CASE REPORT - OPEN ACCESS

International Journal of Diabetes and Case Reports DOI: https://dx.doi.org/10.51521/IJDCR.2022.1101

Contents lists available at bostonsciencepublishing.us

International Journal of Diabetes and Case Reports

A Case of SGLT-2i Induced Euglycemic Diabetic Ketoacidosis in the Setting of Gastrointestinal Stress

Gowry Reddy MD[1], Amisha Tailor MD[2], Anca Tanase MD[3], Jeffrey Kantor MD[4]

[1]*Department of Internal Medicine, Saint Clare's Denville Hospital 25 Pocono Road, Denville, NJ, 07834; greddy3@primehealthcare.com; Phone No: 973-625-6000; ORCID No. 0000-0003-0774-5809*

[2]*Department of Internal Medicine, Saint Clare's Denville Hospital 25 Pocono Road, Denville, NJ, 07834, atailor2@primehealthcare.com; Phone No: 973-625-6000; ORCID No. 0000-0002-4261-8648*

[3]*Department of Internal Medicine, Saint Clare's Denville Hospital 25 Pocono Road, Denville, NJ, 07834 anca88t@yahoo.com; Phone No: 973-625-6000; ORCID No. 0000-0002-3338-574X*

[4]*Department of Internal Medicine, Saint Clare's Denville Hospital 25 Pocono Road, Denville, NJ, 07834; jkantor@primehealthcare.com; Phone No: 973- 625-6000; ORCID No. 0009-0000-6654-7023*

ARTICLE INFO

Article history:
Received 08 November 2022
Revised 17 November 2022
Accepted 19 November 2022
Published 25 November 2022

KEYWORDS:

Empagliflozin

SGLT2i

Euglycemic DKA

Insulin

Stress

ABSTRACT

Euglycemic DKA (euDKA) is a rare, uncommon variant of DKA, characterized by the imbalance between insulin and counterregulatory hormones. Lately, the use of SGLT2 inhibitors is known to incite euDKA, which is often missed on initial presentation. In this case, we present a scenario of a 61-year-old African American male with a history of hypertension, CAD s/p CABG, and type 2 diabetes mellitus on SGLT2i (empagliflozin) with a clinical picture of normoglycemic DKA process. With a pH of 7.14, bicarbonate of 8 mEq/L, anion gap (AG) of 17mEq/L, ketoacidosis, and glucosuria, the patient met criteria for euDKA; however, the initial clinical diagnosis of euDKA was overlooked by the possibility of an underlying infectious gastroenteritis, given his recent history of travel with passengers with similar presentation, causing a delay in euDKA management. The management of euDKA is like that of a typical DKA, inculcating aggressive fluid resuscitation and insulin, followed by a permanent discontinuation of SGLT2i. Thus, this case highlights the importance of understanding SGLT2i induced euDKA and its early diagnostic and timely management to prevent further complications.

Introduction

Diabetic ketoacidosis (DKA) is a metabolic disorder triggered by various precipitants, leading to frequent hospitalization. The metabolic derangements associated with DKA include hyperglycemia, ketonemia, acidosis, induced by prolonged states of starvation, medication nonadherence, etc. Euglycemic DKA (euDKA) is a rare, uncommon variant of DKA, characterized by the imbalance between insulin and counterregulatory hormones, with an elevated glucagon/insulin ratio. It can potentiate significant complications, such as dehydration, if not recognized and managed early with fluids, dextrose, and insulin. A rise of euglycemic DKA, with 2.6-3.2% of DKA admissions, have been found to be attributed to the increased use of sodium-glucose 2 cotransporter inhibitors (SGLT2i) [1,2].

Learning Points

1. Identify etiologies of euglycemic DKA (euDKA)
2. Learn to recognize signs and symptoms of euglycemic DKA (euDKA)
3. Differentiate between symptoms of GI disturbances vs euglycemic DKA (euDKA)
4. Consider euglycemic DKA on initial presentation even if with a normal serum glucose
5. Understand the importance of rare adverse effects of SGLT2i

Case Presentation

A 61-year-old African American male with a past medical history of hypertension, CAD s/p CABG, type 2 diabetes mellitus, presented to the ER after flight travel, with a 1week history of fever, diffuse abdominal pain, nausea, diarrhea, and persistent vomiting followed by a near-syncopal episode. His home diabetic regimen is empagliflozin 25 mg QD and sitagliptin-metformin 50-1000 mg BID.

