Case Report تقرير حالة طبية

EUGLYCEMIC DIABETIC KETOACIDOSIS IN THE SETTING OF SGLT2 INHIBITOR USE

حالة حماض سكري خلوني سوي السكر خلال استخدام مثبطات SGLT2

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ملخص الحالة

يمثل الحماض الخلوني السكري حالة إسعافية واختلاطاً حاداً للداء السكري، يتصف الحماض السكري الخلوني بوجود ثلاثي مخبري: مستوى سكر دم مرتفع لأكثر من 250 ملغ/دل مع حماض استقلابي (درجة PH الدم الشرياني أقل من 7.3 ومستوى بيكربونات أقل من 18 مكافىء/ل)، مع تواجد الأجسام الخلونية في الدم و/أو البول وارتفاع في فجوة الصواعد. تلاحظ نادراً حالات من الحماض السكري الخلوني بمستوى سكر دون 200 ملغ/دل، والتي تعرف بالحماض الخلوني السكري سوي السكر، وهي حالة يمكن حدوثها مع استخدام خافضات سكر الدم الحديثة من نمط مثبطات خميرة ناقل الصوديوم والغلوكوز SGLT2. تعتبر هذه الحالات نادرة ربما بسبب قلة الانتباه لها. سيتم هنا إيراد حالة سريرية لسيدة من سوريا لديها حماض خلوني سكري سوي السكر مترافق مع استخدام مثبطات SGLT2.

ABSTRACT

Diabetic ketoacidosis (DKA) is a medical emergency as acute complication of diabetes mellitus, characterized by the triad of hyperglycemia (blood sugar >250 mg/dl), metabolic acidosis (arterial pH <7.3 and serum bicarbonate <18 mEq/L), and with an increased anion gap and the presence of ketone bodies in the blood and/or urine.[1] Rarely, patients can present with blood glucose (BG) levels of less than 200 mg/dl, which is defined as euglycemic DKA (euDKA). There is an established, though rare, association of DKA with normal glucose values or euDKA with the use of sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors).[2,3] Euglycemic DKA (euDKA), is classically considered rare, but this is perhaps a result of under-recognition and underreporting.[4] We present here a clinical case of euDKA associated with the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in a Syrian patient.

INTRODUCTION

Sodium glucose co-transporter type 2 inhibitors (SGLT2 I) are the newest class of oral anti-hyperglycemic agents that have been approved by the Food and Drug Administration (FDA) for the treatment of diabetes mellitus. SGLT2 inhibitors, such as canagliflozin, dapagliflozin, and empagliflozin, block the SGLT2 protein, which is involved in glucose re-absorption from the proximal renal tubule. This causes an increase in renal glucose excretion and a decrease in blood glucose levels,[5] see Figure 1.

There are strong evidences suggesting that the SGLT2 inhibitors have beneficial effects on decreasing mortality from cardiovascular events, including a lower incidence of myocardial infarction and strokes.[6,7] SGLT2 inhibitors also cause weight loss without any risk of hypoglycemia.[8] In light of these desirable outcomes, SGLT2 inhibitors are an attractive class of medication

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for the management of hyperglycemia in T2DM, concerns have been raised that SGLT2 inhibitors might promote euglycemic ketoacidosis,[9-11] a potentially fatal condition.

Euglycemic ketoacidosis is rare in type 2 diabetic patients, with incidence of ~0.5%.[9-11] Several mechanisms have been proposed for euglycemic ketoacidosis associated with SGLT2 inhibitors, it involves low of insulin production and increase in glucagon secretion, which promotes a shift of glucose to fat metabolism and stimulates ketogenesis.[12-14]

SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, which, in turn, reduces insulin secretion from pancreatic β-cells. The decline in circulating insulin levels results in a lowering of the anti-lipolytic activity of insulin and consequent stimulation of the production of free fatty acids, which are converted to ketone bodies by β-oxidation in the liver. Evidence suggests that the use of SGLT2 inhibitors stimulates the secretion of glucagon, either by a secondary effect mediated by the decrease in insulin secretion or by a direct effect on pancreatic α-cells.[13,14]

Another mechanism of euDKA is by the renal effects of SGLT2 inhibitors; during starvation, renal re-absorption of ketones increases with increase in serum ketone levels, with no apparent excretion threshold, but renal utilization of ketone bodies is reduced.[13,14] By lowering the renal glucose excretion threshold, SGLT-2 inhibition may mimic starvation conditions and cause an increase in ketone production and renal re-absorption.[13]

