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Review

Clinical and biochemical characteristics and analysis of risk factors for euglycaemic diabetic ketoacidosis in type 2 diabetic individuals treated with SGLT2 inhibitors: A review of 72 cases over a 4.5-year period

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ABSTRACT

Background and aims: To study euglycemic diabetic ketoacidosis (euDKA) outcomes associated with sodium-glucose co-transporter 2 inhibitors (SGLT2is)
Methods: Review of 72 euDKA cases in T2DM between September 2015 and January 2020 (PUBMED).
Results: euDKA could occur at any time during SGLT2is treatment, with nausea, abdominal pain and vomiting as main symptoms. Hyperglycemia did not correlate with pH and β-hydroxybutyrates. Low pH and high β-hydroxybutyrates were significantly associated with euDKA. In biguanides users, acidosis was unrelated to lactic acidosis. euDKA occurred during fasting, surgery, acute infection, insulin deprivation (endogenous or exogenous).
Conclusions: These data support avoidance of euDKA risk states in SGLT2i users.

1. Introduction

Sodium-glucose transporter 2 inhibitors (SGLT2is), or gliflozins, are a recent introduction to the therapeutic arsenal for type 2 diabetes mellitus (T2DM) [1]. These new medications (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) allow better glycemic control by inhibiting renal glucose reabsorption. The results of randomized clinical trials have shown that these drugs also lead to a significant reduction in the risk of hospitalization for heart failure in certain patients, independently of the presence or absence of diabetes, and a slowing of the progression of chronic kidney disease and/or a reduction of albuminuria [2–4]. However, rare but serious adverse events such as euglycaemic diabetic ketoacidosis (euDKA) have been reported in type 1 diabetes mellitus (T1DM) and T2DM diabetic patients treated with SGLT2is, both over the course of clinical trials as well as in "real life" [5–30]. These acute euDKA are atypical, as the hyperglycemia is less severe than in ketoacidosis observed in T1DM, hence their classification as "euglycaemic" ketoacidoses. In 2015 and 2016, the Food and Drug Administration of the United States of America and the European Medicines Agency have warned of the potential risk of ketoacidosis when using SGLT2is in T2DM patients [31,32]. A recent meta-analysis by Zelniker et al. concluded that the risk of developing euDKA was 2.2 times higher in T2DM patients treated with SGLT2is compared to patients not treated with these medications [33]. However, it is still an open question whether the incidence of euDKA remains rare due to underdiagnosis and possible under-declaration, as opposed to it being indeed a rare occurrence.

The main purpose of this study was to characterize the clinical and the biological manifestations as well as the risk factors for the occurrence of euDKA in T2DM patients treated with SGLT2is. Furthermore, by understanding the context of the occurrence of euDKA linked with SGLT2is, clinicians can take the necessary precautions to reduce the risk of these events.

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2. Research design and methods

The articles studied were to include a euDKA event in T2DM individuals treated with SGLT2i.

Literature search was conducted on PubMed between September 2015 and January 2020.

An article was included for this study when it had been published in a journal for which the results were peer-reviewed, were published in English or in French, included only T2DM patients, and were presented as a case report or a cases series. Duplicate articles, unpublished articles, randomized control trials, systematic reviews, letters to the editor, and clinical cases relating to euDKA in patients with T1DM or Latent Autoimmune Diabetes in the Adult (LADA) were excluded. The following keyword search was used in PubMed: "Diabetic ketoacidosis" AND "euglycemia" AND "SGLT-2 inhibitors "OR "Sodium-Glucose Transporter 2 Inhibitors" AND "Type 2 Diabetes Mellitus". We reported the results according to PRISMA checklist.

Two authors read and selected the articles over the chosen period. Each selected article was proofread by two authors separately, then they selected or not the articles together. No software was used to analyze the articles for the authors. Furthermore, the data extracted from the articles had to be individual data (and not averages) to avoid the collection of grouped results without specific information for each individual.

The following data were sought and extracted from the clinical cases collected: gender and patient's age at the time of euDKA, duration of diabetes, hypoglycemic medications, length of time (in days) the SGLT2i were taken prior to the occurrence of euDKA, body mass index (BMI), clinical symptoms during the presentation of the euDKA, biochemical test results (A_1c glycated hemoglobin (HbA_1c), blood glucose level associated with euDKA, pH, pressure of carbon dioxide (pCO2), bicarbonate, anion gap, lactate, and capillary β-hydroxybutyrates (β-OHB)). Lastly, the conditions associated with euDKA in patients with T2DM also had to be described. For case reports, all available data were extracted and analyzed; not all case reports necessarily included all the data sought. All the results are summarized in a descriptive manner.

Continuous data are expressed as averages ± the standard deviation (SD), and categorical data are presented as numbers and percentages: n (%). When some of the data were incomplete, the total number (n) of patients for whom this data was available was specified. The clinical and the biological parameters were also subject to Pearson and Kendall's tau-b univariate correlation regression analysis according to a p-value < 0.05. The analysis of the data was carried out using SPSS® software.

3. Results

3.1. Demographics and medication use

In total, over the 4.5 years selected, we have selected 26 articles describing 72 cases of euDKA in patients with type 2 diabetes: 12 cases with canagliflozin, 31 with dapagliflozin, and 29 with empagliflozin, (none involving ertugliflozin, possibly due to the drug being ranked last among the SGLT2i on the market).

For each article included the number of patients with euDKA is listed in Table 1.

