HbA1c measurement

E S Kilpatrick

As methods improve, inherent limitations become more apparent

It is difficult to overestimate the contribution made by glycated haemoglobin measurement (usually in the form of HbA_{1c}) to the management of patients with diabetes mellitus and the reliance now placed on the test by clinicians. Before its introduction as a routine test in the late 1970s and early 1980s, objectively assessing glycaemic control relied on measures such as 24 hour urine glucose excretions[1] and daily blood glucose profiles.[2] By comparison, measurement of HbA_{1c} gave a much more reliable measure of glucose control over the prolonged period of the previous six to eight weeks.[3] The clinical usefulness of the test was cemented by major trials, such as the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes[4] and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes.[5] Both showed that improved glycaemic control, as assessed by HbA_{1c}, could lead to substantial reductions in the risk of developing the microvascular complication of diabetes such as retinopathy, nephropathy, and neuropathy. The UKPDS findings also suggested that the risk of myocardial infarction (the main cause of premature death in diabetes) could be improved by reducing HbA_{1c} values.[6]

> ''The importance that is now placed on HbA_{1c} is demonstrated by the new contract for general practitioners in the UK, which sets glycaemic control targets for diabetes patients''

Based on the publication of these and other studies, target values for HbA_{1c} have evolved over recent years. Currently, in the UK it is recommended that a patient's HbA_{1c} should be between 6.5% and 7.5%, aiming for the lower end of this range if macrovascular complications are present.[7] In the USA, an HbA_{1c} of $< 7.0\%$ is strived for, with values $> 8\%$ requiring major treatment changes in most cases.[8] The importance that is now placed on HbA_{1c} is demonstrated by the new contract for general practitioners in the UK, which sets glycaemic control targets for patients with diabetes.[9] These targets are based entirely on the HbA_{1c} values that general practitioners obtain in their patients and so, for the first time, there will be an element of ''performance related pay'' for these doctors based solely on this particular measurement.

Until recently, the possibility of introducing such national targets would have been impossible because of the differences between HbA_{1c} assays and other methodological problems.[10] These issues are steadily being dealt with. For example, inclusion of fetal haemoglobin as part of the HbA_{1c} result used to be commonplace, leading to spuriously high HbA_{1c} results in some patients,[11] but with contemporary assays this problem is now historical. Most importantly, however, the lack of assay standardisation is now being tackled. Whereas previously the HbA_{1c} value measured differed depending on the assay used, it has now been recommended that laboratories harmonise these results to report a ''DCCT equivalent'' number.[7 12] This is seen as the first step to true standardisation, where the recently published International Federation of Clinical Chemistry (IFCC) reference method[13] will be used either to define true HbA_{1c} values (which will be 1.5–2% lower than DCCT equivalent values) or to ''anchor'' current DCCT/UKPDS numbers to this IFCC ''gold standard''.

Now that most of the assay problems have or are currently being dealt with, the greatest source of concern with HbA_{1c} measurement has become the inherent limitations of the test itself. All the targets mentioned previously are an incentive to try and ensure that the risk of diabetes complications is minimised. However, these targets are based on data for an average patient found in the DCCT and UKPDS studies. This raises two potential issues. The first is how applicable the targets from these studies are to all the patients who participated, and the second is how applicable the findings from these studies are to patients from parts of the world outside the USA and the UK where they were performed. The first concern stems from the fact that there is compelling evidence that patients with the same mean blood glucose can have greatly different HbA_{1c} values, as demonstrated by the DCCT study itself, which showed that patients with a mean plasma glucose of 10 mmol/litre could have an HbA_{1c} value anywhere between 6% and 11%.[14] Some of this variability is undoubtedly caused by limitations in the study, such as the use of a single seven point day plasma glucose profile (converted from laboratory measured whole blood measurements) to compare with the subsequent HbA_{1c} value, but this is partially offset by the power of averaging 18 such comparisons in the 1439 participants throughout the study period. The findings also corroborate those from biological variation studies, which suggest that although ''within individual'' changes in glycated haemoglobin are small, differences between non-diabetic individuals can be as much as 2% HbA_{1c}.[15] The inference from these data is that by slavishly aiming for the same HbA_{1c} in all patients, for some the target is probably unrealistically low (with a high risk of hypoglycaemia if it is attempted to be reached), whereas for others it can be achieved with apparent ease, thereby leaving the patient and clinician falsely reassured.

