Revisiting screening for type 2 diabetes mellitus: the case for and against using HbA1c

INTRODUCTION
Type 2 diabetes mellitus is a major cause of morbidity and premature mortality in the Western world. It is responsible for about 10% of the NHS spend (about £286/second in the UK). Of those diagnosed with type 2 diabetes, 25% are thought already to have evidence of complications indicating that the disease has been present for 4–7 years. Where people have been diagnosed with a pre-diabetes condition, such as impaired fasting glycaemia or impaired glucose tolerance (IGT), a proportion still demonstrate evidence of micro- and macrovascular complications. Research has led to the hypothesis that early detection, particularly in the early stages of the disease, can reduce the incidence of complications.

Many centres and professional bodies have adopted the recent guidance to utilise glycosylated haemoglobin (HbA1c) as a diagnostic tool for diabetes mellitus. Although HbA1c offers much potential in terms of staff time. Increasing research also demonstrated limited reproducibility and, coupled with different cut-off values advocated by the ADA and the World Health Organization (WHO), has led to difficulties in interpreting epidemiological data and limitations in making comparisons between studies.

HbA1c AND ITS USE
HbA1c was introduced as a glycaemic control surrogate in 1976. Its use was initially limited by poor standardisation. Following the National Glycohaemoglobin Standardisation programme in 1996, most UK laboratories use the standard set in the Diabetes Control and Complications Trial (DCCT). Its advantage as a glycaemic control surrogate was that the test could be taken at any time and did not require fasting. It also had the benefit that, as a marker of longer-term hyperglycaemia, it is unaffected by short-term counter-regulatory hormone surges in those who are acutely unwell.

HbA1c has been widely endorsed as a screening tool because it measures long-term glycaemic exposure, which is
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**REFERENCES**


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The fundamental factor underpinning the development of diabetes complications. It does not require the patient to fast and is more useful in the acutely unwell. Currently, the recommendation is to use a cut-off value of ≥48 mmol/mol for diagnosing diabetes. However, the ADA endorsed the additional use of values of 42–47 mmol/mol as indicative of increased risk of developing diabetes. Other evidence in favour of using HbA1c includes:

- **HbA1c** has been the most widely used surrogate for diabetes complications in the literature, for example, the DCCT and UK Prospective Diabetes Studies (UKPDS);
- less within-person day-to-day variability in value. Fasting PG had a day-to-day variability of 5%, and HbA1c variability was 2%;
- a longitudinal study of 1253 subjects, using logistic regression modelling of subjects followed for over 3 years by the Department of Veterans Affairs Medical Centre, showed that HbA1c was the strongest predictor of new cases of type 2 diabetes (defined as either the self-report of a physician’s diagnosis of diabetes, or by HbA1c >7.0% or fasting PG >7.0 mmol/L at 3-year follow-up). The incidence of diabetes was calculated as the number of new cases per person-year of follow-up;

- baseline HbA1c higher than the upper limit of normal in a Japanese population identified a 10-fold rise of diagnosed diabetes over 7 years, regardless of the fasting glycaemic values;
- as a test, HbA1c has a low intra- and inter-individual variability, is more stable than glucose at 37°C, and is not affected by factors such as time of sampling, diet, or stress. Similarly, it does not require the standardisation of diet or physical activity prior to the test necessary for the OGTT; as HbA1c testing does not require fasting, symptomatic patients could be tested at the same visit, saving costs.

From the evidence above it would seem that the decision to use HbA1c was easy, but a number of issues need to be considered.

- **HbA1c** is dependent on the predominant circulating haemoglobin being HbA. It is estimated that 30% of HbA1c assays in use will give clinically significant errors when used in subjects with haemoglobinopathies. US data indicate that 10% of African–American people (26 million) may have an undiagnosed HbE or HbS trait that will not be identified by some HbA1c assays;
- anything that shortens red blood cell survival (such as haemolytic anaemia) may cause artificial lowering of HbA1c as the haemoglobin in the younger red blood cells will have had less exposure. Similarly, HbA1c will be raised in conditions where red cell life is extended (splenectomy or iron deficiency);
- renal failure will increase the levels of carboxymethylated haemoglobin, which may affect HbA1c assays. HbA1c results can be falsely low in diabetic patients with end-stage renal disease;
- **HbA1c** reflects the overall glycaemic control over the lifespan of the red cell and hence is not sufficiently responsive in cases with rapidly rising glucose levels, and therefore should not be used in diagnosing symptomatic patients with type 1 diabetes;
- African–Caribbean and South Asian subjects have HbA1c levels 0.4% higher than white subjects, despite lower fasting PG levels when tested using an OGTT;
- older people age >70 years have 0.4% higher values of HbA1c than those aged 40 years, even after adjusting for glucose levels;
- **HbA1c** has a high inter-assay variability with significant differences identified with standard sample testing between laboratories.

In a number of such cases, alternatives to HbA1c such as fructosamine should be considered, although cut-offs for use as a diagnostic tool have yet to be validated.

**CONCLUSION**

The benefits of being able to use a single non-fasting test has led to the consideration of HbA1c as a screening tool, with advice from the International Expert Committee to recommend values of 48 mmol/mol as diagnostic of diabetes. This has been endorsed by WHO and the Department of Health in the UK. The HbA1c should be interpreted in the light of comorbidities and not used in patients with splenectomy, renal failure, haemoglobinopathies, or significant anaemia. Awaiting further data, it is pragmatic to use unified HbA1c cut-off values, rather than age and ethnicity variances, to aid large screening programmes. HbA1c should be seen as an adjunct to, rather than a replacement for, PG measurements. Indeed, diagnosis of asymptomatic individuals with diabetes using HbA1c will identify a different, albeit overlapping, population from that identified using glucose-based testing.
### Table 1. Diagnostic tests for diabetes with their cut-off values

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Impaired glucose tolerance</th>
<th>Impaired fasting glucose</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>&lt;6</td>
<td>n/a</td>
<td>6.1–6.9</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Fasting capillary blood glucose, mmol/L</td>
<td>15–26% higher plasma glucose when checked from the fingertips&lt;sup&gt;35&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Random plasma glucose, mmol/L</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>&gt;11.1</td>
</tr>
<tr>
<td>HbA1c, mmol/L</td>
<td>&lt;42</td>
<td>n/a</td>
<td>n/a</td>
<td>&gt;48</td>
</tr>
<tr>
<td>2-hour value of OGTT, mmol/L</td>
<td>&lt;7.8</td>
<td>7.8–11.0</td>
<td>n/a</td>
<td>&gt;11.1</td>
</tr>
</tbody>
</table>

n/a = not available. OGTT = oral glucose tolerance test.