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(Article begins on next page)

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Adverse drug reaction: Diabetic ketoacidosis with SGLT2 inhibitors

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A 45-year-old diabetic woman presented with malaise, shortness of breath and nausea for 2 days. She took metformin and insulin and had started canagliflozin 6 weeks earlier to lose weight. Over the previous week she halved insulin dose for improved glycemia.

Her physical examination was remarkable for drowsiness and a rapid (respiratory rate: 28/min) deep breathing pattern.

Serum biochemistry revealed a glucose of 8,9 mml/L and a metabolic acidosis with increased anion gap: pH: 7.18 pO2 104 14 kPa pCO2 4 kPa $HCO3^-$ 14 mmol/L, anion gap: 23 mmol/L (reference range 8–12 mmol/L).

Urine dipstick showed strong (3+) ketonuria.

SGLT2 inhibitors (SGLT2i) are a novel class of antihyperglycemic drugs that is being increasingly used in diabetes. Despite their glycaemic, renal and cardiovascular benefits, they can cause diabetic ketoacidosis (DKA), a serious, life-threatening adverse event. This article aims to inform patients and general practitioners on how to recognize and prevent SGLT2i-associated DKA.

What are SGLT2i?

SGLT2i block Sodium-Glucose Cotransporter-2 (SGLT2) in the proximal renal tubule, inducing glycosuria[1]. Since the first SGLT2i approval to improve glycemic control in T2DM in 2012, SGLT2i use increased rapidly: in a retrospective analysis of UK primary care databases, SGLT2i represented 14% new second-line and 27% new third-line prescriptions for T2DM in 2016[2].

In 2019, indications for T2DM expanded beyond glycemic control to ensure cardiovascular and renal protection[1]; three SGLT2i were also approved for T1DM as an adjunct to insulin to

improve glycemic control in Europe and Japan and rejected by FDA because of a risk of DKA deemed excessively high in this patient population.

Indications and licensing for SGLT2i for diabetes are listed in **supplementary Table 1**. Mechanisms whereby SGLT2i may predispose to ketoacidosis are depicted in **Figure 1**[3, 4 5]. In 2015 the FDA and the EMA, after the review of pharmacovigilance reports , issued warnings about DKA as a rare adverse reaction with SGLT2 inhibitors in both T1DM and T1DM. In addition, they warned about possible "atypical" presentation of DKA, i.e. with normal or mildly elevated blood glucose levels, which can delay diagnosis and treatment **(Box 1)**[6,7,8] .

In 2020, following a review of peri-operative DKA cases in patients taking SGLT2i, both regulatory agencies updated recommendations to include guidance on timing to interrupt and restart SGLT2i and how to monitor for DKA in hospitalized patients **(Box 1)**[9,10].

How do patients present?

Symptoms are similar to those usually seen with DKA, such as polyuria, polydipsia and signs of dehydration, nausea, vomiting, abdominal pain, and altered sensorium[11, 12, 13,14]. However, the analysis of RCTs and of 198 SGLT2i-associated DKA reports from FDA Adverse Event Reporting System(FAERS) database show that 33% of DKA cases in T1DM[15] and 46% of DKA cases in T2DM patients[16] present with normal/mildly elevated blood glucose levels (<13.9 mmol/ l; 250 mg/dL), also referred to as euglycaemic DKA(euDKA)[16,17], which can pose a diagnostic challenge and are addressed by regulatory agencies and NICE recommendations[18,19,20] **(Box 2).**

How common is it?

The epidemiological evidence linking SGLT2 inhibitors to DKA is summarized in **supplementary Table 2.**

High quality meta-analyses of randomized controlled trials(RCTs) indicate SGLT2i use increases the risk of DKA: in T1DM, the relative risk (RR) of DKA with SGLT2i vs. placebo was 4.49 (2.88-6.99)[21] and 3.93 (95%CI: 1.94-7.96)[15], with an absolute rate of 22[21] and 18[15] events per 1000 patient-years. In T2DM, the RR of DKA with SGLT2i as compared with placebo or other antidiabetic drugs(ADs) was 2.31(1.38, 3.27), with an absolute rate of 3 events per 1000 patient-years[22]

The risk of DKA was increased with SGLT2i as compared with other glucose-lowering agents also in real-world observational studies comparing new-users of SGLT2i with new-users of other Ads: the incidence rate ranged 1.3-to-8.8 events per 1000 patient-years in T2DM [23,24,25,26]and was 7.3 events per 100 patients-years in T1DM[27].

