Case Report

# SUCCESSFUL REIMPLEMENTATION OF A VERY LOW CARBOHYDRATE KETOGENIC DIET AFTER SGLT2 INHIBITOR ASSOCIATED EUGLYCEMIC DIABETIC KETOACIDOSIS

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## ABSTRACT

***Objective:*** We report a case of a successful reimplementation of a very low carbohydrate ketogenic diet (VLCKD) after a case of euglycemic diabetic ketoacidosis (euDKA).

***Methods:*** A 42-year-old female with a history of type 2 diabetes mellitus on a self-administered VLCKD was prescribed a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Two weeks after initiation, she presented with nausea and vomiting and was found to be in euDKA which was treated with fluid resuscitation, insulin infusion, and cessation of the SGLT2 inhibitor. She was discharged on insulin and instructed not to resume a VLCKD.

***Results:*** After discharge, the patient experienced rapid weight gain and deteriorating glycemic control and desired to resume a VLCKD. She was referred to a university-based medical weight loss clinic that specializes in a VLCKD. The patient was monitored with daily contact via the electronic health record's patient portal and serial laboratory testing while her carbohydrate intake was slowly reduced and her insulin titrated off. She has safely remained in ketosis for 2 years without a further episode of euDKA.

***Conclusion:*** As the clinical use of SGLT2 inhibitors and the VLCKD both become increasingly common, it is vital for practitioners to be aware that the combination can lead to euDKA. We present a case of successfully resuming a VLCKD after recovering from euDKA and cessation of SGLT2 inhibitor therapy. **(AACE Clinical Case Rep. 2020;6:e330-e333)**

**Abbreviations:**
**euDKA** = euglycemic diabetic ketoacidosis; **SGLT2** = sodium glucose cotransporter 2; **T2DM** = type 2 diabetes; **VLCKD** = very low carbohydrate ketogenic diet

## INTRODUCTION

A very low carbohydrate ketogenic diet (VLCKD) is a popular dietary approach for weight loss and diabetes management (1). A ketogenic diet restricts carbohydrates, usually to less than 50 g per day, to induce metabolic changes that favor fat utilization as the primary energy source via ketone formation (2).

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are increasingly prescribed for the treatment of type 2 diabetes mellitus (T2DM), given their cardiac and renal protective effects (3). They inhibit glucose reabsorption in the proximal tubule of the kidney, leading to glucosuria and reduced blood glucose levels. Diabetic ketoacidosis (DKA) is a known side effect of SGLT2 inhibitors (4). More than 2,500 cases of SGLT2 inhibitor-associated DKA have been reported in the United States Food and Drug Administration Adverse Event Reporting System, prompting new warnings about these risks (4). We report a case of a patient taking an SGLT2 inhibitor for T2DM while following a VLCKD who presented in euglycemic DKA (euDKA) and wished to resume a VLCKD following the episode. To our knowledge, there is no published literature

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about the safety or efficacy of reintroduction of a VLCKD after an episode of euDKA.

## CASE REPORT

A 42-year-old female with a past medical history significant for class III obesity and a 15-year history of T2DM on insulin therapy for 10 years, presented to the hospital complaining of a 2-day history of acute-onset nausea, vomiting, and shortness of breath. Three months prior, she had self-initiated a VLCKD at less than 20 g of carbohydrate per day, and was able to lose weight and dramatically reduce her blood glucose levels. Two weeks prior to admission, given the reduction in blood glucose, her primary care provider discontinued insulin and glyburide; continued her sitagliptin-metformin; and restarted an SGLT2 inhibitor (canagliflozin) which the patient had tolerated in the past.

