Sodium glucose co-transporter-2 inhibitor-induced diabetic ketoacidosis following tooth extraction: Improving awareness among dental practitioners

Short Title: Diabetic ketoacidosis following tooth extraction

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Abstract: Sodium glucose co-transporter-2 inhibitors (SGLT-2i) are a relatively new class of oral glucose lowering agents that improve glycaemic control and also provide significant cardiac and renal benefits. However, SGLT-2i use is associated with a small but significant increased risk of diabetic ketoacidosis (DKA) especially during periods of reduced oral intake such as following dental procedures, bowel preparation for colonoscopy, surgery and concurrent illness. In contrast to typical DKA, in many cases of SGLT2i-associated DKA, the blood glucose is normal or only slightly elevated, giving rise to the term euglycaemic DKA (euDKA). Patients with euDKA often present with non-specific symptoms. Moreover, their normal or only mildly elevated blood glucose levels may lead to delayed diagnosis and treatment and hence potentially life-threatening complications. Not only should patients taking an SGLT-2i be informed about the risk of euDKA, and be provided with SGLT-2i sick day management education, but clinicians should also be alert to this diagnosis.

Keywords: Diabetes mellitus, sodium- glucose co-transporter-2 inhibitor, diabetic ketoacidosis, dental procedures, dental treatments

Introduction. The SGLT-2i class of oral hypoglycaemic medications represents a significant advance in the management of people with type 2 diabetes mellitus (T2DM) as they not only improve glycaemic management but also provide significant cardiovascular and renal benefits1-6. These benefits have also been demonstrated in people without T2DM, and SGLT-2i will be prescribed more widely6-9. It is therefore relevant for dentists to be aware of the increased risk of euDKA associated with SGLT-2i use especially during periods of fasting or reduced oral intake such as...
following some dental procedures\textsuperscript{10,11}. We report a case of severe euDKA in the setting of reduced oral intake following extraction of a single infected wisdom tooth.

**Case Description and Results.** Two days after dental extraction, a 54-year-old woman with a 4-year history of presumed T2DM diagnosed and managed by her General Practitioner presented to the Emergency Department with nausea, vomiting, dizziness, lethargy and poor oral intake. She complained of ongoing tooth socket pain. Fingerprick blood glucose was 11.0 mmol/L (normal range 3.5-7.0 mmol/L). Fingerprick blood ketones and venous blood gas analysis were not performed. The Emergency Department diagnosis was dehydration due to poor oral intake and she was discharged home with paracetamol 1 gm, ibuprofen 400 mg and oxycodone 5 mg for pain relief and advised to increase her oral intake.

She re-presented within 12 hours with ongoing vomiting and dizziness. She had continued to take all her oral hypoglycaemic agents, including her SGLT-2i, empagliflozin 25mg daily. On physical examination, she was clinically dehydrated, her body mass index was 20.1 kg/m\textsuperscript{2} (normal range 20-25), pulse 112 bpm and she had a low blood pressure of 97/62. She was afebrile. Investigations showed a severe metabolic acidosis with an arterial blood gas pH of 6.88 (normal 7.35-7.45), serum bicarbonate <5 mmol/L (normal 21-28 mmol/L), serum ketones 4.7 mmol/L (normal <0.6 mmol/L) and blood glucose on arterial blood gas 10.6 mmol/L (normal 3.0-7.7 mmol/L), HbA1c 8.3\% (general target for good diabetes management ≤7\%).

She was diagnosed with severe euDKA and admitted to the Intensive Care Unit for treatment with intravenous 0.9\% sodium chloride, intravenous potassium chloride and an insulin infusion. Intravenous ceftriaxone 1 g daily and metronidazole 400 mg twice daily were added as empirical treatment for a suspected periodontal abscess that was subsequently excluded by computed tomography. Ketonaemia cleared after 3 days and she was transitioned from intravenous to subcutaneous insulin.

Her pain gradually settled on regular paracetamol 1 gm qid and Difflam lozenges. She began eating and drinking on day 2 of admission and was discharged after seven days on a combination of bedtime basal insulin and meal-time quick acting insulin. Her oral hypoglycaemic medications were ceased.
Post-discharge, she was confirmed to have autoimmune type 1 diabetes, rather than her previously diagnosed T2DM on the basis of a low serum C-peptide of 0.10 pmol/mL (normal 0.33-1.47 pmol/mL) and positive glutamic acid decarboxylase (GAD) antibody level of 41.5 units/mL (normal <5 units/mL), indicating that she will have a life-long requirement for insulin.

**Discussion.** In view of the impressive efficacy of SGLT-2i on cardio-renal outcomes as well as all-cause mortality, the Australian Diabetes Society (ADS) has recommended they may be added as second-line therapy after lifestyle modification and metformin if glycaemic control remains suboptimal. Moreover, it is expected that there will be increasing use of SGLT-2i for their cardiovascular and renal benefits in people without T2DM. While SGLT-2i are not approved for type 1 diabetes, they can be inadvertently prescribed to people with unrecognised type 1 diabetes, such as in the case presented.

