OMD
OXFORD MEDICAL DIAGNOSTICS

Breath Ketone Measurement

David Taylor, Technical Officer

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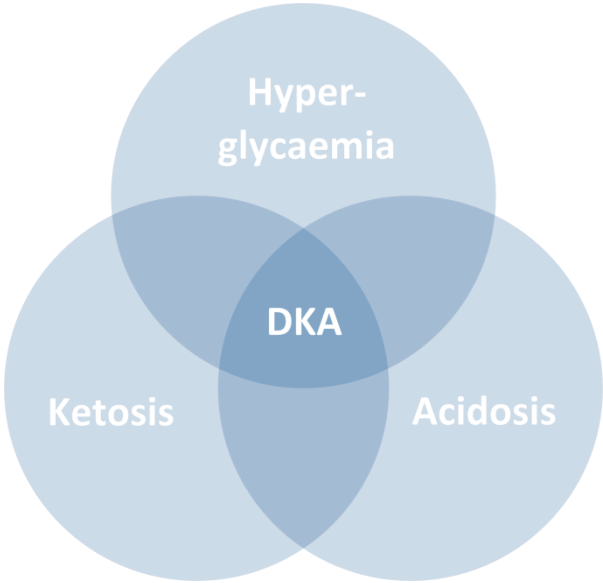
About OMD

- Founded in 2010
  - Spin-out from Department of Chemistry, University of Oxford
  - Based on Begbroke Science Park, Oxford
- Develop optical techniques for non-invasive measurement of clinically relevant Volatile Organic Compounds (VOCs)
  - Measure concentration of certain molecules in exhaled breath as indicators of disease and physiology
  - More affordable approach than conventional analytical equipment e.g. mass spectrometry
- Exhaled breath acetone (BA) – first application
  - Correlates with circulating blood ketone (BK) levels
  - Early detection of diabetic ketoacidosis
  - Potential tool for identifying individuals with undiagnosed diabetes

Diabetic Ketoacidosis (DKA)

- Potentially fatal complication of diabetes
  - Caused by insulin deficiency
  - Mortality rates of 2-10%
- In absence of insulin:
  - Body cannot use glucose as energy source so burns fats to compensate – leads to ketosis
  - Excess ketone bodies cause metabolic acidosis
  - 3 principal ketone bodies: β-OHB, AcAc and acetone
  - Low insulin leads to elevated glucagon to produce glucose from glycogen – rapid onset of DKA
- ~£17.5m per annum in associated acute admissions costs in NHS in England
  - 16,158 admissions in England in 2012/13
  - Excludes expenditure on ambulances, A&E etc.
  - Present in ~25% diagnoses of type 1 diabetes (~35% for children <5 years)



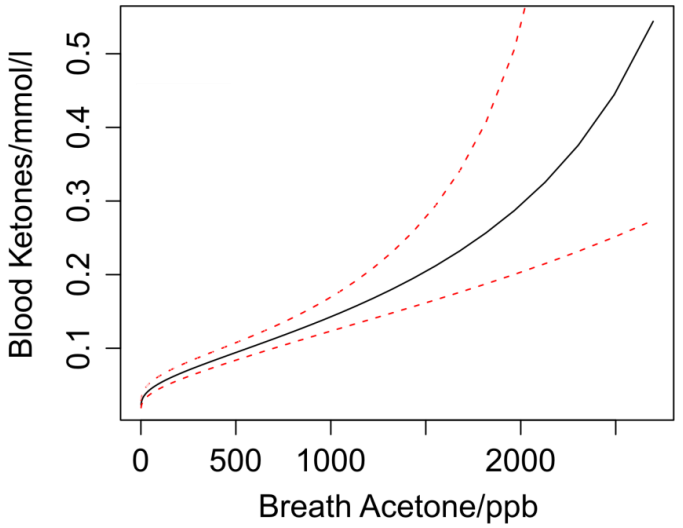
Current Methods for Ketone Testing

- BK testing advised every 4-6 hours on sick days or when blood glucose >16.7 mmol/L
- Urine testing
  - Cheap (£0.06 per test)
  - Urine ketones lag levels in blood by ~2-3 hours
  - Varies with hydration levels and interfering molecules
- BK with electrochemical strips
  - Expensive (£2.06 per test strip)
  - Direct measure of BK levels
  - Influenced by blood pH
- Lifetime of test strips only 6-9 months – high wastage

