Hyperglycaemia in patients with acute ischaemic stroke: how often do we screen for undiagnosed diabetes?

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Summary

Background: Hyperglycaemia is common among patients with acute ischaemic stroke, and may be due to the physiological stress of the acute stroke event or reflect underlying diabetes mellitus. The under-diagnosis of diabetes in the general population, combined with the association of diabetes and stroke, suggests a rationale for screening for diabetes among hyperglycaemic stroke patients.

Aim: To determine how often clinicians screen for diabetes among hyperglycaemic stroke patients without a prior diagnosis of diabetes.

Design: Retrospective medical record review.

Methods: We reviewed the records of acute ischaemic stroke patients admitted at any of ten Connecticut hospitals from May 1996 through December 1998.

Results: We identified 90 acute stroke patients with no prior history of diabetes. The prevalence of hyperglycaemia varied from 31% down to 6%, depending on the maximum glucose cut-off used to define hyperglycaemia: from ≥140 mg/dl (7.8 mmol/l) to ≥200 mg/dl (11.1 mmol/l). Only one of the hyperglycaemic patients (1/90, 1%) had any evidence that a clinician screened or planned to screen for undiagnosed diabetes: one patient had a haemoglobin A1c measured during the hospitalization, none received oral glucose tolerance testing while hospitalized, and no discharge summary included a plan to screen for diabetes as an outpatient.

Discussion: Hyperglycaemic stroke patients without a previous diagnosis of diabetes are not routinely screened for diabetes. This situation represents an opportunity, currently unused, to identify an important and modifiable condition.

Introduction

Hyperglycaemia is common in patients with acute stroke, occurring in up to 60% of patients overall,1–5 and approximately 12–53% of acute stroke patients without a prior diagnosis of diabetes.2,6–9 It has been associated with increased stroke severity and mortality.3,4,8,10–18 Because hyperglycaemia is both common and associated with poor patient outcomes, clinical trials are in progress that evaluate treatment strategies to reduce hyperglycaemia, in an effort to improve stroke outcomes.1,19,20 In the absence of stroke-specific recommendations, current guidelines advise treating hyperglycaemia in stroke patients as one would treat hyperglycaemia in any hospitalized patient, including frequent glucose monitoring and stringent blood glucose control.21,22
Several prior studies have demonstrated that post-stroke hyperglycaemia is associated with worse patient outcomes following an acute stroke, including increased post-stroke mortality.\(^3\)\(^4\)\(^6\)\(^8\)\(^10\)\(^16\)

However, no specific glucose cut-off has been established to define ‘hyperglycaemia’, nor has a cut-off been used consistently in the prior research. For example, Pulsinelli and colleagues found that for a neurological outcome was worse in patients with blood glucose levels >120 mg/dl (6.7 mmol/l).\(^8\) In a systematic review of hyperglycaemia and post-stroke outcomes, Capes and colleagues included 32 studies and found that admission blood glucose >108–144 mg/dl (6–8 mmol/l) was associated with increased in-hospital or 30-day mortality (relative risk 3.1, 95%CI 2.5–3.8, in patients without diabetes vs. 1.3, 95%CI 0.5–3.4, in patients with diabetes).\(^18\)

Although hyperglycaemia is often attributed solely to the physiological stress of the acute stroke event, elevated blood glucose levels may reflect underlying glucose intolerance or diabetes mellitus. Approximately one-third of all patients with diabetes have undiagnosed diabetes (i.e. not recognized by their clinician).\(^23\) Current guidelines recommend screening patients for diabetes if they have one or more risk factors for diabetes (e.g. age ≥45 years, hypertension, lipid abnormality, vascular disease, etc.).\(^24\) The under-diagnosis of diabetes in the general population, together with the strong association of diabetes with stroke (stroke is often due to either micro- or macrovascular disease, and stroke patients often have other risk factors for diabetes),\(^6\)\(^25\) suggests a rationale for screening all hyperglycaemic stroke patients for diabetes. A diagnosis of diabetes in a stroke patient would probably change the clinical management of that patient, specifically with respect to lipid and blood pressure management.\(^26\)\(^27\)

The primary objective of this study was thus to determine the rate of screening for diabetes among hyperglycaemic stroke patients without a prior diagnosis of diabetes. Our study builds on the previous research that has evaluated the prevalence of post-stroke hyperglycaemia, and that has demonstrated the prognostic importance of hyperglycaemia in the acute stroke setting. Some may argue that post-stroke hyperglycaemia must be identified so that euglycaemia can be maintained, in an effort to reduce stroke-related morbidity and mortality. Although we agree with this perspective, we also believe that recognizing post-stroke hyperglycaemia is necessary so that clinicians will screen for previously undiagnosed diabetes, a potent and treatable risk factor for stroke and other vascular diseases.

