



## Standardisation of reporting haemoglobin A<sub>1c</sub>: adoption of the New Zealand Society for the Study of Diabetes (NZSSD) position statement

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The haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) assay has become the gold-standard measurement of chronic glycaemia, providing an integrated index of glycaemic control over the preceding 2–3 months and with elevated values related to increased risk of microvascular and probably macrovascular complications of diabetes mellitus.<sup>1</sup> The present article describes some of the issues related to HbA<sub>1c</sub> and how global initiatives have addressed the non-standardisation of this assay, culminating in a major international consensus statement, with implications for the way HbA<sub>1c</sub> is reported world-wide from clinical laboratories.

At a meeting in Milan on 4 May 2007 a consensus statement on the worldwide standardisation of HbA<sub>1c</sub> measurement was endorsed 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). This statement was published in three journals<sup>1–3</sup> with the recommendation for implementation “globally as soon as possible”.

The key tenets of the consensus statement, with implications for the way HbA<sub>1c</sub> is reported from clinical laboratories are:

- HbA<sub>1c</sub> results are to be reported world-wide in IFCC units (mmol/mol) AND:
- Derived National Glycohaemoglobin Standardisation Program (NGSP) units (%), using the IFCC-NGSP master equation. (*i.e. what is currently reported by clinical laboratories*)
- If the ongoing “average plasma glucose study” fulfils its *a priori* specified criteria, an HbA<sub>1c</sub> derived average glucose value calculated from the A<sub>1c</sub> result will also be reported as an interpretation of the A<sub>1c</sub> results.

After consultation with its membership, NZSSD produced a Position statement (see Appendix 1 at the end of this article) and endorsed recommendations 1 and 2 above, although not 3 for reasons to be discussed. These recommendations have now been implemented in New Zealand clinical laboratories from 03 August 2009.

[http://www.nzssd.org.nz/position\\_statements/standardisation.html](http://www.nzssd.org.nz/position_statements/standardisation.html)

### The background to these recommendations

HbA<sub>1c</sub> came to the fore with the publication of the DCCT trial<sup>4</sup> in 1993 and subsequently the UKPDS study (in Type 2 diabetes).<sup>5</sup> Both studies showed that there was a curvi-linear positive relationship between HbA<sub>1c</sub> values and diabetes complications and enabled the setting of targets for management ( $\leq 7\%$  is desirable)<sup>6</sup>

and in some centres, a change of therapy is recommended at levels above 8%. However, it became apparent at the time of the DCCT trial that there were widely differing HbA<sub>1c</sub> results between laboratories, reflecting widely different analytical principles and also the lack of standardisation between assays.

The DCCT trial employed a high performance liquid chromatography (HPLC) method called the “Biorex-70”. In recognition of the need for better harmonisation between assays, the National Glycohaemoglobin Standardisation Program (NGSP) (<http://www.ngsp.org>) was established in the USA. This organisation developed a network of reference laboratories and produced standards, based on whole blood samples, with HbA<sub>1c</sub> values traceable to the “Biorex-70” method. This enabled traceability of results to the DCCT method and thus to the patients and clinical outcomes in that landmark trial. Working through both manufacturers and clinical laboratories, the NGSP achieved better standardisation and by the year 2001, there was evidence from Quality Assurance Programmes that HbA<sub>1c</sub> results from different laboratories were in much tighter agreement.

However, the problem is that what underlies the HbA<sub>1c</sub> peak on the Biorex-70 chromatogram is not “pure” HbA<sub>1c</sub>, but rather a mixture of substances. HbA<sub>1c</sub> refers strictly to Hb glycosylated at the N-terminal valine residues of the beta chains, whereas the peak contains Hb glycosylated at other sites, some HbF and the “uraemic-adduct” (Hb with urea attached). “Pure” HbA<sub>1c</sub> may represent only 60-70% of what underlies the peak on the chromatogram. For this reason, the International Federation of Clinical Chemistry (IFCC) from the mid 1990s moved to develop a reference method with true primary standards.

The IFCC achieved this using the N-terminal hexa-peptide of the haemoglobin beta chain in both glycosylated and unglycosylated forms and methods based on mass spectrometry or capillary electrophoresis and also developed an international network of reference laboratories<sup>7</sup>. This is now in place with the methods accepted by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) and the IFCC HbA<sub>1c</sub> laboratory network providing reference laboratory services<sup>8</sup>.

