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Re-emergence of a forgotten diabetes complication: Euglycemic diabetic ketoacidosis

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Abstract:

Diabetic ketoacidosis (DKA) is the most common emergency complication of diabetes. Euglycemic DKA (EDKA), on the other hand, has been known for many years but is a rare and under-recognized condition and constitutes a very small proportion of DKA cases. However, in recent years, an increase in the incidence of EDKA has been observed with the widespread use of sodium–glucose co-transporter 2 inhibitors, which have proven benefits in the treatment of diabetes mellitus and its cardiorenal complications, heart failure, and chronic kidney disease. Unlike classical DKA, these patients without significant hyperglycemia can easily be missed in emergency departments. EDKA should be kept in mind in patients with diabetes presenting with DKA but with a blood glucose level <250 mg/dL. The diagnostic and therapeutic approach after clinical suspicion in these patients is similar to classical DKA and is briefly summarized in this review. The most important point in treatment is that these patients are normoglycemic but have a significant insulin deficiency (relative or absolute). Therefore, insulin is the mainstay of the treatment and should be given together with dextrose solutions to avoid hypoglycemia.

Keywords:

Diabetes mellitus, diabetic ketoacidosis, sodium-glucose transporter 2 inhibitors

Introduction

Diabetes mellitus (DM) is one of the most important health problems of our age, characterized by insulin resistance and/or deficiency in insulin secretion. In 2019, its global prevalence was 9.3% (463 million people) and it is estimated that this rate will increase to 10.2% (578 million) by 2030.[1] Acute and chronic complications of DM, which has almost reached a pandemic level, are among the most important causes of morbidity and mortality worldwide. In Turkey, the prevalence of DM was found to be 16.5% in the TURDEP-II study.[2] Despite all the progress made in the treatment of DM, emergency department visits with acute complications of DM are also very common because of its relatively high prevalence.

One of the most important diabetic emergencies is diabetic ketoacidosis (DKA). The components of classical DKA are hyperglycemia (serum glucose >250 mg/dL), increased anion gap metabolic acidosis (anion gap >10–12, serum bicarbonate <18 mEq/L, and/or pH <7.3), and ketosis (ketonemia and/or ketonuria).[3-6] DKA is an urgent complication of DM with a high risk of mortality if not treated promptly and appropriately.[4,7,8] Despite this, the mortality rate is currently <1% with advances in

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diagnosis, treatment, and increased accessibility to health facilities.

Although DKA is more common in patients with type 1 DM, approximately one-quarter of the cases are in patients with type 2 DM.[3,4] DKA frequently occurs in patients with DM with absolute or relative insulin deficiency at initial diagnosis or in the presence of triggering factors such as infections, trauma, acute myocardial infarction, pregnancy, or in the interruption of insulin therapy.[7,9]

Euglycemic DKA (EDKA), unlike classical DKA, is an under-recognized condition with relative euglycemia with a blood glucose level <250 mg/dL, metabolic acidosis, and ketosis.[3,10-14] EDKA was first described by Munro *et al*. in 1973.[13] Subsequently, a larger case series was published by Jenkins *et al*. in 1993.[14] EDKA accounts for approximately 2.6%–7% of DKA cases, depending on the upper limit of reference of blood glucose level.[3,10,11] However, the actual incidence is not known exactly.[7]

In recent years, the use of sodium–glucose transporter 2 (SGLT-2) inhibitors, a group of oral antidiabetic drugs, increased gradually. Therefore, EDKA has started to be seen more frequently. This situation has made EDKA more important to recognize in clinical settings.[3,7,15-21]

SGLT-2 inhibitors are the newest group of antidiabetic agents that have been in use for about 10 years (since 2013). These agents increase renal glucose excretion by inhibiting glucose reabsorption from renal proximal tubules. The resulting glucosuria leads to osmotic diuresis and volume depletion. However, these drugs decrease the clearance of ketone bodies and increase the reabsorption of ketone bodies.[3,22,23] The main agents of this group are empagliflozin, dapagliflozin, and canagliflozin. Although these agents are relatively new, they have quickly taken the top place of the treatment algorithms in type 2 DM treatment due to their cardiovascular and renal benefits and their favorable effects on weight. While studies on their use in patients with type 1 DM are ongoing, they are also used off-label in some patients in clinical settings. Some guidelines recommend their use under close follow-up in appropriate patients with type 1 DM.[18,20,24-30] Beyond diabetes, SGLT-2 inhibitors have proven benefits in the treatment of reduced, mildly reduced, and preserved ejection fraction heart failure and chronic kidney disease in patients without DM.[31,32] SGLT-2 inhibitors have been used in Turkey for about 5 years. Dapagliflozin and empagliflozin are currently licensed and used SGLT-2 inhibitors in Turkey.

