Author/s:
Kong, YW;Morrison, D;Lu, JC;Lee, MH;Jenkins, AJ;O'Neal, DN

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Continuous ketone monitoring: Exciting implications for clinical practice

Yee Wen Kong MBBS[1] | Dale Morrison PhD[1] | Jean C. Lu MBBS[1,2] | Melissa H. Lee PhD[1,2,3] | Alicia J. Jenkins MD[1,2,4,5] | David N. O'Neal MD[1,2,3,4]

[1]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia

[2]Department of Diabetes and Endocrinology, St. Vincent's Hospital, Fitzroy, Victoria, Australia

[3]Werribee Mercy Hospital, Werribee, Victoria, Australia

[4]Australian Centre for Accelerating Diabetes Innovations, Melbourne, Victoria, Australia

[5]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

Correspondence
David N. O'Neal, Department of Medicine, St. Vincent's Hospital Melbourne, University of Melbourne, Fitzroy, 3065, VIC, Australia.
Email: dno@unimelb.edu.au

Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication usually affecting people with type 1 diabetes (T1D) and, less commonly, people with type 2 diabetes. Early identification of ketosis is a cornerstone in DKA prevention and management. Current methods for ketone measurement by people with diabetes include capillary blood or urine testing. These approaches have limitations, including the need to carry testing strips that have a limited shelf life and a requirement for the user to initiate a test. Recent studies have shown the feasibility of continuous ketone monitoring (CKM) via interstitial fluid with a sensor inserted subcutaneously employing an enzymatic electrochemical reaction. Ketone readings can be updated every 5 minutes. In the future, one would expect that commercialized devices will incorporate alarms linked with standardized thresholds and trend arrows. Ideally, to minimize the burden on users, CKM functionality should be integrated with other devices used to implement glucose management, including continuous glucose monitors and insulin pumps. We suggest CKM provision to all at risk of DKA and recommend that the devices should be worn continuously. Those who may particularly benefit are individuals who have T1D, are pregnant, on medications such as sodium-glucose linked transporter (SGLT) inhibitors that increase DKA, people with recurrent DKA, those with T1D undertaking high intensity exercise, are socially or geographically isolated, or those on low carbohydrate diets. The provision of ketone profiles will provide important clinical insights that have previously been unavailable to people living with diabetes and their healthcare professionals.

KEYWORDS
clinical physiology, continuous glucose monitoring, glycaemic control, type 1 diabetes

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a major acute life-threatening complication of diabetes, mostly seen in people with type 1 diabetes (T1D) and less commonly in people with type 2 diabetes (T2D). It is usually defined as a metabolic state in which the individual has either a glucose concentration of more than 11.1 mmol/L (> 200 mg/dL) at presentation, or has been previously diagnosed with diabetes; they must

have a plasma β-hydroxybutyrate concentration of 3.0 mmol/L or higher, or urine ketones of more than 2+ on a standard urine ketone test-stick; and a pH less than 7.3 or a serum bicarbonate of less than 15.0 mmol/L.[1] Blood glucose levels may not always be elevated in DKA, a state referred to as euglycaemic ketoacidosis.[2]

DKA results from a relative or absolute deficiency in circulating insulin associated with elevated glucagon. These, in turn, promote the uncontrolled release of free fatty acids that are converted to ketone bodies, resulting in an anion gap acidosis. Acetoacetate, the primary ketone body, is then converted enzymatically to β-hydroxybutyrate, the predominant circulating ketone body, and non-enzymatically to acetone, which is exhaled[3] (Figure 1). The reduced peripheral uptake of glucose and increased endogenous glucose production results in marked hyperglycaemia and dehydration. The metabolic acidosis, hypovolaemia, electrolyte disturbance and hyperosmolar state stimulate a counter-regulatory hormone response increasing insulin resistance and ketogenesis, further exacerbating the metabolic disturbance, resulting in a downward spiral. If left unaddressed this culminates in altered consciousness, cardiovascular collapse, coma and death.[4]

Contributing factors to the development of DKA include the late recognition of new-onset T1D, poor adherence to insulin therapy, severe catabolic stressors such as sepsis and myocardial infarction, recreational drug use (e.g. amphetamines and cocaine), therapies (e.g. steroids, some antipsychotic agents, sympathomimetic agents, or sodium-glucose linked transporter inhibitors [SGLTinh]).[4]

Although data collected in the United States and Australia prior to the coronavirus disease 2019 (COVID-19) pandemic suggest that DKA-associated mortality is stable or falling, conversely, the incidence of DKA is increasing.[5,6] This increased incidence has implications regarding healthcare costs. For example, in the United States, aggregate DKA-related charges adjusted for inflation increased from $2.2 billion in 2003 to $5.1 billion in 2014.[7] DKA therefore remains of significant clinical relevance, and this review will focus on the potential of continuous ketone monitors (CKMs) to minimize DKA risk. We also recognize that ketoacidosis may occur in the absence of diabetes, such as with starvation,[8] low carbohydrate or ketogenic diets,[9] heavy alcohol intake[10] and pregnancy.[11] For the purposes of this paper, however, we will restrict our focus to the potential benefits of CKMs for people living with diabetes.

