



ABCD position statement on haemoglobin A_{1c} for the diagnosis of diabetes

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Background

The diagnostic criteria for diabetes has slowly developed over the last 50 years. Fundamentally, the diagnosis of diabetes has been determined as the glycaemic threshold for microvascular disease, predominantly retinopathy. By the 1960s, the oral glucose tolerance test (OGTT) had become established as the means by which type 2 diabetes should be identified, but there was inconsistency as to how the test should be performed, in the quantity of glucose that should be ingested and the diagnostic blood glucose cut-offs. These criteria were standardised by the World Health Organization (WHO) in 1980¹ and have evolved since then, with the fasting plasma glucose (FPG) value more central to the diagnosis.²

Ever since the 1980s, when the measurement of haemoglobin A_{1c} (HbA_{1c}) became routine in patients already known to have diabetes, there has been the suggestion that this test could supplant the measurement of blood or plasma glucose as the diagnostic test for the disease. Two recent reports have recommended incorporating HbA_{1c} into the current diagnostic criteria.^{3,4} This ABCD position statement updates these recommendations for the United Kingdom, highlighting the advantages and disadvantages to using HbA_{1c} as a diagnostic test in non-pregnant individuals.

International recommendations

An International Expert Committee on the role of HbA_{1c} in diabetes diagnosis published their report in

June 2009.³ The Committee (comprising members appointed by the American Diabetes Association [ADA], the European Association for the Study of Diabetes [EASD] and the International Diabetes Federation [IDF]) recommended that diagnosis in type 2 diabetes should now usually be made solely on the basis of an HbA_{1c} confirmed to be $\geq 6.5\%$ (48mmol/mol), without the need to measure a plasma glucose concentration in the subject. A 'subdiabetic "high risk" state' would exist for subjects with an HbA_{1c} of 6.0–6.4% (42–46mmol/mol).

Since then, the ADA has ratified the use of both the test and the diagnostic threshold as a fourth way of diagnosing diabetes, the other three continuing to be a fasting glucose value $\geq 7\text{mmol/L}$, a 2hr post-OGTT value of $\geq 11.1\text{mmol/L}$ or, in someone with classic symptoms of diabetes, a random plasma glucose of $\geq 11.1\text{mmol/L}$.⁴ The first three criteria would need confirmation by repeat testing in the absence of unequivocal hyperglycaemia. Where there is a discrepancy leading to one test (HbA_{1c} or glucose) being diagnostic, but the other not, the ADA recommends retesting the raised test and diagnosing diabetes if it remains above the diagnostic threshold. The decision about which test to use is at the discretion of the health care professional. An individual is regarded as being at an increased risk of diabetes with an HbA_{1c} of 5.7–6.4% (39–46mmol/mol).

Updated guidance from the EASD and WHO is awaited.

Using HbA_{1c} to diagnose diabetes

The advantages and disadvantages are summarised in Table 1.

Advantages

No requirement for fasting. HbA_{1c} has the undoubted benefit of being able to test an individual in the non-fasting state without it affecting the result. This could be helpful in the opportunistic identification of patients with glucose intolerance. Compared to glucose, there is also less of an issue in the stability of the measurement after a sample has been taken.

Low biological variability. Biological variability of HbA_{1c} is less than fasting glucose and considerably less than the 2hr post-GTT glucose value (coefficient of variation 3.6 vs 5.7 vs 16.7% in one study).⁵ This potentially means a single measurement is less likely to change significantly on repeat testing.

A measure of prior glycaemia. There is also the argument that, by giving an estimate of glycaemia over the preceding few weeks or months, HbA_{1c} could provide a more complete view of glycaemia than a one-off fasting glucose or the 'artificial' conditions of an OGTT. It is also less affected by the stress hyperglycaemia that can be found during an acute concurrent illness.

Analytical considerations. For much of the time during which HbA_{1c} has been in routine use in the UK it has been dogged by a lack of standardisation in measurement. This meant that results in patients with diabetes could

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Received: 28 May 2010
Accepted: 1 June 2010



vary substantially from one laboratory to another and having a single cut-off to diagnose the disease was inconceivable. From the mid 1990s, UK laboratories have steadily moved over to expressing results aligned to values used in the Diabetes Control and Complications Trial (DCCT-aligned) which has enabled more uniform reporting of HbA_{1c} values nationally. Within the last year there has been the further refinement of calibrating laboratory instruments to the new IFCC standard for HbA_{1c} measurement which, as well as heralding a change of units to mmol/mol, has the potential to bring results from different laboratories even closer together.⁶

Disadvantages

Despite the steady advances in measuring HbA_{1c}, inherent issues with the test mean that there is still potential for the test to give a misleading indication of glycaemia in an individual, and so lead to an inappropriate or missed diagnosis.

