Practice

Cases in primary care laboratory medicine

Glycated haemoglobin (HbA_{1c}) monitoring

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Glycation of haemoglobin to produce HbA_{1c} occurs throughout the 120 day average lifespan of the red blood cell. Repeat testing in less than 120 days or situations that shorten this lifespan will produce HbA_{1c} results that do not fully reflect current diabetic control

This is the fourth article in this series

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This article describes two common scenarios involving the use of glycated haemoglobin (HbA_{1c}) that may be seen in primary care and considers their potential clinical implications in monitoring patients with diabetes.

HbA_{1c} has become established as the monitoring test of choice to assess medium term diabetic control and as a key parameter on which to base changes in management of patients. Common situations exist, however, in which the HbA_{1c} can be misleading. As the average lifespan of a red blood cell is approximately 120 days, in situations in which red cell lifespan is reduced HbA_{1c} may not accurately reflect diabetic control. With increasing emphasis on achieving lower HbA_{1c} values in patients with diabetes, clinicians need to be aware of these situations and understand the limitations of the test methods used.

Summary points

- Glycated haemoglobin (HbA_{1c}) is a reliable indicator of diabetic control in most but not all situations
- Glycation of haemoglobin is non-linear over time and occurs over the whole lifespan of the red blood cell (normally 120 days)
- Situations in which red cell lifespan is reduced may give rise to low HbA_{1c} results
- Testing intervals should not normally be less than two months to take account of the physiological half life
- Practitioners should be aware of situations in which results do not correctly reflect control, when home glucose records may add valuable information
- HbA_{1c} is not a diagnostic test for diabetes and should not be used as a screening test

Case 1

A 60 year old woman was seen for review of her diet controlled type 2 diabetes. She was also taking long term ferrous sulphate treatment because of caecal angiodysplasia. Otherwise, she seemed healthy with no specific problems except for being slightly overweight (body mass index 28). Her blood pressure was 144/94 mm Hg, and her haemoglobin was 12.3 g/dl (reference interval 11.5-16.5 g/dl). Random plasma glucose and HbA_{1c} were measured and found to be 12.0 mmol/l and 7.4% respectively. Urine albumin excretion was also assessed—urinary albumin:creatinine ratio 1.5 mg/μmol (threshold <3.5 mg/μmol to exclude microalbuminuria). This was considered acceptable, and no change in treatment of her diabetes was considered necessary. Over the next year her haemoglobin remained stable; an HbA_{1c} of 6.8% suggested good glycaemic control, and her diabetes treatment was not changed.

The next year two consecutive urine albumin excretion ratios were 5.6 and 7.2 mg/μmol, and fundal examination showed early retinopathic changes. Her blood pressure was 152/98 mm Hg. HbA_{1c} was measured and found to be 6.4% despite a random plasma glucose of 18.9 mmol/l. The patient was asked to record regular daily random home blood glucose measurements for a period of three weeks, the results of which were consistently between 12.4 mmol/l and 21.0 mmol/l. She was started on oral hypoglycaemic agents and advised to monitor her blood glucose and symptoms regularly to determine future treatment. She was also prescribed an angiotensin converting enzyme inhibitor in view of her hypertension and microalbuminuria.

Case 2

A 57 year old man was diagnosed as having type 2 diabetes when he presented with malaise and weight loss and had a fasting glucose concentration of 14.8 mmol/l and HbA_{1c} of 9.7%. He was given dietary advice and reviewed after one month, when his HbA_{1c} was 9.4%. This was considered to be unsatisfactory, and

he was started on metformin 500 mg twice daily, which was increased to 850 mg twice daily two weeks later. He was seen six weeks later, when his HbA_{1c} had fallen to 8.7% and a sulphonylurea was added. Two weeks later the patient collapsed at work and was revived with a sweet drink. A finger prick blood sample was tested for glucose as he was being revived, and this was found to be 5.2 mmol/l. Home blood glucose monitoring started after this episode showed that his blood glucose readings ranged from 2.4 mmol/l before breakfast to 6.8 mmol/l in a post-prandial specimen, and the sulphonylurea was stopped. He had no further similar episodes or symptoms of hypoglycaemia and when reviewed two months later his HbA_{1c} was 7.1%; this fell to 6.6% after a further three months on metformin alone.