	Mild DKA	Moderate DKA	Severe DKA
Plasma Glucose (mmol/L)	>13.9	>13.9	>13.9
Arterial pH	7.25 - 7.30	7.00 - 7.24	<7.00
Sodium Bicarbonate (mEq/L)	15 - 18	10 - 14	<10
Urine Ketones	+	+	+
Serum Ketones	+	+	+
Serum Osmolality (mOsm/kg)	Variable	Variable	Variable
Anion Gap	>10	>12	>12
Mental Status	Alert	Drowsy	Stupor/Coma

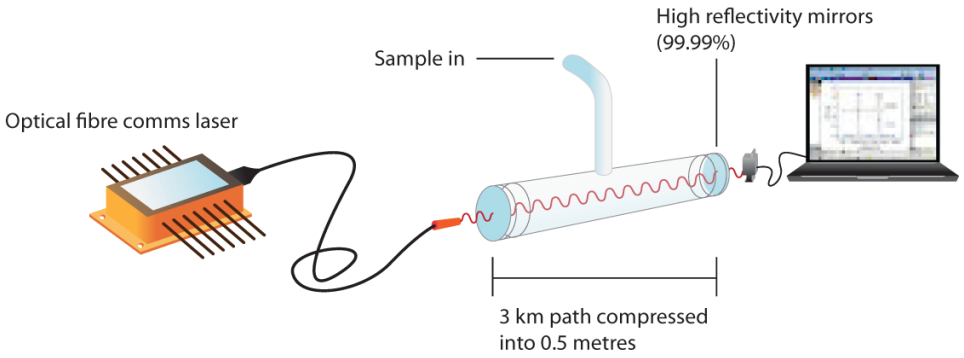
Breath Testing Alternative for BK

- Acetone (a BK) is highly volatile
  - Produced through spontaneous and enzymatic decarboxylation of AcAc
  - Readily diffuses out of blood into air in the lungs
  - Exhaled BA provides a reliable indication of circulating BK levels
- Instantaneous measurement
  - No lag time between exhaled BA and levels in blood
  - Effectively a large “blood” sample
- Less prone to interference than existing methods



Blood β-hydroxybutyrate (mmol/l)	Exhaled Breath Acetone (ppmv)	Action required
<0.6	<3.0	Normal – recheck every 1-2 hours if blood glucose >13.9 mmol/l
0.6 - 1.5	3.0 - 7.0	Insulin required – follow sick day rules, checking ketone and glucose levels every 1-2 hours
1.5 - 3.0	>7.0	Risk of DKA – seek urgent medical attention

Technology: Cavity Enhanced Absorption Spectroscopy

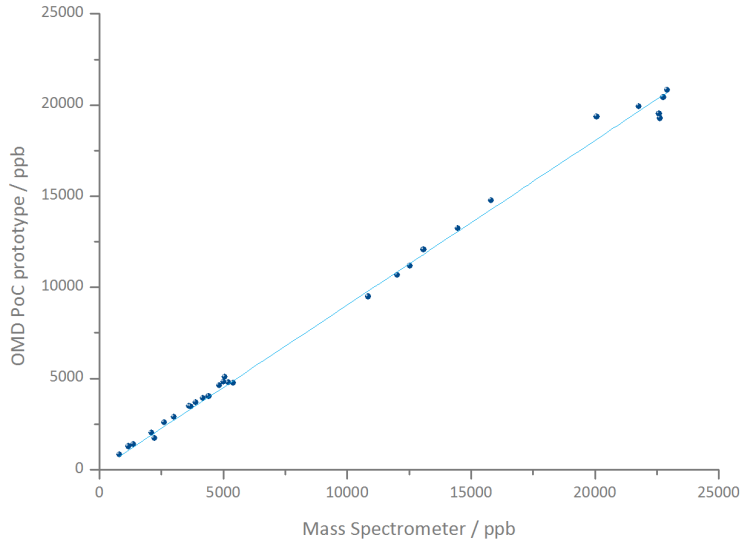


Typical CEAS setup

- All molecules absorb light at characteristic frequencies
- Spectroscopy exploits this effect to identify molecules and measure them quantitatively
- CEAS amplifies the absorption by enclosing the sample between two high-reflectivity mirrors
- Preconcentration method used to treat breath sample prior to measurement – increases sensitivity in small device
- Sub-ppm measurements of acetone readily achieved using this approach

CEAS *vs.* Mass Spectrometry

- Mass spectrometry (MS) is the gold-standard for breath analysis
- 1:1 correlation between OMD's CEAS technology and MS
- Robust technology benefits from investment in telecoms sector
- MS costs ~£250k; with high-volume manufacture, CEAS could cost ~£100.



