Guidance concerning the use of glycated haemoglobin (HbA_{1c}) for the diagnosis of diabetes mellitus

A position statement of the Australian Diabetes Society

Only patients at high risk of undiagnosed diabetes should be tested

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doi: 10.5694/mja15.00041

Reimbursement by Medicare of the costs of measuring glycated haemoglobin (HbA_{1c}) for the diagnosis of diabetes mellitus was recently approved. An HbA_{1c} value of 48 mmol/mol (6.5%) or more constitutes a positive result, suggesting the diagnosis of diabetes mellitus. This test provides an alternative to traditional glucose-based methods of diagnosis; it does not replace them. The correct use of the test may facilitate earlier diagnosis of people with elevated mean blood glucose levels who are at increased risk of long-term diabetes-specific microvascular complications. HbA_{1c} assessment will be used predominantly for the diagnosis of type 2 diabetes mellitus.

It is important that medical practitioners who elect to use the test for diagnostic purposes understand its nature, its limitations and its benefits. The latter were outlined in the position paper of the HbA_{1c} Committee of the Australian Diabetes Society published in this Journal in 2012.[1] We recommend that medical practitioners read the earlier paper in conjunction with this new implementation document. Assessment of HbA_{1c} levels during pregnancy is not discussed in this article.

This position statement of the Australian Diabetes Society is endorsed by the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists.

Summary

- Glycated haemoglobin (HbA_{1c}) assessment for the diagnosis of diabetes mellitus overcomes many practical problems associated with traditional blood glucose measurements.
- However, the test is not without limitations of which the medical practitioner needs to be aware.
- The possibility of an individual having a medical condition that interferes with the test should always be considered, even though these conditions are rare in most Australian communities.
- Appropriately used, HbA_{1c} assessment should provide a cost-effective, efficient and simple tool for the early diagnosis of type 2 diabetes.

Medicare reimbursement

The Medicare Benefits Schedule (MBS) entry for item 66841 describes the test as the "Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in asymptomatic patients at high risk". When used for this purpose, the cost of the test can be reimbursed only once during a 12-month period.[2] The brevity of the MBS description raises certain questions.

1. High-risk patients

Only patients at high risk of undiagnosed diabetes should be tested. These are patients with either (i) a medical condition or ethnic background associated with high rates of type 2 diabetes, or (ii) an Australian type 2 diabetes risk (AUSDRISK) score of 12 or greater, placing them at increased risk of diabetes.[1,3,4]

The HbA_{1c} test should not be used to randomly or systematically screen undifferentiated groups of patients. Without prior knowledge of the medical status of an individual, the test may not correctly diagnose patients as having diabetes (see section 5, below).

2. Asymptomatic patients

Medicare restricts diagnostic HbA_{1c} assessment to asymptomatic patients. However, many symptoms of diabetes are, in isolation, non-specific; eg, tiredness and blurred vision. Patients presenting with such symptoms should be considered asymptomatic and appropriate for HbA_{1c} testing if at high risk of developing diabetes. If one or more symptoms that suggest diabetes are present in a low-risk patient, blood glucose tests should be used.

Patients who have multiple classical symptoms of diabetes (weight loss, polyuria, polydipsia, blurred vision etc.), however, are not asymptomatic, and should have the diabetes diagnosis confirmed by blood glucose assessment; high blood glucose levels would be expected in these cases. Further, patients with rapidly evolving diabetes can theoretically have normal HbA_{1c} levels because blood glucose levels have not been elevated for a significant period of time.

3. Repeat assessment of HbA_{1c} levels

An HbA_{1c} test result of less than 48 mmol/mol (6.5%) indicates that diabetes is unlikely. As the test will have been performed in a high-risk patient, it should be repeated 12 months later, according to the National Health and Medical Research Council (NHMRC) guidelines.[4] These patients should also be given appropriate lifestyle advice.[5,6]

Labelling people with an HbA_{1c} value slightly under 48 mmol/mol (6.5%) with prediabetes is not recommended, as there is uncertainty about using HbA_{1c} levels to define prediabetes. This is consistent with the position of the World Health Organization.[7] However, an HbA_{1c} level of 42–47 mmol/mol (6.0–6.4%) suggests a higher risk of developing diabetes than that based on the AUSDRISK score alone; these individuals will also be at increased risk of the cardiovascular complications.[8,9] They should be

1 Conditions that may reduce glycated haemoglobin (HbA_{1c}) levels

A. Increased erythropoiesis

Iron, vitamin B_{12} or folate administration, erythropoietin therapy, chronic liver disease, reticulocytosis

B. Abnormal haemoglobin

Haemoglobinopathies, haemoglobin F, methaemoglobin

C. Reduced glycation

Aspirin, vitamins C and E, certain haemoglobinopathies, increased intra-erythrocyte pH

D. Elevated erythrocyte destruction

Haemolytic anaemia, haemoglobinopathies, splenomegaly, rheumatoid arthritis, certain medications (eg, antiretroviral agents, ribavirin, dapsone)

E. Assay problems

Haemoglobinopathies,* hypertriglyceridaemia.

