

Euglycaemic diabetic ketoacidosis with SGLT2 inhibitors: is it more than a perioperative problem?

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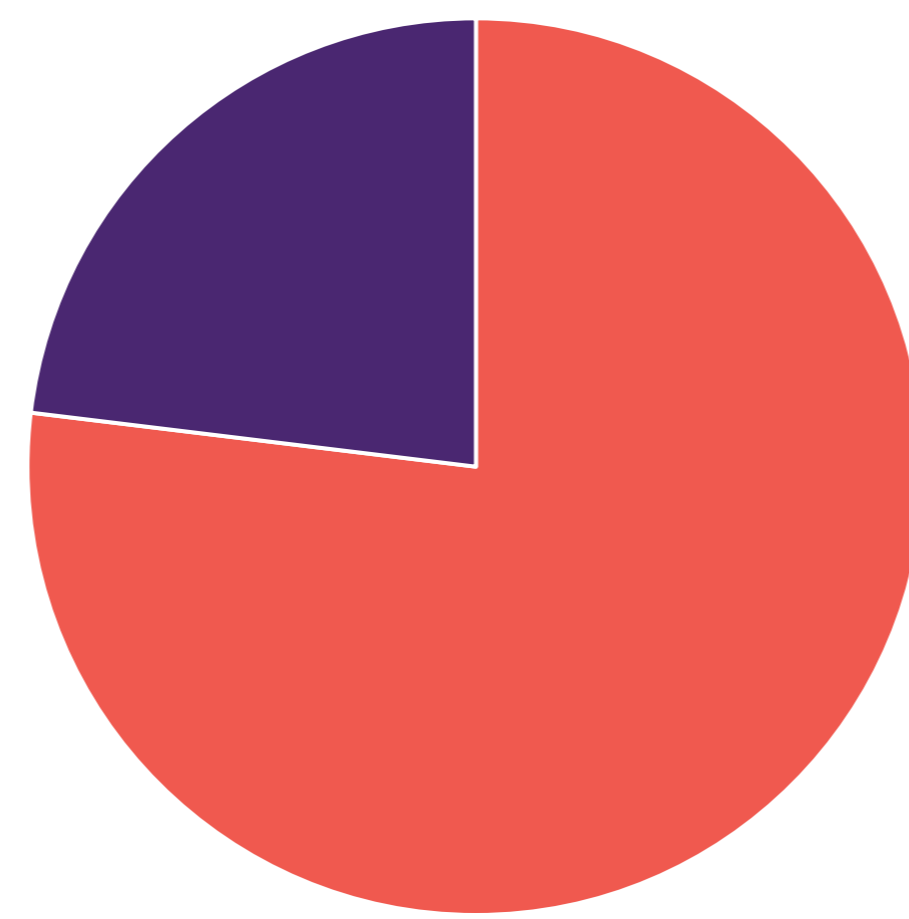
Background

Sodium-glucose co-transporter type 2 inhibitors (empagliflozin, ertugliflozin and dapagliflozin) are second line options for the treatment of type 2 diabetes with favorable benefits such as weight loss, cardio- and renal-protection.

During the post-marketing period, infrequent adverse drug reactions (ADRs) including euglycaemic diabetic ketoacidosis (DKA) emerged, which lead to recommendations about withholding therapy in the perioperative period in 2018.

With the growth in evidence potentially supporting the use of these agents in Type 1 diabetes or in heart failure patients without diabetes, there is an increasing need for vigilance

DKA cases at Austin



- 10 outside perioperative period
- 3 in perioperative period

Contributing factors included dehydration, poor oral intake, low carbohydrate diet, pancreatitis and weaning insulin doses

Be alert to the patient taking a SGLT2i who is severely unwell, with reduced oral intake or dehydration upon admission

Pharmacovigilance at Austin Health

Austin Health's multidisciplinary ADR committee has a reputation for in-depth and prompt reporting of ADRs. Our committee includes pharmacists, infectious disease physicians, clinical pharmacologists, dermatologists and rheumatologists

Each year we report between 300-500 ADRs to the Therapeutic Goods Administration, estimated to make up around 15% of reports from Australian hospitals.

At Austin health, we noticed reports of euglycaemic DKA starting in 2016, with 8 cases in 2018 alone¹ Only 23% of these cases were in the perioperative period.

Case (Year)	Medication & dosage	Severity	Causality	Potential contributing factors
1 (2016)	Empagliflozin 10mg daily	Moderate	Probable	Perioperative setting
2 (2016)	Dapagliflozin 5mg bd	Severe	Probable	Perioperative setting
3 (2017)	Dapagliflozin 10mg daily	Severe	Probable	Type 1 diabetes, unwell for 3 days
4 (2017)	Empagliflozin 10mg daily	Severe	Possible	Concurrent influenza
5 (2018)	Empagliflozin 10mg daily	Severe	Probable	Poor oral intake (narcosis)
6 (2018)	Empagliflozin 12.5mg TWICE a day	Severe	Probable	Worsening weight loss
7 (2018)	Empagliflozin 25mg daily	Moderate	Probable	Concurrent pneumonia
8 (2018)	Dapagliflozin 10mg daily	Moderate	Possible	Low carbohydrate diet
9 (2018)	Empagliflozin 10mg daily	Severe	Probable	Unwell with some vomiting
10 (2018)	Dapagliflozin 5mg TWICE a day	Severe	Probable	5-7 days of loss of appetite
11 (2018)	Dapagliflozin 10mg daily	Severe (died during admission)	Probable	Pancreatitis. Unwell for 10 days prior to admission
12 (2018)	Empagliflozin 25mg daily	Severe	Probable	Weaning insulin, 5 days of gastroenteritis
13 (2019)	Empagliflozin 10mg daily	Severe	Probable	Perioperative period

Case series summary

Of the **THIRTEEN** cases:

- **TEN** were **outside** the perioperative period;
- **TEN** were **euglycaemic** at presentation with blood sugar levels of ≤ 14 mmol/L;
- **TEN** were classified as **severe**;
- **ELEVEN** had the SGLT2i considered as a **probable** cause.

Recommendations

Australian Diabetes Society recommend²:

- Stop 2 days prior and day of surgery;
- Only restart when patient is eating and drinking well;
- Take care if other risk factors for ketoacidosis are present; severe concurrent illness, dehydration, very low carbohydrate diet.

References:

1. McLachlan G, Keith C, Frauman A. Diabetic ketoacidosis with sodium-glucose cotransporter type 2 inhibitors: a case series. Medical Journal of Australia 2019; 211:237

Conclusion

Euglycaemic diabetic ketoacidosis with SGLT2 inhibitors can occur in patients outside of the perioperative period.

Look for elevated blood ketones even without an elevated blood sugar level in patients on an SGLT2i and other contributing factors.

2. https://diabetessociety.com.au/documents/August2019_A_LERT-ADS_SGLT2i_PerioperativeKetoacidosisfinal_000.pdf