Glycated haemoglobin values

Standardisation is essential

EDITOR,—Eric S Kilpatrick and colleagues' observations regarding the problems of assessing control of blood glucose concentrations in diabetes mellitus are important.[1] We agree that standardisation of assessment of glycated haemoglobin concentration is essential for appropriate interpretation of this test. Not only should haemoglobin A_{1c} be specifically measured but normal ranges need to be standardised nationally.

Important developments in diabetes care include the development of local and national registers comprising data conforming to an agreed national dataset. Such registers will be important for comparative analysis to assess success in achieving the objectives of improving metabolic control and monitoring the rates of development or progression of complications of diabetes. Measurement of glycated haemoglobin is essential to assess metabolic control, and its standardisation is therefore essential to permit meaningful comparisons.

We must remember that it is the person with diabetes to whom the result is of primary importance. Different methods in use around Britain, substantially different normal ranges for different assays, and changing assays within a locality may confuse and demotivate both patients and professionals.

In recognition of these considerations the British Diabetic Association is currently working with the Royal College of Pathologists towards the standardisation of assessment of haemoglobin A_{1c} concentration. There is not a simple solution to the present confused situation, but efforts are being made on several fronts.

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1 Kilpatrick ES, Rumley AG, Dominiczak MH, Small M. Glycated haemoglobin values: problems in assessing blood glucose control in diabetes mellitus. *BMJ* 1994;309:983-6. (15 October.)

Methodological discrepancies are not important

EDITOR,—The article on glycated haemoglobin values by Eric S Kilpatrick and colleagues fails to add anything to diabetic care and misses the most important point.[1] It is well known that there is no standardisation in increasing glycated haemoglobin concentration; primary standards do not exist, secondary reference standards are not applicable to different methods, and there is no agreement about which method most accurately mirrors diabetic control.[2-4] The most important clinical factor is the trend of glycated haemoglobin concentration with treatment and the approximate relation of trend in glycated haemoglobin concentration and the results recorded on a patient's diabetic control card. This gives clinicians information on whether patients are compliant and well trained in monitoring glucose concentrations in their own blood or urine and gives some indication of the previous three months' trend in control.

The discrepancies between methods are well characterised through the different quality control and external quality assurance schemes for each type of glycated haemoglobin analyser and are not important unless a laboratory changes its method of analysis, a patient moves districts, or a general practitioner changes laboratory service. Reference ranges for individual instruments are defined from sampled populations, so discrepancies are to be expected between laboratories that use their own sample populations for standardisation. The high labour intensity and slowness of electrophoretic methods may be a major consideration in the choice of method for laboratories with large numbers of samples given the pressure for quick reporting.

The effects of numerical derivation of results by subtraction from initial results which have a significant variance can clearly be seen in figure 2 of Kilpatrick and colleagues' article and cast doubt on the value of such secondary results. Any method comparisons involving significant imprecision on both axes should be compared with Deming's regression analysis and not linear regression. There is also no mention of the common confounder of glycated haemoglobin analysis, haemoglobin variants (especially haemoglobin S and fetal haemoglobin),[5] and no mention of their incidence in the study population. The most interesting analysis that could have come from this study would have been a comparison of patients' glycated haemoglobin fractions with their own capillary glucose records over four months and regular plasma analyses in the laboratory, but unfortunately the relevant data were not presented.

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We prefer short letters that relate to a recently published article and we are unlikely to publish letters longer than 400 words and containing over five references. Letters may be shortened. Your letters should be typed with double spacing and include a word count. All authors need to sign the letter and provide one current appointment and address. We encourage you to declare any conflict of interest. Please enclose a stamped addressed envelope if you require an acknowledgment.

Derive reference range locally

EDITOR,—During the past decade measurement of the glycated haemoglobin concentration has become the gold standard for assessing glucose control in diabetes.[1] Eric S Kilpatrick and colleagues identified a discrepancy between measurements of total haemoglobin A_1 and haemoglobin A_{1c}, but our experience indicates that this may not apply to other laboratories.

