

Blood Ketones: Measurement, Interpretation, Limitations, and Utility in the Management of Diabetic Ketoacidosis

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■ Abstract

Diabetic ketoacidosis (DKA) remains a common medical emergency. Over the last few years, new national guidelines have changed the focus in managing the condition from being glucose-centered to ketone-centered. With the advent of advancing technology and the increasing use of hand-held, point-of-care ketone meters, greater emphasis is placed on making treatment decisions based on these readings. Furthermore, recent warnings about euglycemic DKA occurring

in people with diabetes using sodium-glucose co-transporter 2 (SGLT-2) inhibitors urge clinicians to inform their patients of this condition and possible testing options. This review describes the reasons for a change in treating DKA, and outlines the benefits and limitations of using ketone readings, in particular highlighting the difference between urine and capillary readings.

Keywords: diabetes · diabetic ketoacidosis · ketones · measurement · SGLT-2 · glucose uptake

1. Introduction

Diabetic ketoacidosis (DKA) is the hallmark of absolute insulin deficiency. It occurs predominantly in people with type 1 diabetes, although it is occasionally seen in type 2 diabetes or gestational diabetes as well. Insulin has several actions, depending on the concentration present in the circulation. At a relatively high concentration it is responsible for cellular uptake of glucose, inhibition of glycogenolysis, and stimulation of glycogen synthesis. At a very low concentration, insulin switches off lipolysis and ketogenesis. However, in situations of absolute insulin deficiency or when concentration of counter-regulatory hormones such as glucagon, cortisol, or catecholamines is high (e.g. acute illness), there is little or no insulin-mediated cellular glucose uptake, resulting in the need for an alternative energy substrate.

The metabolic derangement occurring as a result of insulin deficiency causes hormone-sensitive lipase activity to increase in adipocytes and even-

tually the generation of free fatty acids from triglyceride breakdown [1]. The fatty acids are beta oxidized to form acetyl coenzyme A (CoA), which usually enters the tricarboxylic acid (TCA) cycle. However, in this situation of absolute insulin deficiency and fatty acid breakdown, the elevated amount of acetyl CoA entering the TCA cycle overwhelms the enzyme systems, and is then converted into ketone bodies in the liver [2]. These ketones provide an alternative energy substrate, mainly in the form of β -hydroxybutyrate and acetoacetate at an approximate ratio of 10:1 [3]. **Figure 1** shows how increased lipolysis results in the liberation of fatty acids and subsequent production of increased acetyl Co-A concentrations. The acetyl CoA acts as the substrate for hepatic ketogenesis, with the predominant ketones being acetoacetate, acetone, and beta-hydroxybutyrate.

Whilst the vast majority of DKA cases occur in those with type 1 diabetes, recent reports have stated that the use of sodium-glucose co-transporter 2 (SGLT-2) increases the risk of devel-

oping euglycemic DKA [4]. These drugs have an insulin-independent mode of action, and whilst currently licensed only for use in people with type 2 diabetes, are being trialed in those with type 1 diabetes. As glycemic control improves, there is often a subsequent reduction in insulin dose, which increases the risk of developing DKA [5].

2. Prevalence of DKA

How commonly DKA occurs varies geographically. In the UK, the crude one-year incidence in people with type 1 diabetes has been reported as 3.6%, equating to 4.8 episodes per 100 patient years [6, 7]. In the Western Pacific region, the rate amongst children is 10 per 100 patient years [8], but is much lower in some parts of Northern Europe [9, 10]. In North America, the one-year incidence is between 1% and 5% of people with type 1 diabetes [11, 12], corresponding to about 145,000 cases per year [13]. Most cases occur in those with type 1 diabetes, but in some regions up to 50% of

Abbreviations:

CoA	coenzyme A
DKA	diabetic ketoacidosis
SGLT-2	sodium-glucose co-transporter 2
TCA	tricarboxylic acid

cases may be found in those with type 2 diabetes, depending on ethnicity and family history [14, 15]. However, type 1 diabetes patients tend to have the most extensive metabolic derangements, with a pH lower than that in type 2 diabetes patients [16]. Treatment of DKA remains expensive, with individual admission costs estimated to ~\$17,500 in the US [17] and average costs of £886 to £1803 per episode in the UK [18-20].

