**Expert Position Statement**

**Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011**

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**Introduction**

As our understanding of diabetes has evolved over the last 50 years, the diagnostic criteria for diabetes have changed. The diagnosis of diabetes has classically been determined as the glycaemic threshold for progression to microvascular disease, predominantly retinopathy. By the 1960s, the oral glucose tolerance test 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 standardized by the World Health Organization (WHO) in 1980 [1] and have evolved since then, with the fasting plasma glucose value more central to the diagnosis in the USA [2].

Two reports have recommended incorporating haemoglobin A1c (HbA1c) into the current diagnostic criteria [3,4], and, more recently, the WHO [5] has stated:

**WHO recommendation**

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present that preclude its accurate measurement.

An HbA1c of 48 mmol/mol (6.5%) is recommended as the cut-off point for diagnosing diabetes. A value of less than 48 mmol/mol does not exclude diabetes diagnosed using glucose tests.

The SI unit for HbA1c is mmol/mol and is defined as mmol HbA1c per mol HbA0 + HbA1c.

A meeting was organized at the Department of Health with the objective of starting the process of agreeing on how these recommendations might be applied to UK clinical practice. All relevant diabetes and scientific organizations, along with recognized experts, were invited to attend (Appendix 1), with the objective to agree advice for the National Health Service (NHS) in England, Scotland, Wales and Northern Ireland on the use of the new WHO recommendation on HbA1c in the diagnosis of diabetes. Subsequently, there were extensive discussions and consultation with relevant individuals and organizations.

This consensus report provides guidance to clinicians in the UK about the use of HbA1c (also called glycated haemoglobin) in the diagnosis of diabetes. This report has been prepared jointly by: NHS Diabetes, Diabetes UK, the Association of British Clinical Diabetologists (ABCD), the Primary Care Diabetes Society (PCDS), the Association for Clinical Biochemistry (ACB), Community Diabetes Consultants (CDC), Training, Research and Education for Nurses in Diabetes (TREND-UK); along with invited experts referenced in Appendix 1. A brief summary of the consensus was released in 2011 [6]. This full report details the issues.

It is widely recognized that cardiovascular risk in the population increases with increasing HbA1c, and the emergence of diabetic retinopathy is used by the WHO and others, as the point at which diabetes is diagnosed. There has been discussion over many years as to the best measure to diagnose diabetes; measurement of plasma glucose has been the primary determinant, either fasting or following a glucose challenge. However, with improved standardization of HbA1c and good quality assurance, this analyte has now been advocated for diagnosis of Type 2 diabetes.

In developing the recommendations for UK clinicians, the following reports were considered:

1. The 2009 International Expert Committee Report on the role of the HbA1c assay in the diagnosis of diabetes. The report advocated the use of HbA1c for the diagnosis of diabetes [3]. The International Committee concluded that the cut-off for diabetes diagnosis should be an HbA1c ≥ 6.5% (≥ 48 mmol/mol). Individuals with an HbA1c of 6.0–6.4% (42–47 mmol/mol) should be considered at high risk for progression to diabetes; but ‘this range should not be considered an absolute threshold at which preventative measures are initiated’.

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2. In 2010, the American Diabetes Association adopted HbA1c ≥ 6.5% (≥ 48 mmol/mol) for the diagnosis of diabetes and 5.7–6.4% (39–47 mmol/mol) to identify a category for increased risk of future diabetes [4]. The American Diabetes Association report summarizes guidance to ensure national standardization for diagnosing diabetes. It does not replace individual clinical assessment of the patient. In particular, it should be noted that the diagnosis of Type 1 diabetes must not be based on HbA1c; this is likely to be a poor indicator, as patients may have such a rapid rise in glucose that HbA1c is not elevated initially. The priority in these patients is to avoid diabetic ketoacidosis by prompt diagnosis and insulin treatment.

3. The WHO report: *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. This report states: an HbA1c of ≥ 48 mmol/mol (≥ 6.5%) is recommended as the cut-off point for diagnosing diabetes. A value of less than 48 mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests [5].

