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Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial

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Abstract

Aims Diabetic ketoacidosis (DKA), a life-threatening acute complication of Type 1 diabetes, may be preventable with frequent monitoring of glycaemia and ketosis along with timely supplemental insulin. This prospective, two-centre study assessed sick day management using blood 3-hydroxybutyrate (3-OHB) monitoring compared with traditional urine ketone testing, aimed at averting emergency assessment and hospitalization.

Methods One hundred and twenty-three children, adolescents and young adults, aged 3–22 years, and their families received sick day education. Participants were randomized to receive either a blood glucose monitor that also measures blood 3-OHB (blood ketone group, $n = 62$) or a monitor plus urine ketone strips (urine ketone group, $n = 61$). All were encouraged to check glucose levels ≥ 3 times daily and to check ketones during acute illness or stress, when glucose levels were consistently elevated (≥ 13.9 mmol/l on two consecutive readings), or when symptoms of DKA were present. Frequency of sick days, hyperglycaemia, ketosis, and hospitalization/emergency assessment were ascertained prospectively for 6 months.

Results There were 578 sick days during 21 548 days of follow-up. Participants in the blood ketone group checked ketones significantly more during sick days (276 of 304 episodes, 90.8%) than participants in the urine ketone group (168 of 274 episodes, 61.3%) ($P < 0.001$). The incidence of hospitalization/emergency assessment was significantly lower in the blood ketone group (38/100 patient-years) compared with the urine ketone group (75/100 patient-years) ($P = 0.05$).

Conclusions Blood ketone monitoring during sick days appears acceptable to and preferred by young people with Type 1 diabetes. Routine implementation of blood 3-OHB monitoring for the management of sick days and impending DKA can potentially reduce hospitalization/emergency assessment compared with urine ketone testing and offers potential cost savings.

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Keywords Type 1 diabetes, diabetic ketoacidosis, β-hydroxybutyrate, urine ketones, sick day management

Abbreviations DKA, diabetic ketoacidosis; 3-OHB, 3-hydroxybutyrate; HbA_{1c}, glycated haemoglobin

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Introduction

Diabetic ketoacidosis (DKA) is a life-threatening, acute complication of diabetes and contributes to morbidity/mortality and the direct and indirect costs of healthcare [1,2]. There are over 100 000 annual episodes of DKA in the United States, yielding expenditures exceeding 2.5 billion dollars [3–5]. Cerebral oedema, the most devastating complication of DKA, is the leading cause of mortality in children with Type 1 diabetes [1,6]. Thus, it is critical to identify and treat impending DKA.

DKA is theoretically preventable, as the majority of cases have previously diagnosed diabetes. While up to 40% of young children present with DKA at diagnosis, only about 10% of patients treated for DKA have undiagnosed diabetes [7]. Up to 85% of hospitalizations for children with diabetes are secondary to DKA [8] and over 5% of emergency visits for patients with diabetes are for DKA [2,9]. Thus, there is opportunity to reduce the burden of DKA upon healthcare outcomes and costs. It is estimated that 50% of hospital admissions for DKA could be prevented with improved outpatient treatment and better adherence to self-care [3,10,11].

Frequent monitoring of metabolic parameters, including glycaemia and ketosis along with timely interventions with insulin and fluids, may avert emergency management or hospitalization [12]. DKA may be preventable in patients with diabetes if the presence of ketones is recognized early and treatment is initiated [13,14]. Previous reports demonstrate successful outpatient management of ketosis with patient education and 24-h phone access to a healthcare team [15,16].

Despite advances in glucose monitoring, urine ketone monitoring has barely changed since the 1970s [17]. Commercial ketone tests for urine and blood have relied on the nitroprusside reaction in which acetoacetate reacts with nitroprusside to produce a purple-coloured complex. If glycine is added, the test can also detect acetone, although to a lesser degree. The third ketone body, 3-hydroxybutyrate (3-OHB), is not detectable by this standard test, but recent enzymatic methods can rapidly quantify 3-OHB levels in small blood samples for home use [18–23]. The ability to measure blood 3-OHB has the potential to improve sick day management and to reduce progression to and severity of DKA [12,14].