**Methods**

This study was a secondary analysis of a retrospective cohort study evaluating thrombolytic therapy for stroke.\(^26\) We performed a comprehensive medical record review of patients hospitalized with a diagnosis of acute ischaemic stroke at ten acute care hospitals in Connecticut from 1 May 1996 to 31 December 1998. We identified the medical records of patients aged ≥18 years with a principal discharge diagnosis of ischaemic stroke, using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-CM-9) codes 430–438. We defined a stroke as a persistent focal neurological deficit of presumed ischaemic origin lasting more than 24 h.\(^29\) We excluded primary haemorrhagic strokes, but included ischaemic stroke with haemorrhagic transformation. The cohort included all stroke patients who received thrombolytic therapy at any of the ten hospitals (n = 63),\(^23\) and also included a random sample of patients with ischaemic stroke who had not received thrombolytic therapy but who were admitted during the same temporal period as the thrombolysis patients, at one of the participating hospitals (n = 56). The sample size for this study was designed to provide face validity of the results. All of the charts were made available to us; no chart was missing. Institutional review board approval was obtained at all participating hospitals.

Two abstractors, who were unaware of the study hypotheses, abstracted the medical record data using standard definitions. Any coding uncertainties were documented, resolved by consensus, and recorded in a coding dictionary. Inter-rater reliability was assessed by re-reviewing 10% of medical records, and demonstrated complete coding agreement for all abstracted variables.

**Definition of diabetes**

A patient was considered to have a diagnosis of diabetes mellitus if diabetes, diabetic eye disease, or diabetic neuropathy was listed on the admission history, problem list, nursing in-take form, or any Emergency Department documentation. Patients were also considered to have diabetes if they were taking insulin or any oral hypoglycaemic agent at the time of admission.

**Hyperglycaemia measurement**

Our medical record data did not indicate whether a blood sample was obtained in the fasting state; we therefore recorded both the glucose measurements
on admission and the maximum glucose value during the hospital stay. The American Diabetes Association (ADA) has not defined a specific glucose value as being hyperglycaemic, but has defined normal as a fasting glucose concentration of <110 mg/dl (6.1 mmol/l), or a glucose measurement of <140 mg/dl (7.8 mmol/l) during a 2-h oral glucose tolerance test. The ADA has defined diabetes as a fasting glucose ≥126 mg/dl (7 mmol/l), or a glucose measurement of ≥200 mg/dl (11.1 mmol/l) during a 2-h oral glucose tolerance test, or any glucose measurement ≥200 mg/dl (11.1 mmol/l) with symptoms of diabetes. In this context, we created an ordinal scale of the maximum glucose measurement: <120 mg/dl (<6.7 mmol/l), ≥120 to <140 mg/dl (≥6.7 to <7.8 mmol/l), ≥140 to <160 mg/dl (≥7.8 to <8.9 mmol/l), ≥160 to <180 mg/dl (≥8.9 to <10 mmol/l), ≥180 to <200 mg/dl (≥10 to <11.1 mmol/l), and ≥200 mg/dl (≥11.1 mmol/l).

Definition of plan to screen for diabetes

The American Diabetes Association recommends using a fasting plasma glucose measurement to screen for diabetes in non-pregnant adults. For patients hospitalized with an acute stroke, physicians might appropriately delay screening for diabetes until after discharge, if they suspect that fasting plasma glucose measurements were elevated due to the stress of the acute illness. Accordingly, we considered any of the following as documentation of a plan to screen for diabetes: documentation of diabetes or hyperglycaemia as a possible problem on a problem list in a progress note or in the discharge summary; documentation of a plan to screen for diabetes in one of the daily progress notes or in the discharge summary (e.g. ‘will screen for diabetes’ or ‘rule out diabetes’); or an order for a glycated haemoglobin, a haemoglobin A1c (HbA1c), or an oral glucose tolerance test either during the hospitalization; or documentation that a fasting plasma glucose, glycated haemoglobin, a HbA1c, or an oral glucose tolerance test would be ordered as an out-patient. We also recorded whether patients were given insulin or any oral hypoglycaemic medication during their hospital stay or at discharge.

Stroke severity

The National Institutes of Health Stroke Scale (NIHSS) Score was derived from admission neurological examination data. Three stroke severity categories were developed from the NIHSS Score: mild, 0–10; moderate, 11–20; and severe, >20.