Abnormal haemoglobins. Measurement of HbA_{1c} is dependent on the haemoglobin circulating being predominantly HbA. Being able to identify and account for abnormal haemoglobins depends on the particular HbA_{1c} instrument being used, with most being able to discern some haemoglobinopathies but not others.⁷ The potential magnitude of this problem depends also on the prevalence of haemoglobinopathies, which obviously varies from race to race and country to country. As an example, data from the US estimate at least 10% of their 26 million African-American citizens have either an HbS or HbC trait present.⁸ Around one-third of HbA_{1c} instruments in routine use there will give a clinically significant error in the presence of these haemoglobins, some without any indication that a problem might exist.⁷ Patients with haemoglobinopathies can also have altered red cell survival which will influence all HbA_{1c} measurements. Guidance already exists on alerting clinicians to diabetes patients of African, Mediterranean or South-east Asian heritage who may have problems when using HbA_{1c} for monitoring.⁹ The advice would also seem applicable if the test is to be used for diagnosis.

Table 1. Advantages and disadvantages to using plasma glucose and HbA_{1c} thresholds for the diagnosis of diabetes – the recommendations are UK based so omit global considerations

	Advantages	Disadvantages
Fasting and/or post challenge glucose measures	<ul style="list-style-type: none"> Established as the current means of diagnosing diabetes Directly measures the molecule thought to cause diabetes complications Not subject to misleading results due to non-glycaemic factors Smaller differences in results between laboratories compared to HbA_{1c} Less expensive to measure than HbA_{1c} 	<ul style="list-style-type: none"> Requires patient to be tested in the fasting state and for the sample to be analysed promptly May require a glucose tolerance test for diagnosis A measurement of glucose at a single time-point Higher within-individual variability than that of HbA_{1c} Oral glucose tolerance testing laborious and time consuming
HbA_{1c}	<ul style="list-style-type: none"> Established as a means of monitoring patients already known to have diabetes Does not require a fasting sample and is more stable after sample collection than glucose A marker of glucose control over the previous weeks/months Lower within-individual variability than that of glucose Although more costly than glucose, overall cost as part of a screening/diagnostic pathway may not be 	<ul style="list-style-type: none"> Measurement can be misleading in patients with haemoglobinopathies, anaemia or renal failure May differ between patients of different ages and ethnicity Larger differences in results between laboratories compared to glucose A surrogate marker of hyperglycaemia with between-individual discrepancies between glucose and HbA_{1c}

Anaemias. It is widely appreciated that haemolytic anaemia, from whatever cause, can lead to HbA_{1c} values which are lower than expected because of reduced red cell survival. However, iron deficiency anaemia can lead to an inappropriate rise in HbA_{1c} of 1–1.5%, which falls after iron treatment.¹⁰ This common condition, which is known to affect over three million women in the US,¹¹ also seems to influence the HbA_{1c} of non-diabetic subjects, although perhaps not as markedly as in those with the disease.¹²

Patients with renal failure can demonstrate both iron deficiency and haemolytic anaemia, thereby having an unpredictable effect on the HbA_{1c} result. Some instruments are also affected by the carbamylated haemoglobin formed in excess in renal failure.

Ageing and ethnicity. It has been identified that older non-diabetic subjects appear to have higher HbA_{1c} values than younger individuals, being approximately 0.4% higher at 70 years than at 40 years,¹³ even after adjusting for fasting and 2hr glucose. Differences in the HbA_{1c} have also been consistently found between individuals from different races, with Afro-Caribbeans having values 0.4% higher than Europids with apparently the same glucose tolerance.¹⁴ A similar difference has been found between individuals of South Asian descent and Caucasians in the UK.¹⁵ There is currently insufficient evidence to know if Afro-Caribbeans, Asians or elderly people are more hyperglycaemic than their GTT would suggest but, if not, then it is possible that these groups would be



over-diagnosed by a single HbA_{1c} cut-off. In turn, this could necessitate the use of age-related and race-related diagnostic thresholds for HbA_{1c}.

