

Euglycemic diabetic ketoacidosis: another masquerader!**Bhargavi Kumar, Saravanan Thangavelu*, Rajgokul Prabhakar**

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ABSTRACT

Euglycemic ketoacidosis is defined by the triad of euglycemia, metabolic acidosis and ketonemia or ketonuria. In the current era of diabetic management, it is a serious concern with the usage of sodium glucose co-transporter 2 (SGLT2) inhibitors potentiated by a number of precipitating agents. Empagliflozin though a novel oral hypoglycemic agent in this category may also lead to this potential complication. Here we report a 59 year old male, type 2 diabetic who was on empagliflozin and presented with euglycemic ketoacidosis after a binge of alcohol.

Keywords: Empagliflozin, SGLT2 inhibitor, Type 2 diabetes, Euglycemic ketoacidosis

INTRODUCTION

Hyperglycemic states in diabetes like Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar non ketotic coma are widely encountered, well known and therefore easily diagnosed emergencies. However euglycemic ketoacidosis is an often missed relatively less known condition and under reported scenario. A high index of clinical suspicion is warranted to arrive at this diagnosis because the normoglycemia may mask our clinical judgement of DKA.

The management of diabetes mellitus is ever evolving with oral hypoglycemic agents being an area of constant research and updates. Approved by the Food and Drug administration of USA (FDA) in 2014, Sodium glucose co-transporter 2 (SGLT2) inhibitors is a new addition to the already existing broad list of oral hypoglycemic agents for type II diabetes mellitus. Apart from reducing

blood sugars, its spectrum also extends to reducing blood pressure, reduction of weight and cardio protection.¹ It is now included in American Diabetes Association treatment guidelines as one of the add-on agents in dual or triple drug combinations in diabetes as it can effectively reduce HbA1c by 0.5-0.7%. However euglycemic ketoacidosis is a rare but potential complication in this class of drugs for which FDA has released a safety alert in 2015.² Its diagnosis may be delayed owing to the normal sugar levels and needs a strong index of suspicion whenever there is ketonemia or ketonuria in the presence of normal blood sugar levels and high anion gap metabolic acidosis.

CASE REPORT

A 59 year old male presented to the emergency department with abdominal discomfort and orthopnea following a binge alcohol intake. Patient was a chronic smoker and alcoholic for 30 years and a known case of

type 2 diabetes mellitus and systemic hypertension for 5 years. He was on irregular treatment with tablet metformin 500 mg in once daily dosage and had started taking tablet empagliflozin 10 mg once daily for the past 2 years without prescribed medical advice. His concomitant medications included tablet nebivolol 5 mg once daily for systemic hypertension. On examination, the patient was moderately dyspnoeic, tachypnoeic, drowsy, arousable and normotensive. Respiratory system examination showed basal crepitations and abdomen examination showed mild epigastric tenderness.

Preliminary investigations revealed normal sugar levels (169 mg/dl), ketonuria (3+) and elevated HbA1c (10.8%). His complete blood counts, serum procalcitonin, liver, thyroid and renal functions were normal but for low bicarbonate (4.65 mEq/l) and a pH of 7.2. The calculated anion gap was high (27.7). Cardiac functions were normal as evidenced by echocardiogram and biomarkers.

An ultrasonography of the abdomen was done in view of epigastric tenderness and showed a bulky pancreas suggestive of acute pancreatitis. His amylase (956 U/l) and lipase (3873 U/l) were also elevated and lipid profile evaluation revealed hypertriglyceridemia (242 mg/dl). His laboratory parameters are summarised in Table 1.

Noting his ketonuria and high anion gap metabolic acidosis with normal blood sugars we arrived at a diagnosis of euglycemic ketoacidosis in the background of his medication history of empagliflozin therapy which was probably precipitated by alcohol binge and acute pancreatitis. Patient was put on ventilator support and started on intravenous fluids, insulin along with 5% dextrose and bicarbonate correction. The acidosis improved gradually and blood glucose levels were controlled with rapidly acting insulin. After the patient improved symptomatically, he was weaned off and tolerated soft diet.

Table 1: Laboratory parameters of the patient across his days of admission showing his normal sugar values at admission and metabolic acidosis which resolved following treatment.

	Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 10
Sugars (mg/dl)	169	141	132	178	193	299	268
Urine for ketones	+++	+++	++	+	Nil	Nil	Nil
pH	7.2	6.9	7.47	7.4	7.48	7.40	7.41
HCO₃ (mEq/l)	4.65	7.0	14	11.3	18	23.8	24.1
Amylase (U/l)	956	-	-	145	242	-	-
Lipase (U/l)	3873	-	-	639	1158	887	637

On discharge, the patient was counselled regarding diet, insulin therapy, advised alcohol abstinence and was counselled to stop any self-medication of new oral hypoglycemic agents. The patient is now on regular follow up, maintaining average blood sugars of 200 mg/dl. As the patient was apprehensive about continuing insulin, he is now put on oral agents-insulin secretagogues alongside diet and lifestyle modification.

DISCUSSION

There are a multitude of causes leading to metabolic acidosis in diabetics. These include normal anion gap acidosis like renal failure as well as high anion gap states like lactic acidosis and ketoacidosis. Ketoacidosis could be due to diabetic ketoacidosis, starvation ketoacidosis or alcoholic ketoacidosis. Diabetic ketoacidosis may be either hyperglycemic or euglycemic. Thus analyzing the risk factors that contribute to the development of ketoacidosis is very crucial.

Euglycemic ketoacidosis was first observed and reported in a case series by Munro et al who observed that a subset of DKA patients had sugar levels <300 mg/dl.³ Subsequently euglycemic ketoacidosis has been characterized by the triad of euglycemia (blood glucose <250 mg/dl), metabolic acidosis (pH <7.35, bicarbonate <18 mEq/l) and ketonemia or ketonuria.⁴ To explain it

succinctly, euglycemic ketoacidosis is DKA sans marked hyperglycemia. It is mainly described in type 1 diabetes but nevertheless not uncommon in type 2 diabetes. Possible contributing factors include starvation, alcoholism, pregnancy, pancreatitis and drugs. Among drugs, SGLT2 inhibitors are notorious to cause euglycemic ketoacidosis.

SGLT 2 inhibitors act primarily by inhibiting sodium glucose co-transporter 2 in proximal convoluted tubule which mediates 80-90% of glucose absorption in kidney. As a result of this facilitation of glucose excretion by kidney, blood glucose levels are lowered. When the blood glucose levels reduce, the insulin release from pancreas also reduces proportionately tilting the normal insulin: glucagon ratio, thereby favoring ketogenesis. Other proposed mechanisms include release of glucagon by direct SGLT2 inhibition in pancreas, release of kisseptin which inhibits insulin release and also decreased reabsorption of ketones leading to ketonemia.

Empagliflozin has shown meticulous benefits in reducing major cardiac events as evidenced in the 'EMPA-REG OUTCOME' trial.⁵ Since empagliflozin's mechanism of action is independent of beta cell functioning, they are useful in all type 2 diabetes patients as long as estimated glomerular filtration rate is above 45-60 ml/min. Other potential benefits include weight loss (2-3 kg) and

reduction in blood pressure (3-6 mmHg systolic, 1-2 mmHg diastolic) due to natriuresis besides cardioprotection. Though beneficial in numerous aspects, empagliflozin also has adverse effects like genital fungal infections (3-5%), urinary tract infections (1-2%), volume depletion and hypotension. However of serious concern is the development of euglycemic ketoacidosis though reported in less than 0.1% patients. Canagliflozin and dapagliflozin also carry the risk of euglycemic ketoacidosis with reported incidence being 0.8% and less than 0.1% respectively.⁶

On literature review, we noted that Gammons and Counselman have presented a case report of a chronic alcoholic, type 2 diabetic patient on empagliflozin developing euglycemic ketoacidosis with acute pancreatitis similar to our index patient.⁷ So also Candelario and Wykretowicz have presented a type 2 diabetic female who developed euglycemic ketoacidosis while on empagliflozin therapy precipitated by acute cholecystitis.⁸

In our index patient with euglycemic ketoacidosis, the clear culprits were empagliflozin overtly precipitated by his binge of alcohol and pancreatitis. A high index of suspicion alone prompted us to withdraw the offending drug and treat him with insulin and dextrose apart from intravenous fluids in correcting his metabolic acidosis.

CONCLUSION

DKA need not necessarily present with hyperglycemia. High anion gap ketoacidosis should be a red flag to look for euglycemic ketoacidosis which requires both insulin and dextrose in correcting the underlying metabolic derangement. Careful drug history and possible precipitators should be identified and promptly corrected. SGLT2 inhibitors though a novel agent in the treatment of diabetes also comes with its quantum of adverse effects like euglycemic ketoacidosis which is a potential life threatening complication. The key to a successful usage of newer exciting hypoglycemic agents lies in choosing our patients wisely and carefully avoiding those who have other contributing factors for acidosis.

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