



Diabetic Ketoacidosis in Type 2 Diabetes: A Narrative Review of the Presentation That Is Not Expected

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Abstract

Diabetic ketoacidosis is taught as a complication of type 1 diabetes presenting with marked hyperglycaemia. Neither half of that description is reliable. People with type 2 diabetes develop ketoacidosis during states of relative insulin deficiency, and a proportion present with a glucose below the conventional diagnostic threshold of 13.9 mmol/L. Euglycaemic presentations account for approximately 2 to 3 per cent of ketoacidosis overall, but in a systematic review of 34 published cases associated with sodium-glucose cotransporter 2 inhibitors, 71 per cent met euglycaemic criteria. The mechanism is understood: urinary glucose loss lowers plasma glucose, insulin secretion falls, glucagon rises and ketogenesis proceeds while glucose remains near normal. The clinical problem is that the finding which prompts the diagnosis is absent, and the differential considered first includes sepsis, lactic acidosis and renal failure. This review sets out the presentation, the precipitants reported, and the limitations of an evidence base built largely from case reports.

Keywords: Diabetic ketoacidosis; Euglycaemic ketoacidosis; Type 2 diabetes; SGLT2 inhibitors; Diagnostic delay

Introduction

Diabetic ketoacidosis is conventionally defined by a triad of hyperglycaemia, high anion gap metabolic acidosis and ketosis, with a glucose above 13.9 mmol/L among the diagnostic criteria [1,2]. It is taught primarily as a complication of type 1 diabetes.

Both parts of that framing are incomplete. People with type 2 diabetes develop ketoacidosis during states of relative insulin deficiency, most often precipitated by inadequate medication or intercurrent illness [3,4,27]. Ketosis-prone type 2 diabetes has been described as a distinct set of syndromes [27], and the biochemical differences between ketoacidosis in the two types characterised directly [28,29]. And a subset of presentations occur with a glucose below the diagnostic threshold, a variant first described more than fifty years ago and termed euglycaemic ketoacidosis [5,6].

The clinical consequence is diagnostic delay. This review examines how the presentation differs, why the population at

risk has grown, and how far a literature composed largely of case reports can support conclusions.

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, acute medicine and critical care journals were searched for reports of ketoacidosis in type 2 diabetes and of euglycaemic presentation. Search terms combined diabetic ketoacidosis and euglycaemic diabetic ketoacidosis with type 2 diabetes, sodium-glucose cotransporter 2 inhibitor, diagnostic delay and case series. Reference lists of reviews [7,8] were screened by hand for primary sources.

Eligibility: Reports were included if they described ketoacidosis in people with type 2 diabetes with sufficient biochemical detail to characterise the presentation, or synthesised such reports. Individual case reports are identified as such throughout, because they form the majority of this literature

and carry the limitations that implies.

Data extraction and handling: Population, precipitant, glucose at presentation, acid-base findings and the reported course were extracted as published. The study type is stated alongside every observation, since a case report describes what happened to one person and cannot support a statement about frequency. This review reports published findings and does not constitute guidance on the prescription, holding or withdrawal of any medicine. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How the presentation differs: Euglycaemic ketoacidosis is characterised by high anion gap metabolic acidosis and ketonaemia with a blood glucose below 13.9 mmol/L, the threshold that ordinarily forms part of the diagnostic criteria (Figure 2) [5,9]. The acidosis and ketosis are as marked as in conventional presentations; it is the glucose that differs [6,10].

