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Case Report

Sodium-Glucose Co-Transporter 2 Inhibitor-induced Euglycemic Diabetic Ketoacidosis in a Type 2 Diabetes Patient Not Absolutely Insulin-deficient!

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Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral antidiabetic agents. In addition to glucose lowering, they have other advantageous effects on blood pressure and body weight. The use of those agents has increased exponentially after the emerging evidence of cardiovascular protection following the publication of the EMPA-REG OUTCOME study. Although they are relatively safe and effective, they are not without side effects. Perhaps, the most serious complication is euglycemic diabetic ketoacidosis (DKA). Several cases were reported in the literature. We describe a case of severe DKA in association with the use of an SGLT2 inhibitor (empagliflozin) in a 69-year-old male with type 2 diabetes who is not absolutely insulin deficient following knee replacement. The case highlights the increased risk of DKA and the importance of discontinuation of SGLT2 inhibitors before major surgery.

Keywords: Euglycemic diabetic ketoacidosis, insulin deficiency, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes

Introduction

Diabetic ketoacidosis (DKA) is an acute major life-threatening complication of diabetes that mainly occurs in patients with type 1 diabetes mellitus (T1DM), but it is not uncommon in type 2 diabetes mellitus (T2DM). This condition is a complex disordered metabolic state characterized by hyperglycemia, metabolic acidosis and ketonaemia.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a relatively new class of antihyperglycemic agents used as adjunctive therapy to the standard treatment regimens for T2DM. SGLT2 inhibitors are marketed both as single-ingredient products and in combinations with metformin and other oral antidiabetes medications. These drugs lower renal glucose reabsorption and increase urinary glucose excretion resulting in improved glycemia as well as weight reduction.[1] The (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) provided evidence that empagliflozin reduces cardiovascular (CV) mortality and heart failure in high-risk patients with T2DM with a previous CV event (myocardial infarction, stroke, amputation, multivessel coronary artery disease, or coronary artery bypass graft).[2] Following publication of this study, the use of SGLT2 inhibitors increased dramatically.

Side effects of SGLT2 inhibitors include genital fungal infections, urinary tract infections, and hypotension. However, in 2015, regulatory authorities warned that these medications might lead to DKA.[3] This complication seemed to occur mostly in insulin-deficient T2DM patients and those with T1DM. We report here a case of a previously stable patient with T2DM with no obvious evidence of absolute insulin deficiency who developed severe DKA when he was treated with an SGLT2 inhibitor.

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Case Report

A 69-year-old male has T2DM diagnosed in 1995, cleft palate since birth, bilateral cataract surgery, dyslipidemia, hypertension, and right knee osteoarthritis.

He was referred to our tertiary facility in October 2017 to improve his glycemic control; his medications were metformin 1000 mg twice/day, sitagliptin 50 mg twice/day, perindopril 5 mg/day, and atorvastatin 20 mg once/day. He was compliant with all his medications, and he had no osmotic symptoms or symptoms suggestive of hypoglycemia. He was troubled with severe right knee pain restricting his mobility, and he was scheduled for knee replacement. His full systemic examination was unremarkable apart from peripheral neuropathy and mild nonproliferative diabetic retinopathy.

His initial blood investigations showed HbA1c 9.6%, fasting blood glucose 11.0 mmol/L, and normal serum C-peptide. Positive microalbuminuria, serum creatinine 64 μmol/L, eGFR 108 ml/min/1.73 m^2, and LDL 4.38 mmol/L. His liver and thyroid function tests were normal.

He was advised to commence insulin therapy but declined. Therefore, he was started on empagliflozin 10 mg/day along with Pioglitazone 30 mg/day. Atorvastatin dose was increased to 40 mg/day. He returned for review 2 months later. His HbA1c improved to 8.6% but remained suboptimal. He was advised again to commence insulin but maintained his view against starting insulin. He was scheduled for a further appointment in 3 months. However, a month before his diabetes review appointment was due, he was admitted by the orthopedic surgeons for elective right knee replacement, which was uneventful and was discharged 4 days after surgery. During his inpatient stay, his glycemic control was maintained on his usual medications along with variable rate subcutaneous insulin injections.

