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2010 Consensus Statement on the Worldwide Standardization of the Hemoglobin A_{1c} Measurement

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Glycated hemoglobin concentrations (most common hemoglobin A_{1c}; HbA_{1c}) reflect time-averaged blood glucose during the previous 2–3 months and are used as the gold standard for long-term follow-up of glycemic control. Standardization with common calibration was first proposed in 1984 (1). It was only after the publication of the DCCT study in 1993 (2), however, that the issue of international standardization of HbA1c measurements became an important objective for scientists and clinicians. At that time, the lack of international standardization resulted in several countries developing National standardization programs; most notable of these are:

- In USA, the National Glycohemoglobin Standardization Program (NGSP), with the DCCT HPLC method used as primary reference method
- In Sweden, the Mono S ion exchange chromatography designated as the comparison method
- In Japan, use of common calibrators (six calibrators are available for use) with HbA_{1c} values assigned by the Japan Diabetes Society.

A common feature of these national programs is the absence of primary and secondary reference materials. To overcome this lack of reference materials, achieve global standardization, and to meet the requirements of the European Union directive on *in vitro* diagnostic medical devices, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a working group on HbA_{1c} standardization to develop a reference measurement system within the concept of metrological traceability. Such a system has been developed consisting of incubation with the enzyme endoproteinase Glu-C, cleavage of the N-terminal hexapeptide of the β chain, and separation and quantification of glycated and non-glycated hexapeptides by mass spectrometry or capillary electrophoresis (3). The analyte measured is a hemoglobin molecule having a stable adduct of glucose to the N-terminal valine of the hemoglobin β chain (βN-1-deoxyfructosyl-hemoglobin). Pure HbA_{1c} and pure HbA_0 are isolated from human blood and mixed in well-defined proportions to produce a certified primary reference material set used to calibrate the primary reference measurement system (PRMS). The PRMS values are assigned to secondary reference materials (SRMs; whole blood), and the SRMs are used by the manufacturers to calibrate their instruments. A laboratory network has been established to implement and maintain the PRMS (4).

Adopting the new IFCC standardization procedure will result in HbA1c percentage values being lowered because of the higher specificity on the reference method. It has been suggested that lowering the percentage value of the HbA_{1c} reported may lead to poorer glycemic control in some patients (5), and IFCC

has recommended the use of SI numbers of mmol/mol which would minimize the risk of confusion between IFCC percentage units and DCCT/NGSP percentage units (6).

Expressing HbA_{1c} as an average glucose concentration has been widely discussed as there is a convincing linear relationship between HbA_{1c} and average glucose concentration in both adults (7) and children (8). Nevertheless, not all population groups have been evaluated adequately.

The use of the IFCC reference method for calibration purposes has been widely accepted by both clinicians and scientists, and the implementation of this standardization process is ongoing. There has been a considerable debate, however, regarding the number issue, i.e. whether HbA_{1c} should be expressed in percentage units related to the DCCT study or mmol/mol related to the IFCC method. There is an evident need to keep doctors, nurses, and people with diabetes educated to ensure a worldwide understanding of previously reported and upcoming scientific HbA_{1c} results. A first consensus meeting was held in 2007 (9, 10), where it was decided that the new IFCC reference system for HbA_{1c} represents the only valid anchor to implement standardization of the measurement and that HbA_{1c} results were to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.

A second consensus meeting was held at the International Diabetes Federation (IDF) meeting in Montreal on 21 October 2009. The American Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation (IDF), the IFCC and the International Society for Pediatric and Adolescent Diabetes were represented at that meeting, as well as some editors from medical journals and the following statements were approved by these organizations:

1. HbA_{1c} test results should be standardized worldwide, including the reference system and results reporting;
2. The IFCC reference system for HbA_{1c} represents the only valid anchor to implement standardization of the measurement;
3. HbA_{1c} results are to be reported by clinical laboratories worldwide in SI (Système International) units (mmol/mol – no decimals) and derived NGSP units (% – one decimal), using the IFCC-NGSP master equation (DCCT units);
4. HbA_{1c} conversion tables including both SI (IFCC) and NGSP units should be easily accessible to the diabetes community;
5. Editors of journals and other printed material are strongly recommended to require that submitted manuscripts report HbA_{1c} in both SI (IFCC) and NGSP/DCCT units;
6. The reportable term for glycated hemoglobin is HbA_{1c}, although other abbreviations may be used in guidelines and educational material (A1C);
7. The above consensus recommendations apply through 2011, when they will be discussed again at the next consensus meeting at the IDF meeting in Dubai December 2011.

HbA_{1c}-derived average glucose values calculated from the HbA_{1c} results were not included in the consensus because of the above mentioned limitations of this procedure. However, the use of an estimated average glucose (7) in discussion with an individual patient may add to the consultation process, and the availability of such estimation may be advantageous. Agreement should be reached at a local level on how this estimation available.

In a world of increased communication and with the ever increasing availability of information that both lay people and professionals may access via the Internet, it is inevitable that scientific results from studies such as the DCCT will be brought to the attention of interested individuals for decades to come. By reporting in both IFCC and DCCT units ongoing continuity between these reporting systems will be ensured. The submission of manuscripts containing both units will facilitate the alignment of the various HbA_{1c} methods as the master equation will be used in the laboratory instruments for calculating the DCCT units, that is both the IFCC units and the DCCT units will have the same basis. It is therefore of vital importance that all laboratories and other users or instruments for measuring HbA_{1c}, either in the laboratory or at the Point of Care, take part in quality control and quality assessment programs to ensure accurate results (individual countries will vary in the way this is performed). We hope that the recommendation of dual reporting in submitted manuscripts will be adopted promptly by all scientific journals publishing diabetes articles.

Appendix

The International HbA_{1c} Consensus Committee consisted of: for ADA: David Kendall, Sue Kirkman, Sue McLaughlin, Richard Bergenstal, David Sacks, and David Nathan; for EASD: Viktor Joergens and Ulf Smith; for IDF: Jean-Claude Mbanya, Massimo Massi Benedetti, Marg McGill, and Larry Deeb; for IFCC: Garry John and Graham Beastall; for ISPAD: Ragnar Hanas and Thomas Danne.

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