The main characteristics, including type of diabetes, age, and gender were available for the 72 cases.

They were adults (37 males and 35 females), and all of them had T2DM, and their average age was 57.6 ± 14.9 years. In the 72 cases, information on the duration of diabetes was available in 56 patients (12.2 ± 9.9 years), and BMI was reported in 36 patients (27.6 ± 6.2 kg/m^2). For 46 patients (information was not available for the other cases), euDKA has occurred at different times after using SGLT2i (Table 2).

All the patients were taking glucose-lowering drugs prior to the euDKA, and none had new-onset diabetes. Glucose-lowering drugs associated with SGLT2is mostly consisted of biguanide (metformin) (88%) and/or insulin (36.1%) and/or dipeptidyl peptidase-4 inhibitors (27.6%). The presence of cardiac or renal comorbidities was low, respectively 18.4% and 7.8% (Table 2).

3.2. Symptoms and biochemical parameters at euDKA presentation

During the euDKA, most of patients exhibited nausea (48%), abdominal pain (38%), vomiting (36%), and numerous other non-specific symptoms. The most frequent clinical signs were tachypnea (34%), tachycardia (30%), dehydration (14%), and alteration of consciousness (10%) (Table 2). The means of the following biological parameters were HbA_1c 8.9 ± 2.2% (74.5 ± 23.8 mmol/mol), glycemia 282.8 ± 159.2 mg/dl (15.69 mmol/L), pH 7.2 ± 0.17, bicarbonate 10.4 ± 5.8 mmol/L, anion gap 24.8 ± 7.7 mmol/L, β-OHB 5.0 ± 2.3 mmol/L, serum creatinine 1.2 ± 0.5 mmol/L, and lactate 1.7 ± 1.3 mmol/L (Table 2).

3.3. Conditions predisposing to euDKA

Potential risk factors for euDKA associated with SGLT2is were in decreasing order of frequency: prolonged fast (24.2%), surgical intervention (mainly immediate postoperative) (20.8%), acute infection (16.7%), relative insulinopenia, or a recent decrease/cessation of insulin therapy in patients prior to the euDKA (14.2%), dehydration (9.2%), and other causes presented in Fig. 1. None of the 72 cases of euDKA resulted in death.

The clinical alterations on admission improved or disappeared following treatment of the euDKA, the latter usually involves stopping SGLT2is and fasting, and/or giving an intravenous infusion of saline, sodium bicarbonate and insulin. The Pearson correlation coefficient (PC) was significantly negative between the pH and the capillary β-OHB (PC: 0.52; $p = 0.004$), the anionic gap (PC: 0.49; $p < 0.001$), respiratory rate (PC: 0.66, $p = 0.03$) and significantly positive between the bicarbonate (PC: +0.79; $p < 0.001$) and the pCO2 (PC = +0.74; $p < 0.001$).

Furthermore, there was no significant correlation between pH and the level of lactate (PC = −0.03; $p = 0.45$), which rules out *posteriori* that lactic acidosis produced the acidosis. We did not find significant correlations between pH and glycaemia (PC = −0.21; $p = 0.07$), or glycaemia and β-OHB (PC = 0.23; $p = 0.11$) (Fig. 2).

4. Discussion

With respect to the already existing literature, we confirm and provide new information on the association between euDKA and the use of SGLT2is. We observed that euDKA preferentially occurred in middle-aged patients of both genders, with usually a long duration of diabetes (>10 years on average), and already treated with oral glucose-lowering agents and/or insulin. In our review, cardiac or renal comorbidities were not preponderant in patients with euDKA. Moreover, the renal function during the occurrence of the euDKA was satisfactory. An episode of euDKA can therefore occur in individuals without prior cardiovascular and/or renal complications, and considered at low risk at the cardiometabolic level, unlike what is observed in case of lactic acidosis linked to biguanides. Also, we have shown that euDKA could occur at any time during SGLT2i treatment.

In addition, as reported by Burke et *al.* [34] in a systematic review from 2013 to 2016 involving 25 patients with T2DM, we encountered the same symptoms of euDKA in patients treated with

Table 1
Data extracted from the original case reports.

Table 1. Data extracted from the original case reports.

