



Unmasking Type – 1 Diabetes Mellitus Following an Episode of Euglycemic Diabetic Ketoacidosis with SGLT-2 Inhibitor Use: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author NKS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SJ and AM managed the analyses of the study. Author NKS managed the literature searches. All authors read and approved the final manuscript.

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Case Study

ABSTRACT

We describe here the case of a patient with Euglycemic DKA in the setting of SGLT-2 inhibitor use, further evaluation of which led to unmasking of Type-1 Diabetes Mellitus. There have been previous case reports where SGLT-2 inhibitor use has led to unmasking of diabetes mellitus type-1 in patients previously diagnosed with diabetes mellitus type-2.

We had a 57-year-old female with history of type 2 DM since last 10-12 years on Empagliflozin, Liraglutide, Metformin, Glimepiride and Pioglitazone presented with 5-hour history of shortness of breath which was acute in onset and was not associated with any other complaints. On initial evaluation, random blood sugar was 182 mg/dl. ABG showed high anion gap severe metabolic acidosis and Serum ketones levels were high. She was treated with IV fluids in the form of normal saline and was later switched to dextrose infusion when her random blood sugar levels fell below 250 mg/dl, Insulin infusion and Potassium correction along with other supportive measures. her symptoms resolved with treatment over 3-4 days.

We did a literature review on the topic and present here the pathophysiology, Diagnosis, Management and Prevention of SGLT-2 inhibitor induced Euglycemic DKA.

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1. INTRODUCTION

Diabetic Ketoacidosis is considered a medical emergency and is diagnosed by presence of triad of Hyperglycemia (RBS>250 mg/dl), Metabolic acidosis (pH<7.3 and Serum bicarbonate < 18mEq/L) and ketosis. Rarely the patient can present with features of DKA in the presence of blood sugar levels of less than 200 mg/dl and this is defined as Euglycemic DKA [1-4].

We present here a case SGLT-2 inhibitor induced Euglycemic DKA.

2. CASE PRESENTATION

A 57-year-old female, a known case of Type-2 Diabetes Mellitus for the last 10-12 years presented to us with complaints of sudden onset shortness of breath, there was no other associated symptom. She was on Empagliflozin, Liraglutide, Metformin, Glimepiride and Pioglitazone along with Insulin for her glycemic control. She had been on Empagliflozin for the last 6 months at the time of presentation.

On initial clinical evaluation she was dyspneic, tachypneic & tachycardic. General and systemic examination was unremarkable. Random blood sugar level was 182 mg/dl and ABG showed pH of 6.84, bicarbonate (1.7 mEq/L), pCO2 (8 mmHg), lactate (1.7 mmol/L) and anion gap of 28. Her ECG and chest X-ray were unremarkable. Complete blood count showed TLC – 10,500/ μ l, Hb – 10.2 gm/dl and Platelet count – 2,25,000/ μ l.

Her renal and liver functions were within normal limits. Serum amylase was 28 U/L and serum lipase was 32 U/L. 2D-ECHO and detailed cardiac evaluation did not show any abnormality. Her serum β -hydroxybutyrate levels were 6.8 mmol/L.

In view of past history of Type-2 DM and presence of metabolic acidosis along with ketosis diagnosis of Euglycemic diabetic ketoacidosis was made. She was started on IV fluids, insulin infusion and potassium correction in view of euglycemic DKA. Initially her bicarbonate levels did not improve as per the expectation but eventually she responded to the treatment and showed clinical as well as investigatory improvement. Nephrologist opinion was taken and advice was followed. High anion gap metabolic acidosis resolved with continuous treatment over 2 days. Her C-reactive protein levels came out to be 0.8 mg/dl. In view of continuous insulin requirement for maintenance of euglycemia and low CRP levels a diagnosis of type-1 diabetes mellitus was made. The patient also showed improvement CLINICALLY and she was shifted out of the ICU on day 3. Subsequently she was discharged after being monitored in the ward for further 2 days.

Many cases of this rare complication of SGLT-2 inhibitor use have been reported. Most commonly this complication was seen with off-label use in type-1 diabetes mellitus or in patients wrongly diagnosed as having type-2 DM who in fact had latent autoimmune diabetes of adults.

