Review Article

SGLT2 Inhibitor–associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis

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ABSTRACT

Purpose: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the newest class of antihyperglycemic agents available on the market. Regulator warnings and concerns regarding the risk of developing diabetic ketoacidosis (DKA), however, have dampened enthusiasm for the class despite the combined glycemic, blood pressure, and occasional weight benefits of SGLT2 inhibitors. With the goal of improving patient safety, a cross-Canada expert panel and writing group were convened to review the evidence to-date on reported SGLT2 inhibitor–related DKA incidents and to offer recommendations for preventing and recognizing patients with SGLT2 inhibitor–associated DKA.

Methods: Reports covering DKA events in subjects taking SGLT2 inhibitors that were published in PubMed, presented at professional conferences, or in the public domain from January 2013 to mid-August 2016 were reviewed by the group independently and collectively. Practical recommendations for diagnosis and prevention were established by the panel.

Findings: DKA is rarely associated with SGLT2 inhibitor therapy. Patients with SGLT2 inhibitor–associated DKA may be euglycemic (plasma glucose level <14 mmol/L). DKA is more likely in patients with insulin-deficient diabetes, including those with type 2 diabetes, and is typically precipitated by insulin omission or dose reduction, severe acute illness, dehydration, extensive exercise, surgery, low-carbohydrate diets, or excessive alcohol intake. SGLT2 inhibitor–associated DKA may be prevented by withholding SGLT2 inhibitors when precipitants develop, avoiding insulin omission or inappropriate insulin dose reduction, and by following sick day protocols as recommended.

Implications: Preventive strategies should help avoid SGLT2 inhibitor–associated DKA. All SGLT2 inhibitor–treated patients presenting with signs or symptoms of DKA should be suspected to have DKA and be investigated for DKA, especially euglycemic patients. If DKA is diagnosed, SGLT2 inhibitor treatment should be stopped, and the DKA should be treated with a traditional treatment protocol. (*Clin Ther*. 2016;38:2654–2664)

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INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic agents for the pharmacologic management of type 2 diabetes. In guidelines, they are a second-line option in the management of hyperglycemia in type 2 diabetes.[1] Over a span of 6 weeks from May through June 2015, the US Food and Drug Administration, the European Medicines Agency, and Health Canada sequentially raised concerns regarding the unexpected association of diabetic ketoacidosis (DKA) among SGLT2 inhibitor–treated patients.[2–4] Currently, 3 SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are available in Canada and much of the world for the treatment of type 2 diabetes, and their product monographs now carry warnings and precautions regarding potential DKA, which may be euglycemic (defined in the present review as a plasma glucose level <14 mmol/L). Other agents in this class include ipragliflozin, luseogliflozin, and tofogliflozin. Despite a number of review articles summarizing the issue of SGLT2 inhibitor–associated DKA, clinicians require practical advice regarding the prevention and diagnosis of this relatively new clinical entity.[5–7]

DKA is a medical emergency affecting people with diabetes,[8,9] and it may sometimes be the presenting feature of a new diagnosis of diabetes. It has mortality rates ranging from 0.65% to 3.3%[8] and is most often identified in individuals with type 1 diabetes in whom the prevalence has been found to be 4.6 to 8.0 per 1000 patient-years.[9] However, DKA is not exclusive to those with type 1 diabetes.[10,11] Data from a Swedish population study indicated that DKA in persons with type 2 diabetes may account for as much as one third of all DKA cases, with a rate of 0.5 per 1000 patient-years.[11] DKA is often preventable if detected early and with appropriate self-monitoring. Treatment and preventive measures for DKA vary according to the precipitating factors, which include, but are not exclusive to, insulin omission, reduced food or fluid intake, infection, intercurrent events (eg, surgery, myocardial infarction, trauma, abdominal crisis, thyrotoxicosis), alcohol abuse, and use of drugs that can alter carbohydrate metabolism (eg, cocaine, corticosteroids, antipsychotic agents, interferon).

DKA results from a relative or absolute insulin deficiency coinciding with concomitant increases in counter-regulatory hormones that include cortisol, epinephrine, growth hormone, and glucagon. The net effect of this hormonal imbalance is to enhance hepatic gluconeogenesis, glycogen breakdown, and lipolysis while also decreasing cellular uptake of glucose leading to hyperglycemia and increased circulating levels of free fatty acids. When the liver's capacity to oxidize fatty acids is exceeded, ketone bodies accumulate, resulting in an anion gap metabolic acidosis. Although there are no definitive benchmarks for diagnosing DKA, the presence of ketones generally co-presents with a pH <7.3, a serum bicarbonate level ≤ 15 mmol/L, and an anion gap that exceeds 12 mmol/L.[12] Although plasma glucose levels are ≥ 14.0 mmol/L in most cases, euglycemic DKA with glucose levels <14 mmol/L has been reported in young individuals with type 1 diabetes[13] and in pregnant women.[14] However, because many of the reported cases with "euglycemic DKA" have glucose levels that are above normal, our group, in accordance with the American Association of Clinical Endocrinologists and the American College of Endocrinology, deems "euglycemic DKA" a misleading term. For that reason, we support more accurate terminology such as "DKA with lower-than-anticipated glucose levels."[5] Individuals with DKA, including those with euglycemia, may have symptoms of thirst, polyuria, nausea, vomiting, abdominal pain, confusion, sense of air hunger (Kussmaul's breathing), fever, and fruity odor on the breath (acetone), as well as indications of any of the precipitating factor(s).

DKA associated with the use of SGLT2 inhibitors has a somewhat different pathophysiology from classic DKA (discussed later). The major concern regarding SGLT2 inhibitor–associated DKA is that it may present with normal or moderately increased blood glucose levels, which can lead to delays in recognition or diagnosis. Given the potential patient safety concerns regarding delayed diagnosis and treatment, the goals of the present study were 2-fold: (1) to provide a concise review of the prevalence, risk factors, and pathophysiology of SGLT2 inhibitor–associated DKA; and (2) to convey practical, evidence-based recommendations for the prevention and diagnosis of DKA related to SGLT2 inhibitor therapy.

A 7-member panel was convened in January 2016 to review the literature on SGLT2 inhibitor–associated