Received: 4 December 2024 | Revised: 27 January 2025 | Accepted: 29 January 2025

DOI: 10.1111/dom.16252

ORIGINAL ARTICLE

WILEY

Illnesses associated with ketosis including diabetic ketoacidosis during very low carbohydrate and ketogenic diets

Caroline G. P. Roberts MD[1] | Shaminie J. Athinarayanan PhD[1] | Robert E. Ratner MD[2] | Guillermo E. Umpierrez MD[3]

[1]Virta Health, Denver, Colorado, USA

[2]Department of Medicine, Division of Endocrinology, Georgetown University School of Medicine, Washington, District of Columbia, USA

[3]Department of Medicine, Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia, USA

Correspondence
Caroline G. P. Roberts, Virta Health, 3513 Brighton Blvd. Suite 310, Denver, CO 80216, USA.
Email: caroline@virtahealth.com

Abstract

Aims: Ketogenic diets are used by individuals with obesity and type 2 diabetes for improved glycaemic control, reduced appetite and weight loss. However, the risks associated with higher ketone levels, including diabetic ketoacidosis (DKA), in individuals with and without diabetes are not well-documented.

Materials and Methods: We analysed real world data from a single-centre telemedicine clinic specializing in a very low carbohydrate ketogenic diet (VLCKD) as a lifestyle intervention. Illnesses associated with ketosis (IAK) were defined as beta-hydroxybutyrate (BHB) levels ≥3 mmol/L when patients sought in-person care. We estimated the IAK and DKA incidence rate in individuals with and without type 2 diabetes.

Results: In 72 751 patient-years of follow-up, 86 people had IAK (incidence rate 1.18 per 1000 person-years). In 22 347 patient-years of follow-up of people without diabetes, the incidence rate of IAK was 0.04 per 1000 person-years with no DKA cases. In 50 404 patient-years of follow-up in people with type 2 diabetes (PWD), the incidence rates of IAK and of DKA were 1.69 and 1.01 per 1000 person-years, respectively. In 12 763 person-years of follow-up of PWD using SGLT2-inhibitors, the DKA incidence was 2.90 per 1000 patient-years.

Conclusions: Very low carbohydrate ketogenic diets are generally safe with low rates of IAK, including DKA, in people with and without type 2 diabetes. The higher incidence of DKA in PWD on VLCKD who are also on SGLT2-inhibitors may be manageable through at-home monitoring of BHB levels.

KEYWORDS

diabetes complications, dietary intervention, real-world evidence, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Very low carbohydrate ketogenic diets (VLCKDs) are rising in popularity among people with metabolic diseases due to growing awareness of their benefits for glycaemic control, inflammation and weight loss. VLCKDs are characterized by reducing dietary carbohydrate intake to 20–50 g/day (about 4 to 10% of a 2000-kcal/day diet). After several days of VLCKD, glycogen is depleted, and the body breaks down

protein and fat for energy. The increased fatty acid release results in high circulating levels of free fatty acids, which are converted to ketone bodies in the liver. Beta-hydroxybutyrate (BHB) is the primary ketone body, which can be measured in capillary blood on point-of-care devices.[1]

Despite higher levels of BHB, VLCKDs are primarily regarded as safe because healthy subjects can adapt to VLCKD by increasing ketone clearance by peripheral tissue (brain and muscle) and enhancing the kidney's ability to excrete ammonia to compensate for the increased acid production.[2] Therefore, these diets rarely result in significant metabolic acidosis or with a serum bicarbonate concentration of less than 18 mEq/L. However, VLCKD has been linked to cases of ketoacidosis.[3,4] More recently, the risk of illness associated with ketosis (IAK) has increased in individuals with diabetes on SGLT2-inhibitors, particularly during times of intercurrent illness, dehydration, reduced carbohydrate/ketogenic diet and/or metabolic stress, leading to diabetic ketoacidosis (DKA).[5] Therefore, American Diabetes Association and American Association of Clinical Endocrinologists and American College of Endocrinology guidelines warn against adopting VLCKD in patients receiving SGLT2-inhibitors.[6,7]

Few studies have reported on the risk of DKA in individuals with and without diabetes on VLCKDs. Therefore, in this analysis, we examined the incidence rate and characteristics of IAK in people with type 2 diabetes, prediabetes and obesity who follow VLCKD and who employ home fingerstick BHB primarily for biofeedback on dietary adherence and secondarily for safety monitoring. In addition, we explored the added risk of IAK and DKA with the use of SGLT2-inhibitors.

2 | MATERIALS AND METHODS

2.1 | Care model

Virta Health delivers telemedicine care to patients throughout the United States seeking support for lifestyle care for individuals with type 2 diabetes, prediabetes and obesity. Patients with stage 4 or more severe chronic kidney disease, New York Heart Association Class IV heart failure and Child Pugh Class C cirrhosis are excluded from the clinic. Patients are initially counselled to achieve and sustain nutritional ketosis (BHB 0.5–5.0 mmol/L),[8] by restricting carbohydrates to fewer than 30 g per day (or fewer than 50 g if consuming a vegan eating pattern). In addition, protein intake is recommended around 1.5 g/kg of reference body weight, and fat intake is titrated to achieve satiety while enabling weight loss. Levels of carbohydrate restriction and ketones are later individualized based on the patient's personal carbohydrate tolerance and health goals. Patients are encouraged to continue carbohydrate restriction for the entire period while they are under care in the telemedicine clinic. Diabetes medications are adjusted as needed for glycaemic control and to minimize the risk of hypoglycaemia. The frequency of follow-up with patients regarding biomarkers and nutrition therapy is individualized based on patient outreach and health needs and can be as often as daily.

