

Guidelines

The role of HbA_{1c} in the diagnosis of diabetes mellitus in Australia

Position statement of the Australian Diabetes Society, the Royal College of Pathologists of Australasia, and the Australasian Association of Clinical Biochemists

Michael C d'Emden
MD, PhD, FRACP,
Director of Endocrinology
and Diabetes,¹ and
Chair of HbA_{1c} Committee²

Jonathan E Shaw
MD, FRACP, FRCP,
Endocrinologist³

Peter G Colman
MB BS, FRACP, MD,
Director of Diabetes
and Endocrinology⁴

Stephen Colagiuri
MB BS, FRACP,
Professor of
Metabolic Health⁵

Stephen M Twigg
MB BS, PhD, FRACP,
Professor of Medicine⁶

Graham R D Jones
MB BS, DPhil, FRCPA,
Chemical Pathologist,⁷ and
RCPA Representative,
HbA_{1c} Committee⁸

Ian Goodall
FAACB, FAIMS, FFSC(RCPA),
Retired Medical Scientist,⁹
and AACB Representative,
HbA_{1c} Committee¹⁰

Hans G Schneider
MD, FRCPA, FRACP,
Director of Alfred
Pathology Service¹¹

N Wah Cheung
MB BS, PhD, FRACP,
Director of Diabetes
and Endocrinology¹²

¹ Royal Brisbane and Women's Hospital, Brisbane, QLD.

² Australian Diabetes Society, Sydney, NSW.

³ Baker IDI Heart and Diabetes Institute, Melbourne, VIC.

⁴ Royal Melbourne Hospital, Melbourne, VIC.

Diabetes mellitus is a major health problem for Australia. It is associated with the development of a variety of complications that have a significant impact on morbidity and mortality. The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study found an overall diabetes prevalence of 7.4% in a national sample of people aged 25 years or older, with 50% of cases being previously undiagnosed.¹ The long-term complications of type 1 and type 2 diabetes include the microvascular complications of retinopathy, nephropathy and neuropathy, but the major health problem in type 2 diabetes is the increased risk of macrovascular complications, such as coronary artery disease and peripheral artery disease.

It is important to establish the diagnosis of diabetes early in its development, as effective management of the disease has been shown in the United Kingdom Prospective Diabetes Study (UKPDS) to significantly reduce the risk of developing complications.² Furthermore, long-term follow-up of participants during the observational phase of the UKPDS demonstrated that more effective glycaemic control from the time of diagnosis in people with type 2 diabetes conferred a long-term legacy benefit that persisted even though glycaemic control may deteriorate over time.³ This observation implies that strategies that facilitate early detection of diabetes should result in improved outcomes, with major long-term health and cost benefits for Australia.

Traditionally, we have relied on measurement of blood glucose parameters to make the diagnosis of diabetes.^{4,5} The cut-offs used to establish the diagnosis defined elevated blood glucose levels on the basis of an increased risk of diabetes-related complications. Although there is a clear and highly significant relationship between blood glucose levels and cardiovascular disease, there is no threshold level at which cardiovascular disease will occur.⁶ However, microvascular complications, and in particular retinopathy, show a much clearer threshold of glycaemia above which they occur and where glucose-lowering therapy is clearly effective in preventing them.² Thus, the diagnosis of diabetes has been based on blood glucose threshold levels associated with the presence of retinopathy.⁵

However, measuring blood glucose levels is associated with methodological, procedural and practical problems. Day-to-day variation of blood glucose levels is considerable, the concentration *ex vivo* falls quickly even when the

Summary

- For many years, the diagnosis of diabetes has been made through the laboratory-based measurement of fasting or random blood glucose levels, or using the oral glucose tolerance test.
- A glycated haemoglobin (HbA_{1c}) level $\geq 6.5\%$ (48 mmol/mol) is now also acceptable for diagnosing diabetes.
- Caution is needed in interpreting HbA_{1c} test results in the presence of conditions affecting red blood cells or their survival time, such as haemoglobinopathies or anaemia.