2 | CURRENT APPROACHES TO THE PREVENTION, RECOGNITION AND MANAGEMENT OF DKA

The standard management of established DKA has been extensively documented in international guidelines.[4,12,13] The principles are volume replacement, the correction of electrolyte abnormalities, provision of insulin and addressing precipitating factors, all of which should occur in a hospital environment in which the patient is closely monitored.[4] Patients with DKA may range from early presenters who are mildly unwell and have rapid reversal of their metabolic disturbances to late presenters who are severely unwell with marked disturbances in acid–base balance, volume status and electrolyte abnormalities requiring admission to an intensive care unit. Generally, early presentation with a milder metabolic derangement is associated with lower mortality, faster recovery and lower socioeconomic costs.[14]

The first step in the prevention and management of DKA is recognition of the impending or established condition with a ketone measurement. The measurement of ketones requires that the person recognizes that they are at an increased risk of DKA and to proactively initiate a test to confirm the presence of elevated ketones.

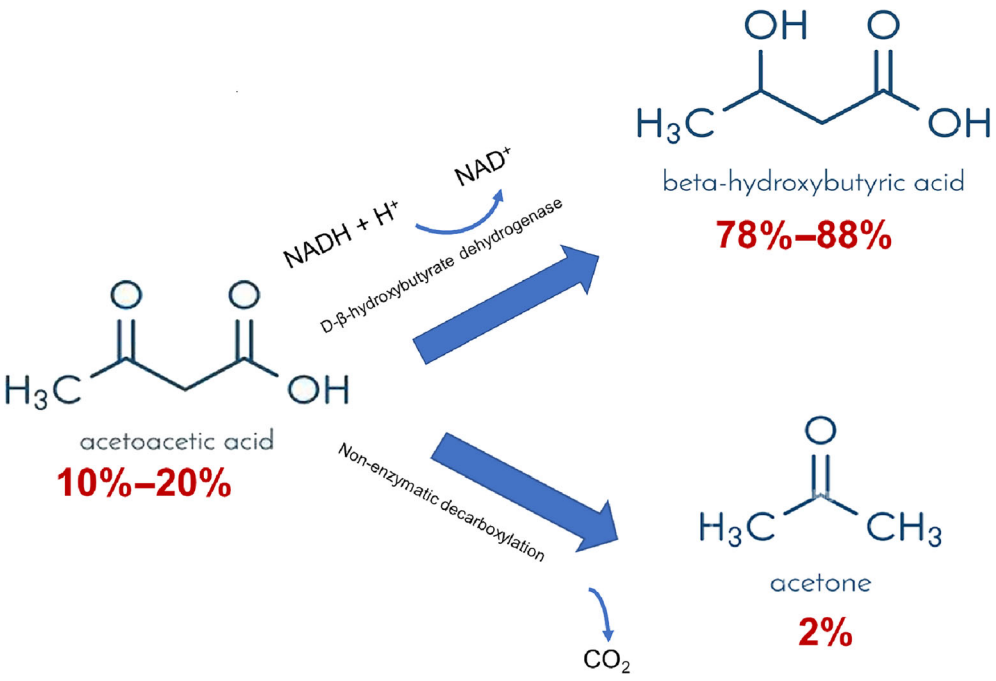


FIGURE 1 An overview of ketone body metabolism (adapted from[3])

Symptoms such as nausea, vomiting and thirst occur late, and hyperglycaemia, which is not invariably present, may not always prompt the person to check their ketone levels. Current available options test for the presence of ketones in urine and blood samples.

2.1 | Urine testing for ketones

Urine testing for ketones is a method that has been available for a long time; it is relatively inexpensive and painless, does not require the user to carry a meter and involves minimal technical skill to implement. However, many patients prefer to avoid doing urine tests. The colour-coded, strip-based test uses a nitroprusside reaction, which provides a semiquantitative measure of acetoacetate and with some brands acetone.[15] The test represents an average of ketones excreted in the urine since the last void, which may delay recognition of impending DKA or its resolution. Importantly with treatment, the circulating pool of β-hydroxybutyrate is oxidized to acetoacetate, which may cause urine ketone readings to rise, while blood β-hydroxybutyrate concentrations are falling. The paradoxical increase in urinary acetoacetate gives the false impression that the condition is not improving. In addition, acetoacetate accounts for approximately only 20% of circulating ketone bodies, impacting the sensitivity of urine testing. False positive results can result from highly pigmented urine and interfering substances, including levodopa and drugs that are present in the blood and/or excreted in the urine as free-sulphydryl compounds.[15,16] Finally, it requires the person to recognize an increased risk of DKA to then initiate testing. This may be difficult because of oliguria from dehydration and acute renal failure or in the absence of a private environment where a urine sample may be obtained.

2.2 | Blood testing for ketones

Current best practice in Australia advises that ketone levels should be checked on finger-prick capillary blood using a handheld meter and ketone testing strips.[17] Blood ketone testing measures β-hydroxybutyrate, which constitutes the major circulating ketone body.[3] There is no clear consensus in the literature as to thresholds of blood ketone levels that should be considered as significantly elevated. In general, levels below 1.0-1.5 mmol/L are considered to exclude DKA, while those above 2.5-3.0 mmol/L suggest the diagnosis or the level at which an urgent medical review should be obtained.[18–24]

Blood testing for ketones has a greater sensitivity and specificity for DKA than does urine testing.[25] A blood sample is usually readily available, and because it provides a measurement quickly it minimizes delays in diagnosis. Although ketone meters may vary in their accuracy depending on their manufacturer, these devices generally represent a mature technology and many combine blood glucose and ketone testing, which means that a person is not required to carry an additional device. Conversely, ketone meters and their blood strips are expensive, ketone strips have a short shelf-life of typically 12 months, and testing is painful and involves blood exposure. As with urine ketone measurements, interfering substances may impact specificity.[26]