Diagnostic Assessment/Treatment

On admission, his vital signs were temperature of 36.4 deg C, BP of 134/59 mmHg, HR of 84, RR of 19 breaths/min, SpO2 92%. Physical exam was significant for dry mucous membranes and generalized abdominal tenderness. Laboratory findings on admission, revealed an acidemia with a pH of 7.144, bicarbonate level of 8 mEq/L, AG of 17 mEq/L, with blood glucose 173 mg/dl, 3+ glucosuria, 3+ ketonuria, trace leukocyte esterase, and proteinuria, with a normal lactate, thus

* Corresponding author.
Gowry Reddy, Department of Internal Medicine, Saint Clare's Denville Hospital 25 Pocono Road, Denville, NJ, 07834; greddy3@primehealthcare.com; Phone No: 973-625-6000; ORCID No. 0000-0003-0774-5809

meeting the criteria for euglycemic DKA. His recent HbA1c was 9.3. CT abdomen and pelvis was performed, showing no evidence of colitis/acute mesenteric ischemia. Significant factors included his recent history of prolonged travel, and passengers with similar symptoms of gastroenteritis. He was started on IV bicarbonate infusion given his acidotic state and initial clinical presentation of gastroenteritis, causing a delay in treatment of his euglycemic DKA. Upon initiation of bicarbonate, his AG significantly worsened on day 2, prompting us to consider a differential diagnosis, including euglycemic DKA as the principal cause of his underlying acidosis. During his hospitalization, given his previous episodes of ketoacidosis with poor glycogen reserve at baseline, the bicarbonate drip was discontinued, in light of worsening AG. He was then initiated on aggressive IV fluids with D5NS and IV insulin infusion at 0.1 U/kg/hr, which corrected the AG and ketosis, resulting in significant clinical improvement. On day 4 of admission, he was counseled on proper diabetic education and medical management, and advised to discontinue his use of empagliflozin, and was discharged on an insulin regimen and glipizide, and to resume his home medication—sitagliptin-metformin BID— to achieve optimal glycemic control.

Discussion

SGLT-2i are newer diabetic medications that have been associated with potential benefits, such as renoprotective and cardioprotective effects, in diabetics often outweighing the risks, such as genitourinary infections and the very rare euglycemic DKA. Recently, there is mounting evidence of euglycemic DKA precipitated by SGLT2i, which presents as a diagnostic obstacle to many physicians, due to its atypical presentation. In this case, various stressors, such as a prolonged fasting state, possible gastrointestinal infection due to recent travel, etc., may have triggered DKA. Other precipitants of DKA include anorexia, gastroparesis, ketogenic diet, pregnancy, excessive alcohol consumption, sepsis/infections, pancreatitis, cirrhosis, cardiovascular events, and recent major surgeries [1,2]. The criteria for euglycemic DKA is defined as the presence of metabolic acidosis (pH <7.3, and serum bicarbonate <18 mEq/L), ketosis, and a blood glucose <200 mg/dl, all of which were met. In euDKA, insulin deficiency and resistance are milder compared to standard DKA, hence, glucose overproduction and underutilization are less [5]. By inhibiting reabsorption of glucose in the proximal tubule, SGLT2i can reduce both fasting and postprandial blood glucose, while also lowering body weight and blood pressure [2,3]. Various SGLT2i, such as empagliflozin, canagliflozin, and dapagliflozin, have shown great efficacy in recent years in controlling diabetes with added protective effects. Although the half-life is 11 to 13 hours, their systemic effects can be prolonged several days after discontinuation, and it should be advised to discontinue at least 3 days prior to anticipating stressors, such as surgery. Overall, treatment of euDKA inculcates aggressive fluid resuscitation with isotonic saline or lactated ringer's solution at the rate of 1 to 1.5 L/hr isotonic fluids during the initial 1 to 2 hours, after which continuous insulin infusion is initiated with concomitant K+ level monitoring, at a rate of 0.05 to 0.1 U/kg/hr. In euDKA, as serum glucose is typically <250 mg/dl, D5 should initially be added to fluids to avoid risk of hypoglycemia and expedite ketosis clearance [9]. If persistent ketoacidosis noted, increment in D5 to D10 is recommended [10-12]. Treatment with fluids should be continued once anion gap closure is achieved. Once euDKA is diagnosed, SGLT2i should be discontinued permanently at the time of recovery from acute phase of illness, to prevent further complications, such as respiratory failure, cerebral edema, myocardial infarction, seizures, coma, and ultimately death [5,13].

