

Euglycemic Ketoacidosis Induced by SGLT2 Inhibitor in Latent Autoimmune Diabetes in Adults: A Case Report

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Received: 17-04-2024 / Revised 16-05-2024 / Accepted 12-06-2024

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DOI: <https://doi.org/10.32553/ijmbs.v8i3.2802>

Conflict of interest: Nil

Abstract:

Background: Euglycemic ketoacidosis (EKA) is a medical condition characterized by the presence of ketoacidosis without significant hyperglycemia. It is particularly challenging to diagnose due to normal or near-normal blood glucose levels. SGLT2 inhibitors, used in managing type 2 diabetes mellitus, are known to cause EKA. This risk is increased in patients with latent autoimmune diabetes in adults (LADA), a type of Type 1 diabetes presented in adult (Hybrid form of diabetes)

Case Report: A 64-year-old male with a history of diabetes mellitus and hypothyroidism presented with shortness of breath, nausea, and dizziness. Despite taking Metformin, Glimepride, Thyroxin, and Empagliflozin, he had poor glycemic control (HbA1c 9%) Physical examination showed generalized vitiligo and tachycardia. Initial laboratory results revealed high anion gap metabolic acidosis with normal blood glucose, consistent with EKA. Extensive diagnostic workup confirmed the presence of LADA and SGLT2 inhibitor induced EKA.

Result: The patient was diagnosed with type 1 diabetes mellitus (LADA) and EKA induced by SGLT2 inhibitors. Management included discontinuation of the SGLT2 inhibitor, initiation of insulin therapy, and monitoring of metabolic parameters.

Conclusion: Euglycemic ketoacidosis induced by SGLT2 inhibitors in patients with LADA is a serious condition requiring prompt recognition and treatment. Clinicians should be vigilant in monitoring adult patients with diabetes and other autoimmune conditions who are on SGLT2 inhibitors for symptoms of ketoacidosis even when blood glucose levels are normal.

Recommendations: Regular monitoring of blood ketone levels in patients on SGLT2 inhibitors. Consideration of alternative glucose-lowering therapies in patients with LADA. Education for patients and healthcare providers on the risks of EKA.

Keywords: Euglycemic ketoacidosis, SGLT2 inhibitors, Latent autoimmune diabetes in adults, Diabetes management, Metabolic acidosis.

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Introduction

A medical condition known as euglycemic ketoacidosis (EKA) is defined as the presence of ketoacidosis without a noticeable rise in blood sugar levels. Because of the normal or nearly normal

blood glucose levels, this illness can be particularly difficult to detect, which can postpone receiving the right care. The usage of sodium-glucose co-transporter 2 (SGLT2) inhibitors, a family of oral drugs

frequently used in the treatment of type 2 diabetes mellitus, is one of the common causes of EKA.

Empagliflozin, canagliflozin, and dapagliflozin are examples of SGLT2 inhibitors that lower blood glucose levels by inhibiting the kidneys' ability to reabsorb glucose and encouraging the excretion of glucose through the urine. These medications have been linked to an elevated risk of EKA [1], despite the fact that they are beneficial for the cardiovascular system and are helpful in regulating blood sugar. Individuals with latent autoimmune diabetes in adults (LADA), a kind of diabetes that combines elements of type 1 and type 2 diabetes, should be especially concerned about this risk.

Due to its gradual onset and manifestation during adulthood, LADA is often mistaken for type 2 diabetes. Similar to type 1 diabetes, LADA is an autoimmune condition where the body's immune system attacks the pancreatic beta cells responsible for producing insulin[2]. By encouraging ketosis, SGLT2 inhibitor use in LADA patients can hasten the onset of EKA. The inhibition of glucose reabsorption leads to decreased insulin levels and increased glucagon levels, both of which can stimulate ketogenesis. Additionally, the underlying autoimmune destruction of beta cells in LADA patients further impairs insulin production, exacerbating the risk of ketoacidosis [3].

