1

Development of a Breath Analysis System for the Early Detection of Diabetic Ketoacidosis in Type I Diabetics

T. P. J. Blaikie*, Dr. I. Campbell*, Prof. G. Hancock**, Dr. R. Peverall*, Dr. G. Richmond*, Prof. G. A. D. Ritchie** and D. Taylor*

*Oxford Medical Diagnostics Ltd., Centre for Innovation and Enterprise, Begbroke Science Park, Begbroke Hill, Woodstock Road, Yarnton, OX5 1PF, U.K.
**Department of Chemistry, University of Oxford, Physical and Theoretical Chemistry Laboratory, South Parks Road, Oxford, OX1 3QZ, U.K.
david.taylor@oxfordmedicaldiagnostics.com

OMD
OXFORD MEDICAL DIAGNOSTICS

Introduction and Objectives

Oxford Medical Diagnostics Ltd. (OMD) is developing a **non-invasive breath acetone test** for the early detection of diabetic ketoacidosis (DKA), a potentially fatal complication of type I diabetes mellitus (TIDM)

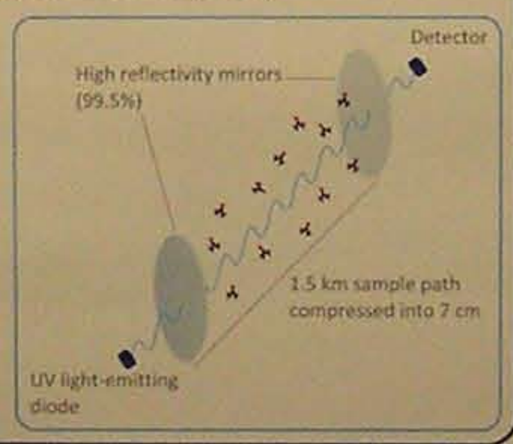
- DKA caused by absolute insulin deficiency
  - Body utilises fat stores for energy rather than glucose, leading to **excessive production of ketone bodies** (*e.g.* **acetone**) and **metabolic acidosis**
  - Cause of **50% of all diabetic hospital admissions** in young persons in the US
  - **>$2bn in annual healthcare costs** associated with treating DKA (~$11k per hospital admission)
- OMD is developing a simple, inexpensive test for measuring breath acetone to aid prevention of DKA

- Present technology based on near-infrared (NIR) laser **absorption spectroscopy** of acetone
- More economic options available by sensing acetone in **ultraviolet (UV) region**
- Current research focused on developing a fully-functional and portable device based on UV spectroscopy of acetone
- This phase of research work is supported by a **£89k grant from the SBRI**

The Technology

- **Cavity Enhanced Absorption Spectroscopy** (CEAS)
- Sample cell enclosed by **high reflectivity mirrors** (R>99.5%)
- Diode laser probes sample
- Extreme pathlength (1 km) in **small physical footprint** (5 cm)

The sensitivity of CEAS is determined by the length of the path of light through the sample. However, a large instrument would not lend itself to use in a clinical environment. To combat this, CEAS has been combined with a **pre-concentration unit** which traps acetone from breath and releases it selectively into the cell for measurement. This enables **sub-ppm quantification of breath acetone**.

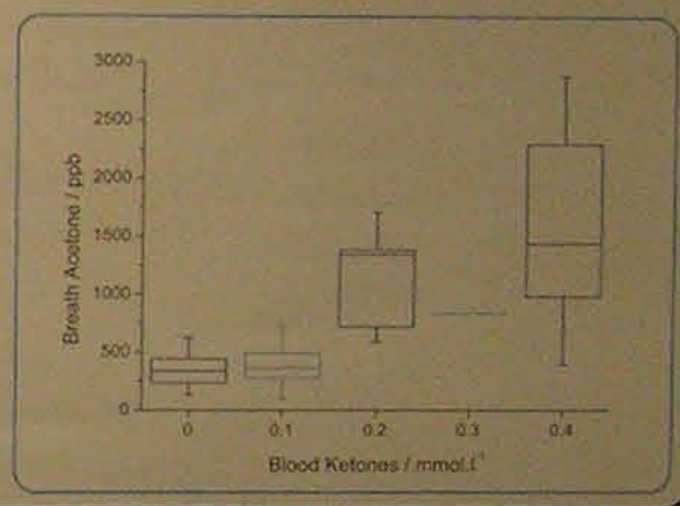


Clinical Evidence

A number of clinical trials have been carried out to establish the link between breath acetone and blood ketones. Of particular note is a study run in conjunction with the Oxford Children's Hospital.