Remote monitoring of capillary BHB and glucose is done using a combined monitor (keto-mojo, Freestyle Precision Xtra) or glucose by CGM (Dexcom, Libre, Medtronic). The medical care team reviews daily values. BHB values are primarily used in coaching patients on dietary changes and food choices, however, patient safety is always on top of mind. Patients logging fingerstick ketones ≥3 mol/L who are taking SGLT2-inhibitor receive an automated message via smartphone application prompting them to seek in-person care if they are experiencing symptoms compatible with DKA. If they are not experiencing symptoms, they are prompted to hydrate. Additionally, the medical care team reaches out to patients logging BHB ≥3 mmol/L to conduct risk assessment and to provide personalized guidance. Patients describing symptoms concerning for DKA are advised to seek in-person care, and the case is flagged for follow-up. Events where patients follow through on the recommendation to seek in-person care are termed 'IAK' and the care team documents the result of the initial laboratory assessment and the course of care by reviewing their medical records.

Due to warnings from the American Diabetes Association[6] and the American Association of Clinical Endocrinology[7] against combining SGLT2-inhibitors with VLCKD due to risk of DKA, the safety protocol is to stop SGLT2-inhibitors a few days before diet changes in people without cardiorenal indications. For people with cardiorenal SGLT2-inhibitor indications, the medications are continued through diet changes to continue to deliver the protective benefits. Diabetes medications, including SGLT2-inhibitors, are started de novo or resumed if needed for persistent hyperglycaemia despite dietary changes. All patients taking SGLT2-inhibitors in combination with carbohydrate restriction receive anticipatory guidance on the risk of DKA, a description of DKA symptoms, caution on avoidable risk factors such as dehydration, fasting and heavy alcohol use, and a safety protocol to hold the medication and hydrate if the ketones rise above 3 mmol/L and resume the medication when the fingerstick BHB falls below 2 mmol/L.

2.2 | Study population

This real world retrospective study used de-identified patient care data from 2015 to 2023, including enrollment descriptives, laboratory values, medication use and diabetes monitoring data (home-monitored glucose, BHB and body weight) of all cases flagged for follow-up due to clinician concern for nascent DKA, generally due to the combination of BHB ≥3 mmol/L and concerning symptoms. The use of de-identified data, which is compliant with the Health Insurance Portability and Accountability Act (HIPAA) standards, exempts this study from needing ethics committee approval, as it does not involve identifiable human subjects.

The primary outcomes were incidence rates of IAK and of DKA in individuals with and without type 2 diabetes. IAK was defined as when a patient who feels ill with a BHB ≥3 mmol/L seeks in-person care. Secondary outcomes included the incidence rates and clinical characteristics of flagged events including ill patients with BHB

≥3 mmol/L who elected not to seek in-person care, and the clinical and laboratory characteristics of IAK, including DKA, incidence rates of IAK and DKA among people taking SGLT2-inhibitors and the difference in risk of DKA associated with SGLT2-inhibitor use.

BHB were recorded from the hospital records. When BHB values were not available from hospital records due to patient recovery at home, or due to missing documentation, the highest fingerstick BHB value within 3 days before or on the date of the event was retrieved. Among the reported IAK, DKA cases were classified based on the 2024 DKA criteria[9] to confirm the presence or absence of DKA. Events lacking laboratory data were adjudicated as DKA if care was provided in an intensive care unit and/or if continuous intravenous insulin infusion was employed. Multiple events in the same person were handled individually.

2.3 | Statistical methods

Enrollment and at-event descriptives, including weight change from enrollment to time of event, were assessed to describe the characteristics of flagged events, IAK, confirmed DKA and non-DKA cases. Means and standard deviations (SDs) were used for continuous variables, while the total number of patients and percentages were used for categorical variables. The differences between cases where in-person care was sought versus not sought, and confirmed DKA and non-DKA cases was assessed using independent t-tests for continuous outcomes and Chi-square tests for categorical variables. The incidence rates of IAK, including IAK in those ever exposed to and never exposed to SGLT2-inhibitor while in the treatment and/or at enrollment, and adjudicated DKA cases were calculated by dividing number of events reported by total patient-years at risk treated in each category during the duration of the study monitoring period from 2015 to 2023.

The association between SGLT2-inhibitor and IAK was assessed using two different approaches: 1) patients who were exposed to SGLT2-inhibitor during dietary treatment, and 2) patients who were exposed to SGLT2-inhibitor during dietary treatment or who had been instructed to stop the SGLT2-inhibitor prior to dietary changes. This analysis was conducted using univariate penalized logistic regression. To further quantify the risk associated with SGLT2-inhibitor use, we calculated the number needed to harm (NNH) using three different approaches: 1) exposure to SGLT2-inhibitor during the treatment period, 2) exposure to SGLT2-inhibitor either during the treatment period or before diet changes and 3) person-days of SGLT2-inhibitor exposure during the treatment period. These NNH values were calculated for IAK and for confirmed DKA cases. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 29.0 and R software version 4.2.2.

2.4 | Data resource and availability

The datasets generated during and/or analysed in the study are available from the corresponding author upon reasonable request.

