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EUGLYCEMIC DIABETES KETOACIDOSIS ASSOCIATED WITH SGLT-2 INHIBITORS - REVIEW OF CASE REPORTS

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ABSTRACT:

AIM: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have gained significant importance in the treatment of type 2 diabetes mellitus. One of the adverse effects while using SGLT-2 inhibitors is euglycemic ketoacidosis (euDKA) - acute life-threatening emergency.

METHODS: The following review of case reports was based on articles published in 2023, obtained from the PubMed databases. Key search terms included “case report”, “sglt-2”, “sglt-2i”, “sodium-glucose cotransporter inhibitors”, “dka”. “eudka”, “euglycemic ketoacidosis”.

RESULTS: In the literature, cases of euDKA correlated with the use of SGLT-2 inhibitors are described.

CONCLUSION: There is a need for greater observation of the frequency of the adverse effects in patients taking sodium-glucose cotransporter inhibitors (SGLT-2i) and for raising awareness

among doctors about the possibility of developing euglycemic diabetic ketoacidosis during the SGLT-2 inhibitors therapy.

Key words: sodium-glucose cotransporter inhibitors; sglt-2 inhibitors; euglycemic ketoacidosis; diabetes mellitus type 2

INTRODUCTION:

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are commonly used medications that have gained significant importance in the treatment of type 2 diabetes mellitus in recent years. SGLT-2 inhibitors target and block the action of SGLT-2 protein in the renal tubules, preventing the reabsorption of glucose. Increased glucose excretion contributes to lowering the blood glucose levels. While SGLT-2 inhibitors are generally well-tolerated, like any medications, they have potential adverse effects. The most frequently reported adverse events with SGLT-2 inhibitors are female genital mycotic infections, urinary tract infections, increased urination, nausea, and constipation. [17]

In 2015 the United States Food and Drug Administration (FDA) issued a warning regarding the risk of diabetic ketoacidosis (DKA) with SGLT-2i. [13] It is a serious complication of diabetes, whose symptoms typically include nausea, vomiting, abdominal pain, weakness, fatigue, shortness of breath, excessive thirst and frequent urination.

Diagnostic criteria for ketoacidosis based on Szczeklik's Internal Medicine [15]:

- mild: blood glucose greater than 13,9 mmol/l (250 mg/dl), arterial pH 7,25-7,30, serum bicarbonate 15-18 mmol/l, anion gap >10 mmol/l, and the presence of ketonemia or ketonuria. The patient is conscious.
- moderate: blood glucose greater than 13,9 mmol/l (250 mg/dl), arterial pH 7,00-7,24, serum bicarbonate 10-14,9 mmol/l, anion gap >12 mmol/l, and the presence of ketonemia or ketonuria. The patient is conscious, but may be disoriented.
- severe: blood glucose greater than 13,9 mmol/l (250 mg/dl), arterial pH less than 7,00, serum bicarbonate less than 10 mmol/l, anion gap >12 mmol/l, and the presence of ketonemia or ketonuria. The patient has disorders of consciousness - dementia or coma.

DKA is more common in type 1 diabetes mellitus than type 2 diabetes mellitus (50-100 and 4,6-8 episodes per 1000 patients, respectively) [9]

Although DKA is typically associated with marked hyperglycemia and resultant dehydration, it can occur with only a moderate increase in blood glucose levels or, in rare instances, in setting

of normal glucose concentrations. This latter, uncommon form of DKA, know as euglycemic or normoglycemic DKA, was originally defined as DKA with blood glucose level of <300 mg/dL, but it is now recognised as that in the presence of blood glucose concentration of <200 mg/dL. [26]

While conducting research on PubMed, we found only 5 case reports of euglycemic diabetic ketoacidosis (euDKA) associated with SGLT inhibitors published in the medical literature in 2023.

MATERIALS AND METHODS

The following review of case reports was based on articles published in 2023, obtained from the PubMed databases. Key search terms included “case report”, “sglt-2”, “sglt-2i”, “sodium-glucose cotransporter inhibitors”, “dka”. “eudka”, “euglycemic ketoacidosis”.

