SGLT2-Inhibitors and Euglycemia Diabetic Ketoacidosis: A Missed Diagnosis

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Abstract

Euglycemic diabetic ketoacidosis (EuDKA), is an uncommon but potentially fatal medical emergency characterized by metabolic acidosis, ketosis, and either normal or near normal blood glucose level. The Diagnosis is delayed due to a lack of hyperglycemia leading to adverse consequences. It's not a routine diagnosis but patients with both types of diabetes mellitus may suffer from it. Since august 2014, after the inclusion of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for the management of diabetes mellitus, the incidence of euglycemia DKA has raised. The other conditions that may contribute to this metabolic disorder include fasting, chronic liver disease, pregnancy, gastroparesis, bariatric surgery, glycogen storage disease, cocaine intoxication, and insulin pump failure. Euglycemic DKA, a diagnosis of exclusion, should be considered in any unexplained metabolic acidosis among diabetic patients, who report to the hospital with nonspecific symptoms not suggesting DKA and have been taking sodium-glucose cotransporter-2 inhibitors. Here we are describing a case of ketoacidosis with normoglycemia caused by empagliflozin in a female suffering from type 2 diabetes mellitus to raise awareness of physicians to minimize the delays in the identification of this life-threatening metabolic disorder.

KeyWords: *Metabolic Acidosis, Hyperglycemia, Diabetes Mellitus, Sodium-Glucose Cotransporter-2 Inhibitors, Empagliflozin.*

INTRODUCTION

Empagliflozin, a sodium-glucose co-transporter inhibitor (SGLT2i), is a newly approved drug by Food and Drug Administration (FDA) for patients suffering from type 2 diabetes mellitus [1]. SGLT2i functions by inhibiting the uptake of glucose in proximal renal tubules, promoting glycosuria [2]. Increased urinary tract infections, genitals fungal infections, and dehydration are among the common side effects [3].

Euglycemic DKA is characterized by high anion gap acidosis (pH < 7.3 or serum bicarbonate < 18 mmol/L), ketosis but either normal plasma glucose or just mild hyperglycemia [4]. Patients usually present with anorexia, nausea, malaise, and tachypnea due to ketonemia and associated ketoacidosis. With a high index of suspicion and prompt investigation for this metabolic acidosis, serum, and urinary ketones can lead to the identification of these patients [5]. Euglycemic DKA might be more common among diabetic patients on SGLT2 inhibitors with lesser body mass index (BMI) and depleted glycogen stores [6]. Episodes may be precipitated by infection, trauma, surgery, missed meals, continuous vomiting, gastroparesis, dehydration, inadequate insulin dosages, and any major illness [7]. The workup for diagnosis consists of arterial blood gas for metabolic acidosis, serum, and urinary ketones, with elevated anion gap and other causes of metabolic acidosis should be excluded. Treatment of Euglycemic DKA is identical to DKA which includes restoration of hydration with intravenous fluid, electrolytes correction, and insulin replacement [8].

We are reporting a rare case of Euglycemic DKA in a female patient, diagnosed case type 2 diabetes mellitus on treatment with oral hypoglycemic presented in the emergency department with fever, vomiting generalized body weakness, and lethargy along with severe metabolic acidosis.

CASE REPORT

A 54 years old female, diagnosed case of type 2 diabetes mellitus for the last 17 years on tab metformin 500mg thrice daily and tab empagliflozin 25mg once daily, the dosage was increased recently from 10mg to 25mg once daily, presented with complaints of fever, vomiting, and generalized body aches and weakness along with swelling on left forearm followed by trauma. On admission, Vital signs were recorded as pulse rate of 99 beats per minute; respiratory rate of 23 breaths per minute, blood pressure of 134/77 mmHg, and temperature of 38.1°C; pulse oximetry showed oxygen saturation of 99% at room air. The patient appeared agitated, and tachypenea with impaired mentation. On examination, dry mucosa was found; the abdomen was soft, mildly tender, and non-distended. The left arm of the patient appeared to be edematous, and tender with a raised temperature of overlying skin suggestive of cellulitis. The rest of the general physical and systemic examination was insignificant.

Laboratory investigations showed serum glucose of 10 mmol/l (180mg/dl), high anion gap metabolic acidosis

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with serum lactate of 2.5 mmol/L (0.05–2.00 mmol/L). The electrocardiogram didn't show any acute change and cardiac enzymes were negative for any acute cardiac insult. The diagnosis of metabolic acidosis secondary to sepsis was made and the patient was admitted to a higher dependency unit. Serum electrolytes, creatinine, BUN (blood urea nitrogen), lipase, amylase, and liver function tests were within normal ranges whereas serum hydroxybutyrate was raised and urine analysis demonstrated ketones in the urine. The patient was treated with broad-spectrum antibiotics along with continuous intravenous hydration with normal saline and other supportive care.

