

What's in a Number? The International Standardisation of HbA1c Results in Diabetes Care

Nearly everybody with diabetes is familiar with the HbA1c test. It features prominently in any review of blood glucose control. The test is used to assess the adequacy of blood glucose control over the preceding two to three months and is now universally used to guide diabetes management.

The importance of this test was not fully recognised until the completion of the landmark US Diabetes Control and Complications Trial (DCCT) for people with Type 1 diabetes in 1993 and the UK Prospective Diabetes Study (UKPDS) for people with Type 2 diabetes in 1998. The DCCT showed that the risk for development and progression of the chronic complications of diabetes in people with Type 1 diabetes is closely related to the degree of blood glucose control as measured by HbA1c. The UKPDS showed similar results for people with Type 2 diabetes.

The correlation between HbA1c levels and outcomes highlighted the need to measure HbA1c accurately and precisely so that results for a person with diabetes can be directly related to studies such as the DCCT and consequently to outcome risks. This involves a consideration of one of the fundamental principles of measurement.

The science of measurement is called metrology and it sets out the requirements for measurement systems including those in laboratory medicine. Amongst these is the requirement for metrological traceability. Put simply, this is the linking of a measurement result from a patient sample through an unbroken chain of calibrations to a commonly accepted international reference. Doing this is a prerequisite to being able to link measurement results to a common reference when using different types of measurement equipment in different locations over

time. The implications of all this are far-reaching. Measurement systems with full metrological traceability will enable the use of international reference ranges and the harmonisation of decision values. All of this may appear esoteric but it will have very important benefits for patient care, the management of long-term conditions, the detection and control of disease, ongoing medical research and the control of healthcare costs.

An important driver for metrological traceability emerged in December 1998 with the publication of the European Directive 98/79/EC on In-vitro Diagnostic Devices. The directive incorporated the requirement for metrological traceability into regulation. Earlier in 1998, in advance of the directive, the EU Commission provided funding to assist the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) in completing its programme to develop a reference method and pure standards for the HbA1c assay. That programme had commenced in 1995, two years after the publication of the DCCT results. The IFCC reference method was published in 2002 and is now the means for the uniform standardisation of HbA1c assays worldwide. Measurements are traceable to an SI unit, the mole (mol), and are expressed in mmol/mol rather than as % which is not an SI unit. The abbreviation, SI, is universally used to signify the International System of Units (*Le Système International d'Unités*), colloquially known as the metric system of measurement. SI is the dominant measurement system used in science.

Both the DCCT and UKPDS predate the requirements for metrological traceability. The HbA1c assay systems used in both of these trials were not specific for HbA1c and were not standardised or calibrated in the true sense and would not now meet the standards required for the proper metrological traceability of the assay.

The principal officers of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), International Diabetes Federation

(IDF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) met at a summit conference in Milan on 4th May 2007. It was agreed that the HbA1c assay results be reported worldwide in IFCC units (mmol/mol) **and** derived DCCT units (%), using the IFCC-DCCT master equation. Countries should introduce the new way of reporting HbA1c results, known as dual reporting, beginning in 2010 after the agreed deadline of 31st December 2009 for manufacturers to have traceability to the IFCC Reference System in place.

For clinicians and people with diabetes, the impact of all these developments will be evident in the laboratory reports giving HbA1c results. For example, an HbA1c (IFCC) result of 42 mmol/mol will be accompanied by a derived HbA1c (DCCT aligned) result of 6.0%; an HbA1c (IFCC) result of 53 mmol/mol will be accompanied by a derived HbA1c (DCCT aligned) result of 7.0%; an HbA1c (IFCC) result of 64 mmol/mol will be accompanied by a derived HbA1c (DCCT aligned) result of 8.0%.

It is important that all involved in diabetes care in Ireland note that under the new system of reporting HbA1c results, each DCCT aligned HbA1c result (expressed as %) will be reported alongside the new HbA1c (IFCC) result (expressed in mmol/mol).

The UK's NHS opted to implement the new arrangements on 1st June 2009, ahead of the deadline for manufacturers, and to report in both 'new' (IFCC) and 'old' (DCCT) units for a two year period with only the 'new' (IFCC) units being reported from 1st June 2011. In doing this, the NHS is going further than what is required by the terms of the International Agreement of 2007.

The HSE's Diabetes Expert Group (EAG) will lead the introduction of the new HbA1c reporting system in Ireland. A subcommittee of the EAG has been appointed for this purpose. The subcommittee members are: Dr. Ned Barrett

(Chairman), Mr. James Conway (Assistant National Director, Office of the CEO), Dr. Graham Roberts, Dr. Tony O'Sullivan, Ms. Louise McMahon and Dr. Obada Yousif. A meeting with representatives of all hospital laboratories in Ireland providing an HbA1c service was held on 25th June. As a result of that meeting, a Project Team was formed and arrangements for the introduction of the new reporting system are well advanced. The agreed commencement date for dual reporting of HbA1c results in Ireland is July 1st, 2010. The Project Manager is Ms. Loraine McGrattan, Health Service Executive, Oak House, Limetree Avenue, Millennium Park, Naas, Co. Kildare.

In Ireland, the Irish External Quality Assessment Scheme for Laboratory Medicine (IEQAS) assesses the accuracy and quality of HbA1c assays in hospital laboratories. For the past six years, IEQAS has been providing these laboratories with specimens assayed by the European Reference Laboratory using the new IFCC Reference Method as part of its quality assessment service. This facility will be used more extensively to demonstrate the full concordance of HbA1c results from Irish laboratories with the IFCC Reference System in the months ahead of the introduction of the new units and dual reporting to the wider diabetes community.

The introduction of the new HbA1c reporting system in Ireland will provide an opportunity for the HSE's Diabetes EAG to emphasise again the importance of good blood glucose control in preventing the costly complications of diabetes.

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