HbA_{1c}: Practicalities and pitfalls

Jane Diggle

HbA_{1c} has been the standard measure for diagnosing type 2 diabetes and monitoring glycaemic control for decades. Although a useful marker of average blood glucose levels and risk of diabetes complications, HbA_{1c} does not provide a complete picture of glycaemic variability, and there are a number of situations in which the test may be inaccurate. This article is a practical review of HbA_{1c} and when it should, or should not, be used in diagnosis, monitoring and setting treatment targets.

What is HbA_{1c}?

HbA_{1c} is a measurement of glycated haemoglobin. Glucose present in the bloodstream spontaneously binds to the haemoglobin in red blood cells in a process called glycation, with the amount of glucose that binds to the haemoglobin directly proportional to the level of glucose at that time.

After binding to the red blood cell, the glucose remains attached for the lifespan of the cell: usually around 12 weeks. Thus, HbA_{1c} provides an indicator of average blood glucose levels over that period.

HbA_{1c} levels may be reported either as a percentage or in mmol/mol. Since 2009, in the UK the standard unit of measurement has been mmol/mol, to align with the International Federation of Clinical Chemistry (see *Table 1* overleaf for conversions).

HbA_{1c} is useful in the diagnosis, prevention and monitoring of diabetes, as it reflects the impact of diet, lifestyle and medication on glycaemic control over the preceding 3 months.

When is HbA_{1c} used in practice?

Monitoring glycaemic control

For decades, HbA_{1c} has been used as the standard measure for monitoring glycaemic control in people living with diabetes. It was demonstrated to be an important predictor of diabetes-related complications in 1993, which led to the recommendation of specific HbA_{1c} targets (DCCT Research Group, 1993).

Other landmark studies, including the UKPDS (Adler et al, 2024), have demonstrated the link between HbA_{1c} and diabetes complications, reinforcing the use of these targets in people living with type 2 diabetes.

A note about glucose variability and hypoglycaemia

HbA_{1c} is a biomarker of glucose control over the preceding 2–3 month period. It does not provide any insight into day-to-day glucose variability or provide evidence of hypoglycaemia. There are circumstances when such information is essential, in particular where a person is treated with blood glucose-lowering therapies associated with hypoglycaemia (e.g. sulfonylureas and insulin). To guide these treatment decisions, self-monitoring of capillary glucose should be utilised or, for individuals on insulin who meet the eligibility criteria, continuous glucose monitoring should be considered.

Diagnosing type 2 diabetes

The use of HbA_{1c} was broadened in 2010, when the American Diabetes Association added it as a diagnostic criterion for type 2 diabetes. It has been standard practice in the UK to use HbA_{1c} for diagnosing type 2 diabetes since 2011, when the World Health Organization (WHO, 2011a) published guidance on its use.

Use of point-of-care devices to assess HbA_{1c}

Point-of-care (POC) testing devices for HbA_{1c} measurement are available and may be used

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Article points

1. HbA_{1c} is useful for diagnosing type 2 diabetes and non-diabetic hyperglycaemia, for monitoring glycaemic control and for agreeing treatment targets.
2. There are a number of situations when HbA_{1c} tests should not be used or should be interpreted with caution, particularly in cases where red blood cell lifespan is altered.
3. In these situations, alternative methods of assessing glycaemia should be considered, including the measurement of fructosamine, self-monitoring of capillary glucose or, where appropriate, continuous glucose monitoring.

Key words

- HbA_{1c}
- Type 2 diabetes
- Diagnosis
- Monitoring

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Table 1. HbA$_{1c}$ unit conversions.

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
6.0%	42	8.0%	64	10.0%	86
6.1%	43	8.1%	65	10.1%	87
6.2%	44	8.2%	66	10.2%	88
6.3%	45	8.3%	67	10.3%	89
6.4%	46	8.4%	68	10.4%	90
6.5%	48	8.5%	69	10.5%	91
6.6%	49	8.6%	70	10.6%	92
6.7%	50	8.7%	72	10.7%	94
6.8%	51	8.8%	73	10.8%	95
6.9%	52	8.9%	74	10.9%	96
7.0%	53	9.0%	75	11.0%	97
7.1%	54	9.1%	76	11.1%	98
7.2%	55	9.2%	77	11.2%	99
7.3%	56	9.3%	78	11.3%	100
7.4%	57	9.4%	79	11.4%	101
7.5%	58	9.5%	80	11.5%	102
7.6%	60	9.6%	81	11.6%	103
7.7%	61	9.7%	83	11.7%	104
7.8%	62	9.8%	84	11.8%	105
7.9%	63	9.9%	85	11.9%	107

DCCT=Diabetes Control and Complications Trial; IFCC=International Federation of Clinical Chemistry.

in some community settings. Such devices offer an immediate test result and operate via a finger-prick blood sample; thus, they do not require a trained healthcare professional to draw a venous blood sample. This clearly offers benefits, particularly in a community setting; however, concerns have been raised around the accuracy of this method. Recently, Sacks et al (2024) explored the advantages and disadvantages of POC HbA$_{1c}$ testing and concluded that, although it is convenient and useful for assessing glycaemic control in individuals with diabetes, it should not be used for diabetes diagnosis, due to lack of accuracy.