3 | RESULTS

Figure 1 shows the case review process and identification of IAK, and adjudication of DKA events. Incidence rates are shown in Table 1. In 72 751 patient-years of follow-up, there were 148 unique flagged health events involving higher ketones, giving an incidence rate of 2.03 per 1000 person-year. Sixty-two incidents in 61 people were resolved at home. All but three such incidents involved PWD. Eighty-six people (85 with type 2 diabetes) went on to seek in-person care for illness in the setting of higher BHB, defined as IAK. The incidence rate of IAK is 1.18 per 1000 person-years. In 22 347 patient-years of follow-up in people without diabetes, there was one IAK, giving an incidence rate of 0.04 per 1000 person-years. This case did not involve an SGLT2-inhibitor, and did not meet the criteria for DKA. SGLT2-inhibitor use in the non-diabetes population was minimal, and there were no IAK events in 154 person-years of follow-up.

In 50 404 patient-years of follow-up in PWD, the incidence rates of IAK and of DKA were 1.69 and 1.01 per 1000 person-years, respectively. There were no deaths. Among PWD, the incidence rate of IAK of those who ever took an SGLT2-inhibitor, including just before dietary change, is 4.23 per 1000 person-years compared to 0.82 per 1000 person-years for those who never took an SGLT2-inhibitor. The incidence rates of DKA in PWD per 1000 person-years is 1.01, 2.90 among those ever on an SGLT2-inhibitor, and 0.37 among those never on an SGLT2-inhibitor. The use of SGLT2-inhibitors in PWD increased the risk of IAK by 4.24-fold ($p < 0.001$), 2.11-fold for non-DKA IAK (not significant) and 7.18-fold for DKA ($p < 0.001$).

Table 2 shows the biomarkers and clinical characteristics of PWD with flagged events including those who recovered at home and those who developed IAK, including events where DKA was ruled in and ruled out. Among flagged events, the presence of nausea and/or vomiting was less common among those who recovered at home than among those who sought care (25% vs. 61%, $p < 0.001$). The highest fingerstick glucose within 3 days of the event were more likely to be under 200 mg/dL (86% vs. 68%, $p = 0.02$) in people who recovered at home than in people with IAK. No other clinical characteristics distinguished these two groups, including SGLT2-inhibitor or insulin use, and fingerstick BHB values that were well above the diagnostic threshold for DKA of ≥3 mmol/L.[9]

Among PWD with IAK, there were no clinical characteristics or biomarkers that distinguished between people with adjudicated DKA and non-DKA events, including risk factors for and markers of insulin deficiency, fingerstick glucose and BHB, SGLT2-inhibitor and insulin use.

Table 3 shows the laboratory values of PWD with IAK, including adjudicated DKA and non-DKA events. Laboratory assessments for ketosis were used for DKA adjudication but results are not included in the table due to heterogeneity of specimen sources and of reporting scales. Of the 51 people with DKA, 26 (54%) had blood glucose ≥200 mg/dL, and 22 (46%) were normoglycemic. A similar percentage of laboratory glucose above and below 200 mg/dL was seen in non-DKA IAK. Although alcohol and lactate may contribute to

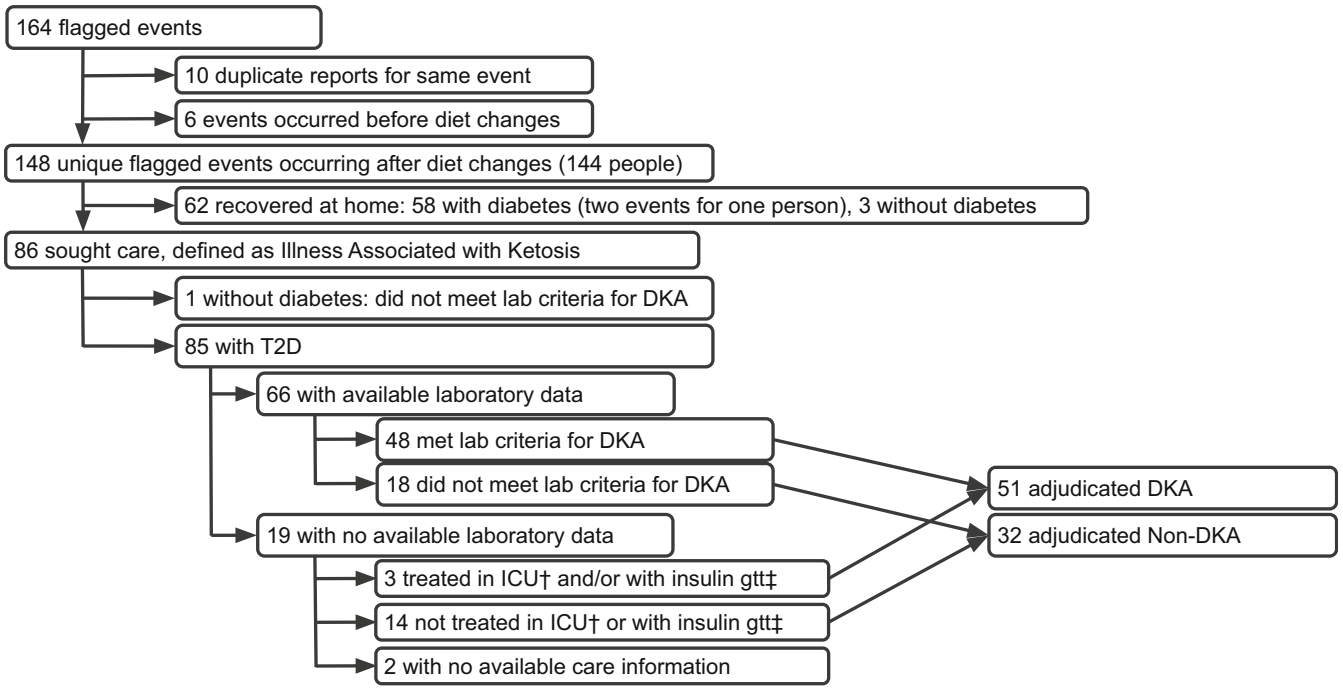

FIGURE 1 Study flow diagram of identification from flagged events to illnesses associated with ketosis and diabetic ketoacidosis adjudication. †ICU, intensive care unit. ‡gtt, continuous intravenous infusion.

