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Editorial

Implementation of haemoglobin A1c results traceable to the IFCC reference system: the way forward

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This issue of the journal contains two papers prepared by scientific groups of the IFCC on the topic of haemoglobin A1c (HbA1c) (1, 2). In the position paper by the Working Group on Standardization of HbA1c (WG-HbA1c), Mosca et al. highlight the achievements of the WG created in 1995 and outline its position on the current situation surrounding HbA1c measurements (1). The second document contains the recommendations on HbA1c nomenclature and unit prepared by the IFCC/IUPAC Committee on Nomenclature, Properties and Units (C-NPU) (2).

It is fascinating to consider the analytical improvements that have occurred since HbA1c was first introduced into clinical laboratories for diabetes monitoring during the late 1970s. At that time methods displayed poor precision and significant differences in the results produced by different laboratories (3). Comparability of HbA1c results among laboratories was considered to be at best difficult or more likely impossible, especially when they originated from different laboratories using different methods.

Result harmonisation by common calibration was first proposed in 1984 by Peterson et al. (4). However, it was only after the publication of the Diabetes Control and Complications Trial (DCCT) study in 1993 (5) that the issue of standardisation of HbA1c measurements became an important objective for scientists and clinicians. The lack of standardisation resulted in the development of several national and regional harmonisation/standardisation programs, with considerable divergence still existing between results obtained in different parts of the world (6, 7). Given the local level of initiatives, a common feature of these programs was the absence of internationally recognised and accepted reference materials and measurement procedures to be used as key elements in assuring the accuracy and comparability of HbA1c measurements at a global level. To definitively address these shortcomings and to achieve a uniform international standardisation of HbA1c measurements, the IFCC established the WG-HbA1c with the aim to develop a complete reference measurement system based on the concepts of metrological traceability, bearing in mind that, in addition to reference methods and materials, essential elements of a comprehensive reference measurement system include definition of the measurand (including the unit) with regard to the intended clinical use and the individuation of reference laboratories that possibly collaborate in a network (8, 9). For this project, the decision was made to define HbA1c as haemoglobin molecules having a special hexapeptide in common, which is the stable adduct of glucose to the N-terminal valine of the haemoglobin β-chain (βN-1-deoxyfructosylhaemoglobin). The rationale was that this quantity is biochemically well characterised, is the major form of HbA1c in human blood, and most of the commercial HbA1c tests claim to measure only this form. Two equivalent reference methods specifically measuring this hexapeptide were then developed, with a combination of high-pressure liquid chromatography (HPLC) and electron-spray mass spectrometry (MS) or, alternatively, a two-dimensional approach using HPLC and capillary electrophoresis (CE) with UV detection (10). The WG-HbA1c was also successful in preparing primary reference materials (purified HbA0 and HbA1c) to calibrate the reference procedures (11). In 2001, the IFCC reference methods were unanimously accepted by the National Societies of Clinical Chemistry following a ballot and published as approved IFCC reference methods (10). In the meantime, a network of laboratories was established, using either the HPLC-MS or the HPLC-CE option.

When comparing calibration of routine measurement systems to the IFCC HbA1c reference system, significant differences in results of routine procedures were found. This change results in HbA1c values being 25%–35% lower than currently reported. From a theoretical point of view, the decision-making system for the routine methods can be adjusted accordingly, and clinicians and patients educated concerning the change. To maintain the value of accumulated clinical experience, correlation of measurement results obtained with the new standardised calibra-

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Table 1 Suggested units and target values for HbA1c when measured with methods traceable to the IFCC reference system. A comparison with the current figures is also given.