However, the issue is that the HbA<sub>1c</sub> results that are IFCC aligned are *lower* than those that are NGSP (or DCCT) aligned by an absolute value of 1-2%. For example, 7% by DCCT would be reported as 5.4% by IFCC. Manufacturers are obliged to use calibrators and controls that are traceable to a higher order reference method (IFCC aligned), though currently use “master equations” to convert HbA<sub>1c</sub> results into values that are NGSP (or DCCT) aligned and which are currently reported.

The main recommendation<sup>1-3</sup> is to use the alternative molar units proposed by the IFCC, namely mmol/mol (haem) for reporting of HbA<sub>1c</sub>.

See Table 1 for equivalent values.

**Table 1. relationships between HbA<sub>1c</sub> in NGSP % units, HbA<sub>1c</sub> IFCC mmol/mol units and estimated average glucose (eAG, mmol/L).**

HbA <sub>1c</sub> NGSP (%)	HbA <sub>1c</sub> IFCC (mmol/mol)	eAG (mmol/L)
5.0	31	5.4
6.0	42	7.0
7.0	53	8.6
8.0	64	10.2

### **Arguments for change to IFCC Units (mmol/mol)**

- Current % unit changes appear small and may be considered unimportant by some patients (e.g. changes of 0.5%).
- The numbers for NGSP units (e.g. 6.8) are similar to those used for blood glucose concentration when measured in mmol/L, which leads to confusion in some patients.
- The IFCC units are scientifically valid and accurately indicate the amount of HbA<sub>1c</sub> present in the sample. By contrast the NGSP units refer to a non-specific assay which measured other forms of haemoglobin in addition to HbA<sub>1c</sub>.

### **Arguments in favour of retaining NGSP % (or DCCT aligned) results.**

- Familiar to patients, carers, educators, doctors, labs, manufacturers.
- These units are used in peer-reviewed literature, brochures, treatment guidelines and on analyser readouts.
- The values relate directly to current evidence (e.g. DCCT, UKPDS, others).
- Any change in units is likely to create mishaps. Described by some authors as potentially leading to “great confusion”.

The argument, however is not a choice of one unit or the other at this time as the recommendation is for the result to be reported with two values reported with each unit. It has been noted that if both units are reported then users will probably look no further than the unit they are familiar with.

### **The proposal to report estimated average glucose (eAG)**

The expression of HbA<sub>1c</sub> as an estimated average plasma glucose (eAG) in addition to the HbA<sub>1c</sub> result is supported in the text of the consensus statement<sup>1-3</sup> as follows: “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 glycaemia in terms and units most suitable to the patients under their care.”

The proposal originally stems from the observed relationship between HbA<sub>1c</sub> and average blood glucose in the DCCT trial.<sup>9</sup> However, the relationship shows a wide scatter of average glucose levels for any HbA<sub>1c</sub>, leading to the suggestion that there is a spectrum from slow to fast “glycators”.

More recently, the A<sub>1c</sub>—derived average glucose study (ADAG)<sup>10</sup> reported the relationship between HbA<sub>1c</sub> measured at the end of 3 months and the weighted average glucose from at least 2 days of continuous glucose monitoring performed four times, and seven-point daily self-monitoring of blood glucose performed at least 3 days per week. This represented approximately 2700 glucose readings per subject and was undertaken in a total of 507 subjects, including 268 patients with Type 1 diabetes, 159 with Type 2 diabetes and 80 normal subjects.

Participants were aged 18-70 and patients with diabetes had stable glycaemic control (HbA<sub>1c</sub> values within 1% over a 6 month period), with a range of HbA<sub>1c</sub> values up to approximately 12%. The study was undertaken in 11 centres in the USA, Europe and Africa. The derived regression equation showed a lower eAG compared with DCCT and with less scatter, thus fulfilling the *a priori* quality criterion that 90% of estimates fell within ±15% of the regression line.

There were no differences in the relationship according to diabetes type or ethnic group, although there was a trend to lower eAG in African Americans. Asian ethnic groups were under represented in the study and children were excluded. Those with haemoglobinopathies, likely to confound interpretation of HbA<sub>1c</sub> were also excluded from the study.<sup>10</sup>

The accompanying editorial<sup>11</sup> and others<sup>12</sup> have advocated introduction of eAG into reporting of results.