DKA typically occurs in people with type 1 diabetes, but up to one-third of cases of DKA occurs in T2DM. In contrast to classical DKA which typically presents in the context of significant hyperglycaemia, SGLT-2i-associated DKA may be missed because it usually presents with normal or only mildly raised blood glucose levels, as seen in this case, hence the term euglycemic DKA. The mechanism by which SGLT-2i promotes ketosis is still incompletely understood. One mechanism is that SGLT-2i increases glucagon levels that result in lipolysis and ketone production especially during periods of fasting or reduced oral intake. Patients with euDKA often present with non-specific symptoms such as abdominal pain, nausea, vomiting and lethargy, and lack the classical symptoms of polyuria, nocturia and marked thirst which is seen with markedly elevated blood glucose. As a result, the diagnosis of DKA may be delayed. Without prompt recognition and treatment, diabetic ketoacidosis can lead to persistent vomiting, hypovolaemic shock, multi-organ failure and death.

In a Melbourne study of 162 cases of DKA in patients with T2DM, 37 were taking SGLT-2i. In that study, the incidence of DKA was 1.02 per 1000 (95% CI, 0.74 to 1.41) in SGLT-2i users vs 0.69 per 1000 (95% CI, 0.58 to 0.82) in non-SGLT-2i users (OR, 1.48; 95% CI, 1.02 - 2.15; p = 0.037). Two cases of SGLT2i-related DKA were
reported to have occurred in the setting of dental abscess\textsuperscript{14}. A recent meta-analysis of ten randomised clinical trials of SGLT-2i involving 71,553 individuals showed an increased relative risk of DKA of 2.23 (95% CI 1.36-3.63), although the total number of DKA cases was not stated\textsuperscript{15}. Outside of clinical trials, the FDA adverse events reporting system database has provided the largest detailed analysis of SGLT-2i associated DKA in 2397 cases and estimated an increased 7.9 (95% CI 7.5-8.4)-fold reported use of SGLT-2i in DKA cases\textsuperscript{16}.

Recognition of the increased risk of SGLT-2i associated DKA led to guidelines from the ADS and the Australian and New Zealand College of Anaesthetists (ANZCA) that advise withholding SGLT-2i on the day of the procedure for day procedures or day surgery, and 2 days before and the day of surgery for major procedures\textsuperscript{17}. They should only be recommenced once oral intake is secure, in order to minimise the risk of developing euDKA.

The mainstay of treatment of euDKA is intravenous hydration and an insulin infusion such as our patient received. Presentation with euDKA prompts re-analysis of an individual’s diabetes classification, as with our patient who was subsequently found to have type 1 diabetes; this was the case in 22\% of the T2DM cohort who presented with DKA in the Melbourne study\textsuperscript{14}.

In Australia, SGLT-2i are presently only available on the Pharmaceutical Benefits Scheme (PBS) for people with type 2 diabetes (Table 1). It is important for dentists and other clinicians to be aware of all these different preparations of SGLT-2i.
Table 1. Sodium-glucose co-transporter 2 inhibitors available in Australia

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Dosage (mg)</th>
</tr>
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<tbody>
<tr>
<td><strong>Empagliflozin-containing products</strong></td>
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<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
<td>10</td>
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<tr>
<td>Empagliflozin/metformin</td>
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<tr>
<td>Empagliflozin/linagliptin</td>
<td>Glyxambi</td>
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<tr>
<td><strong>Dapagliflozin-containing products</strong></td>
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<tr>
<td>Dapagliflozin</td>
<td>Forxiga</td>
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<tr>
<td>Dapagliflozin/Saxagliptin</td>
<td>Qtern</td>
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<tr>
<td>Dapagliflozin/metformin</td>
<td>Xigduo XR</td>
<td>10/500</td>
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<td>extended-release</td>
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<td><strong>Ertugliflozin-containing products</strong></td>
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<td>Ertugliflozin/metformin</td>
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<tr>
<td>Ertugliflozin/sitagliptin</td>
<td>Steglujan</td>
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<td>15/100</td>
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While the absolute risk of euDKA is small, patients and all healthcare providers, including dental practitioners should be aware of the potential risk of SGLT-2i-
associated euDKA around periods of fasting$^{11,14}$. Emergency dental work should not be withheld because a patient is taking an SGLT-2i. Dental practitioners should routinely enquire if patients are taking an SGLT-2i. Straightforward dental care involving dental cleaning and scaling, and tooth fillings do not generally result in reduced food intake, and therefore, it is unnecessary to withhold an SGLT-2i. However, other more significant dental procedures such as tooth extraction, root canal work, tooth implant or dental conditions such as dental abscess or periostitis may result in reduced food intake of variable duration. While there is no specific guidance regarding SGLT-2i use around dental work in the ADS/ANZCA Guidelines, the following general advice is recommended$^{17}$. If it is anticipated that normal eating cannot be resumed within 12 hours, the SGLT-2i should be withheld on the day of the dental procedure and not be resumed until normal oral intake recommences. If patients have not withheld their SGLT-2i on the day of a significant dental procedure, it may not be necessary to cancel the procedure if they are otherwise well. However, they should be instructed to withhold further doses of SGLT-2i until they are eating normally and they should be advised to present to an Emergency Department if they develop nausea or vomiting. Early recognition, diagnosis and treatment of euDKA will prevent significant morbidity and potential mortality.

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