Diagnosis of diabetes: A line in the sand

In the last issue of this journal we included an important statement from a group convened by Rowan Hillson, National Clinical Director for Diabetes in England, which recommended the use of HbA_{1c} for the diagnosis of diabetes throughout the UK (John et al, 2011). An HbA_{1c} level of ≥48 mmol/mol (≥6.5%) has been chosen as the cut-point for diagnosing diabetes. This agreed level aligns with a report issued last year by the World Health Organization (WHO, 2011) recommending that HbA_{1c} can be used as a diagnostic test for diabetes, providing that stringent quality assurance tests are in place in laboratories that use the test.

While this statement had been much anticipated, we should be aware that it has important consequences for people with diabetes and their primary care teams. Primary healthcare professionals are already familiar with the benefits of HbA_{1c} in helping people with diabetes with their ongoing management decisions, as well as a measure of performance in QOF.

Sensitivity and specificity

How sensitive and specific is HbA_{1c} in the diagnosis of diabetes compared with fasting plasma glucose (FPG) and 2-hour plasma glucose? In a population-based analysis of 12 485 participants, the sensitivity (proportion of actual positives that are correctly identified) and specificity (the proportion of negatives that are correctly identified) remained much higher for HbA_{1c} compared with blood glucose, leading to it being described as the "gold standard" test (Selvin et al, 2011). This accuracy for HbA_{1c} was maintained consistently across most age, BMI, and ethnicity groups. The same article went on to suggest that in individuals with an HbA_{1c} level of <48 mmol/mol (<6.5%), but who also have an elevated FPG, the test also predicted the risk of developing diabetes.

In the UK, individuals are thought to be at risk and to have impaired glycaemia when they have an HbA_{1c} level of >42 mmol/mol (>6.0%) and <46 mmol/mol (<6.4%) (Kilpatrick and Winocour, 2010; NICE, 2011). While the cut-point for the diagnosis of diabetes has been chosen as ≥48 mmol/mol (≥6.5%) – as this is the level at which the risk of diabetic retinopathy increases – individuals who are diagnosed using this cut-point have a more unfavourable cardiovascular risk profile than those who are diagnosed using OGTT (Boronat et al, 2010).

What more commonly leads to a discussion among clinical biochemists is people who do not fulfil the diagnostic cut-off of ≥48 mmol/mol (≥6.5%), but have elevated fasting, or 2-hour plasma glucose levels, especially as these latter groups often vary with age and ethnicity. Each test identifies a different group of people who can be diagnosed with diabetes, and although there is considerable overlap, there are differences between the groups. This has implications for people who will be diagnosed with HbA_{1c}, but who might escape this diagnosis with other diagnostic methods.

Advantages and disadvantages of using HbA_{1c}

A clear advantage of using HbA_{1c} for diagnosis for primary care teams is that the person with suspected diabetes does not need to fast, perhaps saving an additional appointment. As well as offering a measure of glycaemia over the preceding 12 weeks, there is less biological variability with HbA_{1c} compared with plasma glucose measurements, which means the measurement is unlikely to change with repeated testing. Moreover, standardising laboratory instruments to the new International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standard has brought laboratories across the UK and Ireland closer together.

Colin Kenny

A new series of Primary Care Diabetes Society (PCDS) CPD modules launches in this issue. Now supported by an educational grant from Boehringer Ingelheim and Eli Lilly and Company, the series begins with Eugene Hughes' updated module on older blood glucose-lowering therapies on page 35. The way the modules are presented online is changing; to read more about the updates, see the PCDS newsletter on page 18.

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There are also disadvantages of the test, however, that may lead to times when an HbA_{1c} level will give primary care teams misleading indications of true glycaemia. Abnormal haemoglobin, both in terms of haemoglobinopathies and the survival time of the red blood cell, may give misleading results. Various anaemias, particularly haemolytic anaemia can affect red blood cell survival and HbA_{1c} results. This may be compounded by renal failure. Being >70 years of age with diabetes can also affect HbA_{1c} levels, which can be 4.4 mmol/mol (0.4 percentage points) higher in such individuals (Pani et al, 2008). An article on page 22 looks at how to individualise the correct target HbA_{1c} levels for older people. To allow people who potentially have diabetes to make informed decisions, primary healthcare professionals will need to be familiar with factors that can interfere with haemoglobin and make testing inaccurate (WHO, 2011).

Primary care team members need to be aware that there are situations where HbA_{1c} should not be used as the sole test to diagnose diabetes. HbA_{1c} reflects glycaemia over the preceding 12 weeks, and so may not be elevated if blood glucose levels have risen rapidly. Typically, all children and young people, people with symptoms suggestive of type 1 diabetes of any age, short duration of diabetes symptoms, people at high risk of diabetes who are acutely ill, those taking medication that may cause a rapid rise in blood glucose levels, or people with acute pancreatitis or who have had pancreatic surgery should not have substantive clinical decisions made on their HbA_{1c} level (John et al, 2011). Another study questioned the validity of the test in adolescents (Lee et al, 2011).

The way forward

Given this clear direction, what should healthcare professionals do now? Primary care teams should accept this diagnostic cut-point as a line in the sand at any one point in time. It is important that practice protocols for diabetes care are updated and all team members are informed of this fundamental change. Most practices are likely to stop doing oral glucose tolerance tests and Jill Hill looks at the future use of this test on page 10. A more difficult group are those with the label of diabetes and an HbA_{1c} level below the 48 mmol/mol (6.5%) threshold, who are not on treatment. Pragmatically, practices may wish the diabetes label be allowed to continue, accepting that such individuals did meet the criteria for diabetes at the time of diagnosis and that many will progress to beta-cell failure. Practices may have recently reviewed their classification of diabetes. A similar exercise of searching for people with diabetes who have been diagnosed by plasma glucose estimates but not confirmed by HbA_{1c} at the agreed level of 48 mmol/mol (6.5%) could be futile as people with established diabetes, initially diagnosed on blood glucose alone, will have seen their diabetes progress and will have considerable cardiovascular risk.

Symptomatic individuals whose HbA_{1c} level is <48 mmol/mol (<6.5%) should certainly be encouraged to seek follow-up at agreed intervals, and sooner if symptoms present. Inevitably, there will be a minority of people for whom the diagnosis will not be clear-cut; as the diagnosis has many medico-legal and driving licence consequences, not to mention the inclusion on QOF registers, such cases should be discussed with a clinical biochemist. Nevertheless, this clear diagnostic level for diabetes is an important development and should be embraced as such by healthcare professionals. ■

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