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Gastric emptying during and following resolution of moderate diabetic ketoacidosis in type 1 diabetes: a case series

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ABSTRACT

Introduction To use the 'gold standard' technique of scintigraphy to quantify gastric emptying (GE) as soon as practicable during an admission with diabetic ketoacidosis (DKA) and following its resolution at least 7 days later.

Research design and methods Five patients with type 1 diabetes, age 29±12 years; Body Mass Index 23±3 kg/m^2; hemoglobin A1c 11.3%±1.9%, were studied during an admission with DKA and following its resolution. Solid and liquid GE were measured using scintigraphy. Solid emptying was assessed via the percentage intragastric retention at 100 min and that of liquid by the 50% emptying time.

Results There was no difference in either solid or liquid GE at the initial study compared with the follow-up. Median (IQR) solid retention was 47±20 versus 38%±33%, respectively; p=0.31, and time to empty 50% of liquid was 37±25 min versus 35±15 min, p=0.31, at the initial and follow-up GE study, respectively.

Conclusions GE of solids and liquids is not affected by moderate DKA, inferring that earlier reintroduction of oral intake may be appropriate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute hyperglycemia has been associated with slowing of both solid and liquid gastric emptying (GE).

WHAT THIS STUDY ADDS

⇒ This study measured GE using scintigraphy during an admission with acute diabetic ketoacidosis and at follow-up at least 7 days later and found no difference in GE rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Earlier reintroduction of oral intake may be appropriate.

INTRODUCTION

Gastroparesis, defined as delayed gastric emptying (GE) in the absence of mechanical obstruction, occurs in about 30%–50% of individuals with longstanding, complicated type 1 diabetes (T1D).[1 2] It may be associated with upper gastrointestinal symptoms, poor glycemic control and delayed oral drug absorption[3] although the concordance of symptoms with the presence of gastroparesis is now appreciated to be weak.[4]

Diabetic ketoacidosis (DKA) results from relative or absolute insulin deficiency in the presence of increased counter-regulatory hormones[5] and may be precipitated by poor adherence to therapy, intercurrent infection or other acute medical conditions.[5] DKA commonly occurs at the initial diagnosis of T1D and has a worldwide incidence of 8–51.3 cases per 1000 patient-years in individuals with T1D.[6] Upper gastrointestinal symptoms occur frequently during DKA and have been attributed to delayed GE, particularly as acute hyperglycemia is known to slow GE of both solids and liquids.[7 8] Moreover, acute gastric dilatation is a recognized, although rare, complication,[9] with attendant increased risk of aspiration pneumonia as a cause of mortality.[10] It is, accordingly, generally assumed that GE is frequently delayed in ketoacidosis. However, there is only anecdotal information about GE during DKA, with an absence of formal measurements. Current management of DKA involves rehydration, potassium replacement, intravenous insulin infusion and reversal of precipitating factors. Nutritional replacement is usually in the form of intravenous dextrose and oral intake is introduced only after biochemical resolution of ketoacidosis[6] due to concerns regarding the potential for GE to be delayed in acute DKA. To test the hypothesis that GE is delayed in DKA, we have now measured GE, using the 'gold standard' technique of scintigraphy,

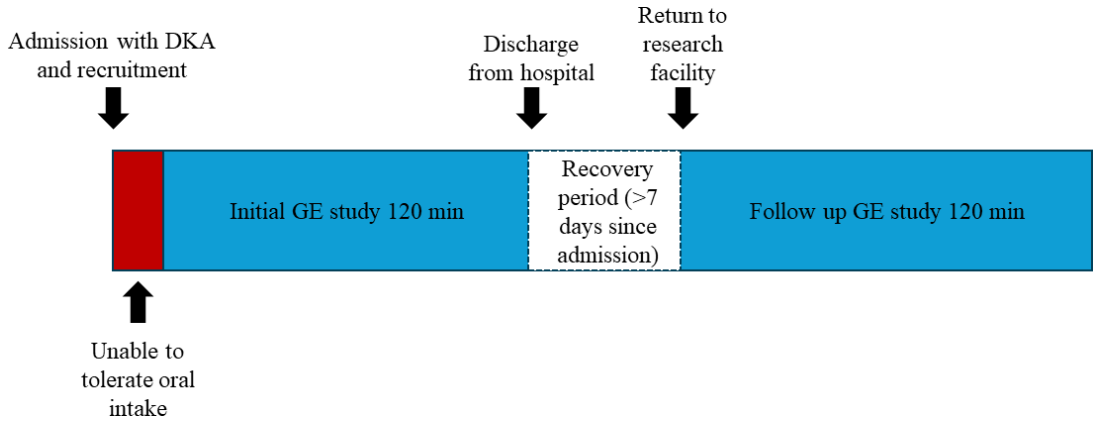

Figure 1 Study protocol. DKA, diabetic ketoacidosis; GE, gastric emptying.

during and following the resolution of ketoacidosis. We assessed GE of both solids and liquids as this may provide insight into what type of oral intake to reintroduce.

