ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY

Research Article

Evaluation of Sodium-Glucose Cotransporter-2 Inhibitors on Euglycemic Diabetic Ketoacidosis in Patients Admitted to an Academic Medical Center

Mikael Habtezion[1], Farnoosh Zough[2], Khaled Bahjri[3], Christopher Hauschild[4], Asya Bookal[5], Ahmed Bahjri[5], Darren Kang[5] and Huyentran N Tran[6]*

[1]PGY-2 Cardiology Resident, Loma Linda University, School of Pharmacy, California, United States

[2]Associate Professor, Department of Pharmacy Practice, Loma Linda University, School of Pharmacy, California, United States

[3]Associate Professor, Pharmaceutical and Administrative Sciences, Loma Linda University, School of Pharmacy, California, United States

[4]Assistant Professor, Department of Pharmacy Practice, Loma Linda University, School of Pharmacy, California, United States

[5]Pharmacy Student Year 4, Loma Linda University, School of Pharmacy, California, United States

[6]Associate Professor, Department of Pharmacy Practice, Director and Coordinator, PGY2 Cardiology Pharmacy Residency Program, Loma Linda University, School of Pharmacy, California, United States

***Corresponding Author:** Huyentran N Tran, Associate Professor, Department of Pharmacy Practice, Director and Coordinator, PGY2 Cardiology Pharmacy Residency Program, Loma Linda University, School of Pharmacy, California, United States.

Received: December 21, 2024; **Published:** January 03, 2025

Abstract

Purpose: Since the approval of sodium-glucose cotransporter-2 inhibitors (SGLT2i), there has been an increase in reported cases of diabetic ketoacidosis (DKA) in patients with type 2 diabetes. While DKA typically presents as hyperglycemic DKA, many of these patients developed euglycemic DKA (euDKA). The incidence of euDKA remains unknown. Given the diagnostic dilemma posed by normoglycemia or lower than expected serum glucose levels, euDKA has been associated with worse outcomes compared to classic DKA, likely due to delays in diagnosis and treatment. This investigator-initiated study aims to evaluate the incidence of euDKA in patients newly initiated on a SGLT2i while admitted to Loma Linda University Health (LLUH) Medical Center.

Methodology: This retrospective cohort study involved collecting data on patients initiated on an SGLT2i while admitted to the LLUH Medical Center. The primary outcome of this study was to evaluate rates of euDKA following inpatient initiation of SGLT2i. As a subgroup analysis, we examined potential risk factors for euDKA, including infection or sepsis, recent surgery or trauma, or recent procedures. We included adult patients over the age of 18 who were started on an SGLTi, regardless of pre-existing conditions.

Study Design: This retrospective cohort study is descriptive and aims to characterize the incidence of euDKA in admitted patients prescribed an SGLT2i.

Results: A total of 1,604 patients who were admitted to LLUH Medical Center and prescribed an SGLT2i were included from December 2016 - September 2023. Regarding the primary outcome of the incidence of euDKA, we were not able to diagnose a single patient. While most patients had lab values for anion gap, and fewer had lab values for arterial pH, none had labs drawn for ketones, either from urinalysis or serum β-hydroxybutyrate.

Conclusion: Our study indicates that clinicians may be missing diagnosis of euDKA in admitted patients prescribed an SGLT2i. Implementing a hospital-wide protocol for these patients may help prevent euDKA from going unnoticed, potentially leading to earlier intervention and improved outcomes. Further research is warranted to investigate the relationship between the timing of SGLT2i initiation and the incidence of euDKA.

Keywords: *Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i); Diabetic Ketoacidosis (DKA); Euglycemic DKA (euDKA); Loma Linda University Health (LLUH)*

Background

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have substantially grown in popularity over the past few years, with expanding indications for their use. Multiple consensus guidelines recommend SGLT2i to improve diabetes, renal and cardiovascular outcomes [1]. As their use rises, so do reports of adverse events, notably diabetic ketoacidosis (DKA) following the 2013 FDA approval of the initial SGLT2i, canagliflozin [2]. Increasing reports of euglycemic diabetic ketoacidosis (euDKA) have also emerged [3]. An analysis of the FDA's adverse reporting system demonstrated a sevenfold higher risk of DKA with SGLT-2i use, with approximately two-thirds of those reported cases fitting the criteria for euDKA [4]. However, there are few studies that specifically describe euDKA events in the setting of SGLT-2i use, likely due to diagnostic challenges.

