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Euglycemic Ketoacidosis and an Absence Seizure in A Type 2 Diabetic On SGLT2 Inhibitors: Case Report and Review of the Literature

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1. Abstract

1.1. Introduction: In recent years, many new antidiabetic drugs have been developed. One class of these new antidiabetic drugs are sodium-glucose cotransporter 2 inhibitors (SGLT2i). SGLT2i are associated with an increased risk of euglycemic ketoacidosis (euDKA).

Case report: We describe an 81-year-old male with type 2 diabetes mellitus (T2DM), who arrived at the emergency department (ED) after a suspected absence seizure. An arterial blood gas (ABG) demonstrated a high anion gap metabolic acidosis. Subsequently, the diagnosis of euDKA was made. A computed tomography (CT) of the brain and electroencephalography (EEG) could not provide a substrate for his seizure. We started with intravenous levetiracetam, an anticonvulsant. He left the hospital in a good condition, 5 days later.

Conclusion: Health care professionals should be aware that a patient can be in diabetic ketoacidosis without having elevated levels of blood glucose. Such a euDKA often has a more atypical presentation due to different underlying pathophysiological mechanisms. In animal models, ketonemia exerts anti-seizure effects, but this has yet to be proven in clinical trials. As such, in our patient, a link between his absence seizure and euDKA remains unclear.

2. Introduction

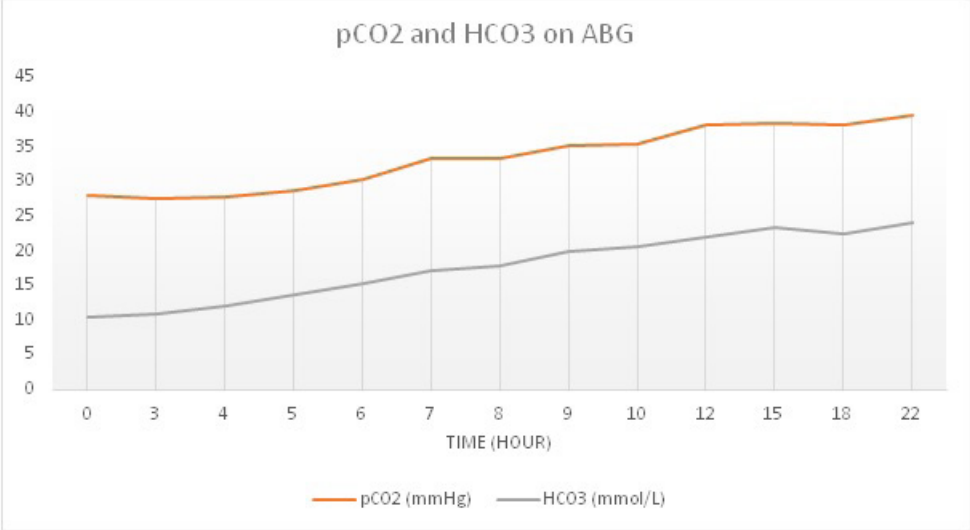
Globally, an estimated 462 million individuals are affected by type 2 diabetes (T2D), meaning good treatment options can have a major impact on patient morbidity and mortality for a huge number of people [1]. One relatively new class of antidiabetics are sodium-glucose cotransporter 2 inhibitors (SGLT2i), also known as gliflozins. They prevent renal glucose reabsorption into the blood by blocking sodium-glucose cotransporter 2 (SGLT2). Under normal physiological conditions, SGLT2 facilitates urinary reabsorption of glucose in the proximal renal tubules [2]. However, SGLT2i use has been associated with a higher prevalence of euDKA [3,4]. Just like hyperglycemic DKA, euDKA is a medical emergency that requires rapid treatment. The cardinal difference between both forms of diabetic ketoacidosis is that euDKA is characterized by milder blood glucose levels, typically <250 mg/dL. This normoglycemia might be misleading as it can delay a timely diagnosis and thus postpone adequate treatment [5,6].

