We describe a case of a 26-year-old female with long-standing type 1 diabetes (T1D), on multiple subcutaneous insulin injections, who had been taking empagliflozin for the past year. She was detected to have severe diabetic ketoacidosis (DKA) with relatively lower blood glucose values during hospitalisation for dengue fever. The factors that precipitated the DKA are discussed, along with the unique challenges in the management of her metabolic status. While sodium-glucose co-transporter-2 (SGLT2) inhibitors have several potential benefits as adjunctive add-on therapy to insulin in T1D, the evidence is limited to short-term studies. However, their off-label use is increasing and there have been concerns related to increased risk of diabetic ketoacidosis. At present, SGLT2 inhibitors are not approved for use in T1D, and the risks should be discussed at length with the patient.

Keywords
Type 1 diabetes, diabetic ketoacidosis, euglycaemic diabetic ketoacidosis, sodium-glucose co-transporter-2 (SGLT2) inhibitors, empagliflozin

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We report a case of diabetic ketoacidosis in a 26-year-old female with long-standing type 1 diabetes (T1D) who was on multiple subcutaneous insulin injections and empagliflozin. Informed consent was taken from the patient for the publication of this report.

Case report
A 26-year-old female, a postgraduate student, with long-standing T1D since the age of 10 presented to the emergency department on the evening of July 2017 with a history of fever for 4 days and a petechial rash over the trunk and upper arms for 2 days. She complained of malaise and loss of appetite but there was no history of rigors or chills, dysuria, diarrhea, vomiting, abdominal discomfort or respiratory difficulty. At presentation, she was conscious and well-oriented and had a fever (temperature 99.8°F), her vitals were stable and she had no hypotension. She had a petechial rash on the upper body and an extensive genital and inguinal mycotic infection, but the rest of the systemic examination was otherwise normal.

For her diabetes, she had been taking multiple subcutaneous insulin injections for several years and her insulin dose requirements had been gradually increasing. Over the past few years, she had gained significant weight and her daily insulin dose was >1 U/kg, but her glycemic control continued to be suboptimal. Her previous endocrinologist had started her on empagliflozin 25 mg per day for the past 1 year. Subsequently, she had substantially reduced her insulin doses due to relatively lower blood glucose values, but self-monitoring of blood glucose (SMBG) was inadequate and she had not followed up with her healthcare practitioner for several months. Her current insulin regimen was 5 units of insulin aspart twice a day with the two largest meals and 16 units of insulin degludec once daily. She had lost some weight, but her current body mass index (BMI) was 29.38 kg/m².

At admission, her random blood glucose by glucometer was 202 mg/dl and she was admitted to the ward for investigations and detailed evaluation. She was started on empirical intravenous ceftriaxone and intravenous saline at a maintenance rate of 75 ml/hour, pending laboratory reports. Aspart was increased to thrice daily with all three meals, degludec was continued and empagliflozin was discontinued. By early morning, her condition had deteriorated and she complained of extreme fatigue and shortness of breath. She had tachycardia and dehydration but there was no hypotension. Fasting blood glucose by glucometer was 203 mg/dl and her glycosylated hemoglobin (HbA1c) was 12.5%. Urinalysis done in the morning revealed ketonuria (80 mg/dl), glucosuria and few yeast cells,
but no bacteriuria. An acid blood gas (ABG) analysis revealed metabolic acidosis with hypokalemia: pH 7.08, PaO\textsubscript{2} 129.8 mmHg, PaCO\textsubscript{2} 25.6 mmHg, HCO\textsubscript{3} 1.6 mmol/l, lactate 1.05 mmol/l, base excess 25.4, anion gap 18.1, sodium 136 mEq/l, and potassium 3.35 mEq/l. Hemoglobin was 16.1 mg/dl, hematocrit was 51.7%, total leucocyte count was 4.56 thousand per μL and platelet count was 163 thousand per μL. Dengue immunoglobulin G and immunoglobulin M antibodies were later found to be strongly positive, while blood and urine cultures were sterile.

With a diagnosis of diabetic ketoacidosis (DKA), she was shifted to the medical intensive care unit and an endocrinology consultation was taken. Standard management protocol for DKA was initiated with intravenous fluids, intravenous insulin infusion and potassium replacement.\textsuperscript{1} Standard management protocol for DKA was initiated with intravenous fluids, intravenous insulin infusion and potassium replacement.\textsuperscript{1} After an intravenous bolus rush of 500 ml of normal saline, she was started on 5% dextrose normal saline as blood glucose remained in the range of 200–230 mg/dl. Her metabolic acidosis resolved, her general condition significantly improved over the next 24 hours, and she started accepting oral liquids and soft diet by the next morning. However, despite resolution of acidosis and blood glucose remaining in the range of 140–180 mg/dl, her ketonuria and glycosuria persisted for the next 5 days. Therefore, insulin infusion and intravenous dextrose saline was continued for the next 48 hours. In standard practice, we switch to subcutaneous insulin once the patient starts eating orally. The insulin dose requirements were in the range of 55–60 units per day for the first 3–4 days, despite intravenous dextrose saline and adequate oral intake. But the total daily insulin requirement increased thereafter and was 92 units per day at the time of discharge on day 8. In routine practice, insulin requirements reduce sequentially following recovery from ketoacidosis and glucotoxicity. We hypothesized that the need for prolonged dextrose infusion was due to the effect of empagliflozin and the subsequent rise in insulin requirements occurred when the glucose-lowering effect of empagliflozin had stopped.