RESULTS AND DISCUSSION

Case patient	1	2	3	4	5	6	7	8	9	10	11
Age (years)	56	43	74	67	61	54	34	28	64	63	70
Sex	female	male	male	female	male	female	male	male	male	male	male
Insulin/oral	oral	oral	insulin + oral		oral	oral	oral	insulin + oral	oral	oral	oral
SGLT-2i type	E	E	E	E	D	D	D	E	D	D	D
Dose (mg)	12,5			25	10		2 x 5	10	5	10	10

Table 1 - basic information about patients (oral - oral medications, D - dapagliflozin, E - empagliflozin)

Report cases:

FIRST CASE: 56-year-old female with a past medical history of type 2 diabetes mellitus (T2DM) presented to the emergency department with a one-week history of chest pain and generalized weakness. [34] She denied nausea, vomiting, abdominal pain, shortness of breath, fever. The patient was diagnosed with diabetes mellitus about one year back. Then she had an episode of DKA and pancreatitis - probably associated with COVID-19 infection. Originally,

she was treated with insulin for three months, and then the therapy was changed to oral medications. For about nine months she was taking oral medications such as: glimepiride 4 mg twice daily, metformin 1000 mg twice daily, and Empagliflozin 12,5 mg. Due to the electrocardiogram (ECG) findings (premature ventricular contractions and ST-segment depression) and non-obstructive coronary artery disease (after catheterisation was performed) the patient was managed under the presumption of myocardial infarction with non-obstructive coronary arteries (MINOCA). Cardiologist recommended aspirin and statin as a treatment. Concurrently, the patient was diagnosed with probable euglycemic DKA due to laboratory results (table 2, table 3). Treating DKA and correcting electrolyte abnormalities with aggressive resuscitation measures such as intravenous fluid administration and initiation of insulin drip lead to resolution of symptoms and ECG abnormalities. Type 1 diabetes mellitus was excluded - GAD antibodies and pancreatic antibodies were negative.

SECOND CASE: 43-year-old Asian man with a past history of myocardial infarction, hypertension, and type 2 diabetes mellitus initially presented to the Veteran Affairs hospital for intermittent chest pain which has been ongoing for several days [7]. He has no further investigation and treatment associated with earlier myocardial infarction. He was taking medication such as atorvastatin, carvedilol, lisinopril, nitroglycerine, aspirin, and empagliflozin. The patient underwent Coronary Artery Bypass Grafting due to ECG findings, high serum troponins levels, and results of coronary artery imaging tests. However, by looking at his laboratory findings euglycemic diabetic ketoacidosis was diagnosed (table 2, table 3). The results of C-peptide, islet cell antibodies, IA-2, ZnT-8, and glutamine acid decarboxylase-65 antibodies were within normal limits, which excluded the possibility of type 1 diabetes mellitus causing euglycemic diabetic ketoacidosis. Further treatment of diabetes relied on subcutaneously administered insulin: glargine 8 Units at bedtime and rapid-acting insulin before meals.

THIRD CASE: 74-years-old male with a history of type 2 diabetes mellitus, hypertension, ischemic stroke, peripheral arterial disease, bilateral non-obstructive renal artery stenosis, chronic right internal carotid artery occlusion, seizures, and vascular dementia presented to emergency department from a local nursing home due to decreased oral intake and dehydration for at least the past week. [28] He was sarcopenic-appearing with dry mucus, hypotension and tachycardia. His diabetic regimen was revealed as both insulin glargine and aspart, and SGLT-2i. Empagliflozin once daily was initiated one month ago. Based on results of laboratory tests the patient was diagnosed with euDKA with acute renal failure (Table 2, table 3). After

admission to an intensive care unit the treatment protocol for diabetic ketoacidosis was started. A week later the patient returned to the nursing home with metformin and subcutaneous insulin as a diabetic treatment.