Analytical considerations. Although IFCC standardisation of HbA_{1c} measurement is an undoubted step forward in improving comparability between laboratories, the technological limitations of measuring HbA_{1c} mean there are still clinically significant differences between laboratories using different instruments from different manufacturers. As part of the UK National Quality Assurance Scheme (NEQAS), the same sample sent to UK laboratories was analysed on 251 instruments in July 2009. The assigned HbA_{1c} value was the proposed diagnostic threshold of 6.5% (48mmol/mol), but reported results varied from 5.8 and 7.2% (40 and 55mmol/mol) [personal communication, Jonathan Middle, UKNEQAS], so the likelihood of being diagnosed with diabetes, or not, would still be partly dependent on the laboratory to which the sample was sent. Currently, most point-of-care HbA_{1c} analysers do not perform satisfactorily enough to be used for diagnostic purposes.

Comparing HbA_{1c} and glucose to diagnose diabetes

The relationship between fasting/2hr glucose and HbA_{1c} within the non-diabetic reference range is not nearly as tight as it is when patients with diabetes are included ($r^2 = 0.26$ for FPG and 0.14 for 2hr¹⁶), so the population of individuals diagnosed using HbA_{1c} is not the same as that when using glucose. Using an HbA_{1c} threshold which will maintain a similar prevalence of diabetes to that currently, only around a half would be diagnosed using both criteria. Consequently, half the subjects diagnosed at present using glucose would not be using HbA_{1c}, and half using HbA_{1c} would not currently be using glucose.

The proposed diagnostic cut-off of 6.5% (48mmol/mol) for HbA_{1c} is above the value that most studies have shown would lead to a diabetes prevalence equivalent to that using plasma glucose, so fewer patients will be newly diagnosed if HbA_{1c} at this level is used alone. In the US NHANES population, 1.6% of adult individuals

had undiagnosed diabetes using this HbA_{1c} threshold, 2.5% if using fasting glucose alone and 4.9% if using 2hr glucose alone.¹⁷ The prevalence of undiagnosed diabetes using any glucose criteria (fasting or 2hr) was 5.1%, and including HbA_{1c} it rose to 5.4%. There is thus more than a three-fold difference in prevalence between the preferred position of the Expert Committee (1.6%) and both the current WHO recommendation (5.1%) and the literal interpretation of the ADA recommendation to use any or all of the tests (5.4%).

Overall, only 25% of individuals with a 'positive' OGTT had an HbA_{1c} $\geq 6.5\%$, while 45% of individuals who exceeded both the fasting and 2hr glucose criteria (1% of the full population) were not diagnosed with diabetes using HbA_{1c}.

Superimposing the effect of ethnicity and ageing has a marked influence on these proportions. Whitehall II data from the UK showed that while 91% of white subjects with an HbA_{1c} $\geq 6.5\%$ had diabetes by GTT, the higher values normally found in Asian and black subjects meant that only 61% and 50% respectively also had glucose diagnosed diabetes.¹⁸ The rise in HbA_{1c} normally with age is probably responsible for only 15% of elderly patients with an HbA_{1c} $\geq 6.5\%$ in the Rancho Bernardo Study having glucose-defined diabetes and one-third actually being completely normoglycaemic above this HbA_{1c}.¹⁹

HbA_{1c} as a test to identify risk of microvascular complications

Identifying patients at risk of developing microvascular complications (particularly retinopathy) has been the basis for diagnosing an individual as having diabetes. The International Expert Committee argued it was more appropriate to use 'moderate' retinopathy (rather than 'any') as an endpoint in identifying an HbA_{1c} threshold for diabetes,³ which is presumably one reason why the prevalence of diabetes using the 6.5% (48mmol/mol) value derived in this way is so much lower than when using current glucose criteria. However, using this logic, the glucose cut-offs may have been expected to rise too.

There is debate around whether HbA_{1c} predicts retinopathy in a

population any differently to that of glucose. Older studies (in Pima Indians, Egyptian and NHANES populations) seemed to favour glucose as the best predictor,²⁰ particularly the 2hr value, while as-yet unpublished data cited in the Expert Committee report has shown HbA_{1c} to be at least as predictive.³

HbA_{1c} as a test to identify risk of macrovascular complications

The diagnosis of diabetes leads to intensive management of cardiovascular (CV) risk factors in addition to hyperglycaemia, with many patients prescribed antihypertensive and lipid lowering agents. As shown, at a 6.5% cut-off far fewer individuals in some populations would automatically receive this treatment consideration. In addition, the move to HbA_{1c} for diagnosis would largely replace the 2hr post-OGTT glucose diagnosis of diabetes and therefore remove impaired glucose tolerance (IGT) as an entity. HbA_{1c} is acknowledged to be poor at identifying patients with impaired fasting glucose (IFG) or IGT,²¹ and those individuals found to be in the Expert Committee 'high risk' state (HbA_{1c} of 6.0–6.4% [42–46mmol/mol]) belong to a group which is about 10 times smaller in size than would be identified as having either IFG or IGT.¹⁷ The alternative categorisation of intermediate glucose intolerance will therefore have a major impact on both CV disease risk estimation and the strategy for ongoing screening for diabetes in this group.

