Clinica Chimica Acta 432 (2014) 157–161

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Implementation of the HbA1c IFCC unit — from the laboratory to the consumer: The New Zealand experience

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ARTICLE INFO

Article history:
Received 7 May 2013
Received in revised form 10 September 2013
Accepted 10 October 2013
Available online 19 October 2013

Keywords:
Harmonisation
HbA1c
Diabetes

ABSTRACT

In 2007, an international consensus statement recommended that HbA1c results should be reported world-wide in IFCC units (mmol/mol) and also the more familiar derived percentage units using a master equation. In New Zealand, the HbA1c IFCC units have been successfully implemented and used exclusively since 3rd October 2011 (following a 2 year period of reporting both units) for both patient monitoring and the diagnosis of diabetes, with a diagnostic cut-off of ≥50 mmol/mol.

The consultation process in New Zealand dates back to 2003, well before the international recommendations were made. It reflects the close cooperation between the clinical and laboratory communities in New Zealand, particularly through the agency of the New Zealand Society for the Study of Diabetes (NZSSD), a key organisation in New Zealand open to all those involved in the care of people with diabetes and the national advisory body on scientific and clinical diabetes care and standards.

There was a phased process of consultation designed to increase familiarity and comfort with the new units and the final step was coupled with the adoption of HbA1c as a diagnostic test with some evidence-based pragmatism around using the rounded cut-off.

Genuine clinical engagement is vital in such a process.

1. Introduction

At a meeting in Milan on 4 May 2007, a consensus statement 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 [1–3], with agreement that the recommendations should be implemented "globally as soon as possible".

The main recommendations were:

1. HbA1c results are to be reported world-wide in IFCC units (mmol/mol) AND:
2. Derived NGSP units (%), using the IFCC-NGSP master equation.
3. If the ongoing "average plasma glucose study" fulfils 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.

2. Implementation of the HbA1c IFCC unit — from the laboratory to the consumer

This article, focusing mainly on HbA1c, describes the background to how these international recommendations came about and the process of consultation that occurred within one country, New Zealand, where the HbA1c IFCC units have been successfully implemented and used exclusively since 3rd October 2011 for both patient monitoring and the diagnosis of diabetes. The consultation process in New Zealand dates back to 2003, well before the international recommendations outlined above were made. It reflects the close cooperation between the clinical and laboratory communities in New Zealand, particularly through the agency of the New Zealand Society for the Study of Diabetes (NZSSD). The discussions and debates were intimately intertwined with the evolution of the international recommendations, thus it is appropriate to give some of the background, outlining the arguments for and against adopting the HbA1c molar units that were presented to the clinical community as part of the consultation process.

NZSSD is a key organisation in New Zealand, being an incorporated society that is open to all those involved in the care of people with diabetes. It has over 400 members including diabetes specialist physicians, diabetes specialist nurses, podiatrists, dietitians, ophthalmologists, general physicians, primary care

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http://dx.doi.org/10.1016/j.cca.2013.10.009

Table 1
HbA1c conversion table.

HbA1c mmol/mol	HbA1c %
20	4.0
30	4.9
40	5.8
42	6.0
44	6.2
46	6.4
47	6.5
48	6.5
49	6.6
50	6.7
52	6.9
53	7.0
54	7.1
56	7.3
58	7.5
60	7.6
70	8.6
80	9.5
90	10.4
100	11.3
110	12.2

physicians, scientists, community health workers and allied industries. NZSSD is the national advisory body on scientific and clinical diabetes care and standards. Its objectives are to promote the study of diabetes and the best standards of care for diabetes in New Zealand.

3. The background to the recommendations

HbA1c became an essential clinical tool after the publication of the DCCT trial [4] in 1993 and subsequently the UKPDS study (in type 2 diabetes) [5]. These showed the relationship between HbA1c and clinical outcomes and enabled the setting of a desirable target for management (53 mmol/mol [7%], with a change of therapy being recommended at levels above 64 mmol/mol [8%]). However, at the time of the DCCT trial it became apparent that there were widely differing results for HbA1c between laboratories, reflecting widely different analytical principles and also the lack of standardisation of these 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 and developed a network of reference laboratories and standards, based on whole blood samples with HbA1c values meticulously assigned by 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 was successful in achieving better standardisation so that by the year 2001 there was evidence from Quality Assurance Programmes that HbA1c results from different laboratories were in much tighter agreement with further improvement evident by 2004 and 2010 [6,7].