Discussion

Both these cases hinge on the average lifespan of a red cell, which is approximately 120 days. A loss of red cells reduces the average age of the red cell pool. The glycation of haemoglobin to produce HbA_{1c} occurs over the lifespan of the cells; approximately 50% occurs in days 90-120, and the remainder occurs before this.[1 2] HbA_{1c} thus represents a weighted average of the blood glucose concentration over the previous two to three months. In the presence of anaemia, blood loss results in a reduction in the average red cell lifespan and HbA_{1c} is lower than would be expected for the degree of chronic hyperglycaemia. If blood loss is sufficient to shorten average lifespan to 90 days, the HbA_{1c} concentration would theoretically be halved and could give the false impression that glucose control is exemplary. In the second case described, insufficient time was allowed for the HbA_{1c} to fall before treatment was intensified, resulting in an avoidable hypoglycaemic episode.

Box 1 lists some potential causes of misleading HbA_{1c} results. Interferences, notably from fetal haemoglobin and haemoglobin variants, have been greatly reduced since most laboratories have moved to more specific high pressure liquid chromatography methods. Such methods produce results that align more closely to the diabetes control and complications trial,[3] on which existing targets for diabetic control are based. The cases above illustrate two of the situations that practitioners should be aware of in order to avoid risks of inappropriately changing diabetic care or believing that control is better than it actually is.

Published targets vary between international organisations, although all recognise the need to achieve better diabetic control and for individualised targets, weighing the benefits of better control against the risk of hypoglycaemia. These targets include $<6.5\%$ (International Diabetes Federation,[4] American College of Endocrinology,[5] UK National Institute for Health and Clinical Excellence (NICE) type 1 diabetes, high cardiovascular risk[6]); 6.5-7.5% (NICE type 2 diabetes[7]); $<7.0\%$ (American Diabetes Association[8] and UK national service framework for diabetes, after first year[9]); and $<7.5\%$ (NICE type 1 diabetes, lower cardiovascular risk[6]). In the United Kingdom, the quality and outcomes framework of the primary care General Medical Services contract sets a remuneration linked quality indicator for HbA_{1c} of $<7.5\%$.[10 11] Regardless of absolute target, these aspirations for improved diabetes control may be difficult to achieve in some patients, and clinicians should recognise that the change in risk corresponding to a change in HbA_{1c} is non-linear. Thus, in a population study in which the mean HbA_{1c} value was reduced from 9% to 7%, approximately 50% of the decrease in events occurred at a mean HbA_{1c} of 8.6%, and 70% at 8.0%; thus small improvements can give rise to large benefits, even if perfection cannot be achieved.[12]

Another common problem that can arise from the use of HbA_{1c} is the misdiagnosis of diabetes because of the use of HbA_{1c} as a diagnostic test instead of the various plasma glucose based cut-offs. Laboratories commonly receive simultaneous blood glucose and HbA_{1c} requests in patients being screened for diabetes. Although this may be reasonable if local point of care testing has revealed a blood glucose concentration indicative of diabetes, indiscriminate use does risk incorrect classification of patients whose HbA_{1c} may be above the population upper reference interval but who do not meet the formal criteria for diabetes. Some of these patients may be found to have impaired fasting glycaemia, which may attract similar lifestyle advice, but the implications for the patient of an incorrect diagnosis are considerable.

Box 1: Examples of potential causes of clinically misleading glycated haemoglobin results

Increased red cell turnover
- Blood loss
- Haemolytic disease (including subclinical)
- Haemoglobinopathies and red cell disorders
- Myelodysplastic disease

Interferences*
- Persistent fetal haemoglobin
- Haemoglobin variants
- Carbamylated haemoglobin in uraemic patients

Timing problems
- Short interval retesting (less than two months)

Imprecision problems*
- Differences between two consecutive results (up to 0.6% or more depending on method) may not reflect a significant change because of variability in methods. Trends are more valuable than small absolute differences between two values

*Interferences are method dependent; many are resolved by methods now in use in hospital laboratories. Individual laboratories will advise on their own methods. Users of point of care testing should, however, be aware of potential interferences with the method used. Similarly, imprecision varies by method and is typically 3-4%

What are the sources of evidence?

The complete guidance supporting the answers given in box 2 may be found in the third review of best practice in primary care pathology published online in the *Journal of Clinical Pathology*.[13] We present here the key recommendations from these reviews.

The guidance points are based on a review of guidelines that have mostly been established by expert consensus. Good evidence exists that complications in

Box 2: Monitoring glycated haemoglobin (HbA_{1c}) in diabetic patients

How frequently should HbA_{1c} be measured in patients with diabetes?

- We recommend:
- A minimum of HbA_{1c} measurement every 15 months in all patients with diabetes
- Ideally, two measurements each year in patients who are meeting goals of treatment and who have stable glycaemic control
- More frequent measurements up to a maximum of four to six a year in patients whose treatment has changed or who are not meeting treatment goals

When should HbA_{1c} be used in the diagnosis of diabetes or in non-diabetic patients?

- We do not recommend that HbA_{1c} should be used in the diagnosis of diabetes or in non-diabetic patients

How are HbA_{1c} values interpreted?

