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DIABETIC KETOACIDOSIS ASSOCIATED WITH EMPAGLIFLOZIN THERAPY : MECHANISMS, RISC FACTORS AND CLINICAL IMPLICATIONS

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Abstract: Empagliflozin, a sodium–glucose co-transporter 2 (SGLT2) inhibitor, is widely prescribed for type 2 diabetes mellitus (T2DM) and heart failure. Despite its proven cardiovascular and renal benefits, rare but serious cases of diabetic ketoacidosis (DKA), including euglycemic DKA (euDKA), have been reported. This article reviews the incidence, mechanisms, risk factors, clinical features, and management strategies of empagliflozin-associated DKA. Early recognition and preventive strategies are essential to balance risks and benefits of therapy.

Introduction

Empagliflozin (Jardiance) is an oral SGLT2 inhibitor that improves glycemic control, reduces cardiovascular events, and provides renal protection in patients with T2DM [1]. However, since 2015, regulatory agencies have highlighted the risk of DKA, particularly euDKA, in patients treated with SGLT2 inhibitors [2]. EuDKA is characterized by significant ketosis and metabolic acidosis despite only mild-to-moderate hyperglycemia, creating diagnostic challenges [3].

Methods

A narrative review was conducted using PubMed, Scopus, and Web of Science databases. Search terms included “empagliflozin,” “SGLT2 inhibitors,” “diabetic ketoacidosis,” and “euglycemic DKA.” Articles published between 2015 and 2025, including randomized controlled trials (RCTs), meta-analyses, case reports, and regulatory advisories, were included.

Results

Incidence

Meta-analyses and real-world studies report low but clinically significant incidence of empagliflozin-associated DKA. A 2024 network meta-analysis found empagliflozin 10 mg increased odds of DKA compared with placebo (OR 2.68; 95% CI 1.11–6.49) [4]. Another meta-analysis of 10 RCTs including 71,553 subjects reported a threefold increased risk of DKA with SGLT2 inhibitors (RR 3.0; 95% CI 1.36–3.63) [5].

In Uzbekistan, empagliflozin-associated DKA incidence was estimated at 0.23% (2.3 per 1,000 patient-years) [6]. Perioperative studies show elevated risk: 0.17% after non-emergency surgery and 1.1% after emergency procedures [7].

Pathophysiology

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Empagliflozin promotes ketogenesis by:

1. Increasing glucosuria, lowering insulin secretion, and stimulating glucagon release [5].

2. Enhancing renal ketone reabsorption [5].

3. Inducing osmotic diuresis, volume depletion, and impaired glucose utilization [3].

Risk Factors

Major risk factors include:

Acute illness, infection, dehydration, or perioperative fasting [2,7].

Low-carbohydrate diets, alcohol intake, and prolonged fasting [2,6].

Insulin dose reduction or discontinuation in insulin-dependent patients [5].

Ethnic differences: higher incidence among NZ Europeans compared to Māori and Asian populations [6].

Clinical Presentation

Patients typically present with nausea, vomiting, abdominal pain, dyspnea, malaise, and metabolic acidosis. Blood glucose is often <14 mmol/L (<250 mg/dL), which may delay diagnosis [2,3].

Management

Immediate discontinuation of empagliflozin.

Standard DKA protocol: IV fluids, insulin infusion, and electrolyte replacement [3,8].

Perioperative prevention: discontinue empagliflozin ≥3 days before elective surgery and resume only after clinical stabilization [1,2].

EuDKA may require longer ketone clearance but carries higher risk of hypoglycemia due to insulin therapy [8].

Prevention

Preventive strategies include patient education on “sick day rules,” perioperative discontinuation, avoidance of ketogenic diets, and maintaining appropriate insulin therapy [2,6].

Discussion

Although the absolute incidence of empagliflozin-associated DKA is low, the condition is clinically significant. RCTs report mixed findings, with some showing no significant increase in DKA compared to placebo, but real-world evidence and case reports confirm the risk in susceptible patients [4–6]. The atypical presentation of euDKA emphasizes the need for clinical vigilance. Preventive strategies and patient education can help minimize risk while preserving empagliflozin’s cardiovascular and renal benefits.

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Conclusion

Empagliflozin remains an important therapeutic option for T2DM and heart failure. However, clinicians must be aware of the rare risk of DKA, especially in perioperative and high-risk scenarios. Vigilance, patient education, and adherence to preventive protocols are essential to maximize benefits and minimize risks.

References (Vancouver Style)

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–2128.

2. Medicines and Healthcare products Regulatory Agency. SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis. Drug Safety Update. 2016. Available from:https://www.gov.uk/drug safety update/sglt2-inhibitors updated

Advice on the risk of diabetic ketoacidosis

3. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care. 2015;38(9):1638–1642.

4. Li Y, Sun H, Jiang F, et al. Risk of diabetic ketoacidosis with SGLT2 inhibitors in adults with type 1 diabetes: a network meta-analysis. Front Endocrinol. 2024;15:1453067.

5. Tang H, Li D, Wang T, et al. Risk of diabetic ketoacidosis with sodium-glucose cotransporter-2 inhibitors: a meta-analysis of randomized controlled trials. Front Pharmacol. 2023;14:1145587.

6. Braatvedt G, et al. The incidence of diabetic ketoacidosis associated with empagliflozin use in Aotearoa New Zealand: a preliminary review. N Z Med J. 2022;135(1555):94–102.

7. Meyer EJ, et al. Perioperative risk of diabetic ketoacidosis in patients taking SGLT2 inhibitors: a population-based cohort study. Anaesthesia. 2025;80(3):259–268.

8. Tuttle KR, et al. Euglycemic DKA management in patients on SGLT2 inhibitors: protocol evaluation. Curr Diab Rep. 2025;25(2):163–170.