The problem, however, is that what underlies the HbA1c peak on the Biorex-70 chromatogram is not "pure" HbA1c, but rather a mixture of substances. Strictly, HbA1c refers to haemoglobin glycated at the N-terminal valine residues of the beta chains, whereas the peak contains Hb glycated at other sites, some HbF and the "uraemic-adduct" (Hb with urea attached). "Pure" HbA1c may represent only 60–70% of what is included in the peak on the chromatogram. For this reason, from the mid 1990s the International Federation of Clinical Chemistry (IFCC) 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 glycated and unglycated forms and methods based on mass spectrometry or capillary electrophoresis and also developed an international network of reference laboratories [8]. This reference system is now in place, with the methods being accepted by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) and the IFCC HbA1c laboratory network providing reference laboratory services [9]. The consensus statement [1–3] states that "the new IFCC reference system for A1c represents the only valid anchor to implement standardisation of the measurement".

An issue resulting from the better specificity of the IFCC reference method is that the HbA1c 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 5.3% by IFCC. Manufacturers are obliged to use calibrators and controls that are traceable to a higher order reference method (IFCC aligned), but use "master equations" to convert HbA1c results into values that are NGSP (or DCCT) aligned and which are still reported in many countries as the only result. Moreover, using IFCC units provides a much closer physiological relationship of HbA1c to mean plasma blood glucose [10]. In particular, it was shown that when HbA1c from the landmark DCCT trial [4] was recalculated into IFCC units, the regression line now passed through the origin and without an intercept, which was not the case using NGSP aligned units.

Because of the potential clinical confusion caused by the difference between IFCC calibrated and NGSP aligned results when both are expressed in % units, and the sometimes acrimonious debate that ensued, the recommendation [1–3] was to use alternative molar units proposed by the IFCC, namely mmol/mol (haem) for reporting of HbA1c, with conversions shown in Table 1.

3.1. Arguments presented for change to IFCC units (mmol/mol)

- Previous % 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 HbA1c present in the sample. By contrast the NGSP units refer to a non-specific assay which measured other forms of haemoglobin in addition to HbA1c.

3.2. Arguments presented 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 clinical 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 was not a choice of one unit or the other at the time of original implementation as the recommendation was for the result to be reported with values in each unit. It had been suggested that if both units were reported then users would probably look no further than the unit with which they are familiar.

4. The proposal to report estimated average glucose (eAG)

The expression of HbA1c as an estimated average plasma glucose (eAG) in addition to the HbA1c result was conditionally supported in the text of the consensus statement [1–3] pending further studies, with the comment that "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 HbA1c and average blood glucose in the DCCT trial [11]. The relationship, however, shows a wide scatter of average glucose levels for any HbA1c, leading to the suggestion that there is a spectrum from slow to fast "glycators". Subsequently, the A1c-derived average glucose study (ADAG) [12] reported the relationship between HbA1c 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 non-diabetic subjects. Participants were aged 18–70 and diabetic subjects had stable glycaemic control (HbA1c values within 1% over a 6 month period), with a range of HbA1c values up to approximately 12%. ADAG 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 ADAG study and children were excluded. Those with haemoglobinopathies, likely to confound interpretation of HbA1c were also excluded from ADAG study [12]. The accompanying editorial [13] and others [14] have advocated introduction of eAG into reporting of results.

4.1. Arguments in favour of routinely reporting the eAG

- Reporting HbA1c in average blood glucose should assist with patient's understanding of the results.
- The test name "HbA1c" is confusing, as haemoglobin usually refers to the red cells.

4.2. Arguments against routinely reporting the eAG

- The nature of the relationship between HbA1c and average blood glucose remains poorly understood.
- There is a considerable scatter around the line used to convert the HbA1c 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.
- This method of reporting may have little benefit in understanding for type 2 diabetic subjects who are not involved in home blood glucose monitoring.