On presentation, the patient had tachypnea (28 breaths per minute), tachycardia (108 beats per minute), a blood pressure of 140/80 mm Hg, and appeared ill. Laboratory testing was significant for metabolic acidosis with carbon dioxide (CO2) of 7 mmol/L and an elevated anion gap of 19 mmol/L (normal, 0 to 10 mmol/L). Blood gas analysis showed a pH of 7.11 and a pCO2 of 16 mm Hg. Urinalysis revealed ketones of 80 mg/dL (normal, <5 mg/dL) and glucosuria at >500 mg/dL. Blood glucose was 152 mg/dL. Serum acetone and β-hydroxybutyrate levels were elevated at 261 mg/L (normal, <20 mg/L) and 73.0 mg/dL (normal, 0.2 to 2.8 mg/dL), respectively. Serum lactate and creatinine were normal. Hemoglobin A1c on admission was 6.7% (50 mmol/mol). She was diagnosed with euDKA, admitted to the intensive care unit and treated with a standardized DKA protocol, including intravenous insulin and fluid resuscitation.

After 4 days, the patient was discharged on 30 units of glargine insulin daily, sitagliptin-metformin 50 mg/1,000 mg twice a day and told not to resume her SGLT2 inhibitor or her VLCKD. She subsequently experienced a rapid weight gain of 9 kg over 6 weeks and desired to resume the VLCKD. As a result, she was referred to a university-based medical weight loss clinic directed by a specialized obesity-medicine physician.

At her initial visit she was taking 85 units of glargine daily and sitagliptin-metformin. The physician and patient collaboratively decided to slowly reinitiate the VLCKD with close monitoring of dietary intake, blood glucose, medication dosage, and home testing of urinary ketones. Laboratory testing was obtained monthly for 3 months and then every 3 months to monitor renal function, CO2, and anion gap. Testing for the presence of antibodies to glutamic acid decarboxylase was obtained to assess for previously undiagnosed type 1 diabetes mellitus and was negative. A fasting C-peptide level was 2.9 ng/mL (normal, 0.8 to 3.1 mg/mL), suggesting residual insulin secretion.

To establish a baseline and ensure close monitoring prior to reinitiating the VLCKD, the patient was required to send daily communications via the patient portal regarding her dietary intake, urinary ketones, insulin dose, and glucose measurements. Her carbohydrate intake was initially restricted to 75 g daily to avoid ketosis. Over the course of the first month of treatment, carbohydrate intake was reduced to 50 g daily without evidence of urinary ketones. At her 1-month follow-up visit, the patient had lost 1.4 kg, laboratory parameters remained normal, and her glargine dose was reduced from 85 to 55 units daily.

In the second month of treatment, carbohydrate intake was reduced to 25 g daily. She developed positive urinary ketones but had no symptoms of nausea or vomiting. She also experienced a 7.6 kg weight loss and glargine was reduced to 5 units daily.

Three months after reinitiating the carbohydrate restricted diet, the patient was able to discontinue her insulin completely (while remaining on sitagliptin-metformin). She has now been followed at the weight loss clinic for 2 years with a total weight loss of 32.7 kg and without any further instances of euDKA or metabolic acidosis. Her T2DM is controlled on metformin 1,000 mg twice daily, glimepiride 1 mg daily, and liraglutide 1.8 mg subcutaneously daily, with hemoglobin A1c values ranging from 6.0% (42 mmol/mol) to 6.6% (49 mmol/mol) (Table 1).

## DISCUSSION

DKA is a known complication of type 1 diabetes mellitus and infrequently seen in T2DM (5,6). EuDKA is a rare variant of DKA and is defined by a blood glucose level of less than 200 mg/dL, glucosuria, and the presence of ketone bodies (7). An increased incidence of euDKA

**Table 1**
**Changes In Body Mass and Insulin Resistance with Reinitiation of Very-Low Carbohydrate Ketogenic Diet (VLCKD)**

| | Baseline | 2 Years on VLCKD[a] | Total change (Δ%) |
|---|---|---|---|
| Weight, kg | 132.6 | 99.9 | –32.7 (24.7) |
| Body Mass Index, kg/m$^2$ | 48.7 | 36.7 | –12 (24.6) |
| Insulin, units/day | 85 | 0 | –85 (100) |
| Hemoglobin A1c, % (mmol/mol) | 6.7[b] (50) | 6.6[c] (49) | –0.1 (1) |

