Clinical implications

- Hysteroscopic surgery for dysfunctional uterine bleeding has significantly less morbidity and a significantly reduced hospital stay and recovery period compared with hysterectomy
- This randomised trial of hysterectomy and hysteroscopic surgery found that 12 months after the conservative surgery around 80% of women were amenorrhoeic or hypomenorrhoeic
- Dysmenorrhoea and premenstrual symptoms also improved in most women after operative treatment for dysfunctional uterine bleeding
- Although satisfaction with hysterectomy was significantly higher, around 80% of the women who would currently have been treated by hysterectomy were entirely satisfied with the effect of hysteroscopic surgery
- Gynaecologists should be encouraged to offer hysteroscopic surgery as first line surgical treatment for dysfunctional uterine bleeding

it is associated with greater morbidity. Hysteroscopic surgery can be recommended and should be encouraged as an alternative for the majority of women when more conservative treatment has failed.

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Glycated haemoglobin values: problems in assessing blood glucose control in diabetes mellitus

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Abstract

***Objective*—To see whether two measures of glycated haemoglobin concentration—the haemoglobin A_1 (HbA_1) value and the haemoglobin A1c (HbA_{1c}) value—assess blood glucose control differently in diabetes.**

***Design*—Diabetic patients had glycaemic control assessed on the basis of HbA_1 and HbA_{1c} values measured by the same high performance liquid chromatography instrument and on the basis of HbA_1 measured by electrophoresis.**

***Setting*—A diabetic outpatient clinic.**

***Subjects*—208 diabetic patients and 106 non-diabetic controls.**

***Main outcome measures*—Glycated haemoglobin concentrations classified according to European guidelines as representing good, borderline, or poor glycaemic control by using standard deviations from a reference mean.**

***Results*—Fewer patients were in good control (25;12%) and more poorly controlled (157;75%) as assessed by the HbA_{1c} value compared with both HbA_1 assays (39 (19%) and 130 (63%) respectively when using high performance liquid chromatography; 63 (30%) and 74 (36%) when using electrophoresis). The median patient value was 8·0 SD from the reference mean when using HbA_{1c}, 5·9 when using HbA_1 measured by the same high performance liquid chromatography method, and 4·1 when using HbA_1 measured by electrophoresis.**

***Conclusions*—Large differences exist between HbA_1 and HbA_{1c} in the classification of glycaemic control in diabetic patients. The HbA_{1c} value may suggest a patient is at a high risk of long term diabetic complications when the HbA_1 value may not. Better standardisation of glycated haemoglobin measurements is advisable.**

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Introduction

Over the past decade measurement of glycated haemoglobin concentration has brought a major advance in the assessment of glycaemic control in diabetes mellitus by providing an objective indication of a patient's overall blood glucose control for the preceding six to eight weeks.[1] The term glycated haemoglobin encompasses both haemoglobin A_1 (HbA_1) and haemoglobin A_{1c} (HbA_{1c}). HbA_1 refers to the non-enzymatic binding of several species of carbohydrate to haemoglobin, whereas in HbA_{1c} the carbohydrate is specifically glucose.[2]

The desirability of good glycaemic control in insulin dependent diabetes mellitus has been reinforced by the diabetes control and complications trial, which showed

an impressive reduction in microvascular complications in intensively treated patients when compared with a group treated conventionally.[3] Though self blood glucose monitoring is an important safety check for patients, technical problems and lack of appeal often make it unreliable as an indicator of glycaemic control.[4,5] Therefore, in routine clinical practice more emphasis is placed on glycated haemoglobin measurement. Hence it is important that the classification of a patient's glycaemic control by using this measurement should be both accurate and reproducible. However, because of differing methods of analysis the stated reference ranges for glycated haemoglobin measurements may vary substantially. This means it is difficult to find a common set of target values for glycated haemoglobin which will be applicable to all analyses. In an attempt to account for this, recent guidelines have been set for patients with insulin dependent and non-insulin dependent disease which define categories of glycaemic control as a HbA_1 or HbA_{1c} concentration so many standard deviations from a particular method's non-diabetic population mean.[6]