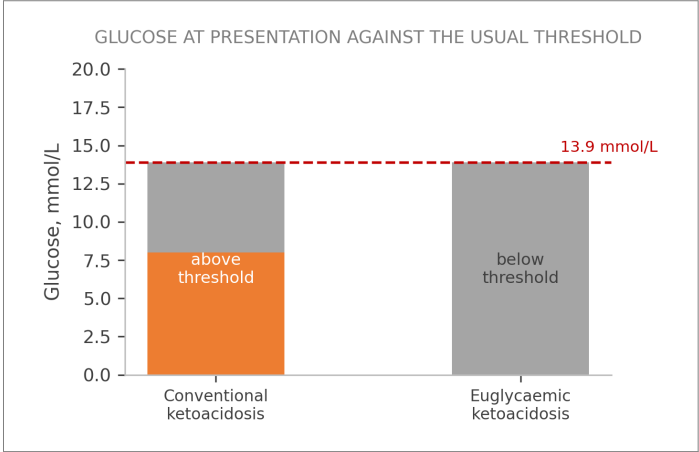


Figure 2: Glucose at presentation against the conventional diagnostic threshold [5,9]

How often it occurs: Euglycaemic presentations have been reported to account for approximately 2 to 3 per cent of ketoacidosis presentations overall (Figure 3) [9]. The proportion is markedly higher in cases associated with sodium-glucose cotransporter 2 inhibitors: in a systematic review of 34 published cases, 71 per cent met criteria for euglycaemic ketoacidosis (Figure 1) [7,11].

Table 1: How the two presentations differ, as described in the published literature [5,9]

Table 2: Presentations described in published reports of euglycaemic ketoacidosis

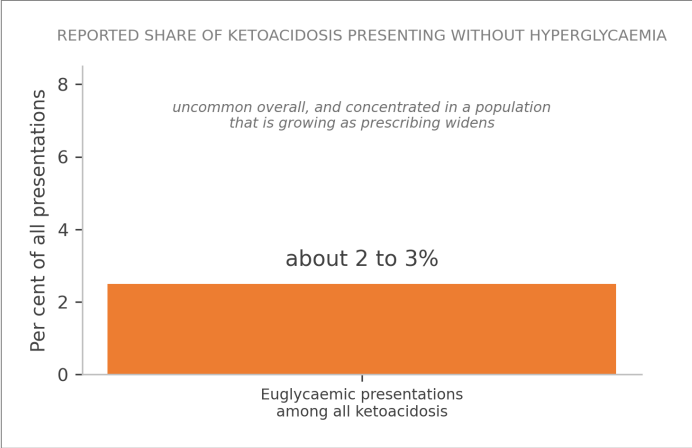


Figure 3: Reported share of ketoacidosis presenting without hyperglycaemia [9]

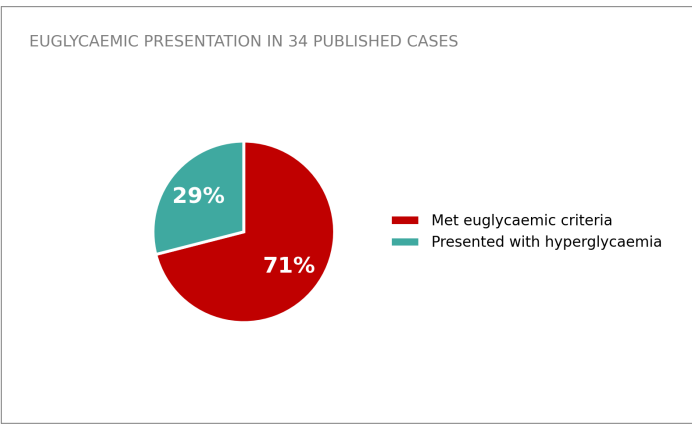


Figure 1: Euglycaemic presentation among 34 published cases associated with SGLT2 inhibitors [7,11]

The mechanism: These agents lower plasma glucose through enhanced urinary glucose excretion. The resulting fall in glucose reduces insulin secretion and promotes glucagon release, which favours lipolysis and hepatic ketogenesis. Combined with increased renal reabsorption of ketone bodies, this produces a biochemical state in which ketoacidosis develops while glucose remains near normal (Figure 4) [7,12,13]. The pharmacological effect may persist beyond several half-lives of elimination [3,14].

