Guidelines and recommendations for testing in diagnosis of DM: The role of HBA1c

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History

1980 WHO

- ✓ Based on oGTT (in non pregnant women)

1997 IEC

- ✓ oGTT criteria supplemented with FPG

2009 IEC members of ADA, EASD and IDF

- ✓ recommended HbA1c as preferred test in T2D
- ✓ HbA1c value 48 mmol/mol (≥6.5%)

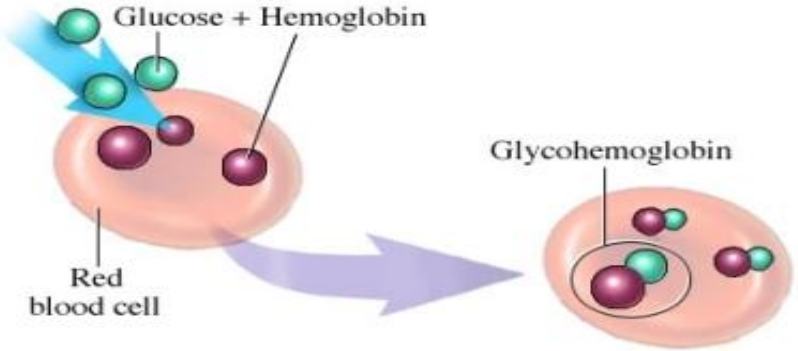
IUPAC-IUB Joint Commission on Biochemical Nomenclature, 1984

Haemoglobin A1c

- ✓glycated haemoglobin
- ✓glycohemoglobin
- ✓glycosylated
- ✓glucosylated haemoglobin
- ✓Hb A1
- ✓Hb A1c

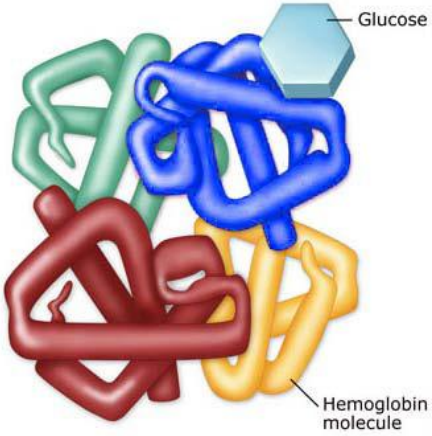
The term glycosylated (glucosylated) is an **enzymatic process** resulting in glycoside (glucoside) compounds.

The term glycated is the **non-enzymatic covalent binding** of glucose or other sugar to free amino groups of proteins – glycated proteins



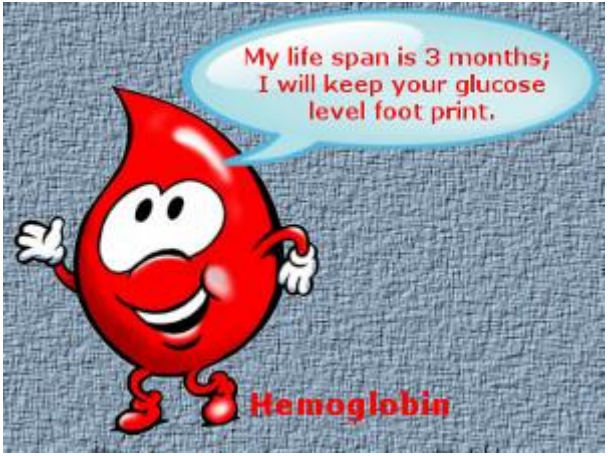
*JCBN - IUPAC-IUB Joint Commission on Biochemical Nomenclature

What is HbA1c?



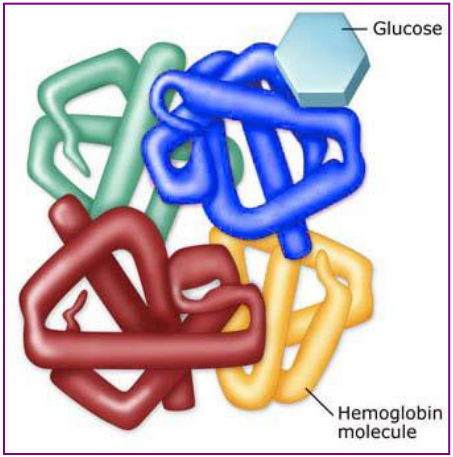
Glycated hemoglobin - stable adduct of glucose to the N-terminal Valine of the Haemoglobin β chain (β N-1-deoxyfructosyl-hemoglobin)