Hence, SGLT2 inhibitors render the body susceptible to acidemia by ketogenesis and continue to produce glycosuria, causing near normal or less abnormally elevated glucose levels than usually seen in DKA.[15]

CASE PRESENTATION

N. M a 55-year-old Syrian female with 10 years type 2 DM, presented to ER with weakness, dyspnea, nausea, vomiting, and mild abdominal pain for the past 2 days, with poor oral intake for the past 1 week due to severe toothache followed extraction, the patient had no fever, chills, alcohol intake. She was previously treated with a combination of metformin 1 g twice daily and gliclazide 80 mg twice daily, with empagliflozin 25 mg once daily being added to the regimen 2 weeks ago.

Physical examination on admission: She was ill looking, with Kussmaul breathing, moderately dehydrated with sunken eyes, dry oral mucosa, and poor skin turgor. Vital signs at presentation were: temperature 36.8 C, pulse rate 127 beats/min, respiratory rate 25 breaths/min, blood pressure 150/95 mm. Hg. Auscultation of the lungs revealed no significant findings. The rest of physical examination was unremarkable.

Laboratory results: See Table 1, blood sugar was

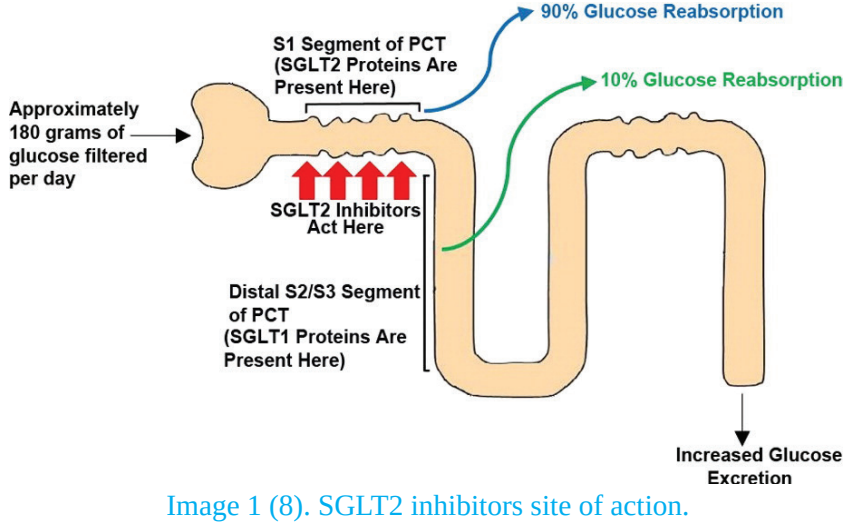

Image 1 (8). SGLT2 inhibitors site of action.

Test	BS	Creatinine	BUN	Sodium	Potassium	Chloride	Leucocyte
Result	160 mg/dl	1.2 mg/dl	50 mg/dl	142 mmol/L	4.0 mmol/L	112 mmol/L	18*109/L
Normal level	100-126	0.5 to 1.1	7-20	135-145	3.6-5.2	98-106	4-11

Test	pH	CO_2	HCO_3	Blood ketones	Anion gap*	Hematocrit	Serum lactate
Result	6.99	20.9 mm Hg	8.0 mEq/L	2 positives	22 mEq/L	55%	8 mg/dl
Normal level	7.35-7.42	35-45 mm Hg	22-29	Negative	<12	35-45	6-16 mg/dL

*Serum anion gap (AG)= Na+ – (Cl- + HCO_3-).

Table 1. Laboratory results upon admission.

found to be mildly elevated (160.0 mg/dl), blood ketones were 2 positives, arterial blood gases showed a picture of severe metabolic acidosis with an elevated anion gap (pH=6.99, CO_2 20.9 mm.Hg, HCO_3^- 8.0 mEq/l, anion gap 26 mEq/l), and serum lactate levels were normal (8 mg/dl). Sodium 142 mmol/l, potassium 4.0 mmol/l, chloride of 112 mmol/l. Renal function test revealed serum blood urea nitrogen of 55 mg/dl and serum creatinine of 1.2 mg/dl. Leucocyte $18x10^9$/l with predominant neutrophils, Haematocrit 55%, amylase 70 U/l (Normal is 40-140 U/l). Urinalysis: Glucose 4+, ketones 3+. CXR (chest X ray) and ECG (electrocardiogram): WNL.

