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Case Report

Sodium-Glucose Cotransporter-2 Inhibitors in Odontogenic Infections

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ABSTRACT

On top of improving glycemic control, sodium-glucose cotransporter-2 inhibitors have been shown to reduce cardiovascular mortality & heart failure hospitalization. Sodium-glucose cotransporter-2 inhibitors have also been gaining momentum as effective reno-protective agents. Recent evidences have shown that sodium-glucose cotransporter-2 inhibitors are transforming the management of heart failure and chronic kidney disease in patients without type 2 diabetes mellitus. In view of the cardioprotective and reno-protective outcomes, as well as the potential benefits that outweigh adverse effects, it is no doubt that there will be continued increased use of sodium-glucose cotransporter-2 inhibitors. However, with use of sodium-glucose cotransporter-2 inhibitors comes risk of adverse effects, in particular diabetic ketoacidosis. Although uncommon, diabetic ketoacidosis is a potentially life-threatening acute metabolic complication. Diabetic ketoacidosis developing during sodium-glucose cotransporter-2 inhibitors use can present with normal blood glucose concentrations (euglycemia). This atypical presentation can delay diagnosis and hence, treatment. It is therefore crucial for dental practitioners to be cognizant of the increased risk of euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors use, especially during periods of reduced oral intake, such as in patients with odontogenic infection. Euglycemic diabetic ketoacidosis is a diagnosis of exclusion and should be considered as a differential in an ill patient on sodium-glucose cotransporter-2 inhibitors, despite normal blood glucose or absent urine ketones. We report a case of starvation ketosis in a patient with well-controlled type 2 diabetes mellitus, after excisional biopsy of right cervical lymph node and extractions of two lower right molars. Although the patient did not develop euglycemic diabetic ketoacidosis peri-operatively, it was an important diagnosis to exclude considering his high-risk profile of developing euglycemic diabetic ketoacidosis and the potential sequelae of missing the diagnosis.

1. Introduction

On top of improving glycemic control, sodium-glucose cotransporter-2 inhibitors (SGLT2-i) have been shown to reduce cardiovascular mortality and heart failure hospitalization [1]. Real world observational data from over 300 000 patients with type 2 diabetes mellitus (T2DM) have confirmed the reduction in heart failure hospitalization and all-cause mortality, in comparison with other blood glucose-lowering agents [2]. SGLT-2i have also been gaining momentum as effective reno-protective agents. Several trials have demonstrated that SGLT2-i can lower the incidence of albuminuria, eGFR decline, progression of kidney disease as well as the need for renal transplantation in patients with T2DM [2-5]. Recent evidences also show that SGLT-2i are transforming the management of heart failure and chronic kidney disease in patients without T2DM [6-10].

In view of the cardioprotective and reno-protective outcomes, as well as the potential benefits that outweigh adverse effects, it is no doubt that there will be continued increased use of SGLT2-i. However, with use of SGLT2-i comes risk of adverse effects, in particular diabetic ketoacidosis (DKA). Although uncommon, DKA is a potentially life-

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threatening acute metabolic complication. DKA developing during SGLT2-i use can present with normal blood glucose concentrations (euglycemia). This atypical presentation can delay diagnosis and hence, treatment.

It is therefore crucial for dental practitioners to be cognizant of the increased risk of euglycemic DKA (EDKA) associated with SGLT2-i use, especially during periods of reduced oral intake, such as in patients with odontogenic infection [11]. EDKA is a diagnosis of exclusion and should be considered as a differential in an ill patient on SGLT2-i, despite normal blood glucose or absent urine ketones. We report a case of starvation ketosis in a patient with well-controlled T2DM, after excisional biopsy of right cervical lymph node and extractions of two lower right molars. Although the patient did not develop EDKA peri-operatively, it was an important diagnosis to exclude considering his high-risk profile of developing EDKA and the potential sequelae of missing the diagnosis.

2. Case Report

A 58 year old male presented to the Department of Emergency Medicine (DEM), Singapore General Hospital with the chief complaint of a gradually enlarging and painful right neck swelling over 2 days. He had a medical history of T2DM with hemoglobin A1c of 7.4% and was on dapagliflozin, gliclazide and metformin. He had previously undergone percutaneous coronary intervention after an episode of non-ST-elevation myocardial infarction, and was on dual antiplatelet therapy (DAPT) of aspirin and ticagrelor for 12 months. Other chronic medications included omeprazole and bisoprolol fumarate. The patient also had an allergy to penicillin.

