what goes where on each page, and mark up—or format—the copy accordingly. It is unlikely to fit perfectly, so don't be afraid to cut. Do not alter the style to make it fit, for example by reducing the typesize; this will destroy your newsletter's hardearned personality. Do not be afraid to add extra lines to stories so that they can fit exactly; often, adding extra paragraph breaks will do.

Now is the time to write headlines and other devices intended to attract the reader. Set the style *before* writing the headlines, which will dictate the size of the type and the number of lines. Put the most important (and logically the longest) story at the top of each page. Graduate the size and lines of headlines accordingly.

Headlines are not labels, but marketing tools. They should contain short, interesting words and, whenever possible, a verb. The top line should be longer than the second to draw the reader's eye down into the story. They should never contain information that is not in the story. Avoid whimsical or punning headlines on every story.

FEEDBACK

Newsletter editors find it hard to know how they are doing, but they should try. An obvious method is to send out a questionnaire with the publication, but response rates will be low. Editors must therefore monitor "Letters to the Editor," ask their readers for

their opinions, or watch to see how quickly (or slowly) piles of their newsletters disappear. These are not scientific methods but are better than the alternative, which is listening to the opinions of a few people with axes to grind or who have little in common with your target readership. You will have complaints, but see them in perspective: newsletters must be judged on the overall flow of information they provide, not on individual items.

Conclusion

Throwing ill-considered newsletters at a communications problem will probably do more harm than good, and will certainly be a waste of resources. On the other hand, a newsletter that is well planned, adequately resourced, and skilfully executed will be a formidable communications tool. Enjoy it; if you do not, then how can you expect others to do so?

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- 2 Strunk W, White EB. *The elements of style*. New York: Macmillan, 1959.
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Lesson of the Week

Diagnostic confusion in diabetes with persistence of fetal haemoglobin

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Persistence of fetal haemoglobin falsely increases estimates of haemoglobin A₁ concentration by charge dependent methods and is not detected by routine electrophoresis. Diagnosis of diabetes should not be based solely on HbA₁ concentration

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Most diabetic clinics in the United Kingdom measure glycated haemoglobin to assess control of diabetes and there is general consensus for its use as a basis for changes in treatment.¹ Methods of estimating glycated haemoglobin concentrations are often charge dependent, separating haemoglobin A from haemoglobin A₁ by electroendosmosis, high pressure liquid chromatography, or ion-exchange chromatography. Presence of abnormal haemoglobins (haemoglobin S, haemoglobin C) with an altered charge may therefore result in misleading results for glycated haemoglobin tests.² These haemoglobin variants are rare except in well defined populations and are readily identified by electrophoresis. Persistence of fetal haemoglobin has also been described as a confounding factor in measuring HbA₁³ but has not been considered to be a common problem in diabetic management.

We report on a medical student and two patients in whom persistence of fetal haemoglobin into adult life gave rise to apparently raised HbA₁ concentrations and was not detected by routine haemoglobin electrophoresis. In the two patients overdependence on the results of glycated haemoglobin concentration at the expense of blood glucose measurement led to misdiagnosis and potentially serious overtreatment of diabetes with oral hypoglycaemic drugs.

Case reports

CASE 1

A medical student was helping with tests on a glucose meter and sent her own blood for estimation

of glycated haemoglobin concentration. This was analysed by ion exchange chromatography⁴ and found to be 11.4% (non-diabetic reference range 6.0-8.5%). Repeated estimation gave a result of 11.0% with a simultaneous non-fasting blood glucose concentration of 4.0 mmol/l. An oral glucose tolerance test gave normal results (fasting blood glucose concentration 4.4 mmol/l, two hour concentration 2.6 mmol/l). No abnormal bands were detected on haemoglobin electrophoresis and repeated estimations of glycation by other methods gave inconsistent results: electroendosmosis 10.8% (non-diabetic range 5.0-7.5%);⁵ affinity chromatography 5.6% (non-diabetic range 5.5-7.5%),⁶ and glycated albumin method 3.2% (non-diabetic range 2.0-5.4%).⁷ The discrepancy was explained by a fetal haemoglobin concentration of 4% (reference range up to 1%).⁸