The purpose of this study was to assess the efficacy of blood 3-OHB monitoring for sick day management of Type 1 diabetes. We performed a 6-month two-centre, prospective, randomized clinical trial comparing blood 3-OHB monitoring with traditional urine ketone testing. We examined the frequency of elevations in blood ketone levels and the presence of ketonuria during episodes of hyperglycaemia and during sick days. Next, we ascertained the incidence of emergency room visits and hospitalizations during 6 months of follow-up care in these two groups. We hypothesized that blood ketone monitoring compared with urine testing would allow more timely home interventions and reduce the need for emergency or hospital interventions.

Methods

Participants

The study population consisted of 123 children and adolescents with Type 1 diabetes cared for at the Joslin Diabetes Center in Boston, Massachusetts, or the New England Diabetes and Endocrinology Center in Waltham, Massachusetts. Eligibility criteria included attained age ≤ 22 years, duration of diabetes ≥ 12 months, insulin dose of ≥ 0.5 U/kg/day if age > 5 years or ≥ 0.3 U/kg/day if age ≤ 5, and routine glucose monitoring ≥ 3 times daily. Patients with recurrent DKA or known emotional problems were excluded. Eligible patients and families were approached sequentially for enrolment over a 3-month interval from mid-December to mid-March. The Committee on Human Studies at each institution approved the protocol.

Materials

Each participant received a blood glucose meter with lancing devices, lancets, and control solutions (Abbott Laboratories, MediSense® Products, Bedford, MA, USA). Participants randomized to the blood ketone group received the Precision Xtra™ System, which measures blood 3-OHB and glucose levels with their respective test strips. The accuracy of capillary 3-OHB measurements has been documented [23,24]. Study participants randomized to the urine ketone group received the Precision QID™ system with blood glucose strips and urine ketone strips (Ketostix®, Bayer Corporation, Elkhart, IN, USA). All participants were given logbooks to record the date and time of insulin dosages, glucose results, blood or urine ketone measurements, and episodes of illness.

Procedures and measures

A trained research assistant explained the study and obtained written consent and assent. Next, the patients were randomized within each site to either the blood ketone or urine ketone group. To ensure equal representation of insulin pump and non-pump users and to avoid confounding by glycaemic control, patients were randomized according to pump status and glycated haemoglobin (HbA_{1c}) (< 8.5% and ≥ 8.5%). Patients/families at each site received identical sick day protocols.

Participants continued routine diabetes care throughout the study, including 24-h access to an on-call physician. Study visits occurred at baseline, 3 and 6 months. At baseline, patients underwent a physical examination, blood sampling for HbA_{1c}, and completed a baseline questionnaire. HbA_{1c} was assayed centrally by automated, high-performance liquid chromatography (reference range 4–6%; Tosoh 2.2; Tosoh Corp., Foster City, CA, USA). The questionnaire assessed specifics of diabetes management, past illnesses and sick day management.

There were 62 patients randomized to the blood ketone (3-OHB) group and 61 to the urine ketone group. All received instructions in the use of their assigned meters for glucose monitoring and in ketone testing procedures. All were encouraged to check glucose at least three times daily and to check ketones during acute illness or stress, when glucoses were elevated (≥ 13.9 mmol/l on two consecutive readings), or with

Table 1 Sick day guidelines for clinical trial

		Blood glucose (mmol/l)		
	Urine ketones	< 13.9	13.9–22.2	> 22.2
Urine ketone group	Negative	No change	5%	10%
	Trace	No change	5%	10%
	Small	0–5%	10%	15%
	Mod/Large	0–10%	15–20%	20%*
		Blood glucose (mmol/l)		
	3-OHB (mmol/l)	< 13.9	13.9–22.2	> 22.2
Blood ketone group	< 0.6	No change	5%	10%
	0.6–0.9	No change	5%	10%
	1.0–1.4	0–5%	10%	15%
	≥ 1.5	0–10%	15–20%	20%*

% refers to percentage of total daily dosage given as regular or lispro insulin. Pump basal rates increased by 20–50% during illness along with additional bolus doses.
*Consider intramuscular insulin.