The swelling approximated 6 cm by 7 cm in size, with no overlying skin erythema and extended to levels 2 and 3 of the neck. Intraorally, the lower right second molar was a root stump and the lower right third molar was grossly carious. However, no obvious signs of odontogenic infection were noted. A computerized tomography (CT) scan of the neck showed enlarged right cervical level 2 lymph nodes with surrounding inflammatory changes and no drainable abscesses. Blood test results revealed leukocytosis (white blood cell count of 18.24×10^9/L), neutrophilia (absolute neutrophil count of 14.73×10^9/L) and monocytosis (absolute monocyte count of 1.31×10^9/L). Serum C-reactive protein (CRP) was also elevated at 29.7 mg/L. A diagnosis of lymphadenitis secondary to odontogenic infection was made. He was discharged with oral clindamycin and metronidazole.

He was then reviewed outpatient in National Dental Centre of Singapore with periapical radiographs of the lower right first molar to lower right third molar. The lower right second molar had extensive loss of tooth structure radiographically, which corresponded clinically with a root stump. Radiographs revealed no apparent periapical radiolucency at the involved teeth. Patient was advised to complete the course of antibiotics and scheduled for a repeat review in a week's time.

Despite compliance to antibiotics, the patient re-presented to DEM with worsening of pain and swelling over his right neck. The right neck swelling had increased to approximately 8 cm by 8 cm. A repeated CT neck revealed an increase in size of the previously noted right cervical level 2 adenopathy, with features suggestive of a developing abscess. There were also features of infection and inflammation in adjacent soft tissues and right sternocleidomastoid. Blood tests showed leukocytosis (white blood cell count of 15.96×10^9/L), neutrophilia (absolute neutrophil count of 11.27×10^9/L), lymphocytosis (absolute lymphocyte count of 3.21×10^9/L) and monocytosis (absolute monocyte count of 1.32×10^9/L). Serum CRP had shot up to 102 mg/L.

The patient was admitted and underwent excisional biopsy of the right cervical lymph node and extractions of lower right second and third molars under general anesthesia on the following day. Pre-operatively, all oral hypoglycemic agents (OHGAs) and ticagrelor were withheld while aspirin was continued. Histopathology revealed that patient had lymphadenitis secondary to Klebsiella infection and reactive lymphoid hyperplasia. He was kept on intravenous clindamycin and metronidazole perioperatively and subsequently changed to oral ciprofloxacin based on culture and sensitivity results.

Subsequently, serum ketones were assessed due to the possible risk of ketoacidosis secondary to the use of SLGT2-I and ongoing odontogenic infection. The patient was noted to have elevated serum ketone levels of 1.4 mmol/L. An endocrinologist opinion was sought. He was diagnosed with starvation ketosis without acidosis (bicarbonate levels were 20.6 mmol/L and blood pH was 7.38). This diagnosis was concluded from the fact that the patient's last dose of SGLT2-i was 2 days prior to surgery, and ketone levels on admission were normal but only subsequently high after a day of fasting. It was noted that the patient had withheld from food intake for an approximate period of 33 hours prior to measurement of serum ketones.

As the patient resumed oral diet, metformin and gliclazide were restarted. Dapagliflozin was halted until the patient was able to tolerate full oral intake. Few days after, a repeat serum ketone revealed normal results. The patient was then discharged well. He was regularly reviewed for dressing change and displayed improvement in clinical signs and symptoms.

3. Discussion

3.1. Ketoacidosis

In this case report, ketonemia was timely identified (ketone levels: 1.4mmol/L) and managed such that no metabolic acidosis occurred (blood pH: 7.38). Nonetheless, it is crucial to keep in mind management strategies when managing a patient with a high risk of developing diabetic ketoacidosis. The most prevalent cause of ketoacidosis is DKA. Other types of ketoacidosis include EDKA, alcoholic ketoacidosis (AKA) and starvation ketoacidosis (SKA). DKA most commonly occur in patients with poorly-controlled DM and is precipitated by an acute infection that triggers uncontrolled hyperglycemia. Other risk factors of DKA include T1DM, non-compliance to insulin or OHGAs and acute major illnesses such as acute myocardial infarction, stroke, sepsis or pancreatitis and surgery. Table 1 summarizes the three types of ketoacidosis, associated laboratory findings as well as appropriate management strategies.

TABLE 1: Differentiation between the three different types of ketoacidosis: DKA, AKA and SKA [12].