**The diagnostic cut-off**

During the meeting, some clinicians suggested an HbA1c cut-off of ≥ 50 mmol/mol as a round number. The WHO states ≥ 48 mmol/mol (≥ 6.5%) and, while this is less memorable, the group agree that 48 mmol/mol should be the level used to adhere to the WHO recommendation. In symptomatic patients, initial management should not await the results of laboratory HbA1c analysis. See below for symptomatic patients suspected of having Type 1 diabetes. In symptomatic patients not suspected of Type 1 diabetes, an immediate finger-prick glucose test (following national guidance on glucose point-of-care test) should be performed to identify those requiring immediate treatment (Fig. 1). An HbA1c request can be sent to the laboratory the same day. One HbA1c result of ≥ 48 mmol/mol would be sufficient to diagnose diabetes in symptomatic patients, providing conditions precluding accurate measurement of HbA1c are excluded. If not, WHO guidance for the use of glucose in the diagnosis of diabetes should be followed. In asymptomatic patients, a single HbA1c result of ≥ 48 mmol/mol is likely to indicate diabetes; however, although uncommon, mistakes can be made during the entire process from taking the blood sample to laboratory error. Therefore, the group agreed with the WHO that, in asymptomatic patients, a second sample should be taken promptly (within 2 weeks) to confirm the diagnosis of diabetes. If one of the two results is below 48 mmol/mol, the patient does not have diabetes and should be monitored as outlined in

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**FIGURE 1** Patients who may need urgent treatment.
Fig. 2, and according to National Institute for Health and Clinical Excellence (NICE) guidance.

Some clinicians have been adding a fasting glucose test to HbA1c in at-risk, asymptomatic patients. Strong objections were raised to this by some group members as fasting is not universally complied with, and is inconvenient for many patients, and the combined results might be equivocal. This may result in a delay in diagnosis. Avoiding the need for fasting is a major benefit of using HbA1c. It was agreed that no fasting or random glucose test is needed for confirmation unless the patient has a condition precluding accurate measurement of HbA1c, in which case WHO guidance for the use of glucose in the diagnosis of diabetes should be followed.

Risk of developing diabetes/complications

Patients whose HbA1c is under 48 mmol/mol (6.5%) may still fulfill WHO glucose criteria for the diagnosis of diabetes. Use WHO glucose testing in patients with symptoms of diabetes or clinically at very high risk of diabetes. The use of such glucose tests is not recommended routinely. The group adopted the term ‘high risk of diabetes’ for patients most likely to progress to diabetes. The WHO did not provide specific guidance on HbA1c criteria for this group. NICE is currently considering the issue. In the interim, the expert reference group advised that clinicians should consider the individual patient’s personal risk of diabetes and provide advice and monitoring accordingly. However, in general, they recommended the following:

- **HbA1c 42–47 mmol/mol (6.0–6.4%)**
  - High risk of diabetes.
  - Provide intensive lifestyle advice.
  - Warn patients to report symptoms of diabetes.
  - Monitor HbA1c annually.

- **HbA1c under 42 mmol/mol (6.0%)**
  - These patients may still have a high diabetes risk (see Appendix 2).
  - Review the patient’s personal risk and treat as ‘high diabetes risk’, as clinically indicated.

Women with previous gestational diabetes who no longer have diabetes post-partum should be followed as high risk, as should those people who had high transient glucose values following a myocardial infarction.

As before, in patients with a condition precluding accurate measurement of HbA1c, WHO guidance for the use of glucose in the diagnosis of diabetes should be followed.

Considerations to be made when using HbA1c for diagnosis

When using HbA1c for diagnosis, it is important to realize that the individuals diagnosed may be different from those identified with plasma glucose (fasting or post-glucose challenge). But it is recognized that there is no single measurement related to hyperglycaemia that can be considered the gold standard in its relation to increased risk for microvascular or indeed

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*HbA1c values >120 mmol/mol likely to indicate marked hyperglycaemia which may need urgent assessment*

**FIGURE 2** Non-urgent situations in adults over 18 years old.
macrovascular complications [3]. Some studies suggest using an HbA1c ≥ 6.5% will maintain a similar prevalence of diabetes to the current diagnostic criteria, but only approximately a half would be diagnosed using both criteria. In contrast, studies from the UK suggest using HbA1c ≥ 48 mmol/mol (≥ 6.5%) could either increase or decrease the prevalence of diabetes compared with using an oral glucose tolerance test, and therefore suggesting there may be regional variation in this relationship [7,8]. Furthermore, it has been clearly demonstrated that the relationship between fasting/2-h glucose and HbA1c within the non-diabetic reference range is not nearly as tight as it is when patients with diabetes are included (r² = 0.26 for fasting plasma glucose and 0.14 for 2-h glucose) [9]. Consequently, up to half the subjects diagnosed at present using glucose would not be diagnosed using HbA1c, and half using HbA1c would not currently be diagnosed using glucose [9].