Statistical methods

Student’s t-test and one-way analysis of variance (ANOVA) were used to assess differences in the maximum glucose measurement according to in-hospital mortality and stroke severity categories.

Results

A total of 119 acute stroke patients were identified, including 93 (78%) who did not have a prior history of diabetes; three patients did not have a glucose measurement during their hospital stay. The baseline characteristics of the 90 patients included in the current study are provided in Table 1.

Prevalence of hyperglycaemia

The maximum glucose measurements ranged from 75 to 250 mg/dl (4.2–13.9 mmol/l), with a median of 122 mg/dl (6.8 mmol/l) (Table 2). Approximately half of the patients had a maximum glucose measurement ≥120 mg/dl (6.7 mmol/l) (Table 3). The prevalence of hyperglycaemia in the cohort varied with the maximum glucose measurement cut-off used: ≥140 mg/dl (7.8 mmol/l), 31% (n=28); ≥160 mg/dl (8.9 mmol/l), 17% (n=16); ≥180 mg/dl (10 mmol/l), 10% (n=9); ≥200 mg/dl (11.1 mmol/l), 6% (n=5) (Table 4).

No statistically significant differences were found when comparing the maximum glucose measurement in patients stratified by admission stroke severity: mean ± SD maximum glucose: 121 ± 25 mg/dl (6.7 ± 1.4 mmol/l) for mild strokes, 137 ± 42 mg/dl (7.6 ± 2.3 mmol/l) for moderate strokes, and 130 ± 37 mg/dl (7.2 ± 2.1 mmol/l) for severe strokes (p=0.16). Similarly, no statistically significant differences were seen when comparing the maximum glucose measurements in patients who died during their hospital stay with patients who did not die: mean ± SD maximum glucose 139 ± 38 mg/dl (7.7 ± 2.1 mmol/l) for patients with in-hospital death, and 128 ± 36 mg/dl (7.1 ± 2.2 mmol/l) for patients discharged alive (p=0.32).

Screening for diabetes

Of the patients without a previous diagnosis of diabetes, none received an oral glucose tolerance test. Only one patient had an HbA1c measurement obtained during their hospital stay. This patient had an admission glucose measurement of 204 mg/dl (11.3 mmol/l), a maximum glucose measurement of 204 mg/dl (11.3 mmol/l), and an HbA1c of 7.1%. None of the patients had a discharge summary that
included a plan to screen for diabetes as an outpatient with a fasting glucose, glycated haemoglobin, a HbA1c, or an oral glucose tolerance test. Accordingly, the rate of screening for diabetes in these stroke patients depended on the definition of hyperglycaemia, and ranged from 4% (1/28) of patients with a maximum glucose of \( \leq 210 \text{ mg/dl} (11.1 \text{ mmol/l}) \), to 20% (1/5) of patients with a maximum glucose of \( \leq 200 \text{ mg/dl} (11.1 \text{ mmol/l}) \).

Use of insulin and oral hypoglycaemic agents

Of the 90 stroke patients without a previous diagnosis of diabetes, 12% \((n = 11)\) were given insulin during their in-patient stay. These 11 patients had maximum glucose measurements that ranged between 93 and 250 mg/dl \((5.2 \text{ and } 13.9 \text{ mmol/l})\) (mean ± standard deviation, \(157 \pm 52 \text{ mg/dl} [8.7 \pm 2.9 \text{ mmol/l}]\)). None of these 11 patients were given an oral hypoglycaemic agent during the hospital stay, and none were given either an oral hypoglycaemic agent or insulin as a discharge medication. None of these 11 patients were screened for diabetes.
Discussion

The prevalence of hyperglycaemia post stroke

Hyperglycaemia is common among acute ischaemic stroke patients without a prior diagnosis of diabetes—ranging between 6% and 31% in our study, depending on the glucose measurement cut-off used to define hyperglycaemia. Clinicians caring for stroke patients should be aware that hyperglycaemia is very common in the acute stroke period, even in patients without a previous diagnosis of stroke. As mentioned above, current guidelines recommend treating hyperglycaemic stroke patients as one would treat any hyperglycaemic hospitalized patient. 21,22

The prevalence of post-stroke hyperglycaemia that we observed (6%–30%) is similar to that seen in previous studies of patients with acute stroke, with or without a previous diagnosis of diabetes. For example, Szczudlik and colleagues found that among 262 consecutive ischaemic stroke patients, 36% had some hyperglycaemia (> 140 mg/dl [7.8 mmol/l] on admission or > 115 mg/dl [6.4 mmol/l] after admission) and 25% met the World Health Organization (WHO) criteria for diabetes.3 Scott and colleagues reported that > 50% of stroke patients had admission blood glucose measurements > 108 mg/dl (6 mmol/l).5 Williams and colleagues found that 40% of stroke patients had admission hyperglycaemia, defined as a random blood glucose ≥ 130 mg/dl (7.2 mmol/l).4