FOURTH CASE: 67-year-old female with a past medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, and atrial fibrillation on apixaban for coagulation presented to the hospital for intractable abdominal pain, shortness of breath, and chest pain. She reported worsening abdominal pain over the last few days, along with nausea and reported episodes of vomiting. [16] The pain was mid-gastric, it radiated to the back and got worse with positional movement. Acute pancreatitis with euglycemic ketoacidosis was diagnosed based on the results of laboratory tests (Table 2, Table 3) and abdominal computed tomography. She denied past medical history of gallstones, autoimmune disease, any alcohol use, or recent trauma. She was taking medications such as atenolol 50 mg, apixaban 5 mg, empagliflozin 25 mg (started two weeks before symptom onset). The patient was treated with subcoutanous inulin, nothing by mouth, intravenous fluid, antiemetics, and intravenous morphine.

FIFTH CASE: 61-years-old man who was admitted to the emergency department with chest pain, generalized weakness, polyuria, vomiting, and nausea for several days. The medical history of patient includes: six years of type 2 diabetes mellitus and 10 years of hypertension. [3] He was taking medications such as amlodipine/perindopril 10/5 mg, metformin 1000 mg twice daily, dapagliflozin 10 mg (added 1 month ago). Dry oral mucosa and decreased skin turgor tonus were the only abnormalities noted on physical examination. Biochemical blood and urine examinations revealed euglycemic ketoacidosis (Table 2, Table 3). Nausea and vomiting were worsened even after administration of intravenous fluid, insulin, and sodium bicarbonate. The patient began to have chest pain and Kussmal respiration and arterial pH decreased to 6,81. Coronary angiography showed left anterior descending artery occlusion and percutaneous coronary intervention was successfully performed. With the continuation of euglycemic diabetic ketoacidosis treatment, the patient's condition was improving. He was discharged with vildagliptin/metformin 50/1000 mg twice daily and insulin glargine subcutaneous 1x 14 unit once daily as a diabetic treatment.

SIXTH CASE: A 54-year-old female with a history of diabetes on metformin and dapagliflozin presented after several days of typical chest pain, accompanied by intractable nausea and vomiting. (36) She has a history of diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, hypertension, and tobacco abuse. Due to ECG findings (ST-elevation in the inferior leads with ST-depression in lead V1-V2) catheterisation was performed

- thrombus in the right coronary artery (RCA) and mild coronary artery disease (CAD) in left anterior descending (LAD) and left circumflex (LCX) arteries. After revascularization and the patient continuously having nausea and vomiting, euglycemic diabetic ketoacidosis was diagnosed based on laboratory findings (table 2, table 3). Her clinical condition improved after intravenous hydration and intravenous insulin treatment.

SEVENTH CASE: A 34-year-old male, diagnosed with T2DM four years before, presented to the emergency room with epigastric pain, nausea, vomiting, generalized body weakness, and shortness of breath. (31) Four days prior to consultation the patient had a motor vehicular accident. Computed tomography scan performed after the accident showed unremarkable results. He was treated with dapagliflozin + metformin (5mg + 1000 mg) twice daily. The patient had not been monitoring their blood glucose levels at home and had not had a follow-up visit in three years. Euglycemic diabetic ketoacidosis was diagnosed based on laboratory results(table 2, table 3) His clinical condition improved through intravenous hydration, insulin therapy, and administration of sodium bicarbonate.

EIGHTH CASE: A 28-year-old male, after post-percutaneous coronary intervention (PCI) to LAD due to non-ST elevated myocardial infarction status performed five days ago and newly diagnosed type 2 diabetes mellitus presented to the emergency department with dyspnea, nausea, vomiting, food intolerance, chills, dizziness, lightheadedness, and constipation for one day. (27) Upon PCI, the patient was started on aspirin, insulin glargine, insulin aspart, metoprolol, rosuvastatin, ticagrelor, pantoprazole, and empagliflozin. A euglycemic diabetic ketoacidosis was diagnosed based on laboratory results (table 2, table 3). The patient clinical condition has improved after administration of sodium bicarbonate, intravenous hydration and intravenous insulin therapy.

