Glycated hemoglobin concentrations (most commonly 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 HbA$_{1c}$ 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 the US, 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 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 meet the requirements of the European Union directive on in vitro diagnostic medical devices (IVD), the 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 $\beta$ 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 $\beta$ chain ($\beta$N-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 HbA$_{1c}$ percentage values being lowered due to 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 IDF meeting in Montreal on October 21st, 2009. The American Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation, the IFCC and the International Society for
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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. HbA1c test results should be standardized worldwide, including the reference system and results reporting.
2. The IFCC reference system for HbA1c represents the only valid anchor to implement standardization of the measurement.
3. HbA1c 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-National Glycohemoglobin Standardization Program (NGSP) master equation (DCCT units).
4. 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 HbA1c in both SI (IFCC) and NGSP/DCCT units.
6. The reportable term for glycated hemoglobin is HbA1c 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.

HbA1c-derived average glucose values (ADAG) calculated from the HbA1c results were not included in the consensus due to the above mentioned limitations of this procedure. However, the use of an estimated average glucose (eAG) (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 to make 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 HbA1c methods as the master equation will be used in the laboratory instruments for calculating the DCCT units, i.e., 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 of instruments for measuring HbA1c, 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


Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References

Worldwide Standardization of HbA1c Measurement

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