She was promptly admitted to the intensive care unit (ICU) and treated for euDKA, the patient was started on intravenous fluids with normal saline to reverse the dehydration, a continuous IV infusion of regular insulin with a second line infusion of 10% dextrose to prevent hypoglycemia, with monitoring of electrolyte abnormalities.

Serial blood gas analyses showed gradual resolution of her ketoacidosis with normalized anion gap and clearance of serum ketones. The patient was discharged from the ICU on day 2 and then to the general ward on day 4 uneventfully, she was discharged with permanent cessation of empagliflozin administration.

DISCUSSION

DKA is classically defined as presence of the triad of hyperglycemia (>250 mg/dl), ketosis, and anion-gap acidosis. euDKA is then DKA without marked hyperglycemia.[4,17] Our patient had ketoacidosis (blood pH 6.99, blood ketones positive), yet blood sugar levels of 160.0 mg/dl are far below the usual means of that in the "traditional" DKA, the diagnosis would thus have been missed if we had ruled out DKA based on the absence of marked hyperglycemia.

Euglycemic diabetic ketoacidosis is a diagnostic challenge for treating physicians, since there is no hyperglycemia. There are many causes of metabolic acidosis in patients in the intensive care unit.[18] The causes of euglycemic diabetic ketoacidosis listed in Table 2.

Fasting
Insulin use prior to hospital admission
Pregnancy
Use of SGLT-2i
Cocaine Abuse
Pancreatitis
Cirrhosis
Use of insulin pump
Sepsis

Table 2. Causes of euglycemic diabetic ketoacidosis.[19-21]

Our patient had ketoacidosis and she is taking SGLT2 inhibitor empagliflozin, with no other cause. Empagliflozin is a SGLT2 inhibitor approved in 2014 by the U.S. Food and Drug Administration to treat DM, either as a single treatment or in combination with other antidiabetics.[22] Experiences with empagliflozin-associated euDKA in the ER are still very limited.[23]

The euDKA in our patient, a type 2 diabetic lady

on empagliflozin caused a sharp spike in the urinary excretion of glucose. Plasma glucose concentrations subsequently fell, further exacerbated by her poor oral intake for the past 1 week.[23,4] Insulin deficiency in our patient's caused a concurrent increase in lipolysis from her peripheral fat tissues, releasing free fatty acids.

These fatty acids were subsequently converted into acetyl-CoA via beta-oxidation by hepatic mitochondria, and acetyl-CoA molecules entered the ketogenic metabolic cycle to produce acetoacetic acid. Acetoacetic acid was then reduced to beta-hydroxybutyric acid; accumulation of these two acids resulted in an elevated anion gap metabolic acidosis. Acetoacetic acid was also decarboxylated to acetone, a ketone body which served as an alternative energy source for our patient in her state of reduced intracellular glucose availability secondary to insulin deficiency.[12] All these metabolic processes thus ultimately manifested as euDKA, Figure 1.[24]

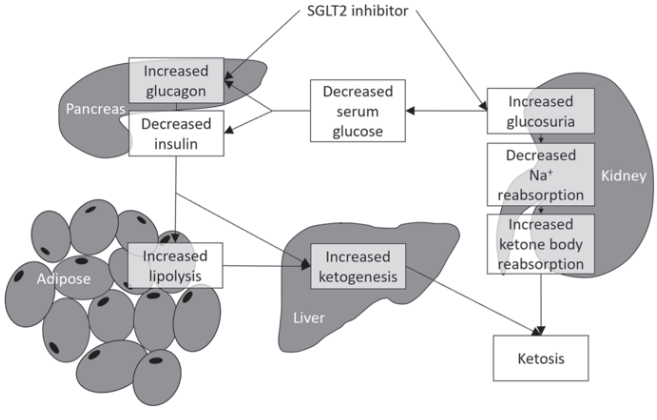

Figure 1. Possible mechanism of euDKA induced by SGLT2 inhibitors.[24] (FFA, free fatty acid; ACC, acetyl-CoA carboxylase; CPT-I, carnitine palmitoyl transferase-I).

Euglycemic diabetic ketoacidosis is a diagnostic challenge, if left untreated, DKA can lead to serious complications including hypokalemia, acute kidney injury, cerebral edema, acute respiratory distress syndrome, shock, and even death.[26]

Our patient was treated successfully for euDKA through correction of fluid loss (intravenous rehydration), correction of hyperglycemia and acidosis with insulin infusion, correction of electrolyte disturbances, particularly potassium, and 10% dextrose infusion to prevent hypoglycemia and allow for continuation of insulin infusion,[16] with permanent cessation of empagliflozin or any kind of SGLT2 inhibitor pills.