Research design and methods

Patients with T1D presenting to the Royal Adelaide Hospital with DKA were eligible. Those with a history of significant gastrointestinal disease, or a requirement for medication known to affect gastrointestinal function (including anticholinergic medications or opioids), were excluded. In five individuals with T1D, GE was measured during an admission for DKA (day 2–4) as soon as the individual was able to tolerate oral intake, and when plasma biochemistry (apart from blood glucose) was within the normal range, at least 7 days later. All participants with DKA were admitted and received standard treatment (intravenous rehydration, intravenous insulin, potassium replacement, assessment and correction of precipitating factors). Antiemetic medications were not administered within five half-lives of the first GE measurement. Diabetic complications were evaluated by a combination of history-taking, physical examination and review of medical records. Autonomic nerve function was assessed at baseline using standardized cardiovascular reflex tests. Parasympathetic function was evaluated by the variation (R–R interval) of the heart rate during deep breathing and the response to standing (30:15 ratio) while sympathetic function was assessed by the fall in systolic blood pressure in response to standing.[11]

Measurement of GE

The test meal comprised 100 g ground beef labeled with 20 MBq 99mTc-sulfur colloid chicken liver, and 150 mL of 10% dextrose labeled with 7 MBq ^{67}Ga-EDTA. The solid meal was consumed within 5 min, followed by the liquid within 1 min. Radioisotopic data were acquired with the subject seated with their back against a gamma camera (GE MPR Single Headed Gamma Camera) at 1-minute frames for the first hour and 3-minute frames thereafter. Time zero (t=0) was defined as meal completion and GE was measured for 120 min. Data were corrected for radionuclide decay, gamma ray attenuation and subject movement using previously described methods[12] and GE curves expressed as percent retention over time derived. For the solid component of the meal, the percentage remaining in the stomach at 100 min (T100) and for the liquid component the time for 50% emptying (T50) were measured.[8 12]

GE was classified as normal or delayed according to an established control range (delayed GE for solids is defined as >61% retention of the meal at 100 min and for liquids, a T50 of >31 min).[1 2] Blood samples were obtained via an indwelling venous cannula at t = −2, 30, 60, 90 and 120 min for measurement of plasma glucose using a hexokinase technique.[2]

The initial GE study was undertaken while the patient was receiving an intravenous insulin infusion. A medical doctor was present during the measurement of GE and the insulin infusion was adjusted according to the results of blood glucose measurements at 60 and 120 min.

Table 1 Participants' baseline characteristics

Case	Age range (years)	Duration T1DM (years)	HbA1c (%)	BMI (kg/m^2)	Retinopathy	Neuropathy	Nephropathy
1	20–29	10	12.4	25.6	Nil	Nil	Nil
2	40–49	8	10.1	23.4	Nil	Nil	Nil
3	20–29	19	10.5	23.0	Yes	Yes	Yes
4	40–49	21	11.3	31.5	Yes	Nil	Nil
5	20–29	10	13.3	22.0	Nil	Nil	Nil

BMI, Body Mass Index; HbA1c, hemoglobin A1c; T1D, type 1 diabetes.

Table 2 Participant biochemistry

Case	Days postadmission of initial study	Days until timing of follow-up study	Bicarbonate on admission (mmol/L)	Bicarbonate at follow-up GE study (mmol/L)	Glucose at commencement of initial GE study (mmol/L)	Glucose at commencement of follow-up GE study (mmol/L)
1	2	7	11	20	8.7	9.4
2	2	9	11	22	9.8	11
3	2	30	13	20	10.8	6.5
4	2	16	13	23	9.6	4.2
5	2	49	12	21	9.6	5.5

GE, gastric emptying.

The second GE study was scheduled at 08:00 hours when half of the participant's usual basal insulin dose was given (figure 1)

Statistical analysis

A paired Wilcoxon test was used to compare GE at the initial and follow-up studies. Data are reported as median±IQR.