Euglycemic ketoacidosis induced by SGLT2 inhibitors in LADA requires prompt recognition and treatment. Clinicians should be aware of this potential complication, particularly in patients presenting with symptoms such as nausea, vomiting, abdominal pain, and difficulty breathing, despite normal blood glucose levels [4]. Early diagnosis and management are critical to prevent severe outcomes.

Understanding the interplay between SGLT2 inhibitors and LADA is essential for optimizing diabetes treatment and minimizing risks associated with these medications.

Case Presentation

Patient Demographics:

The patient is a 64-year-old male.

Chief Complaints:

Upon presentation, the patient reported experiencing shortness of breath, nausea, and dizziness.

Medical History:

The patient's medical history revealed diagnoses of diabetes mellitus and hypothyroidism.

Presenting History:

He presented with a history of shortness of breath, nausea, and dizziness. Notably, he was on multiple medications, including Metformin, Glimepride, Thyroxin, and Empagliflozin, with persistently poor glycemic control indicated by a high HbA1c level of 9%. Recent medication changes were associated with increased urination and recurrent morning hypoglycemia. There was no history of alcohol intake.

Physical Examination:

Physical examination revealed generalized vitiligo, a BMI of 22.8 Kg/m², and normal vital signs except for tachycardia.

Initial Management:

Despite reassurance by his treating physician, the patient remained concerned due to poor glycemic control. Subsequently, another physician adjusted his medication regimen by stopping Glimipride, initiating Inj Glargine 10 units s.c. daily, and maintaining other oral antidiabetic medications.

Table 1: Initial work up Arterial blood gas and other

Parameter	Measured Values	Reference Range
Sodium, mmol/L	134	135-145
Potassium, mmol/L	4.15	3.5-5
Chloride, mmol/L	98	98-108
Creatinine, mg/dL	0.7	0.5-1.2
BUN, mg%	25	7-17
HCO ₃ , mmol/L	10	22-26
Glucose, mg/dL	160	65-99
Anion gap, mEq/L	26	5-15
ABG pH	7.2	7.35-7.45
ABG PCO ₂ , mmHg	22.8	35-45
ABG PO ₂ , mmHg	80	80-100
Lactate, mmol/L	2.5	0.5-2
Urine ketone	+++	Not applicable

Subsequent Presentation:

The patient's subsequent presentation included symptoms of dyspnea, dizziness, dehydration, and tachycardia.

Provisional Diagnosis:

Based on the history and clinical examination, a provisional diagnosis of poorly controlled type 2 diabetes mellitus, hypothyroidism, vitiligo, and dyspnea requiring evaluation was made.

Diagnostic Workup:

Extensive diagnostic workup was performed, including blood tests (Beta hydroxybutyrate, Lipase, Amylase, LFT, KFT, HbA1c, T3, T4, TSH, Anti-TPO antibodies, C-peptide, GAD antibody) and urine ketone analysis. The results revealed a high anion gap metabolic acidosis with a normal blood sugar level, indicative of euglycemic ketoacidosis.

Final Diagnosis:

The final diagnosis comprised type 1 diabetes mellitus (LADA) and SGLT2 Inhibitor-induced euglycemic ketoacidosis.

Ethical considerations:

The study protocol was approved by the Ethics Committee and written informed consent was received from the participant.

Discussion

This case presents a 64-year-old male with a history of diabetes mellitus and

hypothyroidism who presented with symptoms of shortness of breath, nausea, and dizziness. Despite being on multiple medications, his diabetes remained poorly controlled. Recent addition of Empagliflozin was associated with increased urination and recurrent morning hypoglycemia. Subsequent adjustment of his medication regimen did not resolve his symptoms, and he presented again with dyspnea, dizziness, dehydration, and tachycardia.

Extensive diagnostic workup revealed a high anion gap metabolic acidosis with normal blood sugar levels, indicative of euglycemic ketoacidosis, which is a rare complication of diabetes. Further testing confirmed the diagnosis of Type 1 diabetes mellitus (LADA) and identified SGLT2 Inhibitor-induced euglycemic ketoacidosis.

