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Euglycemic ketoacidosis in elderly patients using SGLT2 inhibitors

Euglikemiczna kwasica ketonowa u osób starszych stosujących inhibitory SGLT2

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Abstract

Type 2 diabetes, heart failure, chronic kidney disease and obesity are common conditions in the elderly population. In their treatment, new effective therapeutic strategies are constantly being sought. Sodium-glucose transporter 2 inhibitors (SGLT2i) are a promising group of drugs with proven activity in these indications Euglycemic ketoacidosis (euDKA), which can be difficult to diagnose leading to delays in treatment, is a characteristic but rare side effect of this group of drugs. Factors such as infections, malnutrition, changes in insulin therapy or the perioperative period, which are common in the elderly, can promote the occurrence of this complication. With the aging of the population and the increasing use of flozins, an increase in the number of euDKA cases can be expected. Therefore, it is crucial to develop effective methods for rapid diagnosis, treatment and prevention of this risk in this group of patients. (Gerontol Pol 2025; 33; 38-45) doi: 10.53139/GP.20253301

Keywords: *geriatrics, SGLT2i, euglycemic ketoacidosis, flozins.*

Streszczenie

Cukrzyca typu 2, niewydolność serca, przewlekła choroba nerek i otyłość to częste schorzenia w populacji osób starszych. W ich leczeniu nieustannie poszukuje się nowych, skutecznych strategii terapeutycznych. Jedną z obiecujących grup leków o udowodnionym działaniu w tych wskazaniach są inhibitory transportera sodowo-glukozowego 2 (SGLT2i). Charakterystycznym, choć rzadkim działaniem niepożądanym tej grupy leków jest euglikemiczna kwasica ketonowa (euDKA), której rozpoznanie może być trudne, co może prowadzić do opóźnień w leczeniu. Czynniki takie jak infekcje, niedożywienie, zmiany w insulinoterapii czy okres okołoperacyjny, które są częste u osób starszych, mogą sprzyjać wystąpieniu tego powikłania. Wraz ze starzeniem się społeczeństwa i coraz szerszym stosowaniem flozyn, można spodziewać się wzrostu liczby przypadków euDKA. Dlatego kluczowe znaczenie ma opracowanie skutecznych metod szybkiego rozpoznawania, leczenia oraz zapobiegania temu ryzyku w tej grupie pacjentów. (Gerontol Pol 2025; 33; 38-45) doi: 10.53139/GP.20253301

Słowa kluczowe: *geriatria, SGLT2i, kwasica euglikemiczna, flozyny*

List of abbreviations:

DK – diet ketogenic
DKA – diabetes ketoacidosis
DM1 – type 1 diabetes mellitus
DM2 – type 2 diabetes mellitus
eGFR – estimated glomerular filtration rate
euDKA – euglycemic diabetes ketoacidosis
FAERS – FDA Adverse Event Reporting System
SGLT2i – sodium glucose co-transporter 2 inhibitors
FDA – Food and Drug Administration
HHS – hyperglycemic hyperosmolar state

Introduction

According to the Database of System and Implementation Analysis, 2.65 million people in Poland suffered from diabetes in 2018, accounting for 8% of the country's adult population [1]. Data from the National Health