Both the US Food and Drug Administration (FDA) (in 2015) and the European Medicines Agency issued warnings that the use of SGLT-2 inhibitors may predispose to DKA in 2016.[18,33,34] Blau *et al*. reviewed the US FDA Adverse Event Reporting System for DKA associated with SGLT-2 inhibitor use and found that 71% of reported cases were EDKA. The EDKA risk was higher in patients with type 1 DM and using SGLT-2 inhibitors. SGLT-2 inhibitors used in type 2 DM had a 2- to 7-fold increased risk compared to treatment with other drugs.[35]

The clinical approach to EDKA is similar to classical DKA. However, what makes EDKA important in clinical practice, especially in emergency departments, is the possibility that the disease may be unrecognized due to normal or relatively high blood glucose levels (serum glucose <250 mg/dL). This review aims to increase awareness of EDKA and to review the clinical approach to these patients.

Pathophysiology

The pathophysiology of DKA involves relative or absolute insulin deficiency and increased levels of counter-regulatory hormones (glucagon, cortisol, growth hormone, and catecholamines). This hormonal imbalance causes hyperglycemia by increasing glycogenolysis, and hepatic gluconeogenesis and decreasing peripheral utilization of glucose. Lipolysis increases and generates free fatty acids from adipose tissue. Increased proteolysis generates amino acids. Free fatty acids and amino acids promote gluconeogenesis and ketogenesis. Thus, ketone bodies (beta-hydroxybutyrate, acetoacetate, and acetone) increase in blood and cause metabolic acidosis. Glucosuria and osmotic diuresis caused by hyperglycemia lead to dehydration and hypovolemia.[4,7] Volume depletion further exacerbates elevations of counterregulatory hormones.

Carbohydrate deficiency has a critical role in the pathophysiology of EDKA. Insulin deficiency or insulin resistance is less important than carbohydrate starvation. However, counter-regulatory hormone production does not reduce. The glucagon/insulin ratio increases. Ketogenesis is triggered without a significant change in hepatic gluconeogenesis and peripheral glucose utilization.[7,10,12,36] Fasting or prolonged exercise with depleted hepatic glycogen stores and consequently impaired glycogenolysis triggers EDKA. Since glycolysis intermediates are not available as a result of reduced intracellular glucose oxidation, increased glucagon also promotes lipid oxidation by generating acetyl-CoA and ketone bodies. Nonreduced ketonemia and glycosuria (usually seen with SGLT-2 inhibitors) contribute to EDKA.[7,20,36]

Etiology

Any condition that results in decreased glucose availability or decreased glucose production, decreased

insulin secretion, increased counterregulatory hormone production, and increased glucagon/insulin ratio can cause EDKA. The three most common causes are SGLT-2 inhibitors, pregnancy, and prolonged fasting. The dose of insulin administered before presentation to the emergency department may also cause the patient to present with EDKA-like DKA [Table 1].[3,7]

Sodium–glucose cotransporter 2 inhibitors

SGLT-2 inhibitors may cause EDKA in patients predisposed to DKA through glucosuria, which causes a carbohydrate deficiency state, osmotic diuresis with glucosuria, dehydration, and hypovolemia. Carbohydrate deficiency and hypovolemia stimulate glucagon release. Insulin level also decreases due to decreased glucose. The glucagon/insulin ratio increases. Lipolysis and free fatty acid levels increase. This triggers euglycemic ketogenesis. Other effects of SGLT-2 inhibitors that play a role in the pathophysiology of EDKA are that these drugs increase glucagon release by direct effects on pancreatic alpha cells and inhibit the excretion of ketone bodies from the kidneys.[7,20,22,23,37,38]