TABLE 1 Incidence rates of all events by disease and by SGLT2-inhibitor (SGLT2i) exposure.

		Flagged events		Recovered at home		IAK		No DKA		DKA	
Diagnosis	Person-years of follow-up	N	IR†	N	IR	N	IR	N	IR	N	IR
All	72 751	148	2.03	62	0.85	86	1.18	33	0.45	51	0.70
Ever on SGLT2i	12 917	98	7.59	43	3.33	54	4.18	18	1.39	37	2.86
Never on SGLT2i	59 835	50	0.84	19	0.32	32	0.53	15	0.25	14	0.23
PWD	50 404	144	2.86	59	1.17	85	1.69	32	0.63	51	1.01
Ever on SGLT2i	12 763	98	7.68	43	3.37	54	4.23	18	1.41	37	2.90
Never on SGLT2i	37 654	46	1.22	16	0.42	31	0.82	14	0.37	14	0.37
People without Diabetes	22 347	4	0.18	3	0.13	1	0.04	1	0.04	0	0.00
Ever on SGLT2i	154	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Never on SGLT2i	22 181	4	0.18	3	0.14	1	0.05	1	0.05	0	0.00

Abbreviations: †IR, incidence rate per 1000 person-years; DKA, diabetic ketoacidosis; IAK, illness associated with ketosis; PWD, people with type 2 diabetes.

metabolic acidosis, these data were not systematically obtained in clinical practice, so we are unable to examine their roles. Not shown in the Table 3 are the laboratory values of the case of IAK without diabetes. This individual was acidotic (bicarbonate 13 mg/dL), and ketotic (urine ketones 3+), but was missing the glycaemia criterion due to normoglycaemia (93 mg/dL) and lack of history of diabetes.

In a univariate model, PWD ever taking an SGLT2-inhibitor while in the treatment are 4.3 times more likely than those never on an SGLT2-inhibitor ($p < 0.001$) to have an IAK event. Similarly, people who were ever exposed to SGLT2-inhibitors, whether they were taking SGLT2-inhibitor in the treatment or where these patients de-prescribed SGLT2-inhibitor just prior to dietary change as per our usual care protocol, are 5.9 times more likely than never on SGLT2-inhibitor ($p < 0.001$) to have IAK.

When an SGLT2-inhibitor is added to a VLCKD, the NNH for DKA is 260, and when an SGLT2-inhibitor is added or used before transitioning to VLCKD, it is 223. The NNH for IAK, based on person-days of exposure to SGLT2-inhibitor in a VLCKD, is 33 597, meaning that for every 33 597 person-days of exposure to SGLT2-inhibitor while on a VLCKD, one additional IAK event is expected to occur compared to those not exposed to SGLT2-inhibitor.

The NNH for DKA cases, when SGLT2-inhibitor is used in conjunction with VLCKD or when exposure to SGLT2-inhibitor occurs just before or during VLCKD, is slightly higher, around 308 to 313.

TABLE 2 Characteristics of flagged events, and of illness associated with ketosis (IAK) including diabetic ketoacidosis (DKA) and no DKA in people with diabetes (PWD).