The patient had become afebrile by day 3. The platelet count reduced to 50,000 per μL on day 3 of hospitalization without any evident bleeding tendencies, and then improved over the next few days to recover to 200,000 per μL by day 7. Her hemoglobin was 13.0 g/dl with hematocrit of 40% at the time of discharge. She was discharged on subcutaneous insulin aspart three times a day—20 units before breakfast, 20 units before lunch, and 16 units before dinner, with insulin degludec 36 units once a day. She was counseled about appropriate diet management, regular SMBG, and self-titration of bolus aspart doses based on SMBG. On follow-up, the insulin requirement reduced to 76 units per day a week after discharge, and was 64 units per day after 10 days, with pre-meal values in the range of 100–160 mg/dl and post-meal values ranging between 130 and 250 mg/dl.

**Discussion**

Insulin is the mainstay of pharmacological therapy in T1D. However, despite significant advances in insulin preparations and delivery systems, most patients with T1D do not achieve and maintain glycemic targets. A significant time is spent in hyperglycemia and higher insulin doses are associated with hypoglycemia and weight gain. Several non-insulin antidiabetic agents have been evaluated for their adjunctive role to insulin, including pramlintide, metformin, pioglitazone, glucagon-like peptide 1 (GLP-1) analogs, and dipeptidyl peptidase 4 (DPP-4) inhibitors.\textsuperscript{2} More recently, there has been a keen interest in the role of sodium-glucose co-transporter-2 (SGLT2) inhibitors in T1D. SGLT2 inhibitors promote glucouresis and natriuresis and do not require endogenous insulin secretion for their glucose-lowering effect and, therefore, have a low risk of hypoglycemia. Additional pleiotropic benefits such as moderate reductions in blood pressure, uric acid, body weight, and fat mass, and long-term cardioprotective and renoprotective effects have been demonstrated with their use in T2D.\textsuperscript{3} Thus, SGLT2 inhibition is an attractive therapeutic target in T1D to improve metabolic control.

Several small, short-term studies in type 1 diabetic individuals have explored the potential role of dapagliflozin, empagliflozin, and canagliflozin.\textsuperscript{4–6} Use of SGLT2 inhibitors was associated with improvements in average glucose control, reduced postprandial hyperglycemia and glycemic variability, reduced body weight, and reduced insulin dose requirements.\textsuperscript{5–13} Dual SGLT1/2 inhibitor, sitagliptin, has also demonstrated significant reductions in HbA1c, postprandial glucose, weight, and insulin doses.\textsuperscript{4} A recent systematic review reported that use of SGLT2 inhibitors in T1D was associated with reduction of HbA1c (up to 0.49%) and weight (up to 2.7 kg) and lowered total daily insulin dose, with lower incidence of hypoglycemia.\textsuperscript{8} However, there are several potential concerns with SGLT2 inhibitors, including increased risk of genital mycotic infections, urinary tract infections and volume depletion, and long-term concerns about effects on bone health and amputation risk. The most pressing concern in T1D relates to the potential for increased risk of diabetic ketoacidosis.\textsuperscript{3} There have been several reports of diabetic ketoacidosis with the use of SGLT2 inhibitors in both T1D and T2D.\textsuperscript{7} In phase II and III studies of SGLT2 inhibitors in patients with T1D the incidence of diabetic ketoacidosis has been as high as 3–9%.\textsuperscript{7,10–11} SGLT2 inhibitors can increase the risk of diabetic ketoacidosis by several potential mechanisms.\textsuperscript{5,20} By lowering glucose levels by insulin independent mechanism, they may prompt an inappropriate reduction of insulin doses and increase the risk of ketogenesis. Their use is associated with an increase in glucagon secretion, via a direct effect on pancreatic α-cell and also a compensatory rise due to glucouresis. They may also reduce the renal clearance of ketone bodies. Moreover, blood glucose may be lower than typically seen in diabetic ketoacidosis, which has been described as “euglycemic” diabetic ketoacidosis, leading to a delay in diagnosis.\textsuperscript{21}

The risk of diabetic ketoacidosis is high in individuals with T1D latent autoimmune diabetes and T2D with insulinopenia. In most cases reported so far, including ours, there were clear precipitating factors which could have triggered the ketoacidotic state. Some of these include insulin omission or inappropriate dose reduction, insulin pump failure, acute medical illness or surgery, trauma, dehydration, alcohol intake, or starvation.\textsuperscript{22} Our patient had reduced her insulin doses significantly, had not been monitoring regularly, had poor glycometric control (HbA1c 12.5%), and was hospitalized for dengue fever. Even though her dengue fever was not complicated by dengue shock syndrome or dengue hemorrhagic fever, the overall combination of factors along with the use of SGLT2 inhibitors could have triggered the DKA. Her blood glucose was deceptively lower at first presentation, which led to a few hours’ delay in the diagnosis.

While the off-label use of SGLT2 inhibitors in T1D is increasing, there is a pressing need to appreciate the lack of long-term studies and the increased risk of diabetic ketoacidosis with their use. If used at all,
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the potential risk should be explained to the patient, and caution must be exercised to ensure insulin dose is not significantly reduced and adequate hydration is maintained. SGLT2 inhibitors should be discontinued during any acute illness and prior to planned surgeries.18 Physicians should be aware of the possibility of DKA even if the blood glucose is not significantly elevated, and should maintain a high index of suspicion.9

5. Taylor SI, Blau JE, Rother KI, SGLT2 inhibitors may predispose to hypoglycemia, J Clin Endocrinol Metab, 2015;100:2849–52.
6. Rodbard HK, Peters AL, S, et al., The effect of canagliflozin, a sodium glucose transporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring of patient-reported outcomes among people with type 1 diabetes, Diabetes Care, 2015;38:2654–64.e1.