In observational and pharmacovigilance publications reporting time-to-onset of DKA after SGLT2i initiation, 76.8% to 85.2% of cases of DKA occurred within 180 days of starting SGLT2i therapy, suggesting that patients are at higher risk of developing DKA during the first months of SGLT2i[16, 28, 29, 30, 31,32] ; 70% to 85% of these SGLT2i-associated DKA cases required Intensive Care Unit admission; in observational[26] and pharmacovigilance[29,30 32] reports 1.5-1.9% of all SGLT2i-associated DKA cases were fatal.

A good quality meta-analysis of RCTs documented a dose-response relationship with SGLT2i-associated DKA in T1DM[21] with a 4.9-fold higher rate of DKA with high SGLT2i doses (34 events per 1000 patient-years) as compared to low SGLT2i doses (7 events per 1000 patient-years).

What factors increase the risk?

A predisposing condition or precipitating factor (**Box 3**) could be identified in up to 100% of SGLT2i-associated DKA cases in RCTs[15,33] and in 68-78% of DKA cases reported by observational[24,31] and pharmacovigilance[28,31] studies.

These factors *per se* enhance ketogenesis and may precipitate DKA if occur in patients on SGLT2i. Among these factors, late-onset autoimmune diabetes of adulthood (LADA) is an emerging condition predisposing to SGLT2i-associated DKA: in the canagliflozin T2DM clinical trial program[33] and in an analysis of four US Administrative Claims Databases[26] as many as 50% T2DM patients developing DKA were subsequently diagnosed to have LADA. **(Box 3).**

How is it diagnosed?

Lab tests are required to confirm the diagnosis of DKA.

Increased ketones in blood (β-hydroxybutyrate, BHB≥ 3 mmol/L) or urine (ketonuria ++ or more on urine dip-sticks) and acidosis (serum bicarbonate <15 mmol/L *and/or* blood pH <7.3) indicate diabetic ketoacidosis[22-25].

An elevated serum anion gap[$Na^-(Cl^-+HCO3^-)$> 10 mmol/L] may help rule out other causes of metabolic acidosis if blood ketone testing is unavailable[24].

Blood ketone testing is preferred over urine test-strips as it is a more accurate marker for detecting onset and resolution of ketosis[23,24,25,26,27]. (**Box 1**)

Once a diagnosis of DKA is made in patients taking SGLT2i, other competing causes of ketoacidosis which can occur both in diabetic and nondiabetic people, which usually present as euglycemic ketoacidosis, need to be ruled out. These causes (reviewed in [34]) and hints for differential diagnosis are reported in **Box 4.**

How is it managed?

Once ketosis has developed, a stepwise sequence of remedial actions is recommended to mitigate the risk of progression to DKA (**Box 4**) [35,36] : SGLTi should be discontinued immediately, and rapid acting insulin, carbohydrate and adequate hydration should be undertaken[35,36]. Case series and analyses of RCTs showed that early application of these measures can reverse ketosis and prevent progression to DKA[15,31].

EMA recommends against restarting SGLT2i treatment after DKA, unless another clear cause is identified and resolved (see **Box 2, Box 4**).

However, a case series[31] and an analysis of FAERS[16] documented DKA recurrence in 100% and 50% of cases, respectively, after SGLT2i re-challenge, even after identification and resolution of putative contributing factors (**Box 3**). Consider other antidiabetic drugs in these patients.

How can it be prevented?

The AACE/ACE[37], the National Institute for Health and Care Excellence(NICE)(**supplementaryTable 1**) and two international experts consensus[35,36] proposed a stepwise strategy to minimize the risk of SGLT2i-associated DKA.

This strategy includes

1)Patient selection: when considering SGLT2i for their patients, physicians should first rule out conditions at high risk of DKA in their patients, which are contraindications to SGLT2i (**Box 3**).

2)Patient education: before starting SGLT2i, patients should be informed on when and how to measure ketones (blood ketone measurement is preferred over urine dipstick) and on what actions to take if ketones are elevated. These instructions were provided by 2

international expert consensus and are reported by EMA's Summary of Product Characteristics(SmPC) for every SGLT2i[38]

Ketones should be monitored

- on a regular basis during the initial 1-2 weeks of therapy, regardless of symptoms; then individualize the frequency of ketone testing according to patient's lifestyle and/or predisposing conditions (**Box 3**)
- in the presence of precipitating factors of DKA, regardless of symptoms (**Box** 3), or if symptoms/signs of DKA occur (such as polyuria, polydipsia and signs of dehydration, nausea, vomiting, abdominal pain, and altered sensorium**)(Box 2).**

If ketone elevation occurs, the sequence of remedial actions to be applied is indicated in Box 5: consume at least 30–45 grams of carbohydrates every 2 hours with a correction dose of insulin (1.5 times the usual dose) and drink 300–500 mL of fluids hourly.