		Flagged events in people with diabetes				DKA adjudication of IAK in people with diabetes			
	All flagged events	All	Recovered at home	IAK		No DKA	DKA	Lab data unavailable	
	N = 148	*N* = 144	*N* = 59	*N* = 85	*p*-value	*N* = 32	*N* = 51	*N* = 2	*p*-value
Demographics									
Age at Event, mean years (SD)	56 (9)	56 (8)	58 (8)	55 (9)	NS	57 (8)	54 (9)	54 (0)	NS
Female, *n* (%)	66 (45)	63 (44)	28 (48)	35 (41)	NS	15 (47)	20 (40)	0 (0)	NS
Baseline BMI, mean kg/m^2 (SD)	34 (8)	34 (8)	35 (7)	34 (8)	NS	34 (6)	34 (9)	31 10)	NS
Baseline HbA1c, mean % (SD)	8.3 (1.9)	8.4 (1.8)	8.3 (1.6)	8.5 (1.9)	NS	8.6 (2.2)	8.4 (1.8)	9.8 (0.1)	NS
Diabetes Duration, mean years (SD)	16 (10)	16 (10)	17 (10)	16 (9)	NS	16 (10)	15 (8)	20 (3)	NS
Time to insulin, mean years (SD)	9 (9)	9 (9)	9 (9)	9 (10)	NS	13 (11)	7 (9)	10 (13)	NS
Risk factors for insulin deficiency									
Pancreatic insufficiency risk factors,[a] *n* (%)	11 (8)	11 (8)	2 (3)	9 (11)	NS	4 (13)	5 (10)	0 (0)	NS
Prior History of DKA,[b] *n* (%)	14 (10)	14 (10)	3 (5)	11 (13)	NS	5 (16)	5 (10)	1 (50)	NS
Autoimmunity, *n* (%)	40 (27)	38 (26)	18 (31)	20 (24)	NS	9 (28)	11 (22)	0 (0)	NS
C-peptide,[c] mean ng/dl (SD)	2.4 (2.5)	2.4 (2.5)	1.9 (1.1)	2.6 (2.9)	NS	3.2 (1.7)	2.5 (3.3)	0.1 –	NS
CPRI,[d] mean (SD)	1.3 (1.1)	1.3 (1.1)	1.1 (0.5)	1.4 (1.3)	NS	1.8 (0.5)	1.3 (1.5)	0.2 –	NS
Baseline triglycerides, mean mg/dL (SD)	193 (164)	194 (165)	173 (116)	209 (191)	NS	199 (233)	216 (165)	178 (44)	NS
Baseline HDLc, mean mg/dL (SD)	47 (15)	46 (15)	49 (16)	44 (13)	NS	47 (16)	43 (12)	42 (9)	NS
Tenure at event, mean days (SD)	271 (385)	278 (388)	230 (316)	311 (430)	NS	396 (505)	267 (379)	77 (41)	NS
Weight change, baseline to event, % (SD)	−6.1 (8.7)	−6.1 (8.8)	−6.4 (7.3)	−5.8 (9.7)	NS	−5.2 (8.0)	−6.0 (10.8)	−10.3 (2.2)	NS
Maximum fingerstick home monitoring values, Up to 3 days before event									
Glucose mean mg/dL (SD)	172 (94)	205 (106)	136 (59)	205 (106)	<0.001	222 (106)	194 (105)	111 –	NS
Glucose <200 mg/dL, *n* (%)	105 (77)	101 (76)	51 (86)	50 (68)	0.02	18 (56)	31 (76)	1 (100)	NS
Glucose ≥200 mg/dL, *n* (%)	32 (23)	32 (24)	8 (14)	24 (32)		14 (44)	10 (24)	–	
BHB, mean mmol/L (SD)	4.8 (2.0)	4.8 (2.0)	4.5 (1.4)	5.1 (2.3)	NS	4.7 (2.1)	5.6 (2.4)	3.6 –	NS
BHB <3 mmol/L, *n* (%)	17 (14)	17 (14)	7 (12)	10 (16)	NS	5 (17)	5 (15)	–	NS
BHB 3 – <4 mmol/L, *n* (%)	24 (19)	22 (18)	16 (27)	6 (9)		3 (10)	2 (6)	1 (100)	
BHB 4 – <8 mmol/L, *n* (%)	75 (60)	74 (60)	33 (56)	41 (64)		20 (67)	21 (64)	–	
BHB ≥8 mmol/L, *n* (%)	10 (8)	10 (8)	3 (5)	7 (11)		2 (7)	5 (15)	–	
Symptoms									
Nausea and/or Vomiting, *n* (%)	76 (51)	76 (53)	15 (25)	61 (76)	<0.001	18 (62)	43 (84)	–	NS
Medications at time of event									
Insulin, *n* (%)	49 (33)	49 (34)	17 (27)	32 (38)	NS	11 (34)	20 (39)	1 (50)	NS
Total per day, mean units (SD)	28 (24)	28 (24)	21 (19)	32 (26)	NS	26 (16)	34 (30)	60 –	NS
Units per kg, mean (SD)	0.30 (0.25)	0.30 (0.25)	0.24 (0.24)	0.34 (0.25)	NS	0.30 (0.23)	0.34 (0.27)	0.58 –	NS

(Continues)

TABLE 2 (Continued)

		Flagged events in people with diabetes				DKA adjudication of IAK in people with diabetes			
	All flagged events	All	Recovered at home	IAK		No DKA	DKA	Lab data unavailable	
	N = 148	*N* = 144	*N* = 59	*N* = 85	*p*-value	*N* = 32	*N* = 51	*N* = 2	*p*-value
Metformin, *n* (%)	98 (66)	98 (68)	40 (68)	58 (68)	NS	19 (59)	38 (75)	1 (50)	NS
SGLT2i, *n* (%)	72 (49)	72 (50)	34 (58)	38 (45)	NS	13 (41)	25 (49)	0 (0)	NS
GLP1ra, *n* (%)	45 (30)	45 (31)	14 (24)	31 (37)	NS	11 (34)	20 (39)	0 (0)	NS
DPP4i, *n* (%)	12 (8)	12 (8)	5 (9)	7 (8)	NS	1 (3)	6 (12)	0 (0)	NS
Sulfonylurea, *n* (%)	11 (7)	11 (8)	4 (7)	7 (8)	NS	3 (9)	4 (8)	0 (0)	NS
Thiazolidenedione, *n* (%)	7 (5)	7 (5)	2 (3)	5 (6)	NS	2 (6)	3 (6)	0 (0)	NS

Note: Data available for 80% or more of all flagged events except as indicated.
Abbreviations: CPRI, postprandial C-peptide immunoreactivity index (10); NS, not significant.
[a]Data available for 114 events, 77% of flagged events.
[b]Data available for 117 events, 79% of flagged events.
[c]Data available for 94 events, 64% of flagged events.
[d]CPRI data available for 50 events, 34% of flagged events.

The NNH based on person-days of exposure to SGLT2-inhibitor in a VLCKD is 37 709. The NNH for IAK and adjudicated DKA events was slightly lower in those exposed to SGLT2-inhibitor during or just before VLCKD. This correlates with when these adjudicated DKA events were reported, where approximately 40% were reported within 90 days of enrollment, with the median programme days of DKA events being 125 days. Likely, these events happened early in the dietary changes, especially among those taking SGLT2-inhibitor at enrollment.