Clinicians typically associate DKA with marked elevated glucose levels, whereas euDKA lacks this, creating a diagnostic dilemma. Patients and clinicians may be misled by relatively normal or only mildly elevated point-of-care glucose levels [5] and prematurely rule out a metabolic cause for their symptoms. This can then delay the time to diagnosis and treatment, resulting in worse outcomes for these patients [6]. Compared to DKA, patients with euDKA may present with symptoms such as malaise, anorexia and tachypnea because of ketonemia and accompanying ketoacidosis [7], or even atypical symptoms like chest pain as described in a case report where the diagnosis of euDKA was nearly missed [8]. Given the diagnostic dilemma of normoglycemia or lower-than expected blood glucose levels, euDKA has been shown to have worse outcomes compared to DKA, presenting a pressing need for improved diagnosis and management [9].

The role of SGLT2i in the development of DKA is not fully understood. However, proposed mechanisms include rapid urinary glucose excretion leading to reduced blood sugar, decreased insulin secretion, and increased glucagon release which collectively promote lipolysis and ketogenesis [10]. While the incidence of DKA has been studied in the context of SGLT2i initiation, the occurrence of euDKA remains under-investigated, with current data limited to case reports [11].

Given the limited data on euDKA incidence with SGLT2i, we sought to investigate its occurrence at Loma Linda University Medical Center through a retrospective analysis of patients prescribed an SGLT2i during inpatient admission.

Methods

Trial design and patients

This retrospective descriptive study was conducted at Loma Linda University Health (LLUH) Medical Center, a tertiary academic medical center. Adult patients admitted to LLU Medical Center between December 2016 and September 2023 who were prescribed an SGLT2i during admission were screened for inclusion. Patients were eligible if they were aged 18 years or older and prescribed an SGLT2i, irrespective of the indication. Patients were excluded if they were on dialysis or had a diagnosis of type 1 diabetes mellitus.

Study group

A total of 1,604 patients were identified as having been prescribed an SGLT2i while admitted to LLU Medical Center.

Data collection

Baseline demographic data, including age, sex, weight, comorbidities, and drugs that can increase blood sugar (e.g. prednisone, cyclosporine, olanzapine etc.), vitals, and labs including basic metabolic panel, lactic acid and ketones, were collected on day one of admission. Daily labs were collected for up to 10 days post-initiation of SGLT2i, including arterial blood pH, ketones from urinalysis, β-hydroxybutyrate from serum, basic metabolic panel, and white blood cell count. Patient risk factors for DKA (recent surgery or trauma,

recent infection, history of pancreatitis, etc.) were also collected. We defined euDKA as serum β-hydroxybutyrate ≥ 3.0 mmol/L, arterial pH ≤ 7.3, serum bicarbonate ≤18 mEq/L, serum glucose < 200 mg/dL, and anion gap > 10.

Outcomes

Our primary outcome was to measure the incidence of euDKA in patients prescribed an SGLT2i while admitted to LLU Medical Center.

Results

A total of 1,604 patients admitted to LLU Medical Center and prescribed an SGLT2i were included from December 2016 to September 2023. Regarding the primary outcome of euDKA incidence, no patients were diagnosed with euDKA. While most patients had lab values for anion gap, and fewer had lab values for arterial pH, none had labs drawn for ketones from urinalysis or serum β-hydroxybutyrate.

Discussion

Our study aimed to characterize the incidence of euDKA in admitted patients prescribed an SGLT2i. Our findings reveal a concerning gap, suggesting that clinicians may not be considering a diagnosis of euDKA when working up admitted patients who are prescribed an SGLT2i. This aligns with past literature, which shows that the milder degrees of hyperglycemia and euDKA (often < 200 mg/dL) lead to delayed diagnosis and treatment, with potential adverse metabolic consequences [12]. This diagnostic dilemma of euDKA can delay treatment, as our results suggest, potentially leading to missed diagnoses. For example, a case report from 2023 describes a 56-year-old woman with a history of type 2 diabetes mellitus on empagliflozin who presented to the emergency department (ED) with retrosternal discomfort but denied nausea, vomiting, edema or signs of dehydration. Initially, The ED consulted cardiology; however, her venous blood gas revealed a pH of 7.28 and serum bicarbonate of 13 mEq/, while her basic metabolic panel (BMP) showed serum glucose of 173 mg/dL and an anion gap of 31. She was then admitted to the ICU for the treatment of possible euDKA. Initial serum β-hydroxybutyrate was not collected; however, on day three of admission, her level was 0.3 mmol/L, and her anion gap had closed to 9 [8]. Had her serum β-hydroxybutyrate been collected on admission, elevated levels likely would have been observed. Given the atypical presentation and near-normal serum glucose, the diagnosis and treatment of euDKA were delayed.