RESULTS

Three men and two women, age 29±12 years; Body Mass Index 23±3 kg/m^2; hemoglobin A1c (HbA1c) 11.3%±1.9%, duration of T1D 10±9 years, were recruited (table 1). Three participants had no evidence of microvascular complications, one had retinopathy alone and one had retinopathy, neuropathy and nephropathy. No participant had prior documented macrovascular complications. Baseline autonomic nerve function testing was normal in all participants. All participants had moderate DKA[6] and were normokalemic at the time of the initial and follow-up studies (table 2). The initial GE study was conducted within 48 hours of admission when participants were able to tolerate oral intake.

There was no difference in either solid or liquid GE during DKA compared with after its resolution (figure 2). At the initial study, one participant had delayed solid and liquid emptying and two normal solid, but delayed liquid, GE. The participant with delayed solid and liquid emptying had normal solid GE on follow-up but liquid GE remained delayed. For the participants with normal solid, but delayed liquid GE, the liquid GE remained delayed at the follow-up study.

DISCUSSION

Our study suggests that moderate DKA has little, if any, effect on GE, challenging previous assumptions. One individual had moderately delayed solid emptying during ketoacidosis, which had normalized at follow-up, and in the three individuals with delayed liquid GE at the

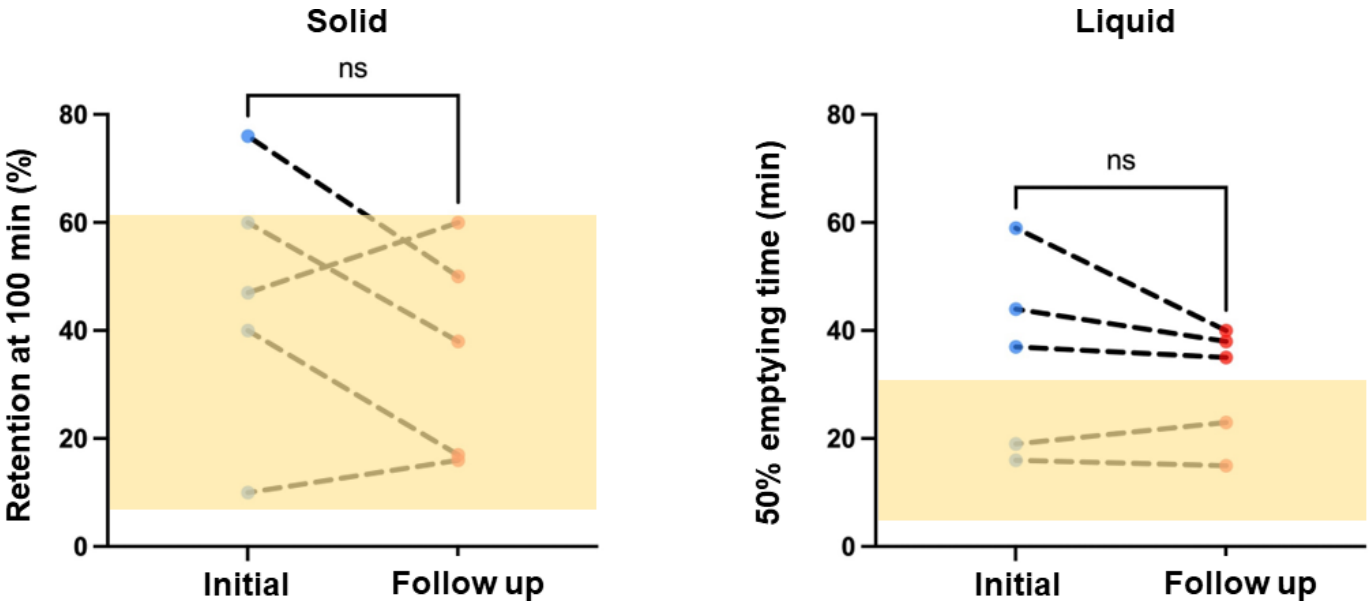

Figure 2 Measurements of solid and liquid gastric emptying (GE) by scintigraphy as soon as practicable following acute diabetic ketoacidosis (DKA) (blue) and after at least 7 days postadmission for DKA (red). The shaded area (yellow) represents the normal range of GE.

initial study, there was no significant change at follow-up. Measurement of nutrient liquid emptying (unlike water) is of comparable sensitivity to measurement of solid emptying for the diagnosis of gastroparesis.[13] Our observations, accordingly, suggest that earlier introduction of oral feeding may be appropriate in ketoacidosis.