CONCLUSIONS

This is a case of life-threatening euDKA as a complication of empagliflozin, a very rare missed diagnosis. FDA issued in May 2015 a drug safety warning on the possibility of diabetic ketoacidosis (DKA) in all people taking SGLT-2 inhibitor pills.[25,12] We should consider the diagnosis of eDKA in a patient whose drug regimen includes any SGLT2 inhibitor, especially if the patient presents with nausea, vomiting, abdominal pain, dyspnea, lethargy, and is clinically dehydrated. These patients should then be investigated with ketone studies and blood gas analyses regardless of blood glucose levels for prompt diagnosis and treatment. Patients started on SGLT2 inhibitors can also be counseled to perform urine dipstick tests to check for ketones if they feel unwell, and seek medical treatment immediately if positive.

REFERENCES

1. *Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335-43.*
2. *Monami M, Nreu B, Zannoni S, et al. Effects of SGLT-2 inhibitors on diabetic ketoacidosis: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2017;130:53-60.*
3. *Kim YG, Jeon JY, Han SJ, et al. Sodium-glucose co-transporter 2 inhibitors and the risk for diabetic ketoacidosis in patients with type 2 diabetes mellitus: A nationwide population based cohort study. Diabetes Obes Metab 2018;20:1852-8.*
4. *Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose co-transporter 2 inhibition. Diabetes Care 2015 Sep;38(9):1687-93.*
5. *Singh M, Kumar A. Risks associated with SGLT2 inhibitors. Curr Drug Saf 2018;13(2):84-91.*
6. *Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2*

diabetes. N Engl J Med 2015;373:2117-28.

7. *Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2(5).*
8. *Madaan T, Akhtar M, Najmi AK. Sodium glucose co-transporter 2 (SGLT2) inhibitors: Current status and future perspective. Eur J Pharm Sci 2016;93:244-52.*
9. *Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100(8):2849-52.*
10. *Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. N Engl J Med 2017 Jun;376:2300-2.*
11. *Ele F, Simona B, Silvia F, et al. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care 2017 Jun;40(6):771-6.*
12. *Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Invest 2016;7:135-8, 11.*
13. *Qiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2i: basic mechanisms and therapeutic perspectives. Diabetes Metab Res Rev 2017 Jul;33(5).*
14. *Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with Dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015 May;21(5):512-7.*
15. *Handelsman Y, Henry RR, Bloomgarden ZT, et al. AACE and ACE position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016;22:753-62.*
16. *Savage MW, Dhatariya K, Kilvert A, et al. The management of diabetic ketoacidosis in adults. Diabet Med 2011 May;28(5):508-15.*
17. *Bonora BM, Avogaro A, Fadini GP. Euglycemic ketoacidosis. Curr Diab Rep 2020;20:25.*
18. *Gauthier PM, Szerlip HM. Metabolic acidosis in the intensive care unit. Crit Care Clin 2002 Apr;18(2):289-308.*
19. *Tarif N, Al-Badr W. Euglycemic diabetic ketoacidosis in pregnancy. SJKDT 2007;18(4):590-3.*
20. *Muppidi V, Meegada S, Challa T, et al. Euglycemic diabetic ketoacidosis in a young pregnant woman precipitated by urinary tract infection. Cureus 2020 March;12(3):e7331.*
21. *Abdin AA, Hamza M, Khan MS, et al. Euglycemic diabetic ketoacidosis in a patient with cocaine intoxication. Case Reports Crit Care 2016;2016:4275651.*
22. *Gangadharan KM, Mather A. Empagliflozin for the treatment of type 2 diabetes. Expert Rev Clin Pharmacol 2014 May;7(3):271-9.*
23. *Meyer EJ, Gabb G, Jesudason D. SGLT2 Inhibitor-associated euglycemic diabetic ketoacidosis:A south australian clinical case series and australian spontaneous adverse event notifications. Diabetes Care 2018;41:e47-9.*
24. *Diaz-Ramos A, Eilbert W, Marquez D. Euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitor use: A case report and review of the literature. Int J Emerg Med 2019;12(1):27.*
25. *Dfarjo P, Kidd KM, Reece JA. A Case of euglycemic diabetic ketoacidosis following long-term Empagliflozin therapy. Diabetes Care 2016 Oct;39(10):e165-6.*
26. *Westerberg DP. Diabetic ketoacidosis: Evaluation and treatment. Am Fam Physician 2013 Mar;87(5):337-46.*