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Fund show that in Poland, PLN 6.073 million was spent on diabetes-related treatment in 2017. Of this amount, PLN 2.825 million (46.5%) was spent on health services and drug reimbursement for people with diabetes, while PLN 3.248 million (53.5%) was spent on treating other comorbidities in patients with diabetes [2]. Type 2 diabetes mellitus (DM2) accounts for 90% of all diabetes cases worldwide [3]. The elderly are the main group of patients with type 2 diabetes, and the number of patients over the age of 65 is constantly increasing. According to estimates, one in five people in this age group is struggling with DM2. In Poland, the average age at first diagnosis of DM2 is 62 [1]. It was reported that between 2013 and 2017, the prevalence of DM2 increased by an average of 3.7% per year. This increase consisted of 1.2% related to the aging of the population and 2.5% due to an actual increase in the number of people diagnosed with diabetes. About 20% of people with diabetes in Poland are unaware of their disease, suggesting that the actual number of patients may exceed 3 million [4]. In addition, older people with diabetes often face a number of comorbidities, such as obesity, heart failure and chronic kidney disease, which affects up to 50% of people over the age of 70 [5]. This is also confirmed by the PolSenior study, which indicates that 80% of seniors over 65 suffer from multimorbidity and take an average of 4.2 prescription drugs. The phenomenon of polypharmacy, which is associated with a higher risk of side effects from individual medications, causes difficulties in adhering to medical recommendations, while in geriatric medicine it is crucial to use the most cost-effective approach to treatment [6]. In response to these challenges, new therapeutic strategies are being sought, among which sodium glucose cotransporter 2 inhibitors (SGLT2i) have gained particular popularity [7]. The mechanism of action of these drugs is to block the SGLT-2 transporter in the renal proximal tubule, preventing glucose reabsorption. As a result, glucose is excreted in the urine, leading to a reduction in blood glucose concentrations. A new chapter in the use of flozins has been opened by the confirmation of their effectiveness in protecting organs such as the heart and kidneys. Other advantages of this group of drugs include a beneficial effect on weight reduction, a reduced risk of hospitalization for exacerbation of heart failure or a reduction in the incidence of cardiovascular incidents. The broad applicability of flozins means that they are increasingly being used in the elderly population for a variety of indications [5,8]. However, these drugs are not without side effects. The literature indicates that their use may increase the risk of urinary tract infections, as well as lead to hypovolemia or hypotonia. This is of particular concern in the elderly, as the consequences of falls in this age group can lead to increased mortality [8]. Euglycemic ketoacidosis (euDKA) is another rare condition associated with their use. Because of its unusual course, its diagnosis and treatment may be delayed, with serious health risks. This is especially true in the elderly, in whom factors specific to the geriatric population, such as malnutrition, irregular insulin use and the presence of infection, may further increase the risk of this complication [9,10]. The aging population and the comprehensive pharmacological properties of SGLT2i make these drugs increasingly important in the treatment of seniors. Improved reimbursement conditions further increase their availability to the elderly. The aim of the present study was to analyze research on the relationship between SGLT2i use and the incidence, treatment and preventability of euDKA in this age group.

Mechanism of action, efficacy and safety of SGLT2i in the elderly

The first SGLT2i drug, canagliflozin, was launched in Europe, including Poland, on November 15, 2013. Currently, dapagliflozin, empagliflozin, and ertugliflozin are also available in Poland. These preparations are taken once a day in oral form [11]. The mechanism of action of these drugs is based on blocking the SGLT2 transporter in the proximal tubule of the kidney, resulting in the occurrence of glucosuria. As a result of this blockade, there is a steady urinary excretion of glucose of 40-80 g per day. In addition, there is some increased sodium excretion, leading to increased osmotic diuresis and decreased intravascular volume. In addition, other positive effects have been proven for this group of drugs. In a meta-analysis of patients with a mean age of 56.9 years, it was shown that the use of SGLT2i reduced HbA1c levels by 0.5-0.7% after 12 weeks of treatment. [12]. The CANVAS trial showed that in patients older than 65 years, treatment with canagliflozin was associated with a 20% reduction in the risk of a composite endpoint including death from nonfatal myocardial infarction, nonfatal stroke and cardiovascular causes. In a subanalysis of the VERTIS-CV trial, ertugliflozin was shown to reduce the risk of hospitalization for heart failure by 36% in patients with a mean age of 64.2 years during a 3.5-year follow-up [13]. Lunati et al. showed that at 12-month follow-up, SGLT2i significantly reduced body mass index in patients with a mean age of 75.4 years [5]. This is explained by the fact that SGLT2 inhibition reduces body weight, initially due to a diuretic effect and then by shifting substrate utilization from carbohydrates to lipids [9]. In a study involving 71.122 subjects with a mean

