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CASE REPORT

EUGLYCEMIC DIABETIC KETOACIDOSIS IN THE CONTEXT OF LATENT AUTOIMMUNE DIABETES AND SGLT2 INHIBITOR THERAPY: CASE REPORT

Felicia DARII[1,2]✉, Daria ROMANIUC[2], Victoria IVANOV[2], Natalia PORCEREANU[3], Olga TAGADIUC[1]

[1] "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2] Institute of Cardiology, Chisinau, Republic of Moldova
[3] "Timofei Mosneaga" Republican Clinical Hospital, Chisinau, Republic of Moldova

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Abstract

Introduction. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as an important therapeutic option in type 2 diabetes mellitus, with proven cardiovascular and renal benefits. However, their use has been linked to rare cases of euglycemic diabetic ketoacidosis (euDKA), a potentially life-threatening complication characterized by metabolic acidosis and ketosis in the absence of marked hyperglycemia. This risk may be heightened in patients with latent autoimmune diabetes in adults (LADA), an autoimmune form of diabetes often misclassified as type 2 diabetes due to its slow progression.

Case presentation. We report the case of a 60-year-old woman initially diagnosed with type 2 diabetes and treated with metformin and dapagliflozin. Shortly after starting SGLT2i therapy, she developed severe euDKA requiring hospitalization. Laboratory evaluation revealed metabolic acidosis, positive ketone bodies, and near-normal blood glucose. Autoimmune testing confirmed the diagnosis of LADA, with elevated antibodies against glutamic acid decarboxylase (anti-GAD) and low C-peptide levels. This case not only

Résumé

Acidocétose diabétique euglycémique dans le context du diabète auto-immun latent et du traitement par inhibiteurs de SGLT2: présentation du cas

Introduction. Les inhibiteurs du co-transporteur sodium-glucose de type 2 (iSGLT2) sont devenus une option thérapeutique majeure dans le diabète de type 2, grâce à leurs effets démontrés sur la protection cardiovasculaire et rénale. Toutefois, leur utilisation a été associée à de rares cas d'acidocétose diabétique euglycémique (ACDe), une complication potentiellement fatale, caractérisée par une acidose métabolique et une cétose en l'absence d'hyperglycémie marquée. Ce risque pourrait être accentué chez les patients atteints de diabète auto-immun latent de l'adulte (LADA), une forme auto-immune souvent confondue avec le diabète de type 2.

Présentation du cas. Nous rapportons le cas d'une femme de 60 ans, initialement diagnostiquée avec le diabète de type 2 et traitée par metformine et dapagliflozine. Peu de temps après l'initiation du traitement par iSGLT2, elle a développé une ACDe sévère

✉ Address for correspondence: Felicia DARII
"Nicolae Testemitanu" State University of Medicine and Pharmacy and Institute of Cardiology, Chisinau, Republic of Moldova
Email: felicia.darii@usmf.md; Phone +37369434463

reflects the diagnostic complexity of LADA, but also raises concern regarding the possible contribution of SGLT2 inhibitors to precipitating ketoacidosis, particularly in patients with unrecognized insulin deficiency. While SGLT2i therapy offers significant clinical benefits, careful patient selection is critical. Screening for pancreatic autoantibodies may help identify patients at higher risk and prevent adverse outcomes.

Conclusions. The clinicians should consider autoimmune diabetes in atypical cases and remain vigilant for signs of euDKA when prescribing SGLT2 inhibitors. Structured screening and close monitoring may improve patient safety without compromising the therapeutic advantages of this drug class.

Keywords: SGLT2 inhibitor, euglycemic ketoacidosis, LADA, anti-GAD antibodies.

List of abbreviations:
Anti-GAD – anti-glutamic acid decarboxylase
Anti-IA2 – anti-tyrosine phosphatase
DKA – diabetic ketoacidosis
EuDKA – euglycemic diabetic ketoacidosis
LADA – latent autoimmune diabetes in adults
SGLT2 – sodium-glucose cotransporter-2
SGLT2i – sodium-glucose cotransporter-2 inhibitors

nécessitant une hospitalisation. Les analyses ont mis en évidence une acidose métabolique, une cétonurie positive et une glycémie proche de la normale. Les examens immunologiques ont confirmé le diabète LADA, avec des anticorps anti-GAD élevés et une insulinopénie marquée (peptide C bas). Ce cas met en lumière la complexité diagnostique du LADA et suggère un rôle déclencheur possible des iSGLT2 dans l'acidocétose, en particulier chez les patients présentant un déficit insulinique méconnu. Un dépistage des autoanticorps pourrait permettre d'identifier les patients à risque et de prévenir les complications.

