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Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke

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Abstract

Background: diabetes mellitus not only increases the risk of ischaemic stroke two- to four-fold but also adversely influences prognosis. The prevalence of recognised diabetes mellitus in acute stroke patients is between 8 and 20%, but between 6 and 42% of patients may have undiagnosed diabetes mellitus before presentation. Post-stroke hyperglycaemia is frequent and of limited diagnostic value and the oral glucose tolerance test assumes that the patient is clinically stable and eating normally. There is a need for a simple and reliable method to predict new diabetes mellitus in acute stroke patients.

Objectives: to determine the prevalence of unrecognised diabetes mellitus and impaired glucose tolerance on hospital admission and 12 weeks later in acute stroke patients with post-stroke hyperglycaemia ≥ 6.1 mmol/l. To measure the accuracy of hyperglycaemia and elevated glycosylated haemoglobin concentration in predicting the presence of unrecognised diabetes mellitus at 12 weeks.

Design: acute (<24 hours) stroke patients (cerebral infarction and primary intracerebral haemorrhage) with admission hyperglycaemia between 6.0 and 17 mmol/l and without a previous history of insulin-treated diabetes mellitus who were

randomised into the Glucose Insulin in Stroke Trial between October 1997 and May 1999 were studied. The Glucose Insulin in Stroke Trial is a randomised controlled trial investigating the benefits of maintaining euglycaemia in acute stroke patients with mild to moderate hyperglycaemia. At 12 weeks, survivors underwent a 75 g oral glucose tolerance test. The positive predictive value and negative predictive value of admission plasma glucose ≥ 6.1 mmol/l and elevated glycosylated haemoglobin concentration in predicting the presence of diabetes mellitus were used to estimate the prevalence of unrecognised diabetes mellitus in a consecutive series of 582 acute stroke admissions.

Results: 582 consecutive acute stroke patients were assessed for eligibility for the Glucose Insulin Stroke Trial, of whom 83 (14%) had recognised diabetes mellitus. One hundred and forty-two patients were randomised and 62 underwent a 3-month oral glucose tolerance test, of whom 26 (42%) had normal glucose tolerance, 23 (37%) had impaired glucose tolerance and 13 (21%) had diabetes mellitus. Admission plasma glucose ≥ 6.1 mmol/l and glycosylated haemoglobin $\geq 6.2\%$ predicted the presence of previously unrecognised diabetes mellitus at 12 weeks with a positive predictive value of 80% and negative predictive value of 96%. The estimated prevalence of unrecognised diabetes mellitus in the total series of acute stroke admissions was 16–24%.

Conclusions: one-third of all acute stroke patients may have diabetes mellitus. For patients presenting with post-stroke hyperglycaemia, impaired glucose tolerance or diabetes mellitus is present in two-thirds of survivors at 12 weeks. Admission plasma glucose ≥ 6.1 mmol/l combined with glycosylated haemoglobin $\geq 6.2\%$ are good predictors of the presence of diabetes mellitus following stroke.

Keywords: stroke, diabetes mellitus, oral glucose tolerance test, elderly

Introduction

Diabetes mellitus (DM) is known to increase the risk of ischaemic stroke by two- to four-fold [1, 2]. DM also confers a poor prognosis following stroke in terms of increased mortality, stroke recurrence and impaired neurological recovery [3, 4]. Recent studies suggest that the prevalence of DM and impaired glucose tolerance (IGT) is increasing in the older population [5]. Post-stroke hyperglycaemia (PSH) is a frequent finding in patients presenting with acute stroke. The prevalence of recognised DM in acute stroke patients is between 8 and 20% but between 6 and 42% of patients may have undiagnosed DM before presentation with stroke [6–9]. This wide estimate reflects the different populations studied, the various criteria used for the diagnosis of DM and the indirect (and non-validated) estimates of DM prevalence provided by blood fructosamine and glycosylated haemoglobin (HbA_{1c}) concentration as measures of persistent hyperglycaemia prior to stroke. A high prevalence of unrecognised DM would partly explain the high prevalence of PSH in acute stroke, which is strongly associated with excess mortality in patients of all ages [10, 11].