age of 61.3 years, it was shown that initiation of SGLT2 inhibitor therapy was associated with a slower decline in estimated glomerular filtration rate (eGFR). The difference in the rate of eGFR decline for SGLT2 inhibitors compared to other glucose-lowering drugs was 1.53 ml/min/1.73 m, per year (95% CI 1.34-1.72; $p < 0.0001$). These results confirm that long-term use of SGLT2i mitigates glomerular damage [14]. In 2023, these drugs were added to the "S-list" and included in the free availability for people over 65 who meet certain criteria [15]. However, it is important to consider the potential side effects of these drugs. Among the most commonly cited side effects of SGLT2i are genital infections. In addition, they can cause kidney damage, dehydration and increase the risk of fractures as a consequence of decreased bone density. One of the more serious conditions associated with the use of these drugs is euDKA, which deserves special attention, especially since it often occurs in the context of triggers such as infections, dehydration or insulinopenia – problems that are commonly encountered in the elderly [12,13,14]. In May 2015, the Food and Drug Administration (FDA) issued a cautionary message that reported 73 cases of euDKA in patients using SGLT2i drugs based on case analysis. It noted that in many situations, euDKA was diagnosed late due to abnormally low glucose levels that deviated from values characteristic of classic diabetic ketoacidosis (DKA), making it difficult to initiate treatment quickly [16]. The literature also reports cases of euDKA in patients without DM2 who were receiving SGLT2i for heart failure and chronic kidney disease [17,18]. It is indicated that euDKA accounts for 10% of initially diagnosed cases of DKA [19]. It is currently estimated that the incidence of euDKA in patients treated with SGLT2i ranges from 0.16 to 0.76 cases per 1000 patients per year [9].

Definition of euglycemic acidosis

EuDKA is defined as an acute, life-threatening condition characterized by increased metabolic acidosis with an elevated anion gap, the presence of ketonemia or ketonuria, and a blood glucose level that does not exceed 250 mg/dl [47,19]. The absence of hyperglycemia distinguishes euDKA from typical ketoacidosis, which is often the first symptom of previously undiagnosed type 1 diabetes [20]. It is its atypical course that its diagnosis, and thus proper treatment, can be significantly delayed which in turn increases the risk of serious, life-threatening complications [17]. Another dangerous acute condition that can occur in people with late-diagnosed or inadequately treated type 2 diabetes is hyperglycemic-hyperosmolar syndrome (HHS). It is characterized by different features compared to DKA and euDKA, such as higher glycemic levels, greater severity of dehydration, and differences in the presence of ketosis and acidosis [21]. The main differences between DKA and euDKA and HHS are included in table I.

EuDKA most often occurs in patients with limited glycogen reserve or high levels of glucosuria, such as from alcohol abuse, liver dysfunction or pregnancy. Other triggers include fever, infections, the postoperative period, a low-calorie diet, cocaine intoxication or a low-carbohydrate diet [17,22]. The pathophysiology of euDKA is assumed to be due to an increased ratio of glucagon to insulin. The mechanism of action of SGLT2i leads to the occurrence of glucosuria, even when blood glucose levels are within normal limits. This results in carbohydrate deficiency and increased glucagon levels. This is followed by increased reabsorption of ketones. In addition, the increased ratio of glucagon to insulin causes lipolysis and an increase in free fatty acids, which are converted into ketone bodies. Physiological disturbances, such as infection or the perioperative period, can lead to an increase in counter-regulatory hormones, which promotes ketosis, increased glycemia and osmotic diuresis. The use of SGLT2i causes continuous glucose diuresis, resulting in lower blood glucose levels [23]. In addition, some authors suggest other mechanisms for the formation of euDKA. It has been shown that phlorizin, the natural compound from which SGLT2 inhibitors are derived, can increase the reabsorption of ketone bodies in the renal tubules. Another study showed increased levels of glucagon, cortisol and catecholamines enhance lipolysis and ketogenesis in SGLT2i-induced hypovo-

Table I. Comparison of metabolic parameters in DKA, euDKA, and HHS. [7,9,19,21]

Parameter	Standard	DKA	euDKA	HHS
Blood glucose concentration [mg/dl]	80-130	>250	<250	>600
pH of blood	7.35-7.45	<7.30	<7.30	>7.30
Bicarbonate concentration [mEq/l]	22-26	<18	<18	>18
Ketones in serum or urine	none	present	present	none/trace
Anion gap [mEq/l]	0	>10	>10	<12
Plasma osmolality [m Osm/kg/H_2O]	280-300	variable	no data	>320

euDKA-euglycemic diabetes ketoacidosis, DKA-diabetic ketoacidosis, HHS-hyperosmolar hyperglycemic state

lemic states [24]. The presence of dementia can hinder effective diabetes management in the elderly [25]. Such changes in therapy, as well as withdrawal of insulin itself or insulin-stimulating drugs such as sulfonylurea derivatives, have been described as a possible cause of euDKA associated with SGLT2i inhibitor therapy [26].