There are a number of factors that may potentially slow GE in DKA. In our study, all participants had suboptimal glycemic management as evidenced by a median HbA1c of 11.3% and two of the five participants had microvascular complications, but none had severely delayed GE. Although acute dehydration slows GE in healthy men, our cohort was clinically euvolemic at the time of the initial study.[14] While the solid and liquid GE were delayed in hyperglycemic clamp studies of individuals with T1D, where changes in blood glucose were abrupt,[8] there is less certainty about the impact of hyperglycemia on GE in the setting of spontaneous elevations in glucose.[15] The effect of metabolic acidosis on GE is uncertain, although in pig models, disordered gastric motility has been reported (although GE was not specifically measured) and rodent models have shown delayed GE during exercise-induced metabolic acidosis.[16 17] Notably, our cohort did not have severe metabolic acidosis (ie, bicarbonate <10 mmol/L). Despite there being multiple factors that have the potential to delay GE in DKA, there was no evidence to suggest delay in either solid or liquid GE in our study. Limitations of this study are the small cohort size, lack of matching of glycemia at the initial and subsequent study and poor baseline glycemic control. GE was not evaluated at the time of significant ketoacidosis as measurement of GE requires oral intake to be considered clinically safe. While our study did not find markedly delayed GE of either solid or liquid nutrients in acute DKA in any of our participants, further and larger studies are required to confirm these findings before considering changes to established clinical practice.

CONCLUSION

GE of solids and liquids is not markedly delayed in moderate DKA.

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Contributors Study concept and design: LP, KLJ, CR and MH. Recruitment and study conduct: LP, CM, LEW and MB. Data analysis: RJJ, LP and MU. Original manuscript draft: RJJ. Critical evaluation of manuscript: All authors. Guarantor: MH. Supervision: KLJ, CR and MH.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital (approval ID 050325b). The study was conducted in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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REFERENCES

1 Horowitz M, Harding PE, Maddox AF, *et al*. Gastric and Oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1989;32:151–9.
2 Horowitz M, Maddox AF, Wishart JM, *et al*. Relationships between Oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 1991;18:229–34.
3 Jalleh RJ, Jones KL, Rayner CK, *et al*. Normal and disordered gastric emptying in diabetes: recent insights into (Patho)Physiology, management and impact on glycaemic control. *Diabetologia* 2022;65:1981–93.
4 Talley NJ, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia *Am J Gastroenterol* 2001;96:1422–8.
5 Karslioglu French E, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. *BMJ* 2019;365:l1114.
6 Dhatariya KK, Glaser NS, Codner E, *et al*. Diabetic ketoacidosis. *Nat Rev Dis Primers* 2020;6:40.
7 Rayner CK, Samsom M, Jones KL, *et al*. Relationships of upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 2001;24:371–81.
8 Fraser RJ, Horowitz M, Maddox AF, *et al*. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990;33:675–80.
9 Scott J, Lloyd-Mostyn RH. Letter: acute autonomic dysfunction in diabetic ketoacidosis. *Lancet* 1976;1:590.
10 Hamblin PS, Topliss DJ, Chosich N, *et al*. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. 1973-1988. *Med J Aust* 1989;151:439, .
11 Horowitz M, Harding PE, Chatterton BE, *et al*. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1–9.
12 Collins PJ, Horowitz M, Cook DJ, *et al*. Gastric emptying in normal subjects--a reproducible technique using a single Scintillation camera and computer system. *Gut* 1983;24:1117–25.
13 Sachdeva P, Kantor S, Knight LC, *et al*. Use of a high caloric liquid meal as an alternative to a solid meal for gastric emptying scintigraphy. *Dig Dis Sci* 2013;58:2001–6.
14 van Nieuwenhoven MA, Vriens BE, Brummer RJ, *et al*. Effect of dehydration on gastrointestinal function at rest and during exercise in humans. *Eur J Appl Physiol* 2000;83:578–84.
15 Aigner L, Becker B, Gerken S, *et al*. Day-to-day variations in fasting plasma glucose do not influence gastric emptying in subjects with type 1 diabetes. *Diabetes Care* 2021;44:479–88.
16 Silva MTB, Palheta-Junior RC, Sousa DF, *et al*. Sodium bicarbonate treatment prevents gastric emptying delay caused by acute exercise in awake rats. *J Appl Physiol (1985)* 2014;116:1133–41.
17 Tournadre JP, Allaouchiche B, Malbert CH, *et al*. Metabolic acidosis and respiratory acidosis impair gastro-pyloric motility in anesthetized pigs. *Anesth Analg* 2000;90:74–9.