The American Diabetes Association (ADA) and World Health Organisation (WHO) recommend the use of fasting blood glucose (whole blood or plasma) with or without a 2-hour post 75 g oral glucose load sample in the diagnosis of DM [12, 13]. However, these criteria assume that the test is performed when the individual is well and clinically stable. The catabolic stress response to stroke elevates blood glucose concentrations and renders the use of plasma glucose [and therefore the use of the oral glucose tolerance test (OGTT) and intravenous glucose tolerance tests] unreliable for the diagnosis of DM and IGT in this clinical situation. It is therefore usually necessary to delay definitive investigations for DM until after the acute phase. Only three small published studies have performed an OGTT following stroke which

demonstrated between 21 and 41% of survivors to have previously unrecognised DM [14–16].

The absence of a simple and reliable diagnostic test for DM in acute stroke means that the true prevalence of DM and IGT in stroke survivors is unknown. Furthermore, investigations some time after stroke are of no value in the acute management of stroke patients with unrecognised DM. However, performing an OGTT at 12 weeks post stroke provides an accurate measure of the prevalence of DM and IGT in survivors and enables the results to be related to admission values for plasma glucose and HbA_{1c}. This allows their value in predicting the presence of DM in acute stroke patients to be calculated.

Patients and methods

Sunderland Royal Hospital is a teaching hospital in the north-east of England serving a catchment population of 330,000 residents. From 1 October 1997 until 31 May 1999 all adult acute stroke patients referred to a centralised admissions unit at Sunderland Royal Hospital were assessed for eligibility for the Glucose Insulin in Stroke Trial (GIST). GIST is a randomised controlled trial investigating the potential benefit of maintaining euglycaemia in acute stroke patients (including both non-insulin treated diabetic and non-diabetic individuals) with mild to moderate hyperglycaemia (admission plasma glucose between 6.0 and 17 mmol/l). The presence of recognised diabetes was based on the patient's reported history of treated DM. Details of the trial methodology have been reported in full elsewhere [17]. Consecutive acute stroke patients presenting within 24 hours of ictus underwent blood sampling for admission plasma glucose (Instrumentation Laboratories glucose oxidase IL-Glucose kit on a Monarch analyser) and HbA_{1c} concentration (high performance liquid chromatography on a Menarini analyser with DCCT aligned results [18]) on

admission irrespective of eligibility for inclusion in the trial. Following informed consent, or informed assent, eligible patients were randomised to receive either a glucose potassium insulin (GKI) infusion for 24 hours, to maintain whole blood capillary glucose values (BM Glycaemie test strip) between 4–7 mmol/l, or control therapy with 154mmol/l (0.9%) ‘normal’ saline.

Randomised participants surviving at 12 weeks underwent a standard 75 g OGTT after an overnight fast. The presence of normal glucose tolerance, IGT and DM were defined according to current WHO criteria [13]. A fasting plasma glucose of <6.1 mmol/l and a 2-hour plasma glucose <7.8 mmol/l represents normal glucose tolerance. A fasting plasma glucose ≥ 6.1 and <7.0 mmol/l together with a 2-hour value ≥ 7.8 and <11.1 mmol/l represents IGT. DM is present when the fasting plasma glucose value is ≥ 7.0 mmol/l or the 2-hour value is ≥ 11.1 mmol/l.

Results of the OGTT were compared with admission plasma glucose and HbA_{1c} concentrations to determine the sensitivity and specificity of these initial measurements in predicting the presence of DM on OGTT at 12 weeks. An HbA_{1c} concentration of <6.2% in patients with DM is considered to represent ideal diabetic control. A concentration of $\geq 6.2\%$ in subjects without a known history of DM was therefore categorised as elevated. The results were then applied to plasma glucose and HbA_{1c} data from a large series of consecutive acute stroke patients to determine the likely overall prevalence of DM in acute stroke. Admission mean plasma glucose, fasting and 2-hour mean plasma glucose on OGTT and admission and 12-week mean HbA_{1c} concentrations were compared between normal glucose tolerance, IGT and DM groups using analysis of variance (ANOVA). The difference in mean HbA_{1c} concentration between admission and 12 weeks was compared within these 3 groups using Wilcoxon Rank Sum analysis. Multiple logistic regression analysis was also performed to determine the risk of unrecognised DM being present for increasing HbA_{1c} values.

