HbA1c is not always reliable in estimating glycaemic control

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Abstract
Glycated haemoglobin (HbA1c) is considered as a cornerstone for assessing long-term glycaemic control. Several studies have established a strong correlation between HbA1c and diabetic comorbidities. However, in certain conditions it can lead to a false interpretation of diabetes control which may result in serious errors in patient management. It is essential clinicians are aware of the conditions that can affect glycated haemoglobin and use alternative methods of glycaemic control if there is a discrepancy between blood glucose readings and HbA1c.

We report a case of a falsely low HbA1c which led to a wrong interpretation of glycaemic control resulting in a major comorbidity. Copyright © 2016 John Wiley & Sons.

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Key words
glycated haemoglobin; HbA1c

Introduction
First described by Rahbar et al. in 1969, HbA1c is an invaluable tool in monitoring long-term diabetes control. Several studies have shown that the level of HbA1c correlates well with the glycaemic control over a period of two to three months.

The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have shown a strong correlation between HbA1c and diabetic comorbidities.1,2 It is a well-established practice to measure HbA1c in all patients with diabetes and is considered a cornerstone for diabetes management. It results from an irreversible non-enzymatic reaction between glucose and the main haemoglobin in adults, HbA, and occurs during the life span of the erythrocyte.3

Case history
A 52-year-old male with a seven-year history of type 2 diabetes, managed in primary care, was referred to the diabetes clinic for painful peripheral neuropathy. Apart from hypertension there was no other significant past medical history. At the time of presentation the patient was on metformin, gliclazide and ramipril. Review of previous results showed an HbA1c ranging between 20–40mmol/mol, GFR 73ml/min, Hb 139g/L, MCV 107fl and proteinuria of 2.65g/24 hours/L. A review of finger prick blood glucose results revealed blood glucose in the range of 15–20mmol/mol. The patient did not report any hypoglycaemic episodes; however, in view of the HbA1c results, the gliclazide dose was initially reduced and later completely stopped. As the blood glucose readings did not correspond to the HbA1c results, continuous glucose monitoring (CGM) was organised on two occasions which confirmed the discrepancy between blood glucose and HbA1c. HbA1c was tested using two different assays at different hospitals with no difference.

Review of medications did not reveal any drugs that could have accounted for the inappropriately low HbA1c. Vitamin B12 and folate levels were within the normal reference range (B12 264ng/L, folate 7.3mg/L) and though the initial results showed macrocytosis subsequently it resolved spontaneously. Haemoglobin electrophoresis, haptoglobin and auto-antibody screen were all normal. Fructosamine levels were also within the normal range. A red cell study was organised which indicated a reduced red cell survival of approximately 22.5 days. A CT scan of the abdomen was organised and showed splenomegaly, but no cause for the splenomegaly could be identified. Considering the results of investigations a diagnosis of falsely low HbA1c secondary to reduced red cell survival due to hypersplenism was established.
In view of the CGM results while the investigations were ongoing, the patient was commenced on insulin to improve glycaemic control. By the time of presentation the patient had already developed severe painful peripheral sensory neuropathy and, despite preventive measures, developed diabetic foot complications (Charcot’s foot, osteomyelitis) leading to below-knee amputation of the left foot.

The patient remains under the follow up of the diabetes service, with glucose monitoring used as a method of diabetes control.

**Discussion**

This case illustrates the importance of clinical awareness when interpreting HbA1c results. They may falsely lead to what may appear to be a good glycaemic control.

The following discussion focuses on the conditions and factors which can affect HbA1c. Although in general HbA1c is a robust marker of glycaemic control, in some conditions the test can be unreliable. In addition, certain drugs can cause a falsely low or high HbA1c. High performance liquid chromatography, immunoassay, capillary electrophoresis, and boronate affinity chromatography are some of the techniques used to measure HbA1c. The newer assays to measure HbA1c can eliminate some, but not all, of the errors.3

**Factors affecting HbA1c interpretation**

Certain conditions can cause inappropriately high or low HbA1c. Any condition which shortens the mean erythrocyte age, such as haemolysis and blood loss, lowers HbA1c regardless of the assay method used. The accuracy of the HbA1c methods can also be affected adversely by the presence of haemoglobin variants. In patients with HbSS, HbCC and HbSC, HbA1c must be interpreted with caution given the pathological processes. In such patients, an alternative method of testing, such as glycated albumin or glycated serum protein, should be considered. Patients with heterozygous variants are usually asymptomatic and have normal red cell survival. In these patients, HbA1c can be used as long as the Hb variant does not interfere with the assay method used or the binding of glucose to haemoglobin.4

In beta thalassemia major, HbA1c can be unreliable as a method of glycaemic control. These patients require regular transfusions, and data from relatively old literature suggest that a high concentration of glucose in the red blood cell (RBC) storage medium promotes glycation of the packed RBCs and raises HbA1c values in transfused patients.5 However, these findings were not confirmed in a study by Spencer et al. which showed HbA1c levels may actually reduce in diabetic patients receiving transfusion because of dilution with RBCs containing typical amounts of HbA1c.6

There are only a few studies that have looked at the effect of beta thalassemia trait and alpha thalassemia on HbA1c. Glycated haemoglobin measurement is not affected in beta thalassemia trait7,8 and in alpha thalassemia except in patients with HBH disease in which HbA1c levels were found to be lower than controls in a recent study.9 More research is needed in this area.