Table 2 Baseline characteristics of patients according to study group

	Urine ketone (n = 61)	Blood ketone (n = 62)
Age (years)	14.33 ± 4.64	13.15 ± 5.01
Duration (years)	7.45 ± 4.57	7.33 ± 4.71
Gender (% male)	39	47
Developmental stage (%)		
Pre-pubertal (TI)	26.2	30.6
Pubertal (TII–TIV)	21.3	24.2
Post-pubertal (TV)	52.5	45.2
Insulin (U/kg/day)	1.0 ± 0.3	0.9 ± 0.3
Insulin regimen (%)		
Two injections/day	4.9	9.7
Three injections/day	27.9	24.2
Four injections/day	41.0	37.1
Five injections/day	4.9	6.5
Pump	21.3	22.6
Frequency of BGM (%)		
≤ 2/day	3.3	1.6
3/day	13.1	16.1
4/day	36.1	29.0
5+/day	47.5	53.2
HbA_{1c} (%)	7.9 ± 1.3	8.3 ± 1.5

No significant differences between groups.
Values are mean ± SD or percentage.

symptoms of ketosis, such as nausea, vomiting or abdominal pain. Participants recorded in the logbook any unusual events such as insulin omission, cold/flu, nausea, vomiting, diarrhoea, or illness. Patients and families were counselled to contact their local diabetes team for sick day management during illness as needed.

Sick day guidelines were reviewed at baseline and at the 3-month visit. Participants received the guidelines within the logbooks specific for each group. Recommendations were based on glucose results and either urine ketone or blood 3-OHB measurements (See Table 1).

Three-month visit

At the 3-month visit, participants returned logbooks and meters, received new supplies (including strips and a new meter) and had HbA_{1c} measurement. Sick day guidelines were reviewed and reinforced.

Final visit

At the 6-month visit, patients had a repeat HbA_{1c} measurement and completed a follow-up questionnaire concerning diabetes care and sick day management, and reviewed intercurrent illnesses, hospitalizations and emergency visits. All meters and logbooks were collected.

Statistical analyses

Data from meters were downloaded and compared with logbooks. Ketone data were examined and assessed against concurrent glucose levels. Comparisons between blood ketone and urine ketone groups were made with respect to the frequency of glucose monitoring, frequency of ketone monitoring during sick days or when glucose levels were ≥ 13.9 mmol/l on two consecutive readings, total number of sick days, total number of hospitalizations and emergency visits, and overall satisfaction with sick day management. Outcomes were analysed according to intention-to-treat groups.

Statistical analyses employed SAS v8.0 for Windows (SAS Institute, Cary, NC, USA) and Microsoft® Excel 2000 (Microsoft Corporation, Redmond, WA, USA). Means ± SD are presented unless otherwise noted. Rates of clinically significant outcomes (hospitalizations and emergency visits) were calculated by summing the number of events and dividing by the person-years of follow-up. Paired and unpaired t-tests and χ^2 analyses were performed. Two-tailed P-values of < 0.05 were considered significant.

Results

Patient characteristics

Participants were aged 3–22 years (13.7 ± 4.9) and had diabetes for 1–15 years (7.4 ± 4.6). At baseline, the blood ketone and urine ketone groups were comparable (See Table 2). In the blood ketone and urine ketone groups, 22.6% and 19.7%, respectively, used insulin pump therapy (NS). Comparable proportions of patients received lispro insulin in both groups.

Of 123 participants, 108 returned monitors and 97 returned study logbooks. The number of returned monitors and logbooks was similar between groups. In total, there were 21 548 days of follow-up with similar rates of follow-up contributed by each group (See Table 3).

Table 3 Monitoring frequency during the 6-month study according to study group

	Urine ketone	Blood ketone
Total follow-up (days)	10 638	10 910
Number of follow-up days recorded in logbooks	6158	6776
Total number of glucose values recorded in logbooks	25 371	28 430
Average number of BG/day		
From meter	4.6 ± 3.0	4.4 ± 1.8
From logbooks	4.0 ± 1.5	4.0 ± 1.5
Average of glucose results from meter (mmol/l)	10.2	10.2
Total number of ketones checked	1798	1866
Number positive	102	42
% positive	5.7%	2.3%
Total numberof glucose values ≥ 13.9 mmol/l	4394	5591
Number of pairs of glucose values ≥ 13.9 mmol/l	1238	2089
Number of ketones checked with pairs of high glucoses	432	705
Number positive	18	23
% positive	4.2%	3.3%
Number of reported sick days	274	304
Number of ketones checked on sick days	168	276
Number positive	26	20
% positive*	15.5%	7.2%

*$P < 0.01$.