	Current[a]	IFCC traceable methods
Reference interval (non-diabetics)	4–6%	20–42 mmol/mol
Target for treatment in diabetics[b]	<7%	<53 mmol/mol
Change of therapy in diabetics[b]	>8%	>64 mmol/mol

[a]Refer to methods aligned to the US National Glycohemoglobin Standardization Program. [b]As recommended by the American Diabetes Association.

tion to results of measurements obtained with the previous calibration should, however, be established. Adjustment of the decision-making criteria is of outstanding importance, since, even if the routine methods are biased from a metrological point of view, clinicians can still reach correct clinical decisions if the decision-making criteria they apply incorporate the same bias. In contrast, they could arrive at incorrect clinical decisions if patient HbA1c results are true with regard to the reference system, but the decision-making criteria are only valid by using the previous calibration for the test. Introduction of a new, even if more specific, measurement system theoretically requires the clinical validation trials to be repeated. In the case of HbA1c, reliable linear relationships between results traceable to the IFCC reference system for HbA1c and previous national and regional recommended methods have been demonstrated, allowing the conversion of analytical and clinical data from one system to another (12). It is therefore possible in practice to translate target values generated in previous landmark clinical studies, using methods not traced to the IFCC system, to maintain the clinical experience. In its document, the C-NPU proposes that "mmol/mol" be used as the unit of measurement for HbA1c; this represents the SI unit for this measurand (2). This option, i.e., the use of a completely different unit (mmol/mol instead of percentage), will avoid confusion when recalculating old HbA1c targets to the new IFCC standardised values if clinical laboratories wish to implement HbA1c results traceable to the IFCC reference system (Table 1). Other advantages of this approach may include a positive impact of changing the scale of reported HbA1c results, allowing clinicians and diabetic patients to better understand the biomarker changes (currently they may perceive small changes in percentage values – although linked to large health effects – as unimportant) and increased potential for future use of HbA1c as a diagnostic tool (13).

The question of reporting IFCC standardised results for HbA1c rather than "DCCT-aligned" results has been debated at some length (14, 15). It was agreed that the best strategy for change should involve a coordinated transition at international level. We think that the two papers published in this journal's issue may further contribute to this evolutionary process of standardisation that parallels the progress of scientific knowledge on the analytical and biochemical aspects.

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Note added to proof

At a type of "summit" meeting on May 4, 2007, representatives from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and IFCC agreed on some consensus statements on the ways to report HbA1c results. Here, we are pleased to present the Consensus Agreement, as follows:

1. ADA, EASD, and IFCC agree that HbA1c results should be standardized worldwide, including the reference system and results reporting.
2. ADA, EASD, and IFCC agree that the IFCC reference system for HbA1c represents the only valid anchor to implement standardization of the measurement.
3. ADA, EASD, and IFCC agree that the HbA1c results are to be reported worldwide in IFCC units (mmol/mol) *and* derived National Glycohemoglobin Standardization Program (NGSP) units (%), using the IFCC-NGSP master equation.
4. ADA, EASD, and IFCC agree that if the ongoing "average plasma glucose study" fulfils its *a priori* specified criteria, an HbA1c derived average glucose (ADAG) value will also be reported as an interpretation of the HbA1c results.
5. ADA, EASD, and IFCC recommend that all glycemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units, and as ADAG.
6. ADA, EASD, and IFCC agree that these recommendations should be implemented globally as soon as possible.

We believe that this Agreement will further contribute to the process of the worldwide comparability of HbA1c results, paralleling the progress of scientific knowledge related to the analytical and biochemical aspects and leading to better care for patients.

The signers of the agreement were:

For IFCC

Prof. Jocelyn Hicks, IFCC President
Prof. Mathias Mueller, IFCC Past President
Prof. Mauro Panteghini, IFCC Scientific Division Chair
Dr. Garry John, IFCC SD WG-HbA1c Chair

For ADA

Dr. Richard Kahn, ADA Chief Scientific and Medical Officer
Dr. John Buse, President-Elect, ADA
Prof. David Nathan, Harvard Medical School

For EASD

Prof. Ele Ferrannini, EASD President
Prof. Robert Heine, President-Elect, EASD