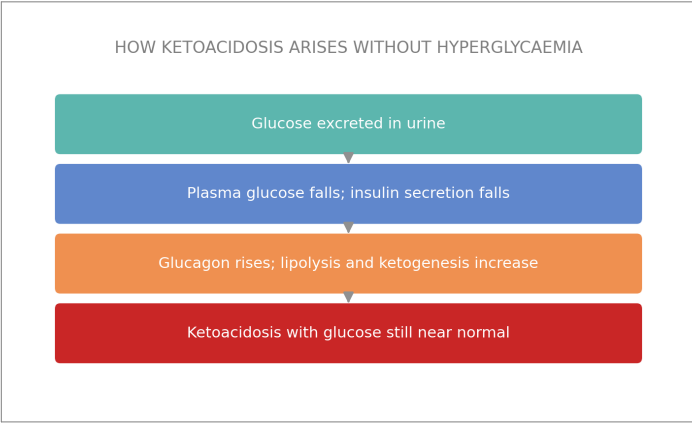


Figure 4: How ketoacidosis arises without hyperglycaemia [7,12,13]

What precipitates it: Reported precipitants include surgery and perioperative stress, acute intercurrent illness, reduced

carbohydrate intake, volume depletion, fasting before procedures and abrupt withdrawal of insulin (Figure 6) [3,14,15]. In one report, transition from long-term insulin to an oral agent preceded the presentation [11]. Older patients have been described as particularly susceptible, with reduced thirst, lower renal function, limited access to food or fluid and multiple comorbidities cited as contributors [9,16].

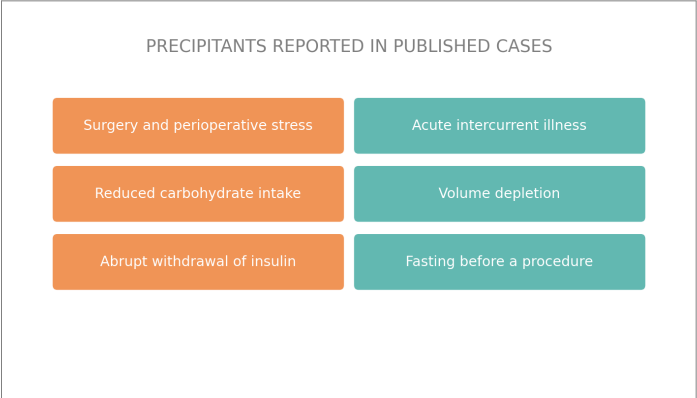


Figure 6: Precipitants reported in published cases [3,14,15]

Feature	Conventional presentation	Euglycaemic presentation
Glucose	Above 13.9 mmol/L	Below 13.9 mmol/L
Anion gap acidosis	Present	Present
Ketonaemia	Present	Present
Prompt to test for ketones	Hyperglycaemia	Frequently absent
Share of presentations	The majority	About 2 to 3% [9]

What it is mistaken for: In the absence of marked hyperglycaemia, the differential considered first has included sepsis, lactic acidosis, renal failure and non-diabetic causes of ketoacidosis (Figure 5) [10,17]. Reported presentations have included acute respiratory distress, unexplained falls and non-specific symptoms such as nausea, vomiting, fatigue and confusion, none of which points towards the diagnosis [9,10,16].

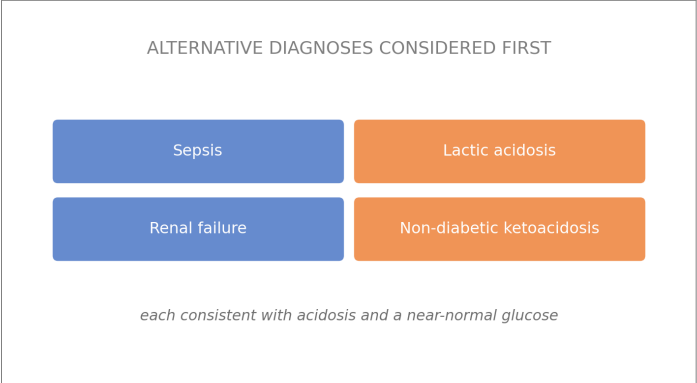


Figure 5: Alternative diagnoses considered before ketoacidosis was identified [10,17]