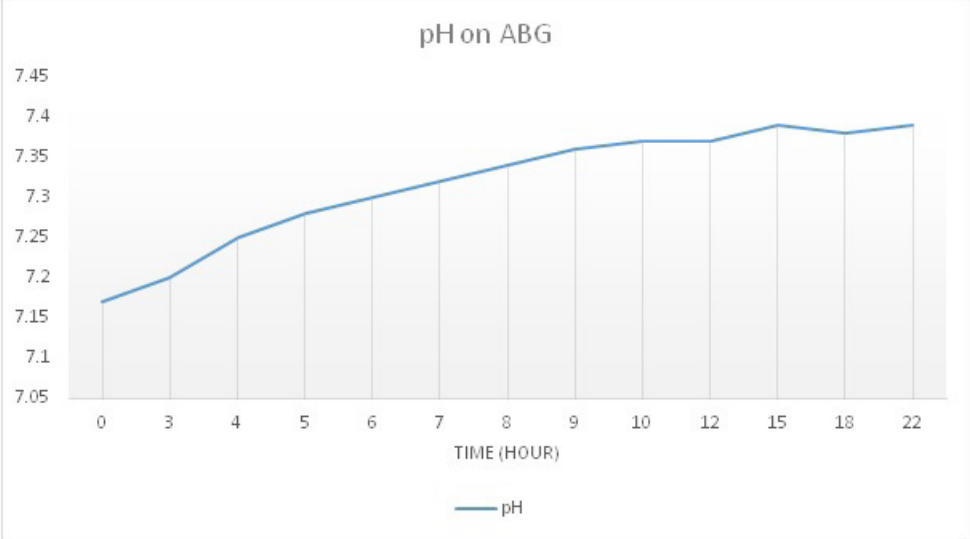
3. Case Report

An 81-year-old male presented to the ED with a decreased level of consciousness, nausea, and vomiting. His complaints had started an hour before admission. According to family members who witnessed the event, he was sitting unresponsive for approximately 10 minutes while maintaining normal muscle tone. He subsequently started hyperventilating and regained consciousness. On admission, his vital signs showed hypertension (170/110 mmHg), blood oxygen saturation of 98% without supplemental O2, a heart rate of 70 bpm, tachypnea (20 breaths per minute), and no fever. We did not withhold any abnormalities on clinical examination. More specifically, a complete neurological exam showed no signs of lateralization, normal pupil functioning, normal sensory and motor function, and a Glasgow Coma Scale (GCS) of 15/15. He

suffered from inadequately controlled T2D for more than 10 years. His most recent HbA1C was 10.4%. In addition, he suffered from diabetic nephropathy, atrial fibrillation, arterial hypertension, hypercholesterolemia, and obesity. His home medication consisted of a statin, an antiplatelet drug and a beta-blocker. His diabetes was treated with insulin, metformin, and a daily dose of dapagliflozin (10mg), a SGLT2i. Our initial differential diagnosis focused on the unresponsiveness and included epilepsy or a transient ischemic attack (TIA). However, a CT scan of the brain and an EEG showed no abnormalities. In contrast, ABG demonstrated a severe high anion gap metabolic acidosis, with normal lactate levels, and normoglycemia. Considering the possible causes for a high anion gap metabolic acidosis: glycoles, (5)-oxoprolin, L-lactate, D-lactate, methanol, aspirin, renal failure, rhabdomyolysis, and keto-acidosis (GOLDMARRK) [7], we checked for ketonemia and found a level of 6.9 mmol/L.

We started with intravenous isotonic crystalloid fluids to correct dehydration and started treatment with 40 ml glucose 20% and a continuous infusion of 5 units of insulin per hour, to activate glucose metabolism and stop fatty acid metabolism. Whilst insulin was administered, potassium levels were closely monitored and corrected as necessary. We performed serial ABG's to monitor the therapeutic effects and titrate insulin therapy as necessary. Within 12 hours, his blood values normalized, and ketonemia was undetectably low. We considered his unusual loss of consciousness at home to be an absence seizure and consequently started intravenous Levetiracetam (2 x 1000 mg/day), an anticonvulsant. He was scheduled for further neurological evaluation and could leave the hospital in a good condition, 5 days after presenting to the ED. Figure 1 represents the ABG values over time during treatment. After 10 hours of treatment, arterial pH and pCO2 were normalized. Arterial HCO3- and ketones returned to normal after 12 hours. Glycaemia always remained between 100 and 200 mg/dL during treatment by carefully titrating glucose and insulin doses. See Figure 1.