In their paper in this issue of the *Journal of Clinical Pathology*, Camargo and Gross have investigated this last group of patients by looking for causes of spuriously low HbA_{1c} values in their Brazilian patients with diabetes.[16] They found that the presence of haemoglobin variants and undiagnosed anaemia accounted for most of these cases. The cosmopolitan nature of their population (certainly in comparison with those in DCCT and UKPDS) probably contributed to the prevalence of haemoglobinopathy, and although the number of affected samples was small (130 patients from 29 657 samples) this is certain to be just the tip of the iceberg because they defined a very low HbA_{1c} as being below their non-diabetic lower reference limit of just 4.7%. Thus, there may have been many other cases where the effect on the HbA_{1c} value was much more subtle but still clinically relevant.

> ''There is compelling evidence that patients with the same mean blood glucose can have greatly different HbA_{1c} values''

Abbreviations: DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; HbA_{1c}, glycated haemoglobin; UKPDS, United Kingdom Prospective Diabetes Study

The findings of their study add to the other known intrinsic problems with HbA_{1c}. These include the spurious values that can be found in patients with renal failure[17] and in those who appear to glycate at unusual rates.[18] Even when patients have none of these abnormalities, the fact that HbA_{1c} measures average glycaemia and says nothing about swings in blood glucose can result in some individuals only achieving their treatment goal at the expense of a poor quality of life, as a result of frequent, disabling, and unpredictable hypoglycaemia.

Taken together, it means that in a health care culture that is being driven increasingly by targets it is important not to lose sight of the fact that patients still need to be assessed as individuals.

J Clin Pathol 2004;**57**:344–345.
doi: 10.1136/jcp.2003.010918

Correspondence to: Dr E S Kilpatrick, Department of Clinical Biochemistry, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK; eric_kilpatrick@hotmail.com

REFERENCES

1 **Gabbay KH**, Hasty K, Breslow JL, *et al.* Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. *J Clin Endocrinol Metab* 1977;**44**:859–64.
2 **Gonen B**, Rubenstein A, Rochman H, *et al.* Haemoglobin A1: an indicator of the metabolic control of diabetic patients. *Lancet* 1977;**2**:734–7.
3 **Goldstein DE**, Little RR, Wiedmeyer HM, *et al.* Glycated hemoglobin: methodologies and clinical applications. *Clin Chem* 1986;**32**:B64–70.
4 **The Diabetes Control and Complications Trial Research Group**. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
5 **UK Prospective Diabetes Study (UKPDS) Group**. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.
6 **Stratton IR**, Adler AI, Neil HAW, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405–12.
7 **Clinical Guideline G**. Management of type 2 diabetes. *Management of blood glucose*. National Institute for Clinical Excellence N0128, September 2002 (www.nice.org.uk).
8 **Clinical** practice recommendations 2003. *Diabetes Care* 2003;**26**:S106–8.
9 http://www.doh.gov.uk/gmscontract/index.htm.
10 **Kilpatrick ES**. Problems in the assessment of glycaemic control in diabetes mellitus. *Diabetic Med* 1997;**14**:819–31.
11 **Paisey RB**, Read R, Palmer R, *et al.* Persistent fetal haemoglobin and falsely high glycosylated haemoglobin levels. *BMJ* 1984;**289**:279–80.
12 **Marshall SM**, Barth JH. Standardization of HbA1c measurements—a consensus statement. *Diabetic Med* 2000;**17**:5–6.
13 **Jeppsson JO**, Kobold U, Barr J, *et al.* Approved IFCC reference method for the measurement of HbA_{1c} in human blood. *Clin Chem Lab Med* 2002;**40**:78–89.
14 **Rohlfing CL**, Wiedmeyer HM, Little RR, *et al.* Defining the relationship between plasma glucose and HbA_{1c}: analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;**25**:275–8.
15 **Kilpatrick ES**, Maylor PW, Keevil BG. Intraindividual variation of glycated haemoglobin: implications for diabetes screening and monitoring. *Diabetes Care* 1998;**21**:261–264.
16 **Camargo JL**, Gross JL. Conditions associated with very low values of glycohemoglobin measured by an HPLC method. *J Clin Pathol* 2004;**57**:346–9.
17 **Weykamp CW**, Penders TJ, Siebelder CWM, *et al.* Interference of carbamylated and acetylated hemoglobins in assays of glycohemoglobin by HPLC, electrophoresis, affinity chromatography, and enzyme immunoassay. *Clin Chem* 1993;**39**:138–42.
18 **Yudkin JS**, Forrest RD, Jackson CA, *et al.* Unexplained variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. *Diabetologia* 1990;**33**:208–15.

HbA_{1c} measurement

E S Kilpatrick

J Clin Pathol 2004 57: 344-345
doi: 10.1136/jcp.2003.010918