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**Case Report**

# An Ongoing Concern of Diabetic Management with SGLT2i - Its Potential Medico-Legal Implication

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## Abstract

Diabetic Ketoacidosis (DKA) is a life-threatening diabetic emergency. There is now an emerging risk of DKA because of a potential adverse effect of the new diabetic medication - Sodium Glucose Transporter 2 inhibitor (SGLT2i) that can lead to diabetic ketoacidosis. This paper shares our experience of unexpected events in two diabetic patients taking SGLT2i, resulting in urgent hospitalization in one case and medical litigation in the other. It also brings to the doctors' attention that ketone breath sensors are now available to diagnose DKA quickly and accurately. They can offer a non-invasive approach to detecting and monitoring DKA in diabetic patients; hopefully, it could have averted similar events and prevented medical litigation in the future.

**Keywords:** ***Diabetes Mellitus, Diabetic Ketoacidosis, SGLT2i, ketone breath sensor, medical litigation.***

## Introduction

Diabetic Ketoacidosis (DKA) is a life-threatening diabetic emergency with severe metabolic acidosis of pH < 7.3 and serum bicarbonate < 18 mmol/L, associated with ketonemia. It occurs in both Type 1 and Type 2 diabetic patients taking diabetic medications when precipitating factors occur, e.g., reduced oral or fluid intake, surgery, vigorous exercise, and infection. Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a new generation of oral diabetic medication available since 2013 for the treatment of Type 2 diabetes. With additional benefits of weight loss and reduction of mortality and morbidity due to cardiovascular and kidney complications, there were 63.2 million prescriptions of SGLT2i worldwide from 2015 to 2020 [1]. As a result, the risks of DKA increased by 2-4 fold, to an incidence of up to 5% in Type 1 Diabetes Mellitus (DM) [2]. Due to the unawareness of the side effects of this medication by medical generalists and surgeons, this case report paper shares our concern about the unexpected events in two diabetic patients taking SGLT2i, resulting in urgent hospitalization and medical litigation in one case.

## Case report

### Case 1

A 54-year-old male patient with no history of diabetes mellitus suffered from thirst, polyuria, and weight loss of 5 kg over one year. He also experienced delayed wound healing for two years. She underwent a body check-up in 2021. Blood tests revealed fasting blood glucose of 18.2 mmol/L, Haemoglobin (Hgb) A1c of 10%, and spot glucose of 20.2 mmol/L. His urine ketone showed 1+, but his renal function test was normal. He was managed in a clinic with Novomix insulin using dose titration. The next day, he had a blood ketone strip ordered and tested, which showed 0.3 mmol/L. Therefore, he was prescribed Dapagliflozin (SGLT2i) 10 mg daily to speed up his glycemic control and allow him to return to Mainland China early for business. A few days later, he felt unwell with dizziness and palpitation but no nausea and vomiting. However, his blood tests showed a fasting blood sugar of 9.7 mmol/L (normal 3.9 – 5.6 mmol/L), serum bicarbonate of 16.6 mmol/L (normal 22-32 mmol/L), and blood ketone of 6.1 mmol/L (normal<0.6 mmol/L). Given the risk of early diabetic ketoacidosis, he was admitted to the hospital for further management. While in the hospital, the dapagliflozin was taken off. He was treated as suffering from euglycemic diabetic ketoacidosis, probably induced by SGT2i and reduced dietary intake. He became well after one week in the hospital and was discharged home on day 7 with conventional antidiabetic treatment, including insulin but without SGLT2i.