Reported presentation	Setting described
Acute respiratory distress	Emergency department, elderly patient [10]
Unprovoked falls	Emergency department, elderly patient [16]
Nausea, vomiting, malaise	Repeatedly across reports [15,17]
Postoperative deterioration	Surgical and anaesthetic literature [3,14]

Reported presentation	Setting described
Vague symptoms after regimen change	Outpatient transition of therapy [11]

The population at risk has widened: These agents are now prescribed for cardiovascular and renal indications as well as for glycaemic control, including in people without marked hyperglycaemia [11,18,19]. The number of people exposed has therefore grown, and increasingly under the care of clinicians whose primary concern is not diabetes [12,20]. Pharmacovigilance and cohort analyses have estimated the excess risk associated with these agents against other glucose-lowering drugs [22,23,24]. Case series from lower-resource settings describe the same presentation with the added difficulty of limited access to ketone measurement [21].

Observation	What follows from it
Glucose may be near normal	The usual prompt to test ketones is absent [5,9]
Acidosis is as severe	Delay carries the same risk as in conventional cases [10]
Prescribing has widened	Exposure extends beyond diabetes services [18,19]
Effect outlasts elimination	Holding the drug does not act immediately [3,14]

Table 3: Features of this presentation and their practical consequence

What the larger datasets show: Beyond the case literature, cohort and pharmacovigilance analyses have compared rates of ketoacidosis between these agents and other glucose-lowering drugs, and clinical programme data have reported event rates within trial populations [22,23,24]. These sources carry denominators that the case reports lack, and they address a different question: how often ketoacidosis occurs, rather than how it presents when it does [24,34].

Ketoacidosis in type 2 diabetes without these agents: The drug-associated form dominates recent publication, but ketoacidosis in type 2 diabetes was described long before these agents existed. Ketosis-prone syndromes have been characterised as a distinct group in which people presenting with ketoacidosis subsequently prove to have preserved beta cell function and can be managed without long-term insulin [4,27]. Comparative studies describe clinical and biochemical differences between ketoacidosis arising in the two types of diabetes [28,29].

Discussion

The diagnostic problem here is unusually clean. Ketoacidosis is normally suspected because the glucose is high, and in this presentation the glucose is not high. Every other element of the syndrome is present and as severe, so the delay arises entirely from the absence of the trigger to look [5,9,10].

That gives a narrow and reasonably firm implication: in a person with diabetes taking one of these agents who presents with acidosis, nausea, vomiting or malaise, the glucose does not

exclude the diagnosis and ketones need measuring [15,17]. This is repeated across the case literature to the point of unanimity, which is unusual, and it is the one recommendation the evidence supports without difficulty.

The evidence base itself needs stating plainly, because it is weak in a specific way. Most of this literature is individual case reports, and the largest synthesis pooled 34 of them [7,11]. Published cases are selected for being instructive, unusual or severe, so the 71 per cent figure describes the published cases and not the underlying population. It cannot be read as the proportion of ketoacidosis in treated patients that is euglycaemic, and the 2 to 3 per cent figure for presentations overall comes from a different sampling frame again [9].

What the mechanism does support is a prediction rather than a frequency. Urinary glucose loss lowering plasma glucose and thereby reducing insulin secretion is a coherent explanation of how ketogenesis proceeds at a normal glucose, and it predicts the precipitants reported: anything that reduces carbohydrate intake or increases counter-regulatory stress [7,12,13]. Surgery, fasting before procedures and acute illness recur across reports for that reason, and the periods when a patient stops eating are the periods of concern [3,14].

The widening of prescribing is the part most likely to matter operationally. These agents are used for heart failure and chronic kidney disease in people who may have no marked hyperglycaemia at all, which places the exposed population partly outside diabetes services [18,19]. A cardiologist or nephrologist starting one of these drugs may not be the clinician who sees the patient acutely, and the acute physician may not connect a normal glucose with a metabolic acidosis. Reports have repeatedly called for clearer holding parameters around procedures and illness [3,14,20]. Perioperative reviews and anaesthetic guidance address this directly [32,33], international consensus on risk management exists for the analogous problem in type 1 diabetes [31], and the concern has been described as predictable, detectable and preventable [30].