While in several previous studies DKA was the presenting feature of type 1 diabetes in up to 30% of cases [11, 21-25], recent data from national surveys in the UK have reported that DKA was the first presentation of type 1 diabetes in adults or adolescents in 3-6% of cases only [26, 27]. In addition, the data from the adult survey of over 280 admissions with DKA also showed that mortality was lower than previously reported, with no deaths in the 2016 data, compared with a mortality of 3.9% and 1.8% in UK populations described previously, and 1.7% mortality described recently in a cohort from China [28-30].

3. Prevention of DKA and ongoing management

Patients with insulin-treated diabetes are taught to measure their glucose concentrations by hand-held point-of-care glucometers. Some meters encourage patients to test for ketones if the glucose concentration is higher than 13.9 mmol/l (250 mg/dl). This is the concentration of glucose required to make a diagnosis of DKA according to

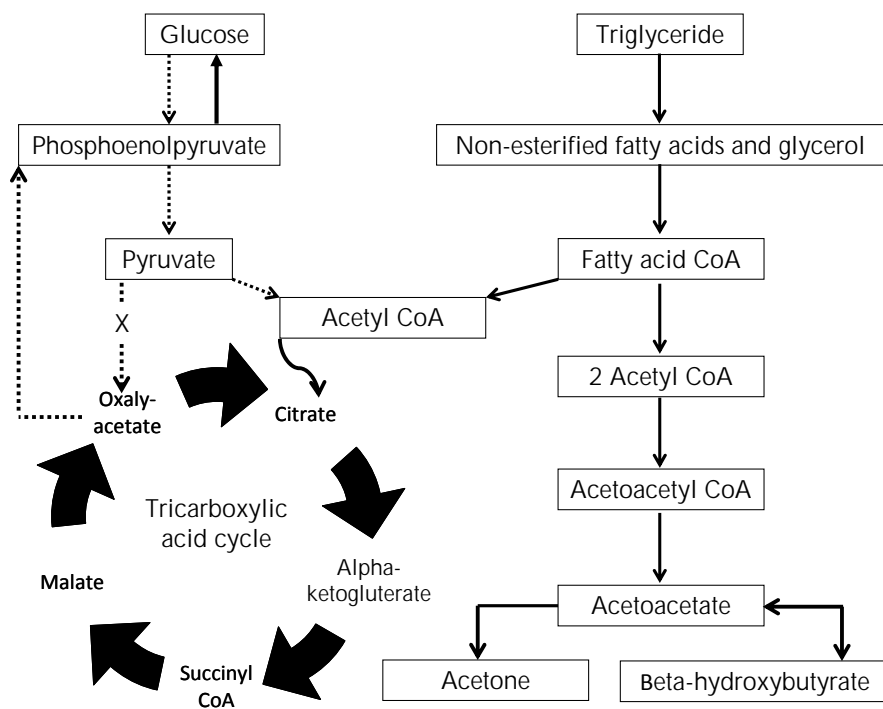


Figure 1. A simplified illustration showing the metabolic pathway for ketogenesis. During insulin deficiency, glucose uptake into cells is limited, and there is a need for an alternative energy substrate. The breakdown of non-esterified fatty acids allows the entry of fatty acid CoA to enter the tricarboxylic acid cycle, thus generating ATP. However, excess fatty acid CoA production leads to the production of acetoacetate (a ketoacid) and beta-hydroxybutyrate (a hydroxyl-acid), causing ketoacidosis in periods of extended insulin deficiency.

the ADA guidelines [17]. If the ketone concentration is high, then patients should follow sick-day rules, see their doctor, or seek urgent medical attention, depending on the concentration and their condition.

