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Empagliflozin-Induced Acute Pancreatitis and Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes Mellitus

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ABSTRACT

Acute pancreatitis and euglycemic DKA, EDKA, are uncommon but potentially fatal complications in diabetic patients on sodium-glucose cotransporter 2 inhibitors (SGLT2). This case report presents the exceptional occurrence of a 49-year-old; male patient diagnosed with empagliflozin-induced EDKA coupled with T2DM as a precursor to acute pancreatitis. Euglycemic DKA may be produced after administering just one dose of SGLT2. On discharge, empagliflozin was managed to stop. Since the initial administration of SGLT2, this diagnosis should be considered a potential consequence. Appropriate medical treatment is made possible by diagnosing and treating this life-threatening condition promptly.

INTRODUCTION

The clinical trifecta of metabolic acidosis, hyperglycemia, and elevated ketone bodies in the urine and blood is known as diabetic ketoacidosis (DKA). Euglycemic DKA (EDKA) is the precursor to a particular group of people whose blood glucose levels are between normal ranges (Nyenwe & Kitabchi, 2016). At the presentation time, 37 out of 211 DKA patients had normal blood sugar levels (300 mg/dL) and a plasma bicarbonate level of 10 mmol/L. Munro *et al.* (1973) were the first to document this phenomenon. Normoglycemia was interpreted as less than 250 mg/dL. Thus, when serum glucose levels are below 250 mg/dL, EDKA is described as a trifecta that includes high anion gap metabolic acidosis with positive urine and serum ketones (Kitabchi *et al.*, 2009). One of the most recent classes of oral drugs for the treatment of T2DM has been legalized, and it is called sodium-glucose cotransporter-2 (SGLT-2) inhibitors. They may be administered to these patients alone or with other medications. They prevent glucose reabsorption in the proximal renal tubule, which lowers blood sugar levels (Sarafidis *et al.*, 2019). The US Food and Drug Administration (FDA) officially warned patients using these medications in 2015 that they are at an elevated risk of developing DKA with unusually mild to moderate glucose spike, or EDKA (Do, n.d.). Therefore, the present case report explores the rare presentation of empagliflozin-induced euglycemic DKA, (EDKA) and acute pancreatitis in a patient with T2DM just 6 days after empagliflozin introduction.

Abbreviations

DKA=Diabetic ketoacidosis, EDKA=euglycemic DKA, SGLT-2=Sodium-glucose cotransporter-2, FDA=

Food and Drug Administration, VBG=Venous Blood Gas, CVA=Cerebral Vascular Accident, HDU=High Dependency Unit, CT= Computed Tomography

METHODOLOGY

Case Presentation

A presentation from a 49-year-old man nonsmoker with a 5-year medical history and worsening type 2 diabetes mellitus due to poor compliance was made to the Mediclinic Al Jowhara Hospital in the United Arab Emirates. Additionally, he had three days' history of upper abdominal pain, nausea, and vomiting. He denies fever, loose motion, melena, cough, or headache. Six days before the presentation, he suffered from CVA with residual right-sided weakness. During his admittance, he was initiated on Aspirin, clopidogrel, Atorvastatin 40mg, Lisinopril 5mg, Linagliptin/Metformin 5mg/1000mg once, and Empagliflozin 25mg.

The initial observational analysis revealed that he was tachypneic but otherwise vitally normal. Other vital signs include his RBG as 11.1 mmol/L, dry mucous membranes, but normal capillary refill time. Additionally, on clinical assessment, there was right lower limb's minor motor impairment, intact sensory functions, normal reflexes, and normal cranial and cerebellar functions were notable. His venous blood gases (VBG) represented pH 7.121, HCO₃ 9.6 mmol/L, pCO₂ 25.4 mmHg, Lactate 2.1 mmol/L, Na 128 mmol/L, Cl 101 mmol/L, and K 5.2 mmol/L and urine showed ketone +3 suggestive of high Anion gap (17.4), severe metabolic ketoacidosis and his HbA1C was 8.1%. The patient's lipase and amylase were elevated at 440 U/L and 354 U/L, respectively, compatible with acute pancreatitis (Table 1). ECG assessment was reported normal, as well as chest X-ray and Abdominal