Diagnosing diabetes using HbA$_{1c}$

An HbA$_{1c}$ of 48 mmol/mol (6.5%) is used as the cut-off point for diagnosis although, as per the WHO (2011a) consensus, a value of less than this does not exclude diabetes diagnosed using other glucose tests (such as fasting glucose or an oral glucose tolerance test). This diagnostic threshold was chosen because it is the point at which the incidence of retinopathy, a common complication that may be present even before the actual diagnosis of diabetes is made, is increased (International Expert Committee, 2009).

WHO (2011a) recommends the following diagnostic criteria for diabetes:

- HbA$_{1c}$ below 42 mmol/mol (6.0%): **Not diabetes**.
- HbA$_{1c}$ 42–47 mmol/mol (6.0–6.4%): **Impaired glucose regulation** or **prediabetes**.
- HbA$_{1c}$ ≥48 mmol/mol (6.5%): **Type 2 diabetes**.

Importantly, individuals with a single elevated HbA$_{1c}$ between 42 and 47 mmol/mol are classified by NICE as having non-diabetic hyperglycaemia (NDH) and being at increased risk of developing type 2 diabetes. NDH is a clinical domain within the current NHS Quality and Outcomes Framework (QOF; NHS England, 2024). Practices are required to report on *"the percentage of patients with non-diabetic hyperglycaemia who have had an HbA$_{1c}$ or fasting glucose performed in the preceding 12 months"*, and this is currently worth 18 points with a threshold of 50–90%.

Progression to type 2 diabetes may be prevented or delayed in people with NDH through lifestyle changes with a focus on diet, weight loss and exercise. Referral to the National Diabetes Prevention Programme (or a local equivalent) is strongly advocated.

The process of using HbA$_{1c}$ to diagnose type 2 diabetes is summarised in *Figure 1* (overleaf).

Situations where HbA$_{1c}$ is not appropriate for diagnosing diabetes

Because an HbA$_{1c}$ test may be performed at any time of day and does not require any preparation such as fasting, it has become the preferred method for diagnosing type 2 diabetes and assessing glycaemic control in those with diabetes. However, test results may be affected by a number of factors that impact the amount of glucose penetrating the red cell membrane, the rate of glycation or the lifespan of red blood cells (Radin, 2014; Kaiafa et al, 2021).

These factors must be considered when reviewing HbA$_{1c}$ results both for the purposes of making a diagnosis and in the ongoing