Euglycemic acidosis with a focus on the elderly population

During the 9-year study period, a gradual increase in the population incidence of DKA was observed, which may be related to the increasing frequency of SGLT2i prescribing [18]. He et al., using data from the FDA Adverse Event Reporting System (FAERS), investigated the incidence of euDKA and DKA after use of flozins. The use of SGLT2i was more frequently associated with the occurrence of euDKA and DKA compared to other hypoglycemic drugs. The median age of patients enrolled was 54.2 years, and the majority of cases occurred in the first month of flozins use. Nausea and vomiting were more common in SGLT2i-induced euDKA compared to classic DKA, whereas acute kidney injury occurred more frequently in cases of classic DKA. It should be noted that acute life-threatening conditions developed in 27.7% of patients using SGLT2i with euDKA and 19.8% with DKA, which was statistically significant. The study authors suggest that this may have been due to the more difficult identification of euDKA [27]. A retrospective analysis of seven cases of patients with a diagnosis of euDKA aged 51 to 74 years showed that euDKA symptoms mimicked those of DKA in the form of accelerated breathing, confusion, thirst, vomiting, abdominal pain, nausea, loss of appetite and weakness [24]. In addition, triggers for euDKA were dehydration, starvation, infection and abrupt termination of insulin therapy. Schwarzfuchs et al. compared the outcomes of patients hospitalized for initially diagnosed classic diabetic ketoacidosis (DKA) in two age groups: under 65 and over 65. They showed that 5.1% of initially diagnosed cases of DKA in patients over 65 were euDKA. An interesting result was that the rate of in-hospital mortality in senior patients was significantly higher, at 16.7%, compared to 1.6% in those under 65. In addition, hospitalization was longer in seniors and the risk of recurrent DKA was higher [28]. Liu et al. described nine cases of patients with symptoms of diabetic ketoacidosis whose glycemic levels were <250 mg/dl. The researchers point out that due to low glycemic levels, treatment was delayed in these patients. In addition, it was proven that DKA was more common in patients over 60 years old [29]. Yun et al. indicate that neurocognitive disorders are more common in older diabetic patients and limit their ability to control glycemic levels. In addition, disorders of the thirst center, nutritional deficiencies, and concurrent use of diuretics may be risk factors for euDKA, increasing the susceptibility of this population [10]. Rathore et al. described the case of a 74-male, nursing home resident with frailty syndrome, malnutrition who developed euDKA. The authors concluded that geriatric individuals residing in nursing homes who are not adequately treated and monitored may be at risk of developing dehydration and eating disorders, which promotes euDKA [30]. Garg et al. described the case of three patients over the age of 60 who developed euDKA after using flozins without accompanying diabetes. In two cases, the inhibitors were used to inhibit the progression of heart failure, and in one case they were used protectively in chronic renal failure. This demonstrates that elderly patients taking SGLT2i for indications other than diabetes are not free of euDKA risk [18]. Yanai et al. proposed potential parameters that can predict the risk of euDKA in elderly patients with DM2. One of them is C-peptide, which is produced in equimolar ratio to endogenous insulin, making its concentration independent of exogenous insulin. The authors indicated that fasting C-peptide concentrations ≥1.6 ng/ml may indicate the relative safety of SGLT2i. Evaluation of changes in triglyceride and non-HDL-C cholesterol levels may also be helpful. An increase in these parameters during SGLT2i therapy may suggest the development of relative insulin deficiency, increasing the risk of euDKA. In contrast, their decrease after one month of treatment indicates the effectiveness of the therapy and improved control of insulin resistance [26]. Castellanoz-Diaz et al. described the case of a 70-year-old woman with type 1 diabetes mellitus (DM1) who was diagnosed with euDKA while on SGLT2i and a ketogenic diet (DK) The patient began therapy with empagliflozin to reduce the number of hypoglycemic episodes, and implemented DK to improve glycemic status and reduce insulin requirements. The ketogenic diet, which involves eating low-carbohydrate, high-fat meals, can induce starvation-like metabolic changes, leading to fat breakdown and production of ketone bodies, resulting in acidosis. The use of SGLT2i likely exacerbated this condition. This case underscores the need for caution in the selection of diet and medications in the elderly, especially in the context of the use of therapies that may increase the risk of acidosis. In addition, Soliman et al. described the case of a 79-year-old patient whose serum beta-hydroxybutyrate levels were elevated for the first four days of hospitalization, while urinary ketones were detectable only on the first and third days. The authors note that the main ketone body excreted in