Table 1. Sequential ABGs of the patient

Parameters	Day 1					Day 2				Day 3
	07:00 PM	09:30 PM	11:00 PM	03:00 AM	08:46 AM	11:30 AM	02:45 PM	06:00 PM	09:00 PM	02:00 PM
pH	6.84	7.26	7.30	7.17	7.10	7.06	7.29	7.42	7.38	7.42
pO2 (mmHg)	169	142	123	144	230	127	103	86	109	84
pCO2 (mmHg)	08	10	12	9	18	8	10	14	12	36
HCO3- (mEq/L)	1.7	4.5	6.8	3.3	5.6	4.8	14.6	14.6	12.6	20.8
BE	-28.3	-22.6	-18.6	-25.2	-24.1	-22.6	-15.4	-15.4	-15.8	-2.4
Lactate (mmol/L)	1.7	1.6	1.2	0.9	2.0	1.0	0.9	0.9	0.8	1.2
RBS (mg%)	195	188	190	148	142	144	138	133	142	128

Table 2. Sequential laboratory investigations of the patient

Parameter	Day 1	Day 2	Day 3
Hb (gm/dl)	10.2	10.5	10.6
TLC (*10 ³ /μl)	10.5	8.7	7.9
Platelet (*10 ³ /μl)	2.25	2.12	2.42
Total bilirubin (μmol/L)	1.8		
SGOT (IU/L)	54		
SGPT (IU/L)	46		
S. Amylase (U/L)	28		
S. Lipase (U/L)	32		
Trop I	0.04		
β-hydroxy butyrate (mmol/L)	6.8	2.9	0.3

3. DISCUSSION

SGLT-2 inhibitors are newest addition to the class of Oral hypoglycemic agents and were approved by FDA for use in type-2 diabetes mellitus in 2013. They have been shown to offer numerous benefits including increased weight reduction, decreasing HbA1c levels along with decreasing the incidence of diabetic nephropathy and cardiovascular complications in diabetic patients [5,6].

SGLT-2 inhibitors exert their effect by inhibiting glucose reabsorption in proximal convoluted tubule through inhibition of sodium glucose co-transporter-2 (SGLT-2). This leads to increased secretion of glucose in urine and hence lower blood glucose levels. The mechanism of SGLT-2 inhibitor induced euglycemic DKA is believed to involve lowering of blood insulin levels in response to lower blood glucose levels and increased blood glucagon levels leading to decreased insulin glucagon ratio. [7] SGLT-2 inhibitors are also believed to increase glucagon levels by stimulating α-cells. Lowered insulin levels lead to increased production of free fatty acids and these free fatty acids are converted to ketones by β-oxidation in the liver. Hence, SGLT-2 inhibitor makes the patient susceptible to acidemia following ketosis and continued glycosuria along with ketosis lead to picture of euglycemic DKA. After their introduction 101 cases of SGLT-2 inhibitor induced DKA were reported till may 2015 which led FDA to release a warning about this concern with SGLT-2 inhibitor use [8,9].

Precipitating factors for euglycemic DKA are similar to Hyperglycemic DKA and include starvation, infection, infarction, Surgery, low

carbohydrate diet, dehydration ,recent reduction in insulin dose andextreme physical activity among others. SGLT2 inhibitors should also be avoided in patients with previous history of DKA, if no precipitating factor for their DKA could be recognized. They should also be used with caution in patients with low β-call reserve (type-2 diabetes patients with low c-peptide levels, latent autoimmune diabetes in adults or in patients with past history of pancreatitis), patient with conditions that lead to restricted oral intake or dehydration, patients in whom insulin dosage has been recently decreased and in conditions of increased insulin requirements like infection, pregnancy etc [10,11].

Other more common side-effects with SGLT-2 inhibitor use include genital fungal infection in men and women, urinary tract infections, constipation, nasal congestion and urinary discomfort. Patient should be well counselled regarding these possible side-effects before initiating SGLT-2 inhibitors [12,13,14].

As per the statement issued by American association of clinical endocrinologists in 2016, any diabetic patient who presents with nausea, abdominal pain, vomiting and/or dyspnea should be evaluated for DKA because SGLT2 inhibitors use can lead to DKA even in the setting of euglycemia or even with only mild elevation in blood sugar levels [15].

For routine major surgical cases, it is recommended to discontinue SGLT2 inhibitors three days before the surgery because SGLT2 inhibitors typically have a half-life of 11 to 17 hours. It is also recommended to avoid inappropriate insulin dose reduction or avoiding insulin dose altogether [15].

4. CONCLUSION

Diabetic ketoacidosis is seen in an estimated 1 out of every 2000 patients suffering from type 1 diabetes mellitus and the number is much lower in patients with type 2 diabetes mellitus. Such a case indicates the need for emergency and critical care physician to remain vigilant in identifying drug-induced causes of DKA. Many such cases can have delayed diagnosis due to low blood glucose levels on presentation. SGLT-2 inhibitors should be used with caution in patients who have low β -cell reserve and in patients with conditions that lead to restricted food intake or severe dehydration. SGLT-2 inhibitors should not be used in patients who might have increased insulin requirement, due surgery or any other acute medical illness.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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