Nathan et al. Translating the A1c Into Estimated Glucose. Diabetes Care 2008; 31:1473-1478, Christchurch Diabetes Center 2009



- The mean erythrocyte life span is approximately 120 days
- The HbA1c value reflects the integrated glucose concentration over the preceding 8–12 weeks

Methodology → ~ 100/35 y two principles



- methods based on charge differences between glycated and nonglycated components (cation-exchange chromatography, agar-gel electrophoresis)
- methods separating glycated and nonglycated components based on structural differences (boronate affinity chromatography, immunoassay)
- most charge-based and immunoassay methods measure HbA1c, whereas other methods quantify 'total glycated haemoglobin'

GHb results reported for the same blood sample can differ considerably among methods.

Nathan et al. Translating the A1c Into Estimated Glucose. Diabetes Care 2008; 31:1473-1478, Christchurch Diabetes Center 2009

Proces to standardisation

1995 IFCC – WG HbA1c standardisation

✓reference procedure with purified primary calibrators,
✓network of reference laboratories and implementation of traceability to the IFCC reference system
✓defined analyte - βN1-deoxifructosyl-haemoglobin
✓recommended units - mmol/mol

1996 – NGSP

✓initiated to standardise GHb test results among laboratories to DCCT-equivalent values
✓manufacturers of HbA1c assays should follow traceability to the IFCC reference method

1997 – IFCC Committee

✓higher-order reference method and reference materials

2001 – Method approved (manufacturers)

Variety of changes in reporting HbA1c

Consensus on reporting HbA1c results

1. A1C test results should be standardized worldwide, including the reference system and results reporting.

2. The new IFCC reference system for A1C represents the only valid anchor to implement standardization of the measurement.

3. A1C results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.

4. 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.

5. Glycemic goals are expressed in IFCC units, derived NGSP units, and as ADAG.

International consensus agreement among the ADA, EASD, IDF, and IFCC signed in Milan, Italy, in 2007. Diabetes Care 2007; 39(9):

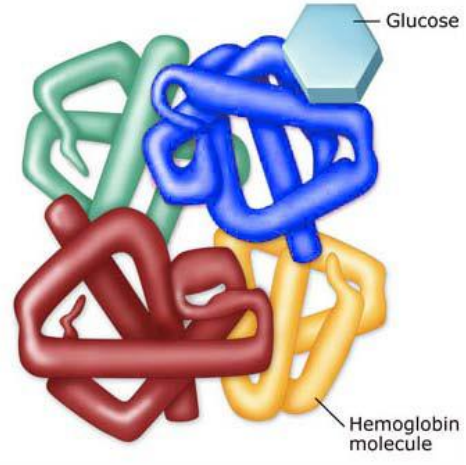
Since June 2011, HbA1c reporting switched from a percentage to mmol/mol

To make sense of the new units and compare these with old units and *vice versa*, a converter was developed

Master equation

Use of HbA1c

- ✓ Diagnosis of diabetes
- ✓ Monitoring glycemic control
- ✓ Risk of micro- and macro vascular complication
- ✓ Emergency
- ✓ Confirm accuracy of self monitoring meters



Every 1% decrease in HbA1c reduces diabetic complications

Stratton et al BMJ 2000; 321: 405-412

Use of HbA1c to Diagnosis of Diabetes

Diabetes confirmed –
HbA1c to be 48mmol/mol (≥6.5%)

'Subdiabetic "high risk" –
HbA1c 42–46mmol/mol (6.0–6.4%)

Increased risk of diabetes -
HbA1c (39–46mmol/mol (5.7–6.4%)

25% of individuals with a 'positive' OGTT had 48mmol/mol,

45% of individuals exceeding both fasting and 2 h glucose criteria were not diagnosed with diabetes using HbA1c. The additional effect of ethnicity and aging has an important role in these proportions.

Undiagnosed type 2 diabetes

- ✓ 2011 Undiagnosed:
  ~7.0 million people*
- ✓ 1 out of 3 people with T2D don't know they have it

*Centers for Disease Control and Prevention. National Diabetes Fact Sheet. 2011. Atlanta, GA
http://diabetes.webmd.com/slideshow-type-2-diabetes-overview

HbA1c - ?