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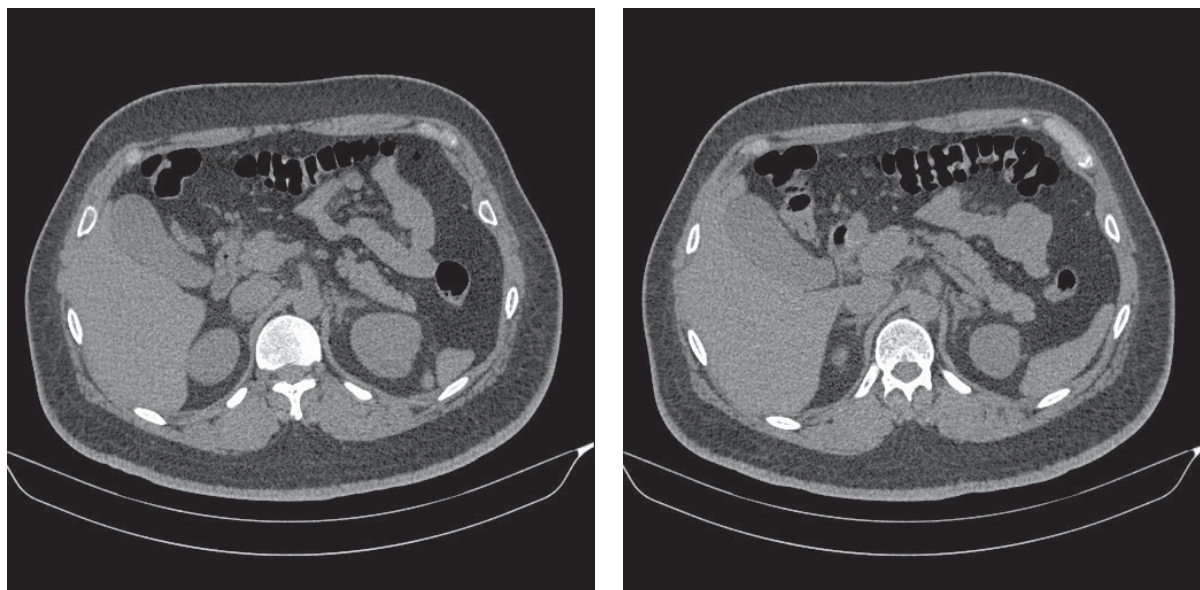


Figure 1: Axial and coronal CT images in venous phase showing minimal peripancreatic fat stranding around the head and body as early features of pancreatitis. No peripancreatic fluid.

Ultrasound. Abdomen CT showed mild enlargement of pancreatic head with subtle peri-pancreatic fat stranding, a picture of mild pancreatitis.

The patient was admitted to HDU for management of EDKA, Linagliptin/Metformin, empagliflozin were held, and intravenous fluids and insulin infusion were initiated with repeated VBG every 2 hours. His pH normalized, ketonuria improved, and the Anion gap closed. He made a good recovery with normalizing pancreatic enzymes

and improved symptoms. Once he could tolerate normal oral intake, he shifted to Sitagliptin/Metformin 100/1000 mg and gliclazide 120 mg. After dietary consultation and education, he was discharged. Upon follow-up visits, he was clinically stable, tolerating his medications with good glycemic control, and his HbA1C became 6.2%. Using the Naranjo algorithm of adverse drug reactions, we concluded that empagliflozin was the most likely culprit for his pancreatitis.

