# Diabetic Ketoacidosis After Sodium–Glucose Cotransporter Inhibitor Initiation Under Advanced Hybrid Closed-Loop Therapy in Type 1 Diabetes

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# **Full title:** Diabetic ketoacidosis after initiation of sodium-glucose cotransporter inhibition under advanced hybrid closed-loop therapy in type 1 diabetes

**Short running title:** DKA in type 1 diabetes under SGLTi and advanced HCL

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**Abstract**

Sodium-glucose cotransporter inhibitor (SGLTi) use is not uncommon in type 1 diabetes (T1D). Not much is known about possible risks or benefits when combining SGLTi with advanced hybrid closed-loop (aHCL). This report describes in detail the daily insulin dosing by the MiniMed™ 780G algorithm in a patient with T1D after SGLTi initiation leading to diabetic ketoacidosis (DKA). Within a few days after start of SGLTi, the aHCL algorithm reduced autobasal and autocorrection doses, while meal bolus insulin doses were reduced mainly due to frequent activation of the 'safe meal bolus'. Taken together, there was a significant 49% reduction in total daily insulin dose after start of SGLTi, leading to insulin doses below the minimum needed to prevent ketone formation. Until more is known about the influence of SGLTi on aHCL algorithm functioning, we recommend caution with SGLTi use in people with T1D on aHCL systems to avoid increased DKA risk.

## Introduction

Sodium-glucose cotransporter inhibitors (SGLTi) are oral anti-diabetes medications, recommended for the treatment of type 2 diabetes due to their beneficial effect on glucose control, and cardiovascular and renal outcomes.[1] Several randomized controlled trials have also shown improvement in glycemic control with SGLTi as adjunct therapy in type 1 diabetes (T1D), along with weight loss and reduction in systolic blood pressure.[2] In Europe, the European Medicines Agency has approved low dose dapagliflozin and sotagliflozin for people with T1D and a Body Mass Index (BMI) >27 kg/m$^2$. However, despite clinical benefits and regulatory approval, there is reluctance to SGLTi use in T1D, due to an increased risk of developing diabetic ketoacidosis (DKA).[3] Here we report a 23-year-old woman with T1D treated with advanced hybrid closed-loop (aHCL) therapy, who developed DKA two weeks after initiation of SGLTi.

## Case Report

The patient was diagnosed with T1D at age 12. As a teenager she had difficult glycemic control, with HbA1c values between 9.0 and 10.7% (74 and 94 mmol/mol), complicated with one severe DKA episode due to non-compliance with insulin injections. Diabetes control improved in the last 6 months since start of aHCL (Medtronic MiniMed$^{TM}$ 780G system), with an HbA1c between 7.3 and 8.0% (56 and 64 mmol/mol). She struggled with overweight for years, with a BMI reaching 42.1 kg/m$^2$, for which her diabetologist recommended SGLTi in the form of empagliflozin 12.5 mg/day.

Two weeks after initiation of SGLTi, the patient presented at the emergency department of a regional hospital because of acute dyspnea on awakening. She complained of polydipsia and polyuria, and had measured a capillary blood ketone level of 6.5 mmol/L at home as instructed according to the international recommendation.[3] She also said she had lost 8 kilos in the past few weeks, partly due to reduced intake of carbohydrates. There were no abnormalities on physical examination, except for sinus tachycardia (127/minute), and an elevated blood pressure (154/101 mmHg). Arterial blood gas was consistent with metabolic acidosis (reference value): pH 7.14 (7.35-7.45), pCO2 1.2 kPa (4.3-6.0), pO2 16.5 kPa (11.1-14.4), bicarbonate 3.1 mmol/L (22-29), base excess 23 (-2.5 to +2.5), lactate 2.1

mmol/L (<1.2). Plasma glucose levels were 19.6 mmol/L (353 mg/dL). Dipstick revealed ketonuria (ketones 4+). The diagnosis of DKA was made, with no clear evidence of contributing factors (i.e. kinked cannula, infection, etc.). Treatment with fluids and intravenous insulin was started with full recovery. The patient was discharged from the hospital 3 days later with resumption of aHCL therapy, but without SGLTi.

