Case report: An unexpectedly low HbA_{1c}

David Morris, Probal Moulik

HbA_{1c} has become a key parameter for diagnosing type 2 diabetes and for monitoring glycaemic control in all types of diabetes. This case study reports on a person who presented with an unexpectedly low HbA_{1c} at an annual hypertension monitoring appointment. The aim of reviewing the case is to provide an understanding of HbA_{1c}, its limitations, and the clinical situations in which it is unreliable and alternative measures of glycaemic control should be sought.

Case history: The presentation

Emily (a pseudonym), age 68 years, had blood tests performed ahead of her annual hypertension monitoring appointment with her GP. The results were as follows:

HbA_{1c}: <20 mmol/mol
Haemoglobin: 105 g/L
Mean corpuscular volume: 112.3 fL
White cell count: 9.3×10^9/L
Platelet count: 411×10^9/L
Sodium: 142 mmol/L
Potassium: 3.5 mmol/L
eGFR: 77 mL/min
TSH: 1 mU/L
Total cholesterol: 2.5 mmol/L;
Non-HDL: 1.7 mmol/L; **HDL:** 0.79 mmol/L
Bilirubin: 27 µmol/L
Other LFTs: Normal range
Urinary ACR: <0.4 mg/mmol

Previous medical history: Hypertension; hyperlipidaemia; hypothyroidism; depression.

Medication: Amlodipine 5 mg once daily, bendroflumethiazide 2.5 mg once daily; atorvastatin 20 mg once daily; levothyroxine 75 µg once daily; citalopram 20 mg once daily.

At review, Emily reported feeling tired but was otherwise asymptomatic. She did not report symptoms suggestive of hypoglycaemia.

On examination, her blood pressure was 132/73 mmHg and her BMI was 28.2 kg/m^2.

How would you respond to these results?

Understanding HbA_{1c}

Under normal circumstances, approximately 97% of adult haemoglobin is haemoglobin A (HbA), which itself is composed of four globin chains: two alpha and two beta chains (Wang and Hng, 2021). When glucose binds covalently to the beta chain of HbA, the resulting form of the molecule then persists until the red cell is destroyed. In people without diabetes, around 6% of HbA is glycated, with the principal contribution, typically around 5%, coming from HbA_{1c} (HbA can be glycated at other sites on the molecule). In people with diabetes, who have higher blood glucose concentrations, the level of HbA_{1c} rises.

HbA_{1c}, then, is a measure of the proportion of HbA within red cells that is glycated. It reflects the prevailing blood glucose levels over the lifetime of the red blood cell: approximately 120 days. It is important to note that glucose levels nearer to the time of HbA_{1c} measurement contribute significantly more to the HbA_{1c} value than those more distant from the time of testing, because red blood cells that are more recently glycated will better survive until the time of the test than older red blood cells (Little and Sacks, 2009).

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Article learning points

- HbA_{1c} is a surrogate marker for plasma glucose levels over the previous 3 months – an average that is skewed to more recent glucose readings.
- HbA_{1c} may be falsely lowered in conditions that reduce the lifespan of red blood cells or increase red cell turnover. Common examples include haemolytic anaemias and hypersplenism.
- Conversely, HbA_{1c} may be falsely elevated in conditions that extend erythrocyte survival or reduce erythrocyte turnover. Common examples include asplenia and deficiencies in iron, vitamin B12 or folate.
- Haemoglobinopathies have a variable effect on HbA_{1c}, and specialist advice should be sought.
- Self-monitoring of blood glucose or continuous glucose monitoring should be used where HbA_{1c} is unreliable. A 75 g oral glucose tolerance test is advised for diagnosis of diabetes in pregnancy. Fructosamine is an alternative measure of glycaemic control to HbA_{1c}, reflecting control over the previous 2–3 weeks.

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Box 1. Situations where HbA_{1c} should not be relied on to diagnose diabetes.

- Symptoms suggesting type 1 diabetes
- Symptomatic children and young adults
- Acute onset of diabetes symptoms
- People at risk of diabetes who are acutely unwell
- People taking medication that can rapidly increase glucose levels (e.g. corticosteroids, antipsychotics)
- Pregnancy

HbA_{1c} thus acts as a surrogate marker for plasma glucose levels over the previous 3 months – an average that is skewed to more recent glucose readings.

Utility of HbA_{1c} in diagnosing and monitoring diabetes

HbA_{1c} is routinely used as a means of diagnosing type 2 diabetes, with a threshold of 48 mmol/mol (6.5%), and is also used as a means of monitoring glycaemic control in all types of diabetes. An important advantage of using HbA_{1c} is that a venous blood sample can be taken at any time, in contrast to fasting plasma glucose and the oral glucose tolerance test (OGTT), both of which require the individual to be fasted and, in the case of the OGTT, detained for a prolonged period. A further benefit of using HbA_{1c} is that it is inherently less subject to the day-to-day variation of other diagnostic tests. HbA_{1c} levels correlate well with diabetes complications.

