Position Statement

Title
Recommended Changes in HbA1c Reporting Units for Australian Laboratories

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Recommended Changes in HbA1c Reporting Units for Australian Laboratories

Position Statement of the Australasian Association of Clinical Biochemists

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Executive Summary

This Position Statement is supported by the AACB Executive and also by the Executive Groups of the Royal College of Pathologists of Australasia (RCPA), Australian Diabetes Society (ADS) and Australian Diabetes Educators Association (ADEA).

Changes in HbA1c Reporting Units are already occurring around the world.

This Position Statement recommends a change in the routine HbA1c reporting unit in Australian laboratories from the current DCCT/NGSP ‘%’ unit to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) unit ‘mmol/mol’.

To facilitate a smooth transition to this new IFCC unit and enable time for promotion and education of the new unit, the AACB recommends a period of dual reporting of both NGSP % and IFCC mmol/mol units after which only the IFCC unit will be reported. Operative dates for changes in HbA1c reporting units are yet to be decided by AACB, RCPA, ADS and ADEA, but are the subject of ongoing discussion.

The AACB does not formally endorse routine reporting of estimated average glucose (eAG) on laboratory reports.

Conversion of old and new units, targets, decision levels, and reference ranges are provided within the AACB Position Statement.

The AACB, in partnership with the RCPA, ADS and ADEA, will actively support their members, and the diabetes industry, and other health professionals to promote and interpret the new units throughout the transition period.
Background

Currently, HbA1c values are reported worldwide in three different units with different calibrators and different values. These are USA (%DCCT/NGSP) using Biorex 70 cation exchange HPLC methodology and calibration, Sweden (%Mono S cation exchange HPLC methodology), and Japan (%K0500 cation exchange HPLC methodology). All these methodologies are relatively non-specific.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) HbA1c Working Group on Standardisation of HbA1c, formed in 1994, which includes Australian participation, has developed reference methodology, purified reference calibrators, and an international network of reference laboratories. The IFCC Network laboratories are monitored twice per year, and now are used to calibrate all HbA1c manufacturers and HbA1c analytical assays and analysers worldwide. (1,2)

The IFCC reference system is not affected by confounding substances responsible for the non-specificity in other methods. IFCC and DCCT/NGSP Unit Conversions are traceable to stable Reference Laboratory comparisons (Master Equations) performed over the past 10 – 12 years. (2)

Conversion formulae between DCCT/NGSP and IFCC units are as follows:-

\[
\text{IFCC HbA1c unit (mmol/mol)} = 10.93 \times \text{DCCT/NGSP unit (%)} - 23.50
\]

\[
\text{DCCT/NGSP HbA1c unit (%)} = 0.09148 \times \text{IFCC unit (mmol/mol)} + 2.152
\]

A guide to the new HbA1c values expressed as mmol/mol is provided in Table 1.

Table 1. Comparison between HbA1c values under old and new reporting units

<table>
<thead>
<tr>
<th>Current DCCT/NGSP aligned HbA1c (%)</th>
<th>New IFCC HbA1c (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>20</td>
</tr>
<tr>
<td>5.0</td>
<td>31</td>
</tr>
<tr>
<td>6.0</td>
<td>42</td>
</tr>
<tr>
<td>6.5</td>
<td>48</td>
</tr>
<tr>
<td>7.0</td>
<td>53</td>
</tr>
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<td>7.5</td>
<td>59</td>
</tr>
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<td>8.0</td>
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<tr>
<td>9.0</td>
<td>75</td>
</tr>
<tr>
<td>10.0</td>
<td>86</td>
</tr>
<tr>
<td>12.0</td>
<td>108</td>
</tr>
</tbody>
</table>


**Targets and Reference Ranges in new units**

- The old DCCT/NGSP target of 7.0%, or now commonly 6.5%, will in future be 53 and 48 mmol/mol respectively.
- The now no-longer recommended ‘Change of Therapy’ level of 8.0% will be 64 mmol/mol.
- The old DCCT/NGSP reference range of 4.0 – 6.0% HbA1c will be reported as 20 – 42 mmol/mol HbA1c.