First Author	Alexander	Badwal	Esmouss	Bonora	Chacko		Chou	Diaz Ramo	Dull		Fukuda	Gajjar	Hamblin														Hernandez	Yeon											
Bibliographic reference	5	6	7	8	20		9	10	21		11	12	30														13	29											
Country	Canada	USA	USA	Italy	Australia		Malaysia	USA	USA		Japan	USA	Australia														Spain	Korea											
Year	2017	2018	2016	2017	2018		2018	2019	2019		2020	2019	2019														2019	2019											
Design	case report	case report	case report	case report	case series		case report	case report	case series		case report	case report	case series (37 T2DM but 14 with description)														case report	case series											
Sex	Male	Female	Female	Female	Male	Male	Female	Female	Female	Male	Male	Male	Male	Female	Male	Male	Male	Female	Female	Male	Male	Female	Male	Male	Female	Male	Male	Female	Male	Female	Female	Male	Male	Male	Female	Female	Male	Male
Age (years)	87	25	39	47	66	55	61	44	55	62	71	28	55	63	60	69	66	47	70	73	48	40	72	74	78	70	52	33	77	23	59	63	70	77	37	55	34	39
BMI (kg/m²)	22.5	NR	30	29.5	NR	NR	NR	NR	NR	NR	NR	33.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	24.2	20.1	23.4	37.8	19.5	18.4	19.6	24.1	29.4	22.3	29.3	24.2
Type of diabetes	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Diabetes duration (years)	7	NR	7	18	7	6	10	NR	NR	14	NR	8	15	13	40	15	20	6	NR	9	19	6	11	31	NR	30	4	2	30	2	9	20	30	19	0	11	0	15
Treatment of diabetes																																						
SGLT2i used before euDKA	Cana	Dapa	Cana	Cana	Dapa	Empa	Dapa	Cana	Dapa	Empa	Empa	Dapa	Dapa	Dapa	Dapa	Empa	Empa	Dapa	Empa	Empa	Cana	Dapa	Empa	Empa	Dapa	Empa	Empa	Dapa	Empa	Dapa	Dapa	Dapa	Dapa	Dapa	Dapa	Empa	Dapa
Duration of use of SGLT2i before euDKA (	875	NR	885	871	NR	2690	15	30	NR	NR	NR	240	NR	90	NR	NR	41	365	NR	210	420	NR	68	365	NR	NR	30	NR	5	380	290	NR	106	NR	20	68	NR	248
Insulin	No	No	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes
Metformin	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glitazone	No	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Sulfonylurea	No	No	No	No	No	No	Yes	No	No	No	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	Yes	No	No	Yes	No	No	Yes	No
Glinid	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
DPP4i	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No
GLP-1 RA	No	No	Yes	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
euDKA symptoms																																						
Nausea	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	No	No
Emesis	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Abdominal pain	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	No	No
Asthenia	Yes	No	Yes	Yes	No	No	No	No	No	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Polyuria	No	No	No	No	No	Yes	No	No	No	No	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Acetone breath	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Weight loss	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Poor oral intake	Yes	No	Yes	No	No	No	Yes	No	No	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Malaise	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Syncope	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Dizziness	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Altered mental status	No	No	No	Yes	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	No	No
Dehydration	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Tachypnea	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	No	No
Tachycardia	Yes	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No
Biochimical parameters during euDKA																																						
Blood glucose (mg/dL)	522	161	167	475	165.7	180	180	163	150	120	259	186	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	300	698	361	493	433	274	359	567	234	434	855	178
AIC (%)	6.5	NR	12	7.4	NR	NR	NR	NR	6.8	7.2	NR	10	9.4	7.4	10.5	7.2	6.6	8.9	6.7	7.5	7	8.3	5.9	7.1	8	6.7	7.8	9.9	11.3	12.8	11.5	8.8	7.6	8.4	8.4	16.6	10.6	6.6
AIC (mmol/mol)	48	NR	108	57	NR	NR	NR	NR	50.8	55	NR	86	79	57	91	55	49	74	50	58	52	67	41	54	64	50	62	85	100	116	102	73	60	68	68	151	92	49
pH	7.3	7.1	7.08	6.9	7.3	7.08	7	7.2	7.1	7.3	6.8	7.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	7.21	7.1	7.22	NR	7.2	7.01	7.4	7.2	7.05	7.15	7.25
PCO2 (mmHg)	33	13	22	9.6	30.2	10	21	29	18	30	11	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bicarbonates (mmol/L)	15	5	6.5	2.1	13.3	6.5	7	14	3.5	15.5	1.9	16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	13.3	4.2	7.4	4.8	10.6	8	3.2	12.1	9.4	3.2	5	13.3
Anionic gap (mmol/L)	17	32	25	37	NR	20	20	18	25	20	NR	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	23.1	32.8	29.1	35.2	33.4	35	32.8	21.9	29.6	20	23.3	13.3
Capillary blood β-hydroxybutyrates (mmo	NR	6.1	NR	5.8	1.8	2	8	NR	5.8	4.6	10	5.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Capillary blood β-hydroxybutyrates elevati	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	Yes
Lactate (mmol/L)	7	1.5	1.4	NR	1.13	1	0.9	NR	1.1	1.7	3.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Creatinin elevation	Yes	No	No	No	No	No	No	NR	No	No	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No
Creatinin (mg/dL)	2.23	NR	0.8	NR	NR	NR	0.8	NR	0.9	0.98	2	0.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.35	1.4	0.8	1.47	1.41	1.2	0.97	2.44	1.13	1.3	1.5	0.56
C-Peptide (nmol/L)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.5	0.5	0.4	0.3	0.8	0.37	0.4	0.5	0.2
Risk factors described for euDKA																																						
Prolonged fast	No	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Physical exercice	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Acute infection	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No
Alcohol	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Diet change	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Insulopenia	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes
Reducing or stopping insulin	Yes	No	No	No	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes
Surgery	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Deshydratation	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Corticoid	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

BMI = body mass index; SGLT2i : Sodium glucose transporter 2 inhibitors; euDKA : euglycemic diabetic ketoacidosis; DPP4i : Dipeptidyl peptidase-4 inhibitors; GLP-1 : Glucagon-like peptide-1; A1C = Haemoglobin A1c.

NR : Not reported. For 14 euDKA [19] confirmed, the pH reported is expressed as an average (+ IQR), unfortunately pH is not included for each case. For this reason, we did not use this average pH in our statistics.

Table 1. Data extracted from the original case reports.