[a]VLCKD included <20 g of carbohydrate daily.
[b]Treated with 85 units of insulin glargine daily and sitagliptin-metformin 50 mg/1,000 mg twice daily.
[c]Treated with metformin 1,000 mg twice daily, glimepiride 1 mg daily, and liraglutide 1.8 mg daily.

has been seen in patients on SGLT2 inhibitors and the pathophysiology of this condition is thought to come from the increased reliance on fatty acid metabolism following medication-induced glucosuria (8). SGLT2 inhibitors decrease circulating blood glucose by increasing its secretion into the urine which exacerbates the paucity of available glucose for metabolism and can worsen ketosis in patients with diabetes. EuDKA is a known risk of SGLT2 inhibitor therapy, initially described in a series of 20 cases between 2013 and 2014 published by the United States Food and Drug Administration (9).

A VLCKD induces a state of ketosis resulting from preferential metabolism of fatty acids and has been shown to improve body weight, glycemic control, and other metabolic parameters (10). In fact, some studies have demonstrated greater weight loss in patients on a VLCKD compared with a low-fat diet (10). The 2019 American Diabetes Association (ADA) Consensus Report included a low or very low carbohydrate diet amongst the many eating patterns that can meet individual needs and preferences in patients with diabetes (11,12).

Though a promising treatment option for patients with both obesity and T2DM, there is an exceedingly rare, but documented risk, that patients on a VLCKD alone may develop ketoacidosis in certain situations such as lactation, pregnancy, and starvation (13-15). Additionally, euDKA has been noted in multiple case reports when the VLCKD is coadministered with SGLT2 inhibitors, 3 of which are referenced here (16-18).

In our case, the patient developed euDKA while on a VLCKD and an SGLT2 inhibitor. Given subsequent weight regain and deterioration of glycemic control, she was eager to reinitiate a VLCKD since the SGLT2 inhibitor had been discontinued. To this end, she was closely monitored by an obesity-medicine physician for signs of metabolic acidosis as dietary carbohydrate restriction was slowly introduced over 2 months, as detailed above.

As the use of SGLT2 inhibitors continues to increase, and the VLCKD is increasingly popular, it is important to be aware of the potential complication of euDKA. Furthermore, it is imperative for health care providers to inquire about their patients' diets prior to initiating SGLT2 inhibitor treatment, as many patients initiate a VLCKD without their physician's knowledge. Given the potential increased risk of euDKA, we advise against SGLT2 inhibitor use in patients following a VLCKD. However, the clinical benefit of SGLT2 inhibitor use in patients with T2DM should not be overlooked. The ADA has recommended that this class of medications be preferentially added in patients with T2DM, diabetic kidney disease, and congestive heart failure (19). The anticipated risks/benefits of each therapeutic approach (i.e., SGLT2 inhibitors and VLCKD) should be discussed with the patient to direct shared decision making. In patients with T2DM who do elect to follow a VLCKD, but otherwise meet indications for SGLT2 inhibitors, alternative therapies (i.e., glucagon-like-peptide-1 agonists) with similar clinical benefits should also be considered (19).

## CONCLUSION

There have been reports of euDKA among patients using SGLT2 inhibitors in the setting of a VLCKD and this combination of therapies should generally be avoided. To this end, it is essential that providers assess patients' dietary patterns prior to the initiation of a SGLT2 inhibitor, and provide guidance about risk factors for euDKA. However, if a patient experiences SGLT2-associated euDKA, there is no current guidance for patients wanting to safely initiate a VLCKD after discontinuation of the SGLT2 inhibitor and resolution of the euDKA. Thus, we describe a case where a patient was safely and effectively able to resume a VLCKD for 2 years without adverse effect. This approach was supervised by an obesity medicine specialist and included a gradual reduction in carbohydrate intake in conjunction with close clinical and laboratory monitoring. Although this is only a single case and might not be applicable to all patients, this account may offer some guidance to those contemplating use of a VLCKD after an episode of SGLT2 inhibitor-associated euDKA.

## DISCLOSURE

The authors have no multiplicity of interest to disclose.

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