	DKA	**AKA**	**SKA**
Etiology	Diabetes is uncontrolled, and there is hyperglycemia, with relative or absolute insulin deficiency. Risk factors that can precipitate extreme hyperglycemia: • Infection • Non-adherence to insulin therapy • Acute major illnesses	Chronic alcohol abuse, liver disease and acute alcohol ingestion	Body is deprived of glucose as the primary source of energy for a prolonged period.
Epidemiology	Occurs more frequently in T1DM; 10-30% of cases occur in T2DM especially in the background of extreme physiologic stress or acute illness.	Correlates with the incidence of alcohol abuse and can occur at any age. Occurs mainly in chronic alcoholics but rarely in binge drinkers.	Mild ketosis usually develops after a 12-14 hours fast but if prolonged such as in cases of extreme socio-economic deprivation or eating disorders, ketoacidosis will progressively develop. May present in cachexia due to underlying malignancy, post-operative or post-radiation dysphagia.
Clinical Presentation	• Abdominal pain • Nausea, vomiting • Hypovolemia • Rapid and deep respiratory effort • Distinct fruity odor to breath due to acetone production		
	(Symptoms associated with hyperglycemia) • Polyuria • Polydipsia • Unintentional weight loss • Weakness • Mentation changes • Lethargy • Obtundation	• Signs associated with alcohol withdrawal such as hypertension and tachycardia	• Signs of muscle wasting including poor muscle mass, minimal body fat, obvious bony prominences, tooth decay, sparse, thin and dry hair • Low blood pressure • Low body temperature
Laboratory Findings	• pH <7.3 • Serum bicarbonate <18 mmol/L • Elevated anion gap values >12 mEq/L		
	• Hyperglycemia - blood glucose >125 mg/dL (fasting) • Leukocytosis - WBC > 11.0 × 10^9/L • Serum sodium may be relatively low • Serum potassium may be elevated (>5.2 mmol/L)	Hypoglycemia - blood glucose <70 mg/dL (fasting) • Hypokalemia <3.5 mmol/L • Elevated transaminases and hyperbilirubinemia due to possible concurrent alcoholic hepatitis	• Hypomagnesemia and hypophosphatemia • Multiple electrolyte abnormalities due to chronic malnutrition • Vitamin deficiencies
Treatment	• Standard initial stabilization - airway, breathing and circulation • Monitoring and replacement of electrolytes (especially potassium) • Correction of hypovolemia with IV fluids		
	Monitoring and replacement of electrolytes (especially potassium), correction of hypovolemia with IV fluids, correction of hyperglycemia with IV insulin	• Monitoring and replacement of electrolytes, correction of hypovolemia with IV fluids and IV dextrose (for induction of endogenous insulin and reduction in counter-regulatory hormones) • Monitoring and replacement of magnesium and phosphate	
		Thiamine replacement should be done parenterally and then maintained orally	• Monitor for refeeding syndrome

EDKA is defined as ketoacidosis (pH <7.3 or serum bicarbonate <18 mmol/L) with a normal or close-to-normal plasma glucose (11-14 mmol/L) [13, 14]. Clinically, patients may not appear to be dehydrated due to the absence of polyuria and polydipsia. However, patients may instead have non-specific symptoms such as nausea, vomiting, abdominal pain, lethargy and tachypnea due to ketonemia and concurrent ketoacidosis. EDKA has a similar presentation to DKA except for the fact that patients generally present with relatively lower blood glucose. A lack of hyperglycemia can mask the underlying DKA, delaying its diagnosis and hence treatment outcomes.

With the rise in the use of SGLT2-i, there is an increase in published case reports on EDKA [15, 16]. Other factors that increase the risk of EDKA include poor oral intake, pregnant women, and treatment with insulin [17]. In view of the lack of hyperglycemia, serum ketones should be checked in patients with nausea, vomiting or malaise. Occasionally, low serum bicarbonate may be the first finding in patients with EDKA. Considering that this patient was on SGLT2-i (dapagliflozin) for DM, it was even more crucial to identify any precedents for development of EDKA. AKA was ruled out from history-taking.

3.2. Oral Hypoglycemic Agent - SLGT2-i in Relation to EDKA

SGLT2-i work by blocking SGLT2-i cotransporters in the early proximal renal tubule which is responsible for reabsorption of 80-90% of glucose filtered by the glomerulus. This results in glucosuria and subsequent decrease in blood plasma glucose concentration [8, 18]. The mechanisms that propagate DKA in susceptible patients include: osmotic diuresis with glucosuria (resulting in a state of carbohydrate deficit), volume depletion and dehydration [16, 18]. Carbohydrate deficit and hypovolemia promote glucagon release, increase glucagon-to-insulin ratio and trigger ketogenesis with euglycemia. There is also a direct effect of SGLT2-i on pancreatic alpha cells which result in glucagon release and inhibition of ketone bodies excretion by kidneys [19, 20].