2.3 | Real-world experience with current ketone testing options

Although there is evidence that continuous glucose monitor (CGM) provision has resulted in a reduction in DKA,[27] this is probably because insulin has been administered to address elevated glucose levels rather than any specific action to determine the presence or absence of ketosis. Indeed, while CGM provision has improved glycaemia, DKA has not yet been abolished.[27] The real-world experience highlights many of the limitations of blood ketone testing. An audit of 205 adults (38 on insulin pumps) attending our T1D outpatient service revealed that 31% did not have in-date ketone testing strips at home and only a minority were carrying these with them.[28] A survey of 2995 people with T1D in the United States found that 32% had no urine or blood ketone testing materials at home, with only 21% checking ketones when nauseated or vomiting and only 18% possessing a blood ketone meter.[29] A report in Switzerland of 333 respondents revealed that 64% did not test for ketones at all.[30] These data support the need for alternative approaches to ketone testing that minimize the burden on the person with diabetes and increase their ability to recognize current or impending DKA.

3 | BREATH-BASED KETONE TESTING

Although not widely available clinically, ketones can also be measured by breath testing. The predominant ketone measured is acetone, which is volatile and exhaled.[31] Advantages include the painless assessment of ketone levels and no necessity for blood exposure or urine collection. Additionally, changes in acetone are dynamic and may provide an early signal of change in a person's metabolic state. Conversely, breath ketone meters are expensive, the test needs to be user-initiated and the person is required to carry an additional device. A proof-of-concept study evaluating a breath ketone analyser (Ketonix, Varberg, Sweden) in 10 adults and nine children with T1D concluded that the device could be used to rule out ketosis in adults, but not in children.[32] However, in general, there is a lack of an evidence base for the accuracy and dynamic range of these devices for those with T1D because they have generally been developed for those pursuing ketogenic diets instead of for medical use.

4 | THE IDEAL KETONE MONITOR

To address the limitations associated with current approaches to ketone testing we propose the following: (i) an ideal ketone testing device would measure ketones over a relevant dynamic range (we suggest 0-10 mmol/L) with automated alerts that would not

require the user to initiate a measurement; (ii) measurements would need to be precise, particularly at the lower end of the measured range, so as not to result in a significant number of false alerts leading to alarm fatigue; (iii) the display should not be noticeable unless required; and (iv) the technology should be integrated with the user's usual glucose-management system so that they are not required to carry an additional device. For example, ketone levels and trend information could be displayed on a smartphone or insulin pump screen. Ideally, discomfort, as well as psychological, financial and physical burdens imposed upon the user, should be minimized. At the same time, the device needs to be reliable and durable (Table 1). A further level of refinement, although not essential, could include instructions regarding the most appropriate response to the information provided. Urine, blood and breath ketone testing do not meet these criteria and therefore other approaches need to be explored.

5 | INTERSTITIAL FLUID KETONE MEASUREMENTS

The continuous interstitial measurement of ketones has the potential to address many of the limitations associated with urine, capillary blood and breath testing. Ketones can be quantified in interstitial fluid using a similar conceptual approach as that taken with CGMs by employing an enzymatic reaction. A sensing element is inserted subcutaneously that utilizes the enzyme β-hydroxybutyrate dehydrogenase (βHBDH). These devices detect the concentration of β-hydroxybutyrate, a ketone body that is highly associated with the onset of DKA. βHBDH belongs to the family of oxidoreductase enzymes that requires the availability of a co-factor, nicotinamide adenine dinucleotide (NAD+), to catalyse the oxidation of βHB to acetoacetate and NADH. NADH is, in turn, oxidized at the electrode surface to generate a current proportional to the concentration of βHB (Figure 1).[33]

Ketone bodies, like glucose, are hydrophilic. They have a molar mass of 104 g/mol, which is less than that of glucose (180 g/mol), and therefore should readily enter the interstitial space, as confirmed by in vivo studies. We include an illustrative example in Figure 2 using a streptozotocin-induced rat model in conjunction with a prototype ketone sensor (PercuSense, Valencia, CA). Abbott (Alameda, CA) have published the first-in-human data regarding interstitial fluid measurements made by their dedicated ketone sensor. The Abbott CKM has 14-day durability and 2.1% signal change, requiring a single retrospective calibration with 82.4% of data pairs within 0.225 mM/20% and 91.4% of data pairs within 0.3 mM/30%.[34] However, given that most healthy people living with diabetes have ketone levels of less than 0.6 mmol/L almost all of the time, calibration by the user (as was required with early versions of the CGM) will be problematic. Therefore, from a practical perspective, commercially available devices will probably be factory calibrated.

There are no published data regarding interfering substances with CKMs and further research is required. Given that a similar approach is employed in interstitial and blood ketone testing, it may be inferred that CKMs could be subject to similar interferences as blood ketone testing, for example, ascorbate.[26] Similarly, there are limited data regarding the lag between blood and interstitial ketone levels. One would expect that the ketone body, with a smaller molar mass than glucose, would more readily diffuse into the interstitial space with minimum lag in the setting of rapidly changing ketone levels, as supported by observations made in our unpublished animal studies (Figure 2). However, further research is required to conform this.

Further development of the device is aimed at developing a system that will combine continuous glucose and ketone monitoring capabilities as a single platform. A CKM would therefore address many of the shortcomings associated with blood ketone testing using a handheld meter.

TABLE 1 Desirable characteristics of ketone testing technologies.

- Accurate at lower end of range
- Relevant dynamic range (0-10 mmol/L)
- Does not require user to initiate check
- Provides trend information and alarms
- Reliable (low failure rate)
- Durable (similar life to other analyte sensors [7-14 days])
- Minimally intrusive unless required
- Single insertion multianalyte platform/insulin cannula
- Signal integrated with other technologies (e.g. AID)
- Factory-calibrated
- Cost-effective

Abbreviation: AID, automated insulin delivery.

