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Case Report

Empagliflozin Induced Euglycemia DKA Unveiling Type 1 Diabetes in a Patient of Pancreatitis-A Case Report

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Abstract

Euglycemic diabetic ketoacidosis due to empagliflozin is a life-threatening metabolic complication of diabetes mellitus which is characterized by normal serum glucose levels, ketonemia and metabolic acidosis. We present a rare case of empagliflozin-induced diabetic ketoacidosis later on unmasked as type 1 diabetes. The aim of this case report is to create awareness among clinicians to consider this diagnosis in patients taking sodium-glucose co-transporter (SGLT-2) inhibitors and act timely so that our prompt action can be life saving for the patients.

Keywords: *Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors; Empagliflozin; Euglycemia DKA; Type 1 Diabetes; Pancreatitis*

Introduction

Sodium-glucose Cotransporter 2 (SGLT2) inhibitors are the newer class of oral diabetes medications which have shown improved cardiovascular and kidney outcomes independent of glycemic control in various trials. The use of this drug has grown rapidly due to its pleotropic effect. A rare but important adverse effect of euglycemic ketoacidosis with its use is worth the concern which is characterised by blood glucose of < 200 mg/dl in the presence of severe metabolic acidosis and ketonemia. In the absence of hyperglycemia, this diagnosis is sometimes missed, hence a strong suspicion is paramount. Here we present a case of a patient who presented in euglycemic ketoacidosis possibly empagliflozin induced. Strong clinical suspicion helped in making a quick diagnosis and managing it aggressively which helped us save his life. This patient was presumed to be having secondary pancreatic diabetes since last 6 months and was revealed to have type 1 diabetes during this admission based on positive Anti GAD antibodies.

Case Report

Young male 45 yrs, chronic alcoholic since 20 years, known chronic pancreatitis since 5 years, was diagnosed to have secondary diabetes 5 years back and was started on insulin as part 14 units sc thrice daily. 2 days prior to the presentation he was travelling due to which he skipped his meals and then started having severe pain abdomen with multiple episodes of vomiting following which he presented to the emergency department. On examination, he was conscious, oriented with presence of tachycardia, tachypnea and signs of dehydration. He was afebrile with BP 120/80 mmhg and HR 112/min. Cardiac, abdominal and respiratory examination was normal. Blood investigations done showed hypokalemia with K of 3.4, Phosphorus 1.7, HbA1c of 10%, Random blood glucose 202 mg/dl, Beta hydroxybutyrate level was 5 mmol/l, urine showing 3+ glucose and ketones 3+, with pus cells. ABG was done which showed high anion gap metabolic acidosis with pH 7.1, pCo_2 9 mmhg, Hco_3 3.4 mmol/land AG of 35 mmol/l, lactate 0.9 mmol/l which worsened despite

giving fluid resuscitation. His Sepsis profile was done which was negative. Random blood sugar was done which was 202 mg/dl. So a possibility of euglycemic ketoacidosis was kept. After ruling out other causes of high anion gap metabolic acidosis like renal insufficiency, lactic acidosis, intoxication, methanol and salicylates, his drugs were reviewed and it was found that he has taken tab empagliflozin 25 mg 3 days prior to his presentation which probably resulted in euglycemic ketoacidosis in this patient. His urine examination revealed presence of pus cells with sterile culture for which he was put on IV antibiotics. Aggressive hydration with IV saline with potassium supplementation was given and thereafter insulin infusion was initiated. Potassium, vital signs, urine output, blood ketones, blood sugars and ABG were monitored frequently.

Table 1 depicts the serial laboratory parameters during the hospital stay. His blood ketones came out negative on 3rd day of his admission following which he was started on basal bolus insulin regime and blood sugars were monitored and controlled. Keeping a possibility of type 1 DM with a strong family history, his C-peptide levels were done which was very low 0.1 mg/ml and fasting insulin levels were normal 2.9 (reference range of 2 - 25 microunit/ml). Anti GAD antibodies were done which was very high 122.54 IU/ml (normal reference value < 10) which confirmed the diagnosis of type- I DM. The patient was explained about the need of life long insulin therapy. His USG abdomen was also done for current pancreatic status which showed atrophic pancreatic changes and dilated main pancreatic duct. His CA19-9 was also done which came out to be mildly raised for which CECT abdomen was done which showed presence of chronic calcific pancreatitis and ruled on any evidence of malignancy and was advised to keep a follow up on CA19-9. With all the above treatment, his sugars were normalised and he was discharged in stable condition with an advise to continue insulin, avoid skipping meals, alcohol abstinence and stop empagliflozin.