The incidence of SGLT-2 inhibitor-associated EDKA and DKA varies according to the characteristics of the studies. In clinical trials, the incidence of DKA was reported as 0.16–0.76 events per 1000 patient-years.[20,39] In the Canadian Network for Observational Drug Effect Studies, the incidence was 1.40 (1.29–1.53) per 1000 patient-years, with a 3-fold increased risk compared to patients using DPP-4 inhibitors. The increased risk of DKA was observed with all three SGLT-2 inhibitors, suggesting a class effect. However, canagliflozin had the highest risk (canagliflozin hazard ratio (HR): 3.58, empagliflozin HR: 2.52, and dapagliflozin HR: 1.86).[40] In a recent meta-analysis by Colacci *et al*., although the absolute rate of DKA was low in patients using SGLT-2 inhibitors (0.6–4.9 events per 1000 patient-years), the risk was 2-fold higher.[21] In recent years, publications on cases of EDKA due to SGLT-2 inhibitors in Turkey are noteworthy.[41,42]

Table 1: Conditions associated with euglycemic diabetic ketoacidosis in patients with diabetes

SGLT-2 inhibitors (especially in patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus with low insulin reserve)
Anorexia/prolonged hunger
Pregnancy
Surgery
Trauma
Infections
Acute coronary syndrome
Acute cerebrovascular diseases
Prolonged physical exercises
Ketogenic diets
Alcohol consumption
Cocaine use
Drugs affecting carbohydrate metabolism (glucocorticoids, high-dose thiazide diuretics, sympathomimetic agents, etc.)
Hepatic and renal diseases
Acute abdomen (appendicitis, gastroenteritis, pancreatitis, cholecystitis, etc.)
Glycogen storage diseases
Pump failure in patients with insulin pumps
Interruption or discontinuation of treatment in insulin-dependent patients

SGLT-2: Sodium–glucose transporter 2

The risk was higher in type 1 DM, type 2 DM with severe insulin deficiency, patients with low glycogen storage, and patients with low body mass index.[15,20,37] Although EDKA may develop at any time after the initiation of SGLT-2 inhibitor treatment, there are data suggesting that EDKA may occur more frequently in the first 2 months of the treatment.[3,15,33,43,44] In the meta-analysis of Liu *et al*., there was a higher risk in the elderly (≥60 years) and in long-term use (>52 weeks).[45] In addition to these studies, there are also a few studies in the literature showing that SGLT-2 inhibitors do not increase the risk of DKA with some methodologic doubts.[46,47] The risk increases in patients using SGLT-2 inhibitors, especially in the presence of other causes that may cause DKA.[7]

We expect SGLT-2 inhibitors, which have recently been recommended with a class 1 level of evidence for the treatment of all types of heart failure, to be used even more widely.[31] This may increase the risk of developing EDKA, especially with inappropriate use of SGLT-2 inhibitors. Although the risk of ketoacidosis in patients without diabetes should be negligible according to large clinical trials, the risk can be reduced further with increased knowledge and awareness.[48]

All these data show that these agents are highly effective and generally safe agents when used in appropriate patients, while their use should be avoided, or caution should be exercised in risky patients.

Diagnosis

The clinical picture is similar to classic DKA. However, the diagnosis may be delayed due to the absence of hyperglycemia. Patients often present with nausea, vomiting, abdominal pain, weakness, and fatigue. Kussmaul respiration may be observed due to metabolic acidosis. Hypotension, tachycardia, dryness of mucous membranes and skin, and a decrease in skin turgor may also be observed due to dehydration. Rarely, neurologic findings, mental disorders, stupor, and coma may be observed in more severe cases with deep metabolic acidosis.[3,5,7] Patients with DM who present with these complaints but who do not have hyperglycemia and who are on SGLT-2 inhibitors should definitely be examined

for EDKA. EDKA should also be kept in mind in patients with DM who do not use SGLT-2 inhibitors but have the conditions as mentioned in Table 1.