Conclusion

Delineation of euglycemic DKA presents as a diagnostic challenge for clinicians in the initial stages resulting in treatment delay and gaps in patient care. Given the presence of normoglycemia, many clinicians omit DKA as the primary diagnosis, as presented in this case. In March 2015, the US Food and Drug Administration (FDA) issued a warning for SGLT2 inhibitors–associated diabetic ketoacidosis, after 20 cases had been reported subsequently followed by 73 cases of diabetic ketoacidosis requiring hospitalization or ER visit [7]. It is crucial for physicians to maintain a high index of suspicion in diagnosing euglycemic DKA by understanding its underlying pathophysiology and the impending adverse, but rare effects of SGLT2i in both type 1 and type 2 diabetes mellitus.

Acknowledgements: None

Contributors

All authors made individual contributions to authorship. GR: involved in the diagnosis and management of this patient, formulation of manuscript, editing, and manuscript submission. AT: involved in diagnosis, editing, and finalizing manuscript. AnT: responsible for overseeing treatment and patient care. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosure Summary: None declared

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

References

1. Plewa MC, Bryant M, King-Thiele R. Euglycemic Diabetic Ketoacidosis. [Updated 2021 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554570/.

2. Guo RX, Yang LZ, Li LX, Zhao XP. Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: case-control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. J Obstet Gynaecol Res. 2008;34(3):324–30. https://doi.org/10.1111/j.1447-0756.2008.00720.x.

3. Plewa MC, Bryant M, King-Thiele R. Euglycemic Diabetic Ketoacidosis. [Updated 2022 Jan 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554570/

4. Candelario N, Wykretowicz J. The DKA that wasn't: a case of euglycemic diabetic ketoacidosis due to empagliflozin. Oxf Med Case Reports. 2016 Jul 27;2016(7):144-6. doi: 10.1093/omcr/omw061. PMID: 27471597; PMCID: PMC4962888.

5. Julio Rosenstock, Ele Ferrannini; Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. *Diabetes Care* 1 September 2015; 38 (9): 1638–1642. https://doi.org/10.2337/dc15-1380

6. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin Ther. 2016;38(12):2654-2664.e1.

7. Kidney Med. 2(2):218-221. Published online February 22, 2020 doi: 10.1016/ j.xkme.2019.12.006

8. Goldenberg RM, Berard LD, Cheng AYY, Gilbert JD, Verma S, Woo VC, Yale JF. SGLT2 Inhibitor-associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis. Clin Ther. 2016 Dec;38(12):2654-2664.e1. doi: 10.1016/j.clinthera.2016.11.002. PMID: 28003053.

9. Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. Br Med J. 1973 Jun 9;2(5866):578-80. doi: 10.1136/bmj.2.5866.578. PMID: 4197425; PMCID: PMC1592207.

10. Bader N, Mirza L. Euglycemic Diabetic Ketoacidosis in a 27 year-old female patient with type-1-Diabetes treated with sodium-glucose cotransporter-2 (SGLT2) inhibitor Canagliflozin. Pak J Med Sci. 2016 May-Jun;32(3):786-8.

11. Wan Azman SS, Sukor N, Abu Shamsi MY, Ismail I, Kamaruddin NA. Case Report: High-Calorie Glucose Infusion and Tight Glycemic Control in Ameliorating Refractory Acidosis of Empagliflozin-Induced Euglycemic Diabetic Ketoacidosis. Front Endocrinol (Lausanne). 2022;13:867647.

12. Bader N, Mirza L. Euglycemic Diabetic Ketoacidosis in a 27 year-old female patient with type-1-Diabetes treated with sodium-glucose cotransporter-2 (SGLT2) inhibitor Canagliflozin. Pak J Med Sci. 2016 May-Jun;32(3):786-8.

13. Dai Z, Nishihata Y, Kawamatsu N, Komatsu I, Mizuno A, Shimizu M, Toya N, Ishimatsu S, Komiyama N. Cardiac arrest from acute myocardial infarction complicated with sodium-glucose cotransporter 2 inhibitor-associated ketoacidosis. J Cardiol Cases. 2017 Feb;15(2):56-60.