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 HbA1c ≥ 48 mmol/mol (≥ 6.5%) had diabetes by glucose tolerance test, the higher values normally found in Asian and black subjects meant that only 61% and 50%, respectively, also had glucose-diagnosed diabetes [7]. The rise in HbA1c that normally occurs with age is probably responsible for only 15% of elderly patients with an HbA1c ≥ 48 mmol/mol (≥ 6.5%) in the Rancho Bernardo Study having glucose-defined diabetes [7]. The rise in HbA1c that normally occurs with age is probably responsible for only 15% of elderly patients with an HbA1c ≥ 48 mmol/mol (≥ 6.5%) in the Rancho Bernardo Study having glucose-defined diabetes [7]. The rise in HbA1c that normally occurs with age is probably responsible for only 15% of elderly patients with an HbA1c ≥ 48 mmol/mol (≥ 6.5%) in the Rancho Bernardo Study having glucose-defined diabetes [7].

Analysis of HbA1c

Laboratory measurement

Measurement of HbA1c is based on changes that occur following glycation of the haemoglobin molecule; the structural change (affinity chromatography and immunoassay) and change in charge (cation exchange chromatography and capillary electrophoresis) are both used by modern analytical methods in clinical laboratories [11]. Modern methods are very reproducible and are standardized to an international reference measurement procedure that ensures they are highly accurate. In addition, factors that interfere with older methods have been eliminated in the majority of modern methods; but any physiological factor that changes the red cell lifespan will affect the HbA1c result.

It is recognized that pre-analytical variation for HbA1c is less than for glucose analysis. However, at present, analytical variance for HbA1c remains greater than that of glucose. There has been considerable improvement in HbA1c measurement in the UK over recent years, and there is a general programme for continued work to improve laboratory performance nationwide.

Laboratories in the UK participate in External Quality Assessment (EQA); there are two providers in the UK [UK National External Quality Assessment Service (NEQAS), Birmingham and Wales External Quality Assessment Scheme (WEQAS), Cardiff], both External Quality Assessment schemes distribute samples to laboratories for analysis and returned results are assessed; this process should ensure that laboratories produce high-quality results. Different analytical principles may have different analytical specifications.

Laboratories issuing HbA1c results for diagnostic purposes must participate in External Quality Assessment and meet quality specifications. There are few published data as to the analytical performance required for HbA1c methods used for diagnosis, but, as a minimum, the within-laboratory imprecision should be < 3% coefficient of variation and between agreement must be within 5% coefficient of variation (using SI units) [12]. Certain methods may not achieve minimum requirements for diagnosis, and as such should not be used for this purpose. Recent data on an External Quality Assessment sample with a target value of 47.5 mmol/mol (assigned by a secondary reference method) and distributed to UK hospital laboratories produced an all-laboratory trimmed mean of 49.6 mmol/mol, and the between-laboratory agreement was 4.3% coefficient of variation. The range of results reported by laboratories was between 40 and 60 mmol/mol.

Point-of-care testing

There are a number of point-of-care testing systems available on the market, and it is likely that this number will increase. As with other point-of-care testing systems, those available for HbA1c analysis are not all as robust as laboratory methods, and may not show the same level of accuracy and precision. Data from the Wales External Quality Assessment Scheme show variable quality for different point-of-care testing analysers. Probably the most comprehensive study was performed by the Australian External Quality Assessment Scheme [13]; these investigators found that HbA1c analysis was performed well in general practice, and point-of-care testing results compared closely with laboratory results (−0.0504% bias). It should be noted that practices taking part in the study had a robust quality system in place, and only one type of analyser was used throughout (DCA 2000 + ; Siemens Healthcare Diagnostics, Camberley, UK).

It is well recognized that point-of-care testing analysers perform less well when operated by non-laboratory personnel; but analytical quality of point-of-care testing analysers used by trained laboratory staff was recently investigated by Lenters-Westra and Slingerland [14]; these investigators suggest that most point-of-care testing devices do not perform to the quality specifications achieved by laboratory methods, and would certainly not be robust enough for diagnostic purposes.

If point-of-care testing instruments are to be used for diagnosis, the analytical quality must match that of clinical laboratories, and the analyser used has to be enrolled in an External Quality Assessment scheme. Always confirm a point-of-care testing diabetes diagnosis with venous laboratory testing.
When HbA1c cannot be used for diagnosis

Those present were in unanimous agreement that HbA1c is not to be used for diagnosis of diabetes in the patients or situations listed below; HbA1c should be measured in such patients as part of clinical assessment but a value < 48 mmol/mol does not exclude diabetes.