Monitoring frequency during follow-up

According to downloaded meter data, participants in the urine ketone group checked their glucose levels an average of 4.6 ± 3.0 times daily, similar to the daily glucose monitoring frequency of 4.4 ± 1.8 in the blood ketone group (NS). Both groups also had comparable frequencies of glucose monitoring based on the logbook data. From the meter downloads, the average glucose was 10.2 mmol/l for the urine ketone group and 10.2 mmol/l for the blood ketone group. Frequency of ketone monitoring was assessed only from the logbooks, as there were no 'downloadable' data from urine ketone testing. There were slightly more logged ketone results in the blood ketone group (1866) compared with the urine ketone group (1798) (NS) (See Table 3).

We next assessed monitoring frequency according to recommendations, including ketone testing when glucose levels were ≥ 13.9 mmol/l on two consecutive measurements or during illness. Ketones checked at other times, such as with pump malfunction, were not compared. Both groups had similar monitoring frequencies in the setting of hyperglycaemia with urine and blood ketones checked during 34.9% and 33.7% of the occurrences, respectively (See Fig. 1), suggesting that the common occurrence of hyperglycaemia (~19% of blood glucose results were ≥ 13.9 mmol/l) was often an insufficient motivation to test for ketones. Next, there were 274 self-reported sick days in the urine ketone group and 304 in the blood ketone group. The frequency of ketone monitoring during sick days was 90.8% for participants checking blood ketones, significantly higher than the monitoring frequency of 61.3% for those checking urine ketones ($P < 0.001$) (See Fig. 1).

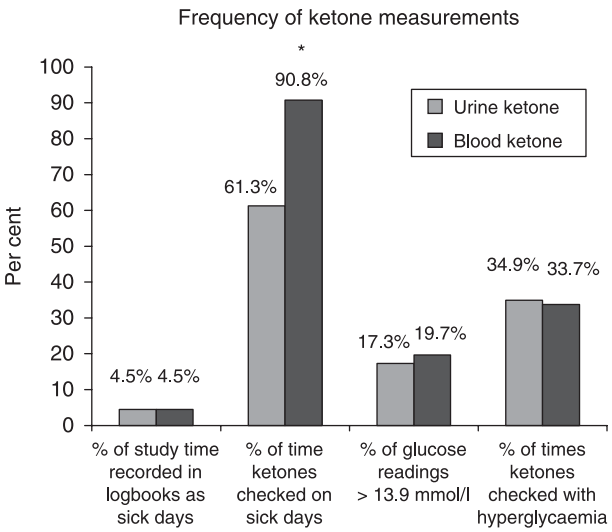

Figure 1 Adherence to ketone monitoring during episodes of sick days and hyperglycemia. The frequency of ketone monitoring during sick days was 90.8% for participants checking blood ketones, which was significantly higher than the monitoring frequency of 61.3% for those checking urine ketones (*$P < 0.001$). There was no difference in monitoring frequency between groups during hyperglycaemia (blood glucose ≥ 13.9 mmol/l).

Glycaemic control during follow-up

Baseline and 3-month HbA_{1c} values were similar in both groups; at 3-months, HbA_{1c} was 7.7 ± 1.2% and 8.1 ± 1.6% (NS) in urine ketone and blood ketone groups, respectively. At the final visit, after controlling for baseline HbA_{1c} levels, there was no

significant difference between groups [7.7 ± 1.2% and 8.3 ± 1.5% (NS) in the urine ketone and blood ketone groups, respectively]. Although absolute HbA_{1c} means differed between groups ($P < 0.03$) at the end of the study, neither group experienced a significant change from baseline.

Frequency of positive ketone determinations

For participants performing urine ketone testing, the majority of measurements, 94.3%, were negative or trace, with 5.7% reported as positive, defined as small, moderate or large. Only 2.6% of results were moderate or large. For participants performing blood 3-OHB monitoring, the majority of measurements, 97.7%, were within the reference range of ≤ 0.5 mmol/l, with 2.3% > 0.5 mmol/l. Only 1.6% of blood ketone results were ≥ 1.0 mmol/l. Virtually all 42 elevated blood ketone results occurred either with hyperglycaemia or during illness, confirming the specificity of blood 3-OHB determination for uncovering impending ketosis or DKA. On the other hand, only 44 of 102 positive urine ketone tests occurred with hyperglycaemia or during sick days, underscoring the potential for false–positive results, for example, after the resolution of an illness.