Results

Between 1 October 1997 and 31 May 1999, 582 consecutive acute stroke patients were assessed on admission of whom 262 (45%) were male. The median age of the patients was 76 years (range 33–97 years). Three hundred and ninety-eight (68%) had admission plasma glucose ≥ 6.1 mmol/l and 83 (14%) gave a history of DM [of whom 78 (94%) were hyperglycaemic]. One hundred and forty-two patients were recruited into the trial of whom 62 (43%) underwent an OGTT at 12 weeks. The reasons for not undergoing an OGTT were death ($n=51$), presence of recognised DM ($n=18$), withdrawal from the trial ($n=6$) and inability to follow the OGTT protocol ($n=5$).

The demographic and clinical characteristics of the remaining 62 participants are given in Table 1. Of these patients 26 (42%) had normal glucose tolerance, 23 (37%) had IGT and 13 (21%) had DM according to WHO criteria. Overall there were 85 randomised participants alive at 12 weeks of whom 31 (36%) had DM and 23 (27%) had

Table 1. Demographic and clinical characteristics of 62 participants who underwent a standard 75 g OGTT at 12 weeks post stroke

Demographic details	<i>n</i> = 62
Median age (range)	75 (40–93)
Gender (male/female)	33/29
Clinical stroke classification	<i>n</i> (%)
Total Anterior Circulation (TACS)	21 (34%)
Partial Anterior Circulation (PACS)	30 (48%)
Lacunar (LACS)	11 (18%)
Posterior Circulation (POCS)	0 (-)
Stroke pathology on CT head	
Cerebral infarction	51 (82%)
Primary Intracerebral haemorrhage	11 (18%)
Prevalence of stroke risk factors	
Hypertension	23 (37%)
Cigarette smoking (current/ex-smoker)	24 (39%)/17 (27%)
Ischaemic heart disease	16 (26%)
Previous stroke	11 (18%)
Previous transient ischaemic attack	3 (5%)
Atrial fibrillation	6 (10%)

IGT. There was no statistically significant difference in the result of the OGTT between clinical stroke subtypes, although unrecognised DM was more prevalent in the lacunar stroke subtype (Table 2). Admission mean plasma glucose and mean HbA_{1c} values were significantly higher in the group diagnosed with DM at 12 weeks compared with those with normal glucose tolerance or IGT. There was no significant difference in admission or 12-week mean HbA_{1c} values between the participants with normal glucose tolerance or IGT. Mean HbA_{1c} values did not show any significant change between admission and 12 weeks within any of the 3 groups.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of admission plasma glucose ≥ 6.1 mmol/l and HbA_{1c} $\geq 6.2\%$ as a diagnostic test for the presence of DM on 12 weeks OGTT were calculated from 61 of the 62 OGTT results (Table 3). Admission HbA_{1c} was not available for one of the participants (found to have normal glucose tolerance) who underwent OGTT. The PPV and NPV values of 80 and 96% were applied to the series of 582 consecutive acute stroke patients assessed between October 1997 and May 1999 to estimate the prevalence of unrecognised DM. One hundred and twenty-seven (22%) were excluded from the analysis because of incomplete data ($n=44$, 8%) and presence of recognised DM ($n=83$, 14%). Of the remaining 455 patients, 94 (21%) had admission plasma glucose of ≥ 6.1 mmol/l and admission HbA_{1c} $\geq 6.2\%$. A PPV of 80% for the test implies that 20% ($n=19$) of these 94 patients may be misdiagnosed as having DM using these criteria. Similarly a NPV of 96% for the test implies that 4% ($n=14$) of the 361 (455 – 94) patients diagnosed as not having DM by these criteria may actually have the disease. Thus between 75 (16%) and 108 (24%) of the 455 patients with no history of DM may have unrecognised DM in addition to the 83 with a recognised history of DM. This results in an estimated total prevalence of DM in the series of 538 hospitalised acute stroke patients in whom data are complete of between 29 ($n=158$) and 36% ($n=191$).