Check blood glucose and ketones every 2 hours for up to 4 hours, seek medical attention if ketosis does not resolve within 4 hrs or if any of these remedies cannot be followed, particularly if you are unable to keep down fluids**.**

If large ketone elevation occurs, usually with symptoms of DKA including abdominal pain, nausea, vomiting, fatigue, malaise, and/or dyspnea, go the Emergency Department wothout delay.

FIGURE LEGEND

Figure 1. Mechanisms for ketoacidosis with SGLT2i.

SGLT2i inhibit SGLT2 on pancreatic islet α-cell and directly stimulate glucagon secretion, which upregulates endogenous glucose production, ketogenesis and lipolysis.

In the kidney, SGLT2 inhibition increases ketone reabsorption.

SGLT2 inhibition-induced glycosuria lowers blood glucose, thereby allowing insulin dose reduction. Insulin reduction further reduces the insulin-to-glucagon ratio, a critical factor in inhibiting hepatic ketogenesis and lipolysis of free fatty acids.

Glycosuria also induces osmotic diuresis and dehydration, which triggers the synthesis if glucagon, cortisol and epinephrine, further contributing to lipolysis and ketogenesis.

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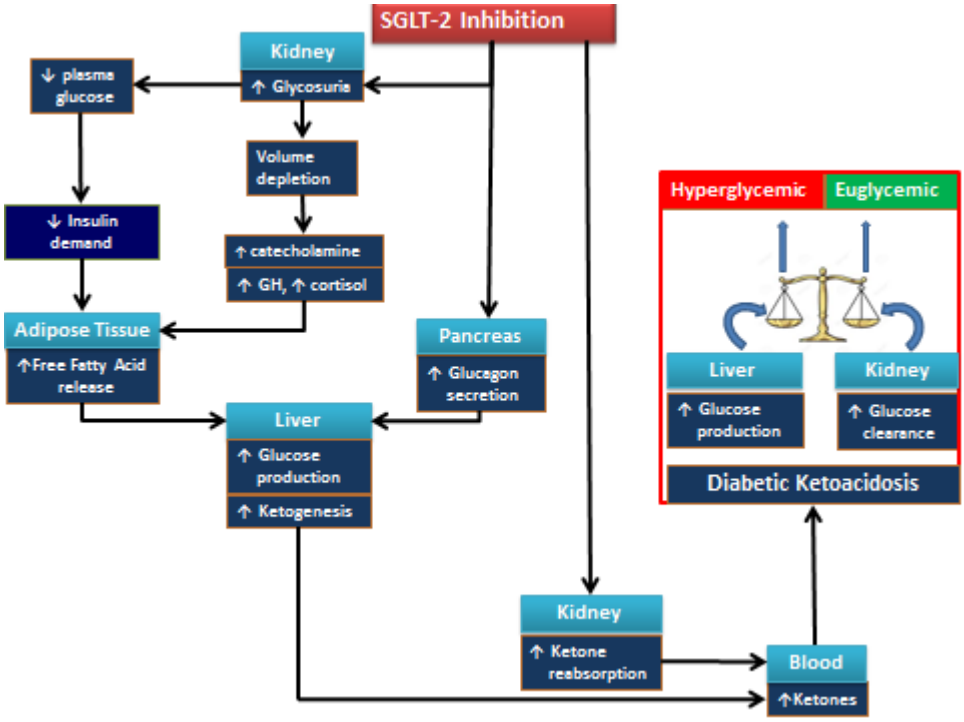
SGLT-2 Inhibition
Kidney
↑ Glycosuria
↓ plasma glucose
Volume depletion
↓ Insulin demand
↑ catecholamine
↑ GH, ↑ cortisol
Adipose Tissue
↑Free Fatty Acid release
Pancreas
↑ Glucagon secretion
Liver
↑ Glucose production
↑ Ketogenesis
Kidney
↑ Ketone reabsorption
Blood
↑Ketones
Hyperglycemic
Euglycemic
Liver
↑ Glucose production
Kidney
↑ Glucose clearance
Diabetic Ketoacidosis

BOXES

Box 1. Safety warnings issued by drug regulatory agencies on DKA associated with SGLT2i use