blood sample is collected in a fluoride-oxalate tube, and interlaboratory levels can vary by at least 14% in a third of cases.^{7,8} The oral glucose tolerance test (OGTT) requires proper pretest preparation, including an appropriate diet for 3 days before the test and a satisfactory period of overnight fasting. The OGTT is also time-consuming, taking at least 2 hours. The glucose load is poorly tolerated by a significant number of people, with nausea, vomiting, delayed gastric emptying and issues of venous access all potentially contributing to an invalid test result. The test often needs to be repeated and has poor patient compliance. A recent study from South Australia showed that only 27% of patients identified on admission to hospital as potentially having diabetes presented for a diagnostic OGTT despite consenting to undertake the test.⁹

The use of glycated haemoglobin (HbA_{1c}) measurement as an alternative diagnostic test overcomes many of these concerns. The HbA_{1c} test is attractive as it measures chronic glycaemia, rather than instantaneous blood glucose levels. HbA_{1c} has been used as an objective marker of average glycaemic control for many years, has an accepted place in the monitoring of patients with diabetes, and is relied on for significant management decisions, such as initiation of insulin therapy. The strength of its relationship with diabetes-related complications was demonstrated in an analysis of the combined data from eight studies conducted between 1988 and 2004, which reported that HbA_{1c} levels were at least as strongly related to the presence of diabetic retinopathy as were blood glucose levels.¹⁰ It is also strongly associated with macrovascular outcomes and mortality.¹¹⁻¹³ Practically, HbA_{1c} measurement provides significant advantages over blood glucose measurement for diagnosis of diabetes. It can be performed at any time of the day, does not require special

Recommendations regarding the use of glycated haemoglobin (HbA_{1c}) testing for the diagnosis of diabetes*

- Measurement of HbA_{1c} level can be used as a diagnostic test for diabetes if analysis is performed in a facility producing acceptable performance in external quality assurance, assays are standardised to criteria aligned to international reference values, and if no conditions which preclude its accuracy are present. It is important to note that HbA_{1c} testing is not currently funded by Medicare for the purpose of diagnosis of diabetes.
- An HbA_{1c} level of $\geq 6.5\%$ (48 mmol/mol) is recommended as the cut-off point for diagnosing diabetes.
- An HbA_{1c} level of $< 6.5\%$ (48 mmol/mol) does not negate a diagnosis of diabetes based on elevated glucose parameters. The existing criteria based on fasting and random glucose levels, and on the oral glucose tolerance test, remain valid, and are the diagnostic tests of choice for gestational diabetes, type 1 diabetes and in the presence of conditions that interfere with HbA_{1c} measurement.

* Level of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system: moderate.¹⁷ ♦

pretest preparation such as a diet or fasting, and is stable when collected in the appropriate specimen tube.

HbA_{1c} has recently been endorsed as a diagnostic test for diabetes by the World Health Organization, the International Diabetes Federation and the American Diabetes Association.^{14,15} The Australian Diabetes Society established an expert committee in 2011, including invited representatives of the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB), to review the available evidence and provide this position statement concerning the role of HbA_{1c} in the diagnostic pathway. Additionally, the committee sought to ensure that its recommendations otherwise concur with recently published National Health and Medical Research Council (NHMRC) guidelines for the detection and diagnosis of type 2 diabetes.¹⁶ A summary of the committee's recommendations is shown in the Box.