Table 2. Mean admission and 12-week values of plasma glucose and glycosylated haemoglobin concentration (HbA_{1c}) categorised by the result of a 12-week 75 g oral glucose tolerance test (OGTT) in 62 stroke survivors with admission plasma glucose ≥ 6.1 mmol/l at the time of stroke

	Normal (<i>n</i> = 26)	IGT (<i>n</i> = 23)	DM (<i>n</i> = 13)	<i>F</i>	<i>P</i>
Total anterior circulation (TACS) <i>n</i> = 21	6 (29%)	9 (43%)	6 (29%)		
Partial anterior circulation (PACS) <i>n</i> = 30	3 (53%)	11 (37%)	16 (10%)		0.62*
Lacunar (LACS) <i>n</i> = 11	4 (36%)	3 (27%)	4 (36%)		
Mean admission plasma glucose (mmol/l)	7.15	7.98	8.52	5.99	<0.01
Mean fasting plasma glucose on OGTT (mmol/l)	5.05	5.20	6.19	8.47	0.01
Mean 2-hour plasma glucose on OGTT (mmol/l)	6.24	9.25	13.79	13.04	<0.001
Mean admission HbA _{1c} (%)	5.72	5.69	6.56	6.28	<0.01
Mean HbA _{1c} at 3 months (%)	5.65	5.60	6.23	97.1	<0.001
<i>P</i> (Wilcoxon Rank Sum for difference between admission and 3-month HbA _{1c})	0.18	0.18	0.14	–	–

**P* value (χ^2 -test) for the difference in OGTT results between stroke subtypes.

The participants found to have DM on OGTT did not have a recognised history of DM prior to the OGTT. *F* and *P* values refer to the results of one-way ANOVA for the difference in mean glucose and HbA_{1c} values between the 3 groups.

The results of the multiple logistic regression analysis are illustrated in Figure 1. Confirmation of DM by OGTT at 12 weeks was used as the dependent variable and admission glucose, admission HbA_{1c} and age were entered as covariates. This analysis included 61 of the 62 individuals who underwent OGTT as the admission HbA_{1c} value was unavailable for one person. The logit(*p*) (log odds = log $p/1 - p$) was shown to increase by 2.58 for each unit increase in HbA_{1c} (sig. = 0.001). The value of *P* was calculated and plotted against admission HbA_{1c}.

Discussion

DM is a well-recognised risk factor for stroke, but the true prevalence of DM in acute stroke is generally underestimated due to the high prevalence of unrecognised DM. By performing an OGTT 12 weeks after stroke the prevalence of unrecognised DM and IGT has been measured accurately in a large group of survivors and the accuracy of admission hyperglycaemia and elevated HbA_{1c} in predicting the presence of DM has been determined. We have confirmed that almost two-thirds of patients with PSH ≥ 6.1 mmol/l either have recognised DM (21%), unrec-

ognised DM (15%) or IGT (27%) at 12 weeks. This demonstrates the importance of proactive investigation for the presence of unrecognised DM in acute stroke patients with even mild-to-moderate hyperglycaemia, who comprised 68% of our stroke population. Secondly, we have shown that 16–24% of our series of acute stroke patients are likely to have unrecognised DM. This implies that around one-third of all acute stroke patients have either known DM or previously undiagnosed DM suggesting that DM is of likely aetiological importance in a greater number of stroke patients than is generally acknowledged. There are also significant implications regarding screening for DM in the local population, as DM and its metabolic control are important predictors of stroke, particularly in older people [19]. Our finding of a high prevalence of unrecognised DM may also partly explain the high prevalence of stroke and the high-standardised mortality rate for stroke in the north-east of England [20].