Agency (date of warning)	**Actions by regulatory agencies**
FDA 2015/05[6]	**Warning to patients and HCPs about**: ∗symptoms/signs of DKA ∗ possible "atypical presentation (i.e. BG levels<13.9 mmol/l; 250 mg/dL) ∗ measures to minimize risk of DKA with SGLT2i
FDA 2015/12[7]	**Safety label update to all SGLT2i:** "Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of BG level. If suspected, discontinue SGLT2i, evaluate and treat promptly. Before initiating SGLT2i, consider risk factors for ketoacidosis. Patients on SGLT2i may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis"
EMA 2016/02[8]	**DKA listed as a rare ADR with SGLT2i** Information for patients and HCP on measures to minimize risk of DKA If DKA is suspected or confirmed, SGLT2i should be stopped immediately and should not be re-started, unless another clear precipitating factor is identified and resolved.
FDA, EMA 2020/03[9,10]	**Safety label update to all SGLT2i**: • interrupt SGLT2i in patients hospitalized for major surgery or acute serious medical illnesses ∗stop canagliflozin, dapagliflozin and empagliflozin at least 3 days, and ertugliflozin at least 4 days before scheduled surgery. ∗ after SGLT2i discontinuation, monitor BG levels (FDA) and ketones (EMA): blood ketone measurement is preferred to urine dipstick (EMA)* *SGLT2i may be re-started once patient's oral intake is restored, ketones are normal and any other risk factors for ketoacidosis are resolved. *report suspected ADR to SGLT2 inhibitors to the Yellow Card Scheme

Abbreviations: BG: blood glucose;

*differently from FDA, EMA recommends monitoring ketones beside BG, because the activity of SGLT2i, and the risk of DKA, lasts several days after drug discontinuation.

Box 2. Clinical features of euglycaemic diabetic ketoacidosis (euDKA) associated with SGLT2 inhibitors

Symptoms/signs
Patients with euDKA may have less polyuria polydipsia and less severe dehydration owing to the milder degree of hyperglycemia-induced osmotic diuresis[16,17], and may instead present with: •ketone-related symptoms: anorexia, nausea and vomiting(51-76% of all euDKA cases), abdominal pain (20%), tachypnoea(19-22%) •vague symptoms: tachycardia(4-44%), malaise(8-22%), tiredness (20-34%), altered mental status(8-15%), dizziness and syncope(4-11%), with or without fever[16,17].
The analysis of case reports and of FAERS database[16,17] reveals that the absence of hyperglycaemia eliminated a vital alert sign that metabolic decompensation was occurring: consequently, patients failed to check for ketones, did not adopt proper treatment and did not seek medical attention. The delayed recognition and treatment of DKA may have contributed to some fatal outcomes[16,17,33]
Consistent with NICE guidance on DKA[18], FDA's Patient Medication Guide[19] and EMA's Summary of Product Characteristics[20] of all SGLT2i recommend to check for ketones in the presence of • suggestive symptoms or • precipitating factors of DKA even if blood glucose levels are <13.9 mmol/l (250 mg/dL)

[a] [18] https://www.nice.org.uk/guidance/ng18/chapter/1-Recommendations#diabetic-ketoacidosis-2

[b] 19 https://www.azpicentral.com/farxiga/farxiga_med.pdf

[c] 20 https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf

Box 3. Predisposing conditions and precipitating factors of DKA in patients taking SGLT2i

Predisposing condition	**Action**	**Precipitating factor**	**Action**
Inability/unwillingness to monitor ketone bodies	SGLT2i contraindicated	Vomiting	Hold SGLT2 inhibitor dose and monitor ketones during acute events
Excessive alcohol use or illicit drug use	SGLT2i contraindicated	Volume depletion/dehydration	Hold SGLT2 inhibitor dose and monitor ketones during acute events
Very-low-carbohydrate / ketogenic diet	SGLT2i contraindicated	Acute infection or illness of any sort	Hold SGLT2 inhibitor dose and monitor ketones during acute events
Pregnancy (ongoing or planned)	SGLT2i contraindicated	Hospitalization for :	*stop