Table 1: Initial and follow up laboratory values

Parameters	Initial	Day1	Day 2	On Discharge
Venous pH (7.36–7.44)	7.121	7.224	7.36	7.439
Serum bicarbonate (21–28 mmol/L)	9.6	11.6	19.2	25.7
pCO ₂ (35–45mmHg)	25.4	22.5	33	39.9
Serum lactate (0.5–1.4 mmol/L)	2.1	1.7	1.6	1.7
Serum sodium (135–145 mEq/L)	128	132	134	134
Chloride (98–107 mmol/L)	101	108	103	99
Serum potassium (3.5–5.0 mmol/L)	5.2	5.7	4.1	3.8
Anion gap (8–16 mmol/L)	17.4	12.4	11.8	9.3
Urine ketone (negative)	+++	++	+	- ve
HbA1C (%)	8.1			
Lipase (0–160U/L)	440 U/L		117	110
Amylase (23–85 U/L)	354U/L		123	78

DISCUSSION

DKA occurs in 1.34/million T2D patients annually (Jensen *et al.*, 2017). In contrast, it is unknown how often euglycemic DKA will occur. The uncommon occurrence of euglycemic DKA may cause a deferment in care and prognosis, which might have significant or fatal consequences (Calçada *et al.*, 2021). A recent family of anti-diabetic medications known as SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) increases the likelihood of euglycemic DKA discrete to the length of treatment (Peters *et al.*, 2015; Somagutta *et al.*, 2021; Taylor *et al.*, 2015). However, the prevalence of EDKA increased after the introduction of sodium-

glucose transporter 2 (SGLT2) inhibitors in some rare cases. Although there have been few reports of DKA in SGLT2i investigations, the precise numbers of EDKA events have not been evaluated (Wibawa *et al.*, 2021). The results of another trial, “the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose)” study, revealed that DKA occurs less frequently than 0.1% of the duration (Rosenstock, 2015; Sampani *et al.*, 2020). Rates of DKA-related occurrences among type 2 diabetic patients on SGLT2 inhibitors ranged from 0.16 to 0.76 events per 1000 patient years (Goldenberg *et al.*, 2016). SGLT2 inhibitors raise the risk of DKA in T2D

patients by seven times (Blau *et al.*, 2017). According to other studies, SGLT2i improves beta cells in the pancreas, increasing lipolysis and raising the concentration of ketone bodies (da Silva *et al.*, 2018). They have also been indicated to activate the pancreatic alpha cells, triggering glucagon production and inducing an imbalance in insulin and glucagon level (Candelario & Wykretowicz, 2016; Pfützner *et al.*, 2017).

The patient, in this case, presented with acute pancreatitis while taking prescribed empagliflozin, and there was no known cause of pancreatitis, such as gallstones or alcohol consumption. The development of pancreatitis with regular exposure to the medication and the symptom treatment response after withdrawal make empagliflozin a plausible cause of pancreatitis. The molecular basis of pancreatitis caused by empagliflozin is unidentified. It is an unusual reaction similar to previous cases of drug-induced pancreatitis because of the immunologic or cytotoxicity effects the drug or its metabolites have on the body.

CONCLUSION

The FDA's warning is supported by multiple pieces of literature that detail many physiologically tenable possibilities for negative consequences of SGLT2 (empagliflozin) inhibitor. The preponderance of the data supports the causative involvement of SGLT2 inhibitors in the pathogenesis of acute pancreatitis and EDKA. Therefore, SGLT-2 inhibitor initiation should be avoided in acute conditions. Since normoglycemia might mask the presence of acidosis, medical professionals should be aware of this diagnosis and immediately begin therapy. Given the nature of the disease, EDKA should be retained in the differential even if it is rare. Patients should be informed about negative consequences and stimuli to prevent recurrences.

