

## Horizon Scan Report 0008

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**Diagnostic Technology:** Point of care blood test for ketones in diabetes patients

**Clinical Question:** In diabetic patients, does a point of care meter to measure blood ketones improve the diagnosis and management of diabetic ketoacidosis compared to standard practice.

**Devices:**

Precision Xtra Advanced Diabetes Management System (Abbott) (blood glucose and ketones)

**Advantages over Existing Technology:**

Earlier diagnosis of capillary blood ketone bodies associated with hyperglycaemia facilitates the prevention of ketoacidosis, as well as prompt treatment (14). Urine ketone strips are semi-quantitative and measurements do not accurately reflect current conditions if the urine has been in the bladder for several hours (e.g. overnight) before testing (1). Bottled strips can lose their accuracy if the bottle has been open for several months. Results can also be affected by medications, giving false-positive results in the presence of drugs containing sulfhydryl groups or false negative reactions (7,8). In some cases, patients may also be unable to provide a urine sample.

**Details of Technology:**

The Precision Xtra from Abbott Diabetes Care is a meter that tests for both blood glucose and blood ketones with the aid of accompanying strips. The meter is portable and the ketone test strip requires 1.5 µl of blood and produces results in approximately 10 seconds. The detection range is between 0.1 and 6 mmol/l and the principle of the test is based on a reader able to measure the current change generated by the reaction produced by the conversion of the ketone 3-beta-hydroxybutyrate (beta-OHB) into acetoacetate in the presence of hydroxybutyrate dehydrogenase that is measured electrochemically. The use of electrochemistry means there is less likelihood of any interference.

**Patient Group and Use:**

- Patients with type 1 or type 2 diabetes mellitus
- Early detection and diagnosis of diabetic ketoacidosis (DKA)
- Monitoring and management of patients with DKA (16)

**Importance:**

The presence of ketones in the bloodstream is a common complication of diabetes, which if left untreated can lead to ketoacidosis. Diabetic ketoacidosis (DKA) remains a leading cause of hospitalization and the main cause of morbidity and death in children and adolescents with type 1 diabetes (1). Diabetes UK reports 2.5 million people diagnosed with diabetes in the UK in 2008 (3.8% prevalence) (2). A recent study reported an increase in the incidence of diabetes amongst children in Europe, with an average annual increase of 3.9% (3). The study also predicted a 70% increase in the incidence amongst children younger than 15 by 2020.

**Previous Research:**

*Accuracy compared to existing technology:*

The Precision Xtra meter (Abbott) measures the ketone beta-OHB in the blood of diabetic patients. When comparing the accuracy of the Precision Xtra meter to a standard laboratory enzymatic method the ketone sensor accurately measured beta-OHB concentrations in patients with DKA (limits of agreement 0.9 to 1.0 mmol/l) or starvation-induced ketonemia (limits of agreement -0.5 to +0.5 mmol/l) within 30s (13).

The utility of blood ketone measurements for predicting DKA was assessed in an emergency department study, which showed that a beta-OHB level of  $\geq 3.0$  mmol/l had a sensitivity of 100% and specificity of 88% for DKA.

In an Emergency Department study of 173 hyperglycaemic patients, point-of-care blood ketone tests (Abbott) were compared to urine dipstick analysis (5). Several cut-off points were evaluated, e.g. at two-cross cut-off points for ketonuria and at the 3 mmol/l cut-off point for ketonemia the two tests had the same sensitivity (100%), but the specificity of 3-beta-hydroxybutyrate (beta-OHB) (94%) was significantly higher ( $P < 0.0001$ ) than that of ketonuria (77%). Overall the study showed that measurement of beta-OHB in capillary blood was faster and more effective than the use of urine dipsticks to detect ketoacidosis. A follow-up study by the same group on the correlation between urine ketones and capillary blood ketones showed a good correlation for low values, but a poor correlation for high values. The study concluded that either test could be used to exclude ketosis, but that the capillary blood ketone test is more accurate to confirm ketoacidosis (11).

A prospective observational study in an emergency department comparing ketone dipstick testing with capillary blood ketone testing, showed that for determining diabetic ketoacidosis the positive likelihood ratio (PLR) of urine ketone dipstick testing was 3 and for capillary blood ketone testing the PLR was 4; and in determining hyperketonemia (both in diabetic ketosis and diabetic ketoacidosis) the PLR was 1.8 and 2, respectively (12).

