Global Harmonization of Hemoglobin A1c

Measurement of glycohemoglobin (GHb) is widely used in patients with diabetes mellitus as a monitor of long-term glycemic control (1–3). In addition, prospective randomized clinical trials, most notably the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have demonstrated that GHb is a measure of the risk for the development of diabetes complications (4,5). GHb is therefore an integral component of the management of patients with diabetes.

GHb comprises several different hemoglobin–glucose adducts, including hemoglobin A1a (HbA1a), HbA1b, and HbA1c. More than 30 different methods are commercially available to measure GHb. Together these factors have led to considerable variation in reference intervals and results reported by different laboratories. When the DCCT was published in 1993, the lack of standardization of GHb methods produced very wide variability among methods, with values ranging from 4.0% to 8.1% on the same blood sample (6). In the United States, the NGSP (previously known as the National Glycohemoglobin Standardization Program) has reduced interlaboratory variation (7). Using a standardization process based on the DCCT reference method, the NGSP has promoted a dramatic improvement in comparability of GHb values among laboratories (3). Data from the 2003 GH2 survey from the College of American Pathologists indicated that ≥98% of participating laboratories use NGSP-certified methods and report results as HbA1c or HbA1c equivalents (3). Analogous standardization programs in Sweden and Japan (8,9), established to harmonize GHb results, have also reduced variability among GHb results. More recently, the IFCC Working Group on HbA1c Standardization prepared primary reference materials of pure HbA1c and HbA0 and developed a reference method for HbA1c (10). They defined HbA1c as the stable adduct of glucose to the N-terminal valine of the β-chain of hemoglobin. In the reference method, hemoglobin is cleaved by endoproteinase Glu-C. The resulting glycated and non-glycated N-terminal hexapeptides are separated by HPLC, followed by quantification by electrospray ionization mass spectrometry or capillary electrophoresis (10). HbA1c is measured as the ratio of glycated to nonglycated N-terminal peptide and is reported as a percentage. Comparison of pooled blood samples revealed a linear relationship between HbA1c results of the IFCC reference method and the standardization schemes in the United States, Japan, and Sweden (11). For example, the calculated regression equation for NGSP

\[ \text{NGSP-HbA1c} = 0.915 \times \text{IFCC-HbA1c} + 2.15\% \]

provides a numeric link between the IFCC and NGSP values (11). An important observation of the comparison is that HbA1c results obtained by the IFCC method are significantly lower (~1.3–1.9% across the relevant HbA1c range) than NGSP results. These findings have generated considerable debate as to how HbA1c should be reported. A brief synopsis of the planned strategy to resolve this issue is outlined below.

A working group, termed the ADA/EASD/IDF Working Group of the HbA1c Assay, was established in 2004 to harmonize HbA1c reporting. Members of the Workgroup included representatives from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF). There was unanimous agreement that the same HbA1c values should be reported globally. The fundamental question was what system should be used. Should HbA1c be reported using the IFCC numbers, which would lead to a pronounced lowering of individual values? Alternatively, should the outcomes-based NGSP/DCCT/UKPDS values be used, which would not change reported results? (Note that the HbA1c assays used in the DCCT and UKPDS were equivalent and the numbers are thus directly comparable.) The advantages and disadvantages of each approach are listed in Table 1. The crucial

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>The reported values reflect the actual values</td>
<td>High cost and prolonged timeline for education necessary to prevent confusion</td>
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<td>Opportunity to reeducate professionals and persons with diabetes about meaning and value of the HbA1c test</td>
<td>Partial or piecemeal implementation will worsen existing differences among laboratories</td>
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<tr>
<td>Opportunity to redefine HbA1c (see below)</td>
<td>Risk of deterioration in glucose control, as experienced in a Swedish study</td>
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<td>Relates HbA1c values to existing evidence base, e.g., UKPDS and DCCT</td>
<td>Lower numbers make it even more difficult to convince patients that small changes in percentage of HbA1c have a big impact on health</td>
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<tr>
<td>Familiar to patients and clinicians</td>
<td>Not the “pure” result</td>
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<tr>
<td>Not the “pure” result</td>
<td>Frequently confused with glucose concentrations in countries where mmol/L is used</td>
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<tr>
<td>Missed opportunity to reinforce the importance of the test</td>
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*Adapted from Ref. (24).*
question is whether to change the numbers. Changing to the more specific IFCC values could potentially create confusion and will require a long education process. Alternatively, the NGSP values, which were used in both the DCCT and UKPDS and are familiar to clinicians and patients, include substances that are not HbA1c.

It was noted that the name of the assay, HbA1c or A1c test, is confusing. Many patients believe the name suggests a blood disorder and has no relationship to diabetes. An important consideration is that the low values (the reference interval for NGSP-certified methods is ~4–6%, whereas that for the IFCC method is 2.8–3.8%) do not convey to patients that a change of 0.5% has a major impact on health. Patients may gain the erroneous impression that they have improved if reference intervals are lowered. This concept is supported by a study of 49 patients, which indicated that metabolic control deteriorated when the HbA1c results were reported on a lower scale (12).