Previous DKA	SGTL2i contraindicated if previous DKA, unless another clear cause of DKA is identified and removed	⁎surgery ⁎acute serious medical illness	canagliflozin, dapagliflozin and empagliflozin at least 3 days, and ertugliflozin at least 4 days before scheduled surgery ⁎ Hold SGLT2 inhibitor dose and monitor ketones during this period
Inappropriate insulin dose reduction	Avoid total insulin dose reduction> 20% If unavoidable, check ketones after reduction	Acute volume depletion/dehydration	Hydrate and monitor ketones
SGLT2i dose	Use lowest SGLT2i dose required to achieve clinical benefit	Vigorous or prolonged exercise	Hold SGLT2 inhibitor at least 72 hours prior to anticipated strenuous exercise event
Insulin pump use	Check ketones with	Insulin pump or	Hold SGLT2

	every pump set change	infusion site failure	inhibitor dose and monitor ketones during this period
LADA [a]	SGTL2i contraindicated. Consider ruling out LADA in T2DM -at high clinical risk of LADA -after a DKA episode with SGLT2i	Travel with disruption in usual schedule/insulin regimen	Hold SGLT2 inhibitor dose and monitor ketones during this period

[a] LADA: late-onset autoimmune diabetes of adulthood. LADA is autoimmune form of diabetes, similar to T1DM, but patients with LADA often show insulin resistance similar to T2DM.

LADA patients have antibodies against pancreatic β-cells, and these cells stop producing insulin more slowly than in T1D patients. Patients with LADA are often initially misdiagnosed as having T2DM due to a residual insulin secretion at the time of diagnosis, but islet autoantibodies cause a subsequent decline in β-cell function. When SGLT2i therapy in initiated on such background of insulin deficiency, SGLT2i can trigger DKA(**Figure 1**).

No guideline-based recommendations are available to guide screening for LADA in T2DM who are candidate for SGLT2i or experienced DKA while taking SGLT2i **.**

Box 4. Differential diagnosis of SGLT2i-associated diabetic ketoacidosis (euDKA).

These causes

usually cause euglycemic DKA.

Condition	Mechanism(s)	Hints for diagnosis
Pregnancy	Pregnancy counter regulatory hormones (progesterone, estrogen, human placental lactogen) induce a maternal catabolic and insulin resistant state to shift all the glucose to the fetus through the placenta	Pregnancy test in women of childbearing age presenting with ketoacidosis
Starvation/ decreased caloric intake	Starvation activates lipolysis and counter-regulatory hormones to trigger ketogenesis	History of weight loss/reduced dietary intake
Excess alcohol intake	Reduced glucose and nutrient intake Unlike DKA, alcoholic KA is characterized by the significant shift in ketone production towards BHB compared with acetoacetate (BHB/atetoacetate ratio of 7:1 vs. a ratio of 3:1 in euDKA), due to the rising NADH/NAD ratio	History, blood ethanol testing. Urine test strips only read acetoacetate and may yield falsely negative results
Cocaine use	Cocaine has anorexigenic actions and stimulates counterregulatory hormone (cortisol, catecholamines) production	Urine drug test
Sepsis	Increased counterregulatory hormone production, catabolic state and insulin	Symptoms/signs of infection

	resistance	
Glycogen storage diseases	Decreased glycogen stores induces accelerated fasting, hypoglycemia and ketosis	Infantile age-at-onset of disease; hereditary disease
Chronic advanced liver diseases	Decreased glycogen stores and gluconeogenesis induce an accelerated fasting condition, leading to, hypoglycemia and ketosis	Clinical examination, blood liver tests

Abbreviations: BHB: β-hydroxybutyrate

Box 5. Patient instructions: remedial actions following ketone testing proposed by international expert consensus reports and recommended by EMA for all SGLT2i: the STICH (**ST**op SGLT2 inhibitor, **I**nject bolus insulin, **c**onsume 30 g **C**arbohydrates, **H**ydrate) **and the STOP DKA protocol**(**S**top SGLT2 inhibitor, **T**est ketones, **O**ral ingestion of fluid and carbohydrates, **P**rotocol instructions for supplemental insulin and carbohydrates)[51,52]

Pre-hospital management of SGLTi-associated DKA		
Blood ketone (BHB)	**Urine ketone (acetoacetate)**	**Actions**
<0.6 mmol/L **Normal**	Negative.	No action needed
0.6 - 1.5 mmol/L **Ketosis**	Trace or Small +	**Stop** SGLT2i **Insulin**: Inject bolus rapid-acting insulin based on carbohydrate intake (hourly): 5-10% TID supplemental insulin or 1.5 x correction bolus plus usual bolus to cover carbohydrates **Carbs**: Consume 30-45 g rapidly absorbed carbohydrates every 2 hours **Hydrate**: drink water 300-500 ml/hourly
		Check blood glucose after 2 hrs to avoid hyperglycemia and hypoglycemia Check blood/urine ketones every 2 hours Seek medical attention if levels persist and symptoms present after 2-4 hours
1.6 - 3.0 mmol/L **Impending DKA**	Moderate ++	Follow treatment recommendations listed above Seek immediate medical attention if unable to ingest fluids and/or ketone levels and symptoms persist 2-4 hours after taking carbs-insulin-fluids
>3.0 mmol/L **Probable DKA**	Large +++/++++	Go to emergency department without delay Stop taking SGLT2i. Apply STICH sequence of actions as above

