Is Australia ready to use glycated haemoglobin for the diagnosis of diabetes?

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HbA_{1c} may be a practical alternative to blood glucose for the diagnosis of diabetes

For more than 15 years, glycated haemoglobin (HbA_{1c}) has been recommended as the key tool for assessing glycaemic control in people with diabetes. Only in 2009 did the first advice to use HbA_{1c} levels for diabetes diagnosis appear, using a cut-point of $\geq 6.5\%$.[1] To date, no clear argument has been articulated to explain why HbA_{1c} levels have been deemed superior to laboratory-determined blood glucose levels for determining the need for insulin therapy, but not for diagnosing diabetes; however, it is likely that implications of the former are greater than those of the latter, for both individuals and society.

Blood glucose values are considered the gold standard for diabetes diagnosis, but they have significant limitations. Day-to-day variability in glucose levels is considerable, and the glucose concentration in a plasma sample falls within a short period, even if the blood has been collected in a fluoride tube. In addition, when stable samples are tested in two different laboratories, the results will differ by at least 14% in more than a third of cases.[2] Furthermore, even when using a single laboratory, only 70% of people with a blood glucose value that indicates a diagnosis of diabetes have the diagnosis confirmed by repeat testing 2 weeks later, compared with 83% for HbA_{1c}.[2]

So, is HbA_{1c} the answer to the challenges of diabetes diagnosis? Until recently, the problem with HbA_{1c} has been the concern that results vary considerably between laboratories. In the 1990s, laboratory differences of more than two percentage points were not uncommon, but the United States National Glycohemoglobin Standardization Program (NGSP) has progressively driven improvements in assay standards. The latest results from the largest global survey of quality of HbA_{1c} measurement show that, for reference samples with HbA_{1c} levels of 4.0%–6.0%, 91% of more than 3000 laboratories could obtain an HbA_{1c}value that was within 6.0% of the target.[3] In a recent Australian study, whole blood samples were sent to more than 200 laboratories and more than 90% obtained HbA_{1c} values that were within 6% of the median.[4] Thus, for a sample with a median value of 5.3%, over 90% of laboratories obtained values within the range 5.0%–5.6%, and for a median value of 7.4%, over 90% obtained values within the range 7.0%–7.8%. In addition, combined data from eight studies conducted between 1988 and 2004 (using assays in eight different laboratories, none of which may have performed as well as those available now) showed that HbA_{1c} levels were at least as strongly correlated with diabetic retinopathy as were blood glucose levels.[5]

HbA_{1c} is not without limitations. First, an HbA_{1c} test is more expensive than a fasting glucose test, but costs about the same as an oral glucose tolerance test. The extra cost of using HbA_{1c} instead of fasting glucose as the initial blood test needs to be weighed up against the potential for the HbA_{1c} test (which does not require the patient to fast) to be used more widely, to identify more undiagnosed cases of diabetes, and to save money by preventing complications of diabetes. To our knowledge, no cost–benefit analyses comparing the HbA_{1c} test with the fasting glucose test have been published — this should be a high priority. Second, HbA_{1c} can be unreliable in the presence of haemoglobin variants or alterations in red blood cell turnover. Most HbA_{1c} assays are now able to adjust for the most common haemoglobin variants, but where there is uncertainty relating to the reliability of HbA_{1c}, blood glucose will remain the preferred test.

If the potential exists to use HbA_{1c} for the diagnosis of diabetes, how can a practitioner know whether a particular laboratory can be relied on? A joint working party of the Australian Diabetes Society, the Royal College of Pathologists of Australasia, and the Australasian Association of Clinical Biochemists is developing a formal laboratory and clinical framework within which the diagnosis of diabetes by HbA_{1c} testing can be undertaken. In the meantime, it would be reasonable to think that a laboratory can be relied on, in the context of using HbA_{1c} as a diagnostic tool, if the routine coefficient of variation is $\leq 3.0\%$ (the 2010 accreditation target used by the NGSP) and the external quality assurance results are consistently within the Royal College of Pathologists of Australasia Quality Assurance Programs method-specific performance targets (allowable limits of performance). This information should be available from laboratories on request.

Practical aspects of using HbA_{1c} for the diagnosis of diabetes remain to be finalised. One option may be to request a fasting glucose test and HbA_{1c} test at the same time, with the HbA_{1c} to be performed only if the fasting glucose level is ≥ 5.5 mmol/L. This strategy would limit the additional costs of HbA_{1c} testing while

decreasing the number of patients who are lost to follow-up for an oral glucose tolerance test.

The cost of an HbA_{1c} test that is used for diagnosis is not currently reimbursed by Medicare. However, when used appropriately, the HbA_{1c} test appears to be at least as useful for diagnosing diabetes as a blood glucose test. Australia may soon be ready to join countries such as the United States and Japan in using HbA_{1c}, a *measure* of chronic glycaemia, for the diagnosis of diabetes, a *disease* of chronic glycaemia.

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References

1 International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009; 32: 1327-1334.
2 Kirkman MS, Kendall DM. Hemoglobin A_{1c} to diagnose diabetes: why the controversy over adding a new tool? *Clin Chem* 2011; 57: 255-257.
3 Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A_{1c} measurement and goals for improvement: from chaos to order for improving diabetes care. *Clin Chem* 2011; 57: 205-214.
4 RCPA Chemical Pathology Programs. Program information circular: glycohaemoglobin program, whole blood samples, 22/06/09. http://www.rcpaqap.com.au/chempath/documents/uploadedfiles/455_Whole%20Blood%20Samples%20270809.pdf (accessed Mar 2011).
5 Colagiuri S, Lee C, Wong T, et al. Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. *Diabetes Care* 2011; 34: 145-150.

Provenance: *Commissioned; not externally peer reviewed.*

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