Iron deficiency can result in falsely elevated HbA1c as well as fructosamine. In late pregnancy, HbA1c is increased in both diabetic and non-diabetic individuals due to iron deficiency.10 The described mechanism is an increase in malondialdehyde, a marker of oxidative stress, in patients with iron deficiency anaemia which enhances glycation of the haemoglobin.11,12 Iron replacement therapy has shown to reduce both HbA1c and fructosamine levels in diabetic and non-diabetic patients with iron deficiency.13,14 Other methods of glycaemic assessment should be used in these patients, such as glucose monitoring, at least until the iron deficiency has been successfully treated. In diabetic patients on dialysis, HbA1c underestimates glycaemic control and measuring glycated albumin is advised.

Conditions affecting HbA1c are summarised in Table 1.

**Table 1. Conditions causing inappropriately high or low HbA1c**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Low HbA1c</th>
<th>High HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemolysis</td>
<td>Dapsone, Ribavirin, Antiretroviral, Trimethoprim, Sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Impaired glycation</td>
<td>Vitamin C, Vitamin E</td>
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<td>Altered haemoglobin</td>
<td>Hydroxyurea</td>
<td></td>
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<tr>
<td>Assay interference</td>
<td></td>
<td>Aspirin (large doses), Chronic opiate use</td>
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</tbody>
</table>

**Table 2. Drugs causing inappropriately low or high HbA1c**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Low HbA1c</th>
<th>High HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemolysis</td>
<td>Dapsone</td>
<td></td>
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<tr>
<td>Hypertriglyceridaemia</td>
<td></td>
<td></td>
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<tr>
<td>Chronic liver disease</td>
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<tr>
<td>Certain haemoglobinopathies</td>
<td></td>
<td></td>
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<tr>
<td>Vitamin B12 deficiency</td>
<td></td>
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<tr>
<td>Uraemia</td>
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<tr>
<td>Hyperbilirubinaemia</td>
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<tr>
<td>Alcoholism</td>
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<td>Fetal haemoglobin</td>
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**Drugs causing inappropriately low or high HbA1c**

Certain drugs have been reported to cause inappropriately low or high HbA1c. Different mechanisms have been postulated by which these drugs can interfere with HbA1c.

Drugs such as dapsone, ribavirin and antiretrovirals cause haemolysis...
and can lower the HbA1c as a result of reduced erythrocyte lifespan. Similarly, hydroxyurea may falsely lower HbA1c by causing a shift from HbA to HbF. Aspirin in large doses used chronically can lead to falsely elevated HbA1c due to acetylation of haemoglobin. Anti-oxidants such as vitamin C and E in high doses can falsely lower HbA1c by interfering with the glycation of haemoglobin. Chronic use of opiates reportedly can increase HbA1c by interfering with the assay, but the exact mechanism is unknown.

Drugs causing inappropriately low or high HbA1c are summarised in Table 2.

Conclusion
Glycated haemoglobin, though a robust marker, can sometimes lead to the wrong interpretation of glycaemic control and may result in serious errors. It is essential clinicians are aware of the conditions that can affect HbA1c.

In situations where there is a suspicion of a falsely low or high HbA1c, the results should be correlated with blood glucose readings and, in the case of a discrepancy, alternative methods of glycaemic assessment should be used and potential causes investigated.

Key points
- HbA1c, in general a robust marker of diabetes control, can be unreliable in certain conditions and may lead to serious errors in patients’ management.
- Alternative methods of glycaemic control should be used if there is a discrepancy between blood glucose and HbA1c.
- It is essential clinicians are aware of the conditions that can affect HbA1c and should correlate HbA1c results with blood glucose readings.

Declaration of interests
There are no conflicts of interest declared.

References

POEMs
Low HbA1c, BP and cholesterol in elderly patients with type 2 associated with high mortality

Clinical question
Is there an association between mortality and glycaemic control, blood pressure levels and cholesterol levels in patients with type 2 diabetes who are older than 80 years?

Reference

Synopsis
These authors evaluated a population-based primary care database in the UK to identify nearly 26 000 patients older than 80 years with type 2 diabetes. The database includes data on physical examinations, test results, diagnoses and medications. The researchers mined this database for all they could: clinical data, comorbidities, number of clinic visits, classes of prescribed medication, smoking status, and so forth. Approximately half the cohort were women, one-third had co-existing cardiac disease, and about half had diabetes for at least 10 years. Approximately 10% of the patients were older than 90 years. There was a median of two years of follow up, during which about 4500 patients died (17%, 105 per 1000 person-years). The authors estimated the mortality, adjusting for a variety of factors, including age, sex and duration of diabetes. Similar to other studies, the relationship between mortality and glycaemic control as measured by HbA1c and blood pressure levels followed a U-shaped pattern, with the nadir for HbA1c between 7% and 7.4% (59–57nmol/mol) and for blood pressure between 150/90mmHg and 135/95mmHg. For each of these, the mortality progressively worsened with lower and higher HbA1c or blood pressure levels. The relationship between total cholesterol and mortality was more curvilinear, with the highest mortality associated with the lowest cholesterol levels and an asymptotic decrease as cholesterol levels increase.