Careful assessment of the evolution of our patient's daily insulin administration and carbohydrate intake in relation to SGLTi use, reveals interesting mechanisms that contributed to the onset of DKA (Figure 1). Within a few days after start of SGLTi, the aHCL control algorithm reduced autobasal and autocorrection doses (panel A and B). Meal bolus insulin doses were already reduced in the week prior to initiation of SGLTi (panel C), as a result of lower carbohydrate intake by our patient (panel D). After start of SGLTi, meal bolus insulin doses remained at a lower level, not only due to lower carbohydrate intake, but also due to frequent activation of the 'safe meal bolus' ('S' in panel C). This specific feature of the MiniMed™ 780G system reduces the calculated meal bolus when the algorithm predicts an excessive risk of post-bolus hypoglycemia if the full calculated bolus were administered. In our case, the safe meal bolus feature frequently reduced meal bolus doses by 13.6 to 42% on 10 out of 14 days after start of SGLTi, compared to only 5.5 to 6.4% on 3 out of 14 days before start of SGLTi. Taken together, there was a significant 49% reduction in total daily insulin dose in the 2 weeks after start of SGLTi compared to 14 days before. In terms of glycemic control, glucose levels decreased immediately in the first days after start of SGLTi (panel E), resulting in an increase in time in range (panel F). However, from day 4 after start of SGLTi, glucose levels and time in range gradually returned to levels observed before start of SGLTi, but without a subsequent increase in autobasal, autocorrection or meal bolus doses.

**Discussion**

In this case report, we describe in detail the deleterious insulin dose reduction by a Medtronic MiniMed™ 780G aHCL algorithm after SGLTi initiation in a person with T1D leading to DKA. Reporting this potential DKA risk is clinically relevant, as the MiniMed™

780G system is increasingly used in Europe and will enter the US market in Q2 2022, while use of SGLTi in people with T1D is not uncommon.

Our case resembles a previously published case report describing DKA in a patient on a Medtronic MiniMed™ 670G system in whom concomitant use of SGLTi was accompanied by an automatic reduction in basal insulin,[4] but several interesting mechanisms specific to the response of the MiniMed™ 780G to the introduction of SGLTi were revealed. The autonomous decrease in both basal and bolus insulin doses resulted in almost halving of the total daily insulin dose leading to the development of DKA due to insulin doses below the minimum needed to prevent ketone formation. This is especially dangerous when additional risk factors for DKA (e.g. infection, insulin pump failure, patient characteristics, low carb diet) are present. Although SGLTi might help in decreasing postprandial hyperglycemia when using automated insulin delivery,[5] our case warns against the use of SGLTi in people with T1D on the MiniMed™ 780G system. Additionally, until more is known about the influence of SGLTi on aHCL algorithm functioning, we recommend caution with SGLTi use in people with T1D on aHCL systems to avoid increased DKA risk. As recently reviewed by Pasqua et al,[6] clear understanding of the effects of SGLTi on the algorithm should be obtained before considering SLGTi in people on aHCL systems. This should allow for specific recommendations to avoid DKA development on top of careful patient selection and education on self-measurement of capillary blood ketones (specifically beta-hydroxybutyrate) as advised by the international consensus.[3]

**Authorship Confirmation Statement**

M.M.V. collected and discussed the data, wrote the manuscript, and made the figures. C.M. and P.G. discussed the data, and wrote the manuscript. M.M.V. and P.G. are the guarantors of this work, and take responsibility for the content of the article.

**Author Disclosure Statement**

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Therapeutics, Pfizer, and Zealand Pharma. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for C.M. from Medtronic, Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme, Eli Lilly, Roche, Abbott, ActoBio Therapeutics, and Novartis; C.M. serves or has served on the speakers bureau for Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme, Eli Lilly, Boehringer-Ingelheim, AstraZeneca, and Novartis. Financial compensation for these activities has been received by KU Leuven. P.G. serves or has served on the advisory panel for Novo Nordisk, Sanofi-Aventis, Boehringer-Ingelheim, Janssen Pharmaceuticals, Roche, Medtronic, and Bayer. Financial compensation for these activities has been received by KU Leuven. P.G. serves or has served on the speakers bureau for Merck Sharp and Dohme, Boehringer-Ingelheim, Bayer, Medtronic, Insulet, Novo Nordisk, Abbott, Roche, and Dexcom. Financial compensation for these activities has been received by KU Leuven. KU Leuven received for P.G. non-financial support for travel from Sanofi-Aventis, A. Menarini Diagnostics, Medtronic, and Roche. All disclosures were unrelated to the present work.