Using HbA$_{1c}$ to diagnose type 2 diabetes

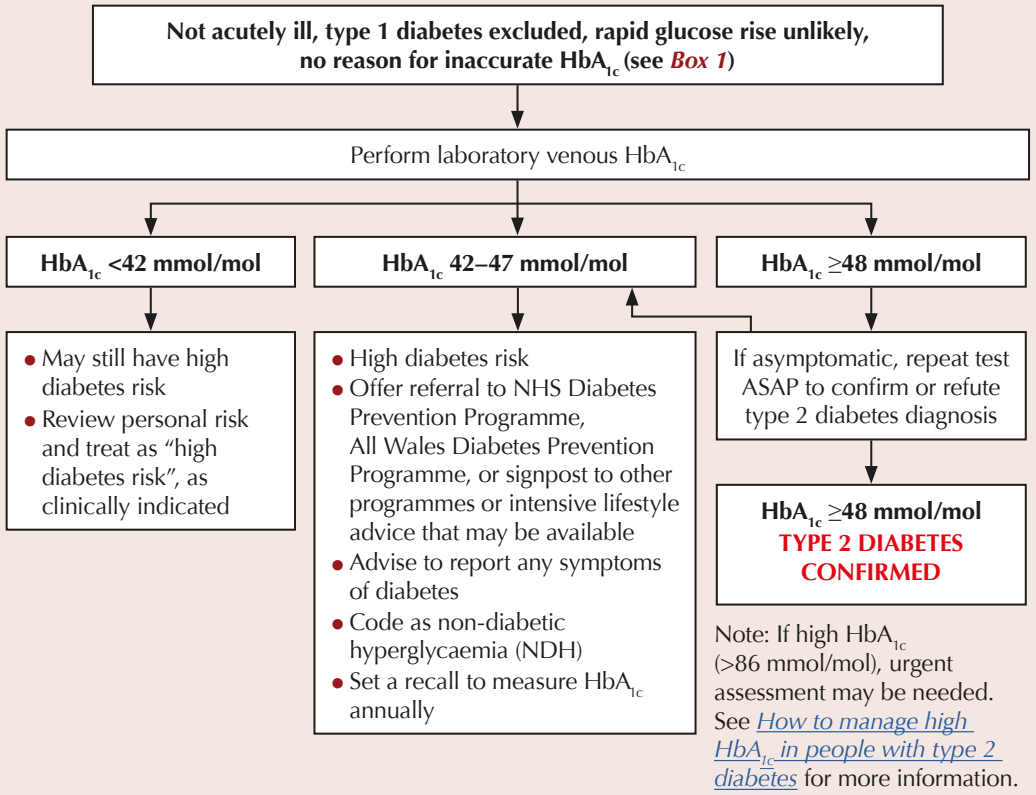

Figure 1. Using HbA$_{1c}$ to diagnose type 2 diabetes. Adapted from NICE (2012) and John et al (2012).

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management of diabetes. In particular, there are situations where it is not appropriate to use HbA$_{1c}$ to diagnose diabetes (*Box 1*).

Using HbA$_{1c}$ to monitor glycaemic control

In relation to HbA$_{1c}$ monitoring and agreeing targets, NICE (2022b) NG28 recommends the following:

Measure HbA$_{1c}$ levels in adults with type 2 diabetes every:

- 3 to 6 months (tailored to individual needs) until HbA$_{1c}$ is stable on unchanging therapy.
- 6 months once the HbA$_{1c}$ level and blood glucose-lowering therapy are stable.

Target setting

Clinicians are advised to discuss and agree an individual HbA$_{1c}$ target and encourage the person to reach their target and maintain it, unless there are resulting adverse effects (including hypoglycaemia) or their efforts to achieve their target impair their quality of life.

- For those managed either by lifestyle and diet, or lifestyle and diet combined with a single drug not associated with hypoglycaemia, aim for an HbA$_{1c}$ of 48 mmol/mol (6.5%).
- For those on a drug associated with hypoglycaemia, aim for an HbA$_{1c}$ level of 53 mmol/mol (7.0%).

Box 1. Situations where HbA$_{1c}$ is not appropriate for diagnosing diabetes.

- **ALL** children and young people.
- People of any age suspected of having type 1 diabetes.
- People at high diabetes risk who are acutely ill (e.g. those requiring hospital admission), or post severe trauma or cardiovascular event.
- People taking medication that may cause rapid glucose rise (e.g. steroids, antipsychotics).
- People with acute pancreatic damage, including pancreatic surgery.
- Pregnancy.
- People with end-stage renal disease.
- People being treated for HIV infection with antivirals.
- Interpret HbA$_{1c}$ with caution if abnormal red blood cell lifespan (see *Table 3*).

Note: Be aware that severe hyperglycaemia in people with acute infection, trauma, circulatory or other stress may be transitory and is not diagnostic of diabetes (NICE, 2022a).

Table 2. Factors to consider when setting clinically appropriate glycaemic goals in older people with type 2 diabetes (Hambling, 2020).

Functional status	Glycaemic range
Healthy or relatively healthy Fit and functionally independent Relatively longer anticipated life expectancy Managed on diet alone or oral glucose-lowering therapies associated with low risk of hypoglycaemia	HbA$_{1c}$ 53*–59 mmol/mol (7.0–7.5%)
Complex/intermediate health or social care needs, with intermediate life expectancy or mild–moderate frailty and requiring oral glucose-lowering therapies Fit older people requiring sulfonylurea or insulin therapy	HbA$_{1c}$ 53–64 mmol/mol (7.0–8.0%)
Very complex/poor health/frail Older people with complex/intermediate health or social care needs and/or mild frailty requiring insulin therapy	HbA$_{1c}$ 59–69 mmol/mol (7.5–8.5%)
End-of-life palliative care	Avoid symptomatic hyper-/hypoglycaemia

*HbA$_{1c}$ <53 mmol/mol (7.0%) may be considered acceptable in some fit older people on monotherapy associated with low risk of hypoglycaemia, although reviewing the ongoing need for medication should be considered.