NINTH CASE: A 64-year-old male who is overweight (body mass index: 28,2 kg/m2) and has T2DM was transferred to the emergency department of Toyama Red Cross Hospital after losing consciousness following severe chest pain while driving, resulting in a car crash into the roadside wall. (14) He has atrial fibrillation and ST segment depression in lead II, III, aVF and V5-V6 in ECG. The patient was treated with dapagliflozin for the past 6 months and restricted diet for the past 2 months. Coronary angiography, performed after resolving euDKA, revealed diffuse coronary vasospasm and 90% stenosis of RCA. The patient was diagnosed with vasospastic angina, as well as euDKA based on laboratory test results (table 2, table 3). Insulin therapy, sodium bicarbonate, intravenous hydration, apixaban and aspirin were administered.

TENTH CASE: A 63-year-old male with non-obese T2DM, mitral regurgitation, and atrial fibrillation was transferred to emergency department of Toyama Red Cross Hospital with excruciating chest pain from exertion, nausea, upper abdominal pain, appetite loss for the past 3 months, and general malaise for 2 months. (19). He was taking dapagliflozin for glycemic control. In addition to atrial fibrillation, the ECG showed ST segment depression in leads V5-V6 and a flat T wave in leads II, III, and aVL. There was no organic stenosis in coronary angiography, but the baseline image showed spasticity. The patient was diagnosed with vasospastic angina, as well as euDKA based on laboratory test results (table 2, table 3). After administering insulin therapy and intravenous hydration, serum ketones returned to normal.

ELEVENTH CASE: A man in his seventies after planned heart catheterization, due to fatigue, weakness, dyspnea on exertion, and abnormal stress test result, presented acute mental status changes, including aphasia and severe agitation. (20) He was treated with glipizide, metformin, dapagliflozin and lisinopril. Computed tomographic scan of the head showed no acute intracranial hemorrhage, mass, or parenchymal changes. The patient was diagnosed with encephalopathy secondary to hypertension. Based on laboratory test results euDKA was diagnosed (table 2, table 3). After administration of euDKA treatment the patient's mental status improved.

CASE	1	2	3	4	5	6	7	8	9	10	11
Glucose (mg/dl)	173	107	185	188	171	135	230	154	163	112	117
Sodium (mmol/L)	135	137	145	138	136		134	135	144	138	140
Potassium (mmol/L)	2,5	4,3	6,6	4,2	5,03	3,2	5,2	5,8	4	5,6	4,3
Chloride (mmol/L)		104	106	89	102		97,7	101	105	97	106
Bicarbonate (mmol/L)	13	18	8	15	5,6		1,88	< 5	13	15,3	
Anion gap (mmol/L)	31	15	31	24	34	high	35,34	undec.	25,8	26	20
HbA1c (%)	7,1	11,2		10,2			14	11,1	9,1	6,5	
pH	7,28		7,09		7,09	< 7,35	6,79	7,05	7,67	7,3	< 7,35

pCo2 (mmHg)	32,2						63,08	25,5	11,8	29,3	17
Beta-hydroxybutyrate mmol/L	0,3		31,5			0,4		9	1,3	8,6	3,38
BUN (mg/dL)		23	207	26	23				19	25	
Creatinine (mg/dL)		0,77	10,2	0,81	1,02		normal		0,78	0,99	
Lactic Acid (mmol/L)		1,3	4,4	3,5				2,1			

Table 2 - The table shows the values of laboratory parameters in blood for individual patients described in the case reports. BUN - blood urea nitrogen, undet. - undetectable

CASE	1	2	3	4	5	6	7	8	9	10	11
Urine Glucose		positive		positive	positive		positive	positive			positive
Urine ketones		positive		positive	positive	positive	positive	positive	positive	positive	positive

Table 3 - The table shows the values of laboratory parameters in urine for individual patients described in the case reports.