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## Figure Legends

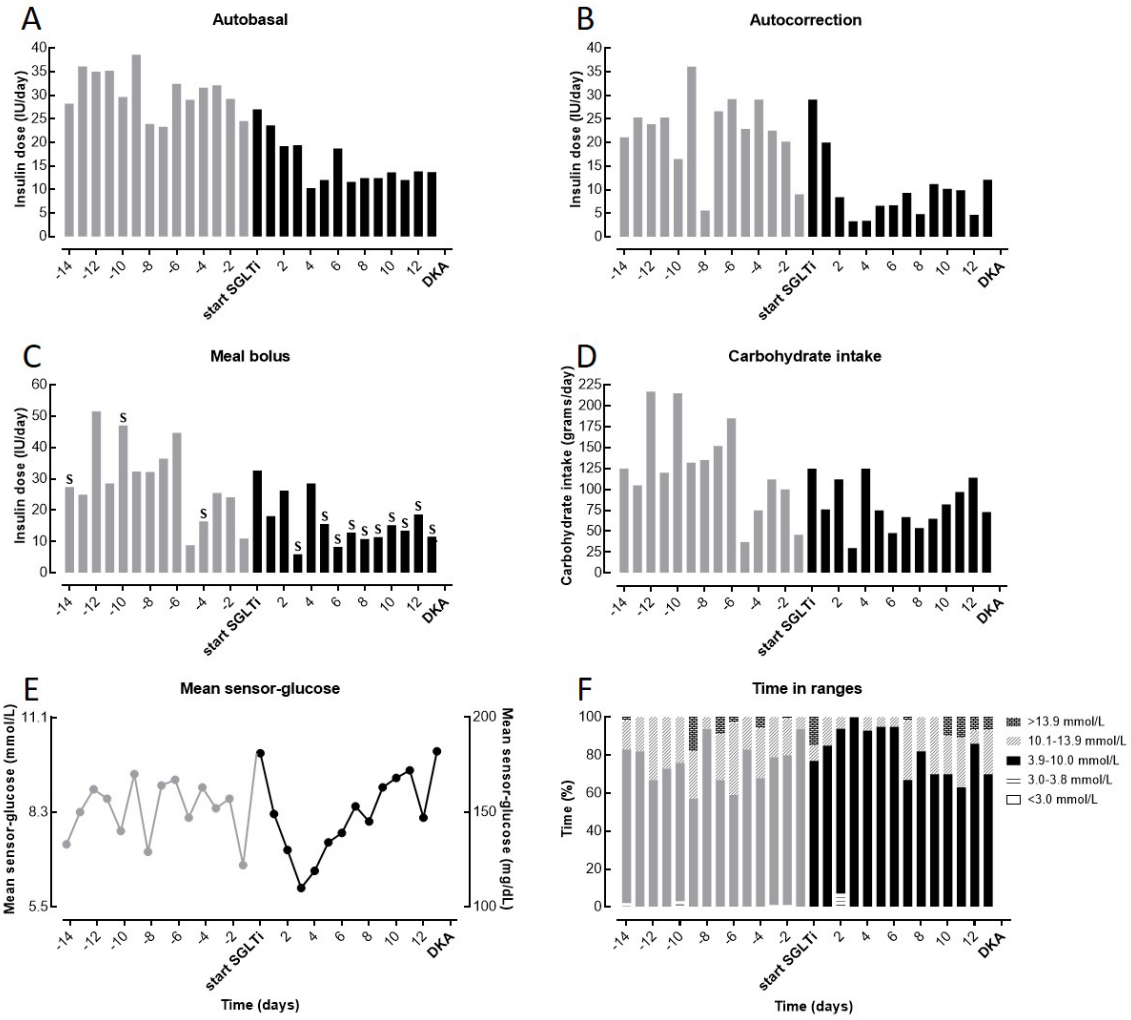


**Figure 1:** Graphical representation of daily autobasal (panel A), autocorrection (panel B), and meal bolus doses (panel C), carbohydrate intake by our patient (panel D), mean sensor-glucose (panel E), and time in ranges (panel F), in relation to initiation of sodium-glucose cotransporter inhibition (SGLTi) and onset of diabetic ketoacidosis (DKA). Grey bars and lines represent the period before start of SGLTi, black bars and lines represent the period after start of SGLTi. In panel C, 'S' indicates activation of the 'safe meal bolus' feature during one or more meal boluses on that specific day. All data are based on daily Ambulatory Glucose Profiles as reported in CareLink™. Sensor usage was on average >70%, SmartGuard™ usage was on average >95%.

SGLTi=sodium-glucose cotransporter inhibition. DKA=diabetic ketoacidosis.