Table II. Summary of studies on euDKA and DKA in the elderly

Study	Description of the study	Conclusion
Garg et al. [18]	Description of 3 cases of patients over 60 years of age without concomitant DM2 who developed euDKA after using SGLT2i for another indication.	Episodes of euDKA have been reported in patients over the age of 60 without type 2 diabetes mellitus (DM2) during the use of flosins to treat heart failure and chronic kidney disease. The use of SGLT2i in people without diabetes does not completely eliminate the risk of euDKA.
Castellanoz-Diaz [22]	A case of a 70-year-old woman with DM1 who was diagnosed with euDKA as a result of simultaneous use of DK and SGLT2i.	Concomitant use of DK and SGLT2i can exacerbate ketogenesis and acidosis. The elderly are more likely to have conditions such as dehydration, which further exacerbate these conditions. Therefore, it is important to consider the patient's diet when selecting drug therapy.
Solinam et al. [22]	Case report of a 79-year-old patient with euDKA following treatment with empagliflozin in DM2.	Serum ketone levels were elevated for the first four days of hospitalization, while they were detected in urine only on the first and third days. The authors suggest that a better way to determine ketones is to measure their concentration in serum, since urine tests can be insufficiently sensitive and lead to overlooking the presence of ketones.
Mengchum et al. [24]	Retrospective analysis of 7 cases of euDKA patients aged 51 to 74 years.	The authors indicate that the symptoms seen in patients with euDKA mimicked those seen in DKA. The authors pointed to dehydration, prolonged starvation, severe infection, and discontinuation of insulin as predisposing factors. In each case, the researchers showed reduced insulin levels.
Yanai et al. [26]	Design of a study in which the use of TG determination and non-HDL-C cholesterol levels may be a marker of response to SGLT2 treatment in the elderly.	Assessment of C-peptide levels and lipid levels may be predictive of the development of euDKA in the elderly and assess tolerance of SGLT2i treatment.
He et al. [27]	Evaluation of the association between euDKA and DKA incidence and SGLT2i use based on reported side effects from the FAERS database.	The median age of euDKA onset was 54.1 years. Vomiting (18.5% vs. 10.2%, $p < 0.0001$) and nausea (13.1% vs. 11.1%, $p = 0.134$) were more common in euDKA compared to DKA, while acute kidney injury was more frequently observed in DKA (21.5% vs. 11.7%, $p < 0.0001$). Life-threatening conditions occurred more frequently in euDKA than in DKA (27.7% vs. 19.8%, $p < 0.0001$). Deaths were rare (2.9% in euDKA vs. 2.4% in DKA, no significant difference).
Schwarzfuchs et al.[28]	Analysis of clinical features and outcomes of patients over 65 and under 65 years old who were initially diagnosed with DKA.	A high rate of euDKA was observed in both study groups. The in-hospital mortality rate for patients older than 65 years was 16.7% compared to 1.6% in those younger than 65. Older patients with DKA had higher prolonged hospitalization and a higher likelihood of recurrence.
Liu et al. [29]	A review of 39 papers involving 60850 patients on examining the effect of SGLT2i on the occurrence of DKA in patients with DM2.	The authors point out that DKA resulting from SGLT2i may be neglected if there is mild to moderate hyperglycemia, which can lead to a delay in diagnosis and treatment. In the analysis, the authors note that in 9 cases of patients, their glucose levels were lower than <250 mg/dl, leading to a delay in diagnosis and treatment implementation.
Rather et al. [30]	Case report of a 74-year-old male nursing home resident who developed euDKA.	The authors report that symptoms of euDKA can be difficult to differentiate from DKA, uremia or poisoning. In addition, they note that in patients using SGLT2, elderly frailty syndrome and malnutrition may exacerbate insulinopenia and thus increase the risk of euDKA.

euDKA-euglycemic diabetes ketoacidosis, DKA-diabetic ketoacidosis, DM1-type 1 diabetes melitus, DM2-type 2 diabetes mellitus, SGLT2i-sodium-glucose cotransporter-2 inhibitors DK-ketogenic diet, FAERS- FDA Adverse Event Reporting System, TG-triglycerides

acidosis is beta-hydroxybutyrate, and to a lesser extent acetoacetic acid and acetone. This is clinically relevant because test strips only detect acetoacetate. As a result, researchers recommend determining ketones in serum [22]. A summary of studies on euDKA and DKA in the elderly is included in table II.