6 | DISPLAYING CKM INFORMATION

The CKM display should consider burden, by minimizing the number of devices and screens needed and the risk of information overload. Ideally, CKM information would be integrated as part of the same device screen providing the glucose readings. We suggest that if the ketone levels are below 0.6 mmol/L then a numerical value need not be provided, and a simple green light could be displayed indicating that the ketone sensor is functioning, and that the levels are not a matter of concern. Above this level, numerical values indicating ketone levels should be displayed; these could be colour-coded to reflect rising clinical urgency as they increase. Because ketone-level fluctuations are not as rapid as those of glucose, the display could be updated every 5-15 minutes. Trend arrows would be useful, indicating the rate and direction of change in ketone levels. We suggest a horizontal arrow if ketone levels are changing at less than 0.25 mmol/L/h, a single up or down arrow if ketone levels are increasing or decreasing between 0.25 and 0.5 mmol/L/h, and two trend arrows if levels are changing at more than 0.5 mmol/L/h. Alarms could be linked to specific ketone thresholds or a high rate of change. We suggest thresholds for alarms at 1.0 or 1.5 mmol/L and rate-of-change alarms at more

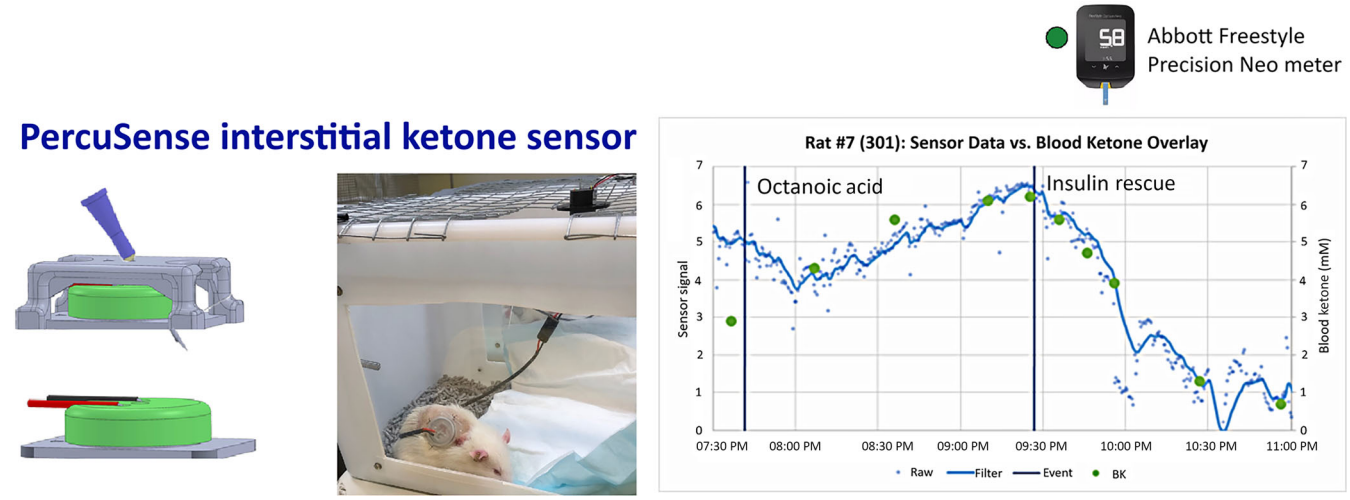
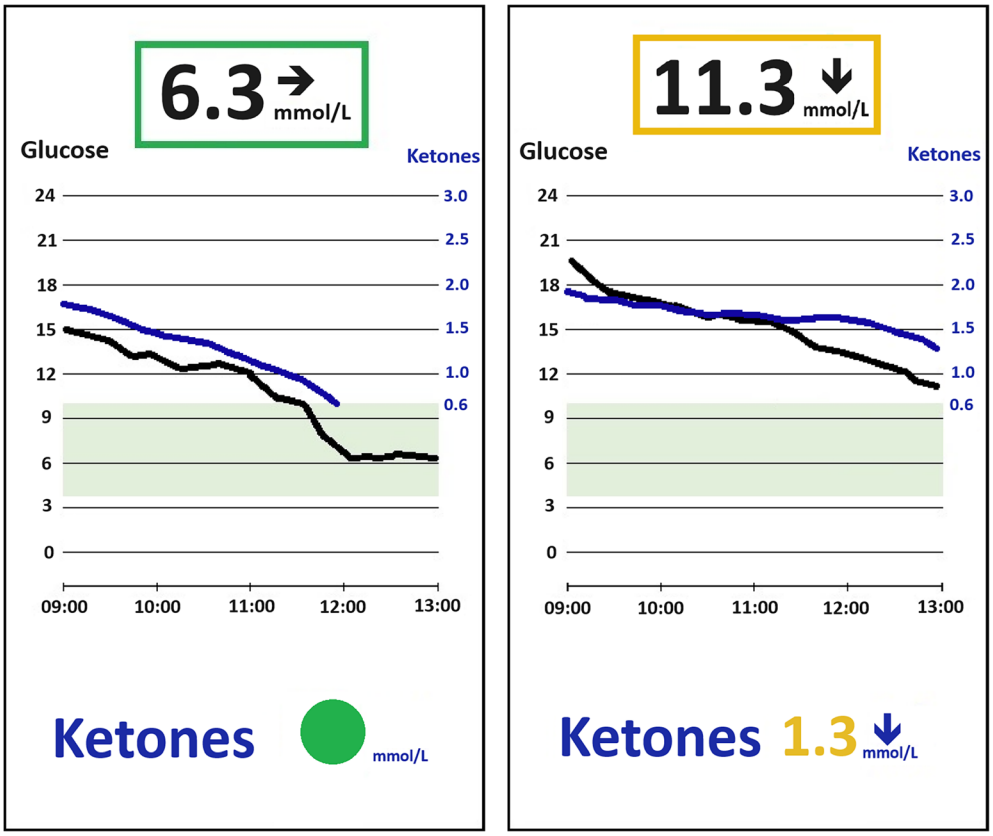


