DIABETIC KETOACIDOSIS WITH LOWER-THiAN-ANTiCiPiTED GLUCOSE LEVELS WITH SGLT-2 INHIBITOR CANAGLIFLOZIN: A CASE REPORT AND REVIEW OF THE LITERATURE.

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ABSTRACT
We describe a case report of a patient who presented with euglycemic diabetic ketoacidosis (eDKA), six days after starting treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitor, Canaglifluzin. ‘Euglycemic diabetic ketoacidosis’ or ‘DKA with lower-than-anticipated glucose levels’ (as recommended by AACE/ACE) is a rare, challenging and easy to miss the diagnosis A 41-year-old male with a history of type 2 Diabetes Mellitus presented with uncontrolled hyperglycemia. Canaglifluzin (SGLT2 inhibitor) was added to his anti-diabetic regimen of Metformin and Sitagliptin. Six days later, he presented with symptoms of diabetic ketoacidosis with normal blood glucose of 131 mg/dl. The patient was further investigated with arterial blood gas analysis and serum ketone studies, keeping in view of the potential of euglycemic diabetic ketoacidosis (euDKA) with SGLT2 inhibitor use. The clinical picture and lab values of the patient were consistent with diabetic ketoacidosis (DKA), although it is rare in type 2 DM. Blood glucose was in the normal range which could have delayed the diagnosis if the physician was not vigilant. If one had only focused on the blood glucose, then this potentially fatal condition could have been missed. However, when other causes of anion gap metabolic acidosis were excluded and the lab values of urine ketones, elevated beta-hydroxybutyrate, reduced bicarbonate, and normal lactate interpreted, it leads to the diagnosis of SGLT2 inhibitor-associated euglycemic DKA. We performed a literature review of this topic and discuss the history of euglycemic diabetic ketoacidosis, risk factors, pathophysiology, diagnosis, management, and prevention of SGLT2 inhibitor-induced euDKA.

KEYWORDS
SGLT2i, euglycemic diabetic ketoacidosis, euDKA, DKA, history, clinical picture, laboratory values.

INTRODUCTION
The sodium-glucose cotransporter-2 (SGLT2) inhibitors are a newer class of anti-diabetic drugs indicated for the treatment of type 2 diabetes mellitus. Reversible inhibition of SGLT2 receptors in the proximal tubules of the kidney is their primary mechanism of action, resulting in decreased glucose reabsorption and increased glucose excretion in urine. Their use has tremendously increased due to their favorable profile, including good glycemic control, weight loss and reduction in blood pressure. SGLT2 inhibitors are also the focus of attention because of their side effects like genitourinary tract infections, hypovolemia and especially, ketoacidosis which is the most serious of all. Type 1 diabetic patients are prone to diabetic ketoacidosis due to complex biochemical mechanisms. But Euglycemic Diabetic Ketoacidosis(euDKA) or DKA with lower-than-anticipated glucose levels is an entity encountered in type 2 diabetic patients treated with SGLT2 inhibitors. Blood glucose levels in euglycemic diabetic ketoacidosis seen after SGLT2 inhibitor use are usually lower than 250 mg/dL, hence delaying patient diagnosis.

Case Presentation
A 41-year-old male with a past medical history of DM type 2 and Hypertension, on Metformin 1000mg and Sitagliptin 100mg (DPP-4 inhibitor) and Lisinopril 20mg, presented to the clinic with uncontrolled hyperglycemia with glycated hemoglobin of 11.7%. Canaglifluzin 100mg (SGLT2 inhibitor) was added to his oral hypoglycemic regimen. Six days later he presented to the hospital with a chief complaint of blurred vision, lightheadedness, nausea, vomiting, and abdominal pain. On examination, he had tachycardia and tachypnea; his other physical examination including cardiovascular, respiratory, abdominal and neurological was unremarkable. Blood chemistry was significant for normal glucose levels of 131mg/dL, bicarbonate 14meq/l, anion gap 20, creatinine 0.8mg/dl, urine, and serum positive for ketones, elevated beta-hydroxybutyrate of 5.7mmol/l, and arterial blood gas showed a pH of 7.16. Serum lactate acid, amylase and lipase were normal. The patient was admitted with findings consistent with euglycemic diabetic ketoacidosis. Canaglifluzin was stopped immediately after the confirmation of the diagnosis and the patient was treated conservatively with intravenous fluids, insulin with dextrose. The symptoms resolved, with a reduction in the anion gap to 11 within 24 hours. Canaglifluzin was discontinued indefinitely and the patient was discharged with the diagnosis of SGLT2 inhibitors induced euDKA.