4 | DISCUSSION

This real world data analysis supports the overall safety of VLCKD for people with metabolic diseases, including type 2 diabetes, prediabetes and obesity. IAK, including DKA, are rare events and almost exclusively affect PWD. Observational studies of DKA incidence rate in PWD ranges from 0.6 to 2.3 per 1000 person-years.[11–17] Our incidence rate of IAK (1.69 per 1000 person-years), including both DKA (1.01 per 1000 person-years) and non-DKA events (0.63 per 1000 person-years) in PWD on VLCKD, falls in this same range, and our DKA incidence rate in PWD not taking SGLT2-inhibitors (0.37 per 1000 person-years) is slightly lower.

The 2.90 per 1000 person-year incidence rate of DKA in PWD on VLCKD and SGLT2-inhibitors in this analysis is comparable to published incidence rates of 0.5 to 4.9 per 1000 person-years in real world data analyses of SGLT2-inhibitor exposure in PWD not specifically following VLCKD.[11,14,16–19] Real world analyses estimate the increased risk of DKA for PWD on SGLT2-inhibitors compared to non-SGLT2-inhibitor medications to be from nil to 2.85-fold.[11,12,15–19] Meta-analyses of clinical trial data report a similarly increased risk of DKA related to SGLT2-inhibitor use ranging from none to 2.5-fold increase.[12,20–26] In an analysis of DKA cases from FDA Adverse Event Reporting System (FAERS), the increased risk from adding SGLT2-inhibitors to diabetes care with no specific dietary pattern was estimated to be sevenfold,[27] which is similar to our calculated 7.18-fold increased risk. The fold increase in our analysis is affected by the relatively low incidence of DKA in PWD not taking SGLT2-inhibitors.

There is evidence of increased IAK, including DKA, early in the combination of VLCKD and SGLT2-inhibitor use, as evidenced by the lower NNH when an SGLT2-inhibitor is added or used just before transitioning to VLCKD, possibly suggesting that the likelihood of developing problems wanes as exposure time increases. It is valuable to understand this risk as the addition of SGLT2-inhibitor use to VLCKD may be helpful for patients who stand to benefit from the non-diabetes effects of these medications when there is a safety protocol in place.

The incidence of glucose concentration ≤ 200 mg/dL among patients with adjudicated DKA in this population is higher than the reported incidence of about 10%.[9] A possible explanation is that the very low carbohydrate nutrition plan prevents higher blood glucose while not preventing ketoacidosis. A less likely explanation is that some of the people adjudicated as DKA were suffering from other causes of acidosis that do not cause hyperglycaemia, such as alcoholic ketoacidosis, starvation ketoacidosis or lactic acidosis in combination with physiologically elevated BHB from low carbohydrate intake. Still, they met the glycaemic criterion for DKA based on their prior history of diabetes. The absence of data on other anions is an important limitation of this analysis, leaving open questions about the contribution of other anions to the acid burden in these patients.

The impact of routine BHB monitoring for biofeedback and of our remote monitoring care model and safety protocols on IAK and DKA incidence rates is unknown. Specifically, the influence of immediate automated guidance to hydrate for higher BHB levels and of the anticipatory guidance for people taking SGLT2-inhibitors to hold

TABLE 3 Laboratory values for illness associated with ketosis (IAK) including diabetic ketoacidosis (DKA) and no DKA in people with diabetes (PWD).

	DKA adjudication of IAK in people with diabetes			
	IAK in People with Diabetes	No DKA	DKA	
	N = 85	*N* = 32	*N* = 51	*p*-value
Glucose,[a] mg/dL	251 (153)	225 (136)	262 (159)	NS
<200 mg/dL, *n* (%)	33 (49)	11 (58)	22 (46)	NS
≥200 mg/dL, *n* (%)	34 (51)	8 (42)	26 (54)	
Bicarbonate,[b] mmol/L	14.9 (5.5)	20.8 (3.4)	12.7 (4.4)	<0.001
Bicarbonate ≥20 mmol/L, *n* (%)	14 (21)	11 (61)	3 (6)	<0.001
Bicarbonate 18 – <20 mmol/L, *n* (%)	9 (14)	6 (33)	3 (6)	
Bicarbonate 15 – <18 mmol/L, *n* (%)	11 (17)	0 (0)	11 (23)	
Bicarbonate 10 – <15 mmol/L, *n* (%)	21 (32)	1 (6)	20 (42)	
Bicarbonate <10 mmol/L, *n* (%)	11 (17)	0 (0)	11 (23)	
Anion Gap,[c] mmol/L	20.8 (6.0)	16.7 (3.8)	22.3 (6.0)	<0.001
Anion Gap 10 – <12 mmol/L, *n* (%)	4 (6)	2 (11)	2 (4)	NA
Anion Gap ≥12, *n* (%)	62 (94)	16 (89)	46 (96)	
Arterial or Venous pH,[d] mean (SD)	7.2 (0.1)	7.4 (0.1)	7.2 (0.1)	<0.001
pH ≥7.30, *n* (%)	15 (30)	10 (100)	5 (13)	<0.001
pH 7.25 – <7.30, *n* (%)	8 (16)	–	8 (20)	
pH 7.00 – <7.25, *n* (%)	22 (44)	–	22 (55)	
pH ≤7.00, *n* (%)	5 (10)	–	5 (13)	

Note: Data available for 80% or more of all flagged events except as indicated.
Abbreviation: NS, not significant.
[a]Data available for 67 events, 79% of IAK in PWD.
[b]Data available for 66 events, 78% of IAK in PWD.
[c]Anion gap data are shown for the events where bicarbonate is less than 20 mmol/L. Anion gap was calculated as follows: Anion Gap = Sodium – (Chloride + Bicarbonate).
[d]Data presented for 51 events, 60% of IAK in PWD and 98% of events where bicarbonate is less than 20 mmol/L.