**Discussion**

**Why does the AACB support the changeover to IFCC units?**

The AACB supports the staged replacement of the current NGSP ‘%’ unit with the new IFCC ‘mmol/mol’ unit for the following reasons:

1. The adoption of the reporting of HbA1c in IFCC units is consistent with recommendations in the published consensus statement produced jointly by the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Diabetes Federation (IDF), following a meeting in Milan on 4 May 2007 (3). These recommendations included:
   - A1c test results should be standardised worldwide, including the reference system and results reporting.
   - The new IFCC reference system for A1c represents the only valid anchor to implement standardisation of the measurement.
   - A1c results are to be reported worldwide in IFCC units (mmol/mol), and derived NGSP units (%) using the IFCC-NGSP master equation (3).

2. Due to the highly specific nature of the IFCC standardisation system, the new IFCC unit provides results which are more scientifically valid and accurately reflect the true HbA1c concentrations in patient samples.

3. The numerical values for the IFCC units are significantly different to those of the current NGSP units (for example 42 mmol/mol compared to 6%) and are therefore less likely to be confused with the numerical results seen with plasma glucose results (of the order of 5-10 mmol/L).

**Why does the AACB not endorse Estimated Average Glucose (eAG)?**

The May 2007 Milan meeting also recommended that if ‘the ongoing ‘average plasma glucose study’ (4) fulfils its “a priori- specified” criteria, an A1c-derived average glucose (ADAG) value [now more commonly termed estimated average glucose (eAG)] will also be reported as an interpretation of the A1c results.’
The AACB is concerned about selected aspects of the now-completed ADAG study and the general transferability of results of this study. Therefore the AACB does not formally endorse routine reporting of estimated average glucose (eAG) on laboratory reports at this time. However eAG may be used at the discretion of the individual clinician as an educational tool for people with diabetes. This lack of endorsement of eAG is also supported by RCPA, ADS, ADEA and the New Zealand Society for the Study of Diabetes (NZSSD) in addition to all European Union countries, except for Denmark, that have set protocols and dates for the HbA1c Unit change.

In summary, the ADAG study (4) was performed in eleven centres in the USA, Europe and Africa in an attempt to define the exact relationship between HbA1c and glucose. The study included a total of 507 subjects, including 268 patients with Type 1 diabetes, 159 patients with Type 2 diabetes and 80 non-diabetic subjects. Patients were between 18-70 years, and diabetic subjects had stable control, defined as HbA1c values within 1.0% HbA1c over a six month period, with a range of HbA1c up to approximately 12% HbA1c. The a-priori quality criterion for the ADAG study was that 90% of values should fall within plus or minus 15% of the regression line.

Issues of concern about the ADAG study include:

- There was considerable scatter around the regression line used to convert HbA1c results to eAG, and consequentially gross discrepancies between any HbA1c value and the possible range of eAG values. This effectively means that the precise values achieved by current HbA1c assays would be replaced with an imprecise value of HbA1c if converted to eAG via the ADAG regression line/equation,

- The relatively small number of patients for such a major worldwide study; with very limited numbers in every patient category, very few patients with poor control, Asian ethnic groups were underrepresented and children excluded from the study

Further arguments against routinely reporting eAG include:

- The potential for significant patient and clinician confusion over the response to eAG (decision about long term management changes) and single blood glucose measurement (decision about immediate treatment changes),

- The range of values in patients using calculated eAG is much narrower than from spot glucoses. For example spot glucoses of 7.0 and 10.2 mmol/L are close and well within the variation of even well controlled diabetic patients, but the HbA1c results which generate these two values as an eAG are markedly different as HbA1c. These are 6.0% and 8.0% respectively, which represent the upper limit of normal of HbA1c and the old ‘Change of Therapy’ for diabetic management/treatment changes for severely tightening diabetes control and increasing diabetes medications,

- Most Type 2 diabetics perform very limited home glucose monitoring and the number of patients with eAG measured as eAG in their homes is negligible.
**Changeover in Units Across the World**

The changeover to different HbA1c units across the world has commenced in earnest; however individual countries have different viewpoints on their choice of reporting units and the time frame of implementation. Table 2 summarises progress made in various countries (information correct at the time of writing, June 2010).