The values of 80 and 96% for PPV and NPV mean the presence of unrecognised DM can be diagnosed in individual acute stroke patients with hyperglycaemia with an acceptable degree of accuracy. In particular, the NPV of 96% infers that patients with HbA_{1c} < 6.2% almost certainly do not have DM, even in the presence of admission hyperglycaemia ≥ 6.1 mmol/l. As any threshold for defining an elevated HbA_{1c} concentration in subjects without DM is somewhat arbitrary, a multiple logistic regression analysis was also undertaken. The results of this analysis clearly showed the increasing odds of demonstrating unrecognised DM on OGTT at 12 weeks with increasing admission HbA_{1c} concentration (Figure 1).

The measurement of HbA_{1c} is a rapid and simple investigation. Our study used DCCT-aligned HbA_{1c} measurements, which are more accurate than older assays. In the presence of hyperglycaemia and no history of DM a result of $\geq 6.2\%$ early in the post-stroke period would influence acute stroke management in terms of frequency of blood glucose monitoring, use of insulin and early implementation of a low sugar diet and drug therapy. These simple changes in management would certainly improve the metabolic control of these patients and may also improve prognosis, although

Table 3. Summarised OGTT results in 61 survivors at 12 weeks post stroke

Admission values	DM present	DM absent	Total
Plasma glucose ≥ 6.1 mmol/l			
+ HbA _{1c} $\geq 6.2\%$	12	3	15
Plasma glucose ≥ 6.1 mmol/l			
+ HbA _{1c} < 6.2%	2	44	46
Total	14	47	61
Sensitivity = $12/14 \times 100 = 86\%$			
Specificity = $44/47 \times 100 = 94\%$			
PPV = $12/15 \times 100 = 80\%$			
NPV = $44/46 \times 100 = 96\%$			

Results are compared with admission plasma glucose and HbA_{1c} values and the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) calculated for admission hyperglycaemia and elevated HbA_{1c} in predicting the presence of unrecognised DM on OGTT 12 weeks later. All participants had admission plasma glucose ≥ 6.1 mmol/l at the time of stroke.

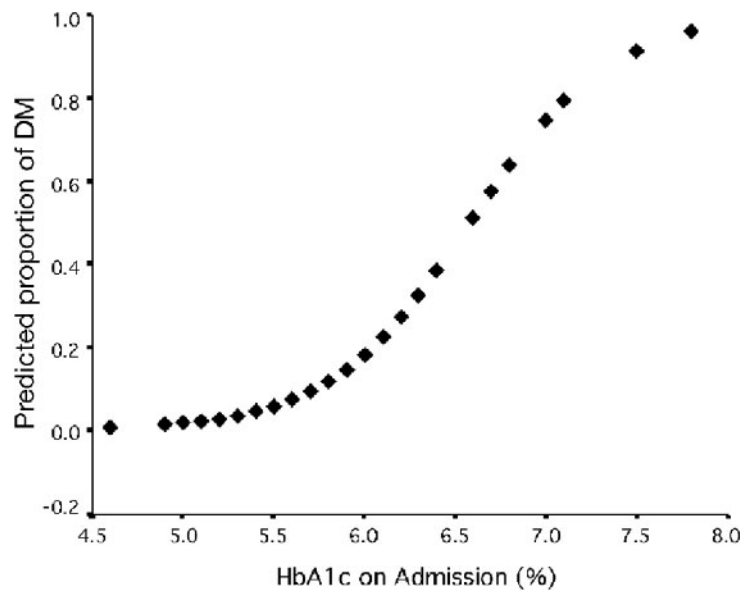


Figure 2. Predicted proportion of patients with unrecognised DM according to increasing HbA_{1c} values ($n = 61$).

this remains to be confirmed by a randomised controlled trial. Patients with a recognised history of type 1 or type 2 DM, who comprise 8–20% of acute stroke patients, are clearly at increased risk of significant hyperglycaemia and are more likely to require exogenous insulin to maintain optimum blood glucose concentrations. However, our findings suggest that there is a greater percentage of patients in whom PSH is the first presentation of DM and who are at increased risk of early neurological deterioration through the presence of DM [21].