### **Arguments in favour of routinely reporting the eAG**

- Reporting HbA<sub>1c</sub> with an estimated average blood glucose should assist with patient's understanding of the results.
- A number of clinicians in Australasia have already expressed a preference for this type of additional reporting.
- If patients can gain an improved understand of the meaning of the HbA<sub>1c</sub>, improved outcomes may be achieved.
- The test name “HbA<sub>1c</sub>” is confusing as haemoglobin usually refers to the red cells.

### **Arguments against routinely reporting the eAG**

- The nature of the relationship between HbA<sub>1c</sub> and average blood glucose remains poorly understood.
- There is considerable scatter around the line used to convert the HbA<sub>1c</sub> results to eAG in the DCCT, ADAG and other studies.
- The term “Average Blood Glucose” has different meanings depending on the method used to determine it. For example average glucose can be obtained

from many home blood glucose meters with limited testing, more detailed meter testing (e.g. 7 times per day) or continuous monitoring.

- There is the possibility of confusion over the response to eAG (decisions about long term management changes) and single blood glucose measurement (decision about immediate changes).
- The range of values reported in patients using calculated eAG is much narrower than from random glucoses. While the eAG values are clearly significant in terms of HbA<sub>1c</sub> values, they may be seen as being not significant if they were fingerprick glucose readings—e.g. random glucose readings of 7.0 mmol/L and 10.2 mmol/L are close, however the HbA<sub>1c</sub> results that generate these values as eAG are markedly different (6% and 8%).
- This method of reporting may have little benefit in understanding for patients with Type 2 diabetes who are not performing home blood glucose monitoring.
- At this time we are unaware of any evidence that reporting in this manner will improve outcomes.

Manufacturers of Point of Care testing devices will also need to make adjustments in order to allow for two (HbA<sub>1c</sub> in % and mmol/mol) or possibly three (also eAG) results to be displayed on a screen or printout. Until these adjustments are made, they will lag behind in the changeover process.

A corollary to all of the above is the additional recommendation,<sup>1-3</sup> namely that “glycaemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units, and as estimated average glucose”. This recommendation is a vital adjunct to the main recommendations. If reporting of laboratory results is changed, then the documentation available to doctors, diabetes educators and patients must also be expressed in the relevant units.

## **The process of making change**

A recent multidisciplinary meeting in the UK with wide representation has considered these issues.<sup>13</sup> The use of IFCC molar units is supported but with recognition of the major educational requirements and lengthy period of dual reporting. The reporting of eAG was not supported at this time although further research was recommended<sup>13</sup>. Other editorials also have not been supportive of reporting of eAG.<sup>14</sup> NZSSD has consulted its Membership, having presented all the information above and reviewed the feedback in the formulation of its Position Statement, the key points of which were implemented in New Zealand on 3 August 2009.

In Australasia there ideally needs to be broad consensus between the clinical and laboratory organisations. Stakeholders for the clinical side include the Australian Diabetes Association (ADA), the New Zealand Society for the Study of Diabetes (NZSSD), the Australia Diabetes Educators Association (ADEA), the Royal Australasian College of Physicians (RACP) and the Royal Australian College of General Practitioners (RACGP).

Patient representative groups through Diabetes Australia and Diabetes New Zealand (DNZ) should also be included in the process. The Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists

(AACB) are the laboratory professional bodies involved with this issue. In Australia, the issues are still being deliberated with no firm plan of action set.

**Competing interests:** None known.

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## **Appendix 1. NZSSD Position Statement on standardisation of reporting units for HbA<sub>1c</sub> and application of estimated average glucose (eAG)**

New Zealand (NZ) clinical laboratories should implement dual reporting of HbA<sub>1c</sub> in both molar units (mmol/mol) and currently reported DCCT-aligned units (%), as recommended in a consensus statement from ADA, EASD, IFCC and IDF, published in 2007. After a period of two years from the time of implementation it is envisaged that only molar units will be reported.

Although explicit times have been set in the United Kingdom (1 June 2009 for initiation of dual reporting and 1 June 2011 for reporting only molar units), it is most important that implementation is coordinated across NZ laboratories, ideally in synchrony with Australia. The NZ clinical laboratory community should cooperate to achieve dual reporting in a standardised format.

There is some evidence in support of also reporting estimated average glucose (eAG), although this has not received universal endorsement. It is recommended that eAG may be used at the discretion of individual practitioners as an educational tool at the point of delivery of care to patients with diabetes. It is not recommended that eAG should appear on laboratory reports at the present time, although there should be flexibility to adopt this if a strong Australasian commitment emerges.

The above recommendations should be supported by educational tools and resources, which should be adapted to meet local requirements.