- All children and young people.
- Pregnancy—current or recent (< 2 months).
- Suspected Type 1 diabetes, no matter what age (Appendix 3).
- Short duration of diabetes symptoms.
- Patients at high risk of diabetes who are acutely ill (HbA1c ≥ 48 mmol/mol confirms pre-existing diabetes, but a value < 48 mmol/mol does not exclude it and such patients must be retested once the acute episode has resolved).
- Patients taking medication that may cause rapid glucose rise; for example, corticosteroids, antipsychotic drugs (2 months or less). HbA1c can be used in patients taking such medication long term (i.e. over 2 months) who are not clinically unwell.
- Acute pancreatic damage or pancreatic surgery.
- Renal failure.
- Human immunodeficiency virus (HIV) infection.

Where blood glucose levels may have risen too fast to influence HbA1c levels, use immediate finger-prick capillary glucose measurement (equipment, staff and the healthcare facility must comply with national guidance for capillary glucose testing). In symptomatic or unwell individuals, if glucose is > 11.0 mmol/l, test blood or urine for ketones and, if they are positive, seek same-day specialist diabetes advice. For children and teenagers under 18 years of age contact the specialist paediatric diabetes team the same day. Finger-prick testing must be confirmed by same-day laboratory venous glucose testing, but do not delay seeking advice whilst awaiting the result (Fig. 1).

Factors to consider when using HbA1c for diagnosis

Clinical judgement is needed for each patient to consider the possibility of conditions that might cause inappropriate exclusion or inclusion in the diabetes-diagnosed category (Fig. 2). If in doubt, discuss the patient with your local laboratory or specialist diabetes team.

It was agreed that laboratories should print concise warning information for clinicians on the laboratory report.

Factors to be considered include:

Abnormal haemoglobins (variant haemoglobins)

Measurement of HbA1c is dependent on the haemoglobin circulating being predominantly HbA. The presence and prevalence of haemoglobinopathies (non-HbA) varies from race to race and country to country. As an example, data from the USA estimate at least 10% of their 26 million African-American citizens have either an HbS or HbC trait present [8]. Being able to identify and account for abnormal haemoglobins depends on the particular HbA1c instrument being used, with most being able to discern some haemoglobinopathies, but not all [15,16]. Some will not indicate the presence of haemoglobinopathies when producing a result [10]. Patients with haemoglobinopathies may also have altered red cell survival, which will influence all HbA1c measurements.

Anaemia

It is widely appreciated that haemolytic anaemia, from whatever cause, can lead to HbA1c values that are lower than expected because of reduced red cell survival. However, iron deficiency anaemia can lead to an inappropriate rise in HbA1c of 11–16 mmol/mol (1–1.5%), which falls after iron treatment [17]. This common condition, which affects over 3 million women in the USA [18] also seems to influence the HbA1c of people without diabetes, although perhaps not as markedly as in those with the disease [19]. Iron deficiency may therefore lead to over diagnosis. Patients with renal failure can demonstrate both iron deficiency and haemolytic anaemia, thereby having an unpredictable effect on the HbA1c result.

Altered lifespan of the red cell

Decreased HbA1c

Recent commencement of erythropoietin therapy will result in a decrease in HbA1c because of increased red cell production and therefore reduction in the average red cell lifespan. Decreased erythrocyte lifespan will occur with some haemoglobinopathies, splenomegaly, rheumatoid arthritis or with drugs such as antiretrovirals, ribavirin and dapsone.

Increased HbA1c

Increased erythrocyte lifespan, as with splenectomy.

Ageing

Older people without diabetes appear to have higher HbA1c values than younger individuals, being approximately 4 mmol/mol (0.4%) higher at 70 years than at 40 years [20], even after adjusting for fasting glucose and 2-h glucose.

Ethnicity

Differences in HbA1c have also been consistently found between individuals from different races; with Afro-Caribbeans having values 4 mmol/mol (0.4%) higher than white Europeans with apparently the same glucose tolerance [21]. A similar difference has been found between individuals of South Asian descent and white Europeans in the UK [22].
Summary
The WHO was very clear that an HbA1c of 48 mmol/mol (6.5%) and above is diagnostic of diabetes. They were less clear regarding results that fell below 48 mmol/mol. The WHO recognize that individuals with HbA1c values below the cut-off point may still have diabetes, but give no guidance on how to investigate further. It is important that these individuals, who may be at increased risk of developing diabetes, are monitored correctly; a recommended scheme is given in Fig. 2; following these recommendations will ensure at-risk people are not overlooked and will be monitored closely.

Even although it is not recommended to combine HbA1c with glucose measurement for diagnosis, the WHO did not discount the value of a fasting glucose and an oral glucose tolerance test to diagnose diabetes in selected individuals; it is the responsibility of the investigating doctor to choose how best to diagnose on an individual basis.