The committee concluded that HbA_{1c} can have an important place in the diagnostic pathway and can be used to establish the diagnosis of diabetes. An HbA_{1c} level $\geq 6.5\%$ (48 mmol/mol) is recommended as the cut-off point for diagnosing diabetes. In an asymptomatic patient with a positive test result, the test should be repeated to confirm the diagnosis. The use of HbA_{1c} measurement will simplify the diagnostic process and may lead to earlier diagnosis of more patients with diabetes. However, HbA_{1c} should not be used as a general screening test for diabetes; initial screening should be on the basis of the Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) score, as recommended in the NHMRC guidelines.¹⁶ Furthermore, it must be noted that the HbA_{1c} assay is not currently funded by Medicare as a diagnostic or screening test for diabetes, although funding for this purpose is being sought. Medicare payments for HbA_{1c} testing currently require evidence that the patient has diabetes, such as a statement to this effect on the request form.

There are some important caveats. If used as a diagnostic test, the HbA_{1c} assay needs to be reliable and consistent across Australia. There have been problems in the past with HbA_{1c} test results varying considerably between

5 Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, NSW.

6 University of Sydney, Sydney, NSW.

7 St Vincent's Hospital, Sydney, NSW.

8 Royal College of Pathologists of Australasia, Sydney, NSW.

9 Melbourne, VIC.

10 Australasian Association of Clinical Biochemists, Sydney, NSW.

11 Alfred Health, Melbourne, VIC.

12 Westmead Hospital, Sydney, NSW.

Michael_d'Emden@health.qld.gov.au

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laboratories. In the United States, the National Glycohemoglobin Standardization Program (NGSP) has progressively driven improvements in assays,¹⁸ resulting in better-quality results around the world. The variability of HbA_{1c} values within Australia is now acceptably low. In a recent Australian study, whole blood samples were sent to more than 200 laboratories, and more than 90% of HbA_{1c} results fell within 6% of the median.¹⁹ Although the variation between laboratories remains even lower for blood glucose assays, when the pretest issues (eg, day-to-day variation in glucose levels, the fall in plasma glucose levels after the sample has been taken) are also considered, the HbA_{1c} test performs at least as well as glucose testing. Further improvements in standardisation of HbA_{1c} measurements should be achieved following the development of a national whole blood external quality control program by the RCPA Quality Assurance Programs and the AACB.

When applying HbA_{1c} testing for the diagnosis of diabetes, some medical conditions may affect the test and cause falsely high or low readings. The test's accuracy is affected principally by conditions that affect red blood cell survival time or non-enzymatic glycation of haemoglobin. A reduced red blood cell survival time will lower the HbA_{1c} level and may lead to a false negative result. Red blood cell survival time is reduced in any haemolytic anaemia, and it can also be reduced in chronic renal failure, severe liver disease and anaemia of chronic disease. Vitamin B₁₂ and folic acid deficiencies may shorten red blood cell survival time. A common clinical situation that shortens red blood cell survival time occurs when patients undergo regular phlebotomy for medical indications (eg, haemochromatosis) or because they are regular blood donors. Iron deficiency may also have an impact on red blood cell survival and the HbA_{1c} level. The congenital variants of the haemoglobin molecule (haemoglobinopathies), which may be relatively common in certain ethnic communities (eg, African, Mediterranean) in Australia, affect glycation to a variable amount, principally due to interference with the laboratory measurement of HbA_{1c} level. Many newer laboratory methods are reducing this problem. The NGSP provides a summary of the effect of common haemoglobinopathies on measurement of HbA_{1c} levels using various methods (<http://www.ngsp.org/interf.asp>). However, any inexplicably high or low HbA_{1c} test result or discrepancy between glucose and HbA_{1c} levels should alert the medical practitioner to a potential problem.

Simplistically, HbA_{1c} may not be the appropriate test to confirm the diagnosis of diabetes in patients with any significant chronic medical disease, any anaemia or any abnormality of red blood cell structure.^{7,8,20} If any of these conditions exist, the diagnosis should be based on measures of blood glucose levels using existing criteria (fasting or random glucose level, and OGTT). These issues will be addressed in another publication from the Australian Diabetes Society, as will the place of HbA_{1c} in the clinical pathways for diagnosing diabetes.

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