The issues in relation to estimated average glucose are presented for the sake of completeness and because they formed an integral part of the deliberations that took place around HbA1c, although it was eventually decided in New Zealand (see below) that they should not be formally reported by the clinical laboratory. It should also be noted that although eAG was included in the initial recommendations [1–3], it was not included in a follow-up consensus statement emanating from the IDF meeting in 2009 [15] on account of limitations, including the findings of the ADAG study [12].

5. The process of making change

The original consultations in New Zealand took place in 2003, when one of the authors (MC) addressed a meeting of the NZSSD Physicians, outlining the background to the work of the IFCC working party and the move towards a reference method for HbA1c. It was indicated that this might involve results that would not necessarily agree with the DCCT (%) units, although the proposal to adopt molar units was not evident at the time. The Physicians were favourably receptive to the arguments presented in support of change and it is our belief that this greatly facilitated the course of the subsequent consultation process and changes that occurred.

Following the publication of the consensus statement [1–3], another author (CF) addressed the NZSSD Physicians in 2008. On this occasion, the recommendations were more definitive and it was agreed that the wider Membership of NZSSD should be canvassed with a view to determining exactly which of the recommendations (if any) should be adopted. NZSSD thus consulted its Membership, presenting all the information above and reviewed the feedback before formulating a Position Statement. The landmark Position Statement (below) was endorsed by the Executive of the NZSSD on February 20 2009.

NZSSD Position Statement (2009) on standardisation of reporting units for HbA1c and application of estimated average glucose (eAG).

New Zealand (NZ) clinical laboratories should implement dual reporting of HbA1c 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 Australasia. 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.
http://www.nzssd.org.nz/position_statements/standardisation.html

The statement allowed some flexibility to be in synchrony with Australian recommendations when their Position Statement emerged, although it now appears that far more progress has been made in New Zealand compared with Australia.

Around the time of the consultations in New Zealand, we were aware of a multi-disciplinary meeting in the UK, with wide representation, that had considered the same issues [16]. They concluded that the use of IFCC molar units was supported but with recognition of the major educational requirements and lengthy period of dual reporting that would be required. The reporting of eAG was not supported at this time (concordant with the feedback received in New Zealand) although further research was recommended [16]. Other editorials had not been supportive of eAG [17]. It seemed eminently sensible to us in New Zealand that a period of dual reporting without precipitously dropping the more familiar DCCT (%) units would enable clinicians to gain familiarity with the new units. It was recommended, however 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, thus taking into account the practices of individual patients and using specially formulated charts within the diabetes clinics.

The Position statement was then widely distributed within the New Zealand laboratory community for comment and feedback. Given that the Position Statement emanated from NZSSD, it was considered to be authoritative and most importantly to represent endorsement from the wider diabetes clinical community. Laboratories were supportive of the proposals and a date for implementation of a 2-year period of

dual reporting was set to begin on 3rd August 2009, allowing time to ensure adequate preparedness and also for adequate priming of other clinical and consumer bodies including those representative of patients.

As part of that process, information was sent from NZSSD to all Primary Healthcare Organisations in New Zealand. Each clinical laboratory prepared its own newsletter for circulation to all client doctors, especially in primary care. Information was provided through the medium of the patient organisation, Diabetes New Zealand. Publications were submitted to New Zealand Doctor (circulated in primary care) and the New Zealand Medical Journal [18], although the latter underwent a protracted review process and appeared at a date that was far too late to be of any benefit around the time of implementation. It was clearly signalled from the outset that this was strictly a period of dual reporting and that the intention was to move to exclusive adoption of the molar units from 1st August 2011.

We deliberated at the time whether we should have undertaken a much broader consultation process with other professional bodies prior to the implementation of dual reporting, such as occurred in the UK, although we were of the opinion that NZSSD had very strong currency and that any recommendations emanating from this organisation would have sufficient authority. Constraints of time, funding and logistics also precluded this option.

Dual reporting (of both molar IFCC and DCCT (%) units) was implemented on 3rd August 2009, with very little feedback received at the time, either against or in favour. One physician commented that it would have been preferable to have quoted more rounded figures for targets e.g. 50 mmol/mol instead of 53 mmol/mol (equivalent to 7%). Ironically, in subsequent deliberations and with the move towards adopting HbA1c for diagnosis of diabetes, that is exactly what came to be adopted in New Zealand, based on both evidence and practical considerations.