- As the absolute risks and benefits of lower targets are currently unknown, we recommend:
- A general diabetes control and complications trial aligned HbA_{1c} target of $<7.5\%$ (and an ideal target of $<6.5\%$ to 7.0%), which should be individualised for each patient, noting life expectancy and age, the incidence of hypoglycaemia, comorbid conditions, and the potential for considerable inter-individual differences in mean blood glucose values and HbA_{1c} concentrations

diabetes are improved by better control, largely based around the diabetes control and complications trial and the UK prospective diabetes study,[3 14] although the evidence base for desirable monitoring intervals is weaker, as these trials did not aim to examine periodicity of monitoring. The physiology of HbA_{1c} described above, however, forms a logical basis for avoiding very frequent testing, as no data assessing rate of change over short periods exist.

The guidance makes little reference to situations in which HbA_{1c} measurement is known not to be valid.[15] These are established from observational studies and follow from the physiology of HbA_{1c}. No evidence is available on the use of HbA_{1c} in these situations. Theoretically, if the factor influencing HbA_{1c} is stable, changes in the value over time might still reflect changes in diabetic control even if absolute values cannot be compared with target values. However, as situations of increased haemoglobin turnover are often not stable, if these values are interpreted at all this should logically be combined with home glucose measurement as an indicator of day to day control.

Useful websites

Lab Tests on Line (UK) (www.labtestsonline.org.uk)—A comprehensive guide for patients on laboratory tests and their use

Cochrane Library (www.nelh.nhs.uk/cochrane.asp)—Information and systematic reviews on evidence based medicine; the Cochrane collaboration is beginning reviews on laboratory diagnostic testing

JCP Online (www.jclinpath.com)—Website (subscription) containing electronic access to the *Journal of Clinical Pathology*, with full content of the questions and answers examined in this article

Clinical Evidence (www.clinicalevidence.com)—Summaries of current evidence based management guidelines

PRODIGY (www.prodigy.nhs.uk)—Clinical decision making guidelines designed principally for general practitioners

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1 Goldstein DE, Little RR, Lorenz RA, Malone RI, Nathan D, Petereson CM. Tests of glycemia in diabetes. *Diabetes Care* 1985;18:896-909.
2 Beach KW. A theoretical model to predict the behavior of glycosylated hemoglobin levels. *J Theor Biol* 1979;81:547-61.
3 Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the diabetes control and complications trial. *Am J Cardiol* 1995;75:894-903.
4 European Diabetes Policy Group. A desktop guide to type 2 diabetes mellitus. *Diabet Med* 1999;16:716-30.
5 American College of Endocrinology consensus statement on guidelines for glycemic control. *Endocrine Practice* 2002;8(suppl 1).
6 National Institute for Health and Clinical Excellence. Type 1 diabetes: diagnosis and management of type 1 diabetes in adults. Clinical guideline 15, full guideline, main section. www.nice.org.uk/pdf/cg015_full guideline_adults_main_section.pdf (accessed 3 Oct 2005).
7 National Institute for Health and Clinical Excellence. Management of type 2 diabetes—managing blood glucose levels. Guideline G. www.nice.org.uk/pdf/NICE_INHERITEG_guidelines.pdf (accessed 3 Oct 2005).
8 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2005;28(suppl 1):S4-36.
9 Department of Health. National service framework for diabetes: standards. Download intervention details and draft service models. March 2002. www.dh.gov.uk/assetRoot/04/03/28/42/04032842.pdf (accessed 30 August 2006).
10 NHS Confederation. Quality and outcomes framework. Accompanying guidance document. 2003. www.nhsconfed.org/docs/quality_and_outcomes_framework_guidance.pdf (accessed 3 Oct 2005).
11 NHS Employers. Revisions to the GMS contract 2006/7. www.nhsemployers.org/primary/index.cfm (accessed 3 May 2006).
12 Rohlfing CL, Weidmeyer H-S, Little RR, England JD, Tennill A, Goldstein DE. 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.
13 Smellie WSA, Forth J, Bareford D, Twomey P, Galloway MJ, Logan ECM, et al. Best practice in primary care pathology: review 3. *J Clin Pathol* 2006;59:781-9.
14 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.
15 Kilpatrick E. HbA_{1c} measurement. *J Clin Pathol* 2004;57:344-5.

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Interactive case report

Fever of unknown origin

This case was described on 2 and 9 September (*BMJ* 2006;333:484, 541). Debate on the patient's management continues on bmj.com (http://bmj.bmjjournals.com/cgi/eletters/333/7566/484). On 20 September we will publish the case outcome together with commentaries on the issues raised by the management and online discussion from relevant experts and the patient's parents.

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