Based on strong findings obtained from large clinical randomized studies, SGLT-2 inhibitors are recommended in cardiovascular, endocrine, and renal studies.[3,5,18, 30]. In clinical recommendation of the Polish Diabetological Society, the drugs recommended to be considered as first-line treatment for initiating pharmacological therapy for type 2 diabetes mellitus are SGLT-2 inhibitors. Especially preferred for individuals with cardiovascular diseases, multiple risk factors, or patients with chronic kidney disease. [2]

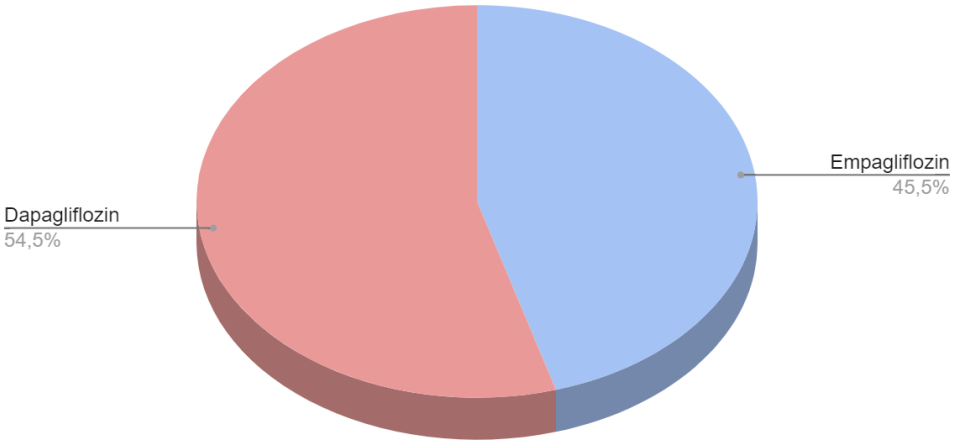

Figure 1 shows SGLT-2 inhibitors used in reviewed report cases.

In the summary of product characteristics for Forxiga, the only available dapagliflozin on the Polish market, ketoacidosis is described as a "rare adverse reaction". Manufacturer AstraZeneca recommends discontinuation treatment in patients hospitalized due to major surgical procedures or acute severe illness. It is not recommended to resume SGLT-2 inhibitor treatment in patients who previously experienced ketoacidosis while using SGLT-2 inhibitors unless another clear cause has been identified and removed. [10] A similar recommendation is found in the summary of product characteristics of empagliflozin produced by Boehringer Ingelheim (Jardiance) [11]. SGLT-2 inhibitors induce urinary glucose excretion ranging 50-100 g/day - that glucose loss may constitute a significant portion of daily carbohydrate availability. If the glucose availability decreases, the amount of insulin produced by pancreatic beta-cells decreases as well - this results in increased glucagon levels due to reduced paracrine inhibition by insulin [24], and possibly decreased glucose transport into alpha cells (mediated by SGLT-). [4]
The elevated glucagon/insulin rate activates lipases and the release of free acids and hepatic ketone production. [29]

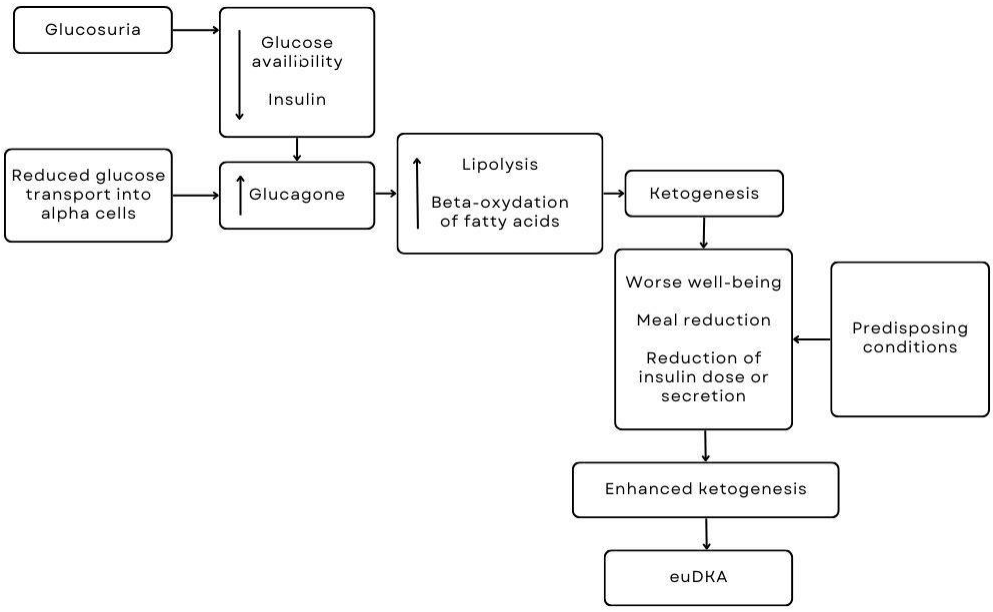

Figure 2. Possible mechanism of euglycemic ketoacidosis induced by SGLT-2 inhibitors.

