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Recommendations for the implementation of international standardization of glycated hemoglobin in Italy[1)]

GLAD Working Group (A_{1c} delegates WG): Andrea Mosca (coordinator)[1,*], Maria Teresa Branca[2], Mariarosa Carta[3], Maria Ludovica Genna[4], Carlo B. Giorda[5], Rosangela Ghidelli[6], Germana Ghislandi[7], Dario Iafusco[8], Annunziata Lapolla[9], Vera Buondonno Lombardi[10], Carlo Augusto Lovagnini Scher[11], Maurizio Marra[12], Gerardo Medea[13], Franco Meschi[14], Andrea Pizzini[15], Francesco Rossi[16], Raffaele Scalpone[17], Gianni Tofini[18], Mariella Trovati[19] and Martina Zaninotto[20]

[1] Delegate from Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica (SIBioC), Università degli Studi di Milano, Italy
[2] Delegate from Operatori Sanitari di Diabetologia Italiani (OSDI), ASL Lecce, Italy
[3] Delegate from Società Italiana di Medicina di Laboratorio (SIMeL), ULSS6 Vicenza, Italy
[4] Delegate from Associazione Italiana Patologia Clinica e Medicina Molecolare (AIPaCMeM), Azienda Ospedaliera RN Cardarelli, Napoli, Italy
[5] Delegate from Associazione Medici Diabetologi (AMD), ASL Torino 5, Torino, Italy
[6] Delegate from OSDI, Azienda Ospedaliera S. Anna, Como, Italy
[7] Delegate from Associazione Italiana Diabetici (FAND), Milano, Italy
[8] Delegate from Società Italiana di Endocrinologia e di Diabetologia Pediatrica (SIEDP/ISPED), II Università di Napoli, Napoli, Italy
[9] Delegate from Società Italiana di Diabetologia (SID), Università degli Studi di Padova, Italy
[10] President of FAND, Milano, Italy
[11] Delegate from AMD, ASL 3, Monza, MI, Italy
[12] Delegate from SIMeL, INRCA IRCCS, Ancona, Italy
[13] Delegate from Società Italiana di Medicina Generale (SIMG), Azienda Ospedaliera di Brescia, Italy
[14] Delegate from SIEDP/ISPED, IRCCS S. Raffaele, Milano, Italy
[15] Delegate from Federazione Italiana Medici di Famiglia (FIMMG), ASL Torino 2, Torino, Italy
[16] Delegate from AIPaCMeM, Azienda Ospedaliera RN Cardarelli, Napoli, Italy
[17] President, Associazione Italiana per la Difesa dei Diabetici (AID), Ospedale INI, Grottaferrata, Roma, Italy
[18] Delegate from AID, Ospedale INI, Grottaferrata, Roma, Italy
[19] Delegate from SID, Università degli Studi di Torino, Italy
[20] Delegate from SIBioC, Azienda Ospedaliera di Padova, Italy

Abstract

This document is issued by the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) and a number of other National Scientific Societies and Associations in order to promote a coordinated plan for implementing the standardization of glycated hemoglobin (HbA_{1c}) measurement in Italy according to the recommendations by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Changes in reporting HbA_{1c} results, new units, how to relate old and new units, a timeline for changes and definition of the analytical goals are the main issues discussed.
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Keywords: Diabetes Control and Complication Trial; external quality assessment; National Glycohemoglobin Standardization Program.

Introduction

Glycated hemoglobin (HbA_{1c}) is routinely measured in patients with diabetes mellitus to monitor their glycemic and metabolic control in the medium to long term (1, 2). This practice is the outcome of several randomized clinical trials, the most important of which are the ''Diabetes Control and Complication Trial'' (DCCT) and the ''UK Prospective Diabetes Study'' (UKPDS). These studies demonstrated a close correlation between glycemic control, as evaluated by measuring HbA_{1c}, and the risk of onset and progression of chronic diabetic complications (3, 4).

To enable their use worldwide, HbA_{1c} measurement procedures needed to be standardized. Thus, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) formed a study group to address this issue in 1995 (IFCC WGHbA_{1c}). Thanks to the activities of the WGHbA_{1c}, a reference measurement procedure is now available (5), two primary reference materials have been produced (6), an international network of reference laboratories for HbA_{1c} has been implemented (7) and master equations have been devel-

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*Corresponding author: Prof. Andrea Mosca, Università degli Studi di Milano, L.I.T.A.Via Fratelli Cervi 93, 20090 Segrate, Italy
E-mail: Andrea.mosca@unimi.it
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oped to convert the findings obtained with the IFCC reference system into results aligned with the system of the ''National Glycohemoglobin Standardization Program'' (NGSP) (8).