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REFERENCES

- Blau, J. E., Tella, S. H., Taylor, S. I., & Rother, K. I. (2017). Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. *Diabetes/ metabolism research and reviews*, 33(8), e2924.
- Calçada, M. B., Fernandes, L., Soares Costa, R., Montezinho, S., Martins Duarte, F., Frutuoso, L., & Freitas, A. R. (2021). *Euglycemic Diabetic Ketoacidosis after a Single Dose of Empagliflozin in a Patient with Pancreatitis. Clinics and Practice*, 11(2), 216-218.
- Candelario, N., & Wykretowicz, J. (2016). The DKA that wasn't: a case of euglycemic diabetic ketoacidosis due to empagliflozin. *Oxford medical case reports*, 7, 144-146.
- Da Silva, P. N., da Conceição, R. A., do Couto Maia, R., & de Castro Barbosa, M. L. (2018). Sodium-glucose cotransporter 2 (SGLT-2) inhibitors: a new antidiabetic drug class. *Medchemcomm*, 9(8), 1273-1281.
- Do, W. Y. C. (n.d.). FDA Issues Multiple Warnings For Newest Class of Diabetes Drugs.
- Goldenberg, R. M., Berard, L. D., Cheng, A. Y., Gilbert, J. D., Verma, S., Woo, V. C., & Yale, J.-F. (2016). SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. *Clinical therapeutics*, 38(12), 2654-2664. e2651.
- Jensen, M. L., Persson, F., Andersen, G. S., Ridderstråle, M., Nolan, J. J., Carstensen, B., & Jørgensen, M. E. (2017). Incidence of ketoacidosis in the Danish type 2 diabetes population before and after introduction of sodium-glucose cotransporter 2 inhibitors—a nationwide, retrospective cohort study, 1995–2014. *Diabetes care*, 40(5), e57-e58.
- Kitabchi, A. E., Umpierrez, G. E., Miles, J. M., & Fisher, J. N. (2009). Hyperglycemic crises in adult patients with diabetes. *Diabetes care*, 32(7), 1335-1343.
- Munro, J., Campbell, I., McCuish, A., & Duncan, L. (1973). Euglycaemic diabetic ketoacidosis. *Br Med. J.*, 2(5866), 578-580.
- Nyenwe, E. A., & Kitabchi, A. E. (2016). The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism*, 65(4), 507-521.
- Peters, A. L., Buschur, E. O., Buse, J. B., Cohan, P., Diner, J. C., & Hirsch, I. B. (2015). Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes care*, 38(9), 1687-1693.
- Pfützner, A., Klonoff, D., Heinemann, L., Ejksjaer, N., & Pickup, J. (2017). Euglycemic ketosis in patients with type 2 diabetes on SGLT2-inhibitor therapy—an emerging problem and solutions offered by diabetes technology. *Endocrine*, 56(1), 212-216.
- Rosenstock, J. F. E. (2015). Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. *Diabetes care*, 38(9), 1638-1642. <https://doi.org/doi:10.2337/dc15-1380>.
- Sampani, E., Sarafidis, P., & Papagianni, A. (2020). Euglycaemic diabetic ketoacidosis as a complication of SGLT-2 inhibitors: epidemiology, pathophysiology, and treatment. *Expert Opinion on Drug Safety*, 19(6), 673-682.
- Sarafidis, P., Ferro, C. J., Morales, E., Ortiz, A., Malyszko, J., Hojs, R., Khazim, K., Ekart, R., Valdivielso, J., & Fouque, D. (2019). SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrology Dialysis Transplantation*, 34(2), 208-230.
- Somagutta, M. R., Agadi, K., Hange, N., Jain, M. S., Batti, E., Emuze, B. O., Amos-Arowoshegbe, E. O., Popescu, S., Hanan, S., & Kumar, V. R. (2021).

- Euglycemic diabetic ketoacidosis and sodium-glucose cotransporter-2 inhibitors: a focused review of pathophysiology, risk factors, and triggers. *Cureus*, 13(3).
- Taylor, S. I., Blau, J. E., & Rother, K. I. (2015). SGLT2 inhibitors may predispose to ketoacidosis. *The Journal of Clinical Endocrinology & Metabolism*, 100(8), 2849-2852.
- Wibawa, K., Kuhuwaël, F. V., Putra, C. R. J., Widiastuti, S. U., & Suciadi, L. P. (2021). Euglycemic diabetic ketoacidosis associated with empagliflozin in patients hospitalized with acute pulmonary embolism. *Clinical Diabetology*, 10(2), 204-208.