One day after discharge, he was re-admitted due to severe postoperative knee pain. On admission, his temperature was 36.5°C, and pulse rate was 107 beats/mint. Respiratory rate was 20 and blood pressure was 135/71 mmHg, oxygen saturation was 100%. He was alert and oriented and there were mild swelling and tenderness over the right knee with a clean surgical wound. His blood investigations are shown in Table 1 confirming a diagnosis of DKA. Therefore, he was transferred to the intensive care unit, and DKA was treated along the lines of standard DKA management. 24-h posttreatment, DKA resolved. While inpatient he dropped, his hemoglobin and required transfusion of 4 units of blood. Upper gastrointestinal endoscopy revealed active peptic ulcer, and he was started on proton pump inhibitor. He was started on a premixed insulin aspart (Novomix 30/70) in addition to metformin. All his other oral agents including empagliflozin were discontinued. He was reviewed in the clinic 3 weeks after discharge, and his HbA1c has improved significantly to 6.5% with normal hemoglobin.

Table 1: Results of the laboratory investigations of the patient and reference ranges

Test	Results	Normal range
Hb	11.8	13.00-17.00
Na	132 mmol/L	136-144
K	4.90 mmol/L	3.60-5.10
Creatinine	54 mmol/L	80-115
Glucose random	11.9 mmol/L	-
Ketones in urine	3+	Negative
Blood glucose capillary	12.2 mmol/L	-
Blood ketones	4.0 mmol/L	<0.6
Urea	7.0	2.90-8.20
Lactic acid	2.4 mmol/L	0.4-2.0
HbA1c (%)	8.9	<5.7
C-peptide	0.53	

Hb: Hemoglobin, HbA1c: Glycated haemoglobin

Discussion

DKA is a rare but serious adverse event seen increasingly with all SGLT2 inhibitors[3]. Multiple proposed theories are exploring the link between SGLT2 inhibitors and DKA. Decreased secretion of insulin from pancreatic islet cells in response to the lowering of blood glucose via urinary excretion has been proposed.[4] This results in a reduced insulin and its antilipolytic activity, leading to increased free fatty acid production.[4] Other evidence suggests that SGLT2 inhibitors stimulate the secretion of the counter-regulatory hormone glucagon, which in turn contributes to the overproduction of ketone bodies.[5,6] One animal study suggests that SGLT2-I might decrease the renal clearance of ketone bodies.[4] The ultimate result is stimulation of the ketogenesis, and an increase in serum ketones, which predisposes to ketoacidosis. This effect is potentiated by the event of physiologic stresses such as starvation or dehydration.[6-8] Although definitive causation has not been established, the association between SGLT2 inhibition and DKA is plausible.

Although to some extent, it is somewhat complicated, one hypothesis regarding the occurrence of DKA in this setting is that some patients may be misdiagnosed as T2DM when they have antibody-mediated ketoacidosis-prone type of diabetes giving them low beta cell reserve. This would lead to insufficient insulin levels when a patient is stressed by an acute illness. In the setting of SGLT2 inhibitors-induced increased glucagon levels, this would permit ongoing hepatic ketogenesis and peripheral lipolysis, leading to the DKA.[5,6]

Typically, DKA is associated with hyperglycemia above 14 mmol/L (250 mg/dL); however, for many patients in the reported cases and our patient, the blood glucose level was lower at presentation. This euglycemic DKA may be under-recognized and result in delayed treatment with the necessary aggressive intravenous hydration and insulin. It is crucial to rule out other potential causes of DKA including major illness, dehydration, and inadequate insulin intake as it was done in our case. The dosage of SGLT2 inhibitors does not appear to correlate with the development of new DKA.

In line with recommendations from international bodies, SGLT2 inhibitors should be discontinued in severe intercurrent illnesses and before major surgery, although our patient gave the history of severe osteoarthritis on his right knee, but he failed to bring to our attention when his knee replacement is planned, which apparently should have alerted us to plan to stop the SGLT2 inhibitors beforehand.

Conclusions

SGLT2 inhibitors are increasingly prescribed by clinicians due to their proven ability to lower HbA1c and cardiovascular benefits. However, physicians need to be aware of the rare serious side effect of euglycemic DKA in patients with T2DM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient consented for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and outstanding efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author's contributions

All authors contributed to the care of the patient, drafting of the case report, revision, and approval of its final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is usually required for single-case reports at our institution.

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