Urine versus blood ketones

This new series of articles is designed to provide practical tips on key tests for patients with diabetes.

Here, Dr Sarah Brewster, Dr Louise Curtis and Dr Ruth Poole examine the parameters regarding ketone measurement and highlight practical points to bear in mind.

Introduction
Confusion exists among both people with diabetes and health care professionals over when to measure ketones, which method to use, and how to interpret the results. This article is designed to provide a background on what ketones are, when and how to measure them, and some practical points to consider.

What are ketones?
Ketones are produced when fatty acids are metabolised in the liver in the absence of glucose as an energy source. This process is known as ketogenesis, and results in the formation of three different types of ketone bodies: 3-beta-hydroxybutyrate (3-β-OHB) comprising 78% of the circulating ketone bodies, acetoacetate 20%, and acetone the remaining 2%.1

As demonstrated in Figure 1, during ketogenesis acetoacetate is the main product. This is reduced in the mitochondria to form 3-β-OHB, and also undergoes spontaneous decarboxylation to form acetone, a substance which can be detected on the breath as a sweet odour.

The principal ketone bodies, 3-β-OHB and acetoacetate, are transported from the liver to tissues where they are used as a source of energy. The brain is an organ that relies on ketones in states of relative carbohydrate deficiency, as it is unable to break down fatty acids itself.1

What causes an elevation in ketones?
In the normal physiological state, ketones are undetectable in either the blood or urine. Any circumstance where fat is the main source of energy will cause a rise in ketones (Box 1). Ketoacidosis occurs when the excess of ketones, which are strong organic acids, dissociate resulting in the production of hydrogen ions which exceed the homeostatic buffering capacity in the blood.1

How are ketones measured?
Urine testing for ketones has been available for more than 50 years.2 It relies on the nitroprusside test where nitroprusside reacts with acetoacetate to produce a purple-coloured complex. This method of measuring ketones has a number of flaws and has been widely superseded by the point of care measurement of 3-β-OHB in capillary blood. The latter method relies on a rapid enzymatic assay and has been proven to be accurate in numerous studies.3,4

Urine ketones
Method: A fresh urine sample is collected, a reagent strip is dipped into the urine, the strip is then removed and tapped on the side of the pot to remove any excess urine, and after a specified amount of time (10–15 seconds), a colour change on the strip is compared to a colour array on the side of the ketone stick pot. The change in colour is semi-quantitative; yellow indicates the absence of ketones, and deepening shades of purple indicate: trace, small, moderate, large or large-large concentration of ketones as referenced on the pot.

Urine strips available: The urine strips available in the UK include: Bayer Keto-Diastix and GlucoRx KetoRx sticks.
Test tips

Urine versus blood ketones

- Starvation
- Low carbohydrate diet
- High-fat diet
- Diabetic ketoacidosis
- Exercise
- Pregnancy and lactation
- Severe illness
- Alcoholic excess
- Isopropyl alcoholic poisoning
- Salicylate poisoning
- Growth hormone or cortisol deficiency
- Rare inborn errors of metabolism

Box 1. Circumstances when ketones may be raised

Limitations of urine ketone testing
- Urine ketones (acetoacetate) are only a surrogate measurement of the clinically relevant capillary ketones (3-β-OHB). In diabetic ketoacidosis (DKA) the 3-β-OHB:acetoacetate ratio increases from 1:1 to 5:1.1 With treatment of DKA, 3-β-OHB is oxidised back to acetoacetate. As a result, 3-β-OHB will decrease, but acetoacetate will increase. Measuring acetoacetate with urine sticks may therefore initially underestimate the severity of DKA and then continue to yield positive readings after the resolution of DKA.
- Urine ketone testing is a semi-quantitative test which only indicates if large, moderate, small or trace amounts of ketones are present. This can introduce user variability in the interpretation of the colour change.
- The osmotic diuresis that can occur in hyperglycaemia results in large volumes of urine produced. This inevitably results in dilution of the measurable urinary ketones and under-representation of capillary ketones. Similarly, hydration status can affect results with dehydration leading to false positive results and excessive fluid intake leading to false negative results.
- A urine sample is required and this may delay the diagnosis if this is difficult to obtain.
- Measurements do not accurately reflect current conditions if the urine has been in the bladder for several hours.
- Drugs can affect results; medications containing a sulphydryl group, for example captopril, and levodopa can cause false positives. Vitamin C may lead to a false negative result.5

### Table 1. Ketone meters available and the cost of their associated ketone strips

<table>
<thead>
<tr>
<th>Blood ketone meter</th>
<th>Compatible ketone strips</th>
<th>RRP (per 10 strips)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freestyle Optium Neo</td>
<td>FreeStyle Optium blood beta-ketone test strips</td>
<td>£21.14</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td>GlucoMen Lx Two</td>
<td>GlucoMen LX β-Ketone test strips</td>
<td>£21.06</td>
<td>A Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoRx HCT &amp; Ketone Monitoring System</td>
<td>GlucoRx HCT Ketone Test Strips</td>
<td>£9.95</td>
<td>GlucoRx Ltd</td>
</tr>
</tbody>
</table>