A retrospective examination of seven-point capillary blood glucose profiles obtained during the DCCT identified a linear relationship between HbA1c and mean blood glucose (MBG) (13). Conversion of the HbA1c values from the study by Rohlfing et al. (13) to IFCC numbers yields a relationship of

\[
\text{MBG (mmol/L)} = 1.84 \times \text{IFCC-HbA1c}
\]

If this relationship can be confirmed in a prospective study, there will be an opportunity to report HbA1c to indicate mean blood glucose. Advantages of this approach include clear revision of the test with a new reference interval that will avoid confusion (although substantial reeducation will be necessary); a simplification of the range, allowing an individual with diabetes to understand his/her own target value (particularly if already using home glucose monitoring); and increased potential for future use as a diagnostic modality. Disadvantages include the possibility that the simple proportionality may not apply to all populations or to extremes of HbA1c, that results will be reported in different units in different countries (mmol/L and mg/dL), and that instruments will report out a value after manipulation by a conversion factor rather than a direct measurement.

Notwithstanding these caveats, the Workgroup decided to proceed with the innovative approach to implement the new standard. A series of steps were recommended (Table 2). The first three recommendations should be executed immediately. The IFCC reference method should be adopted as the global standard for calibration of all instruments and methods that measure HbA1c. Manufacturers have been directed that they should not change the values that are reported. Thus, the DCCT/UKPDS numbers, which are the most widely used at present, should continue to be used. Similarly, the current ranges and numbers should continue to be reported in those countries, e.g., Japan and Sweden, that use values different from those of the DCCT/UKPDS.

Several initiatives were proposed for the next 6 months to 3 years. In addition to determining whether there are retrospective data that can link HbA1c to MBG, prospective studies are planned. The goal is to ascertain whether the linear relationship between HbA1c and MBG is confirmed by prospective analysis in different populations worldwide. Finally, programs to inform and educate both professionals and the general public about the new reporting system will be planned.

The recommendations have been endorsed by the ADA, EASD, IDF, and NGSP. The CDC is participating and supports the approach of the initiative. A follow-up meeting was held in September 2004 at which several critical questions that need to be answered were identified: Is there a relationship between HbA1c and MBG in type 1 and type 2 diabetes and in all ethnic groups? Is the relationship the same at different MBG concentrations? Do fluctuations in glucose concentrations at the same MBG value alter HbA1c? Is the relationship between HbA1c and MBG stable when MBG is increasing and decreasing? Do medications or pregnancy alter the relationship?

A subcommittee was established to design the core protocol for the prospective analysis. The charge to the subcommittee includes developing the protocol, preparing a document for the Request for Proposals, participating in selecting the successful proposals, and inviting input into the study design from the experts at the centers selected for participation. The main Working Group will review the proposals and make the final selection. The fundamental concept is that HbA1c will be compared with MBG. The latter will be derived from 48-h continuous glucose monitoring, supplemented by measurement of capillary blood glucose at least eight times a day. Concurrent HbA1c measurements will be performed. Patients with type 1 and type 2 diabetes (in stable glycemic control), as well as healthy controls, will be evaluated. A timetable was established to expedite the process. The protocol should be completed and resources obtained by January 2005. Funds have been set aside by the EASD and

### Table 2. Recommendations of the ADA/EASD/IDF Working Group of the HbA1c Assay.

| Immediate | 1. Adopt the IFCC reference method as the new global standard for calibration of HbA1c assays by manufacturers  
| 2. Use the new IFCC methodology to anchor an “international certification process” within the existing international laboratory networks  
| 3. Direct manufacturers not to change the HbA1c values reported until further work (outlined below) has been completed, i.e., DCCT/UKPDS range and numbers will continue to be used  |
| Next 3 years | 1. Determine whether there are other retrospective data that can be used to link HbA1c to MBG. In particular, data for patients with type 2 diabetes would be valuable  
| 2. Design and conduct prospective studies on diverse populations worldwide to confirm/establish the HbA1c/MBG relationship  
| 3. Plan public and professional information programs about the new reporting system  |

*Adapted from Ref. (14).
ADA. Centers should be selected by April 2005 and patients recruited by June 2005. Studies should be completed by June 2006 to allow preliminary findings to be reported at the 19th IDF World Diabetes Congress in December 2006.

The results of the planned studies are expected to enhance our understanding of the relationship between HbA1c and MBC. In addition, it is hoped that the findings will lead to an improved method to monitor long-term glycemic control. It is very encouraging that so many major organizations that have an active interest in improvement of the health of individuals with diabetes are working together on this initiative. We eagerly look forward to true global harmonization of HbA1c.

The members of the ADA/EASD/IDF Working Group of the HbA1c Assay are as follows: Jean Claude Mbanya (IDF; Chair); Robert Heine (EASD); Edward Horton (ADA); Ryuzo Kawamori (IDF); Sally Marshall (IDF); Jørn Nerup (EASD); Tony O'Sullivan (IDF); Thomas Pieber (EASD); Ambady Ramachandran (IDF); Robert Rizza (ADA); Frank Vinicor (ADA); Kor Miedema (IFCC); David Sacks (NGSP); staff, Richard Kahn (ADA).

References

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