DISCUSSION
Diabetic ketoacidosis is a severe and life-threatening metabolic complication of type 1 diabetes mellitus. It can rarely occur in patients with type 2 diabetes mellitus. It is a medical emergency characterized by a triad of hyperglycemia (blood sugar >250mg/dl), anion gap metabolic acidosis (anion gap >10, arterial pH<7.3 and serum bicarbonate <18meq/l), and ketosis with positive serum ketones and elevated beta-hydroxybutyrate. It is caused by an absolute or relative insulin deficiency and increased levels of counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone. This results in hyperglycemia, lipolysis, increased production of free fatty acids and ketone bodies. Classic signs and symptoms of DKA include polyuria, polydipsia, nausea, vomiting, abdominal pain, visual disturbance, lethargy, altered sensorium, tachycardia, tachypnea, Kussmaul respirations and acetone smell to the breath [1]. Euglycemic DKA, on the other hand, presents with glucose levels <250mg/dl and is, therefore, challenging to identify. Historically, euglycemic DKA was first described by Munro et al. in 1973, as diabetic ketoacidosis with a blood glucose level of <300mg/dl. Jenkins et al. reported 23 cases of euDKA in 1993 based on the Munro criterion. They proposed a glucose level of less than 10mmol/l (<180mg/dl) as a criterion for euDKA [2]. Euglycemic DKA is characterized by blood glucose levels <200mg/dl, anion gap metabolic acidosis and positive serum and urine ketones. Eu-DKA can, therefore, present without hyperglycemia and the symptoms of dehydration, making it challenging to identify. This can result in delayed diagnosis and treatment leading to adverse metabolic complications. The common causes of euglycemic DKA are pregnancy, insulin-deficient diabetes, SGLT2 inhibitor (SGLT2i) use, decreased calorie intake and after bariatric surgery, glycogen storage disease and chronic liver disease. The less common causes are acute pancreatitis, heavy alcohol use or cocaine abuse, gastroparesis and muscle dystrophy [3]. With the increasing use of SGLT2i and their association with euDKA, they are now becoming the representative of euDKA.

SGLT2 inhibitors are new oral hypoglycemic drugs, approved in March 2013 by the FDA. They are indicated for the treatment of type 2 DM as a second line to Metformin or as a first-line in patients who are unable to tolerate Metformin or in combination with other anti-diabetics. SGLT2 is a sodium-dependent glucose transporter protein responsible for reabsorbing glucose from the proximal renal tubule. SGLT2 decreases blood glucose independently of insulin secretion by reversibly inhibiting SGLT2 protein. SGLT2-induced glucosuria depends on the amount of glucose filtered by the kidneys which depend on plasma blood concentration [4]. SGLT2i exerts favorable effects beyond glycemic control with
reduced glycated hemoglobin. The EMPA-REG OUTCOME study concluded that SGLT2 decreases all-cause mortality, cardiovascular mortality and hospitalization for heart failure. They cause weight loss without a risk of hypoglycemia, lowers blood pressure by decreasing arterial stiffness and reduces oxidative stress by decreasing uric acid levels. The major side effect is genitourinary infections due to high urine concentration of glucose, osteoporosis with an increased risk of fractures, euDKA and volume depletion (rarely) [5, 6].

The increased risk for diabetic ketoacidosis with SGLT2 is a concerning situation. After case reports of DKA in patients taking SGLT2, a drug safety warning was issued by the US Food and Drug Administration on May 15, 2015. The relative normal glucose levels lead to delayed diagnosis and treatment of this potentially life-threatening situation. Randomized studies in T2DM patients showed the incidence of DKA was twice in SGLT2 treated group compared to the control group. FDA adverse event reporting system (FAERS) reports a seven-fold increase in the risk of DKA in SGLT2 treated T2DM patients [7]. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology convened a conference in October 2015 and gave position statements after evaluating cases of SGLT2-associated euDKA.

The mechanism of SGLT2 associated euDKA is unclear. There are several proposed mechanisms for underlying pathophysiology. SGLT2 inhibitors induce persistent glycosuria lowering blood glucose levels and this decreases insulin secretion from beta cells of the pancreas. This increased insulin levels triggers gluconeogenesis and also SGLT2 directly stimulates alpha cells in the pancreas to increase glucagon secretion. This insulinenopia and increased glucagon results in increased glucagon/insulin ratio. This promotes a ketogenic state with gluconeogenesis, glycosgenesis and lipolysis and ketogenesis [3]. The kidneys also play an important role in the pathogenesis of euDKA by decreasing plasma volume due to decreased sodium reabsorption and increasing ketone reabsorption. Therefore, urine ketones are not a sensitive marker of DKA. SGLT2 inhibitors also predispose to a negative fluid and sodium balance and can worsen the hypovolemic state of DKA, particularly in the setting of nausea and poor oral intake. Hypovolemia, decreased blood glucose and metabolic stressful situations stimulate counter-regulatory hormones such as catecholamines, cortisol, and growth hormone, which further increase insulin resistance, lipolysis, and ketogenesis [8, 9].

