



## Sodium–Glucose Cotransporter 2 Inhibitors and Diabetic Ketoacidosis: A Case Series From Three Academic Institutions

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Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have recently been associated with diabetic ketoacidosis (DKA). Initial case reports were largely among patients using SGLT2i off label in the setting of type 1 diabetes and were unusual because of limited associated hyperglycemia (1). More recently, the problem has been specifically noted in patients with type 2 diabetes (2). Meta-analysis of data from initial randomized controlled trials of SGLT2i suggests little risk of DKA (<0.1%) in patients with type 2 diabetes (3).

To better define the scope of the problem in clinical practice, we conducted a search of three academic health care systems' electronic health records. The study was approved by institutional review boards. Patients were selected from all emergency and inpatient encounters between 1 January 2013 and 30 April 2016 that contained the diagnosis codes for ketosis or acidosis (ICD-9 codes: 250.10, 250.11, 250.12, 250.13, 276.2, 790.6; ICD-10 codes: E08.10, E08.11, E09.10, E09.11, E10.10, E10.11, E13.10, E13.11, E11.65, E11.69, E87.2) and had an SGLT2i noted in a medication list. Individuals who met prespecified criteria for DKA with arterial pH <7.3, venous pH <7.27, serum bicarbonate <18 mEq/L, positive urine or serum ketones

per institutional laboratory cutoffs, or an anion gap >10 were included.

A total of 11,197 individuals had a prescription for SGLT2i documented in a medication list and 39 individuals met the criteria for DKA. Details are provided in Supplementary Table 1. Of the DKA cases, 74% appeared to have type 2 diabetes. Glucose  $\leq$ 300 mg/dL was noted at presentation of DKA in 26 of the 39 cases (72%). The mean glucose at presentation was 328 mg/dL, median 266 mg/dL, and range 125–904 mg/dL. With respect to precipitating causes, 49% had nausea/vomiting, although it is unclear if that was a cause, contributor, or consequence of the DKA; 67% had an obvious other precipitating event such as surgery, insulin dose reduction, or decreased oral intake and weight loss.

This is the largest and most comprehensive case series of DKA associated with the use of SGLT2i. Uncertainty about the incidence rate of DKA among SGLT2i-treated patients in our institutions is substantial because we do not have claims data confirming that prescriptions were filled, we likely missed cases that were undiagnosed or incompletely assessed, and some of the cases listed were prescribed SGLT2i by practitioners whose prescribing is not reflected in our

electronic health records. The relatively lower presenting glucose observed in the setting of SGLT2i-associated DKA is likely due to the proposed pathologic mechanisms (4). It is unclear if there are specific characteristics that make some patients more predisposed.

DKA in the setting of SGLT2i therapy is unusual in that it disproportionately affects those with type 2 diabetes and often presents with glucose <300 mg/dL, making recognition challenging. We would recommend a high index of suspicion for DKA in patients taking SGLT2i with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting. While its occurrence is unusual, we should counsel patients on the signs, symptoms, and possible precipitants of DKA even in the setting of type 2 diabetes when prescribing SGLT2i.

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