**Table 2. Summary of progress made by selected countries for change in HbA1c reporting units**

<table>
<thead>
<tr>
<th>Country</th>
<th>Old Units</th>
<th>Reporting of Dual Units</th>
<th>Global Unit</th>
<th>eAG/ADAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%DCCT</td>
<td>%DCCT, mmol/mol</td>
<td>mmol/mol</td>
<td>- to be</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Commencement date</td>
<td>- Commencement date</td>
<td>reported</td>
</tr>
<tr>
<td>Australia</td>
<td>%DCCT</td>
<td>To be confirmed</td>
<td>To be confirmed</td>
<td>No</td>
</tr>
<tr>
<td>Austria</td>
<td>%DCCT</td>
<td>No dates yet</td>
<td>No dates yet</td>
<td>No</td>
</tr>
<tr>
<td>Denmark</td>
<td>%DCCT</td>
<td>1/1/2010*</td>
<td>No dates yet</td>
<td>Yes</td>
</tr>
<tr>
<td>Finland</td>
<td>%DCCT</td>
<td>3/3/2010**</td>
<td>No dates yet</td>
<td>No</td>
</tr>
<tr>
<td>Germany</td>
<td>%DCCT</td>
<td>1/1/2009</td>
<td>1/1/2010</td>
<td>No</td>
</tr>
<tr>
<td>Italy</td>
<td>%DCCT</td>
<td>1/1/2010</td>
<td>1/1/2012</td>
<td>No</td>
</tr>
<tr>
<td>Netherlands</td>
<td>%DCCT</td>
<td>6/4/2010</td>
<td>1/1/2011</td>
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<tr>
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<td>%DCCT</td>
<td>1/8/2009</td>
<td>1/8/2011</td>
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<tr>
<td>UK</td>
<td>%DCCT</td>
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<td>1/6/2011</td>
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<tr>
<td>Sweden</td>
<td>%Mono S</td>
<td>Mono S, mmol/mol</td>
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<tr>
<td></td>
<td></td>
<td>1/9/2010</td>
<td>1/1/2011</td>
<td>No</td>
</tr>
<tr>
<td>USA***</td>
<td>%DCCT</td>
<td>%DCCT</td>
<td>%DCCT</td>
<td>****</td>
</tr>
</tbody>
</table>

* Denmark is reporting dual units (%DCCT, mmol/mol) as from 1/1/2010, together with automatic eAG to produce all three units on laboratory reports.

** Finland is reporting dual units (%DCCT, mmol/mol) as from 3/3/2010. eAG can be reported but is not mandatory. eAG must be requested separately to HbA1c.

*** The USA has not announced any changes in their HbA1c Units. They do not report any pathology in SI Units at all.

**** The USA Position on eAG is detailed as “the American Diabetes Association (ADA) and the American Association for Clinical Chemistry (AACC) have determined that the correlation (r=0.92) obtained in the ADAG study (Reference 4) is strong enough to justify reporting both an A1c result and an estimated average glucose (eAG) when a clinician orders the A1c test.” Diabetes Care 2010; 33 (Supplement 1): S19.
Conclusion

The AACB very strongly supports the change of HbA1c units from the current %DCCT/NGSP to be expressed as IFCC mmol/mol. An appropriate transition period to the new units will allow clinicians and diabetes health professional's time to familiarise and educate themselves with the new reporting system and be able to interpret the results for their patients. However in the long term it is not desirable to maintain two reporting methods for the same assay and the old NGSP% unit should be ultimately abandoned.

References