First Author	Jhaveri	Lau			Lin	Menghoum							Meyer								Nappi	Owais	Pace	Papadokostaki	Peters		Pujara	Sharma				Yeo
Bibliographic reference	22	25			14	27							28								15	18	23	16	24		17	26				19
Country	Australia	Canada			Taiwan	Belgium							Australia								Italy	Pakistan	USA	Greece	USA		USA	USA				Korea
Year	2019	2017			2018	2020							2018								2019	2016	2018	2019	2015		2017	2018				2019
Design	case series	case series			case report	case series							case series								case report	case report	case series	case report	case series		case report	case series				case report
Sex	Female	Male	Male	Male	Female	Male	Male	Male	Female	Male	Male	Male	Female	Female	Male	Male	Male	Female	Female	Female	Female	Male	Male	Female	Male	Female	Female	Female	Female	Female	Female	Female
Age (years)	43	41	54	58	54	74	72	52	71	73	51	74	67	59	53	70	82	67	45	75	67	42	66	75	64	58	64	50	56	57	46	63	23
BMI (kg/m²)	NR	NR	30.6	23.2	23.7	32.7	34	31	29.7	23	24	32.6	25.8	NR	NR	NR	NR	NR	NR	NR	NR	21.5	NR	NR	NR	26.6	26.5	32.8	26	41.8	25	45.5	30.9	NR
Type of diabetes	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Diabetes duration (years)	5	NR	NR	NR	NR	18	17	4	17	3	15	9	14	NR	47	NR	10	14	11	10	NR	5	7	NR	NR	10	2	6	NR	5	0	0	20	2
Treatment of diabetes																																	
SGLT2i used before euDKA	Empa	Empa	Empa	Empa	Empa	Empa	Cana	Dapa	Dapa	Empa	Empa	Empa	Empa	Empa	Empa	Dapa	Dagu	Dapa	Dapa	Dapa	Dapa	Empa	Empa	Cana	Dagu	Empa	Cana	Cana	Empa	Cana	Cana	Cana	Empa	Dapa
Duration of use of SGLT2i before euDKA (days)	NR	NR	NR	NR	NR	60	870	90	540	2	15	875	1095	21	NR	14	60	90	180	180	NR	30	1	NR	NR	240	877	884	365	872	873	874	NR	730
Insulin	Yes	No	Yes	No	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No
Metformin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Glitazone	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No
Sulfonylurea	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No
Glinid	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
DPP4i	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No
GLP-1 RA	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No
euDKA symptoms																																	
Nausea	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
Emesis	Yes	No	Yes	No	No	Yes	No	No	Yes	No	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes	No	No
Abdominal pain	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	Yes	Yes	No	No	Yes	No	No	No	No	Yes	No	Yes	Yes
Asthenia	No	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No
Polyuria	No	No	No	No	No	No	No	Yes	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
Acetone breath	No	No	No	No	No	No	No	No	Yes	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No	No	No
Weight loss	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No	No	No
Poor oral intake	Yes	No	No	No	No	No	Yes	No	No	Yes	No	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Malaise	No	No	No	No	No	No	Yes	No	No	Yes	Yes	No	Yes	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Syncope	No	No	No	No	No	No	No	No	No	Yes	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No	No	No
Dizziness	No	No	No	No	No	No	No	No	No	No	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	No	No	No	No	No	No	No	No	No
Altered mental status	No	No	No	No	No	No	No	No	No	Yes	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No
Dehydration	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	NR	NR	NR	NR	NR	NR	NR	NR	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Tachypnea	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No
Tachycardia	No	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	NR	Yes	No	No	No	Yes	No	No	No	No	No	Yes	No	Yes
Biochimical parameters during euDKA																																	
Blood glucose (mg/dL)	343	250	216	111	172	217	178	280	238	112	198	157	151	336	623	248	522	122.5	174	270	535	299	202	224	225	203	150	169	202	377	235	203	400	148
AIC (%)	NR	11.7	9.2	7.6	6.4	10.6	8.7	9	9.4	9.4	8.2	13.4	5.6	6.8	7.6	9.6	13.4	9.3	6.5	10.2	NR	12	7.1	8.2	7.3	7.1	9.8	7.8	8.2	12.1	12	11.4	12.4	NR
AIC (mmol/mol)	NR	104	77	59.6	59.6	92	72.2	73.4	77.4	80	66.6	123.5	38.6	51	60	81	123	78	48	88	NR	107.7	54	66	56	54.4	83.6	62	66	109	108	92	112	NR
pH	6.8	7.3	7.2	7.3	7.3	7.08	7.2	NR	7.4	7.6	7	7.3	7.4	NR	6.9	7.3	7.2	7.3	NR	7.1	6.9	6.9	7.15	NR	NR	7.3	7.1	NR	7.3	7.4	7.2	7	7.2	7.02
PCO2 (mmHg)	NR	NR	32	36	32	19.1	20.1	NR	28.9	28.8	6.9	29.6	40	NR	NR	NR	NR	NR	NR	NR	NR	9	19.5	NR	NR	21	NR	NR	13	31.6	16.2	20.4	20	NR
Bicarbonates (mmol/L)	6	14	14	17	16	5.6	10.3	22	22	18	1.7	19	28	6	3	14	11	14	13.8	7.7	7	1.8	7.5	15	16	10.9	10	14	15	16	9	8	9	1.8
Anionic gap (mmol/L)	28	18	15	14	12	19.4	NR	19	21	30	17	18	40	48	32	34	26	24	26	42	31	24.9	19	19	29	17	18	25	19	24	23	22	23.8
Capillary blood β-hydroxybutyrates (mmol/L)	NR	NR	5.3	4.6	0.9	NR	6	3	1.9	1.6	6.4	6.4	1.3	NR	5.2	5.8	6	7	7	6.2	7	NR	NR	4.62	4.9	NR	NR	NR	8	NR	NR	NR	NR	1.6
Capillary blood β-hydroxybutyrates elevation	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lactate (mmol/L)	NR	NR	1.1	1.4	2.8	1.8	1.4	NR	1.2	1.15	2.1	1.2	1.4	NR	NR	NR	NR	NR	NR	NR	1.3	NR	NR	NR	NR	1.1	NR	1.4	NR	NR	NR	NR	NR	1.6
Creatinin elevation	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	No	NR	NR	NR	NR	NR	NR	NR	Yes	NR	NR	NR	NR	Yes	No	No	No	NR	NR	NR	NR	No
Creatinin (mg/dL)	NR	NR	1.5	0.6	0.6	NR	0.48	2.3	0.8	0.78	1.3	0.8	1	NR	NR	NR	NR	NR	NR	NR	1.7	NR	NR	NR	NR	1.33	1.2	0.8	1.4	NR	NR	NR	NR	0.8
C-Peptide (nmol/L)	NR	NR	NR	NR	NR	NR	1	1.2	0.6	1.1	0.2	0.5	0.2	NR	NR	NR	NR	NR	NR	NR	0.43	NR	NR	NR	NR	1.4	NR	0.6	NR	NR	NR	NR	NR	NR
Risk factors described for euDKA																																	
Prolonged fast	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	Yes
Physical exercice	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Acute infection	Yes	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes
Alcohol	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Diet change	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Insulopenia	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No
Reducing or stopping insulin	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Surgery	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No
Deshydratation	Yes	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Corticoid	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