Adapted from Gallagher et al (2009).[12]

* The common heterozygote haemoglobinopathies do not cause problems with most current assays, but you should contact your laboratory for further information. ◆

counselled about lifestyle measures (weight loss, dietary change, exercise) and assessed for other modifiable cardiovascular risk factors (hypertension, dyslipidaemia, smoking). Unless they develop symptoms of diabetes, additional blood glucose measurements should not be performed to diagnose diabetes. They may have blood glucose levels consistent with impaired fasting glucose, impaired glucose tolerance, or diabetes, but, with an HbA_{1c} level below 48 mmol/mol (6.5%), they are at minimal risk of developing microvascular complications.[10] Even if diagnosed with diabetes or prediabetes, lifestyle advice should be the major intervention. Their HbA_{1c} levels should be re-assessed 12 months later.

4. Confirmation

The NHMRC guidelines indicate that abnormal blood glucose levels in an asymptomatic patient should be confirmed to establish a diagnosis of diabetes. A single elevated HbA_{1c} result is accepted by Medicare as evidence for established diabetes, although other organisations (WHO, American Diabetes Association) recommend that diagnoses made by HbA_{1c} testing be confirmed by follow-up testing.[7,11]

2 Implementation recommendations regarding glycated haemoglobin (HbA_{1c}) testing for the diagnosis of diabetes

- HbA_{1c} assessment should be considered in asymptomatic patients at high risk of developing diabetes (AUSDRISK score ⩾ 12 or pre-existing medical condition or ethnic background associated with high rates of type 2 diabetes).
- If one or more diabetes symptoms are present in a patient at low risk, blood glucose levels should be used for diagnosis.
- Patients who have multiple symptoms suggestive of diabetes mellitus are not asymptomatic, and their blood glucose levels should be assessed.
- An HbA_{1c} level ⩾ 48 mmol/mol (6.5%) suggests that the patient has diabetes mellitus.
- An HbA_{1c} level < 48 mmol/mol (6.5%) suggests that the patient does not have diabetes mellitus. As the test has been performed in a high-risk patient, the test should be repeated 12 months later.
- A confirmatory test should be performed on another day, ideally as soon as possible and before any lifestyle or pharmacological interventions are commenced.
- Be aware of conditions that may invalidate the test results. ◆

The diagnosis of diabetes has employment, insurance, financial and lifestyle implications, so it is important that it is correct. Although a more reliable laboratory measure than blood glucose levels,[1] HbA_{1c} levels do vary within a narrow range over time, both in individuals and during the measurement process. Errors during sample labelling and handling can also occur. It is therefore recommended that a confirmatory test be performed on a different day, ideally as soon as possible and before any lifestyle or pharmacological interventions commence; if delayed, a normal follow-up result may reflect the effects of treatment. A result below 48 mmol/mol (6.5%) does not confirm diabetes, and these patients should generally be advised that they do not have diabetes. They are, however, at high risk of its developing, and they should be managed accordingly (section 3).

If both HbA_{1c} and glucose levels are elevated in an individual, the diagnosis of diabetes is confirmed. If only one of the values is elevated, the relevant test should be repeated to confirm the diagnosis.

There is an apparent conflict between these practice guidelines and the Medicare regulations (one diagnostic HbA_{1c} test in a 12-month period). Medicare recognises a single elevated HbA_{1c} measurement as establishing a diabetes diagnosis; this entitles the patient to four monitoring HbA_{1c} tests in each subsequent 12-month period. We therefore recommend that the first monitoring test be performed before any interventions are initiated. A positive result in this test confirms the diagnosis and sets the baseline for clinical management. A result below 48 mmol/mol, if the test is performed appropriately, means that the patient should be classified as not having clinical diabetes, but they should have a further diagnostic HbA_{1c} test 12 months later.

5. Abnormal measurements

In a small but important minority of people, HbA_{1c} levels are not a reliable indicator of plasma glucose levels. An inappropriately low HbA_{1c} value is the major concern, as the diagnosis of diabetes will be missed in such patients. The possibility of medical conditions that invalidate the HbA_{1c} result should be considered in all patients with an unexpectedly low HbA_{1c} result, as discussed in our earlier paper.[1] In summary, HbA_{1c} assessment may not be appropriate in patients with significant chronic medical disease, anaemia or abnormalities of red blood cell structure (Box 1). A full blood count may reveal red blood cell abnormalities suggestive of a haemoglobinopathy or haemolytic anaemia, but a normal full blood count does not exclude the possibility of such conditions. Certain ethnic communities more frequently have underlying haemoglobin abnormalities, and this should be discussed with the testing laboratory when appropriate. Emerging methodologies are minimising this problem.

Competing interests: No relevant disclosures.

Provenance: Not commissioned; not externally peer reviewed. ■

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