When evaluating the original recommendations for non-insulin dependent diabetes published in 1988[7] we found that measurement of HbA_{1c} by agglutination inhibition placed significantly more patients in the poorly controlled group than HbA_1 measured by electrophoresis.[8] The aim of this study was to ascertain whether a discrepancy remained when both HbA_1 and HbA_{1c} were measured simultaneously on one instrument by the same method (high performance liquid chromatography). If such a disparity existed, then the interchangeable use of HbA_1 and HbA_{1c} for the measurement of glycaemic control would require reappraisal.

Subjects and methods

Two methods of glycated haemoglobin analysis were used. HbA_1 and HbA_{1c} were measured individually by high performance liquid chromatography (Hi-AutoAlc, Model 8121, Kyoto Daiichi Kagakiu, Japan); HbA_1 was additionally measured by an electrophoretic method (Ciba Corning Diagnostics, Halstead, Essex). Between batch imprecision (coefficient of variation) was less than 4·5% for each analysis at a mean HbA_{1c} concentration of 8·2%.

A locally derived reference range (mean with 2 SD) for the high performance liquid chromatography and electrophoretic methods was compiled by studying 106 non-diabetic subjects (42 male, 64 female; median age 36 (range 16-82) years), comprising hospital staff and families.

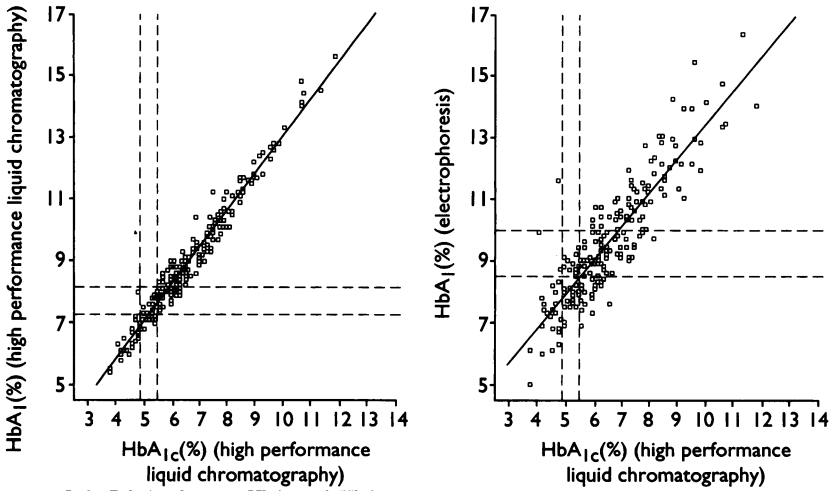

FIG 1—*Left: Relation between HbA_1 and HbA_{1c} concentrations (as measured by high performance liquid chromatography) in diabetic patients (y=1·20x+1·01; r=0·982). Right: Relation between HbA_1 concentrations (as measured by electrophoresis) and HbA_{1c} concentrations (as measured by high performance liquid chromatography) (y=1·10x+2·37; r=0·891). Dashed lines represent 3 and 5 SD limits*

TABLE I—*Reference population statistics and derived glycaemic control categories (n=106)*

	HbA_{1c} (%) (high performance liquid chromatography)	HbA_1 (%) (high performance liquid chromatography)	HbA_1 (%) (electrophoresis)
Reference population statistics:			
Mean	4·02	5·88	6·30
SD	0·28	0·46	0·75
Coefficient of variation (%)	7·1	7·8	11·9
Derived glycaemic control categories:			
Good (<3 SD)	<4·87	<7·25	<8·55
Borderline (3-5 SD)	4·87-5·44	7·25-8·17	8·55-10·05
Poor (<5 SD)	>5·44	>8·17	>10·05

TABLE II—*Diabetic patient statistics and glycaemic control according to European guidelines for patients with insulin dependent diabetes mellitus (n=208)*

