



Ketones and diabetes

Three types of ketones are produced from the breakdown of fatty acids: 3-beta-hydroxybutyrate, acetoacetate and acetone. This process, known as ketogenesis, occurs when there is insufficient glucose as an energy source. Normally, ketones are undetectable in either the blood or urine. Circumstances where fat becomes the primary energy source (e.g. starvation, low-carbohydrate diet, high-fat diet, exercise, alcohol excess and severe illness) will cause a rise in ketones.¹

Diabetic ketoacidosis (DKA) is an abnormal metabolic state caused by a build-up of ketones in the body. It is characterised by hyperglycaemia, acidosis and ketonaemia. It is usually the result of an absolute or relative insulin deficiency.

This life-threatening

complication of diabetes is more likely to occur in those with type 1 diabetes. However, it can occur as the initial presentation in those not yet diagnosed with type 1 diabetes; in latent autoimmune diabetes in adults (LADA); pancreatogenic diabetes; and even type 2 diabetes, most likely in association with sodium–glucose cotransporter 2 (SGLT2) inhibitors.²

It is evident that COVID-19 infection in people with or without previously diagnosed diabetes increases the risk of hyperglycaemia with ketones, DKA and hyperosmolar hyperglycaemic state (HHS). In response, JBDS-IP has produced advice on inpatient management (bit.ly/2TVNVyw). While this guidance does not apply directly to primary care or

to the management of those with milder symptoms (with or without a positive test for COVID-19), it does raise important issues relating to sick-day management and ketone testing in the community.

Key points

Those with diabetes at risk of DKA should be made aware of the signs and symptoms (see **Box 1**). Every person with diabetes should:

- Understand the sick-day guidance.
- Know how and when to self-monitor blood glucose and ketones, and how to act on the results (if this is appropriate and has been recommended by their diabetes team/doctor or nurse). (See * below.)
- Know when to seek medical advice.

Box 1. Signs of DKA³

- Excessive thirst
- Polyuria
- Dehydration
- Shortness of breath and laboured breathing
- Abdominal pain
- Leg cramps
- Nausea and vomiting
- Mental confusion and drowsiness
- Ketones can be detected on the person's breath (pear-drop smell), or in the blood or urine.

These signs and symptoms may develop over 24 hours, but can appear much faster, even within a couple of hours.

How are ketones measured?

Ketones may be measured in the urine or blood. The most accurate way of testing is to use a meter that can measure blood ketone levels; Diabetes UK

publishes a list of these devices (bit.ly/2XQ4rkT). Individuals with type 1 diabetes should have access to this testing method.

Urine strips show the

presence of ketones by changing colour (typically deepening shades of purple as ketone levels rise). Urinary ketones may be under-represented in dilute

samples (e.g. when there is polyuria due to hyperglycaemia) and there can be false positive results with dehydration and poor urine output.

When should individuals with diabetes check for ketones?

As DKA is more common in type 1 diabetes, these individuals should have access to ketone testing and understand when to test.

Diabetes UK advises those with type 1 diabetes to check blood glucose levels at least every 4 hours, including during the night, and check ketones generally if blood glucose is ≥ 15 mmol/L (or ≥ 13 mmol/L for those using an insulin pump; bit.ly/2N2sAQI). It

acknowledges that individuals may be given different targets by their diabetes healthcare provider, but stresses that when ketones are detected they should contact their diabetes team.

Practical information for healthcare professionals (HCPs) on managing diabetes in the context of COVID-19 is available at: bit.ly/33EJ48I

Whenever DKA is suspected (regardless of diabetes type), ketones should be measured.



***In practice, most individuals with type 2 diabetes will not have access to either urine or blood ketone testing equipment. For those prescribed an SGLT2 inhibitor combined with insulin, provision of blood ketone meters should be considered given the increased risk in these individuals. Every person prescribed an SGLT2 inhibitor should be given specific advice about the risk of euglycaemic DKA and advised to consult**

their doctor or nurse if they become ill (even if blood glucose levels are not high). Primary care teams should be aware of the need to test for ketones in this situation and should have a supply of blood ketone meters readily available.