When we changed our analytical method to automated ion exchange chromatography (Glycomat, Ciba-Corning) we established our own reference range for a healthy population (n=100). The mean (SD) concentrations for this group were 5·9 (0·6)% and 4·8 (0·5)% for haemoglobin A_1 and haemoglobin A_{1c} respectively. We subsequently categorised 360 diabetic patients as having good, borderline, or poor control by the criterion of a concentration <3, 3-5, or >5 SD from the mean in the healthy population.[3] When categorised by haemoglobin A_1 concentration 82, 107, and 171 fell into each group respectively, which was in close agreement with the classification by haemoglobin A_{1c} concentration (91, 120, and 149 respectively). Furthermore, 313 patients fell into the same category whichever variable was used, and of the 47 who were classified differently, none were classified as having good control by one method and poor by the other. Thus, in contrast with the conclusions of Kilpatrick and colleagues, the risk of developing microvascular complications would not have been assessed differently by either method.

Haemoglobin A_{1c} is the only specific adduct of glucose to haemoglobin A. Our results showed, however, that levels of non-glucose haemoglobin adducts (haemoglobin A_{1a1}, haemoglobin A_{1a2}, haemoglobin A_{1b}) were well correlated with haemoglobin A_{1c} ($r=0·742$, $P<0·0001$); consequently the former could provide an index of diabetic control in their own right. At present there is no consensus on whether haemoglobin A_1 or haemoglobin A_{1c} is preferred in diabetic care. While Kilpatrick and colleagues' call for more uniformity in measurements of glycated haemoglobin echoes widely held views,[4] in practice the consistency between haemoglobin A and haemoglobin A_{1c} seen in our results suggests that either measurement would suffice. Clinicians should not be dissuaded from using this valuable tool for assessing glycaemic control provided that results are interpreted in relation to a reference range derived locally. Efforts towards universal standardisation would ensure comparability among laboratories, simplify the audit procedure when several hospitals are involved, and ease the interpretation of results when patients' care is transferred.

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1 Diabetes Control and Complications 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.
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Authors' reply

EDITOR,—A S Wierzbicki and colleagues think that trends in glycated haemoglobin concentration should be used with little referral to their absolute value. Accordingly, they must think that a patient with a stable haemoglobin A_{1c} concentration of 12% should be treated in a similar manner to one with a stable value of 6%. In the light of the diabetes control and complications trial, which showed an impressive reduction in microvascular complications with improved absolute glycated haemoglobin values,[1] this opinion must be held by only a minority of clinicians.

How are we to achieve reductions in the incidence of long term diabetic complications without establishing a standard by which we can compare the glycaemic control of our own diabetic patients with those participating in complications trials? It is well known that standardisation for glycated haemoglobin does not exist, but what we showed was the extent to which the same diabetic patients may have their glycaemic control categorised differently because of this lack of standardisation between assays.

With regard to our statistical analysis, our way of comparing the glycated haemoglobin methods had no relevance to the European classification of patients into good, borderline, or poor control. Likewise patients' concentrations of fetal haemoglobin were not pertinent to our chosen assay by high performance liquid chromatography since fetal haemoglobin was not included in the result for glycated haemoglobin. We read with interest the findings of Hassan and colleagues, which are at odds with those of our study and previous publications.[2,3] While there is little doubt that their Glycomat results are analytically correct, their interpretation may be artefactual owing to the inclusion of fetal haemoglobin concentrations in this glycated haemoglobin assay. The random error introduced by fetal haemoglobin is likely to have a greater relative effect on the bias and standard deviation of their reference range population when using haemoglobin A_{1c} than it is when measuring haemoglobin A_1.[4] Therefore, this may affect the subsequent classification of diabetic control when European guidelines are used. We too found a significant correlation between non-glucose haemoglobin adducts and haemoglobin A_{1c} concentration ($r=0{\cdot}66$), but this disguised the fact that these adducts did not rise as quickly as haemoglobin A_{1c} in diabetic patients, which was part of the reason for the discrepancy we found when comparing haemoglobin A_1 and haemoglobin A_{1c}.

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1 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.
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Urinary tract infection in children

GPs may not use same criteria

EDITOR,—Linda Pead and Rosalind Maskell report the proportion of children under 12 in the population served by a public health laboratory in a relatively affluent part of Britain in whom the child's general practitioner suspected a urinary tract infection sufficiently to ask for laboratory confirmation.[1] They also report the criteria used and the proportions of boys and girls. Miscellaneous imaging studies showed that an appreciable number of the children with positive findings had underlying or secondary abnormalities of the urinary tract.