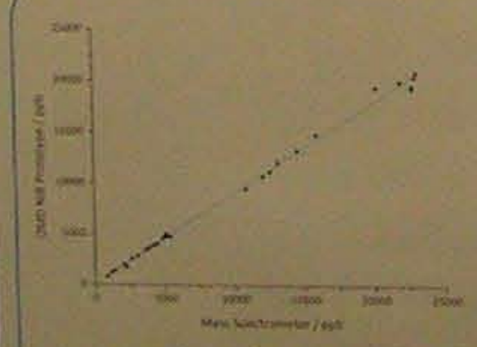
- 113 children aged 7-18 years, all with TIDM
- Breath acetone measured using mass-spectrometry
- Compared against a reference, OTC blood ketone monitor
- Clear relationship is observed
- Large variation due to quantisation of blood ketone monitor

Illustrates the potential for using breath acetone concentration as a predictive marker of blood ketone levels

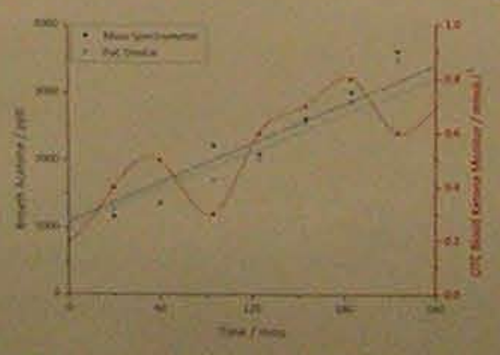


Performance of NIR Device

- NIR system tested extensively both in routine development and in internal clinical evaluations conducted at OMD



Left:
- Data from non-diabetic individuals; breath acetone enhanced by fasting or exercise
- End tidal breath samples analysed on NIR device and 'gold-standard' mass spectrometer
- **1:1 correlation** validates the OMD method
- **R^2 co-efficient of 0.996**



Right:
- Data from healthy, non-diabetic individual after overnight fast and 10 km run
- End tidal breath samples analysed every 30 minutes on NIR device and 'gold-standard' mass spectrometer
- Corresponding blood ketone measurements using OTC monitor as a comparison
- Good agreement between mass spectrometer and NIR device
- Comparison limited by accuracy of existing blood ketone monitor; all results shown fall within accuracy limits of the ketone monitor

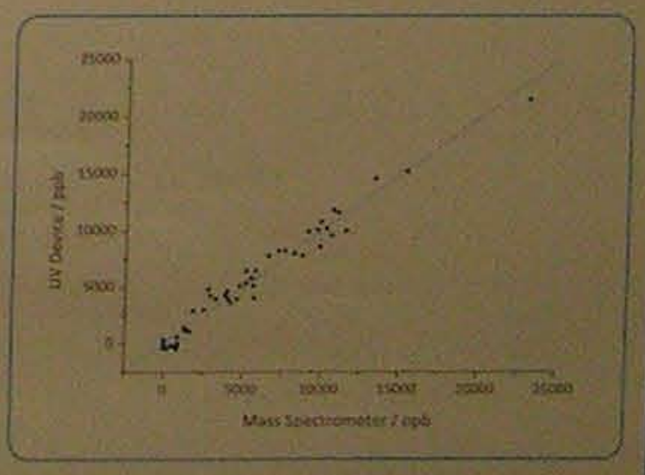
- These data highlight the market need that OMD seeks to address with their technology

The Move Towards a Marketable Product

The successful uptake of OMD's technology into the highly-competitive diabetes healthcare market necessitates a cost-effective product. It is therefore crucial that the cost of goods is driven down so far as is possible. To address this, a wavelength shift from the near-infrared to the ultraviolet is envisaged.

- NIR-CEAS relies on laser-based technology which is expensive
- LEDs centred in the UV offer a far more economic approach
- However, optical technology in the **UV is less well advanced**

Some initial data trialling the UV-CEAS technology in conjunction with sample pre-concentration are shown on the right



- All samples are from mixtures of various calibrated gas sources
- A **1:1 relationship** with mass spectrometer is clearly observed
- **Detection limit of 1.5 ppm** is promising and improvements to this are being made to approach that of the NIR system

Future developments

- **Commercialise** current technology for the early detection of DKA
  - Industrial design team already secured to make this technology ready for market
  - Some early concept designs are shown below
- **Further miniaturisation** of the technology for home use
  - 7 cm optical cavity, currently
  - Tests on a **2 cm cavity** (above right) to begin imminently
- **Other applications** inside and outside medical sector

Concluding remarks

OMD has developed a device based on CEAS technology for the rapid and non-invasive measurement of breath acetone. In the first instance, this technology will be applied to the early detection of DKA in type I diabetics to reduce hospital admission rates and to improve the long-term health of the patient.

Early efforts have focused on a NIR system which is accurate but expensive. To drive down costs, work has commenced on a cheaper, UV based system which shows great promise. This work has been made possible through an SBRI grant.

Please contact us for possible collaborative projects.

Acknowledgements

We are grateful for the help of the clinical team in the Oxfordshire Children's Diabetes Service. Clinical studies were funded by the Department of Chemistry at the University of Oxford. Development funding for the NIR device was provided by the Technology Strategy Board. The development of a device with an ultraviolet light source is funded by the Small Business Research Initiative (SBRI).