	Day0	Day1A	Day1 B	Day2	Day3	Day4	Day5	Day6
pH	7.18	7.07	7.2	7.35	7.5			7.48
Pco_2	9	8	12	12	29			38
Hco_3	7.8	5.1	8.1	12.4	25			28
Anion gap	35	32	30	28	10			10
Sodium	129	134			135	139	139	137
Potassium	3.4	3.7			3.2	3.0	3.9	4.2
phosphorus	1.7	1.2			<1	4.8		5.5
Beta hydroxybutyrate	7	5.1		5		4.6	1.2	0.1
Lactate	0.9	1	0.9	0.7				1.1
Glucose	202	164	164	168	114		300	140
Creatinine	0.89	0.8			0.5			0.38
BUN	7	5.6			2.9			4.2
Hematocrit	45.9				37.5		38	
Chloride		102			103	100	102	105

Table 1: *Depicting the serial laboratory parameters during the hospital stay.*

Discussion

The ADA diagnostic criteria for DKA include hyperglycemia (blood glucose > 250 mg/dL), metabolic acidosis (arterial pH < 7.3 and serum bicarbonate < 18 mEq/L) and ketosis [1].

Euglycemic DKA was initially described as severe ketoacidosis with a blood glucose level less than 300 mg/dL, but currently it has been changed to < 200 mg/dL [2].

The mechanism of action of SGLT-2 inhibitor is to inhibit the renal glucose reabsorption, increasing urinary glucose excretion and thereby lowering the blood glucose levels. The reduced blood glucose levels will lead to decreased insulin release from beta cells, stimulating alpha cells thereby increasing glucagon production. Glucagon aid in hepatic ketogenesis which results in ketone body production in the setting of normal glucose levels referred to as euglycemic ketoacidosis [3].

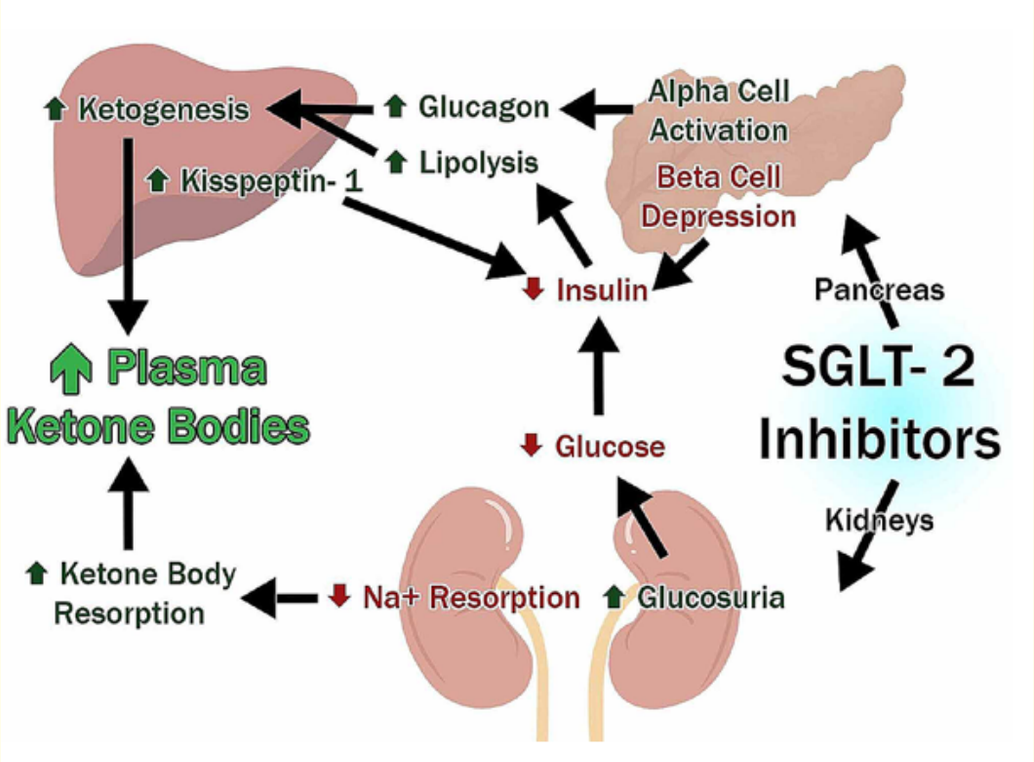

Figure 1: *Shows the multifactorial pathogenesis of euglycemic DKA due to SGLT-2 inhibitors [4].*

The common adverse effects are increased risk of urinary tract infection, genital mycotic infections, volume depletion.