In patients with clinical suspicion, serum glucose levels, serum electrolytes (sodium, potassium, phosphorus, calcium, and magnesium), renal and liver function tests, venous or arterial blood gas samples, and serum and/or urine ketone levels should be evaluated. Leukocyte levels, sedimentation, C-reactive protein, procalcitonin, and serum lactate levels may be evaluated in differential diagnosis and determination of triggering factors if clinically necessary. Further laboratory tests (blood culture, urine culture, amylase, lipase, troponin, etc.,) and imaging methods (chest radiography, electrocardiogram, abdominal ultrasonography, thorax computed tomography, abdominal computed tomography, etc.,) may be used if needed.

There are three ketone bodies that form and accumulate in DKA: acetoacetic acid, beta-hydroxybutyric acid, and acetone. Urinary ketone bodies are detected by nitroprusside tests, whereas serum ketones can be detected by nitroprusside testing or by direct measurement of beta-hydroxybutyrate levels. Direct measurement of serum beta-hydroxybutyrate eliminates the problems associated with nitroprusside testing (false-positive or false-negative results).[5,49] Therefore, The American College of Endocrinology recommends the use of serum beta-hydroxybutyrate levels for the detection of ketosis in EDKA.[3,15] A serum beta-hydroxybutyrate level >3 mmol/L is considered significant. If it is not available, serum acetoacetate and/or urine ketone can be used. However, their sensitivity and specificity are lower.[3] Especially in patients using SGLT-2 inhibitors, urinary ketone reabsorption may increase, and urinary ketone measurement may cause false-negative results.[3,15] The diagnostic criteria for EDKA and its comparison with DKA are shown in Table 2.

In the differential diagnosis, other causes of metabolic acidosis with increased anion gap should be excluded. These include alcohol intoxication, lactic acidosis, renal failure, metformin, salicylate, and tricyclic antidepressant intoxications. Ketoacidosis caused by excessive alcohol intake, decompensated chronic liver disease, sepsis, and fasting ketosis should also be kept in mind.[7] Acidosis is not expected in fasting ketosis. In metabolic acidosis caused by sepsis, serum lactate level is high in the absence of marked ketosis. Ketoacidosis caused by excessive alcohol intake is seen in patients with chronic alcohol use and malnutrition. Differentiation with EDKA may be difficult. Some experts consider this condition as a subtype of EDKA.[10,50]

Table 2: The diagnostic criteria for euglycemic diabetic ketoacidosis and its comparison with diabetic ketoacidosis

	EDKA	DKA
Blood glucose levels (mg/dL)	<250	>250
Arterial pH	<7.3	<7.3
Serum bicarbonate levels (mEq/L)	<18	<18
Anion gap (mEq/L)	>10	>10
Ketone levels	Ketonemia and/or ≥2+ urine ketones	Ketonemia and/or ≥2+ urine ketones

EDKA: Euglycemic DKA, DKA: Diabetic ketoacidosis

Treatment

The principles of treatment are the same as for classical DKA. The basic principles are replacement of fluid deficit, correction of serum electrolyte abnormalities, and providing appropriate intravenous insulin infusion. In addition, intravenous dextrose solution infusion with insulin is also needed both to prevent hypoglycemia that may occur as a result of insulin infusion and to improve carbohydrate deficiency. Triggering factors should be evaluated and treatments should be organized for them, if any. If SGLT-2 inhibitor use is present, the drug should be discontinued. If an infectious disease is suspected, appropriate antibiotic treatment should be initiated.[51]

