HbA1c: What’s going on with HbA1c?

Prof. Eric S. Kilpatrick
Department of Clinical Biochemistry
Hull Royal Infirmary/Hull York Medical School
What’s going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes
What’s going on with HbA1c?

• HbA1c: a brief history

• How should we report HbA1c?

• Using HbA1c to diagnose diabetes
HbA$_1$c: Historical Aspects

1962: Huisman and Dozy

Increases in minor fractions of haemoglobin in four diabetic patients treated with tolbutamide.

1968: Rahbar

‘Diabetic haemoglobin component’ found in 49 Iranian diabetic patients.

1968: Rahbar

Component the same structure as the previously described HbA$_1$c
**Minor Components of HbA**

<table>
<thead>
<tr>
<th>Haemoglobin</th>
<th>Modification</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>A_{1a1}</td>
<td>fructose 1,6-diphosphate</td>
<td>0.2</td>
</tr>
<tr>
<td>A_{1a2}</td>
<td>glucose-6-phosphate</td>
<td>0.2</td>
</tr>
<tr>
<td>A_{1b}</td>
<td>carbohydrate (?)</td>
<td>0.5</td>
</tr>
<tr>
<td>A_{1c}</td>
<td>glucose</td>
<td>4</td>
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</tbody>
</table>

HbA_1
HbA$_{1c}$: Historical Aspects

**HbA$_{1c}$ correlated with:**

- **Plasma ‘glucose brackets’**

- **Daily mean plasma glucose**
  Gonen B *et al.* Lancet 1977; ii; 734-737

- **24 hour urinary glucose excretions**
  Gabbay KH *et al.* J Clin Endocrinol Metab 1977; 44: 859-864

- **Glucose control over past 6-8 weeks**
  Goldstein D *et al.* Clin Chem 1986; 32(Suppl): B64-70
DCCT: Risk of Microvascular Complications

DCCT: Risk of Severe Hypoglycaemia

Graph showing the rate of severe hypoglycaemia (per 100 patient-years) against glycosylated hemoglobin (%) with three curves, each representing different conditions or treatments.
HbA$_{1c}$: Historical Aspects

HbA$_{1c}$ correlated with:

- Plasma ‘glucose brackets’

- Daily mean plasma glucose
  Gonen B et al. Lancet 1977; ii; 734-737

- 24 hour urinary glucose excretions
  Gabbay KH et al. J Clin Endocrinol Metab 1977; 44: 859-864

- Glucose control over past 6-8 weeks
Model of Glycated Haemoglobin Formation

![Graph showing HbA1c (%)](image)

- **HbA1c (%)**
- **Red Cell Age**
  - 0-1 month
  - 1-2 months
  - 2-3 months
  - 3-4 months
Model of Glycated Haemoglobin Formation

\[ y = 2x - x^2 \]

% of HbA1c Value

Months Prior to Sampling
Playing the odds

If I develop diabetes tomorrow

• What are the chances I will remain complication-free for the rest of my life?
DCCT: risk of retinopathy progression

% Risk of Retinopathy progression in next year

HbA1c (%)
Cumulative risk

Probability of retinopathy progression vs. HbA1c (%) for 1 year.

HbA1c (%)
Cumulative risk

Probability of retinopathy progression

HbA1c (%)

1 year
5 years
Cumulative risk

Probability of retinopathy progression

- 1 year
- 5 years
- 10 years

HbA1c (%) vs. Probability of retinopathy progression
Cumulative risk

Graph showing the probability of retinopathy progression over time for different HbA1c levels. The x-axis represents HbA1c (%) ranging from 6 to 10, and the y-axis represents the probability of retinopathy progression ranging from 0 to 1.

Key:
- 1 year
- 5 years
- 10 years
- 20 years

The graph indicates an increasing probability of retinopathy progression as HbA1c levels rise, with the highest risk observed at higher HbA1c levels and over longer periods.