The use of point-of-care ketone monitoring has been shown to prevent DKA and reduce unnecessary hospital admissions [31, 32]. However, the availability of bedside ketone meters in hospital is limited [33], and even if meters are available, staff is not available over 24 hours or able to use them appropriately [33]. Finally, the same UK national survey showed that quality assurance schemes for ketone meters were not as widely available as those for bedside glucose meters [33]. Despite these limitations, point-of-care testing devices for ketones are becoming more commonly used in the management of inpatient dysglycemia.

4. Confounders and interference

Bedside capillary ketone meters usually measure β -hydroxybutyrate. Previous data have shown that, at high concentrations, these measurements may have a wide coefficient of variation. Therefore, a quality assurance scheme must be in place to enable calibration with laboratory analyzers, using dilution methods if necessary to ensure accuracy [34, 35].

Glucose meters may also show inaccurate readings in different circumstances, including abnormal hematocrit, changes in oxygen concentrations or pH, presence of peripheral edema, hyperuricemia, hyperlipidemia, and the use of paracetamol (acetaminophen), vitamin C, or dopamine. Many of these issues are discussed in detail elsewhere [36]. One study has investigated whether ketone meters can also be affected, in particular when hematocrit is low. The authors showed that the Optium Freestyle[®] meter (Abbott Laboratories Ltd, Berkshire, UK) ketone reading can be artificially elevated [37]. However, the impact of hematocrit has been minimized in the StatStrip[®] (Nova Biomedical, Cheshire, UK) ketone device because it has an in-built correction factor for hematocrit interference [37]. With the use of vitamin C, both types of meters were affected, with the Optium Freestyle[®] providing falsely high ketone readings, and the StatStrip[®] showing low readings [37]. What remains unknown is what concentration of vitamin C is needed in the sample to interfere with a reading, or how much needs to be ingested before the accuracy of the meter is degraded. The questions of the kind of substances that interfere with the readings and of their quantitative impacts remain

largely unanswered, and need to be investigated in more detail.

Many hand-held ketone meters use β -hydroxybutyrate dehydrogenase coupled with electrochemical detection. This method has a reasonable correlation with the previous standard spectrophotometric method of detection [32, 38]. However, the issue of decreasing precision with large coefficients of variation still exists, especially at high ketone concentrations (>5.0 mmol/l) [39, 40]. However, the measurement of capillary ketone concentrations can provide a rough indication as to whether treatment is working. The measurement of ketone concentrations can be carried out either by using a point-of-care meter or a blood gas machine [41]. The UK DKA guidelines suggest that ketone concentrations should decrease by 0.5 mmol/l per hour when fluid and insulin treatment is working properly [41].

5. Further limitations of urine and blood testing

Limitations of urine and blood testing are shown in **Table 1**. Urine ketones are no longer recommended for use in the management of DKA for several reasons:

1. The urine ketone stick test (Ketostix[®], Bayer Diabetes, Berkshire, UK) is a relatively cheap method of detection that—unlike plasma ketone measurement—requires no special equipment, and does not require any training to use. The urine test uses a nitroprusside reaction, first described in 1908, and gives a semi-quantitative measure of acetoacetate [42]. However, this test does not detect β -hydroxybutyrate, the predominant metabolite (a hydroxyl-acid, not a ketone) present in DKA. Because of the imbalance between the concentration of acetone and β -hydroxybutyrate, the quantity of ketones measured in the urine does not equate to the plasma ketone concentration.
2. Patients with DKA are dehydrated such that urine output is low. It may take several hours until urine is produced again, which delays treatment instigation unnecessarily.
3. Any estimation of urine ketones collected in this way will be an average of the concentration within the urine held in the bladder since the last void.
4. Finally, if treatment is initiated once and acidosis disappears, β -hydroxybutyrate is oxidized to acetoacetate causing urine ke-

tone readings to rise, even if blood β -hydroxybutyrate concentrations are dropping. The paradoxical rise in urinary acetate would give the false impression that the condition is not improving [43].

Despite these limitations, it is clear that urine ketones are still commonly used, particularly in low-resource environments [30]. Some of the differences and limitations associated with measuring ketones in blood and urine are shown in **Table 1**. Because of the benefits of plasma ketone readings, they should be used as part of the sick-day rules that patients with type 1 diabetes apply

when they are not well to ensure that they do not develop ketoacidosis. These sick-day rules are shown in **Table 2**.