Fluid replacement constitutes the first step of treatment. Fluid replacement should be given at a rate of 15–20 mL/kg/h (approximately 1–1.5 L) in the first 1–2 h. The recommended fluid is 0.9% sodium chloride (isotonic saline, NaCl) solution. After 0.9% saline solution replacement for the first 1–2 h, fluid resuscitation should be continued at a rate of 4–14 mL/kg/h (250–500 mL/h). The fluid to be given in this period is decided according to the calculated corrected serum sodium (Na^+) levels (corrected Na^+ = Measured Na^+ +2 × [(serum glucose - 100)/100]). If the corrected serum Na^+ level is high or normal, 0.45% NaCl solutions should be used, while 0.9% NaCl solutions should be used if it is low. It is aimed to replace the total fluid deficit (approximately 6–8 L) in 24–36 h.[6,51,52] There are also opinions that the first fluid of choice in treatment should be balanced crystalloids (Plasmalyte, Ringer's Lactate, etc.).[3,7,53,54] In the second stage, if the serum potassium (K^+) level is >3.5 mEq/L, intravenous insulin infusion should be started at a rate of 0.05–0.1 unit/kg/h. In addition to intravenous insulin infusion, intravenous 5% dextrose infusion should also be started. If hypoglycemia occurs, 10% dextrose infusion may be used. If the initial K^+ level is <3.5 mEq/L, potassium replacement should be given first, and then intravenous insulin infusion can be started. If the K^+ level is between 3.5 and 5.5 mEq/L, it is recommended to keep the serum K^+ level between 4 and 5 mEq/L by adding 20–30 mEq

K^+ to each 1 L of intravenous solutions. If the initial K^+ level is >5.5 mEq/L, potassium replacement should be postponed.

Renal function, volume status, cardiac reserves, and urine output should be taken into consideration while regulating fluid and K^+ replacement. Phosphate support may be required in patients with serum phosphate levels <1 mg/dL. Sodium bicarbonate replacement is not recommended unless pH <7.0.[3,6,51] The patient's blood glucose level should be maintained between 150 and 200 mg/dL by adjusting the rates of dextrose and insulin infusion. Until the patient starts taking in food orally and the acidosis and ketonemia/ketonuria improve, intravenous dextrose and insulin infusion should be continued. During the treatment, serum glucose, urea, creatinine, electrolyte levels, and blood gas samples should be monitored every 2–4 h in addition to hourly fingerstick capillary glucose sampling. Subcutaneous insulin therapy may be started after the acidosis resolves (pH >7.3 and serum bicarbonate >18 mEq/L) and the patient starts oral food intake. Intravenous insulin infusion should be continued for 1–2 h after subcutaneous insulin is administered to avoid hyperglycemia.

It is important to review the patient's DM treatment plan. Restarting SGLT-2 inhibitors should be carefully considered in patients who develop EDKA due to SGLT-2 inhibitor use. The choice should be taken in accordance with the estimated benefit-loss from the course of treatment. Caution should be taken into consideration in patients with a high risk of EDKA/DKA recurrence and other precipitating factors. If it is chosen to restart the SGLT-2 inhibitor, treatment should not begin until the triggering factors of EDKA have been resolved. If there is no triggering factor other than the use of SGLT-2 inhibitor, it would be a better option not to start the SGLT-2 inhibitor again.

To reduce the risk of EDKA, the treatment should be stopped in patients who use SGLT-2 inhibitors and have other risk factors for DKA. "Sick day rule" should be explained to patients in detail. Patients should temporarily stop SGLT-2 inhibitor in situation of vomiting, diarrhea, inability to eat or drink, acute illness, heavy and prolonged exercise, and at least 48 h before planned surgery.[3,7,15,20] It would be more appropriate not to start SGLT-2 inhibitors without replacing insulin in patients with low insulin reserve. Patients at risk for DKA who are on SGLT-2 inhibitors for possible clinical benefits should be warned, informed, and followed up closely.

Conclusion

With the widespread use of SGLT-2 inhibitors in recent years, EDKA cases, which have been increasing in frequency among DKA cases, should be taken into consideration, especially in emergency departments. Patients who present with symptoms resembling those seen in a DKA clinic but who have normal blood glucose levels should certainly be evaluated for EDKA. It should be kept in mind that the use of SGLT-2 inhibitors, prolonged fasting, pregnancy, infections, alcohol use, and chronic liver diseases are risk factors for EDKA. Missing these patients may have serious and fatal consequences. Identifying patients at risk, clinical suspicion, accurate diagnosis, and rapid and appropriate treatment can be life-saving.

Author contributions statement

- Murat Dagdeviren: Conceptualization, methodology, investigation, software, resources, data curation, writing – original draft
- Tolga Akkan: Conceptualization, methodology, investigation, software, resources, data curation, writing – review and editing
- Derun Taner Ertugrul: Conceptualization, methodology, investigation, writing – review and editing, supervision.

Conflicts of interest

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