FIGURE 2 Prototype PercuSense (Valencia, CA) CKM tested in a rat model with streptozotocin-induced DKA followed by insulin rescue. Blue dots = raw CKM data. Solid blue line = filtered data. Green dots = reference capillary blood ketone measurements (Abbott Freestyle Precision Neo meter). CKM, continuous ketone monitor; DKA, diabetic ketoacidosis.

FIGURE 3 Proposed display of continuous ketone data on the same screen as continuous glucose data in an ambulatory setting. The screen on the left shows a glucose level of 6.3 mmol/L, which is stable, and a ketone level of less than 0.6 mmol/L where no values or trend arrows are displayed. The screen on the right shows a glucose level of 11.3 mmol/L that is trending downward and ketone levels of 1.3 mmol/L, which are also trending downward.



than 0.5 mmol/L/h. Finally, the CKM display could also provide a graph with a trace analogous to that of a CGM[35] (Figure 3).

We also propose that the ketone and glucose data are able to be concurrently uploaded to a web-based platform, processed by software and integrated as part of a single report. This report could incorporate a profile across the 24-hour cycle with the average percentage of time spent in various ketone ranges according to the time of day. In addition, we suggest displaying a bar graph with the percentage of time spent with ketones less than 1.0 mmol/L (green), 1.0-1.5 mmol/L (yellow), 1.6-3.0 mmol/L (orange) and more than 3.0 mmol/L (red). CKM use would be reflected in % time that the ketone sensor was used (Figure 4). The provision of ketone profiles in free-living people with diabetes will provide important previously unavailable insights into the natural history of ketone levels in health and illness.