Conclusions. Il est essentiel de considérer un diabète auto-immun dans les tableaux atypiques et de surveiller attentivement les signes d'ACDe lors du recours aux iSGLT2.

Mots-clés: inhibiteur SGLT2, acidocétose euglycémique, LADA, anticorps anti-GAD.

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent a relatively new class of oral antidiabetic agents used in the treatment of type 2 diabetes mellitus. Through their mechanism of action, which involves the inhibition of renal glucose reabsorbtion at the level of the proximal tubules, these drugs promote glucosuria and reduce blood glucose levels. Clinical trials have demonstrated benefits that extend beyond glycemic control, including a significant reduction in cardiovascular risk and slowing of renal disease progression. Consequently, this pharmacological class has been rapidly incorporated into international guidelines recommendations for the management of diabetes mellitus, heart failure, and chronic kidney disease[1,2].

Although SGLT2i are generally well tolerated, they have been associated in rare cases with the development of euglycemic diabetic ketoacidosis (euDKA). This atypical form of ketoacidosis is defined by the presence of metabolic acidosis and either ketonemia (>3.0 mmol/L) or ketonuria (2+ or higher), in the absence of significant hyperglycemia (blood glucose ≤13.9 mmol/L). It represents a notable diagnostic challenge – especially when no obvious risk factors are present[3,4]. The underlying pathophysiological mechanisms are complex and involve reduced insulin availability, increased glucagon secretion, and stimulation of hepatic lipolysis and ketogenesis. These processes are further amplified by glucosuria-induced energy deficit, which promotes excessive ketone body production[5].

The risk becomes particularly relevant when SGLT2i therapy is initiated in patients with latent autoimmune diabetes in adults (LADA), a condition that is frequently underdiagnosed at the early stages of the disease[6]. LADA is considered an intermediate form between type 1 and type 2 diabetes, characterized by the presence of β-cell-specific autoantibodies (such as anti-GAD) and anti-tyrosine phosphatase (anti-IA2)) and a gradually progressive decline in insulin secretion[7].

We present the case of a woman with previously undiagnosed LADA who developed severe ketoacidosis during treatment with an SGLT2i. This case highlights the importance of recognizing atypical diabetes phenotypes and considering pancreatic autoantibody screening prior to initiating therapies that may exacerbate insulin deficiency.

Case presentation

A 60-year-old female patient was admitted to the Cardiology Institute (Chisinau, Republic of Moldova)

on December 12, 2024, with severe dyspnea, tachypnea, persistent abdominal pain, constipation, and generalized weakness. There was no prior history of clinically confirmed cardiovascular disease.

In October 2024, while abroad, the patient was diagnosed with type 2 diabetes mellitus, with an initial blood glucose level exceeding 20 mmol/L. Early-stage treatment included metformin 1000 mg/day; however, glycemic control remained suboptimal, with blood glucose levels persistently ranging between 15 and 18 mmol/L. As a result, in November, her treatment regimen was intensified to metformin 2000 mg/day in combination with dapagliflozin 10 mg/day. Self-monitored blood glucose levels subsequently ranged between 7 and 14 mmol/L, with no reported episodes of hypoglycemia.

Beginning on December 8, 2024, the patient reported a progressive worsening of her general condition, characterized by pronounced dry mouth, dyspnea, and abdominal discomfort. On December 12, she was admitted to the hospital with a presumptive diagnosis of pulmonary arterial thromboembolism and metabolic ketoacidosis.

On admission, clinical examination revealed a heart rate of 115 bpm, blood pressure of 130/85 mmHg, respiratory rate of 35–40 breaths/min, and oxygen saturation (SpO_2) of 99–100%. The abdomen was tender on palpation. Arterial blood gas test indicated severe metabolic acidosis with pH 7.03, base deficit –25.8 mmol/L, anion gap 30.9 mmol/L, bicarbonate level 2.7 mmol/L, and strongly positive urine ketone bodies (++++). Glycated hemoglobin (HbA1c) on admission was 9.8%.