- If HbA$_{1c}$ levels are not adequately controlled by a single drug and rise to ≥58 mmol/mol (7.5%):
  - Reinforce advice about diet, lifestyle and adherence to drug treatment, and
  - Aim for HbA$_{1c}$ 53 mmol/mol (7.0%), and
  - Intensify drug treatment.
- Consider relaxing the target HbA$_{1c}$ on a case-by-case basis and in discussion with the individual, with particular consideration for people who are older or frailer, if:
  - They are unlikely to achieve longer-term risk-reduction benefits (e.g. people with reduced life expectancy).
  - Tight blood glucose control would put them at high risk if they developed hypoglycaemia (e.g. those at risk of falling, those with impaired awareness of hypoglycaemia, or those who drive or operate machinery as part of their job).
  - Intensive management would not be appropriate (e.g. those with significant comorbidities).

Notably, QOF allows for looser glycaemic control in people with frailty, with indicator IND180 being: *"The percentage of patients with diabetes with moderate or severe frailty, on the register, in whom the last IFCC-HbA$_{1c}$ is 75 mmol/mol or less in the preceding 12 months."*

Resource

NICE patient decision aid on agreeing HbA$_{1c}$ targets

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Illustrative HbA$_{1c}$ targets for older people depending on their functional status are listed in *Table 2* (Hambling, 2020).

Monitoring glycaemic control in people with type 1 diabetes

An assessment of HbA$_{1c}$ levels is still included as part of the diabetes review for individuals with type 1 diabetes within the NICE (2022c) NG17 guideline. The guidance recommends that HbA$_{1c}$ be measured every 3–6 months in adults with type 1 diabetes (providing there are no circumstances that would render the test invalid – see *Table 3* overleaf). Adults with type 1 diabetes should be supported to aim for a target HbA$_{1c}$ level of ≤48 mmol/mol (6.5%), to minimise the risk of long-term vascular complications, although an individualised target should always be considered, with avoidance of problematic hypoglycaemia a priority.

However, an increasing number of people with type 1 diabetes are choosing to use continuous glucose monitoring devices and will use these (alongside capillary blood glucose measurements when needed) to monitor and self-manage their glucose levels. The three key glucose metrics used to do this are time in range (TIR), time below range and time above range (see Milne, 2023 for more information). There is a good correlation between HbA$_{1c}$ and percentage TIR, and on average a TIR of 70% corresponds to an HbA$_{1c}$ level of approximately 53 mmol/mol (7.0%) (Beck et al, 2019).

In the future, there may be a transition to using percentage TIR as the preferred metric for assessing glycaemic control and risk of diabetes complications (Vigersky and McMahon, 2019).

What can interfere with HbA$_{1c}$ and when to interpret tests with caution

Any condition that prolongs or shortens the lifespan of red blood cells, or reduces or increases their rate of regeneration, can affect how long the cells are exposed to glucose, resulting in increased or decreased HbA$_{1c}$ values. See *Table 3* for a list of situations where HbA$_{1c}$ tests may be inaccurate.

HbA$_{1c}$ should be interpreted with caution in people with abnormal haemoglobin type, such as haemoglobinopathy, including sickle cell trait.

Black people (including those with potentially undiagnosed sickle cell trait) may need further evaluation when considering an HbA$_{1c}$ test result, as the result may underestimate past glycaemia.

In pregnancy, red blood cell lifespan is reduced from around 120 to 90 days. HbA$_{1c}$ values reduce in the second trimester, plateau at 20–24 weeks and increase in the third trimester.

Interpretation of HbA$_{1c}$ should be approached with caution in older adults because the concentration of HbA$_{1c}$ increases as people age (Masuch et al, 2019). A few studies have explored the underlying mechanisms and suggested that a decreased red blood cell count caused by a reduction in cell turnover could lead to an increased red blood cell lifespan, thus increasing the levels of HbA$_{1c}$ (Wu et al, 2017). It has also been proposed that the cellular damage that occurs with aging, including altered enzyme activity, decreased membrane lipids and increased cell fragility, might accelerate glycation of haemoglobin and result in higher HbA$_{1c}$ levels (Rooney et al, 2021).

Official guidelines do not suggest using different reference values based on age for making the diagnosis of type 2 diabetes; however, it has been argued that definitions of prediabetes in older adults do not have the same prognostic meaning as they have in younger individuals (JN Learning, 2021). A more relaxed approach to target setting is advocated in most guidelines, including NICE, for older frailer individuals living with diabetes, as highlighted earlier.