There are many conditions predisposing to euglycemic ketoacidosis, for example: anorexia, gastroparesis, fasting, use of ketogenic diet, alcohol use disorder, pregnancy, pancreatitis, glycogen storage disorders, surgery, infection, cocaine toxicity, cirrhosis, insulin pump use. [23] These include low reserves of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin. [12]

ECG changes

Electrolyte abnormalities in the course of DKA can cause transient changes in ECG such as ST depression, prolongation of the QT interval, abnormalities of the T wave, and prominent U waves. [6, 14] The pathomechanism of their formation is probably secondary primarily to hyperkalemia. [6, 14]. In the literature ST-segment elevation mimicking myocardial infarction due to hyperkalemia is described as “pseudoinfarction” pattern. (21,33). The authors found several case reports describing patients with ECG changes in the course of DKA, which resolved after correcting the potassium levels. [21, 25, 32, 35, 8, 22]. In addition to transient ST elevation, the described patients also exhibited intraventricular conduction disturbances or bundle branch block. The changes occurred at potassium levels of 7,2-8,9 mmol/L.

CASE	1	2	3	4	5	6	7	8	9	10	11

Potassium (mmol/L)	2,5	4,3	**6,6**	4,2	5,03	3,2	5,2	**5,8**	4	**5,6**	4,3

Table 4. Potassium levels in described report cases.

In described report cases only two patients have elevated potassium level (Table 4) and only one of them has ECG abnormalities. The authors found one case report where a pseudo-infarct pattern occurs in DKA with normokalemia. [1]

It should be noted that in 6 patients (Table 5), ECG changes were associated with chest pain and changes observed in coronary angiography. Therefore, this is not a pseudo-infarct pattern. In cases of chest pain and ECG changes, a thorough diagnostic process should be conducted, including biochemical tests, imaging studies, and angiography, to exclude acute coronary syndrome before diagnosing a pseudo-infarct pattern.

CASE	**1**	**2**	3	4	**5**	**6**	7	8	**9**	**10**	11
chest pain	**yes**	**yes**	no	yes	**yes**	**yes**	no	no	**yes**	**yes**	no
ECG changes	**ST-depression**	**T-wave inversion**	no	no	**ST-elevation**	**ST-elevation, ST-depression**	no	ST-depression	**ST-depression**	**ST-depression, flat T wave**	no
troponin levels ng/dL	**negative**	**positive > 600**	stable	-	**161, 186**	**0,13**	-	-	-	-	-
Coronarography findings	**MINOCA - CAD 30% stenosis of LAD**	**multivessel disease, high-grade stenosis: LAD, LCX, RCA, apical hypokinesis**	-	-	**occluded LAD**	**ruptured 90-95% ulcerated plaque with thrombus in the RCA, mild CAD is LAD, LCX**	-	not performed (PCI five days ago)	**vasospasm, 90% stenosis of RCA**	**vasospasm**	-

Table 5 - Comparison of symptoms and tests for acute coronary syndrome in described cases. ("-" - not performed, CAD - coronary artery disease

CONCLUSION:

SGLT-2 inhibitors are increasingly prescribed medications not only in patients with diabetes mellitus but also in others due to cardio-renal protective profile. The number of available preparations on the market is increasing. However, it should be remembered that these are not medications free from adverse effects, including life-threatening ones. There is a need for

greater observation of the frequency of the adverse effects in patients treated with SGLT-2 inhibitors and for raising awareness among doctors about the possibility of developing euglycemic diabetic ketoacidosis, while treatment.

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