It is our belief that a significant majority of the diabetes clinical community did genuinely embrace the IFCC molar units from an early stage, with many clinicians using only molar units in their clinical correspondence and this was almost universal as the period of dual reporting moved towards exclusive adoption of the IFCC molar units. This again reflected a positive outcome for the extensive groundwork and consultation that had been undertaken, dating back to 2003.

In the two year period of dual reporting, the debate regarding the role of HbA1c for diagnosis of diabetes gathered momentum. The supporting evidence will not be covered in detail here but HbA1c was endorsed as a diagnostic test by both the American Diabetes Association (ADA) and the World Health Organisation (WHO) [19,20], with a diagnostic cut-off of 6.5% (48 mmol/mol). These issues were deliberated at length by NZSSD. It was decided to adopt a more radical proposal of setting the diagnostic cut-off at a higher level of 50 mmol/mol and to synchronise this formal recommendation for diagnosis with the exclusive adoption of molar units for HbA1c. The rationale was firstly to make the molar units more memorable by using a rounded figure and secondly to maximise specificity for the diagnosis of diabetes [21]. It was recognised that sensitivity would necessarily be lower and that maybe up to 30% of cases may be 'missed' who would have been diagnosed on oral glucose tolerance testing. NZSSD contended, however that these cases were not strictly 'missed' given that they would fall into a pre-diabetic category (HbA1c 41–49 mmol/mol) where lifestyle adjustment would be implemented along with the recommendation to be re-tested in 6–12 months. Furthermore, the level of 50 mmol/mol fits within the estimates of the cut points based on relationship to retinopathy, on which the ADA and WHO recommendations were based [22] and the level of 6.5% chosen by those organisations is itself a pragmatic choice within that range.

The date of 1st August 2011 was therefore set for the exclusive adoption of molar units along with the application of HbA1c as a diagnostic test. This again necessitated the preparation and dissemination of recommendations and educational materials from the NZSSD, regarding the use of HbA1c for diagnosis of diabetes. In particular, there are a number of *caveat* situations, for example haemoglobinopathy, abnormal red cell turnover or iron deficiency anaemia where glucose based criteria are still preferred for diagnosis.

Despite the fact that it had been signalled from the outset that this was strictly a period of dual reporting and that the intention was to move to exclusive adoption of the molar units from 1st August 2011, not everybody was prepared for the changeover and some even denied any knowledge that such a proposal had ever existed.

As the date for implementation drew nearer, it became apparent that many primary care organisations used software systems that could not process the molar units for the purposes of collating

Table 2
Reporting and interpreting glycated haemoglobin (HbA1c) results/values (www.nzssd.org).

When performed in those with confirmed diabetes	
HbA1c value (mmol/mol)	Individual targets should be set using these suggestions
Less than 50	Excellent control; increased risk of hypoglycaemia if on insulin/sulphonylureas
50–54	Very good control; some risk of hypoglycaemia if on insulin/sulphonylureas
55–64	May be appropriate and acceptable in many individuals but higher than ideal from clinical trial evidence. Microvascular complication risk increases exponentially above around 55 mmol/mol
65–79	Suboptimal glycaemic control. Consider more intensive treatment. Microvascular complication risk increases exponentially above around 55 mmol/mol
80–99	Poor glycaemic control. More intensive treatment recommended. Microvascular complication risk increases exponentially above around 55
100 or more	Very poor glycaemic control. Warrants immediate action
HbA1c may be misleading in some situations (e.g. haemoglobinopathies, increased red cell turnover or after recent blood transfusion).	
When performed for diagnosis/CV risk screening	
HbA1c value (mmol/mol)	Comment
40 or less	Virtually excludes diabetes. No need to repeat until next scheduled CVD risk assessment
41–49	Abnormal glucose tolerance Recommend diet/lifestyle changes and assess/manage all CV risk factors Repeat annually unless symptomatic in interim
50 or greater	Supports diagnosis of diabetes (in asymptomatic people must be confirmed on a second sample after an interval) Recommend diet/lifestyle changes and assess/manage CV risk factors Start regular retinal, microalbuminuria, renal function and foot screening

Glucose-based diagnostic criteria should always be used in situations where HbA1c is unreliable (e.g. haemoglobinopathies, increased red cell turnover or after recent blood transfusion).