This new method of diagnosing diabetes will identify a different cohort as having diabetes than is currently being diagnosed; but the process of investigation that does not require a fasting sample makes investigation easier, allowing more people to be investigated.

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None.

Competing interests
None declared.

References
9 van’t Riet E, Alonsoa M, Rijkezljuijzen JM et al. Relationship between A1c and glucose levels in the general Dutch population. Diabet Care 2010; 33: 61–66.

Appendix 1

Members of the expert group
George Alberti, WHO committee on HbA1c, Chair Diabetes UK
Barbara Bain, Professor of Diagnostic Haematology, Imperial College
Ian Barnes, National Clinical Director Pathology, Department of Health
Julian Barth, President Association for Clinical Biochemistry

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HbA\textsubscript{1c} for diagnosis of diabetes mellitus

When to use HbA\textsubscript{1c} for diagnosis

Risk factors—any two present

- Overweight
- Family history
- Over age 30 years if Maori/Asian (Indian subcontinent)/Pacific Island descent
- Over age 40 years if European
- Diabetes in pregnancy
- Had a big baby (more than 4 kg)—not in immediate post-natal period
- Inactive lifestyle, lack of exercise
- Previous high blood glucose/impaired glucose tolerance

Associated risk factors—supports risk factors

- Circulation/heart problems
- Smoker
- High blood pressure
- Diet high in saturated fat

Presence of possible symptoms for over 2 months—supports risk factors

- Tiredness
- Thirst
- Passing lots of urine or bed wetting
- Infections/boils/rashes
- Weight loss
- Blurred vision
- Slow healing
- Sensation change

Severe mental illness

- Prior to starting antipsychotic medication
- On an antipsychotic medication for greater than 2 months

When NOT to use HbA\textsubscript{1c} for diagnosis

A diagnosis of diabetes using glucose measurement must be considered in:
All children and young people:

- Pregnancy—current or recent (< 2 months)
- Suspected Type 1 diabetes, no matter what age
- Short duration of diabetes symptoms
- Patients at high risk of diabetes who are acutely ill (HbA1c ≥ 48 mmol/mol confirms pre-existing diabetes, but a value < 48 mmol/mol does not exclude it and such patients must be retested once the acute episode has resolved)
- Patients taking medication that may cause rapid glucose rise; for example, corticosteroids, antipsychotic drugs (2 months or less). HbA1c can be used in patients taking such medication long term (i.e. over 2 months) who are not clinically unwell
- Acute pancreatic damage or pancreatic surgery
- Haemoglobinopathies (HbS, HbC, etc.)
- Anaemia (haemolytic and iron deficiency)
- Renal failure
- HIV infection

What to consider when using HbA1c for diagnosis

- Age
- Ethnicity

Where HbA1c measurement may be, or is known to be, inappropriate, test using existing fasting glucose and/or glucose tolerance test

In all cases, apply clinical judgement to keep the patient safe.

Appendix 3

Diagnosing Type 1 Diabetes in Primary Care

Person presents with one or more symptoms suggestive of diabetes:

- Thirst
- Polyuria, new onset bedwetting
- Polydipsia
- Weight loss

- Recurrent infections
- Patient, carer or family member suspects diabetes

Assess the patient & perform finger prick blood glucose

Patient ill* and finger prick glucose ≥ 11.1 mmol/L

(e.g. vomiting, dehydration, confusion, hypotension, collapse)

- Diabetes likely. Possible diabetic ketoacidosis

ADMIT VIA 999 AMBULANCE IMMEDIATELY

Patient not ill but finger prick glucose ≥ 11.1 mmol/L

- Diabetes likely:

Seek diabetes specialist advice same day especially if ketones present in blood or urine.

Send venous sample to laboratory for glucose and HbA1c analysis but do not wait for result. Call paediatric or medical on call team if specialist unavailable

Patient not ill and glucose 7.0–11.0 mmol/L

- Diabetes possible:

Send venous sample to laboratory for glucose and HbA1c analysis (HbA1c confirms diabetes if ≥48 mmol/mol; but a result <48 mmol/mol does not exclude diabetes).

Tell patient or carer to contact GP straight away if symptoms worsen:

Review within 3 days

- Diabetes unlikely:

Review if symptoms persist

Individuals at increased risk of developing Type 1 diabetes include:

Autoimmune Family History e.g. Type 1 diabetes, thyroid disease, coeliac disease, pernicious anaemia, Addison’s disease.