There is a reasonable objection to the emphasis in this literature. Ketoacidosis associated with these agents is uncommon, they carry demonstrated cardiovascular and renal benefit, and a review dwelling on a rare adverse presentation risks distorting the balance [18,19,30]. The response is that the argument here concerns recognition rather than prescribing: nothing in the case literature bears on whether these drugs should be used, only on what to measure when a patient taking one becomes unwell.

What would improve the evidence is straightforward and largely absent. Prospective surveillance with a defined denominator, recording glucose at presentation in every episode of ketoacidosis, would establish what proportion is euglycaemic in a treated population rather than in a published sample [24,25]. Until that exists, the frequency figures in this article should be read as descriptions of a literature and not of a population [7,9].

Study limitations

The limitations belong to the underlying literature and are substantial. Most reports are individual cases, which cannot establish frequency, causation or the characteristics of those affected, and are subject to publication bias towards the unusual and the severe [7,11,15]. The largest synthesis pooled 34 published cases, which is a sample of the literature rather than of patients [7]. Definitions of euglycaemia in this context vary between reports, with thresholds of 13.9 and 11.1 mmol/L both used, which affects what counts as a euglycaemic case [5,17]. The 2 to 3 per cent figure for the share of all ketoacidosis derives from a different population and sampling frame from the case series [9]. Denominators are almost entirely absent, so no incidence can be calculated from these sources [12,20]. Reports come disproportionately from settings with ready access to ketone and acid-base measurement, and case series from elsewhere note that limited diagnostic resources compound the difficulty [21]. And ketoacidosis in type 2 diabetes unrelated to these agents, including ketosis-prone presentations, is less well represented in the recent literature than the drug-associated form, which may distort the overall picture [4,8,26,34]. Definitions of ketoacidosis in adults have themselves been the subject of methodological review [25].

2. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. "Diabetic ketoacidosis". *Nat Rev Dis Primers* 6(2020):40.
3. Case report authors. "SGLT2 inhibitor-induced euglycemic diabetic ketoacidosis: a case report". *Mayo Clin Proc Innov Qual Outcomes* 4(2020):337-341.
4. Umpierrez GE, Smiley D, Kitabchi AE. "Narrative review: ketosis-prone type 2 diabetes mellitus". *Ann Intern Med* 144(2006):350-357.
5. Munro JF, Campbell IW, McCuish AC, Duncan LJP. "Euglycaemic diabetic ketoacidosis". *BMJ* 2(1973):578-580.

Conclusion

Ketoacidosis in type 2 diabetes is not rare and does not always announce itself with a high glucose. Roughly 2 to 3 per cent of presentations occur below the conventional threshold, and among published cases associated with sodium-glucose cotransporter 2 inhibitors that proportion was 71 per cent. The acidosis is as severe; only the finding that usually prompts the diagnosis is missing, which is why sepsis, lactic acidosis and renal failure are considered first. The practical conclusion is a single sentence: in a patient taking one of these agents who is acidotic, unwell or vomiting, a normal glucose does not exclude ketoacidosis. The frequency figures behind that sentence rest on case reports and should be treated as descriptive rather than epidemiological.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

- Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. "Hyperglycemic crises in adult patients with diabetes". *Diabetes Care* 32(2009):1335-1343.
- Modi A, Agrawal A, Morgan F. "Euglycemic diabetic ketoacidosis: a review". *Curr Diabetes Rev* 13(2017):315-321.
- Burke KR, Schumacher CA, Harpe SE. "SGLT2 inhibitors: a systematic review of diabetic ketoacidosis and related risk factors in the primary literature". *Pharmacotherapy* 37(2017):187-194.
- Nasa P, Chaudhary S, Shrivastava PK, Singh A. "Euglycemic diabetic ketoacidosis: a missed diagnosis". *World J Diabetes* 12(2021):514-523.
- Falls case authors. "When falls reveal acidosis: unmasking sodium-glucose co-transporter 2 inhibitor-induced euglycemic diabetic ketoacidosis". *Cureus* (2025).
- Case report authors. "Euglycemic diabetic ketoacidosis with sodium-glucose transport protein 2 inhibitors". *Cureus* 17(2025):e80531.
- Almascati Y, Alhumaiqani A. "Euglycemic diabetic ketoacidosis triggered by sodium-glucose cotransporter 2 inhibitor use in a patient with type 2 diabetes mellitus". *Cureus* 17(2025):e84170.
- Goldenberg RM, Berard LD, Cheng AYY, Gilbert JD, Verma S, Woo VC, et al. "SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis". *Clin Ther* 38(2016):2654-2664.
- Ogawa W, Sakaguchi K. "Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors". *J Diabetes Investig* 7(2016):135-138.
- Case report authors. "Fall, fracture, and two episodes of euglycemic diabetic ketoacidosis". *Cureus* 14(2022):e26069.
- Case report and review authors. "SGLT-2 inhibitor-associated euglycemic diabetic ketoacidosis: a case report and a literature review". *Cureus* 14(2022):e26043.
- Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. "Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition". *Diabetes Care* 38(2015):1687-1693.
- Novel presentation authors. "A novel presentation of euglycemic diabetic ketoacidosis associated with SGLT2 inhibitor and weekly GLP-1 agonist: case report". *Clin Case Rep* (2025).
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. "Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes". *N Engl J Med* 373(2015):2117-2128.
- Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. "Dapagliflozin in patients with chronic kidney disease". *N Engl J Med* 383(2020):1436-1446.
- Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. "American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis". *Endocr Pract* 22(2016):753-762.
- Case series authors. "Euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter 2 inhibitors: a case series and clinical reflections". *Clin Case Rep* (2025).
- Erondu N, Desai M, Ways K, Meininger G. "Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program". *Diabetes Care* 38(2015):1680-1686.
- Fralick M, Schneeweiss S, Paterno E. "Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor". *N Engl J Med* 376(2017):2300-2302.
- Wang Y, Desai M, Ryan PB, DeFalco FJ, Schuemie MJ, Stang PE, et al. "Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents". *Diabetes Res Clin Pract* 128(2017):83-90.
- Dhatariya KK. "Defining and characterising diabetic ketoacidosis in adults". *Diabetes Res Clin Pract* 155(2019):107797.
- Umpierrez GE, Korytkowski M. "Diabetic emergencies: ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia". *Nat Rev Endocrinol* 12(2016):222-232.
- Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. "Syndromes of ketosis-prone diabetes mellitus". *Endocr Rev* 29(2008):292-302.
- Newton CA, Raskin P. "Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences". *Arch Intern Med* 164(2004):1925-1931.

29. Barski L, Nevzorov R, Rabaev E, Jotkowitz A, Harman-Boehm I, Zektser M, et al. "Diabetic ketoacidosis: clinical characteristics, precipitating factors and outcomes of care". *Isr Med Assoc J* 14(2012):299-303.
30. Rosenstock J, Ferrannini E. "Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors". *Diabetes Care* 38(2015):1638-1642.
31. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. "International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors". *Diabetes Care* 42(2019):1147-1154.
32. Milder DA, Milder TY, Kam PCA. "Sodium-glucose co-transporter type-2 inhibitors: pharmacology and peri-operative considerations". *Anaesthesia* 73(2018):1008-1018.
33. Thiruvengkatarajan V, Meyer EJ, Nanjappa N, Van Wijk RM, Jesudason D. "Perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors: a systematic review". *Br J Anaesth* 123(2019):27-36.
34. Bonora BM, Avogaro A, Fadini GP. "Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature". *Diabetes Obes Metab* 20(2018):25-33.

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