With regard to CV risk prediction, there is evidence that HbA_{1c} may be superior to fasting glucose alone in predicting future CV events.²² However, post-prandial hyperglycaemia, even with all its inherent variability, has usually been shown to be superior, again compared to both fasting glucose and HbA_{1c}.²³ Other studies have also shown a relationship between increasing HbA_{1c} and increasing CV risk,²⁴ but the test appeared to add little to the CV risk already identified using known risk factors such as blood pressure and cholesterol.²⁵

Type 1 diabetes

Although the discussion around using HbA_{1c} for diagnosis centres on type 2 diabetes, the ADA also makes it

**Table 2.** Suggested diabetes screening algorithm for the UK

1. Consider laboratory testing of HbA_{1c} as an alternative test in adults without conditions known to affect HbA_{1c} measurement. Do not use if type 1 diabetes is suspected
2. If HbA_{1c} <5.8% (40mmol/mol) then diabetes excluded
3. If HbA_{1c} >7.2% (55mmol/mol) on 2 occasions then diabetes diagnosed*
4. If HbA_{1c} 5.8–7.2% (intermediate HbA_{1c}), or an HbA_{1c} >7.2% is not confirmed, use existing fasting glucose and/or glucose tolerance test criteria to confirm or exclude diabetes
5. Where HbA_{1c} measurement may be, or is known to be, inappropriate, test using existing fasting glucose and/or glucose tolerance test criteria
6. Annual testing is suggested for patients identified as having intermediate HbA_{1c}, IFG or IGT on initial screening

*Repeat testing can be at any time after the initial request and is mainly to ensure a sample mix-up could not have occurred.

applicable to patients with type 1 diabetes. There are two concerns in applying HbA_{1c} to this clinical situation. Firstly, it is recognised that rapidly evolving hyperglycaemia in type 1 diabetes may not be immediately reflected in a raised HbA_{1c}, thereby potentially delaying any diagnosis.⁴ Secondly, as the laboratory turnaround time of HbA_{1c} samples is seldom nearly as rapid as glucose, this too could introduce a critical delay.

Applicability of HbA_{1c} limitations in known diabetes

The disadvantages of HbA_{1c} in diabetes diagnosis also apply to patients with known diabetes where population HbA_{1c} targets are used to inform management of hyperglycaemia. However, ABCD's view is that there is a distinction in using HbA_{1c} for diagnosis and for monitoring. Firstly, for an individual subject a diagnosis of diabetes often has lifelong major lifestyle, insurance and psychological implications as well as meaning they will be recommended to use the health care system much more frequently than before diabetes was identified. There is, therefore, an especial duty to patients to ensure that there is the least chance of misdiagnosing hyperglycaemia, one way or the other. By doing so, it also makes sure that health care resources are targeted in the most appropriate way. Secondly, while there may be an argument that race and age-specific HbA_{1c} targets be considered for patients with diabetes, these

measurements are often supported by that of blood glucose, so discrepancies between them can usually be identified. Lastly, the magnitude of the discrepancy in diabetes will likely, at worst, mean a treatment change is considered sooner or later than is ideal; however, when applied to using HbA_{1c} as a diagnostic test it could, as shown above, lead to either incorrect diagnosis in some normoglycaemic subjects or false reassurance – and therefore a missed diagnosis – in some with unequivocal hyperglycaemia.

Alternative HbA_{1c} strategies

Glucose measurement will always need to be an option for diagnosing diabetes, either because HbA_{1c} is known to be unreliable in an individual or because the health care budget in some countries may not support HbA_{1c} measurement.

