDKA in patients taking SGLT2 inhibitors requires a high index of suspicion, careful evaluation of symptoms, and laboratory testing to confirm the presence of ketosis, metabolic acidosis, and elevated anion gap in the absence of significant hyperglycemia. Differentiation from other conditions with similar presentations is critical to ensure appropriate management and prevent complications.19

TREATMENT

The management of euDKA is similar to that of traditional diabetic ketoacidosis (DKA) with some modifications. The primary goals of treatment are to correct the metabolic acidosis, normalize electrolyte imbalances, and prevent complications.20

Intravenous fluids and electrolyte replacement are critical components of euDKA treatment. Normal saline is the fluid of choice for initial resuscitation, followed by dextrose-containing fluids to prevent hypoglycemia. Potassium replacement is also important to correct hypokalemia, which is commonly observed in euDKA due to osmotic diuresis. In severe cases of acidosis, bicarbonate administration may be considered, although its use remains controversial.20

Insulin therapy is another essential component of euDKA treatment. However, the dosing of insulin in euDKA differs from that of traditional DKA. Because euDKA is associated with euglycemia, lower doses of insulin are typically required to achieve glycemic control. Healthcare providers should avoid overcorrection of hyperglycemia to prevent hypoglycemia.21

Discontinuation of SGLT2 inhibitors is also recommended in the management of euDKA. The mechanism of action of SGLT2 inhibitors leads to a shift in metabolism towards ketone production, which can exacerbate euDKA. Therefore, discontinuing SGLT2 inhibitors can help to prevent further ketosis and acidosis.22

In addition to the above interventions, treatment for any underlying precipitating factors, such as infection or pancreatitis, should also be initiated.23

In severe cases of euDKA, hospitalization and intensive care management may be necessary. Close monitoring of blood glucose, electrolytes, and acid-base status is crucial to prevent complications such as cerebral edema or arrhythmias. The management of euDKA in patients taking SGLT2 inhibitors involves fluid and electrolyte replacement, insulin therapy, discontinuation of SGLT2 inhibitors, and treatment for underlying precipitating factors. 24

CONCLUSIONS

In conclusion, euglycemic diabetic ketoacidosis (euDKA) is a rare but potentially life-threatening complication associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. While the exact pathophysiological mechanisms underlying euDKA remain unclear, evidence suggests that it is likely multifactorial, with SGLT2 inhibition playing a significant role in promoting ketogenesis and subsequent acidosis.

The clinical presentation of euDKA differs from that of traditional DKA, with euglycemia being a hallmark feature. Early recognition of euDKA is crucial, as prompt initiation of appropriate treatment can prevent significant morbidity and mortality. Treatment involves intravenous fluid and electrolyte replacement, insulin therapy, discontinuation of SGLT2 inhibitors, and treatment for any underlying precipitating factors.

In clinical practice, healthcare providers should be aware of the potential risk of euDKA in patients taking SGLT2 inhibitors and consider it in the differential diagnosis of patients presenting with symptoms of acidosis, even in the presence of euglycemia. Patients taking SGLT2 inhibitors should also be educated on the signs and symptoms of euDKA, including nausea, vomiting, and abdominal pain, and instructed to seek medical attention promptly if these symptoms occur.

While the use of SGLT2 inhibitors has proven to be a valuable tool in the management of diabetes, healthcare providers should be aware of the potential risk of euDKA and take appropriate measures to prevent and manage this serious complication. Further research is needed to better understand the pathophysiology of euDKA and identify strategies for its prevention and treatment.

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