Treatment of euglycemic acidosis

Treatment of euDKA is similar to that of DKA, with the absence of hyperglycemia. It includes discontinuation of SGLT2i, replenishment of fluid volume, correction of electrolyte disturbances and administration of insulin. According to the British Diabetes Association's 2023 guidelines, 10% glucose solution should be started immediately at a rate of 125ml/h as glucose levels are low. Initial insulin dose of 0.1 units/kg/h. If glucose levels continue to fall, the dose should be reduced to 0.05 units/kg/h to avoid hypoglycemia [31]. Although blood glucose levels are lower in euDKA than in DKA, simultaneous administration of insulin and glucose is necessary to correct metabolic acidosis and prevent hypoglycemia. It is crucial to monitor electrolyte levels, especially potassium, bicarbonate and glucose throughout therapy. In severe cases, it is advisable to consider the prophylactic use of low-molecular-weight heparin. DKA is consi-

dered cured when the patient is able to take food orally, and test results show: pH is >7.3, bicarbonate concentration >15.0 mmol/l, and serum ketone concentration <0.6 mmol/l. The same values are recommended for euDKA [7,32]. According to the FDA communication, the use of SGLT2i should be discontinued immediately until another clear cause of the disease is identified and eliminated. Therapy can be resumed once the patient's condition is stabilized. However, special caution should be exercised in patients with infections, changing insulin doses or alcohol abuse [33]. To minimize the risk of euDKA, it is recommended that SGLT2i be discontinued at least three to five days before planned procedures, during acute illness or prolonged fasting. In patients with nausea, vomiting or malaise during SGLT2i therapy, blood or urine ketone levels should be measured regardless of blood glucose levels [34]. Education of patients and caregivers of the elderly themselves is also key. It is recommended that patients be provided with a prescription for strip tests to monitor ketone bodies. If they feel unwell or have symptoms of acidosis, report urgently to the nearest hospital. Patients should be made aware of the risk of euDKA, especially when changing their diet and modifying insulin therapy [22,32]. In addition, researchers suggest the use of new markers, such as C-peptide and triglycerides, which can help predict the risk of acidosis from SGLT2i treatment in the elderly [26].

Summary

DM2, heart failure, chronic kidney disease are significant health challenges in the elderly population. SGLT2i, which have shown high efficacy in the aforementioned indications, are increasingly being used to treat these conditions. Nevertheless, the use of these drugs is associated with the risk of side effects, such as genital infections, hypovolemia and weakness. A particularly dangerous, though rare, complication is euDKA. This is a condition characterized by the presence of ketonemia and metabolic acidosis with normal or slightly elevated glucose levels, which distinguishes it from classic diabetic ketoacidosis. Due to its insidious course, euDKA in elderly patients often remains difficult to diagnose or overlooked, especially in the context of other medical procedures associated with numerous comorbidities. Among the triggers of euDKA are conditions common in the elderly population, such as malnutrition, infections, the perioperative period and neglect of insulin therapy. Diagnosis is further complicated by the similarity of euDKA symptoms to other conditions, such as DKA, uremia and poisoning. It should be noted that cases of euDKA have also been reported in elderly patients using flozins to treat conditions other than DM2. This shows that the elderly may be at risk for this complication regardless of the original diagnosis. Due to the pleiotropic effects of SGLT2i, their relatively low cost when reimbursed, and their convenience of use, the popularity of these drugs in the treatment of seniors is expected to continue to grow. With this growth and the problem of an aging population, an increased number of euDKA patients can also be expected. It is therefore crucial to conduct further research on markers that will predict the efficacy and safety of flozins in this group of patients. No less important is the prevention and education of patients and their caregivers. Physicians should be especially vigilant for patients with suspicious symptoms and routinely determine ketone levels in such cases so as not to overlook euDKA.

Conflict of interest
None

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