Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

CONSENSUS COMMITTEE*

The hemoglobin A1C (A1C) assay has become the gold-standard measurement of chronic glycemia for over two decades. Anchored in the knowledge that elevated A1C values increase the likelihood of the microvascular complications of diabetes (and perhaps macrovascular complications as well), clinicians have used A1C test results to guide treatment decisions, and the assay has become the cornerstone for the assessment of diabetes care.

The clinical world has assumed that the A1C assay reflects average glycemia over the preceding few months. However, the data supporting that premise are not exceptionally robust (1–5); glucose concentrations were not measured frequently enough to compute a true "average." To gain a better understanding of the relationship between A1C and average blood glucose, an international study has been initiated to document this relationship, using frequent capillary measurements and continuous glucose monitoring. The results of this study will be known around September 2007. Although some clinicians are already providing patients with their "average blood glucose," by simply converting the current A1C test results (6) to a term more relevant to the values obtained from patient self-monitoring, the results of the study will hopefully provide a more accurate conversion algorithm.

Based on the work of the National Glycohemoglobin Standardization Program (NGSP) in the U.S. and other similar programs in other parts of the world, the current A1C assay has been harmonized on reference methods that measure a mixture of glycated hemoglobins (7–9). However, to achieve a more uniform standardization of A1C measurements, it is desirable to have a reference method that measures only a well-defined analyte. Accordingly, after several years of work, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a new reference method that specifically measures the concentration of only one molecular species of glycated A1C (10,11). Results by the new reference method have also been compared with the results obtained by current methodologies (12), and the relation between the assays can be expressed by simple regression equations ("master equations"). Of note, the new reference method is only used to standardize the A1C assay and cannot be used by clinical laboratories in their measurement of A1C.

In keeping with the measurement of other analytes, the IFCC has also suggested that the test results be provided in scientifically correct units, i.e., mmol/mol (13). The impact of both changes proposed by the IFCC would be to significantly change the numeric results provided to clinicians. For example, an A1C value of 5% would become ~33 mmol/mol and an 8% would be ~65 mmol/mol.

What are the implications of the above activities?

The advent of a new reference method to standardize the A1C results, along with the anticipated documentation that the assay does indeed indicate average blood glucose, has led to a variety of proposed changes in the reporting of A1C test results worldwide. To reach an agreement on a course of action, a meeting was held in Milan, Italy, on 4 May 2007, at which a consensus agreement emerged. The following statements have been approved by the American Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation, and the IFCC:

1. A1C test results should be standardized worldwide, including the reference system and results reporting.
2. The new IFCC reference system for A1C represents the only valid anchor to implement standardization of the measurement.
3. A1C results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.
4. If the ongoing "average plasma glucose study" fulfills its a priori–specified criteria, an A1C-derived average glucose (ADAG) value calculated from the A1C result will also be reported as an interpretation of the A1C results.
5. Glycemic goals appearing in clinical guidelines should be expressed in

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*A list of the Consensus Committee members can be found in the APPENDIX.

This article is being simultaneously published in 2007 in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

Abbreviations: ADAG, A1C-derived average glucose; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc07-9925

IFCC units, derived NGSP units, and as ADAG.

All the organizations agreeing with this consensus statement propose that these recommendations be implemented globally as soon as possible. We believe this agreement will further contribute to the worldwide comparability of A1C results, paralleling the progress of scientific knowledge related to the analytical and biochemical features of A1C testing. Expressing test results in scientifically correct units along with a clinically relevant interpretation of those results is not an uncommon practice (e.g., creatinine and estimated glomerular filtration rate). Consequently, clinicians will have the opportunity to convey the concept of chronic glycemia in terms and units most suitable to the patients under their care.

APPENDIX

Consensus Committee

For the IFCC: Jocelyn Hicks, PhD; Mathias Muller, MD; Mauro Panteghini, MD, PhD; and Garry John, PhD. For the American Diabetes Association: Larry Deeb, MD; John Buse, MD, PhD; David M. Nathan, MD; and Richard Kahn, PhD. For the European Association for the Study of Diabetes: Ele Ferrannini, MD, and Robert Heine, MD. For the International Diabetes Federation: Martin Silink, MD, and Jean-Claude Mbanya, MD.

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