### Table 2. Comparison between urine and capillary ketone measurement

<table>
<thead>
<tr>
<th>Urine ketone measurement</th>
<th>Capillary ketone measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures acetoacetate</td>
<td>Measures 3-beta-hydroxybutyrate</td>
</tr>
<tr>
<td>User dependent test with some subjectivity</td>
<td>Objective test</td>
</tr>
<tr>
<td>Semi-quantitative result</td>
<td>Quantitative result</td>
</tr>
<tr>
<td>Results may lag behind clinical status</td>
<td>Results reflect current clinical status</td>
</tr>
<tr>
<td>Sample can be practically difficult to obtain</td>
<td>Sample easy to obtain, even in unconscious patients</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Test strips expire after 6 months once pot is opened</td>
<td>Each test strip is individually foil wrapped with a shelf life of 12–18 months</td>
</tr>
<tr>
<td>Consumables are more cost effective</td>
<td>Consumables are more expensive</td>
</tr>
<tr>
<td>Test can be carried out anywhere, with no meter required</td>
<td>Requires a specific meter that needs calibration</td>
</tr>
<tr>
<td>Urine ketone strips are visually read. People with diabetes often have impaired colour vision</td>
<td>–</td>
</tr>
</tbody>
</table>

- Test strips exposed to air degrade over time and both manufacturers of the strips quote an expiry of six months after opening.
- Urine ketone strips are visually read. People with diabetes often have impaired colour vision.

Cost of urine strips: The National Health Service indicative price of 50 Keto-Diastix is £3.06, and £2.55 for 50 GlucoRx KetoRx sticks.6

**Blood ketones**

Point-of-care ketone meters have become more available since 2010 when the Joint British Diabetes Societies Inpatient Care Group published guidelines on the management of DKA in adults, which recommended measurement of capillary ketones and now represents best practice for DKA.7

**Method:** A blood sample can be taken and sent to the laboratory, but more frequently a bedside capillary finger-prick test is done. This is a similar method to testing for capillary blood glucose and requires 0.8–1.5µL or 1 drop of blood. The time taken for the results varies according to the device but it is usually 10 seconds (cf. 5 seconds for capillary glucose measurement). It provides a rapid, quantifiable and reliable measurement of blood 3-β-OHB, and is a method that facilitates prompt and accurate diagnosis and management of DKA.

**Devices available:** Three portable blood ketone meters are available on prescription in the UK at the time of writing. See Table 1. The choice of meter is determined by
Test tips

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The diagnostic criteria for diabetic ketoacidosis

All 3 of the following must be met:
• pH <7.30 and/or HCO₃ <15mmol/L
• Blood glucose >15mmol/L
• Ketones >3mmol/mol

(Joint British Diabetes Societies, 2011)

Box 2. Diagnostic criteria for diabetic ketoacidosis

local and patient preference, and meters are provided free of charge to NHS organisations and to individuals with diabetes.

Comparison

Table 2 provides a comparison between urine and capillary ketone measurement.

Although the consumables of the capillary ketone meters are more expensive than those of urine ketone measurement, a number of studies have shown: capillary ketone measurement to facilitate earlier detection and management of DKA; a better correlation with the severity of DKA than urine and venous blood ketones; and reduced rate of hospital admission in those able to measure capillary ketones at home compared to those given the stick to measure urinary ketones. As such, the overall cost-effectiveness and economic impact are favourable.

When to measure ketones?

Ketones should be measured when DKA is suspected. Patients with type 1 diabetes are advised to check ketones when their blood glucose exceeds 15mmol/mol, they have a concurrent illness or are vomiting. A diagnosis of DKA is made when all three of the criteria listed in Box 2 are met.

Patients with type 2 diabetes can also have DKA. This may occur in patients with a long duration of type 2 diabetes or in patients with ketosis-prone diabetes, a condition most commonly seen in patients of Afro-Caribbean origin. A correlation has been made with SGLT2 inhibitors although the pathophysiology underlying this is unclear.

If a patient is not known to have diabetes, then ketone testing should be considered in the presence of symptoms suggestive of DKA, or in the presence of a metabolic acidosis of unknown cause. Other special circumstances in which to consider measuring ketones include: hyperemesis in pregnancy, a patient with suspected pancreatic insufficiency who is acutely unwell, or the first presentation of suspected diabetes.

While the presence of ketones may be due to underlying illness or starvation (see Box 1), if the urine ketones are greater than a trace or the blood ketones are greater than 0.6mmol/L, then type 1 diabetes should be considered.

Some people measure their ketones when on a low carbohydrate weight-loss programme to try and establish if they are burning their fat stores. This is not advocated by health care professionals.

Table 3 is a summary of how patients with diabetes are advised to interpret their ketone reading when self-testing at home (based on Diabetes UK advice).

Table 3. How to interpret capillary ketones in a patient with diabetes

<table>
<thead>
<tr>
<th>Ketone reading</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.6mmol/L</td>
<td>Normal; no action required</td>
</tr>
<tr>
<td>0.6–1.5mmol/L</td>
<td>Indicates that more ketones are being produced than normal. Ensure adequate fluid intake and repeat after 1 hour</td>
</tr>
<tr>
<td>1.6–3.0mmol/L</td>
<td>Indicates potential diabetic ketoacidosis. Need to interpret in clinical context. Patient advised to contact diabetes health care team</td>
</tr>
<tr>
<td>&gt;3mmol/L</td>
<td>Seek urgent medical attention; could be in diabetic ketoacidosis</td>
</tr>
</tbody>
</table>

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Declaration of interests

There are no conflicts of interest declared.

References


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