There are situations, however, when HbA_{1c} should not be used as a diagnostic test for diabetes, notably when glucose levels have risen rapidly (see *Box 1*). In such situations, HbA_{1c} will not accurately reflect current levels of glycaemia (Farmer, 2012; John, 2012). Remember that HbA_{1c} does not indicate glucose variability, such that two individuals with very different glucose profiles could return the same HbA_{1c}.

Case history: Managing Emily's presentation

Emily was started on home glucose monitoring, which documented a couple of low glucose episodes (2.8 and 3.6 mmol/L) pre-breakfast, and she reported feeling anxious at those times, with her stomach churning. She was asked to use Lucozade, which did not help her symptoms. At this stage, referral to the endocrinologist was made due to concern about spontaneous hypoglycaemia.

Endocrinologist's assessment: Absence of typical Whipple's triad (symptoms of hypoglycaemia, plasma glucose concentration <3.0 mmol/L and resolution of the symptoms after the plasma glucose concentration is raised) suggested that hypoglycaemia was not a significant concern. The presence of anaemia and raised bilirubin indicated the possibility of haemolysis and that this could account for the low HbA_{1c}.

Investigations: **HbA_{1c}:** <20 mmol/mol. **Fasting plasma glucose:** 5.7 mmol/L. **Haemoglobin:** 109 g/L. **Vitamin B12:** 364 ng/L. **Ferritin:** 360 µg/L. **Folate:** 2.6 µg/L (borderline low). **9 am cortisol** (as advised by endocrinology): 340 nmol/L (normal range). **Fructosamine:** not analysed (due to laboratory error). **Antinuclear antibodies:** positive. **ANCA/RF/CCP antibodies:** negative. **Myeloma screen:** negative. **Blood film:** Anisocytosis, polychromasia, spherocytes, raised reticulocyte count (12.4%). A **direct antiglobulin** (Coombs) test was positive.

Conclusion: Subsequently, fingerprick glucose readings were all >4 mmol/L, confirming that Emily's low HbA_{1c} result did not match up with her measured glucose levels. These results strongly suggested the cause of the low HbA_{1c} to be haemolysis, due to an autoimmune haemolytic anaemia. Emily was referred urgently to the haematologist.

Unrepresentative HbA_{1c} results

Conditions that reduce the lifespan of red blood cells and trigger increased erythrocyte turnover mean there is less time for glycation of red cells to occur and that HbA_{1c} may, therefore, be falsely lowered (Radin, 2014; Wang and Hng, 2021). In contrast, and unlike in Emily's case, extended erythrocyte survival or reduced erythrocyte turnover can lead to falsely elevated HbA_{1c} values (see *Table 1*).

Haemoglobinopathies have a variable effect on HbA_{1c}, and specialist advice should be sought (Radin, 2014). Blood transfusions can falsely lower or raise HbA_{1c}, depending on the diabetes status of donor and recipient. It is also worth being aware that, for given levels of glycaemia,

non-Caucasian populations have slightly higher HbA_{1c} values than Caucasians (Herman and Cohen, 2012). HbA_{1c} values should not be relied on in cases of severe anaemia (Hb <100 g/L).

Alternatives to HbA_{1c} for assessing glycaemic control

Clearly, other means of assessing glycaemia need to be utilised in situations where it is suspected HbA_{1c} could be unreliable. As in Emily's case, self-monitoring of blood glucose (SMBG) can be undertaken, or if necessary some form of continuous glucose monitoring (CGM).

In pregnancy, the 75 g OGTT remains the gold standard for diagnosing diabetes (NICE, 2020). Thereafter, SMBG or CGM can be used to monitor glucose levels and direct treatment.

Serum fructosamine is an alternative measure of glycaemic control in situations where red cell turnover invalidates HbA_{1c}, although it has not been validated as a measure of longer-term glycaemic control or as a predictor of diabetes complications (Rodin, 2014). The test measures glycation of proteins, principally albumin, and reflects glycaemic control over the previous 2–3 weeks, given that the half-life of albumin is around 20 days. However, fructosamine testing would be unreliable in the presence of hypoalbuminaemia.

Conclusion

HbA_{1c} is a pragmatically useful surrogate marker for average glucose control over the preceding 3 months, albeit weighted towards more recent glucose levels. There are clinical situations, however, when HbA_{1c} should not be relied on either to diagnose diabetes or to accurately reflect glucose levels. Unrepresentative HbA_{1c} values can arise through altered erythrocyte lifespan. Under these circumstances, alternative means of assessing glycaemic control should be undertaken. ■

Table 1. Causes of falsely low and falsely high HbA_{1c} readings.

Falsely low HbA_{1c} result	Falsely high HbA_{1c} result
Hypersplenism	Asplenia
Haemolytic anaemia	Iron, vitamin B12, folate deficiencies
End-stage renal failure – reduced erythrocyte survival	Metabolic disturbances affecting HbA_{1c} assay: severe hypertriglyceridaemia, severe hyperbilirubinaemia, uraemia
Blood loss	
Erythropoietin-stimulating agents	
Pregnancy – reduced erythrocyte survival/ increased erythropoietin	

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Further reading

How to correctly diagnose and classify diabetes

A quick guide for primary care on ensuring that diabetes is diagnosed correctly and accurately.

Diabetes & Primary Care **24**: 107–10

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