CASE 2

A 71 year old man with a history of hypertension and a previous myocardial infarction was admitted to hospital acutely unwell with chest pain. This was diagnosed as pleurisy associated with a chest infection. He was noted to have a random blood glucose concentration of 11.5 mmol/l and an HbA₁ concentration of 15.0% (electroendosmosis; reference range 5-7.5%). Although tests with glucose oxidase reagent strips in the ward gave readings of 4-10 mmol/l and no other raised blood glucose concentration was recorded in the laboratory, non-insulin dependent diabetes was diagnosed. He was treated initially with diet and referred to the diabetes service. A confirmatory oral glucose

tolerance test was not performed and blood glucose testing was not routinely performed in that clinic. His HbA_{1c} concentration during follow up was never less than 11.0% and more typically was around 13.0% despite claimed adherence to diet and maximum doses of tolbutamide. Treatment was changed to glibenclamide, but after episodes of sweating gliclazide was introduced, which was eventually increased to the maximum dose. Apart from non-progressive microalbuminuria he had no evidence of microvascular complications at annual review over six successive years. The result of a single clinic estimation of blood glucose concentration was 3.2 mmol/l, and while he was admitted to hospital for control of blood pressure his blood glucose concentration was 4.0 mmol/l. During admission glucose oxidase reagent strip readings were all in the range 4.9 mmol/l. No action was taken on the basis of these results. His HbA_{1c} results remained in the range 11.0-13.0% throughout this time.

Eventually, insulin treatment was agreed and he was taught home blood glucose monitoring. However, all his results were in the range 3-4 mmol/l despite good technique. When questioned directly he described frequent episodes of evening sweatiness and dizziness relieved by food but was not aware that these were hypoglycaemic symptoms. When gliclazide was stopped these symptoms were abolished, with little change in his home blood glucose concentrations.

One month after stopping treatment an oral glucose tolerance test gave a fasting plasma glucose concentration of 5.3 mmol/l and a two hour concentration of 9.8 mmol/l, which is classified as impaired glucose tolerance by the World Health Organisation.⁹ His HbA_{1c} concentration was still 11.3% but enzyme immunoassay¹⁰ of HbA_{1c} gave a result of 3.4% (non-diabetic range 2.8-5.0%).

CASE 3

A 40 year old obese man (body mass index 33.2 kg/m²) with a 10 year history of intermittent episodes of severe abdominal pain which had not been relieved by vagotomy and pyloroplasty was referred to a general surgeon for further investigation. Chronic relapsing pancreatitis was diagnosed, with heavy alcohol consumption being the most likely cause. He was found to have a raised HbA_{1c} concentration of 9.7% (electroendosmosis; non-diabetic range 5.0-7.5%) despite a normal blood glucose concentration. The surgeon suggested a sugar free diet and weight reduction. All his subsequent blood glucose test results were in the range 4.0-6.0 mmol/l, but HbA_{1c} results were in the range 11.0-14.0%.

He was referred to the diabetes clinic as an established diabetic patient. Because of the discrepancy between blood glucose and HbA_{1c} concentrations haemoglobin electrophoresis was performed and found to give normal results, but he had no oral glucose tolerance test. Initial management was further dietary advice. After one year his weight had fallen by 3 kg but HbA_{1c} concentration had not changed. He was noted still to be drinking alcohol and to have a mild peripheral sensory neuropathy. He was treated with tolbutamide, which was increased to the maximum dose over several months, during which time his HbA_{1c} concentration remained greater than 10.0%. He gained weight and complained of episodes of confusion and headache, sweating, and shaking which were not severe. He was taught home blood glucose monitoring. His symptoms were attributed to his alcohol consumption and his home blood glucose concentrations (which were always less than 7 mmol/l) to poor technique. However, the result of a casual blood glucose measurement in the clinic agreed with his home values. Despite normal results of repeat haemo-

globin electrophoresis a sample was sent to another hospital to measure total glycated haemoglobin concentration by affinity chromatography, which gave the result 4.8% (non-diabetic reference range 5.5-7.5%). Tolbutamide was stopped and his symptoms disappeared; a specific assay for fetal haemoglobin gave a result of 5.7% (reference range less than 0.5%). Simultaneous HbA_{1c} and total glycated haemoglobin concentration measured at this time were 11.3% (electroendosmosis) and 4.6% (affinity chromatography) respectively.

An oral glucose tolerance test performed several weeks after stopping tolbutamide gave normal results (fasting plasma glucose concentration 4.7 mmol/l, two hour concentration 3.8 mmol/l).

Discussion

In some diabetes clinics blood glucose is not routinely measured because of the great variability dependent on timing of meals and treatment, but HbA_{1c} is measured to estimate diabetic control and aid management. These cases show potential problems in attempting to diagnose and manage diabetes based on concentrations of HbA_{1c} alone. The first problem is the presence of persistently raised fetal haemoglobin concentration. Raised fetal haemoglobin concentrations give falsely high HbA_{1c} concentrations when charge dependent assay methods are used, such as electroendosmosis⁵ and ion exchange chromatography.¹¹ Although previously reported in a mother and daughter both with diabetes, this has been thought to be a clinical curio rather than a genuine source of diagnostic confusion.³