What the paper does not tell us is whether general practitioners in other areas are likely to use the same clinical criteria for requesting such studies and, if they do so, whether other laboratories and imaging departments would report comparable findings; nor is it clear what fundamental questions such studies would be likely to answer. Surely what we need to know is the proportion of girls and boys in each cohort who sooner or later are likely to develop a urinary tract infection of sufficient severity to damage their kidneys in such a way as to lead to hypertension or renal insufficiency, or both; whether this depends partly on predisposing anomalies of the urinary tract as regards to both frequency and severity of infection; in what ways such cases usually present clinically; and how early diagnosis and treatment affect prognosis. Only when such knowledge is available will we be able to assess the cost effectiveness of attempting to identify children at risk.

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1 Pead L, Maskell R. Study of urinary tract infection in children in one health district. *BMJ* 1994;309:631-4. (10 September.)

Consider severity of abnormalities

EDITOR,—Linda Pead and Rosalind Maskell found urinary infections to be much commoner in children than is generally believed.[1] They rightly point out a considerable logistic problem if all children are to be investigated, as is generally recommended.[2] Although they did not investigate all cases, their figures suggest different risks of underlying renal disease for the different ages at presentation. Thus a newly diagnosed abnormality was found in 20 of 626 cases for girls aged 6-12 (1 in 31). In 27 of the 66 girls with a newly diagnosed abnormality, however, the abnormality was minor and would not be disastrous if missed; so a major abnormality was found in 1 in 43. Although readers are not given details, I suspect that the more severe defects (severe reflux, reflux with scarring, obstruction) were more likely to be present in the children under 5.

What would help address the debate over logistics is a more detailed breakdown of authors' figures by age and sex to give the incidence of important newly diagnosed urinary tract abnormalities for each age group. By important I mean abnormalities that needed surgery or had appreciable potential for impairing renal function long term. We should examine critically any policy that results in *x* ray departments being inundated with children in whom the incidence of abnormal findings is low.

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1 Pead L, Maskell R. Study of urinary infection in children in one health district. *BMJ* 1994;309:631-4. (10 September.)
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Authors' reply

EDITOR,—The breakdown of children with newly diagnosed abnormalities by age and sex for which J F B Dossetor asks is given in tables III and VII of our paper. Sixty three (85%) of those found to have major abnormalities were aged 5 or under. Dossetor's reasoning with regard to the rate of abnormalities in girls aged 6-12 is unclear. The 27 of 66 referred to were the figures for abnormalities in girls of all ages.

When considering the implications of our study it is important to remember that only a minority of the children with infections were investigated, that investigation was often limited to ultrasonography, and that awareness of the problem of urinary tract infection in children was high. Some of the children found to have apparently minor abnormalities on ultrasonography—for example, those with kidneys of appreciably different size—may indeed have had renal scarring. It is difficult to compare our figures with the few available from elsewhere. For example, those of Jadresic *et al* refer to numbers of specimens received rather than to numbers of children from whom they came.[1] Seemingly, however, the overall rate of referral of urine specimens in our study was close to that of the practitioners with the highest referral rate in theirs.

When the diagnosis is not suspected as readily as it was in our study the desirable objective of recognising abnormalities as early as possible may not be achieved. It is unwise, therefore, to assume that abnormalities are unlikely to be found in older children.

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1 Jadresic L, Cartwright K, Cowie N, Witcombe B, Stevens D. Investigation of urinary tract infection in childhood. *BMJ* 1993;307:761-4.

Floating eye clinic

EDITOR,—I recently paid a brief visit to the Russian eye hospital ship moored in Gibraltar's territorial waters and am now in a better position to comment on Giles Tremlett's news item[1] than I was in my previous letter.[2]

Firstly, the eye clinic's operation accords with Gibraltarian law concerning the licensing of medical practitioners. A firm of solicitors handled the details whereby ophthalmologists from Moscow receive secondary registration to practise while carrying out their tour of duty on the ship.

I found the ophthalmologists' examination of patients to be thorough and admired the computerisation of all the findings, which can readily be retrieved. A small army of interpreters are on board, facilitating communication with patients. There are also facilities for providing English