Cumulative risk

Probability of retinopathy progression

HbA1c (%)
Cumulative risk

Probability of retinopathy progression

HbA1c (%)

1 year
5 years
10 years
20 years
30 years
Cumulative risk

HbA1c (%)

Probability of retinopathy progression

- 1 year
- 5 years
- 10 years
- 20 years
- 30 years
- 40 years

HbA1c (%)

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Probability of retinopathy progression

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

6 7 8 9 10
Cumulative risk

Probability of retinopathy progression vs. HbA1c (%)

- 1 year
- 5 years
- 10 years
- 20 years
- 30 years
- 40 years
- 50 years
Playing the odds

- 46 years old
50:50 odds of developing retinopathy

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<tr>
<th>HbA1c mmol/mol</th>
<th>Age (years)</th>
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<tr>
<td>108 (12%)</td>
<td>51</td>
</tr>
<tr>
<td>97 (11%)</td>
<td>52</td>
</tr>
<tr>
<td>86 (10%)</td>
<td>55</td>
</tr>
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<td>75 (9%)</td>
<td>61</td>
</tr>
<tr>
<td>64 (8%)</td>
<td>74</td>
</tr>
<tr>
<td>53 (7%)</td>
<td>98</td>
</tr>
<tr>
<td>42 (6%)</td>
<td>154</td>
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What’s going on with HbA1c?

• HbA1c: a brief history

• How should we report HbA1c?

• Using HbA1c to diagnose diabetes
Interlaboratory variation HbA1c

Overall CV (%) vs. Date


% DCCT aligned methods
Interlaboratory variation HbA1c

Overall CV (%) vs Date

NGSP programme - Dec'96
Menarini Standardisation meeting - Sep '98
UK Consensus statement - Jan '00
IFCC standardisation adopted by manufacturers Jan '04

% DCCT aligned methods

Sample 1
Sample 2
CV Trendline
**DCCT calibration: the de facto standard**

**Cons**

- Not a true standardised measurement
  - The best technology the 1980s could muster
  - Not the true HbA1c concentration
- Tracability of values to DCCT/UKPDS may be lost in time
  - Dependent on upkeep of the 1980s HPLC instrument
IFCC – Working Group on Standardisation of HbA1c

• Established in 1995
• Remit
  -To establish a definition of the analyte Hb that is irreversibly glycated at one or both N-terminal valines of the beta chains.
  -Establish a Primary Reference Material
  -Develop a Reference Method
  -Implement standardisation through a lab network
First step:
- haemoglobin is cleaved into peptides by the enzyme endoproteinase Glu-C

Second step:
- glycated and non-glycated N-terminal hexapeptides of the β-chain are separated and quantified by:
  1. HPLC and electrospray ionisation mass spectrometry OR
  2. two-dimensional approach using HPLC and capillary electrophoresis with UV-detection

## DCCT vs. IFCC HbA1c

<table>
<thead>
<tr>
<th>DCCT HbA1c (%)</th>
<th>IFCC HbA1c (%)</th>
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<tr>
<td>6</td>
<td>4.2</td>
</tr>
<tr>
<td>7</td>
<td>5.3</td>
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<td>8</td>
<td>6.4</td>
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<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>8.6</td>
</tr>
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Middle J. Proceedings of the ACB National Meeting 2003
## DCCT vs. IFCC HbA1c

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<td>64</td>
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<tr>
<td>9</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
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*Clin Chem Lab Med 2007;45:1081-1082*
Consensus meeting on reporting glycated haemoglobin (HbA1c) and estimated average glucose (eAG) in the UK

- Convened at the request of Dr Sue Roberts, National Director for Diabetes
- Representatives of 18 UK professional organisations and of the diagnostic industry
- Meeting held on 23rd January 2008
HbA1c reporting in the UK

- IFCC and DCCT numbers to be ‘dual reported’ as of June 2009
- As of June 2011, removal of the DCCT numbers
## DCCT vs. IFCC HbA1c