Is there a correlation between average glucose and HbA$_{1c}$?

Individuals with diabetes sometimes share self-monitored capillary glucose readings that do not seem to correspond to their current HbA$_{1c}$ value (being either much higher or much lower than expected). Although a linear relationship between mean glucose and HbA$_{1c}$ levels across a range of glycaemia has been proposed (see *Table 4*), it is important to note that individuals with the same HbA$_{1c}$ value may have glucose concentrations across a broad range, and the estimated mean glucose ranges for various HbA$_{1c}$ levels overlap. This has important practical implications because, for example, a person

Table 3. When to interpret HbA$_{1c}$ with caution (Gallagher et al, 2009; Radin et al, 2014).

Increases HbA$_{1c}$ ▲	Decreases HbA$_{1c}$ ▼
Erythropoiesis	
▲ Iron deficiency ▲ Vitamin B12 deficiency ▲ Decreased RBC production ▲▼ Pregnancy (increased in third trimester)	▼ Administration of erythropoietin, iron or vitamin B12 ▼ Reticulocytosis ▼ Chronic liver disease ▲▼ Pregnancy (reduced in first trimester)
Glycation	
▲ Alcoholism/chronic alcohol ingestion ▲ Chronic renal failure ▲ Decreased RBC pH ▲▼ RBC transfusion (variable effects) ▲▼ Genetic determinants (variable effects)	▼ Chronic ingestion of aspirin, vitamin C or vitamin E ▼ Certain haemoglobinopathies ▼ Increased RBC pH
RBC destruction (increased or decreased RBC lifespan)	
▲ Asplenia	▼ Haemoglobinopathies ▼ Splenomegaly ▼ Rheumatoid arthritis ▼ Drugs such as antiretrovirals, ribavirin, interferon-alpha, dapsone
Interference with HbA$_{1c}$ assays	
▲ Severe hyperbilirubinaemia ▲ Uraemia/carbamylated haemoglobin ▲ Alcoholism/chronic alcohol ingestion ▲ Large doses of aspirin ▲ Chronic opioid use	▼ Hypertriglyceridaemia ▲▼ Haemoglobinopathies (variable effects)
Altered haemoglobin	
▲▼ Fetal haemoglobin (variable effects) ▲▼ Haemoglobinopathies (variable effects) ▲▼ Methaemoglobin (variable effects)	

RBC=red blood cell.

Table 4. HbA$_{1c}$ and estimated mean glucose equivalents (Nathan et al, 2008).

HbA$_{1c}$	Estimated mean glucose	95% CI (mmol/L)
31 mmol/mol (5.0%)	5.4 mmol/L	4.2–6.7
42 mmol/mol (6.0%)	7.0 mmol/L	5.5–8.5
53 mmol/mol (7.0%)	8.6 mmol/L	6.8–10.3
64 mmol/mol (8.0%)	10.2 mmol/L	8.1–12.1
75 mmol/mol (9.0%)	11.8 mmol/L	9.4–13.9
86 mmol/mol (10.0%)	13.4 mmol/L	10.7–15.7

CI=confidence interval.

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A practical approach to providing efficient and effective support for people with high HbA$_{1c}$.

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recording a mean glucose level of 8.3 mmol/L could have an HbA$_{1c}$ anywhere between 42 and 64 mmol/mol, which would require different approaches to management.

Conclusion

Although HbA$_{1c}$ offers a number of practical advantages and has come to be regarded as the gold standard for both diagnosing and monitoring diabetes, it is important to recognise its limitations. It is not appropriate for diagnosing diabetes in certain clinical circumstances, and there are conditions that can give rise to falsely high or low results. In these situations, alternative methods of assessing glycaemia should be considered, including the measurement of fructosamine, self-monitoring of capillary glucose or, where appropriate, continuous glucose monitoring. ■

Additional information

LabTestsOnline (https://labtestsonline.org.uk/tests/hba1c-test) provides more detailed information, including how the HbA$_{1c}$ test is used, when it is requested and what the results mean, as well as answering other commonly asked questions about the HbA$_{1c}$ test.

As part of its series of Information Prescriptions, Diabetes UK has produced a single-page document explaining what HbA$_{1c}$ is, when a high HbA$_{1c}$ is a problem and how a person can lower their HbA$_{1c}$. These can be personalised to include individual HbA$_{1c}$ target levels and goals, downloaded and saved into the person's electronic medical record, and even shared via email or text. Information Prescriptions are available at: https://www.diabetes.org.uk/for-professionals/supporting-your-patients/information-prescriptions/information-prescriptions-qa

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