	HbA_{1c} (high performance liquid chromatography)	HbA_1 (high performance liquid chromatography)	HbA_1 (electrophoresis)
Diabetic patient statistics:			
Median (%)	6·3	8·6	9·4
SD from reference mean	8·0	5·9	4·1
% Above reference mean	56·7	46·2	48·4
Glycaemic control category:			
No (%) with good control	25 (12·0)	39 (18·8)*	63 (30·3)**
No (%) with borderline control	26 (12·5)	39 (18·8)*	71 (34·1)**
No (%) with poor control	157 (75·5)	130 (62·5)**	74 (35·6)**

*P=0·0005, **P<0·00001 compared with HbA_{1c} (high performance liquid chromatography).

During the same period 208 samples from consecutive patients (114 male, 94 female; 90 insulin treated, 118 non-insulin treated; median age 60 (range 13-94) years) attending the diabetic outpatient clinic were analysed by both high performance liquid chromatography and electrophoresis. All samples were analysed within three days of collection.

Diabetic patient samples were categorised according to European guidelines for insulin dependent diabetes mellitus. These define good glycaemic control as a HbA_1 or HbA_{1c} value less than 3 SD from a method's non-diabetic population mean. Borderline control is between 3 and 5 SD and poor control is above these limits.[6]

Statistical analysis was by the McNemar test for paired samples and the χ^2 test for unpaired proportions. The Gaussian distribution of the reference samples was verified by Kolmogorov-Smirnov one way analysis. STATGRAPHICS software (Statistical Graphics System, Rockville, Maryland; Statistical Graphics Corporation, 1986) was used throughout.

Results

Table I shows the results of glycated haemoglobin measurements obtained from the reference population for each analysis with their respective good, borderline, and poor control limits. The spread (SD) of each assay's reference values is also expressed as a percentage of the method mean (sample coefficient of variation).

Figure 1 shows good correlation between the two HbA_1 assays and HbA_{1c}. HbA_1 measured by electrophoresis also correlated with HbA_1 measured by high performance liquid chromatography (y=0·90x+1·61; r=0·888).

Table II, however, shows significantly fewer patients classified in good control and more as poorly controlled with HbA_{1c} (high performance liquid chromato-

graphy) compared with both HbA_1 assays. This was true for both insulin treated and non-insulin treated patients (no significant difference). The clinic patient median HbA_{1c} (high performance liquid chromatography) value was proportionally higher than HbA_1 (both by high performance liquid chromatography and electrophoresis) when compared with values in the reference population. Constituents of HbA_1 other than HbA_{1c}—that is, HbA_{1a1}, HbA_{1a2}, and HbA_{1b}—were estimated by subtracting the HbA_{1c} value from HbA_1. The median diabetic patient value for this was 2·30%, which represented a 24% increase above the non-diabetic mean of 1·86%.

Figure 2 shows why more patients were classified as poorly controlled when HbA_{1c} was measured. The distribution of diabetic samples in which HbA_{1c} (high performance liquid chromatography), HbA_1 (high performance liquid chromatography), and HbA_1 (electrophoresis) values were measured is shown as a function of the SD from their respective method means.

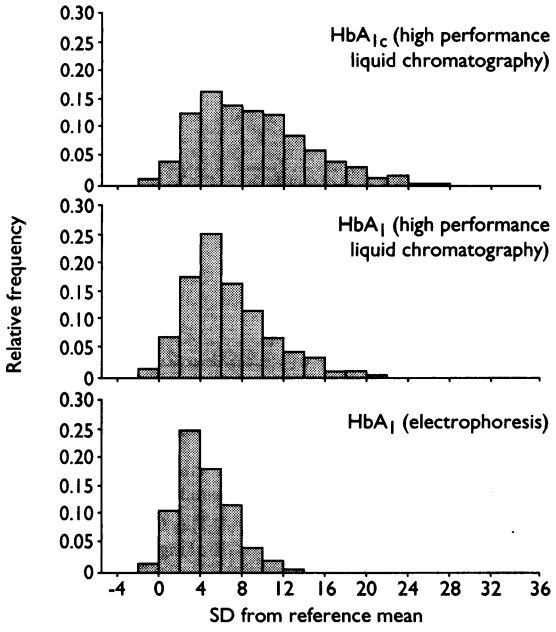

FIG 2—*Distribution of diabetic patient samples as function of SDs from respective method means*