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*Clin Chem Lab Med 2007;45:1081-1082*
Middle’s Manipulation

• ‘I have discovered and easy way to remember how (to convert DCCT to IFCC numbers)’
• ‘The master equation for the relationship between NGSP and IFCC HbA1c 'numbers' is IFCC% = 10x(NGSP% + 2.15) / 0.915’
• ‘It turns out that this yields an easy to remember 'conversion guide' of: IFCC mmol/mol = (DCCT% x 11) – 24’

Jonathan Middle, ACB mailbase 29/1/08
Kilpatrick’s Kludge

- minus 2 minus 2

DCCT
7%
Kilpatrick’s Kludge

- minus 2 minus 2

DCCT  -2
7%  5

Eric Kilpatrick, ACB mailbase 30/1/08
Kilpatrick’s Kludge

- minus 2 minus 2

<table>
<thead>
<tr>
<th>DCCT</th>
<th>-2</th>
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<tr>
<td>7%</td>
<td>5</td>
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Eric Kilpatrick, ACB mailbase 30/1/08
Kilpatrick’s Kludge

- minus 2 minus 2

DCCT  -2  -2  IFCC
7%  5  3  53mmol/mol

Eric Kilpatrick, ACB mailbase 30/1/08
Kilpatrick’s Kludge

- DCCT
  - 4%
  - 5%
  - 6%
  - 7%
  - 8%
  - 9%
  - 10%
Kilpatrick’s Kludge

- DCCT
  - 4%: 2
  - 5%: 3
  - 6%: 4
  - 7%: 5
  - 8%: 6
  - 9%: 7
  - 10%: 8
Kilpatrick’s Kludge

<table>
<thead>
<tr>
<th>DCCT</th>
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<tr>
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Kilpatrick’s Kludge

- DCCT

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<td>9%</td>
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<td>5</td>
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<tr>
<td>10%</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
Kilpatrick’s Kludge

- DCCT
  - 4%  20
  - 5%  31
  - 6%  42
  - 7%  53
  - 8%  64
  - 9%  75
  - 10% 86
<table>
<thead>
<tr>
<th>DCCT</th>
<th>IFCC (mmol/mol)</th>
</tr>
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<tbody>
<tr>
<td>4%</td>
<td>20</td>
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<td>75</td>
</tr>
<tr>
<td>10%</td>
<td>86</td>
</tr>
</tbody>
</table>
What’s going on with HbA1c?

• HbA1c: a brief history
• How should we report HbA1c?
• Using HbA1c to diagnose diabetes
How do we diagnose diabetes currently?

- If a fasting plasma glucose (FPG) is $\geq 7.0\text{mmol/L}$
  and/or
- A 2hr post-OGTT plasma glucose is $\geq 11.1\text{mmol/L}$
A New Look at Screening and Diagnosing Diabetes Mellitus

Objective: Diabetes is underdiagnosed. About one third of people with diabetes do not know they have it, and the average lag between onset and diagnosis is 7 yr. This report reconsiders the criteria for diagnosing diabetes and recommends screening criteria to make case finding easier for clinicians and patients.

An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in nonpregnant individuals. The report of the International Expert Committee represents the consensus view of its members and not necessarily the view of the organizations that appointed them. The International Expert Committee hopes that its report will serve as a stimulus to the international community and professional organizations to consider the use of the A1C, for the diagnosis of diabetes.

Type 2 diabetes has a more gradual onset, with slowly rising glucose levels over time, and its diagnosis has required specified glucose values to distinguish pathologic glucose concentrations from the distribution of glucose concentrations in the nondiabetic population. Virtually every scheme for the classification and diagnosis of diabetes in modern times has relied on the measurement of plasma (or blood or serum) glucose concentrations in timed samples, such as fasting glucose; in casual samples independent of prandial status; or after a standardized metabolic stress test, such as the 75-g oral glucose tolerance test (OGTT).

