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Revisiting screening for type 2 diabetes mellitus:

the case for and against using HbA1c

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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.[1] 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 this regard, it is not yet entirely clear how it should be used in clinical practice in the context of existing tests.

THE PROBLEM OF SCREENING

Evidence of microvascular and macrovascular disease is present in the 25% of newly-diagnosed cases of type 2 diabetes mellitus and also in those thought to be in a pre-diabetes state, therefore this has led to difficulties in deciding the cut-off levels for a clear diagnosis (Table 1).

The random plasma glucose (PG) sample is cheap and easy to do, and the diagnosis of type 2 diabetes mellitus in screened patients is conclusive if the values are ≥11.1 mmol/L. Lower values are more difficult to interpret. Research evidence correlating a diagnosis of diabetes, using a random glucose level, with the existence of complications is not available, possibly because of the methodological flaws in deciding cut-off values when the studies were designed. Studies that used a fasting glucose for diagnosis were able to show a correlation with complications, particularly retinopathy (odds ratio 1.6 per standard deviation in glucose levels, 95% confidence interval = 1.3 to 2.1),[2] leading the American Diabetes Association (ADA) to endorse this as the favoured method of diagnosis. Practically, however, this test requires a second visit to the healthcare facility for the test to be taken while fasting.

The oral glucose tolerance test (OGTT) is thought to demonstrate the altered physiological response to a glucose load, and is also able to diagnose IGT in those individuals who have glucose values between normal and those diagnostic of diabetes. It is more sensitive (because it includes the measurement of a 2-hour glucose in addition to the initial fasting baseline sample) than if a fasting glucose sample alone was used, and is thought to diagnose 2% more individuals with diabetes. The OGTT requires a second visit and is more expensive in terms of staff time. Increasing research also demonstrated limited reproducibility[3] 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).[4] 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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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;[5]
- 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 HbC 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 carbamylated haemoglobin, which may affect HbA1c assays. HbA1c results can be falsely low in diabetic patients with end-stage renal disease.[6]
- 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;[7]
- 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[8] 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.[9] 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

	Normal	Impaired glucose tolerance	Impaired fasting glucose	Diabetes
Fasting plasma glucose, mmol/L	<6	n/a	6.1–6.9	>7
Fasting capillary blood glucose, mmol/L	15–26% higher plasma glucose when checked from the fingertips[10]	n/a	n/a	n/a
Random plasma glucose, mmol/L	n/a	n/a	n/a	>11.1
HbA1c, mmol/L	<42	n/a	n/a	>48
2-hour value of OGTT, mmol/L	<7.8	7.8–11.0	n/a	>11.1

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