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 previouslyundiagnosed. 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. 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. 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. 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. 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. Thus, the diagnosis of diabetes has been based on blood glucose threshold levels associated with the presence of retinopathy.

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 blood sample is collected in a fluoride-oxalate tube, and interlaboratory levels can vary by at least 14% in a third of cases. 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.

The use of glycated haemoglobin (HbA1c) measurement as an alternative diagnostic test overcomes many of these concerns. The HbA1c test is attractive as it measures chronic glycaemia, rather than instantaneous blood glucose levels. HbA1c 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 HbA1c levels were at least as strongly related to the prevalence of diabetic retinopathy as were blood glucose levels. It is also strongly associated with macrovascular outcomes and mortality. Practically, HbA1c 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 pretest preparation such as a diet or fasting, and is stable when collected in the appropriate specimen tube.

HbA1c has recently been endorsed as a diagnostic test for diabetes by the World Health Organization, the International Diabetes Federation and the American Diabetes Association. 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
HBₐ₁c 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. A summary of the committee’s recommendations is shown in the Box.

The committee concluded that HBₐ₁c can have an important place in the diagnostic pathway and can be used to establish the diagnosis of diabetes. An HBₐ₁c level ≥ 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 HBₐ₁c measurement will simplify the diagnostic process and may lead to earlier diagnosis of more patients with diabetes. However, HBₐ₁c 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. Furthermore, it must be noted that the HBₐ₁c 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 HBₐ₁c 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 HBₐ₁c assay needs to be reliable and consistent across Australia. There have been problems in the past with HBₐ₁c test results varying considerably between laboratories. In the United States, the National Glycohemoglobin Standardization Program (NGSP) has progressively driven improvements in assays, resulting in better-quality results around the world. The variability of HBₐ₁c 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 HBₐ₁c results fell within 6% of the median. 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 HBₐ₁c test performs at least as well as glucose testing. Further improvements in standardisation of HBₐ₁c 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 HBₐ₁c 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 HBₐ₁c 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 HBₐ₁c 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 HBₐ₁c level. Many newer laboratory methods are reducing this problem. The NGSP provides a summary of the effect of common haemoglobinopathies on measurement of HBₐ₁c levels using various methods (http://www.ngsp.org/interf.asp). However, any inexplicably high or low HBₐ₁c test result or discrepancy between glucose and HBₐ₁c levels should alert the medical practitioner to a potential problem.

Simplistically, HBₐ₁c 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. 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 HBₐ₁c in the clinical pathways for diagnosing diabetes.

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