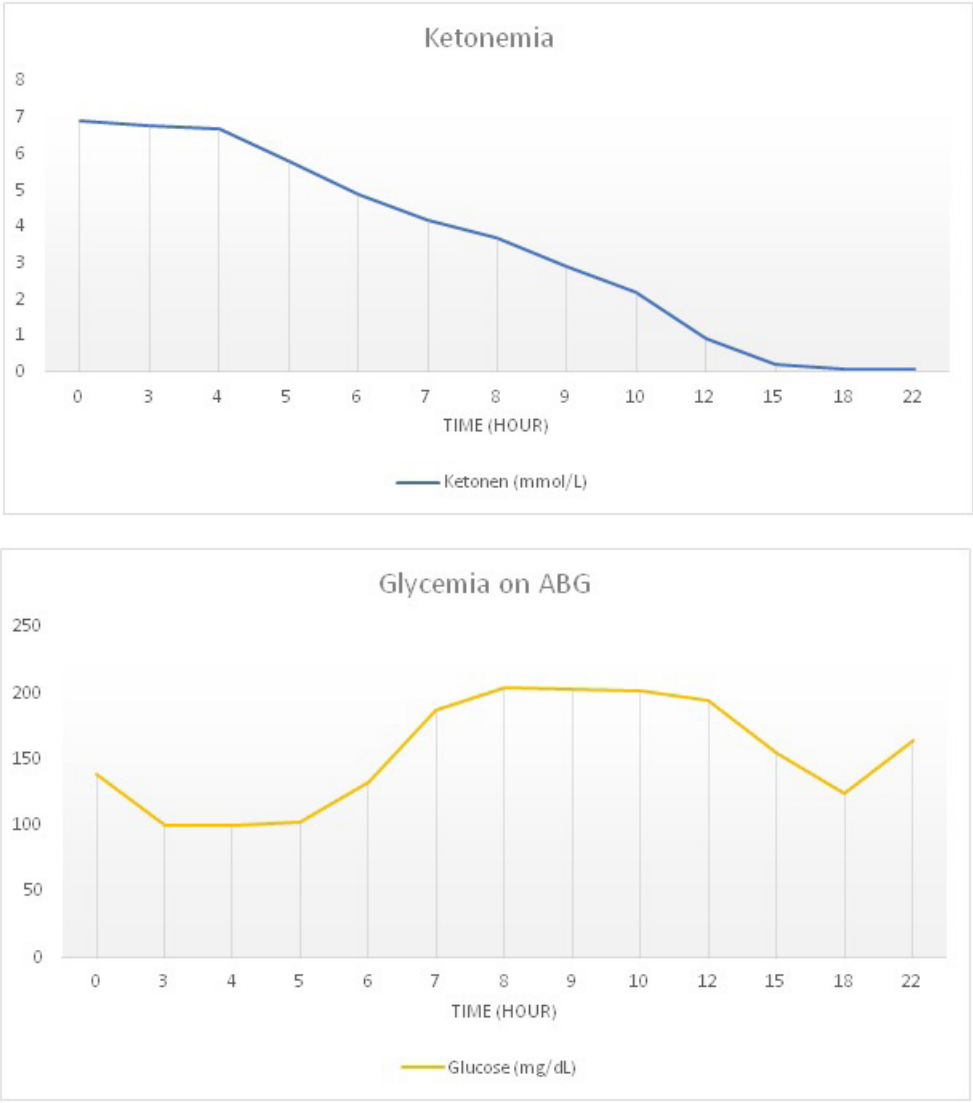


Figure 1: Different lab values over time.

4. Discussion

4.1. Differences Between DKA and euDKA

DKA is a life-threatening complication of type 1 diabetes mellitus (T1D), and much less commonly of T2D. Classically, DKA is characterized by a triad of ketosis, acidosis, and hyperglycemia. Ultimately, this triad is caused by a decrease in circulating insulin levels, combined with elevated counter-regulatory hormones such as: glucagon, growth hormone, glucocorticoids and catecholamines. Causes for the hormonal changes that facilitate DKA include major illness, reduced food and fluid intake or decreased exogenous insulin dosing. As a result, the body switches to lipids as its primary source of energy, which leads to the production of ketone bodies. In euDKA, however, the underlying pathophysiological mechanism is different and is either due to decreased glucose production by the liver or by enhanced urinary excretion of glucose due to an excess of counter-regulatory hormones. Insulin deficiency and resistance are also milder than in DKA. There are several risk factors for euDKA such as low caloric intake, heavy alcohol consumption, pregnancy, cocaine abuse, pancreatitis, sepsis, liver disease, and notably, exogenous insulin administration closely before admission [2]. Hyperglycemic DKA is typically associated with blood glucose levels of > 250 mg/dl [5,8]. However, euDKA is characterized by normal blood glucose levels, which poses a potential challenge for a timely diagnosis of this condition. Therefore, we suggest a more ketonic-centered diagnostic approach as both forms of DKA do present with elevated ketonemia. Since euDKA is associated with much milder blood glucose levels, it does not lead to osmotic diuresis meaning that a timely diagnosis is even further complicated by the absence of polydipsia and polyuria, typical clinical features of hyperglycemic DKA. Patients with euDKA are more likely to present with atypical complaints such as malaise, anorexia, tachypnea, and tachycardia [6].