Risk factors for SGLT2 associated euDKA include latent autoimmune diabetes of adulthood, diabetes, surgery or peri-operative preparations, prolonged fasting or dietary restriction or sudden drastic changes in diet notably low-carb intake or 'keto-diet', hypovolemia, infection, severe injury, acute coronary syndromes, stroke, alcohol abuse, physical exertion, dose reduction of insulin secretagogues, insulin omission or inappropriate dose reduction and acute medical illness [3, 8]. Patient factors associated with the development of euDKA are poorer beta cell function reserve, longer duration of diabetes, poorer control of diabetes and lower BMI [2].

DKA is rarely seen in type 2 DM and the normal glucose can cause misinterpretation of the patient's condition, causing a delay in treatment. The diagnosis can be challenging for those unfamiliar with SGLT2 and its association with euDKA since blood gas analysis and ketone studies are not a part of routine labs. When suspected, serum and urine ketones should be checked to reduce the time to diagnosis and treatment. EuDKA, as with DKA, needs immediate evaluation and treatment. The AACE/ACE recommends measurement of beta-hydroxybutyrate and arterial pH for the diagnosis of SGLT2 associated euDKA. Normal or mildly elevated blood glucose does not exclude this diagnosis in patients using SGLT2. Differential diagnosis of starvation ketoacidosis can be considered but it is usually mild with pH above 7.3 and bicarbonate >18, keto-anions <5mmol/l (in DKA, keto-anions higher). Other causes of acidosis like excess alcohol consumption or toxic alcohol ingestion, salicylate or TC poisoning, lactic acidosis, RTA can be excluded with a careful history, clinical evaluation, and labs [3].

The mainstay of treatment of euDKA is immediately stopping SGLT2 inhibitors and traditional DKA treatment protocol. Due to reversible action of SGLT2, recovery is expected with discontinuing the drug and aggressive fluids administration to correct dehydration, insulin with dextrose to correct anion gap and bicarbonate levels and electrolyte replacement. The other important step is preventing SGLT2-induced DKA by ensuring that SGLT2 inhibitors are prescribed carefully through an accurate selection of patients. SGLT2 should be discontinued when recipients develop any precipitating condition. The ACEA recommends stopping SGLT2, 24 hours prior to anticipated surgery or invasive procedures or stressful physical activity. For emergency surgery, SGLT2 should be stopped immediately and the patient should be monitored. Insulin should not be stopped or the dose reduced too fast after starting patients on SGLT2. Patients should be educated regarding adequate hydration and adequate calorie intake without any sudden drastic dietary changes while using SGLT2. Physicians should avoid using SGLT2 in patients with poor oral intake, alcohol dependence or pregnancy [3, 8]. Patients can be suggested to measure ketones by urine dipstick test at home when they have symptoms suggestive of DKA and a history of a trigger, like acute illness or excessive alcohol use or low-calorie intake due to nausea or vomiting. If positive they should immediately visit their physician for possible management of euDKA [10]. Routine testing is not recommended in asymptomatic patients using SGLT2. For now, the risk-benefit ratio favors the use of SGLT2 but physicians should be clinically vigilant when encountered with a patient using SGLT2 [8].

CONCLUSIONS

In conclusion, SGLT2 inhibitor-induced euDKA has nonspecific signs and symptoms and can present without the classical laboratory findings of DKA. Clinicians should have a high index of suspicion for patients treated with SGLT2. The patients, with a history of SGLT2 use and, signs and symptoms of DKA, even in the absence of hyperglycemia, should be suspected of euDKA. The detailed history and clinical evaluation with complete lab work with blood gas analysis, blood and urine ketones including beta-hydroxybutyrate level, must be done to ensure that the diagnosis is not missed and timely interventions are made to manage this serious condition. Patients who are started on SGLT2 should be informed about the possibility of this potentially life-threatening adverse effect and educated about common triggers like alcohol abuse, acute illness, low-calorie diet, etc. Measuring urine ketone bodies can be suggested to patients but not routinely recommended.

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