- Haemoglobinopathies – HbS; HbC; et
- Anaemias - haemolitic; sideropenic
- Kidney diseases patients
- HIV infection
- Age (0.4 – 1.5%)
- Ethnicity (0.4 – 1.5%)
- Smoking

HbA1c – advantages

- ✓ Established for monitoring patients known to have diabetes
- ✓ Does not require a fasting sample and is more stable after sample collection than glucose
- ✓ Marker of glucose control over the previous weeks or months
- ✓ Lower within person variability than with glucose

Use of HbA1c Monitoring Glycemic Control

Recommended*

- ✓ at least biannually in all diabetic patients
- ✓ quarterly in patients whose therapy has changed or who failed to meet treatment goals

* recommended for non pregnant patients with either type 1 or type 2 diabetes.

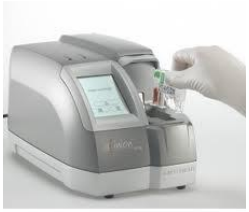
utmost importance the consider the race- and age-specific HbA1c target, as well as different causes leading to misinterpretation of HbA1c, such as haemoglobinopathies, anaemia, renal failure, HIV infection, etc.

Use of HbA1c to identify risk of micro- and macrovascular complication

- ✓ HbA1c 48mmol/mol – predictive risk of microvascular complication (rethinopathy)
- ✓ HbA1c may be superior than FPG in predicting macrovascular complication (CV events)
- ✓ Relationship between increasing of HbA1c and CV risk

Every 1% decrease in HbA1c reduces diabetic complications

Use of HbA1c in emergency



Point-of-care (POC) HbA1c - not sufficiently accurate to use it for the diagnosis of diabetes.

Although several POC HbA1c assays are NGSP certified, due to the lack objective and ongoing documentation of performance proficiency testing POC HbA1c instruments should not be used for diagnosis or screening.

Use HbA1c to confirm accuracy of self monitoring meters

Analytical consideration
Different instruments - technologies

NEQAS – 2009

Results from 251 instruments

Target value 48 mmol/mol (6.5%)

Values obtained from 40 – 55 mmo/mol (5.8 -7.2%)

Kilpatrick ES et al: ABCD Position statement on Hemoglobin A1c for the diagnosis of diabetes. Pract Diab; 2010; 27(6)1-5.

HbA1c POCT

Annual Point of Care Proficiency Testing

The POCT quality is not satisfy and is not recommended Knowledge, skills and experience

Kilpatrick ES et al: ABCD Position statement on Hemoglobin A1c for the diagnosis of diabetes. Pract Diab; 2010; 27(6)1-5.

2011 - The National Academy of Clinical Biochemistry published - Guidelines and Recommendation for laboratory analysis in the diagnosis and management of diabetes mellitus

Sacks *et co*, endorsed by AACC and ADA: NACB Diabetes Mellitus. http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/diabetes. 2014

The Guidelines revealed important recommendations concerning HbA1c :

1) HbA1c should be measured routinely in all patients with diabetes to document their degree of glycemic control
2) Laboratories should use only HbA1c methods that are certified by the NGSP as traceable to the DCCT reference
3) The manufacturers of HbA1c assays should show traceability to the IFCC reference method.
4) Related to the reference intervals, it is recommended that laboratory should determine its own reference interval even if the manufacturer has provided one.

Sacks et all, endorsed by AACC and ADA: NACB Diabetes Mellitus. http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/diabetes. 2014

The Guidelines revealed important recommendations concerning HbA1c :

5) In clinical settings, patient with HbA1c results below the lower limit of reference interval or very high (140 mmol/mol; >15%) HbA1c should be verified by repeat testing,

6) HbA1c values that are inconsistent with clinical presentation should be investigated further.

The Guidelines emphasise the importance of HbA1c interpretation, which requires close laboratory-physician interaction

Sacks et all, endorsed by AACC and ADA: NACB Diabetes Mellitus. http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/diabetes. 2014

Conclusion

The existence of formal recommendations is crucial for standardization of the criteria, methods and procedures in various clinical conditions, however, a number of questions remain that require additional research for the recommendations to resolve all the shortcomings observed to date.

Thank you for your attention!