Relied on distributions of glucose levels, rather than on the relationship of glucose levels with complications, to diagnose diabetes despite emerging evidence that the microvascular complications of diabetes were associated with a higher range of fasting and OGTT glucose values (11,13–15). The diagnostic glucose values chosen were based on their association with decompensation to “overt” or symptomatic diabetes.

When selecting the threshold glucose values, the NDDG acknowledged that “there is no clear division between diabetics and nondiabetics in the FPG concentration or their response to an oral glucose load,” and consequently, “an arbitrary decision has been made as to what level justifies the diagnosis of diabetes.” The diagnosis of diabetes was made when 1)
Diabetes should be diagnosed when A1C is $\geq 6.5\% \ (48\text{mmol/mol})$. Diagnosis should be confirmed with a repeat A1C test.

If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.
HbA1c ≥ 6.5% (48 mmol/mol)
OR
FPG ≥ 7.0 mmol/l
OR
2-h plasma glucose ≥ 11.1 mmol/L during an OGTT
OR
In a patient with classic symptoms….
   a random plasma glucose ≥ 11.1 mmol/L

‘The decision about which test to use to assess a specific patient for diabetes should be at the discretion of the healthcare professional’
Advantages in using HbA1c

- Assesses glycaemia over previous weeks/months
- Lower biological variability than FPG or 2hr
- Already used to guide management
- IFCC standardisation should help with harmonising results between labs
Advantages in using HbA1c

• Does not require a fasting sample
• Does not require a fasting sample
• Does not require a fasting sample
• Does not require a fasting sample
• Does not require a fasting sample
• Does not require a fasting sample
• Does not require a fasting sample
Problems in using HbA1c

- Can give spurious results in:
  - Haemoglobinopathies
    HbS, HbC etc
  - Anaemia
    haemolytic
    iron deficiency
  - Renal failure
  - HIV infection
  - Ethnicity
  - Ageing
Problems in using HbA1c

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  - Haemoglobinopathies
    HbS, HbC etc
  - Anaemia
    haemolytic
    iron deficiency
  - Renal failure
  - HIV infection
  - Ethnicity
  - Ageing
Effect of haemoglobinopathies on HbA1c methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Interference (Yes/No)</th>
<th>Hb C trait</th>
<th>Hb S trait</th>
<th>Hb E trait</th>
<th>Hb D trait</th>
<th>Elevated HbF</th>
<th>Carbamyl-Hb</th>
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<tr>
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<td>No</td>
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<td>Pointe Scientific Hemoglobin A1c</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>Primus Boronate Affinity HPLC</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Bio-Rad Deeside (previously Provalis)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>MicroMat (also sold by Cholestech as GDX)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td></td>
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<td>Randox Haemoglobin A1c</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (&gt;10%)</td>
<td></td>
</tr>
<tr>
<td>Roche Cobas Integra</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Roche Cobas Integra Gen2</td>
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For People of African, Mediterranean, or Southeast Asian Heritage: Important Information about Diabetes Blood Tests

When to Suspect that a Patient with Diabetes Has a Hemoglobinopathy

People who carry one gene for a hemoglobinopathy are often unaware. Several situations may indicate the presence of a hemoglobinopathy:

- when results of self-blood-glucose monitoring have a low correlation with A1C results
- when an A1C result is different than expected
- when an A1C result is more than 15 percent
- when a patient’s A1C test result is radically different from a previous test result following a change in laboratory A1C methods

Problems in using HbA1c

- Can give spurious results in:
  - Haemoglobinopathies
    - HbS, HbC etc
  - Anaemia
    - haemolytic
    - iron deficiency
  - Renal failure
  - HIV infection
  - Ethnicity
  - Ageing
Effect of Fe deficiency anaemia on HbA1c

- 50 patients (30 women, 20 men, mean age 35.7 ± 11.9 years) with IDA and 50 controls
- HbA1c in healthy group 5.9% ± 0.5%
- HbA1c in IDA 7.4% ± 0.8% (p<0.001)
- Following 3 months iron HbA1c 6.2% ± 0.6%