the medication until BHB levels drop could effectively prevent nascent IAK and DKA from evolving and reduce the incidence of events compared to unmonitored settings. Notably, the enhanced DKA risk mitigation plan including intermittent BHB monitoring, that was initiated during the Tandem 1 and 2 studies appeared to reduce, but did not eliminate, the added risk of DKA for people with type 1 diabetes randomized to sotagliflozin.[28] Significantly, in our population of people with type 2 diabetes or no diabetes and with expected higher background BHB levels due to carbohydrate restriction, little of the clinical data available through remote monitoring and prior to the in-person assessment were associated with the need for in-person care versus the ability to recover at home, and with the diagnosis of DKA or non-DKA. This included fingerstick BHB levels that overlap with traditionally concerning values,[1,9] highlighting the need for randomized, controlled trials to understand safe and unsafe BHB levels in people following VLCKD on and off SGLT2-inhibitors employing various monitoring methods, including continuous ketone monitoring,[29] and the importance of clinical oversight and judgement. In unmonitored settings, appropriate anticipatory guidance regarding avoiding triggers and recognizing symptoms of DKA may prevent cases, and/or lead to early diagnosis.

While the incidence of IAK in people without type 2 diabetes was very low, the small number of events precludes exploration of risk factors. The total number of person-years of follow-up of people without diabetes taking SGLT2-inhibitors was minimal, limiting our ability to determine the incidence rate of IAK under these specific circumstances.

As the clinic excludes people with known type 1 diabetes, significant renal or hepatic disease or advanced heart failure, the incidence of IAK and DKA in people following VLCKD with these comorbidities remains an open question. Data on insulin deficiency markers in our population were limited to C-peptide and postprandial C-peptide immunoreactivity index[10] which did not correlate with disease severity. We did not have sufficient data available on autoimmune diabetes markers, limiting our ability to explore vulnerability to DKA in this population.[22] Under-detection of IAK and DKA in this analysis is possible for patients not testing BHB or not reporting in-person assessment to the care team. However it is notable that patients typically interact with the app and their care team nearly daily.

A major strength of this study is the use of a large real world clinical practice dataset, which provides valuable insights into rare events that are unlikely to be studied in controlled settings like randomized

controlled trials. The large number of patient-years of care delivered nationwide is another key strength, enhancing the credibility of our analysis despite the inherent uncertainties in retrospective research. However, the study has limitations, including the potential for bias introduced by the self-selection of individuals with unique characteristics into this dietary pattern. This limitation does not negate the findings, as all dietary patterns are ultimately self-selected. Additionally, the use of de-identified data restricts the ability to explore nuanced clinical details and contextual factors, such as the severity of DKA events. Nevertheless, the de-identified data was robustly linked to related data points for individuals across time, enabling us to study all events comprehensively while maintaining patient privacy. This linkage allowed us to evaluate outcomes irrespective of individual participation levels or adherence to the programme. Despite these limitations, hypothesis-generating retrospective real world analyses, like this one, are valuable for identifying areas for further investigation, such as the role of advanced BHB monitoring in diverse populations.

In conclusion, this analysis underscores the overall safety of carbohydrate-restricted nutrition therapy, particularly VLCKD, for individuals with metabolic diseases such as type 2 diabetes, prediabetes and obesity. We report that IAK, including DKA, are rare and occur at rates comparable to those observed in real world data in individuals with type 2 diabetes who are not following carbohydrate restriction, including in the setting of SGLT2-inhibitor use, when BHB is monitored. Warnings against combining SGLT2-inhibitors and VLCKD may be able to be lightened if these findings are confirmed, which could benefit individuals who have indications for SGLT2-inhibitors and who wish to follow VLCKD. This approach may be especially beneficial for patients at risk for cardiorenal complications mitigated by SGLT2-inhibitors.[30] These insights contribute to a growing body of evidence supporting the efficacy and safety of VLCKD in managing metabolic conditions, paving the way for more informed and individualized treatment plans.

AUTHOR CONTRIBUTIONS

C.G.P.R. conceived of the work and was responsible for manuscript drafts. C.G.P.R., S.J.A. and R.E.R. reviewed raw data and developed the analytical approach. S.J.A. was responsible for statistical analyses. All authors contributed to interpretation of the work, critically reviewed and revised the manuscript and approved the manuscript for submission.

ACKNOWLEDGEMENTS

Thank you to Amy McKenzie, PhD; Kayla Cunningham, MD; Greeshma Shetty, MD; and Alexandra Villasante, MD for early comments and suggestions.

FUNDING INFORMATION

No funding was received for this work.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16252.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST STATEMENT

C.G.P.R. and S.J.A. are employees of Virta Health and have been offered stock options. R.E.R. is a former employee of Virta Health and has been offered stock options.

GUARANTOR STATEMENT

S.J.A. is the guarantor of this work, and as such, has full access to the data and takes responsibility for the integrity and for the data and the accuracy of the data analyses.

PRIOR PRESENTATION

Data in this article were partially presented at the American Diabetes Association 84th Scientific Sessions in Orlando, FL, 21–24 June 2024.