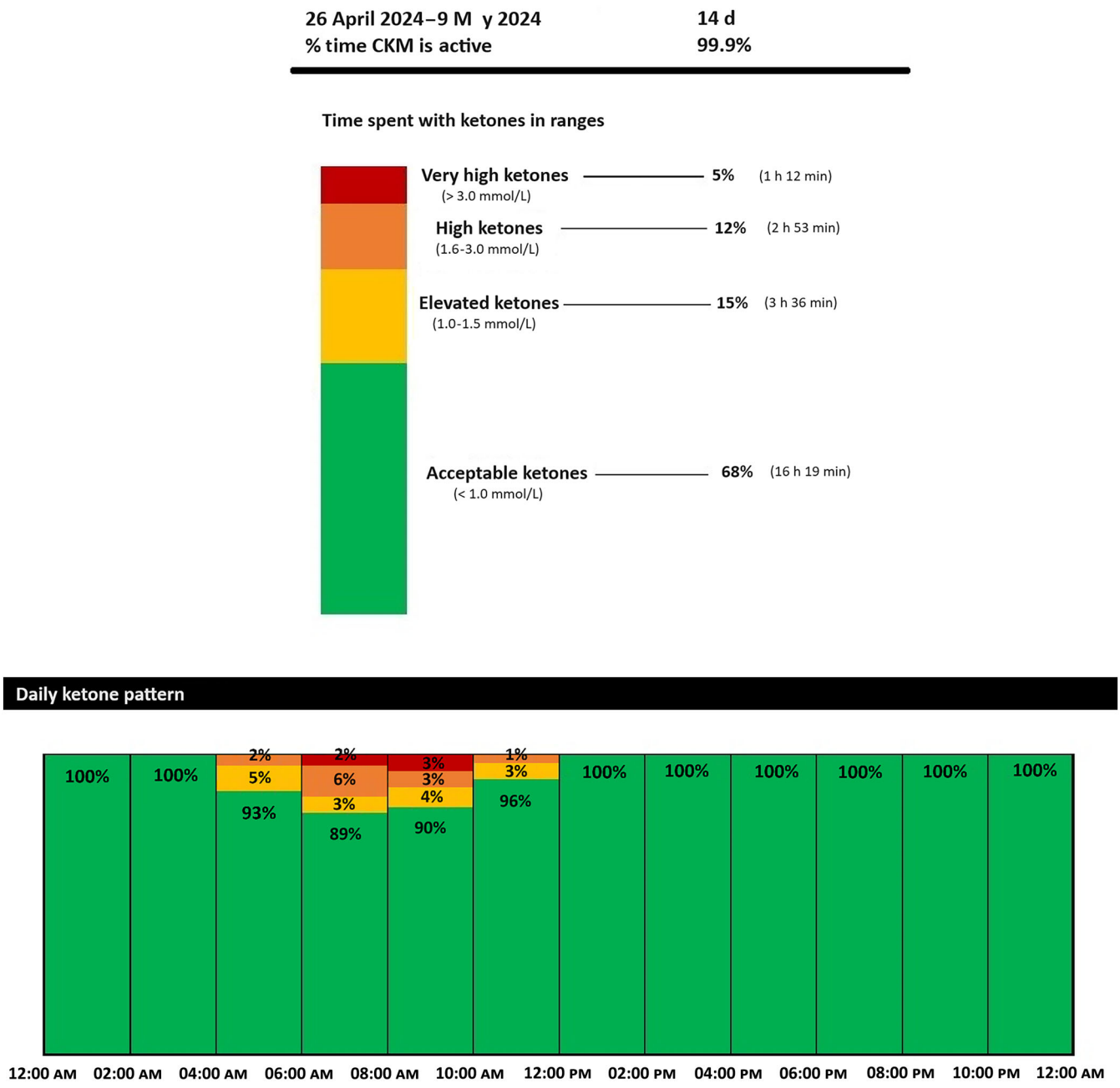


FIGURE 4 Proposed example of 14 days of continuous ketone data that have been uploaded and processed. The upper panel shows a bar graph displaying time spent in acceptable (< 1.0 mmol/L), elevated (1.0-1.5 mmol/L), high (1.6-3.0 mmol/L) and very high ranges (> 3.0 mmol/L). The lower panel displays a proposed ambulatory ketone profile report profiling 14 days of data according to the time of day. CKM, continuous ketone monitor.

7 | RESPONDING TO CKM INFORMATION

The rationale behind the use of a CKM in an ambulatory setting would be to pre-empt DKA rather than to recognize and manage the fully established condition. In support of this approach, Song et al.[36] reported that maximum fasted blood ketone levels of 0.8 mmol/L or higher, as determined by point-of-care testing, predicted future DKA. It should also be noted that in the EASE,[37] DEPICT[38,39] and TANDEM[40] studies, levels of up to 0.8-1.0 mmol/L were not uncommon. Indeed, these minor elevations in ketones may provide part of the protective effect of SGLTinh therapies.[41] Therefore, we suggest that responses to CKM data should be initiated early at ketone levels of either 1.0 or 1.5 mmol/L, as levels below these thresholds effectively exclude DKA.[18–24] Conversely, ketone levels of more than 3.0 mmol/L are consistent with a diagnosis of DKA.[18–24] Levels between 1.5 and 3.0 mmol/L represent an intermediate 'transition zone' providing a window of opportunity to avert DKA. It should be noted that until these CKM devices are approved for non-adjunctive

TABLE 2 Proposed responses to continuous ketone monitor thresholds.

	Acceptable	Elevated	High	Very high
Ketone (mmol/L)	< 1.0	1.0-1.5	1.6-3.0	> 3.0
Response	• No action • (Correct high glucose)	• No action • Observe trends • (Correct high glucose) • Review in 2 h	• Check insulin delivery • If missed insulin dose administer now • Consider hydration • Correct high glucose (eat) • Review in 1 h • Observe trends	• Check insulin delivery/change set • If missed insulin dose administer now • Correct high glucose with pen (eat) • Seek medical help • Hydrate now • Review in 1 h

Note: The colours in the table correspond to the colours in Figures 3 and 4 relating the ketone ranges, urgency, and suggested responses to the proposed display of ketone data in real time and post-upload for retrospective review.

use, confirmation with a finger-prick ketone measurement would be recommended.

In addition, there may be subgroups (e.g. low carbohydrate diet, low basal insulin dose, female sex, low body mass index [BMI], pregnancy, the use of ketogenic medications such as SGLTinh, constitutive β-hydroxybutyrate levels close to 1.0 mmol/L, and use of an insulin pump) and situations (e.g. acute illness, fasting for religious reasons or procedures) where an individual is at greater risk of DKA and alert thresholds may need to be customized accordingly. However, any proposed customized response thresholds need to be formally tested and the optimum settings for alerts have yet to be determined.

The use of trend arrow information adds a further dimension, providing an opportunity for early intervention with predictive alarms. For example, a single arrow indicating an increase in ketone levels of 0.25 to 0.5 mmol/L/h could mean that a response initiated at a threshold of 1.5 mmol/L would provide a 2-hour window for intervention before a level of 2.0-2.5 mmol/L was reached, thus ensuring a greater element of safety and particularly relevant to those at an increased risk of DKA. However, this would entail the cost of a greater number of alarms and raise the possibility that carbohydrate eaten may not necessarily have been required. As is the case with thresholds, any proposed responses to trend arrows will need to be formally tested.

Should an alert inform a person that ketosis is developing, we recommend that a response algorithm based on a modification of the STICH (STop, Inject, Carbohydrate and Hydrate) protocol be followed to preempt DKA risk.[42] The key steps involved in this protocol include (i) verifying ketosis and identifying conditions that cause ketosis; (ii) STopping the SGLTinh, Injecting bolus insulin, consuming 30 g of Carbohydrate and Hydrating; (iii) monitoring ketone levels every 1-2 hours; and (iv) seeking medical care (such as presenting to the emergency department if ketones persist at > 2.5 mmol/L) if ketosis does not resolve or if symptoms of DKA appear, such as abdominal pain, nausea and vomiting. At any elevated CKM level, before taking any further action, it is recommended that the individual checks their ketones with a capillary blood reading using a blood ketone meter. Conversely, should a person experience any symptoms of ketosis despite the CKM indicating normal levels, then confirmation with a blood ketone measurement is strongly recommended. Examples of potential response algorithms for those on insulin pumps and multiple daily injections are listed in Table 2. However, an evidence base providing details of the optimum responses to minimize the risk of DKA is urgently needed.

TABLE 3 Those with T1D at increased risk of DKA who may particularly benefit from a CKM.

• Pregnant women
• Individuals with recurrent DKA
• Taking medications that increase the risk of DKA
• On very low carbohydrate diets
• High intensity exercise
• Socially and geographically isolated
• Fasting for procedures
• Hospitalized/acutely unwell

Abbreviations: CKM, continuous ketone monitor; DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

8 | CKMs: WHO MAY BENEFIT MOST?