A PPV of 80% may reflect the inaccuracy of HbA_{1c} and admission glucose level in predicting the presence of DM. Alternatively the two (12%) patients with DM on OGTT who had a normal admission HbA_{1c} may have had ‘starvation induced high post glucose load’ [22]. This is a recognised complication of under-nutrition that may be present in a proportion of stroke patients with persisting dysphagia. It is characterised by a normal or near-normal fasting plasma glucose but a pronounced plasma glucose response to a glucose load and may be a consequence of reduced muscle mass with abnormal muscle glycogen storage and metabolism. The presence of this abnormal response to OGTT in these patients would need to be reassessed by a repeat OGTT following a period of adequate supplemental nutrition.

A criticism of our methodology is that the prevalence of unrecognised DM on admission is inferred from the presence of DM 12 weeks later. If patients were to develop DM in the intervening period then this method of estimating the admission prevalence of DM would be inaccurate. However, mean HbA_{1c} values did not rise between admission and 12 weeks and the 2 patients with unrecognised DM who had admission HbA_{1c} < 6.2% also had a normal HbA_{1c} at 12 weeks. Furthermore, the only study to perform serial OGTTs following stroke did not demonstrate any deterioration in glucose tolerance between OGTTs at 1 week and 12 weeks following stroke [16].

We recognise that in asymptomatic hyperglycaemic individuals with an abnormal OGTT result, the WHO recommends repeating the test in order to confirm a definite diagnosis of diabetes. A second OGTT was not feasible in this study of frail stroke survivors. It is possible that some patients were misclassified as diabetic due to low carbohydrate diet post-stroke and the use of only one OGTT, thus leading to inaccuracy in the calculated sensitivity and specificity [23]. However, the stability of HbA_{1c} values between admission and 12 weeks suggests that the majority of participants were correctly classified as diabetic or not diabetic using our methodology.

A limitation of the study is that only the subgroup of patients with admission plasma glucose of ≥ 6.1 mmol/l were potentially eligible for randomisation into GIST and hence for 12 weeks OGTT. It is therefore not possible to calculate the accuracy of HbA_{1c} in predicting the presence of DM in patients with admission glucose < 6.1 mmol/l. However, the high prevalence of admission hyperglycaemia ≥ 6.1 mmol/l (68%) in all acute stroke patients and the low prevalence of admission normoglycaemia (6%) in those patients with known DM indicate that the measurement of HbA_{1c} is accurate and of value in predicting the presence of DM in the majority of acute stroke patients.

In conclusion we have demonstrated that unrecognised DM may be more prevalent than recognised DM in hospitalised acute stroke patients. Patients with DM are at greatest absolute risk of vascular disease and the early identification of DM or IGT in stroke patients is important to enable intensive management of blood pressure, cholesterol and anti-platelet therapy in order to reduce risk of recurrence and improve long-term prognosis [24].

Our results suggest that survivors should routinely undergo active investigation for the presence of DM in the recovery phase after stroke. This is particularly important in older people, who form the majority of acute stroke patients and are at increased risk of macrovascular complications of

DM. The finding of admission hyperglycaemia plus an elevated HbA_{1c} concentration is a good predictor of the presence of unrecognised DM in acute stroke and would assist in its early diagnosis and treatment.

Key points

- DM is known to increase the risk of ischaemic stroke and is associated with increased mortality and reduced functional recovery.
- Admission hyperglycaemia (≥ 6.1 mmol/l) plus raised HbA_{1c} concentration predicts unrecognised DM in acute stroke patients, with a sensitivity of 86% and specificity of 94%.
- Previously undiagnosed DM may be more prevalent than known DM in hospitalised patients with acute stroke.

Contributors

J. F. Scott, C. S. Gray, J. E. O'Connell and K. G. M. M. Alberti planned the study. J. F. Scott randomised the participants and performed the 12-week OGTTs. J. E. O'Connell and C. S. Gray supervised the inpatient care of study participants. J. F. Scott, C. S. Gray and J. M. French undertook the statistical analysis and all authors contributed to the writing of the manuscript.

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Ethics

Ethical approval to undertake this study was obtained from Sunderland local research ethics committee.

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Conflicts of Interest

Professor Gray is Principal Investigator to the Glucose Insulin in Stroke Trial. The other contributors are members of the trial steering committee and safety committee (JMF).

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