Options for incorporating HbA_{1c} into the diagnostic process other than replacing glucose have been suggested. One option has been to combine measurement of fasting glucose and HbA_{1c},²⁶ meaning that HbA_{1c} is being used as a surrogate for the 2hr post-GTT result. An added attraction is the recent evidence that increasing fasting glucose and HbA_{1c} are both independently predictive of subsequent diabetes development.²² By combining the two tests it has been shown that this could obviate the need for around half of current OGTTs.²⁶

Another suggestion has been to make the HbA_{1c} thresholds for ruling

out or ruling in diabetes lower and higher than suggested by the ADA in order to triage patients for further glucose testing. By using a 'rule out' HbA_{1c} cut-off of ≤5.5% (37mmol/mol) and a 'rule in' threshold of ≥7.0% (53mmol/mol), three-quarters of the AusDiab population could be excluded from further investigation.²⁷ A further analysis of these data has shown that a 'rule out' threshold of <5.8% (40mmol/mol) would still have a negative predictive value of 98.3% and a 'rule in' cut-off of >6.7% (50mmol/mol) would have a positive predictive value of 100%, leaving 10% of the population (HbA_{1c} 5.8–6.7% [40–50mmol/mol]) requiring glucose testing to confirm or refute hyperglycaemia [personal communication, Lu Zhong]. The applicability of these thresholds to populations of different ages and races and to individuals in the UK has yet to be established. Since ageing, ethnicity and iron deficiency all appear to raise HbA_{1c}, it means the uncertainty mainly involves the 'rule in' threshold. ABCD would therefore suggest the testing principle given in Table 2, being aware that the limits may need to change when further data become available.

Research agenda

In considering HbA_{1c} as a diagnostic test for diabetes in the UK we suggest the following key areas for research:

- Continued industry and laboratory initiatives to bring HbA_{1c} values in UK laboratory analysers from different manufacturers closer to both the IFCC reference HbA_{1c} method and to one another.
- Further examination of any effect of ageing and ethnicity on HbA_{1c} values in the UK population.
- Exploration of desirable UK thresholds for a 'rule in, rule out' strategy using HbA_{1c} which will account for any effect of ageing or ethnicity on these values.
- Comparing HbA_{1c} as a predictor of retinopathy with the current UK strategy of fasting glucose values possibly cascading on to a GTT.

Conclusions

ABCD can understand the appeal of using HbA_{1c} as a diagnostic test for diabetes and of the practical advantages it confers compared to glucose

**Table 3.** Possible causes of discrepancy between plasma glucose and HbA_{1c}

- Haemoglobinopathies
 - HbS, HbC etc
- Anaemia
 - haemolytic
 - iron deficiency
- Renal failure
- HIV infection
- Ethnicity
- Ageing
- Smoking

measurement. The current glucose criteria for diagnosis remain somewhat arbitrary and the testing process itself has well documented limitations. However, at this moment, there are unresolved concerns which could feasibly lead to HbA_{1c} being much more likely than glucose to completely misdiagnose an individual as having diabetes or not. The possible requirement for further testing to exclude conditions such as anaemia or haemoglobinopathies, as well as having to account for patient age and ethnicity, may make the simplification of diagnosis using HbA_{1c} measurement alone anything but.

ABCD recommends against using HbA_{1c} to diagnose when type 1 diabetes is suspected, appreciating that this statement is complicated by the difficulty in sometimes distinguishing type 1 from type 2 diabetes at initial presentation.

For type 2 diabetes, the complete supplanting of a plasma glucose diagnosis with HbA_{1c} seems premature given current evidence. However, there may be potential for using a laboratory-measured HbA_{1c} to triage patients for further glucose testing or to be used in combination with fasting glucose in diagnosis. The feasibility of using either of these successfully in a UK population is a research priority. Subjects with conditions known to affect HbA_{1c} values would still require exclusion (Table 3). For others, if HbA_{1c} is to be used in a diagnostic algorithm, ABCD recommends that current plasma glucose criteria be used to confirm or exclude diabetes in patients with equivocal HbA_{1c} values.

Conflict of interest statement

There are no conflicts of interest.

Key points

- An International Expert Committee report has recommended that HbA_{1c} be used as the preferred test for diagnosing diabetes. The American Diabetes Association has since added this test as an option for diagnosis
- The test has a number of potential advantages compared to glucose in identifying patients as having diabetes
- Persistent analytical differences between laboratories and inherent limitations in HbA_{1c} in assessing glycaemia mean that a single HbA_{1c} threshold for diabetes could miss subjects with hyperglycaemia while identifying some individuals without
- ABCD recommends continuing to diagnose most patients with type 2 diabetes using existing glucose criteria, but can see a role in the UK for HbA_{1c} to triage patients into those who do or do not need further glucose testing

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