Discussion

The results of the diabetes control and complications trial have provided the best objective guide for desirable glycaemic control limits to prevent microvascular complications in insulin dependent diabetes mellitus. In that study the median HbA_{1c} concentration in intensively treated patients was 4 SD from the mean non-diabetic value whereas the median in the conventionally treated group was 8 SD from the mean.[3] In our study the median diabetic value was 4·1 SD from the non-diabetic mean when using electrophoretically measured HbA_1, 8·0 when using HbA_{1c} (measured by high performance liquid chromatography), and 5·9 when using HbA_1 measured by high performance liquid chromatography. Thus, depending on the method of measuring glycated haemoglobin, our diabetic clinic patients could be described as equivalent to either the intensively treated group, the conventionally treated group, or about midway between. Though our study included non-insulin dependent patients, it has been suggested that the results are likely to be equally applicable to this group.[9]

In the United Kingdom the variety of assays for glycated haemoglobin is shown by the submission of samples to the national external quality assessment scheme from participating laboratories. In October 1993 the scheme reported four different instruments for HbA_1 measurement (Corning electrophoresis being the commonest) together with eight instruments for HbA_{1c} analysis (high performance liquid chromatography being the commonest). This study has clearly shown that there is considerable discrepancy in the classification of glycaemic control when comparing the electrophoretic HbA_1 method with HbA_{1c} high performance liquid chromatography. As assessed with European guidelines, 74 (36%) of our patients were poorly controlled (>5 SD) when electrophoresis was used as compared with 157 (75%) when HbA_{1c} was measured by high performance liquid chromatography. This is consistent with our previous findings when comparing electrophoretically measured HbA_1 values with HbA_{1c} measured by an agglutination inhibition method.[8]

The discrepancy is not confined only to the electrophoretic HbA_1 assay. This study has also shown that a substantial disparity between HbA_1 and HbA_{1c} categorisation remained even when patient specimens were measured by using the same high performance liquid chromatography instrument, time of analysis, and reference range samples. Significantly more patients had poor control as assessed by HbA_{1c} values than by HbA_1 (75% *v* 63%). The reasons for this appear twofold. Firstly, the spread (SD) of the non-diabetic HbA_1 reference population results was relatively greater than that of HbA_{1c} (7·8% *v* 7·1% of the mean reference value). Thus more diabetic samples fell within 3 and 5 SD when HbA_1 was measured rather than HbA_{1c}. Secondly, in comparison with non-diabetic values, patient HbA_{1c} values were proportionally higher than HbA_1 (median value 57% *v* 46% greater than the reference mean). The implication is that this was due to the concentration of glycated analytes of HbA_1 other than HbA_{1c} (HbA_{1a1}, HbA_{1a2}, and HbA_{1b}) rising less rapidly than the concentration of HbA_{1c} itself.

There remained a significant difference in the classification of glucose control between the two HbA_1 methods. A total of 130 (63%) patients were poorly controlled when high performance liquid chromatography was used and 74 (36%) when electrophoresis was used. This was due to the electrophoretic assay exhibiting a comparatively higher reference range SD (11·9% of the mean *v* 7·8%). This disparity was likely to be due in part to the fact that, unlike the chosen high performance liquid chromatography method, both glycated and non-glycated fetal haemoglobin co-