Laboratory and imaging investigations excluded pulmonary arterial thromboembolism and other potential causes of metabolic acidosis. Despite intensive therapeutic measures, the patient exhibited persistent ketoacidosis and ketonuria throughout hospitalization. Oral antidiabetic agents were discontinued upon admission, and insulin therapy was initiated. Intravenous Actrapid was administered via continuous infusion, followed by a basal–bolus insulin regimen using Lantus (Glargine) and Novorapid (Aspart), with dosages titrated according to blood glucose levels and carbohydrate intake.

Due to the atypical progression of the disease, LADA was suspected. The diagnosis was subsequently confirmed by markedly elevated anti-GAD antibody levels (559 IU/mL; reference range <10 IU/mL), along with reduced C-peptide concentrations (0.066 ng/mL; reference range 1.1–4.4 ng/mL), and low serum insulin levels (1.68 µIU/mL; reference range 2.6–24.3 µIU/mL).

Discussion

Diabetic ketoacidosis (DKA) represents a life-threatening metabolic emergency characterized by hyperglycemia, metabolic acidosis, and ketosis (ketonemia and/or ketonuria). It results from an absolute or relative deficiency of insulin, combined with elevated levels of counter-regulatory hormones such as glucagon, cortisol, growth hormone, and catecholamines. A particularly challenging presentation of this condition is euglycemic diabetic ketoacidosis (euDKA), in which blood glucose levels remain within the reference range or are only mildly elevated (<13.9 mmol/L). This atypical glycemic pattern may obscure clinical recognition and contribute to delays in the initiation of appropriate treatment[8].

Over the past decade, the use of SGLT2 inhibitors has been associated with significant clinical benefits, as demonstrated by large randomized trials such as EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF. These studies have established the role of SGLT2i in the management of type 2 diabetes, heart failure, and chronic kidney disease, due to their glucose-lowering effects, significant reduction in major cardiovascular events, and the slowing of renal disease progression. However, the expanding therapeutic indications have renewed concerns about their safety, particularly regarding the risk of diabetic ketoacidosis[9-11].

SGLT2i are the pharmacological agents increasingly associated with the onset of euDKA. They reduce glucose reabsorption and enhance urinary glucose excretion by inhibiting the SGLT2 cotransporter in the proximal convoluted tubule. Prolonged glucosuria leads to a decrease in blood glucose levels, which induces a compensatory reduction in insulin secretion. This state of relative insulin deficiency promotes increased lipolysis and stimulates hepatic ketogenesis, resulting in the accumulation of ketone bodies – acetone, acetoacetate, and β-hydroxybutyrate[12]. Additionally, glucosuria is associated with a mild volume depletion, which further stimulates glucagon secretion and potentiates ketogenesis[13]. This metabolic vicious cycle is maintained despite relatively normal glycemia, due to continued renal glucose loss, thereby delaying the diagnosis of DKA.

This pathobiochemical mechanism is of particular concern in individuals with LADA, a slowly progressive autoimmune form of diabetes characterized by the presence of β-cell-specific autoantibodies and a gradual decline in insulin secretion. Clinically, LADA often resembles type 2 diabetes in its early stages, leading to frequent misclassification and delayed initiation of insulin therapy[14]. Current evidence consistently highlights the diagnostic challenges

associated with LADA, with studies indicating that approximately 5–12% of adults initially diagnosed with type 2 diabetes are, in fact, patients with LADA, who are anti-GAD positive and progressively evolve toward severe insulin deficiency[15].

When SGLT2i are administered to patients with undiagnosed LADA, the underlying autoimmune-mediated β-cell destruction combined with the insulin-lowering effects of glucosuria, may act synergistically to precipitate euDKA. Because residual endogenous insulin secretion is typically present at the time of LADA diagnosis, these patients are often initially managed with oral antidiabetic agents, including SGLT2 inhibitors, in the absence of autoimmune screening. However, the progressive decline in insulin secretion increases the risk for ketoacidosis, even in the absence of severe hyperglycemia. This risk is further amplified under conditions of physiological stress, such as acute illness, infection, surgery, myocardial infarction, prolonged fasting, or during ongoing SGLT2 inhibitor therapy, all of which contribute to reduced insulin availability and enhanced ketogenesis[16].