All the producers of systems/reagents for HbA_{1c} have been involved in this alignment to the IFCC reference system. Also, secondary reference materials will soon be produced in cooperation with the Institute for Reference Materials and Measurements (IRMM).

In May 2007, in an attempt to adopt a common strategy for implementation of a new reference system, a group of experts representing the principal scientific societies – the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the International Diabetes Federation (IDF), and the IFCC met to voice an opinion on a standardized method, the unit to be used, and the feasibility of reporting, in addition to the HbA_{1c} value, an estimated average glucose (eAG) concentration [A_{1c}-Derived Average Glucose (ADAG)] on the strength of the results of a clinical trial that was not yet completed at this time.

The conclusions reached at this meeting (9) were the following:

1. All HbA_{1c} test results should be standardized worldwide, including the reference system and the method used for reporting results.
2. The new IFCC reference system for HbA_{1c} represents the only valid tool for obtaining standardized HbA_{1c} measurements.
3. HbA_{1c} results should be reported everywhere in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.
4. If the ongoing ADAG study fulfills the criteria specified a priori, then an ADAG value calculated from the HbA_{1c} result should also be reported for interpretation of the HbA_{1c} value.
5. All HbA_{1c} values appearing in clinical guidelines as targets for glycemic control should be expressed in IFCC units (mmol/mol), and NGSP units (%), and with a value for the eAG.

Following publication of this document, there was a second meeting involving representatives of the IFCC and the companies that manufacture this test. At this meeting, further issues were agreed upon and were subsequently published (10). The points are summarized below.

- All manufacturers of the diagnostic test should be aligned to the IFCC reference system by December 31, 2009, at the latest.
- The name of the test will be HbA_{1c} and not A_{1c} (as used primarily in the USA).
- All the instruments brought onto the market after January 1, 2011 should report results in IFCC units (mmol/mol) and in derived units, as in the NGSP system (%).
- The analytical systems should not report the eAG value, calculated on the basis of the results of the ADAG study, together with the HbA_{1c}. Laboratory professionals can report this finding using their laboratory computer system.
- The control materials used for external quality assessment (EQAS) should be commutable and have an HbA_{1c} assigned using the IFCC reference method. The limit for total allowable error should be clearly defined in the EQAS programs.
- The $WGHbA_{1c}$ will be available to provide diagnostic support for manufacturers during the process of alignment to the IFCC reference system.

What now remains to be dealt with is the reference system's deployment at the end user level (at public health laboratories and diabetes treatment centers, amongst general practitioners and patients). In Italy, a working group was created for this purpose. This group established a set of objectives, as explained below, with recommendations for accomplishing each of these goals.

Aims

The main aims of the working group were:

- to establish the total allowable error for HbA_{1c} measurements;
- to provide a statement on the feasibility of reporting the eAG value, calculated using the equation in the ADAG study, together with the HbA_{1c} measurement;
- to decide which units to be used for reporting HbA_{1c};
- to decide on the phases and timing of the process for implementing the standardized method at the national level in Italy;
- to design strategies for a related information campaign.

The total allowable error for HbA_{1c} measurement

The goal for the total error of a laboratory test result can be defined on the basis of data on the biological variability, the state of the art of the measurement methods used, and related clinical utility criteria. By choosing the last of these, we can make recommendations (according to evidence-based medicine) by starting from the results of the DCCT study. In this study, patients with poor glycemic control had $HbA_{1c} > 8\%$, and values in patients with good glycemic control were $< 7\%$ (3). Based on these results, we concluded that the goal for total error in HbA_{1c} measurements should not exceed $\pm 0.5\%$ of the true HbA_{1c} value. To correctly classify a subject who has a true HbA_{1c} value of 7.5%, measurement error must not exceed 0.5% in absolute terms (equating to a relative total error of 6.7%), in order to avoid classifying the subject as having poor glycemic control ($HbA_{1c} > 8\%$), or good control ($< 7\%$).

Since the total error of a single measurement derives from the combination of its imprecision and bias (11), different combinations of imprecision and bias can comply with this limit (e.g., CV = 3.0% and bias = 1.8%; or CV = 1% and bias = 5.1%). However, the recommendation that was agreed

upon was that imprecision should preferably be no more than 2% (12).

Recommendation no. 1

1. The goal of the total allowable error is ±6.7% (as a percentage fraction of the absolute HbA_{1c} value).
2. The long-term imprecision of the method should be no more than 2%.
3. Participating in EQAS programs, in which commutable materials are used, and adopting HbA_{1c} values assigned using the IFCC reference measurement procedure, are the best way to establish whether measurements that are obtained meet the standards for total error stated above.