Clinical implications

- Improved glucose control in diabetic patients reduces the risk of long term microvascular complications
- HbA_1 and HbA_{1c} are glycated haemoglobins commonly measured to give an indication of glycaemic control over the preceding six to eight weeks
- In this series HbA_1 measurement classified fewer patients as poorly controlled and more as well controlled in comparison with HbA_{1c}
- Patients may thus appear to be at less risk of long term complications when HbA_1 concentration rather than the more specific HbA_{1c} concentration is measured
- Until standardisation to HbA_{1c} measurement occurs doctors should be aware that care is required with the interpretation of glycated haemoglobin measurements

migrates with HbA_1 in the electrophoretic and some other assays and so is included in the HbA_1 result.[10] Nearly half of patients with insulin dependent diabetes mellitus have fetal haemoglobin concentrations exceeding 0·5%.[11] Not only may this lead to spuriously raised HbA_1 values in some patients but it may also lead to an increase in the imprecision (and therefore reference range) of the assay as a whole.[11]

In conclusion, we have found substantial differences in the classification of glycaemic control in diabetic patients when using HbA_1 measurement rather than HbA_{1c}. In relation to the diabetes control and complications trial this inconsistency may have considerable consequences for the long term wellbeing of diabetic patients and may also influence the allocation of resources towards their treatment. Therefore, this study reinforces the need for more standardisation in the methods used for measuring glycated haemoglobin values. Adopting a standardised HbA_{1c} would allow the development of clear guidelines for clinicians based on both recent and subsequent complications trials.

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Indication for computed tomography of the brain in patients with first uncomplicated generalised seizure

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Abstract

***Objectives*—To assess the yield of emergency computed tomography of the brain in patients with a first generalised epileptic seizure and to evaluate a four item screening questionnaire on alcohol misuse (CAGE questionnaire) as a triage tool to avoid unnecessary scans in cases of seizures related to withdrawal from alcohol.**

***Design*—Prospective, observational.**

***Setting*—Medical casualty unit in a university hospital.**

***Patients*—119 adult patients presenting to casualty within one hour of a generalised seizure.**

***Measurements*—A clinical examination focusing on focal neurological symptoms, the CAGE questionnaire, and computed tomography of the brain with contrast enhancement.**

***Results*—Computed tomography showed a focal, structural lesion of the brain in 40 patients (34% (95% confidence interval 25% to 42%)). In 20 patients (17% (10% to 24%)) an important therapeutic intervention resulted. The presence of a focal neurological deficit had a sensitivity of 50% and a specificity of 89% in predicting focal lesions on computed tomography. Answering "yes" to fewer than two CAGE questions had a sensitivity of 90% and specificity of 44% in identifying patients with focal computed tomography lesions. Focal lesions were not detected on computed tomography in any of the 35 patients (0% (0% to 10%)) who showed no focal neurological symptoms and answered "yes" to two or more CAGE questions.**

***Conclusions*—The diagnostic yield of computed tomography of the brain in adults after a first generalised seizure is high. Combined with the clinical examination, the CAGE questionnaire can reliably identify patients with uncomplicated seizures related to withdrawal from alcohol, in whom computed tomography may not be absolutely necessary.**

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CAGE questionnaire for detecting alcohol misuse

C Have you ever felt you should *Cut down* on your drinking?

A Have people *Annoyed* you by criticising your drinking?

G Have you ever felt bad or *Guilty* about drinking?

E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*Eye opener*)?

Introduction

Up to 5% of the population are estimated to have a convulsion at some stage in their life.[1,2] Patients who have a generalised epileptic seizure for the first time are often seen first in a casualty department; the doctors who see them there are often unsure about further evaluation.[3] Imaging of the brain, usually with computed tomography is recommended as part of the diagnostic investigation for every adult patient after a first convulsion.[4,5] The data on the effectiveness of this strategy in identifying patients with treatable lesions, however, are conflicting.[6-11] The value of routine computed tomography has been questioned, particularly in patients with seizures related to withdrawal from alcohol, who represent a large proportion of patients seen in casualty departments with first generalised seizures.[12-15]

We assessed prospectively the yield of routine computed tomography of the brain performed within 24 hours in adults presenting to a casualty department after a first generalised epileptic seizure. We also assessed whether the number of scans could be reduced if the CAGE questionnaire—a simple, four item, validated screening tool for alcohol misuse—was used to identify patients with uncomplicated seizures related to withdrawal from alcohol (see box).[16,17]