This case highlights the importance of recognizing atypical presentations of diabetes and the potential complications associated with medication changes, particularly with SGLT2 Inhibitors. It underscores the need for vigilant monitoring and appropriate management strategies, especially in patients with longstanding diabetes and recent medication adjustments.

EKA induced by SGLT2 inhibitors in patients with LADA is increasingly

recognized as a significant clinical challenge. This condition, characterized by ketoacidosis without marked hyperglycemia, can lead to diagnostic delays and severe outcomes if not promptly identified and managed. Recent case reports and literature reviews have highlighted the complexity of diagnosing and treating EKA in patients on SGLT2 inhibitors. For example, there's a case of a woman who developed empagliflozin-associated EKA despite discontinuing the medication before hospital admission. The case underscored the role of surgical stress and decreased carbohydrate intake in precipitating EKA and the difficulty in diagnosis due to near-normal glucose levels [5].

Another case involved a patient with EKA complicated by hypertriglyceridemia. This case highlighted the diagnostic challenge posed by significant lipemia, which interfered with serum ketone measurements, and emphasized the necessity of recognizing EKA symptoms despite normal glucose readings [6]. Similarly, a study discussed a patient who developed EKA six days after starting canagliflozin, underscoring the need for vigilance in patients with normal blood glucose levels but with symptoms indicative of metabolic acidosis [7].

Extended recovery times in patients with EKA have also been reported. A case involving prolonged recovery in a post-percutaneous coronary intervention patient was discussed. The study suggested that EKA associated with SGLT2 inhibitors might require longer treatment durations than typical diabetic ketoacidosis, particularly in the presence of other comorbid conditions [8]. Another severe case described EKA that was refractory to standard treatment and renal replacement therapy, highlighting the need for aggressive management strategies and the potential for severe complications [9].

Clinical guidelines and risk factors specific to LADA patients using SGLT2 inhibitors

have been proposed to mitigate these risks. A study reported a series of cases where LADA patients developed ketoacidosis while on SGLT2 inhibitors, recommending cautious use and close monitoring in this patient group [10]. Another study also emphasized the importance of accurate diagnosis, noting that several patients initially diagnosed with type 2 diabetes were later found to have LADA after presenting with EKA, highlighting the need for careful patient selection and monitoring [11].

The challenge of misdiagnosed LADA was further highlighted by a report of a case in which SGLT2 inhibitor-induced EKA unmasked LADA in a patient previously presumed to have type 2 diabetes. This case underlined the necessity of distinguishing between different diabetes types to ensure appropriate treatment and avoid severe complications [12].

Conclusion:

The case emphasizes the critical importance of careful monitoring and management in patients with diabetes, particularly when initiating or adjusting medication regimens. The occurrence of euglycemic ketoacidosis, albeit rare, underscores the need for clinicians to remain vigilant for atypical presentations and potential complications, especially with newer classes of antidiabetic medications like SGLT2 Inhibitors. This case highlights the necessity of a comprehensive diagnostic approach and timely intervention to ensure optimal patient outcomes and prevent life-threatening complications in individuals with diabetes mellitus.

Recommendation: Regular monitoring of serum ketone levels in patients on SGLT2 inhibitors. Deliberation over alternative glucose-lowering treatments in patients with LADA is advisable. Educating both patients and healthcare providers about the risks of EKA is essential.

Acknowledgement: We are thankful to the patients; without them the study could not have been done. We are thankful to the supporting staffs of our hospital who were involved in patient care of the study group.

List of abbreviations:

EKA: Euglycemic ketoacidosis
 SGLT2: Sodium-glucose co-transporter 2
 LADA: Latent autoimmune diabetes in adults
 HbA1c: Hemoglobin A1c
 BMI: Body mass index
 s.c.: Subcutaneous
 LFT: Liver function test
 KFT: Kidney function test
 T3: Triiodothyronine
 T4: Thyroxine
 TSH: Thyroid-stimulating hormone
 Anti-TPO antibodies: Antithyroid peroxidase antibodies
 GAD antibody: Glutamic acid decarboxylase antibody
 ABG: Arterial blood gas

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