There has been some debate in the literature as to which concentration of ketones should be considered 'significant'. Because concentrations of up to 0.25 mmol/l may commonly be found after an overnight fast, concentrations above 0.3 mmol/l have been regarded as significantly elevated [44-47]. However, several studies have compared bedside values with laboratory samples [48, 35, 49], and found a consensus that, using either method, a value of 3.0 mmol/l should be used as the cut-off for diagnosing DKA, or at the very least, the concentration at which urgent medical attention should be sought [35, 41, 47, 50].

Previous work has shown that urine ketone testing and capillary testing had sensitivities of 95-100% in diagnosing DKA (using 3.0 mmol/l as cut-off), but that the capillary testing was significantly faster, and had higher specificity (78-94% vs. <50%) [49-55]. Thus, whilst capillary and urine ketone concentrations are both excellent at ruling out DKA, the use of capillary ketones has the advantage of sparing unnecessary time and expensive laboratory investigation because their use is likely to reduce the number of false positive results. This is important because hyperglycemic patients with the hyperosmolar hyperglycemic syndrome need treatment very different from that of DKA [41, 56].

6. Link between ketone concentration and severity

Whilst ketone concentrations may appear to be related to the severity of DKA, it has been shown that this is not the case. Several groups have correlated ke-

Table 1. Comparison of the advantages and disadvantages of ketone measurement methods

Plasma ketones		Urine ketones	
Advantage	Disadvantage	Advantage	Disadvantage
Measures the current plasma ketone concentration, allowing diagnostic certainty, and subsequent management plan			Reading is an average of urine ketone concentration since last void; management may be delayed
Allows for timely change of treatment as necessary			Length of time to resolution of DKA may be overestimated
Fast, immediate measurement			Urine sample collection may be delayed due to dehydration
Greater sensitivity and specificity for DKA			Lower sensitivity and specificity for DKA
Measures beta-hydroxybutyrate, the predominant ketone in DKA			Measures only acetoacetic acid, not beta-hydroxybutyrate
	Potentially painful	Painless	
	Equipment (meter) needed	Readings can be read off the bottle	
	Meter needs regular quality assurance testing	No quality assurance needed	
	Staff who is able to use the meter required (if in hospital)	No technical skill required to use the equipment	
Individually wrapped ketone strips have a long shelf life			Ketone strips have a relatively short shelf life
	Relatively expensive	Relatively cheap	
	Meter may be inaccurate at readings outside the range it is designed for		
	Interference caused by other substances (e.g. vitamin C), giving inaccurate results		Interference caused by other substances (e.g. vitamin C), giving inaccurate results

tone concentrations (point-of-care and laboratory) with serum bicarbonate, anion gap, and arterial pH. They have reported correlations between -0.33 and -0.76 for pH, between -0.25 and -0.74 for serum bicarbonate, and between 0.16 and 0.59 for anion gap [35, 48, 57-60]. In essence, these correlations—many of which were statistically significant—are not sufficiently robust to allow for the ketone concentrations to be used as a marker for the severity of DKA.

Because of possible wide coefficients of variation at high ketone concentrations, bedside ketone meters should only be used to assess whether treatment is working and to make sure that ketone concentrations are decreasing rather than to judge the severity of DKA. Although it is acknowledged that ketone concentrations should decrease by 0.5 mmol/l/hr [41], at high ketone concentrations, the large coefficient of variation may make more accurate measurements difficult. However, from a clinical and practical perspective, ketone reduction considerations should be taken into account, in combination with the other biochemical and physical findings, when treating a patient with DKA. Certainly, by the time changes need to be carried out in the intravenous insulin infusion rate (e.g. from a fixed rate intravenous insulin infusion to a variable rate) or in fluids (e.g. from 0.9% sodium chloride solution to 10% dextrose), when the glucose concentration falls below 14.0 mmol/l (252 mg/dl) again, the ketone concentration should be <0.6 mmol/l, which is within the range where the meter is accurate. The meter is considered to be accurate up to a ketone concentration of 3.0 mmol/l, which is the threshold for the diagnosis of DKA.