Another study in an emergency care setting compared the results of this point-of-care test with standard clinical measures for accuracy in predicting DKA (4). 160 patients who presented with blood glucose levels of  $> 6.4$  mmol/l were tested for beta-OHB and the diagnosis of DKA was made by clinicians using standard clinical criteria without knowledge of the beta-OHB test. Cross-classification of DKA versus beta-OHB yielded sensitivity of 98% (95% CI = 91% to 100%), specificity of 85% (95% CI = 78% to 91%), with a positive likelihood ratio of 6.7 (95% CI = 4.2 to 10.8), and negative likelihood ratio of 0.02 (95% CI = 0.003 to 0.1) at the manufacturer-suggested beta-OHB level of 1.5. The study concluded that the point-of-care test for beta-OHB was as sensitive as more established indicators of DKA and that it was more useful than glucose alone for the diagnosis of DKA.

Management and monitoring of DKA using the Precision Xtra meter has also been investigated (10). 68 children presenting to an emergency department with DKA were treated using a standard protocol (monitoring of venous pH, partial pressure of CO<sub>2</sub> (pCO<sub>2</sub>), bicarbonate, glucose, blood urea nitrogen, and electrolytes), while also measuring venous beta-OHB levels using standard laboratory measures as well as the Precision Xtra meter. The meter readings significantly correlated with pH, bicarbonate and pCO<sub>2</sub> at all points of measurement. The beta-OHB laboratory and meter reading were also showed good correlation ( $r = 0.92$ ;  $P < 0.0001$ ). Real-time beta-OHB measurements may therefore replace repeat laboratory measurement in the management of DKA. However this requires further evaluation.

#### *Impact compared to existing technology:*

One study evaluated the utility of blood beta-OHB testing during sick days in children (9). Children (mean age around 14 years) were randomized in two groups. One group was instructed to supplement insulin based on urine test results, whereas the other group was randomized to using beta-OHB monitoring and correlating insulin supplementation. At 6 months follow-up, the group using beta-OHB measurements showed a reduction in the number of hospitalisation and emergency visit by 60% and 38%, respectively, compared to the ketonuria group. The authors concluded that sick days guidelines with careful monitoring of capillary glucose and beta-OHB associated with adequate supplemental insulin may prevent or reduce the occurrence of DKA episodes compared to ketonuria guidelines.

#### **Guidelines and Recommendations:**

In 2004, the American Diabetes Association (A.D.A) recommended that currently available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis and that blood ketone testing methods that quantify beta-OHB are available and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis (15).

#### **Cost-effectiveness and economic impact:**

Use of the POCT meter would avert the need for A&E assessments and hospitalizations. However there is limited evidence to support this. Laffel et al. found in a study of 123 children, adolescents and young adults aged 3-22 years that

the use of POC blood ketone testing compared with urine testing resulted in 60% fewer hospitalizations and 40% fewer emergency assessments (9). In a small study conducted by Vanelli and colleagues on 33 children, they found that in comparison to urine testing blood POCT for ketones led to earlier discharge from intensive care, reduced numbers of clinical assessments and lab investigations resulting in total savings of 3000 Euro (17, 18).

Further research is required to assess the cost-effectiveness of implementing POC blood tests for ketones within a UK general practice setting.

### Research Questions:

- (a) Who are the potential users of this technology, e.g. general practitioners, district nurses, paramedics, urgent care?
- (b) Can ketone measurement be used in primary care in the early assessment of patients presenting with symptoms suggestive of ketoacidosis?
- (c) Should ketone measurement be used by patients who are considered at risk of developing ketoacidosis?
- (d) What is the role of ketone measurement in managing patients with hyperglycaemia?
- (e) What is the role in early interventions for children to avoid hospitalisation?
- (f) What is the cost effectiveness of ketone measurement in primary care?
- (g) What are the potential barriers to introduction of point of care HbA<sub>1c</sub> testing in primary care, e.g. Consumables, quality control, reproducibility, QC, linking to practice IT, training, time involved, sample throughput etc? (*although these are generic POCT issues*)

### Suggested next step:

- 1) Cross sectional study of utility and accuracy in primary care
- 2) Health economic analysis of blood ketone POCT

### Expected outcomes:

POC blood tests for diabetes allow for rapid and accurate diagnosis and monitoring of diabetic ketoacidosis.

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This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford  
Contact details: Dr. Annette Plüddemann; [Email: horizonscanning@dphpc.ox.ac.uk](mailto:horizonscanning@dphpc.ox.ac.uk)