Another case report from 2023 describes a man in his seventies with coronary artery disease, history of type 2 diabetes on dapagliflozin, stroke, and hypertension. After a procedure in the cath lab, the patient developed acute mental status changes, including aphasia and severe agitation, prompting the initiation of a stroke code and admission to the cardiac intensive care unit. a full stroke work up was completed and eventually came back negative; however, the patient continued to exhibit confusion overnight. Lab tests drawn 12 hours after the initial procedure showed anion gap metabolic acidosis with an elevated ß-hydroxybutyrate level of 3.38 mmol/L and a glucose level of 117 mg/dL, prompting the treatment of euDKA. These atypical presentations demonstrate how easily an euDKA diagnosis can be missed, leading to delay in treatment [13].

Given the atypical presentation of euDKA without signs of dehydration and possibly with symptoms like chest pain and altered mental status [8], there are a significant challenge for early and accurate diagnosis and a stark need for change.

Given our alarming results, we propose instituting a protocol for admitted patients prescribed an SGLT2i. We recommend obtaining early labs for arterial blood gas for all patients admitted who are taking an SGLT2i. If arterial blood gas reveals a pH < 7.3, subsequent serum β-hydroxybutyrate should be obtained in patients with metabolic acidosis. Combined with anion gap, serum glucose and serum bicarbonate levels from the basic metabolic panel, clinicians will have a comprehensive picture of whether or not these patients are in euDKA. These steps can prevent missed diagnoses and improve outcomes for this disease state that can have profound complications if not properly identified and treated.

Limitations of the Study

Our study has several limitations. its retrospective design limits our ability to establish causality between euDKA and SGLT2i and to control for confounding variables. Additionally, as a single-center study, our findings may not be generalizable to other healthcare settings with different patient populations and care practices; however, our study provides a foundation for future multi-center studies.

Conclusion

In conclusion, our study provides concerning evidence that clinicians may be missing diagnoses of euDKA in admitted patients prescribed an SGLT2i. Instituting a hospital-wide protocol for these patients may help prevent euDKA from going unnoticed, potentially leading to earlier intervention and improved outcomes. Further research is needed to validate the finds and improve clinical outcomes.

Bibliography

1. Davies MJ., *et al*. "Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)". *Diabetes Care* 41.12 (2018): 2669-2701.
2. European Medicines Agency. "Review of diabetes medicines called Sglt2 inhibitors started: risk of diabetic ketoacidosis to be examined" (2015).
3. Bilgin S., *et al*. "A case of euglycemic diabetic ketoacidosis due to empagliflozin use in a patient with type 1 diabetes mellitus". *Journal of College of Physicians and Surgeons Pakistan* 32.7 (2022): 928-930.
4. Blau JE., *et al*. "Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data". *Diabetes/Metabolism Research and Reviews* 33.8 (2017): 10.
5. Peters AL., *et al*. "Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium glucose cotransporter 2 inhibition". *Diabetes Care* 38.9 (2015): 1687-1693.
6. Modi A., *et al*. "Euglycemic diabetic ketoacidosis: a review". *Current Diabetes Reviews* 13.3 (2017): 315-321.
7. Nasa P., *et al*. "Euglycemic diabetic ketoacidosis: A missed diagnosis". *World Journal of Diabetes* 12.5 (2021): 514-523.
8. Tiwari K., *et al*. "Misleading presentation: Chest pain masking euglycemic diabetic ketoacidosis possibly induced by empagliflozin". *Cureus* 15.11 (2023): e49402.
9. Barski L., *et al*. "Euglycemic diabetic ketoacidosis". *European Journal of Internal Medicine* 63 (2019): 9-14.
10. Singh AK. "Sodium-glucose co-transporter-2 inhibitors and euglycemic ketoacidosis: wisdom of hindsight". *Indian Journal of Endocrinology and Metabolism* 19.6 (2015): 722-730.
11. Julio Rosenstock and Ele Ferrannini. "Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors". *Diabetes Care* 38.9 (2015): 1638-1642.
12. A Modi., *et al*. "Euglycemic diabetic ketoacidosis: a review". *Current Diabetes Reviews* 13.3 (2017): 315-321.
13. Klinkner G and Steingraber-Pharr M. "Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitor therapy: a case report". *AACN Advanced Critical Care* 34.1 (2023): 27-32.

Volume 13 Issue 1 January 2025