One of the key changes in the UK DKA guidelines has been the move towards the use of venous blood samples rather than arterial blood samples for gas measurement procedures [41]. This is because the differences between the two types of samples are so small that they make no real difference [61, 62]. Also, measurement of arterial blood gases involves painful procedures, and are not free of risk.

7. Cost

Very few of the available point-of-care glucose meters also measure ketones. In the UK, there are currently 38 different glucose meters, of which

Table 2. Simple sick-day rule

Unwell?
Never stop taking your insulin or tablets (except SGLT-2 inhibitors)
Wee – test it for ketones every time you go to the toilet; test your blood glucose every 2-4 hr
Eat normally or replace meals
Liquidity – drink plenty of water, or sugar-free drinks to avoid dehydration
Lighten the load – have a rest

only 2 can also measure ketones [63]. A full list of glucose meters and their characteristics, which also indicates which meter can measure ketones, can be found elsewhere [64]. The small number of meters that can measure ketones means that they are more expensive than glucose-only meters. Also, the strips themselves cost significantly more than the glucose strips. For example, in the UK, 50 blood glucose testing strips for the FreeStyle Optium Neo® (Abbott Laboratories Ltd, Berkshire UK) cost £15.71, while 50 ketone strips for the same meter cost £105.70. This is in contrast to the £3.06 needed for 50 urine ketone sticks (Ketostix® (Ascensia Diabetes Care, Basel)). However, this high cost has to be weighed against the fact that the use of point-of-care meters in aiding the diagnosis and subsequent management of DKA has major advantages over urine ketone estimation. Further benefits of using blood ketone meters are that readings are available in real time, and that accuracy between venous and capillary samples is comparable [38].

Not least, it has been shown that the use of ketone meters is associated with reduced emergencies and hospitalizations and a shorter recovery time [65]. Their use can also help in the initial diagnosis of DKA [41]. Whilst the American Diabetes Association guidelines suggest that a diagnosis of DKA should be made only if a blood glucose concentration is >250 mg/dl (13.5 mmol/l), they acknowledge that about 10% of all cases could be associated with euglycemic DKA [17]. In this regard, the use of ketone meters is even more advisable in patients treated with SGLT-2 inhibitors, as this class of antidiabetic agents is associated with an increased risk of developing euglycemic DKA which may increase the prevalence [66]. Thus, the performance of point-of-care ketone measurement is becoming a key element in the diagnosis of DKA independent of the admission glucose values.

It is clear that the provision of a ketone meter alone is not sufficient to reduce DKA. Patients and healthcare professionals need to be educated on how to use the technology. This is important when using ketone measurement as a means of admis-

Table 3. What to do when you are not well? Practical recommendations for diabetes patients including the monitoring of ketone levels

Severity	Why follow a procedure?	What to monitor?	What action should be taken?
General	When you are ill your body becomes much more resistant to the insulin you produce or take by injection. This means your blood glucose levels can rise.	You need to monitor your blood glucose and ketone level more frequently, at least every 2-4 hours for your glucose, and twice a day for your ketones. Also, check with your usual diabetes care provider.	Never stop taking your insulin; you may need more than you take normally. Also, check with your usual diabetes care provider.
Minor illness	Your blood glucose may be within normal ranges or raised, but ketones should remain negative	As above	As above
More severe illness	Your blood glucose may be raised (i.e. more than 17.0 mmol/l) and lots of ketones may be present (more than 1.0 mmol/l).	Keep checking your glucose levels at least 4 times a day and your ketones at least twice a day.	If the ketones rise to 3.0 mmol/l or more, recheck them within 2 hours. If they remain high for 12 hr or more, seek urgent medical help.