4.2. SGLT2i and euDKA

Under normal physiological conditions, SGLT2 facilitates the urinary reabsorption of glucose in the proximal renal tubules. SGLT2i work by blocking SGLT2 in the proximal renal tubules, prevent-

ing renal glucose reabsorption, ultimately resulting in an absolute or relative insulin deficiency and an increase in glucagon. These hormonal changes trigger the body to switch to lipids as primary energy source, resulting in lipolysis and ketogenesis. A large multicenter study demonstrated that SGLT2i use is associated with a small but significant increased risk for DKA in T2D. The incidence of euDKA was 1.02 per 1000 (95% CI, 0.74 to 1.41 per 1000) in SGLT2i users vs 0.69 per 1000 (95% CI, 0.58 to 0.82 per 1000) in non-SGLT2i users (OR, 1.48; 95% CI, 1.02 to 2.15; P = 0.037) [4].

4.3. Diagnosis and Management of euDKA

Euglycemic ketoacidosis can be misleading due to its atypical clinical presentation and concomitant euglycemia. The differential diagnosis includes all other causes of metabolic acidosis with an elevated anion gap [7]. Physicians also have to search for the underlying etiologies triggering euDKA. A blood gas, either venous or arterial, should be drawn to evaluate glycemia, lactate, electrolytes, and acid-base disturbances. Ketonemia should be determined on a venous blood sample. The measurement of urinary ketones is no longer recommended to confirm DKA. The nitroprusside reaction, which is a common method to measure urinary ketones, does not detect β-hydroxybutyrate, the predominant ketone in ketoacidosis. Even when urinary β-hydroxybutyrate is measured, the use of blood ketones is much faster and has a higher specificity [9]. The management of euDKA consists of rapidly treating dehydration and acidosis using IV fluids and insulin, whilst monitoring and correcting electrolyte disturbances when necessary. Isotonic fluids are the first choice for IV fluid resuscitation. The rate of fluid resuscitation is dependent upon the clinical state of the patient. Subsequently, patients should be started on a fixed-rate intravenous insulin infusion using a weight-based formula (0.1U/kg/h) with concomitant glucose administration to avoid hypoglycemia secondary to the large amounts of insulin that are necessary to correct the acidosis. Physicians should be watchful for iatrogenic hypokalemia that can occur during treatment, which can cause arrhythmias. Before treatment, acidemia causes an extracellular shift of potassium, leading to a falsely elevated serum potassium. During normalization of blood pH, potassium will flow back into the intracellular compartment and thus cause a drop in serum potassium. As insulin will also lead to an intracellular shift of potassium, a dual mechanism pushes potassium back into the cells. In patients with a serum potassium <3.3mEq/l, to prevent iatrogenic hypokalemia, fluid and potassium replacement should be initiated before insulin therapy [10]. Treatment targets are as for hyperglycemic DKA: reducing blood ketone concentration by 0.5 mmol/L/h; elevating bicarbonate with 3.0 mmol/L/h; keeping serum potassium between 4.0 and 5.5 mEq/L. Should these targets not be met, one has to increase the dose of fixed-rate insulin infusion [11].

4.4. Epileptic Seizures and DKA

Our patient initially presented with a suspected epileptic seizure. It was at the venous lactate measurement to exclude tonic-clonic seizures that we noticed a severe high anion gap metabolic acidosis and subsequently diagnosed an euDKA. The CT of the brain showed no abnormalities that could provide a substrate for an epileptic seizure, nor was the EEG suggestive. We questioned whether the ketoacidosis might be a potential trigger for his absence seizure. Contradictory, ketosis is thought to prevent epileptic seizures. The ketone bodies Beta-hydroxybutyrate (βHB) and acetoacetate (AcAc) exert anti-seizure effects in animal models, but this still has to be proven in humans [12] Therefore, we cannot rule out nor confirm a connection between his euDKA and his seizure.

5. Conclusion

Health care professionals should be aware that a patient can be in diabetic ketoacidosis without having elevated levels of blood glucose. Such an euDKA often has a more atypical presentation due to different underlying pathophysiological mechanisms. When treating with insulin, extra attention should be paid to avoid iatrogenic hypoglycemia as glycemia is already at normal levels. In animal models, ketonemia exerts anti-seizure effects, but this has yet to be proven in humans. As such, in our patient, a link between his absence seizure and euDKA remains unclear.

6. Keypoints

• euDKA is characterized by blood glucose levels <250mg/dL, acidosis and ketosis.

• euDKA is associated with different triggers such as: SGLT2i use, pregnancy, low caloric intake, heavy alcohol consumption, pancreatitis, sepsis, cocaine abuse, liver disease and insulin use close before admission.

• Associate a glucose solution at the start of fixed-rate insulin infusion to avoid iatrogenic hypoglycemia and be watchful for iatrogenic hypokalemia.

• Ketonemia exerts anti-seizure effects in animal-models but it has yet to be confirmed in humans.

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