One could argue that all people with T1D, diabetes secondary to pancreatic insufficiency (Type 3c), and those with cystic fibrosis-related diabetes who have a low C-peptide level may benefit from a ketone sensor. The rationale for those with T2D is less compelling, although a case could be made for those treated with ketone-promoting medications such as SGLTinh and certain classes of antipsychotic agents. The need for a CKM may be unpredictable (e.g. acute illness, and insulin pump failure), but the consequences of DKA are catastrophic. Therefore, we suggest that a CKM should be worn continuously. However, resource availability may determine the prioritization of allocation to those with T1D who are at an increased risk of DKA (Table 3).

8.1 | Pregnancy in women with T1D

Pregnancy promotes ketosis, with predisposing factors including the increased insulin resistance with pregnancy-associated hormones and

the increase in maternal metabolic rate.[43] Factors that may precipitate DKA in pregnancy include hyperemesis, infection and the physiological stress of labour, as well as the use of steroids and β-mimetics.[44] While maternal mortality is rare with DKA complicating pregnancy, foetal mortality ranges from 10% to 35%.[45,46] Emphasis should therefore be focused on DKA prevention, and a CKM could facilitate early recognition and prompt pre-emptive measures being taken to reverse the ketotic state.

8.2 | Those with a history of recurrent DKA

A range of factors may contribute to episodes of recurrent DKA. These include adolescence, younger age of T1D onset, poor baseline glycaemic control, psychological factors including depression and diabetes distress or burnout, financial deprivation and substance abuse.[47] Those with more than five DKA admissions have a marked increase in long-term mortality.[48] Interventions in those individuals presenting with recurrent DKA should primarily address underlying educational needs and behavioural factors that have resulted in repeated presentations. However, the use of a CKM may provide a useful adjunct to warn the person of an impending metabolic derangement, providing them with an opportunity to act to avoid further episodes of DKA.

8.3 | Medications that increase the risk of DKA

Therapeutic agents affecting carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, pentamidine, antipsychotic agents and SGLTinh, may increase the risk of DKA.[49] While the therapeutic actions provided by each of these agents may potentially be lifesaving, they come at an increased risk of DKA, with SGLTinh as the exemplar.

SGLTinh may play a key role in the prevention and management of the cardiovascular-kidney-metabolic syndrome because this class of agent has multiple benefits, including improved glucose levels (reducing HbA1c and glycaemic variability without increasing severe or total hypoglycaemia); reducing heart failure; improving weight control; reducing cardiovascular mortality; and providing renoprotection in people with diabetes, thereby addressing some of the fundamental issues contributing to the syndrome.[39,50] Although most available data pertain to people with T2D, these agents also have the potential to substantially improve glucose control and weight, and reduce the development of complications in those with T1D.[51]

Despite these potential benefits in people with T1D, the use of SGLTinh as adjunctive therapy to insulin has generally been associated with a significantly increased risk of DKA, which may occur without hyperglycaemia. Data from studies of selective SGLT2 inhibition and a dual SGLT2/1 inhibition as adjuncts to insulin in T1D showed a higher incidence of DKA with these agents versus placebo.[52–54] For example, a pooled European analysis reported that over 52 weeks of treatment, the incidence of adjudicated DKA was numerically higher with sotagliflozin 200 or 400 mg/day than with placebo (2.9% and 3.8%, respectively, vs. 0.2%).[53] The mechanism remains unclear, although contributing factors may relate to a reduction in insulin dose, a carbohydrate deficit, and increased glucagon release leading to upregulation of lipolysis and ketogenesis. Therefore, to date, SGLTinh have in general failed to receive approval in the United States (US Food and Drug Administration) and Australia (Therapeutic Goods Administration) for use to control glucose levels in people with T1D.[55] In addition, although the European Medicines Agency initially approved sotagliflozin and dapagliflozin as an adjunct to insulin therapy in adults with T1D with a BMI of more than 27 kg/m^2, in November 2021 this was withdrawn because of an unacceptable risk of DKA.[55]

SGLTinh therapy may be viable in people with T1D if an intervention is able to shift the risk–benefit balance in favour of benefit; for example, if the risk of DKA could be monitored and addressed. Guidelines aimed at minimizing DKA risk with these agents have focused on the avoidance of alcohol and low carbohydrate diets, and the avoidance of extreme physical activity, and with cessation of any precipitating medications while ill or fasting for surgical procedures. In addition, early recognition of impending DKA enabling the implementation of pre-emptive measures, such as SGLTinh cessation, administration of an insulin bolus, eating carbohydrate and hydration, may favourably alter the risk–benefit balance.

8.4 | People with T1D on a very low carbohydrate diet

Low (< 130 g/d) and very low (< 20-50 g/d) carbohydrate diets have been embarked upon by some individuals with T1D for weight loss, and as a way of improving their glucose levels. The benefits and safety of minimizing carbohydrate intake remains open to debate.[56] Carbohydrate reduction is accompanied by an increase in fat and protein intake to maintain caloric intake and daily insulin doses are reduced accordingly. Ketosis is a risk with these diets, and we would suggest that a high degree of vigilance is maintained upon embarking on these diets, particularly during the early stages. A CKM would provide increased visibility of excursions in ketone levels and the daily carbohydrate intake could be adjusted accordingly to determine the minimum carbohydrate intake that does not incur unacceptable levels of ketosis.