Data comparing OMD's CEAS technology, obtained using the current prototype device, and a gold-standard mass spectrometric method. All of these data are for breath samples acquired in 1 L breath bags for normal, healthy subjects without diabetes. BA levels were elevated through fasting (up to 36 hours for BA >20 ppm).

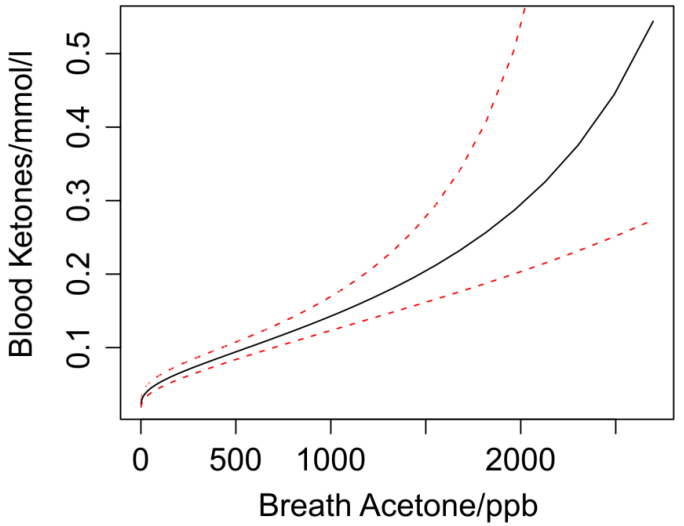
Clinical Data

Study Objective

- **Conducted at Oxford John Radcliffe Hospital, sponsored by Oxford University**
- Establish relationship between breath acetone, blood ketones and blood glucose
- 113 juveniles with type 1 diabetes
- Published in the Journal of Breath Research

Study Protocol

- Blood ketone, blood glucose and breath samples taken during regular clinic visit
- Breath tested for acetone content using mass spectrometry and compared with standard finger prick measurements of ketones and glucose
- OMD sub-contracted to analyse breath samples using mass spectrometry



Blood ketone vs. exhaled breath acetone levels (measured using mass spectrometry) from 113 juveniles with type 1 diabetes under tight glycaemic control at routine clinical appointments. Calibration plot from an inverse regression analysis in which a Gamma Generalised Linear Model was successfully fitted ($\chi^2 = 99.49$). Dashed red lines indicate 95% confidence limits.

Product Development

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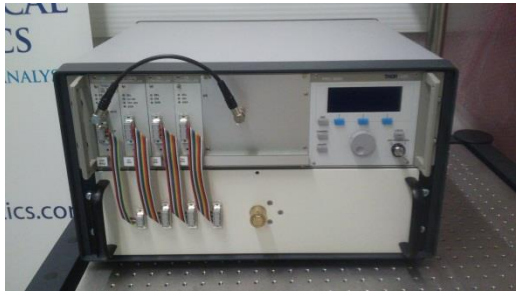
Dec 2011

Alpha device



- Bench top instrument
- 45 cm cavity
- Expensive, complex componentry

Current

Prototype

- iPad Footprint
- Portable
- 7 cm cavity
- Simplified – reduced number of components
- Direct breath sampling demonstrated

Q1 2017

LiteAir

- Industrial design for mass manufacture
- Disposable items included to aid breath sampling
- Image is of a conceptualised block model

Summary

- New breath test for the non-invasive measurement of blood ketone levels
- Robust, reliable technology addresses key problems with existing ketone testing methods
- Strong clinical support for BA as an indicator of BK levels
- Currently in product development phase, producing 20 prototypes for clinical evaluation in late 2015
- Device to be suitable for clinical and home-use settings
    - Clinical – rapid identification of DKA and potentially undiagnosed people with diabetes
    - Home use – routine monitoring on sick days and during hyperglycaemic episodes
- Market launch anticipated in 2017

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Thank you for listening

Contact Details

Oxford Medical Diagnostics Ltd.,
Centre for Innovation & Enterprise,
Begbroke Science Park,
Begbroke Hill, Woodstock Road,
Begbroke, OX5 1PF
United Kingdom

www.omdiagnostics.com

Tel.: +44-(0)1865-854888
Fax.: +44-(0)1865-854889