We also examined the frequency of positive ketonuria and hyperketonaemia in the setting of persistent hyperglycaemia and during sick day episodes. With hyperglycaemia, 4.2% of urinary ketones were positive, while 3.3% of blood ketones were > 0.5 mmol/l. During self-reported sick days, 15.5% of urinary ketone measurements were elevated compared with 7.2% of blood ketone measurements ($P < 0.01$).

Frequency of emergency room use and hospitalization

There were 33 episodes of acute illness or metabolic decompensation necessitating emergency assessment or hospitalization during the 6-month prospective study. The causes were mainly hyperglycaemia, although a small percentage was secondary to hypoglycaemia. Patients in the blood ketone group contributed 10 638 patient-days of follow-up (29.1 patient-years) and patients in the urine ketone group contributed 10 910 patient-days of follow-up (29.9 patient-years). There were 11 episodes of acute complications (8 ER visits and 3 hospitalizations among 10 patients) in the blood ketone group and 22 episodes (14 ER visits and 8 hospitalizations among 15 patients) in the urine ketone group. The need for emergency assessment, treatment and hospitalization was reduced by close to 50% in the blood ketone group compared with the urine ketone group with incidence rates of acute complications 38 per 100 patient-years in the blood ketone group and 75 per 100 patient-years in the urine ketone group ($P = 0.05$) (See Fig. 2).

Satisfaction

At the end of the study, we assessed satisfaction with blood ketone measurements compared with urine ketone determinations in the blood ketone group, as this comparison could not be made in the urine ketone group. In the blood ketone group, 70% reported that they preferred to check blood ketones to urine ketones. As confirmation, 50% more participants measured blood ketones during sick days than those testing urine ketones. The latter finding supports the ease with which blood monitoring can be performed compared with urine testing in the current era of intensive diabetes management that stresses blood monitoring.

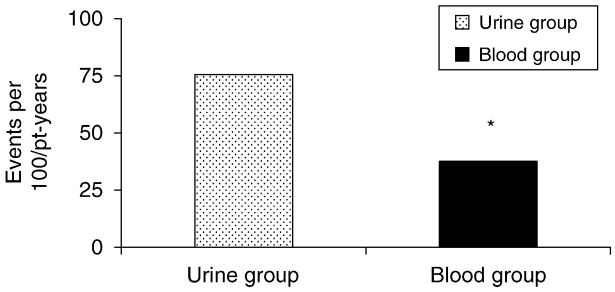

Figure 2 Incidence rates of acute events (emergency room use and hospitalizations) during 6-month follow-up according to study group. The blood ketone group experienced a significantly lower rate of acute complications compared with the urine ketone group with incidence rates of acute events of 38 per 100 patient-years and 75 per 100 patient-years in the blood and urine ketone groups, respectively (*$P = 0.05$).

Discussion

This two-centre randomized trial demonstrated a significant reduction in the occurrence of acute complications requiring hospitalization or emergency assessment for patients with T1DM using a blood ketone monitor compared with patients performing urine ketone testing. This study also demonstrated the ease with which such new technology could be implemented. While the efficacy of monitoring blood ketones had not previously been established in an ambulatory population, the accuracy of the capillary 3-OHB measurements has been documented [23,24]. This investigation demonstrated that the incidence rate of acute events requiring hospitalization or emergency assessment was reduced by 50% in the blood ketone group compared with the urine ketone group ($P = 0.05$). The identification of elevations in ketone levels likely provided an opportunity for timely sick day management [14–16].

Notably, paediatric and young adult patients with Type 1 diabetes frequently experience hyperglycaemia, even in the absence of sickness, and are at increased risk for ketosis [25,26]. The wide fluctuations in blood glucose underscore the routine challenges of matching exogenous insulin with carbohydrate intake and physical activity as well as the exacerbations associated with sick days and the body's counter-regulatory responses promoting ketogenesis, hyperketonaemia or ketoacidosis [17].