In-hospital management of SGLT2i-associated DKA
Treatment should follow existing guidelines for DKA: restore fluid and electrolyte losses via isotonic saline infusion, which should precede ketogenesis suppression via insulin infusion. In euDKA early introduction of a dextrose containing solution is needed to avoid hypoglycemia and keep glycaemia in the range 8,3-13.9-mmol/L(150-250 mg/dL), until the anion gap, and ketone levels normalize.

Abbreviations: BHB: ß-hydroxybutyrate

References: [51,52], EMA's SmPC(https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf)

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Pre-hospital management of SGLTi-associated DKA		
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		Check blood glucose every 2-4 hrs to avoid hyperglycemia and hypoglycemia Check blood/urine ketones every 2 -4 hours until resolution Seek medical attention if levels persist and symptoms present
1.6 - 3.0 mmol/L **Impending DKA**	Moderate ++	Follow treatment recommendations listed above Seek immediate medical attention if unable to ingest fluids and/or ketone levels and symptoms persist

>3.0 mmol/L **Probable** **DKA**	Large +++/++++	Go to emergency department without delay Stop taking SGLT2i. Apply STICH sequence of actions as above
In-hospital management of SGLT2i-associated DKA		
Treatment should follow existing guidelines for DKA: restore fluid and electrolyte losses via isotonic saline infusion, which should precede ketogenesis suppression via insulin infusion. In euDKA early introduction of a dextrose containing solution is needed to avoid hypoglycemia and keep glycaemia in the range 8,3-13.9-mmol/L(150-250 mg/dL), until the anion gap, and ketone levels normalize.		

Abbreviations: BHB: ß-hydroxybutyrate

References: [27,28], EMA's SmPC(https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf)

Box "What you need to know"

- DKA is a rare, life-threatening complication of SGLT2i treatment. Patients on SGLT2i must know symptoms/signs, predisposing conditions and precipitating factors of DKA.
- in the presence of suggestive symptoms/signs, predisposing conditions or precipitating factors, patients should check urine or blood ketones. Blood ketone measurement is preferred over urine dipstick.
- If ketosis is detected, a well-defined sequence of actions should be applied to prevent DKA development with SGLT2i

Box "Education into practice"

- why are you choosing SGLT2i instead of other glucose-lowering drugs in this diabetic patient??

do you spend enough time with patients candidate for SGLT2i discussing DKA symptoms, predisposing factors and precipitating conditions of DKA?

- what aspects of a DKA risk minimizing strategy would you discuss with your patient before commencing SGLT2i?
- guidelines and regulatory authorities now favor blood ketone over urine ketone measurement: for monitoring ketosis: how do you position regarding this recommendation?

Box "How patients were involved in the creation of this article"

We arranged a live Tweet chat with 12 T2DM patients on SGLT2i for their views on an initial draft of this article. All agreed to participate. Based on their feedback we now highlight the importance of checking ketone levels if they have predisposing conditions and precipitating factors

for DKA, irrespective of symptoms. Patients emphasized that general physicians educate patient on strategies to minimize the risk for DKA and the need for providing a blood ketone meter to patients taking SGLT2 inhibitors. We are grateful for their input.

Box "Sources and selection criteria"

We searched PubMed, EMBASE, Cochrane Database of Systematic Reviews, international trial registries, and drug regulatory agencies' websites through July 15th 2020 by using the following search terms: ketoacidosis, diabetic, DKA, euglycemic diabetic ketoacidosis, euDKA, ketone, ketosis, acidosis, sodium glucose cotransporter 2 (SGLT2) inhibitors. We prioritized articles on humans, scientific society (ADA, EASD, ESC, NICE, British Diabetes Societies) guidelines, expert reviews and articles providing mechanistic insights into DKA. We included in our analysis 307 records (13 systematic reviews, 161 RCTs, 30 records from regulatory agencies,13 consensus/guidelines 59 case series and 31 reviews on SGLT2 inhibitor-associated DKA).

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