### Case 2

This 61-year-old lady had Type 2 DM for seven years. She was on multiple antidiabetic medications, including metformin, gliclazide, pioglitazone, and sitagliptin. She consulted an endocrinologist for unsatisfactorily controlled diabetes with fasting blood sugar of 8.1 mmol/L, HbA1c of 8.5%, with weight loss of 0.5 kg over two

months. She was prescribed a GLP1 receptor agonist (GLP1-RA) - Trulicity (dulaglutide) 1.5 mg weekly and Jardiance (SGLT2i) 10 mg daily. After four days on the new medications, she called the clinic for nausea and was advised to stop the GLP1-RA injection. Two days later, she was hospitalized through the Accident and Emergency Department because of persistent poor oral intake and vomiting for two days with severe tiredness. Investigations at the hospital showed blood pH 7.09 (normal 7.35 to 7.45), anion gap 25 mmol/L (normal 4 to 12 mmol/L), and urine ketone strip showed +++. She was diagnosed suffering from diabetic ketoacidosis (DKA) and was admitted to the Intensive Care Unit. The Jardiance (SGLT2i) was stopped, and she received treatment with intravenous insulin + dextrose infusion. A complaint was subsequently lodged to the Hong Kong Medical Council (– a medical professional regulatory body in Hong Kong) against the doctor for not being aware that SGLT2i would increase the risk of ketoacidosis and failing to recognize the dangerous condition when consulted. The doctor lost the case, and disciplinary action was taken against him.

## Conclusion

Although diabetic ketoacidosis is uncommon in patients with type 2 DM, it occurs mostly in those with longstanding DM with significantly reduced beta cell function. However, there is now an emerging risk of DKA because of a potential adverse effect of the SGLT2i [3]. SGLT2i works by inhibiting the sodium-glucose co-transporter-2 (SGLT-2) in the proximal tubules in the kidneys. It reduces renal reabsorption of glucose and increases glucose excretion. Thus, it lowers the blood glucose level, with an action independent of insulin [4]. With the increasing use of SGLT2i in type 2 DM management, a condition called euglycaemic DKA (EDKA) has increased in incidence [5]. In EDKA, the blood glucose is either mildly elevated or normal; the diagnosis of DKA might be delayed or missed [6]. The purpose of this paper is to arouse the awareness of doctors towards the risks of SGLT2i that can unexpectedly lead to diabetic ketoacidosis. For patients on SGLT2i, in the event of non-specific symptoms such as nausea, vomiting, abdominal discomfort, and dizziness or tiredness, they should be checked for glucose levels, ketosis, and acidosis. Even though conventional blood tests are more accurate, they are invasive, and the ketone result is not readily available. Though non-invasive, Urine tests for glucose and ketone are inaccurate, eventually requiring additional blood tests. This will also delay the treatment of a dangerous diabetic ketoacidosis.

With advancing medical technology, ketone breath sensors have been invented and marketed, making diagnosing DKA quick and accurate. Monitoring ketone levels in certain DKA precipitating conditions will be more cost-effective than blood ketone measurements. A novel device, KetoMetrics (from AusMed Global Limited, Hong Kong), has been listed in the USA Food and Drug Administration (USA-FDA) Listed Medical Devices for detecting ketone in the breath [7]. It can further enhance the non-invasive approach to detect and monitor DKA in diabetic patients. As there is an escalating number of patients taking SGLT2i, it is anticipated that this will lead to a higher incidence of ketoacidosis in the community. The clinical awareness of this SGLT2i-related DKA and the availability of a handy and portable ketone breath test device in a clinic or hospital emergency room could have averted the two reported events and prevented medical litigation.

## Abbreviations

DKA: Diabetic Ketoacidosis
DM: Diabetes Mellitus
EDKA: Euglycaemic Diabetic Ketoacidosis
GLP1-RA: GLP1 receptor agonist
SGLT2i: Sodium-Glucose CoTransporter 2 inhibitor
USA-FDA: USA Food and Drug Administration

## Declarations

## Ethical Approval and Consent to participate

Not applicable

## Consent for publication

Both authors agree and consent to the publication of this paper.

## Availability of supporting data

Not applicable

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## Authors' contributions

Both WSF Wong and VTF Yeung were responsible for the design and writing of the paper.

## Potential Conflict of Interest

Dr. Wong and Dr. Yeung are honorary medical advisors to AusMed Global Limited, Hong Kong. The authors understand the importance of disclosing potential conflicts of interest and ensuring that the provided information is accurate and based on the best knowledge available.

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