Further tips for staying safe during illness:

- If you are vomiting, you do not necessarily need to eat, but keep sipping fluids to prevent dehydration.
- If you do not feel like eating normal meals, try to eat foods that are easy to digest, e.g. soup, milk.
- If your blood glucose falls below the normal range, sip sugary drinks, e.g., fruit juice, sweetened tea, or non-diet cola.
- Adjusting your insulin doses will help to control blood glucose levels.
- If your illness is not resolving, you should see your doctor to determine whether you need further treatment.
- If you are vomiting and unable to keep fluids down, and/or if you cannot manage to reduce your blood glucose or ketone levels then you need to contact the hospital as an emergency.

sion avoidance. Previous work has shown that urine ketone strips can be used as a means of admission avoidance in an adult population when combined with advice by telephone [67]. Other authors have looked at the use of capillary ketone meters in a pediatric population and found that overall emergency room visits and admissions were significantly reduced (not just for DKA) [68]. These data suggest that the use of ketone meters in the prevention of DKA and subsequent hospitalization make the technology cost-effective. However, this is a conclusion derived from different findings rather than a hypothesis that has been formally tested in a well-designed clinical trial. Neither has a trial been performed to show that the use of bedside ketone meters in those already admitted with DKA is associated with a shorter length of hospital stay than laboratory ketone measurements.

8. The management of suspected euglycemic DKA with SGLT-2 inhibitor use

Diabetic ketoacidosis should be suspected in any patient who uses this newer class of agent and who presents with classic symptoms. The diagnosis should be made using the three usual criteria:

1. History of diabetes (regardless of presenting glucose)
2. A pH of <7.3 with a serum bicarbonate concentration of <15 mmol/l
3. A plasma ketone concentration of >3.0 mmol/l [41]

The anion gap may also be raised. In this scenario, the drug should be stopped, and the DKA treated as per local guidelines, but using the pH value, bicarbonate concentration, and anion gap as markers, rather than glucose.

In an attempt to prevent SGLT-2 inhibitor-associated DKA, the drug should be avoided, or stopped, during

times of extreme stress, e.g. prior to major surgery, as the patient may be in a catabolic state, or during hospitalization for major illness. Another condition that may predispose to SGLT-2 inhibitor-associated DKA is the very-low-calorie diet. In this regard, it is important that all patients, those with type 1 and type 2 diabetes, are well-informed about the sick-day rules (Tables 2 and 3). Usually, sick-day rules apply to patients on regular insulin therapy and state that the medication must never be stopped irrespective of the patient's wellbeing. Currently, SGLT-2 inhibitors are not licensed for use in type 1 diabetes, but clinical trials are underway, and an increasing proportion of type 1 diabetes patients is using them already. Many people with type 2 diabetes are also on insulin and SGLT-2 inhibitors. It is thus important to understand the sick-day rules in such a way that the continuance of insulin therapy is ensured, but the

use of SGLT-2 inhibitors is stopped when a patient is unwell (**Table 2**).

9. Summary and future work

In the last few years, national guidelines have embraced the use of new technologies that allow the focus to be on the 'K' and the resultant 'A' in the treatment of DKA, rather than on the 'D'. There are major advantages to measuring capillary ketone concentrations using point-of-care devices, namely equivalent sensitivity and superior specificity to urine ketone testing, when making the initial diagnosis of DKA. Another advantage is the reduced time to diagnosis compared with laboratory methods. The use of bedside point-of-care ketone devices has also changed the ongoing management of DKA. However, there are also concerns about the wide and regular use of ketone meters, namely the cost of testing strips and the degree of accuracy when ketone concentrations are high.

Given the potential difficulties with urine ketone measurements, attention needs to be paid to ensuring that plasma ketone testing is easy to use and affordable even in low-resource environments, and that it does not require specialist equipment other than commonly used hand-held, point-of-care glucose meters. Work needs to be done to ensure the accuracy of ketone meters at a wider concentration to minimize false positive and false negative readings, to avoid potential errors in diagnosis and management of this potentially life-threatening disease. At the same time, technologies need to be developed to minimize the number of substances that interfere with the readings. Finally, further work also needs to be done to determine the best way to use this new technology.

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