BMI = body mass index; SGLT2i : Sodium glucose transporter 2 inhibitors; euDKA : euglycemic diabetic ketoacidosis; DPP4i : Dipeptidyl peptidase-4 inhibitors; GLP-1 : Glucagon-like peptide-1; A1C = Haemoglobin A1c.

NR : Not reported. For 14 euDKA [19] confirmed, the pH reported is expressed as an average (+ IQR), unfortunately pH is not included for each case. For this reason, we did not use this average pH in our statistics.

Table 2
Clinical characteristics, drugs used and biochemical values of T2DM patients treated with SGLT2i and diagnosed with euglycaemic diabetic ketoacidosis.

Agent	**All**		**canagliflozin**		**dapagliflozin**		**empagliflozin**	
Baseline characteristics	***mean ± SD (n) or n (%)***							
Total number of T2DM patients diagnosed with euDKA	72		12	*(16.7)*	31	*(43.1)*	29	*(40.3)*
Age (years)	57.6 ± 14.9		57.2 ± 13.11		55.8 ± 17.4		60.8 ± 12.5	
Gender (Male/Female)	37/35		5/7		13/18		19/10	
Diabetes duration (years)	12.2 ± 9.9	*(56)*	8.1 ± 7.3	*(10)*	11.7 ± 9.1	*(24)*	14.7 ± 11.4	*(22)*
BMI (kg/m^2)	27.6 ± 6.2	*(36)*	31.9 ± 7.6	*(9)*	25.8 ± 6.1	*(13)*	26.5 ± 3.9	*(14)*
Glucose-lowering drugs								
Number of patients:	72		12		31		29	
Insulin	26	*(36.1)*	5	*(41.6)*	9	*(29.0)*	12	*(41.3)*
Oral antidiabetic drugs:	58	*(80.5)*	11	*(91,6)*	25	*(80.6)*	22	*(75.8)*
- Biguanides	51	*(88.0)*	6	*(54,5)*	24	*(96.0)*	21	*(95.4)*
- DPP4is	16	*(27.6)*	4	*(36.3)*	8	*(32.0)*	4	*(18.1)*
- Sulfonylureas	10	*(17.2)*	1	*(9.1)*	6	*(24.0)*	3	*(13.6)*
- GLP-1 receptor agonists	5	*(8.6)*	1	*(9.1)*	1	*(4.0)*	3	*(13.6)*
- Glitazones	3	*(5.2)*	1	*(9.1)*	0	*(0)*	2	*(9.0)*
- Glinides	1	*(1.7)*	0	*(0)*	1	*(4)*	0	*(0)*
- Not reported	14	*(24.1)*	1	*(9.1)*	6	*(24.0)*	7	*(31.8)*
SGLT2is use before euDKA (days)			30 to 885	*(11)*	14 to 730	*(19)*	1 to 2690	*(16)*
Number of patients with described comorbidities:	38		11		9		18	
- GFR <60, micro or macroalbuminuria	3	*(7.8)*	1	*(9.0)*	0	*(0)*	2	*(11.1)*
- Cardiovascular disease	7	*(18.4)*	1	*(9.0)*	3	*(33.0)*	3	*(16.6)*
Number of patients with symptoms and clinical manifestations on admission	50		11		19		20	
Symptom								
- Nausea	24	*(48)*	7	*(63.6)*	5	*(26.3)*	12	*(60.0)*
- Stomach-area (abdominal) pain	19	*(38)*	3	*(27.2)*	5	*(26.3)*	11	*(55.0)*
- Emesis	18	*(36)*	5	*(45.4)*	4	*(21.0)*	9	*(45.0)*
- Appetite disorders	11	*(22)*	4	*(36.3)*	2	*(10.5)*	5	*(25.0)*
- Asthenia	10	*(20)*	4	*(36.3)*	2	*(10.5)*	4	*(20.0)*
- Polyuria	5	*(10)*	1	*(9.0)*	2	*(10.5)*	1	*(5.0)*
- Weakness	5	*(10)*	1	*(9.0)*	0	*(0)*	4	*(20.0)*
- Weight loss	2	*(4)*	0	*(0)*	1	*(5.2)*	1	*(5.0)*
- Acetone smell in exhaled air	1	*(2)*	0	*(0)*	1	*(5.2)*	0	*(0)*
Clinical manifestation								
- Tachypnea	17	*(34.0)*	5	*(45.0)*	3	*(16.0)*	9	*(45.0)*
- Tachycardia	15	*(30.0)*	5	*(45.0)*	3	*(16.0)*	7	*(35.0)*
-Dehydration	7	*(14.0)*	0	*(0)*	2	*(11.0)*	5	*(25.0)*
- Consciousness disorders	5	*(10.0)*	2	*(18.0)*	0	*(0)*	3	*(15.0)*