The emerge of its rare but serious side effect of euglycemic diabetic ketoacidosis is worth a concern and physicians should be well versed with these risks with this medication so that any serious and life-threatening event can be avoided. In 2015, FDA approved a safety warning for SGLT2 inhibitor induced ketoacidosis after total of 73 cases were reported from March 2013 - May 2015 requiring emergency hospitalisations and were complicated due to delayed diagnosis in view of normal blood glucose levels at presentation [5].

All patients with LADA and type1 lack endogenous insulin production causing inability to overcome the increase in glucagon levels due to SGLT2 inhibitors which leads to unsuppressed hepatic ketogenesis [6] and hence this class of drug should be used with caution in type1 and LADA.

A systematic review revealed that two-thirds of all cases were T2DM while nine out of twenty five were later diagnosed with latent autoimmune diabetes after resolution of DKA [7]. Further CANVAS trial showed that in patients who were taking canagliflozin, six out of twelve were diagnosed with either autoimmune or tested positive for GAD65 antibodies after DKA was developed [8].

Several trials have shown beneficial effects like reduction in body weight and blood pressure due to natriuresis causing ameliorated cardiovascular and renal outcomes. So as per the ADA guidelines, SGLT-2 inhibitors are recommended as a monotherapy or an adjunct to metformin as the benefits outweigh the risks [9]. The patient and the family should be made aware of the risks and adverse events and of the measures to mitigate these risks.

Euglycemic DKA is more commonly seen in type 1 than type 2 DM and that is why the American association of clinical endocrinologists produced a consensus statement urging caution with off label use in type 1 diabetes. In our case also, patient was initially being treated as diabetes secondary to pancreatitis and on evaluation was found to have underlying type 1. A retrospective analysis showed that DKA due to SGLT2 inhibitors developed in situations like off-label use in patients with type 1 diabetes mellitus, missed diagnoses of type 1 diabetes mellitus, or latent autoimmune diabetes of adulthood [10].

Insulinopenia either absolute or relative (e.g. acute illness and reduced oral intake) leads to reduced glucose use, increased lipolysis, and increased free fatty acid transport to the liver. Glucagon levels increase, leading to free fatty acid oxidation and ketosis [11].

After initiation of SGLT2 inhibitor therapy, the approximate time taken for DKA to develop is around 2 weeks which may or may not be precipitated by an event like acute illness (e.g. infection and surgery), reduced oral intake, state of volume depletion, stressful physical activity, marathon runs and reduced insulin dose [11]. As per endocrinology clinical practice guidelines, this class of drugs should be withheld atleast 24 hours in all such circumstances though the effect of drug may persists beyond 2 - 3 days with ketonemia and glucosuria persisting for around 9 - 10 days post discontinuation. Similar case reports have been published recently where the unusual presenting symptoms resulted in delayed diagnosis. Acute abdomen mimicking peritonitis was seen with the use of dapagliflozin in a case report by Wang., *et al* [12]. Two other case reports highlighted the importance of careful covid 19 vaccination in patients receiving SGLT-2 due to high risk of ketoacidosis [13]. A case with blood sugar level of 75 mg/dl at presentation [14] while another who recently started a ketogenic diet also developed ketoacidosis while having SGLT-2 inhibitors [15]. These varied presentations specify the importance of detailed history taking in patients who are on SGLT-2 inhibitors.

Conclusion

This was a case where SGLT-2 use resulted in diabetic ketoacidosis with skipped meal and alcohol intake being the precipitating factors. Also, the patient was being treated as secondary pancreatic diabetes while the diagnosis was further changed to type-1 due to positive results of Anti GAD antibodies. There should be a high clinical suspicion and detailed drug history should be taken whenever a patient presents in euglycemic ketoacidosis so that the offending drug can be withdrawn and further such episodes can be prevented. Clinicians should always keep a high suspicion for underlying type 1 and LADA in such cases so that long term need of insulin can be explained to the patients to prevent any similar further episode. Before initiating this class of drug, the possible adverse effects and the measures to mitigate these risks should be well explained to the patient and the family.

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