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
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 (HbA1c) 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 HbA1c. 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 HbA1c 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 154 mmol/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 HbA1c concentrations to determine the sensitivity and specificity of these initial measurements in predicting the presence of DM on OGTT at 12 weeks. An HbA1c concentration of < 6.2% in patients with DM is considered to represent ideal diabetic control. A concentration of ≥ 6.2% in subjects without a known history of DM was therefore categorised as elevated. The results were then applied to plasma glucose and HbA1c 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 HbA1c concentrations were compared between normal glucose tolerance, IGT and DM groups using analysis of variance (ANOVA). The difference in mean HbA1c 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 HbA1c 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-two (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 admitted to OGTT. The PPV and NPV values of 80 and 96% for the test implies that 20% (n = 19) of these 94 patients may have unrecognised DM at 12 weeks compared with those with normal glucose tolerance or IGT.

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 HbA1c 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 HbA1c values between the participants with normal glucose tolerance or IGT. Mean HbA1c 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 HbA1c ≥ 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 HbA1c 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 ≥ 6.1 mmol/l and admission HbA1c ≥ 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).
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 HbA1c, and age were entered as covariates. This analysis included 61 of the 62 individuals who underwent OGTT as the admission HbA1c 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 HbA1c (sig. = 0.001). The value of P was calculated and plotted against admission HbA1c.

**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 HbA1c 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%), unrecognised 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 northeast 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 HbA1c < 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 HbA1c 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 HbA1c concentration (Figure 1).

The measurement of HbA1c is a rapid and simple investigation. Our study used DCCT-aligned HbA1c measurements, which are more accurate than older assays. In the presence of hyperglycaemia and no history of DM a result of 26.2% 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...
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 HbA1c and admission glucose level in predicting the presence of DM.Alternatively the two (12%) patients with DM on OGTT who had a normal admission HbA1c 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 HbA1c values did not rise between admission and 12 weeks and the 2 patients with unrecognised DM who had admission HbA1c < 6.2% also had a normal HbA1c 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 HbA1c 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 HbA1c in predicting the presence of DM in patients with admission glucose < 6.1 mmol/l.

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 HbA1c 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 (≥26.1 mmol/l) plus raised HbA1c 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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