- Respiratory rate (breaths/min)	23.7 ± 10.6	*(10)*	26 ± 7.2	*(3)*	22.7 ± 5	*(3)*	22.8 ± 16.8	*(4)*
- Heart rate (bpm)	112.9 ± 19	(15)	122.8 ± 26.9	*(5)*	116.7 ± 11.7	*(3)*	104.3 ± 12	*(7)*
Biochemical parameters								
A1C (%)	8.9 ± 2.2	*(63)*	9.4 ± 2.2	*(11)*	9.3 ± 2.3	*(26)*	8.5 ± 2.2	*(26)*
A1C (mmol/mol)	74.5 ± 23.8	*(63)*	78 ± 23.3	*(11)*	78.1 ± 23.8	*(26)*	69.5 ± 24	*(26)*
Blood glucose (mg/dL)	282.8 ± 159.2	*(58)*	260.3 ± 133.7	*(11)*	299 ± 159.6	*(25)*	275.7 ± 174.7	*(25)*
pH	7.2 ± 0.17	*(51)*[a]	7.2 ± 0.15	*(9)*	7.2 ± 0.13	*(21)*	7.2 ± 0.2	*(21)*
PCO2 (mmHg)	22.4 ± 9	*(29)*	22.7 ± 8	*(8)*	20.7 ± 7.5	*(6)*	22.9 ± 10.5	*(15)*
Bicarbonates (mmol/L)	10.4 ± 5.8	*(58)*[a]	10.9 ± 4.3	*(11)*	10.3 ± 5.7	*(25)*	10.3 ± 6.8	*(22)*
Anionic gap (mmol/L)	24.8 ± 7.7	*(55)*	21.4 ± 5.9	*(11)*	27.1 ± 6.9	*(23)*	23.9 ± 8.7	*(21)*
Capillary β-hydroxybutyrate (mmol/L)	5 ± 2.3	*(30)*[a]	5.4 ± 0.7	*(3)*	5.3 ± 2.1	*(16)*	4.4 ± 2.8	*(11)*
Lactate (mmol/L)	1.7 ± 1.3	*(23)*	2.8 ± 2.8	*(4)*	1.2 ± 0.26	*(6)*	1.6 ± 0.7	*(13)*
Creatinine (mg/dL)	1.2 ± 0.5	*(42)*	1.1 ± 0.7	*(5)*	1.2 ± 0.5	*(16)*	1.2 ± 0.4	*(14)*
C-peptide (nmol/L)	0.59 ± 0.35	*(19)*	1.2 ± 0.3	*(2)*	0.5 ± 0.3	*(11)*	0.5 ± 0.3	*(6)*

T2DM: Type 2 diabetes mellitus; euDKA: euglycaemic diabetic ketoacidosis; BMI = body mass index; SGLT2i: Sodium glucose transporter 2 inhibitor; euDKA: euglycemic diabetic ketoacidosis.
DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1: Glucagon-like peptide-1; A1C = Haemoglobin A1c.
In addition, for 14 euDKA(30)confirmed, the pH reported is expressed as an average (+IQR), unfortunately pH is not included for each case. For this reason, we did not use this average pH in our statistics.
[a] If the number of pH, bicarbonate or ketones is not equal to 72, it is because in 7 articles, the pH value is not present, on the other hand the presence or the value ketone and HCO3 are present (see Table 1).

SGLT2is in our review.

In most of the described case reports, the euDKA is characterized biologically by moderate hyperglycemia (<250 or 300 mg/dl (13.8 or 16.65 mmol/L)) with increase serum anion gap level (range of normal values often 8−10 mEq/L), and accumulation of ketone bodies (hydroxybutyric acid), for which the pathological threshold is > 0.6 mmol/l. The average HbA_1c at admission was elevated, indicating perfectible glycemic control over the course of 2−3 months preceding the euDKA episode.

We also demonstrated that metabolic acidosis was not related to lactic acidosis (as in the case of biguanides), indeed lactatemia was not high, and the correlation was not significant between pH and lactatemia ($p = 0.47$) whereas it was significant between pH and β-OHB. Moreover, glycemic levels at admission did not necessarily reflect the severity of the euDKA [35], we did not find significant correlations between glycaemia and pH or levels of β-OHB (Fig. 2).