ORCID

Caroline G. P. Roberts https://orcid.org/0000-0002-0237-1038
Shaminie J. Athinarayanan https://orcid.org/0000-0001-5427-6748
Guillermo E. Umpierrez https://orcid.org/0000-0002-3252-5026

REFERENCES

1. Arora S, Menchine M. The role of point-of-care β-hydroxybutyrate testing in the diagnosis of diabetic ketoacidosis: a review. *Hosp Pract*. 2012;40:73-78.
2. Cahill GF Jr. Starvation in man. *N Engl J Med*. 1970;19(282):668-675.
3. Shah P, Isley WL. Ketoacidosis during a low-carbohydrate diet. *N Engl J Med*. 2006;354:97-98.
4. de Amorim ALB, Rodrigues EF, Sussi EL, Neri L d CL. Carbohydrate restriction during lactation: a systematic review. *Nutr Res*. 2024;125:91-100.
5. Juneja D, Nasa P, Jain R, Singh O. Sodium-glucose Cotransporter-2 inhibitors induced euglycemic diabetic ketoacidosis: a meta summary of case reports. *World J Diabetes*. 2023;14:1314-1322.
6. American Diabetes Association Professional Practice Committee. 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47:S77-S110.
7. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract*. 2016;22:753-762.
8. Volek JS, Kackley ML, Buga A. Nutritional considerations during major weight loss therapy: focus on optimal protein and a low-carbohydrate dietary pattern. *Curr Nutr Rep*. 2024;13:422-443.
9. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. *Diabetes Care*. 2024;47:1257-1275.
10. Saisho Y. Postprandial C-peptide to glucose ratio as a marker of β cell function: implication for the Management of Type 2 diabetes. *Int J Mol Sci*. 2016;17:744.
11. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363:k4365.
12. Colacci M, Fralick J, Odutayo A, et al. Sodium-glucose Cotransporter-2 inhibitors and risk of diabetic ketoacidosis among

adults with type 2 diabetes: a systematic review and meta-analysis. *Can J Diabetes*. 2022;46:10-15.e2.
13. Jensen ML, Persson F, Andersen GS, et al. Incidence of ketoacidosis in the Danish type 2 diabetes population before and after introduction of sodium–glucose cotransporter 2 inhibitors: a Nationwide, retrospective cohort study, 1995–2014. *Diabetes Care*. 2017;40:e58.
14. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83-90.
15. Davis TME, Davis W. Incidence and associates of diabetic ketoacidosis in a community-based cohort: the Fremantle diabetes study phase II. *BMJ Open Diabetes Res Care*. 2020;8:e000983.
16. Htoo PT, Tesfaye H, Schneeweiss S, et al. Effectiveness and safety of empagliflozin: final results from the EMPRISE study. *Diabetologia*. 2024;67:1328-1342.
17. Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med*. 2017;376:2300-2302.
18. Douros A, Lix LM, Fralick M, et al. Sodium–glucose Cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. *Ann Intern Med*. 2020;173:417-425.
19. Kim YG, Jeon JY, Han SJ, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. *Diabetes Obes Metab*. 2018;20:1852-1858.
20. Yang S, Liu Y, Zhang S, et al. Risk of diabetic ketoacidosis of SGLT2 inhibitors in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized controlled trials. *Front Pharmacol*. 2023;14:1145587.
21. Tang H, Li D, Wang T, Zhai S, Song Y. Effect of sodium–glucose cotransporter 2 inhibitors on diabetic ketoacidosis among patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care*. 2016;39:e123-e124.
22. Erondu N, Desai M, Ways K, et al. Diabetic ketoacidosis and related events in the Canagliflozin type 2 diabetes clinical program. *Diabetes Care*. 2015;38:1680-1686.
23. Liu J, Li L, Li S, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2020;22:1619-1627.
24. Lin DS, Lee JK, Chen WJ. Clinical adverse events associated with sodium–glucose cotransporter 2 inhibitors: a meta-analysis involving 10 randomized clinical trials and 71,553 individuals. *J Clin Endocrinol Metab*. 2021;106:2133-2145.
25. Sridharan K, Sivaramakrishnan G. Risk of diabetic ketoacidosis associated with sodium glucose Cotransporter-2 inhibitors: a network meta-analysis and meta-regression. *J Clin Med*. 2024;13:1748.
26. Bhattarai M, Salih M, Regmi M, et al. Association of Sodium-Glucose Cotransporter 2 inhibitors with cardiovascular outcomes in patients with type 2 diabetes and other risk factors for cardiovascular disease: a meta-analysis. *JAMA Netw Open*. 2022;5:e2142078.
27. Blau JE, Tella SH, Taylor SI, et al. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. *Diabetes Metab Res Rev*. 2017;33:e2924.
28. Peters AL, McGuire DK, Danne T, et al. Diabetic ketoacidosis and related events with Sotagliflozin added to insulin in adults with type 1 diabetes: a pooled analysis of the in tandem 1 and 2 studies. *Diabetes Care*. 2020;43(11):2713-2720.
29. Kong YW, Morrison D, Lu JC, Lee MH, Jenkins AJ, O'Neal DN. Continuous ketone monitoring: exciting implications for clinical practice. *Diabetes Obes Metab*. 2024;26(Suppl 7):47-58.
30. Neuen BL, Jun M, Wick J, et al. Estimating the population-level impacts of improved uptake of SGLT2 inhibitors in patients with chronic kidney disease: a cross-sectional observational study using routinely collected Australian primary care data. *Lancet Reg Health West Pac*. 2023;43:100988.

How to cite this article: Roberts CGP, Athinarayanan SJ, Ratner RE, Umpierrez GE. Illnesses associated with ketosis including diabetic ketoacidosis during very low carbohydrate and ketogenic diets. *Diabetes Obes Metab*. 2025;27(5):2531-2539. doi:10.1111/dom.16252