Acta Haematol 2004;112:126-128
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  - Ageing
HbA1c and ethnicity in the Diabetes Prevention Programme

Mean HbA1c in subjects with IGT:

- 5.78% for whites
- 5.93% for Hispanics
- 6.00% for Asians,
- 6.12% for American Indians
- 6.18% for blacks

After adjusting for age, sex, BP, BMI, fasting glucose, glucose AUC, corrected insulin response, and insulin resistance

*Diabetes Care* 30:2453–2457, 2007
A shift to an HbA1c-based diagnosis for diabetes will have substantially different consequences for diabetes prevalence across ethnic groups.

Diabetes Care 2010; 33:580-582
Racial differences in HbA1c

HbA1c difference. Black vs. White, NHANES III

**Problems in using HbA1c**

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    - HbS, HbC etc
  - Anaemia
    - haemolytic
    - iron deficiency
  - Renal failure
  - HIV infection
  - Ethnicity
  - Ageing
HbA1c and age

Fructosamine (μmol/L) vs. HbA1c (%)

Age (years)

QJM 1996; 89: 307-312
‘A1C increases with age even after multivariate adjustments for gender, fasting and 2hPG.

......................... (it) suggests that non-glycemic factors may contribute to the relationship of A1C with age.’

Pandi.....and Nathan
HbA1c and diabetes diagnosis: ensuring the correct result

Further tests
- Haemoglobinopathy screen
- FBC, ferritin, haptoglobin
- Urea, creatinine

Other factors
- Ethnic background
- Age
Glucose and diabetes diagnosis: ensuring the correct result

- Make sure the patient is fasting
The proposed cut-off for diagnosis
A New Look at Screening and Diagnosing Diabetes Mellitus

Objective: Diabetes is underdiagnosed. About one third of people with diabetes do not know they have it, and the average lag between onset and diagnosis is 7 yr. This report reconsiders the criteria for diagnosing diabetes and recommends screening criteria to make case finding easier for clinicians and patients.

Conclusions: The main factors in support of using HbA1c as a screening and diagnostic test include:
Diabetes should be diagnosed when A1C is $\geq 6.5\%$ (48mmol/mol). Diagnosis should be confirmed with a repeat A1C test.

If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.

Diabetes Care 2009 32: 1327-1334
**HbA1c vs. OGTT**

**US NHANES**
- 1.6% of the population had HbA1c ≥ 6.5%
- 5.1% undiagnosed using FPG or 2hr criteria
- 25% of patients with a +ve GTT had an HbA1c ≥ 6.5%
- 55% of patients with FPG ≥ 7mmol/L AND 2hr ≥ 11.1mmol/L had an HbA1c ≥ 6.5%

*Diabetes Care 2010 33:562–568*
HbA1c of $\geq 6.5\%$ for diagnosis

- Will not identify half to two thirds of patients diagnosed using current criteria
- Will the ‘missing third’ now be the ‘missing two thirds’?
- Will it delay diagnosis in these two thirds?
- Is it acceptable that someone with a haemoglobinopathy etc is 2-3 times as likely to be diagnosed as someone without?
What about type 1 diabetes?

Could HbA1c criteria lead to a (critical) delay in diagnosis?
HbA1c to diagnose diabetes

- HbA1c for diagnosis has its attractions
- Using a ‘simple’ HbA1c measurement to diagnose diabetes may not be so simple
- Individual patients risk being wrongly diagnosed because of non-glycaemic factors
- Populations risk having their diagnoses delayed
But Doctor, WHO
Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

*Abbreviated Report of a WHO Consultation*
An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%.

GRADE quality of evidence: moderate
GRADE strength of recommendation: conditional
What’s going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes
Where from here?

- IFCC (SI) numbers seem destined to be widely used in most countries outside the US
- It seems likely HbA1c will become a diagnostic test for diabetes in the UK
- It is still unclear exactly how it will be implemented.