8.5 | High intensity exercise

High intensity exercise elicits a robust counter-regulatory response and, particularly in the fasting state, may be associated with an increase in ketone levels following exercise that may coincide with a reduction in glucose.[57,58] A reduction in insulin dose may be maladaptive. For example, automated insulin delivery (AID) algorithms use glucose levels as their primary input and do not consider ketone levels. The postexercise fall in glucose levels would result in a reduction in insulin delivery following exercise, at the potential risk of a further

increase in ketone levels. A more appropriate response under these circumstances would be for the AID system to signal the need for the individual to ingest carbohydrate.[59] Ketone levels are not routinely measured following exercise, particularly if glucose levels are falling. A CKM could provide an appropriate alert.

8.6 | Geographically and socially isolated people with T1D

Those individuals with T1D who are socially and geographically isolated are not necessarily at an increased risk of DKA. However, once DKA occurs, limited social supports and access to medical care may delay treatment, which could adversely impact morbidity and mortality.[60] An early alert of impending DKA may allow the person to alter their trajectory towards metabolic decompensation. In support of this we note that DKA-related mortality in a large United States-based cohort of people during the COVID-19 pandemic was several orders of magnitude higher than that observed prepandemic, even in those without a co-existent COVID-19 infection.[61] Although the details were not documented, delays in presentation may have been a significant contributing factor.[62]

9 | THE CKM AS A DIAGNOSTIC TOOL

The initial diagnosis of T1D versus T2D versus latent autoimmune diabetes in adults (LADA) is usually based upon the patient's clinical presentation in conjunction with blood ketone measurements, antibody testing and C-peptide levels, with therapies using insulin or oral agents started based on the assessment outcome. When screening for ketosis, a single point-of-care blood test would be more economical than inserting a CKM. Therefore, at the time of initial presentation and diagnosis, the main use of the CKM, which uniquely tracks ketone levels over time, would not be so much to make the diagnosis but to determine a response to therapy. However, a more substantial role for the CKM could be envisaged in tracking the evolution of the rapid decline in beta-cell function during the honeymoon period (usually 1-2 years)[63] in those diagnosed with T1D/LADA. By contrast, the decline in beta-cell function in those with T2D is usually much more gradual (5%-10% per year)[64] and manifests with hyperglycaemia that is refractory to non-insulin therapy prior to any issues with ketosis. We therefore suggest that a CKM may be useful in tracking the progression of beta-cell failure with autoimmune diabetes.

10 | CKMs IN HOSPITAL

In-hospital use of a CKM may be beneficial in some scenarios. Examples of this include patients presenting to the emergency department and those admitted to hospital for tracking responses to therapy, helping guide transition out of an intensive care unit through to discharge. Those at an increased risk of DKA during their inpatient stay could also be provided with a CKM. These inpatients could include those with a history of T1D or T2D who are on SGLTinh and are critically unwell, or have been fasting for prolonged periods, or treated with high dose steroids, or have an eating disorder, or are in isolation rooms.[65]

It should be noted that the CKMs used in a hospital would need a more dynamic range, because of the higher ketone levels in those who are unwell and the requirement to track those with DKA established. This in contrast to devices used in an ambulatory setting, which would primarily be used for the early detection of ketosis, following which it would be expected that patients would present themselves at hospital once DKA was established. In addition, these devices need to display a robust performance under conditions where the patient may be severely dehydrated or acidotic and in a hospital environment where they may be receiving multiple medications. The capacity for healthcare professionals to readily follow the CKM and its alerts are key to the implementation of this technology.

For those who wish to read further on the subject, please refer to the review by Jaromy et al.[65]

11 | CONCLUSIONS

Incorporating a CKM into the routine care of people living with T1D will represent a significant step in the evolution of technology to better address the needs of those living with the condition. To date, the continuous monitoring of physiological analytes in the management of diabetes has understandably been glucose-centric given that the circulating levels of this analyte may be subject to rapid changes of substantial magnitude with major adverse consequences should they exceed a narrow physiological range. By reducing the burden of care while simultaneously enhancing situational awareness, particularly if this can be achieved with minimal incremental cost, we suggest that the continuous measurement of ketones represents a logical progression of current management that will increase safety as part of self-monitoring by people living with T1D.

Feasibility has been shown, although there is still much that remains to be determined. This includes optimization in the way ketone data are displayed, thresholds at which alerts occur, the processing of uploaded information, and minimization of cost and physical burden to the user. The latter may be achieved by combining ketone sensing with the measurement of other analytes as part of a single platform and integration of CKM data into AID systems, which represent the current standard of care.[66]

However, we recognize that the CKM represents a very new technology, and while there are sound theoretical reasons why these devices may be of significant benefit to people living with diabetes, an evidence base is lacking that includes responses to ketone levels and the thresholds at which these are initiated. We advocate strongly for further research, which is required to determine the optimum user responses to CKM information and the impact of CKM use on DKA hospitalizations. We agree that trials with DKA as an endpoint may represent a challenge because of low incidence rates. We could use CKM time spent above 1.5 and 3.0 mmol/L as surrogate endpoints, or

alternatively study high-risk groups such as those treated with SGLTinh or patients with recurrent DKA.

As with an airbag in an automobile, we anticipate that standards for future AID and monitoring systems used for people with T1D will mandate incorporation of a ketone sensor. You may rarely need to use one, but it could save your life.

AUTHOR CONTRIBUTIONS

DNO wrote the first draft of the manuscript. All the authors critically reviewed and revised the manuscript. All the authors approved the manuscript for submission.

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Data sharing not applicable - no new data generated.

ORCID

Dale Morrison https://orcid.org/0000-0002-3613-4946
David N. O'Neal https://orcid.org/0000-0002-0870-4032

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