The student in case 1 was unlikely to have been classified as having diabetes given the circumstances under which HbA_{1c} was measured. Nevertheless in cases 2 and 3, in which an apparently raised HbA_{1c} concentration was taken as diagnostic of diabetes without a confirmatory diagnostic blood glucose or oral glucose tolerance test result the consequences were potentially more serious. In case 2 the diagnosis was incorrect by World Health Organisation criteria⁹ as a single raised blood glucose value occurred while he was acutely unwell. A raised HbA_{1c} concentration resulted in diabetes being diagnosed without further blood glucose estimation and overtreatment with oral drugs for several years. The ultimate diagnosis of impaired glucose intolerance rather than diabetes mellitus is hard to interpret as some people with previously appropriately diagnosed diabetes may be reclassified as having impaired or even normal glucose tolerance on retesting after prolonged dietary modification.¹²

The patient in case 3 was also misdiagnosed as having diabetes because of a persistently raised HbA_{1c} concentration, despite never having had a diagnostic blood glucose result or an oral glucose tolerance test. He received inappropriate treatment with sulphonylureas, resulting in symptomatic hypoglycaemia which was not appreciated because of his raised HbA_{1c} concentration and assumed continuing high alcohol intake. The misdiagnosis was questioned only when his blood glucose concentration was seen to be normal on diet alone. Nevertheless, he is at increased risk of developing diabetes because of his previous chronic pancreatitis.¹³

In most people fetal haemoglobin concentrations start to fall during the third trimester of pregnancy and reach low concentrations (less than 0.5%) by the end of the first year of life.¹⁴ Hereditary persistence of fetal haemoglobin is recognised¹⁵ but in general has no clinical consequences. The several variants of this condition are distinguished by fetal haemoglobin concentration and type of inheritance,¹⁶ but the Swiss type has at least a 2% prevalence in European and Oriental

populations.¹⁷ Affected individuals have fetal haemoglobin concentrations of 2-4%, which are too low to be detected in routine haemoglobin electrophoresis as performed for haemoglobinopathies. The preferred sensitive test is acid denaturation of a haemolysate and elution from an ion-exchange column.⁸

When fetal haemoglobin is added to a blood sample in vitro the HbA₁ concentration seems to rise when measured by electroendosmosis or ion exchange chromatography, every 1% of fetal haemoglobin causing an overestimation of HbA₁ by 1.5-2%.¹¹ In our patients the discrepancy between HbA₁ concentration measured by electroendosmosis and total glycated haemoglobin concentration by affinity chromatography was a little less: 5.2% for case 1 and 6.7% for case 3 when the mean measured fetal haemoglobin concentrations were 4.0% and 5.7% respectively.

IMPORTANCE OF FETAL HAEMOGLOBIN IN DIABETES

Why is this an important clinical point rather than a curio as first suggested in 1984? Firstly, over the past few years the consensus in the management of diabetes has become to achieve near normal HbA₁ concentrations in most diabetic patients to reduce the risk of microvascular complications.¹ Reliance solely on HbA₁ concentrations would lead to much more troublesome hypoglycaemia in patients in whom there is a discrepancy of perhaps 2.0% between true and measured HbA₁ results as is likely in the 1-2% of people with hereditary persistence of fetal haemoglobin. Of particular concern is evidence that fetal haemoglobin concentrations rise to abnormal levels (greater than 1%) in 15% of normal pregnancies¹⁸ and also that the prevalence of a slightly raised fetal haemoglobin is greater in children with diabetes than in a control group.¹⁹ These are two groups of patients with diabetes in whom normal HbA₁ concentrations are thought particularly important but in whom over-treatment leading to symptomatic hypoglycaemia or chronic neuroglycopenia could have particularly serious consequences.

Measures of long term glycation have a well established place in managing diabetes.^{1,20} To minimise the problems of false high readings, a non-charge dependent method for the estimation of glycation should be used. These include the thiobarbituric colorimetric method,²¹ affinity chromatography,^{6,22} or enzyme immunoassay.¹⁰ However, charge dependent methods, which overestimate glycated haemoglobin concentration when the fetal haemoglobin concentration is raised, are still used by most laboratories participating in the UK national external quality assessment scheme for glycated haemoglobins.²³

The wider acceptance of measures of glycation since the early 1980s may have led to a reluctance to use the oral glucose tolerance test in diagnosing diabetes, on grounds of cost or convenience since a raised HbA₁ concentration is assumed to reflect a previous significantly raised blood glucose concentration. These cases show the occasional dangers attached to that assumption. Even were this not so, it is clear that none of the measures of glycation are sufficiently discriminating to be used in the diagnosis of diabetes.²⁴⁻²⁶ If diabetes is considered a possibility and fasting or casual blood

glucose concentrations are not diagnostic, there should be no substitute for an oral glucose tolerance test.

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