Citation: Diggle J (2020) Ketones and diabetes. *Diabetes & Primary Care* 22: 49–50

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How to interpret results

The table below provides a useful reference for the interpretation of blood and urine ketone tests.⁵

Blood ketone concentration	Urine ketone dipstick	Interpretation
<0.6 mmol/L	Negative	Normal range
0.6–1.5 mmol/L	Trace or +	Potential problem; keep monitoring; seek medical advice if unwell
1.6–3.0 mmol/L	++	High risk of ketoacidosis; seek medical advice urgently
>3.0 mmol/L	+++ / ++++	Likely ketoacidosis; immediate medical review needed

Sick-day guidance

How to advise on sick day rules, a guide for healthcare professionals, can be found at: bit.ly/39zBPjB

During intercurrent illness, people with diabetes should follow sick-day guidance. Diabetes UK provides clear information to help people with diabetes cope when they are unwell: bit.ly/2NcETJX

It also publishes helpful advice on when to test for ketones: bit.ly/2XnLVBo

 **DKA requires urgent hospital admission.**

SGLT2 inhibitors and DKA

SGLT2 inhibitors (used mostly in the treatment of type 2 diabetes) are associated with an increased risk of DKA; in 2006, both the Medicines and Healthcare products Regulatory Authority (bit.ly/24eXtSC) and European Medicines Agency (bit.ly/2SDJYwg) issued warnings. DKA is rare, but atypical euglycaemic DKA may occur (i.e. DKA without marked hyperglycaemia), so individuals should be alerted to this. Given that most will not have access to self-monitoring of either blood glucose or ketones, it is essential they recognise the typical signs of DKA (see [Box 1](#)), which can be non-specific.

HCPs should be aware of situations that may predispose to DKA with SGLT2 inhibitor use, including^{4,5}:

- Type 1 diabetes, LADA, pancreatogenic diabetes
- Sudden reduction in insulin dose
- Acute illness/infection
- Dehydration
- Surgery
- Alcohol excess
- Fasting (carbohydrate restriction, ketogenic diet)
- Corticosteroid therapy

These factors are especially relevant in the light of COVID-19. People with type 1 diabetes who are being treated with an SGLT2 inhibitor by their specialist team are particularly at risk and should stop taking it during the pandemic. This does not apply to those with type 2 diabetes, unless they are admitted to hospital or are at risk and have been advised to stop this medication.

SGLT2 inhibitors should be stopped in all people admitted to hospital, as highlighted in *Diabetes at the Front Door* (bit.ly/2TVNVyw). In the community setting, a degree of clinical judgement is required in relation to when SGLT2 inhibitor drugs should be stopped in the context of illness.

Providing a person follows the sick-day guidance (bit.ly/39zBPjB), stays well hydrated and is able to eat (albeit little and often), they do not need to automatically stop SGLT2 inhibitors (or indeed the other drugs listed in SADMANS – sulfonylureas, ACE inhibitors, diuretics, metformin, ARBs or NSAIDs). Indeed, poor glycaemic control is likely to increase susceptibility to infection and poorer outcomes, so

optimal blood glucose control should remain a priority. The danger lies in acute illnesses that lead to dehydration, in which case these drugs should be temporarily stopped.⁶ This important distinction is highlighted in a position statement by the Think Kidneys campaign (bit.ly/37w3pit). Useful advice to support clinical decision-making in care homes is provided in guidance published by a National Stakeholders Covid-19 Response Group (bit.ly/2XRHnCa).

Diabetes is a predictor of more serious complications of COVID-19. A recent article by a panel of international experts offers guidance and practical recommendations on the management of diabetes during the COVID-19 pandemic (bit.ly/2YHFBFB).

In groups that are particularly vulnerable to COVID-19 infection, such as those with multiple comorbidities (e.g. hypertension, cardiovascular disease and chronic kidney disease), there should be extra vigilance and surveillance for signs of deteriorating health, and a lower threshold for admission to hospital.

References

¹Brewster S, Curtis L, Poole R (2017) *Practical Diabetes* **34**: 13–15

²ABCD (2016) *Position Statement on the risk of diabetic ketoacidosis associated with the use of sodium-glucose cotransporter-2 inhibitors*. bit.ly/3dl1RtS

³Down S (2020) How to advise on sick day rules. *Diabetes & Primary Care* **22**: [in press], bit.ly/39zBPjB

⁴Morris D (2019) SGLT2 inhibitors – moving on with the evidence. *Journal of Diabetes Nursing* **23**: 77, bit.ly/3dnsMFn

⁵Ali A et al (2019) *Diabetes Ther* **10**: 1595–622

⁶Bornstein SR et al (2020) *Lancet Diabetes Endocrinol* **8**: 546–50