It took many years for blood glucose monitoring to gain routine acceptance over urine glucose testing. However, with the current emphasis on intensive management, it is not

surprising that a technology for blood ketone monitoring would be readily accepted. Healthcare providers need additional experience with the interpretation of results and ensuing treatment recommendations before this approach is routinely implemented [11,27]. Indeed, practice recommendations published by the American Diabetes Association already note that blood ketone methods are preferred over urine ketone testing [28].

Previous studies have utilized blood ketone measurements in inpatient, research, and outpatient settings [24,26,29–32]. In the inpatient setting, investigators have demonstrated that normalization of 3-OHB levels prevents recurrence of ketonuria during resolution of ketoacidosis and reduces length of stay [29,31]. Others have studied the development of ketosis with sequential measurements of plasma and capillary 3-OHB and urine ketone measurements after discontinuation of insulin pump therapy [24]. Plasma determinations were made with a laboratory spectrophotometric method; capillary measurements were obtained using the electrochemical method (Precision Xtra meter); and ketonuria was measured semi-quantitatively (Ketodiastix). This study confirmed the similarity of plasma and capillary measurements ($r = 0.94$) and demonstrated that screening for ketosis was improved with capillary measurements compared with urinary ketone determinations [24]. The diagnosis of ketosis was significantly delayed by more than 1 h when it was based upon ketonuria rather than ketonaemia. Additionally, these investigators found that plasma and capillary ketone levels were more frequently positive (≥ 0.5 mmol/l) than concurrent urinary ketone determinations when blood glucose levels were ≥ 13.9 mmol/l.

In our investigation, the blood and urine groups performed blood glucose monitoring with similar frequency and maintained similar HbA_{1c} values throughout the study. They also experienced similar rates of sick days and hyperglycaemia. Notably, significantly more patients randomized to blood ketone measurements checked their ketones during sick days than did patients randomized to urine ketone measurements even though both groups received similar education about sick day management. Over 90% of the blood ketone group measured blood ketones during sick days compared with only 60% of the urine ketone group measuring urine ketones during sick days. Consistent with this finding, 70% of the families in the blood ketone group reported they would be more likely to check blood ketones than urine ketones.

There were several episodes of acute complications during the 6-month study, occurring at a rate similar to hyperglycaemic and hypoglycaemic events reported in the literature [33–35]. There were 60% fewer hospitalizations and 40% fewer emergency assessments in the blood ketone group compared with the urine ketone group, yielding an overall significant 50% reduction in need for costly hospitalization and emergency room use. While blood ketone monitoring strips are more costly than urine ketone strips, there remains great opportunity for overall cost savings with reduced rates of hospitalization and emergency assessments, which serve as the main cost-drivers for escalating health care costs. Future studies of cost-effectiveness are needed.

Blood 3-OHB measurements appear to be more specific than urine ketone determinations. Over 8% of urine ketone measurements were either moderate or large during sick days compared with about 4% of blood ketone measurements. The lack of specificity and resulting low positive predictive value for urine ketone measurements most likely result from the delay with which it takes urine ketones to clear once appropriate treatment is initiated [24,32]. If urine ketones remain positive, there is potential for subsequent hypoglycaemia if supplemental doses of insulin are given. Wallace and colleagues have shown that with initiation of appropriate insulin therapy, blood 3-OHB levels fall with a half-life of approximately 90 min [30]. On the other hand, clearing of urine ketones is dependent not only upon interruption of ketogenesis with insulin administration but upon the state of hydration and the rate of conversion of 3-OHB to acetoacetate.

Diabetic ketoacidosis remains a costly problem associated with significant morbidity and mortality with opportunities for prevention [11,27]. A report by Vanelli *et al*. documented cost savings associated with managing DKA by normalizing blood 3-hydroxybutyrate levels [32]. Increased awareness of sick day guidelines with careful monitoring of blood glucose and blood 3-OHB, along with timely supplemental insulin and hydration, may enhance the management of ketosis and prevent or reduce the occurrence and severity of diabetic ketoacidosis and offer cost savings. Adherence to sick day guidelines will possibly be improved with blood ketone testing, as blood 3-OHB monitoring appears to be more acceptable than traditional urine ketone testing. The efficacy of blood ketonemonitoring supports the need to disseminate this approach to healthcare providers, health delivery systems, and patients at risk for ketosis who are likely to benefit, including paediatric patients, pump users and patients with Type 1 diabetes.

Competing interests

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