During first 48 hours, the patient remained acidotic and his symptoms did not improve. The patient also went into acute kidney injury with an acute surge in serum creatinine (S.Cr). The patient was then labeled as EuDKA secondary to empagliflozin since no other etiological factor contributing towards this high anion gap ketoacidosis (DKA) could be identified.

The patient was then shifted to ICU with continuous intravenous hydration and insulin infusion was commenced as per the protocol of DKA along with the close clinical examination and regular monitoring of his blood investigations. On day 3 Acidosis started to resolve and the anion gap began to narrow intravenous fluids insulin infusion was continued till day 5 then subcutaneous insulin was started after the resolution of acidosis. Serum creatinine also improved and returned to near baseline. The basic metabolic panel trend throughout the hospital course is summarized in Table **1**.

After clinical improvement patient has discharged on tab sitagliptin 50 mg once daily, insulin regular 8 units subcutaneously thrice daily, and insulin glargine 20 units at bedtime.

Table 1: Basic metabolic panel.

Day of admission	01	02	03	04	05	06	07
Arterial pH	6.9	6.9	7.0	7.30	7.36	7.39	7.36
HCO3 on ABGs(mEq/l)	5.4	6.2	12	18	21	21	22
Urinary ketones	4+	4+	4+	2+	2+	1+	1+
Anion gap	27	26	22	18	14	12	11
WBC(x109)	74	42	35	25	22	22	14
S.Cr(mg/dl)	1.1	2.9	2.2	1.9	1.5	1.4	1.2

DISCUSSION

DKA and EuDKA are considered rare but serious adverse effects of the SGLT2 inhibitors (SGLT2i).

Diabetic ketoacidosis (DKA) is a well-recognized life-threatening pressing complication caused by diabetes mellitus (DM), primarily among patients suffering from type 1 DM; but it may also be triggered in type 2 DM by any acute insult to the body like infection, trauma or acute coronary syndrome. Hyperglycemia (typically plasma glucose levels >13.9 mmol/L (>250 mg/dL) is a diagnostic hallmark of DKA constituting the diagnostic triad with metabolic acidosis and ketosis evident by ketonemia/ketonuria [9, 10]. EuDKA is defined as severe metabolic acidosis (pH < 7.3), bicarbonate < 18mEq/L, and anion gap > 12 with blood glucose levels < 250 mg/dL with ketonemia [11]. To be precise, EuDKA is defined as DKA either with normoglycemia or without significant hyperglycemia.

Kidney glomeruli freely filter glucose and 90% of its reabsorption occur at proximal tubules by sodium-glucose co-transporters 2. The inhibition of SGLT2 causes glycosuria and lowers blood glucose values [12-14]. The FDA-approved SGLT2 inhibitors include canagliflozin, empagliflozin, dapagliflozin, and ertuliflozin. The drugs act by reducing renal threshold by approximately 55% and lower HbA1c by 0.5-1%.

Ketoacidosis is caused by two main mechanisms due to the deficiency of insulin. Firstly, the stimulation of free fatty acid release that moves through the bloodstream to the liver causes ketogenesis. Secondly, SGLT2i promotes glucagon release from alpha cells of the pancreas, lowering the insulin-to-glucagon ratio. Raised levels of glucagon interfere with the metabolism of fatty acid by limiting the synthesis of malonyl-CoA, eventually enhancing beta-oxidation and ketoacid production [15, 16].

Our patient reported fever and left arm cellulitis along with severe acidotic pH on arterial blood gas analysis (ABGs). This presentation of a patient with euglycemia resulted in a delay in the diagnosis and treatment of our patient. Once insulin infusion was started, the anion gap has begun to narrow down, and bicarbonate levels increased to normal, supporting further the diagnosis of EuDKA.

EuDKA is managed exactly in the same way as DKA. To minimize the potential risk of EuDKA with SGLT2 inhibitors, Recommendations from the American College of Endocrinology and American Association of Clinical Endocrinologists include cutting down alcohol consumption, avoiding starvation or diminished intake of carbohydrates, and withholding SGLT2i at least 24 hours before elective surgery [17]. Our diabetic population in general lacks knowledge regarding their disease [18]. Awareness of triggering factors may help to prescribe SGLT2i and hold them under any condition that may potentiate DKA [19]. After an episode of ketoacidosis, the patient should not be prescribed an SGLT2 inhibitor again. Although not recommended in the literature it is worth checking ketonemia and ketonemia among patients being treated with SGLT1 inhibitors regardless of serum glucose levels.