Table 3
What to do following a screening test for type 2 diabetes (www.nzssd.org).

Result	Action	Why
Symptomatic		
HbA1c ≥ 50 mmol/mol and, if measured, fasting glucose ≥ 7.0 mmol/L or random blood glucose ≥ 11.1 mmol/L	No further tests required	Diabetes is confirmed
Asymptomatic		
HbA1c ≥ 50 mmol/mol and, if measured, fasting glucose ≥ 7.0 mmol/L or random glucose ≥ 11.1 mmol/L	Repeat HbA1c or a fasting plasma glucose	Two results above the diagnostic cutoffs, on separate occasions are required for the diagnosis of diabetes[a]
HbA1c 41–49 mmol/mol and, if measured, fasting glucose 6.1–6.9 mmol/L	Advise on diet and lifestyle modification. Repeat the test after 6–12 months	Results indicate 'pre-diabetes' or impaired fasting glucose[a]
HbA1c ≤ 40 mmol/mol and, if measured, fasting glucose ≤ 6 mmol/L	Retest at intervals as suggested in cardiovascular risk factor guidelines	This result is normal

[a] When HbA1c and fasting glucose are discordant with regard to diagnosis of diabetes, repeat testing at an interval of 3–6 months is recommended. The test that is above the diagnostic cut point should be repeated — if the second test remains above the diagnostic threshold then diabetes is confirmed. If the second result is discordant with the first then subsequent repeat testing at intervals of 3–6 months is recommended. Patients with discordant results are likely to have test results near the diagnostic threshold.

information, in particular for submission to the Ministry of Health (MoH) for audit purposes and for use in cardiovascular risk calculators. This led to a protracted and acrimonious exchange of correspondence between NZSSD, the MoH, primary care organisations and software vendors. From the laboratory perspective, IT issues included standardisation of messages sent via HL7 to practice management systems and discussion around appropriate LOINC codes. The date for changeover was put back from 1st August 2011 and a date of 3rd October eventually agreed. The MoH undertook a process of intermediation and arbitration that eventually facilitated the change.

An updated Position Statement (September 2011) was issued, the full body of which can be accessed via the NZSSD website. A summary of the recommendations is given in Tables 2 and 3.

Following implementation, the number of (non-pregnancy) OGTTs declined dramatically in all areas, coupled with a more than doubling of HbA1c requests. Increases had been expected, but the actual volume received was a surprise, as MoH figures had suggested that substantial numbers of HbA1c were already being used unofficially for diagnosis in primary care. A factor in the increase has almost certainly been the coincident instruction from the MoH that cardiovascular risk screening and detection of diabetes are auditable priorities, with the instruction to increase the percent of the eligible population screened from the current levels of around 60–65% to 90%, by July 2014.

http://www.health.govt.nz/new-zealand-health-system/health-targets/2012-13-health-targets

Fasting plasma glucose has been part of the cardiovascular risk assessment in New Zealand, but clearly is being replaced by HbA1c. The move towards using non-fasting lipids in the initial risk assessment is also a factor in the preference for HbA1c in the risk assessment.

Given the importance of HbA1c for diagnosis, there has also been increased awareness for detection of possible haemoglobin variants and other factors that may potentially confound the interpretation as well as the robustness of analytical performance. This has significantly increased laboratory workload and follow-up procedures.

6. Conclusion

The successful adoption of IFCC molar units for HbA1c in New Zealand was the result of a robust consultation process through NZSSD that dated way back before any definitive recommendations were made internationally. It was a phased process designed to increase familiarity and comfort with the new units and the final step was coupled with the adoption of HbA1c as a diagnostic test with some evidence-based pragmatism around using the rounded cut-off of 50 mmol/mol for diagnosis. We are fortunate in New Zealand to have close collaboration between the diabetes clinical and laboratory communities. It cannot be understated just how important genuine clinical engagement is in such a process.

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