This review confirms the relevance of assaying capillary ketones (β-OHB) and pH to establish a suspected diagnosis of euDKA in

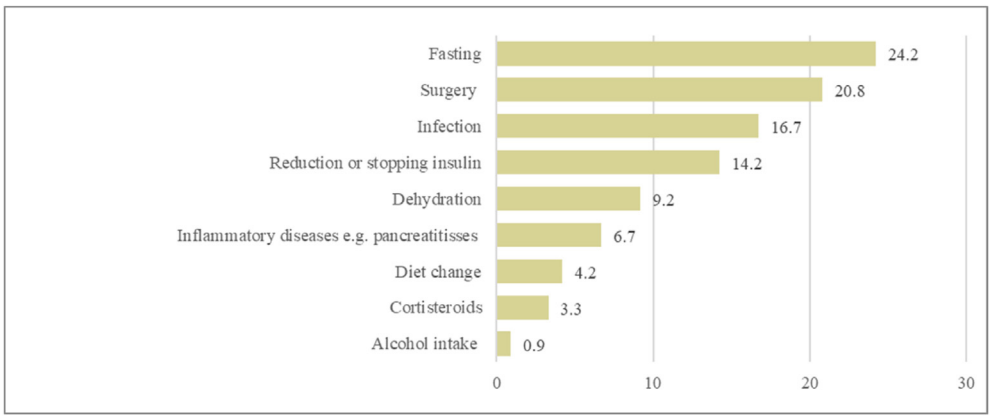

Fig. 1. Frequency (%) of conditions associated with euDKA in patients with T2DM treated with SGLT2i.

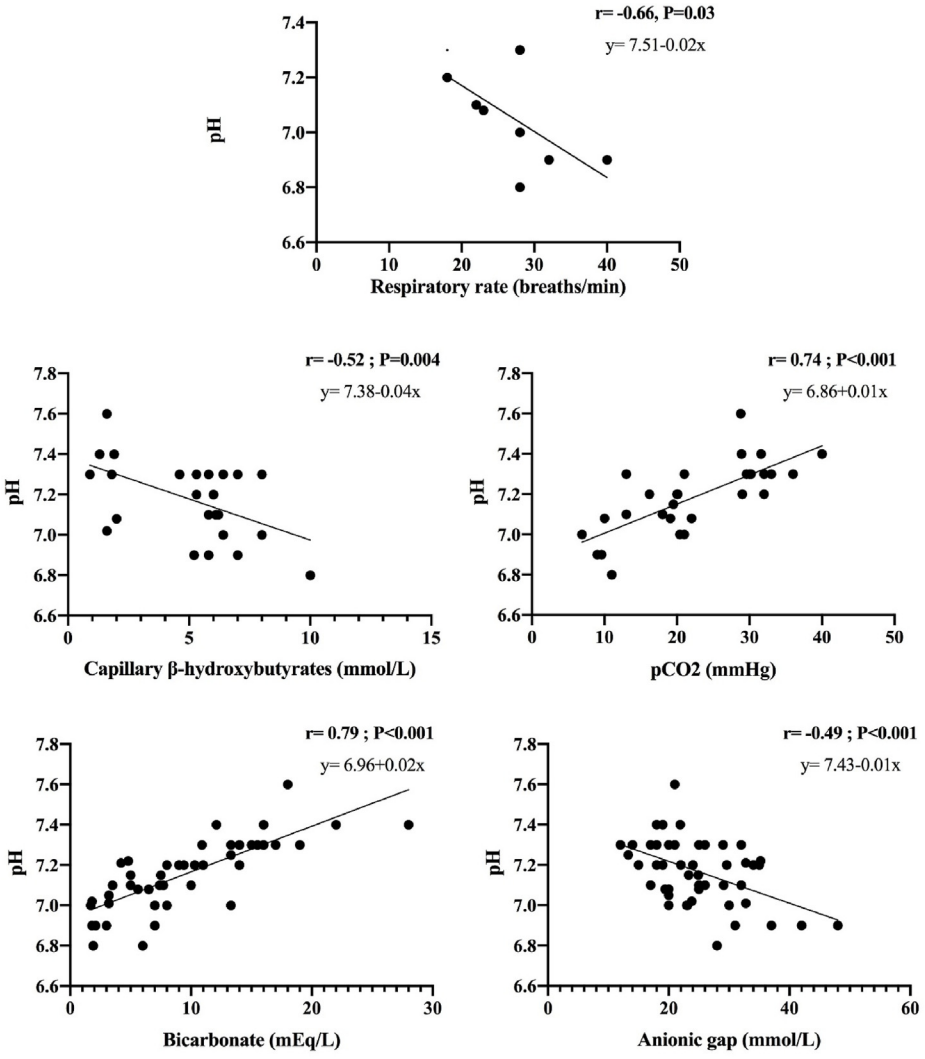

Fig. 2. Correlation between pH and clinical or labs variables associated with euDKA.

patients treated with SGLT2is. It needs to be kept in mind, however, that confounding incorrectly low results of β-OHB can occur in patients who are dehydrated, hypotensive, in a state of shock, or exhibiting a hyperosmolar hyperglycemic syndrome.

In terms of the triggering events associated with euDKA, we noted that physical stresses such as a surgical intervention or a severe infection, prolonged fasting, or a reduction of insulin dosage represent most conditions identified as likely promoters of euDKA (Fig. 1). The role of these enabling factors is best explained by several pathophysiological mechanisms involving *(i)* a change in

the insulin/glucagon ratio, *(ii)* an accumulation of ketone bodies, and/or *(iii)* a decrease in the blood volume.