In parallel, pharmacovigilance reports and observational studies have highlighted an increased risk of euDKA associated with SGLT2i compared to other oral antidiabetic agents[17,18]. Regulatory agencies such as the FDA and EMA have issued safety alerts emphasizing the need for careful clinical evaluation prior to initiating therapy and close monitoring for early signs of ketoacidosis[15,19].

Establishing a definitive causal relationship between SGLT2 inhibitor use and the onset of DKA in patients with LADA remains a complex clinical and scientific challenge. In the case presented, the development of ketoacidosis temporally coincided with the initiation of SGLT2i therapy. However, the subsequent identification of anti-GAD antibodies highlights the need to assess whether DKA was primarily triggered by the effect of SGLT2i or by the natural course of autoimmune β-cell failure and progressive insulin deficiency.

From one perspective, accumulating clinical evidence, including randomized trials and multiple case reports, supports the potential of SGLT2i to trigger DKA, even in patients without previously diagnosed autoimmune diabetes. Pathobiochemical mechanisms support the plausibility of euDKA through reduced insulin synthesis, increased glucagon secretion, and enhanced ketogenesis[20,21].

Conversely, LADA is inherently associated with an increased risk of DKA, due to the progressive decline in endogenous insulin secretion. In many cases, the diagnosis of LADA is delayed due to phenotypic overlap with type 2 diabetes mellitus. The use of agents such as SGLT2i, which reduce the required insulin dose, may mask the progressive β-cell dysfunction until the development of an acute episode of metabolic decomepnsation becomes clinically apparent[22].

Screening for LADA, using clinical risk scores and pancreatic autoantibody testing, may enable safer use of SGLT2 inhibitors. Additional studies are required to develop evidence-based recommendations regarding the clinical evaluation and management of patients who develop DKA during SGLT2i therapy. Recent guidelines recommend testing for pancreatic autoantibodies, especially anti-GAD, in patients with atypical diabetes onset or rapid progression to insulin dependence[23].

In our case, a definitive unidirectional causal relationship between SGLT2i therapy and DKA could not be established. A multifactorial interaction is more likely, with SGLT2 inhibitor therapy serving as a precipitating factor in the context of underlying and progressing LADA. This case highlights the critical importance of accurate diabetes classification and the need to reconsider both diagnosis and treatment approach when conventional treatment fails to achieve adequate metabolic control.

Although the number of published DKA cases in patients with LADA treated with SGLT2 inhibitors remains limited, available reports confirm a potential synergistic risk between the autoimmune β-cell failure characteristic of LADA and the ketogenesis-promoting effects of SGLT2 inhibition. Implementation of structured screening strategies, combining clinical risk assessment with autoantibody testing, could significantly improve the safety profile of SGLT2i in routine practice. Furthermore, accumulating evidence suggests that SGLT2 inhibitors should be avoided or discontinued in patients with suspected autoimmune diabetes, particularly in the context of marked insulin deficiency or clinical situations predisposing to ketogenesis, such as prolonged fasting, acute infections, or surgical stress[24,25].

Conclusions

The presented case underscores the importance of early diagnosis of LADA before initiating treatment with SGLT2 inhibitors. Careful patient selection, particularly in those with clinical features suggestive of progressive insulin deficiency, is essential to reduce the risk of euDKA.

Although the use of SGLT2 inhibitors is associated with an increased risk of ketoacidosis, this potential adverse risk should not preclude their use. The cardiovascular, renal, and metabolic benefits of SGLT2 inhibitors remain well-established, continuing to support their recommendation in clinical practice.

Author Contributions:

Conceptualization, O.T., V.I.; clinical diagnosis, paraclinical investigations, treatment decisions and follow up of the patient, F.D., D.R., V.I., N.P.; writing – original draft preparation, F.D., D.R.; writing – review and editing, O.T., F.D. and N.P. All authors reviewed and approved the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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