Reporting average glucose based on the HbA_{1c} measurements

Converting HbA_{1c} measurements into average glucose estimates might improve the understanding and interpretation of the HbA_{1c} values. A recently published clinical trial prompted the recommendation that the mean blood glucose, or eAG, estimated on the basis of HbA_{1c} measurements be used (13). However, the study in question had several weaknesses that need to be considered. For instance, it did not include any adolescents, pregnant women, patients with renal disease or individuals of Asian ethnicity. In addition, the eAG confidence intervals were so wide that these data would be of little clinical value. Unlike other calculated laboratory parameters [e.g., glomerular filtration rate based on the concentration of serum creatinine and the individual's gender and age; or low density lipoprotein (LDL) cholesterol based on total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides], converting HbA_{1c} into eAG by means of an equation containing only numerical factors does not add any useful clinical information to the HbA_{1c} value alone.

Recommendation no. 2

Reporting eAG based on HbA_{1c} measurements using the equation proposed by the ADAG study has many limitations. We do not recommend systematic use of the eAG.

Units and new numbers for HbA_{1c}

The IFCC reference method enables direct and specific measurement of the portion of hemoglobin that is glycated, in particular, the terminal hexapeptides of the β-chain of hemoglobin. To define the analyte precisely, the introduction of a new unit (mmol/mol) was proposed because the previous unit (%) was not aligned with the international system of measurements (SI) (14). Using the new IFCC reference system involves a change in units used and new reference intervals, i.e.,

- reference interval (for non-diabetic individuals) (DCCT-aligned results): 4.0–6.0%;
- reference interval (for non-diabetic individuals) (IFCC-aligned results): 20–42 mmol/mol.

Table 1 Relationship between the NGSP-aligned HbA_{1c} values (used in DCCT) and IFCC-aligned HbA_{1c} values.

NGSP-aligned, %	IFCC-aligned, mmol/mol
4.0	20
5.0	31
6.0	42
7.0	53
8.0	64
9.0	75
10.0	86

The relationship between these two methods for reporting results is as follows: DCCT-aligned HbA_{1c} (%) = 0.0915 × IFCC-aligned HbA_{1c} (mmol/mol) + 2.15. The relationship between HbA_{1c} values expressed in different units is shown in Table 1.

It is important to emphasize that standardization with the IFCC reference method reduces the uncertainty of the final result because conversion of the result using the equation mentioned previously (15) introduces another uncertainty, that has been calculated and subsequently proven (16). For instance, if a sample measured using the IFCC system has an HbA_{1c} value of 53 mmol/mol, and this value is associated with an uncertainty of 0.42 mmol/mol (0.8%), the subsequent processing in NGSP/DCCT units will raise this uncertainty to 0.47 mmol/mol (0.9%). Though this increase in the uncertainty is small, it cannot be ignored.

Another benefit derived from the use of mmol/mol units is that this enables an approximate 10-fold amplification in the number that is obtained. Thus, so small changes in HbA_{1c} should be easier to identify.

Recommendation no. 3

1. HbA_{1c} should be measured using methods calibrated to the IFCC reference system.
2. The result should be reported in mmol/mol and % units derived using the conversion equation described above.
3. For a limited period of time, the HbA_{1c} value will be expressed in laboratory reports using conventional units (%) followed by the IFCC units (mmol/mol). The conventional units will subsequently be omitted.

Phases and timing

Recommendation no. 4

Beginning on January 1, 2010, HbA_{1c} results will be expressed in units aligned with the DCCT system (%) and in standardized IFCC units (mmol/mol). Next, beginning on January 1, 2012, HbA_{1c} results will be expressed in IFCC units (mmol/mol) only.

Information campaign

An information campaign should be organized that focuses on all stakeholders (medical laboratories, general practitioners, diabetologists and diabetic patients, and all medical specialists involved in managing diabetic patients) to ensure a synchronous and smooth transition to the new IFCC reference system throughout the country. This campaign will be conducted by all of the scientific societies and associations involved in writing this document, using whatever means of communication they have at their disposal (e.g., memos to members, reports at conferences, articles in journals, ''ad hoc'' papers, etc). This effort shall be consistent with the timing of the transition to the new IFCC reference system.

If necessary, the authors of this document will be willing to produce specific material to support those involved in the information campaign, and specific material will be prepared for use by diabetic patients.

Conclusions

Laboratory professionals should ask manufacturers of diagnostic kits for evidence of their alignment to the IFCC reference system in order to establish, beginning with the production process, alignment with the reference system and the related uncertainty. They should check and monitor their alignment by routinely participating in EQAS programs that use commutable control materials, with titers assigned using the reference measurement procedure, considering the previously-mentioned limit for total error as the analytical goal.

Using the recommendations contained in this document and suitable surveillance of the procedures will hopefully contribute significantly to reducing inter-laboratory variability in the measurement of HbA_{1c}, and to providing a better service for patient care.

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