(i) Insulin/glucagon ratio

The euDKA occurs preferentially in diabetic patients exhibiting reduced residual insulin secretion (e.g., long-lasting T2DM with low *C*-peptide or LADA) or secondary diabetes in the context of acute/chronic pancreatitis, or even because of prolonged fasting [34–36].

In such diabetics, the risk of euDKA is greater, as SGLT2i selectively decrease the insulin/glucagon ratio. Indeed, because of their mode of action, SGLT2i produce a substantial glycosuria. The glucose-lowering effect of SGLT2i, which is in the order of 20–25 mg/dL (1.11–1.39 mmol/L) after fasting or postprandially, decreases the stimulus for insulin production by the β cells [37]. This decrease in endogenous (or exogenous) insulin leads to a reduction in portal and systemic insulinemia, with a corresponding decrease of glucose entry into target tissues in which glucose entry is mediated by insulin, eventually leading to increased lipolysis in white adipose tissue; raised levels of free fatty acids; and increased hepatic ketogenesis. Furthermore, an increase in glucagonemia was observed with SGLT2i, which enhances the expression of the preproglucagon gene by a direct effect on pancreatic α cells. This relative SGLT2i-driven hyperglucagonemia promotes, in the liver, the secretion of kisspeptin-1**,** which in turn inhibits residual insulin secretion. Hence an increase in glucagonemia can, besides an effect on the denominator of the insulin/glucagon ratio, potentially reduce the absolute insulinemia by decreasing residual insulin [38–41].

(ii). Accumulation of ketone bodies

It was also hypothesized that SGLT2is can decrease kidney clearance of ketone bodies, as well as promote their systemic accumulation. Indeed, phlorizin, a non-selective inhibitor of the SGLT1 and SGLT2 cotransporters, increases renal tubular reabsorption of acetoacetate, a ketone body [42].These two mechanisms *(i) and (ii)* combined lead to the accumulation of ketone bodies, even when blood glucose levels are barely increased [40].

(iii) . Hypovolemia

SGLT2is promote hypovolemia via glycosuria and natriuresis. This hypovolemia induced by enhanced diuresis leads to direct activation of β1-adrenergic receptors, resulting in glucagon release and secretion of counter-regulatory hormones (cortisol and catecholamines), the latter exacerbating lipolysis and ketogenesis [43].

A combination of the three conditions *(i), (ii), and (iii)* can be encountered during surgical intervention, hemorrhagic shock, and/or severe sepsis [44].

Lastly, recent studies have shown that there can be a degree of variability in the expression of SGLT2 receptors, which contributes to a degree of variability in the pharmacological responses to SGLT2i [45,46].

Therefore, on 19 March 2020, the FDA [47] proposed stopping SGLT2is, 3 or 4 days (3 days for dapagliflozin, empagliflozin, and canagliflozin, or 4 days for ertugliflozin) before surgery under general anesthesia. Given that the average half-life of SGLT2 is approximately 12.5 h, it suggests that clinicians suspend SGLT2i for a period longer than 48 h prior to a major surgical intervention to ensure complete elimination of the medication before the surgery.

Subsequent resumption of SGLT2is should be envisaged on a case-by-case basis, once the acute period (surgery, sepsis, and fasting) has ended. However, according to some medical societies [48], once euDKA has been diagnosed, it is recommended to discontinue forever the SGLT2is.

Our review of the literature confirms the results of previous publications [34,49] as regards the symptoms, laboratory values, and the clinical presentation of euDKA in patients with T2DM. We also show that euDKA occurs in middle-aged patients with on average more than ten years of diabetes, even in the absence of cardiac or renal comorbidities.

The strengths of this review are the number of described cases, exclusively with T2DM; the analysis of individual data; and the fact of having quantified the metabolic severity of euDKA based on the levels of β–OHB, in addition to the glycemic values at admission. Lastly, we show for the first time that despite the substantial use of metformin in these patients, lactic acidosis was an unlikely driver to the metabolic acidosis. We also found the same frequency of predisposing factors for euDKA as reported previously, except for LADA, because these clinical cases were not retained [34].

Our study has several limitations.

Although an in-depth literature search was carried out, not all articles regarding euDKA and SGLT2is could be identified. Our survey only involved one bibliographic database in two languages. The collected data are, therefore, limited, which makes it hard to apply the conclusions to the entire population of people with T2DM treated with SGLT2is. Although it has some limitations, this study was able to assemble a compilation of information based on the published literature detailing the cases of euDKA in patients with T2DM.

5. Conclusion

The increasing use of SGLT2is can in certain situations be associated with euDKA. Health professionals need to be more aware of this diagnosis in patients taking these medications and exhibiting unexplained symptoms such as nausea, vomiting, and abdominal pain. Probing for ketonuria or ketonemia should be undertaken in patients exhibiting the above-mentioned symptoms, even in the absence of frank hyperglycemia. SGLT2is should be used cautiously in certain patients exhibiting known risk factors predisposing to euDKA.

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No applicable.

Availability of data and material

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Authors' contributions

NM and PO independently performed the literature search.
NM, PO, and MPH drafted, revised, and finalized the manuscript.

Declaration of competing interest

The other authors declare that they have no conflict of interest.

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