Although the precise incidence rate of SGLT2-i associated with DKA is unknown, clinical trials of SLGT2-i with T2DM have reported incidence of 0.16 to 0.76 events per 1000 patient-years [16, 21]. Other studies have also proven that risk of DKA was almost three-fold higher with SGLT2-i than dipeptidyl peptidase-4 inhibitors. This was observed with dapagliflozin, empagliflozin and canagliflozin, suggesting a class effect [22].

3.3. Fasting in Relation to EDKA

Reduced nutritional intake especially with concurrent illnesses, such as odontogenic infections, in patients with T2DM can also precipitate EDKA [23, 24]. Prolonged fasting results in a carbohydrate deficit state and reduction of glycogen stores, leading to the use of alternative energy sources like free fatty acids. Ketogenesis from lipolysis, combined with reduced glycogen store that maintain a euglycemic state, sparking off EDKA. However, fasting-induced EDKA should be discerned from starvation ketosis where metabolic acidosis is not present (serum bicarbonate >18mmol/L or serum pH >7.3) [13, 25].

In our case report, it is evident that ketosis likely arose due to patient's prolonged starvation (approximately 33 hours) instead of associated SGLT2-i use and the background of T2DM. This can be concluded from the fact that there was only mild ketosis that arose the day after the operation, with lack of evidence of metabolic acidosis as reflected by normal serum bicarbonate of 20.6 mmol/L and normal blood pH of 7.38. Ketone levels were normal pre-operatively and the patient's last dose of SGLT2-i was taken 2 days prior to the surgery. This significantly lowered the risk of developing EDKA peri-operatively.

3.4. Peri-Operative Considerations

In the peri-operative management of patients on SGLT2-i, it is crucial to ensure that the drug is withheld even when there are no other predisposing factors that might precipitate ketoacidosis such as dehydration and acute illness. Surgery itself poses a physiological stress that may be enough to result in development of DKA. The American Diabetes Association recommends discontinuation of SGLT2-i 3 to 4 days before surgery [26] whereas the Australian Diabetes Society recommends for cessation at least 3 days pre-operatively [27]. This is because the elimination half-life of SGLT2-i ranges from 11 to 13 hours and the pharmacodynamic effects may persist for multiple days. Hypoglycemic drugs should not be restarted until the patient is clinically well, normo-glycemic and able to resume normal nutritional intake.

SGLT2-i should be stopped immediately for patients who are undergoing emergency surgery [28]. Post-operatively, these patients should preferably be admitted to a ward with the capability of early recognition and management of DKA. In cases where there is insufficient time for SGLT2-i cessation prior to surgery, it is essential to monitor the patient post-operatively for any signs and symptoms of ketoacidosis. Studies have also supported that the use of intravenous insulin has helped to reduce risk of DKA in patients who are unable to stop their medications pre-operatively [29]. This can be considered in emergency cases where SGLT2-i cannot be stopped in time, especially when patient is nursed in intensive care postoperatively.

Recognition of starvation ketonemia is also crucial, especially in patients who have fasted for prolonged periods of time prior to surgery. Although infrequently reported, in cases where patients have other diagnosed comorbidities, prolonged starvation can eventually culminate in metabolic ketoacidosis. Regardless, it would be useful to consider preoperative serum glucose and serum ketones for a patient with unexplained ketosis, to promptly manage any potential precedents for metabolic acidosis.

4. Conclusion

This case highlights the importance of identifying risk factors that might predispose one to an episode of ketoacidosis, in particular patients using SGLT2-i for diabetes management. In cases of odontogenic infections or dental trauma where patients may have to undergo emergency dental surgeries, it is crucial for dentists to employ necessary peri-operative measures to avoid an episode of ketoacidosis. Early recognition of DKA or EDKA is crucial to prevent delay in management and potential life-threatening consequences. Although the medical community has been widely educated on this, there is still much room for education amongst dental practitioners, considering that not many case reports are available in the dental journals regarding SGLT2-i and the associated risks of

ketoacidosis. As part of holistic clinical practice, dental practitioners should routinely enquire if patients are on SGLT-2i and take the necessary precautions as suggested.

Ethics Approval and Consent to Participate

Ethics approval was not required for this study.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing Interests

None.

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None.

Author Contributions

SKL and RHN conceptualized the case report, oversaw supervision of draft-writing as well as review and editing the drafts. CTYQ wrote the original draft, and reviewed and edited the manuscript under the guidance of SKL and RHN. All authors read and approved the final manuscript.

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