CONCLUSION

High anion gap metabolic acidosis, either with or without hyperglycemia is a serious side effect of SGLT2 inhibitors. With the introduction of SGLT2 inhibitors, euglycemic DKA has become more prevalent. It is recommended to

identify the etiologies of this potentially lethal outcome. Thus, physicians should consider EuDKA in their differential diagnosis among patients prescribed SGLT2i who report to a healthcare facility with nonspecific signs and symptoms. Prompt diagnosis and timely treatment can improve morbidity as well as mortality and reduce hospital stays. Patients should be routinely informed as well regarding the undesirable effects of empagliflozin (including EuDKA) and the precipitating triggers to diminish the adverse events and complications.

CONSENT FOR PUBLICATION

Written informed consent was taken from the patient.

CONFLICT OF INTEREST

There is no conflict of interest among the authors.

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Declared none.

AUTHORS' CONTRIBUTION

Muhammad Nadeem Ahmed Khan: Data curation and Visualization, writing of the final manuscript.

Sana Jabeen: Provision of Data, writing of initial draft, literature search.

REFERENCES

1. Ray GM, Rodriguez C, Schulman SM, Sarangarm P, Bardack M, Bouchonville MF. Empagliflozin-induced diabetic ketoacidosis unmasking a type 1 diabetes diagnosis. Clin Pract Cases Emerg Med 2019; 3(2): 140-3. DOI: https://doi.org/10.5811/cpcem.2019.2.41795
2. Adachi J, Inaba Y, Maki C. Euglycemic diabetic ketoacidosis with persistent diuresis treated with canagliflozin. Intern Med 2017; 56(2): 187-90. DOI: https://doi.org/10.2169%2Finternalmedicine.56.7501
3. Candelario N, Wykretowicz J: The DKA that wasn't: a case of euglycemic diabetic ketoacidosis due to empagliflozin. Oxf Med Case Reports 2016; 2016(7): 144-6. DOI: https://doi.org/10.1093/omcr/omw061
4. Modi A, Agrawal A, Morgan F. Euglycemic diabetic ketoacidosis: a review. Curr Diabetes Rev 2017; 13(3): 315-21. DOI: https://doi.org/10.2174/1573399812666160421121307
5. Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. Eur J Intern Med 2019; 63: 9-14. DOI: https://doi.org/10.1016/j.ejim.2019.03.014
6. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care 2015; 38(9): 1687-93. DOI: https://doi.org/10.2337/dc15-0843
7. Legaspi R, Narciso P. Euglycemic Diabetic Ketoacidosis Due to Gastroparesis, A Local Experience. J Ark Med Soc 2015; 112(5): 62-3.
8. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. World J Diabetes 2021; 12(5): 514-23. DOI: https://doi.org/10.4239%2Fwjd.v12.i5.514
9. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32(7): 1335-43. DOI: https://doi.org/10.2337%2Fdc09-9032
10. Islam T, Sherani K, Surani S, Vakil A. Guidelines and controversies in the management of diabetic ketoacidosis–A mini-review. World J Diabetes 2018; 9(12): 226-9. DOI: https://doi.org/10.4239/wjd.v9.i12.226
11. Plewa MC, Bryant M, King-Thiele R. Euglycemic Diabetic Ketoacidosis (2022). Accessed: March 11, 2022: https://www.ncbi.nlm.nih.gov/books/NBK554570/.
12. Abu-Abed Abdin A, Hamza M, Khan MS, Ahmed A. Euglycemic diabetic ketoacidosis in a patient with cocaine intoxication. Case Rep Crit Care 2016; 2016: 4275651. DOI: https://doi.org/10.1155/2016/4275651
13. Le Neveu F, Hywel B, and Harvey JN. Euglycaemic ketoacidosis in patients with and without diabetes. Practical Diabetes 2013; 30(4): 167-71. DOI: https://doi.org/10.1002/pdi.1769
14. Pfützner A, Klonoff D, Heinemann L, Ejskjaer N, Pickup J. Euglycemic ketosis in patients with type 2 diabetes on SGLT2-inhibitor therapy-an emerging problem and solutions offered by diabetes technology. Endocrine 2017; 56(1): 212-6. DOI: https://doi.org/10.1007/s12020-017-1264-y
15. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 2016; 7(2): 135-8. DOI: https://doi.org/10.1111/jdi.12401
16. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, *et al.* Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015; 21: 512-7. DOI: https://doi.org/10.1038/nm.3828
17. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, *et al.* American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016; 22(6): 753-62. DOI: https://doi.org/10.4158/ep161292.ps
18. Ali M, Khan MNA, Patel MJ. Pattern and knowledge of HbA1C testing among diabetic patients at the Indus Hospital (TIH), Karachi. Liaquat National Journal of Primary Care 2022; 4(2): 102-5. DOI: https://doi.org/10.37184/lnjpc.2707-3521.4.19
19. Goldenberg RM, Berard LD, Cheng AY, Gilbert JD, Verma S, Woo VC, *et al.* SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin Ther 2016, 38(12): 2654-64.e1. DOI: https://doi.org/10.1016/j.clinthera.2016.11.002