The prevalence of hyperglycaemia that we observed was also similar to that in previous studies of stroke patients without a prior history of diabetes. For example, Pulsinelli and colleagues found that 14/31 (45%) non-diabetic stroke patients had admission blood glucose measurements > 120 mg/dl (6.7 mmol/l).8 Similarly, Riddle and Hart found that 21/40 (53%) stroke patients without a prior diagnosis of diabetes had an elevated HbA1c > 10%.9

Screening for undiagnosed diabetes in patients with post-stroke hyperglycaemia

Only one patient out of 90 without a prior diagnosis of diabetes had any evidence of screening or intention to screen for diabetes, and the rate of screening for diabetes in hyperglycaemic stroke patients without a prior diagnosis of diabetes was at best 20%.

We do not intend to suggest that all patients with hyperglycaemia during their stroke hospitalization have overt diabetes. Patients who are acutely ill may have elevated glucose values, and this phenomenon is especially complex in patients hospitalized with a disabling stroke. For example, if a patient with baseline impaired glucose tolerance has a stroke and is unable to walk, their reduced activity may convert impaired glucose tolerance to overt diabetes. In this manner, a patient hospitalized with an acute stroke may have hyperglycaemia both from the physiological stress and from the impaired exercise. Regardless of the cause of the hyperglycaemia, however, the patient can benefit from diabetes screening. Diabetes is a risk factor for recurrent stroke, myocardial infarction, and death, and early identification and treatment can lead to reductions in its late effects, including vision loss and neuropathy, which may be particularly disabling in the post-stroke population.

Strengths and limitations

Our retrospective study design is well suited to a study of physician practices, because physicians’ behaviour may be altered when aware that monitoring is taking place, or in the setting of a prospective research protocol. Medical record reviews have been used by others to determine whether hospitalized patients with hyperglycaemia had progress notes that commented on the hyperglycaemia or possible diabetes.16,33 Levetan and colleagues found that of 1034 consecutively hospitalized adults, 130 (13%) had at least one episode of hyperglycaemia. Umpierrez et al., in a study of 1886 adult patients admitted to a hospital found that 718 (38%) had hyperglycaemia, 223/1886 (12%) without a prior diagnosis of diabetes and 495/1886 (26%) with a prior diagnosis of diabetes.16

Given the medical record design, we cannot ascertain whether patients were screened for diabetes after discharge from the hospital. Although a physician who cares for a patient hospitalized for acute stroke might take note of the hyperglycaemia and plan to screen for diabetes after discharge (and not record that intention in the hospital medical record), many patients are cared for by one group of clinicians when they are in the hospital and another group when they are in the out-patient setting. In such a situation, the out-patient clinicians might be unaware of hyperglycaemia that occurred during the hospitalization, if it was not documented in the progress notes or discharge summary.

A potential limitation of this study is that we were not able to determine whether glucose measurements were obtained in the fasting state, although clinicians caring for patients would have known if glucose measurements were taken while fasting. Therefore, an elevated glucose measurement might
have prompted a physician to obtain a fasting glucose measurement later during the hospital stay. If that fasting glucose measurement was <126 mg/dl (7 mmol/l), then the physician would have effectively screened that patient for diabetes, and may simply not have documented this in the medical record. If this scenario occurred, then we may have underestimated the rate of screening.

The generalizability of our research findings should be assessed within the context of our sampling strategy, the patients included in our cohort, the physicians who cared for them, the hospital settings where they were cared for, the geographical distribution, and the study time-period. The current study population included both patients who were assembled for another research project and patients who were evaluated specifically for this study. The current study cohort included the full spectrum of cerebrovascular disease (from mild stroke to severe stroke), a wide spectrum of patient characteristics (although the majority were White and elderly, and many had received thrombolytic therapy for their stroke), and all stroke subtypes of ischaemic (not haemorrhagic) stroke. The patients in this cohort were cared for by physicians with a variety of subspecialty training, although most patients had a general internist as the primary attending physician and a neurologist as a consulting attending physician. Many patients were also cared for by resident physicians. A variety of hospital types (academic and community) were included in this study, but they were geographically restricted to the state of Connecticut. The study included patients hospitalized from 1996 to 1998. Since the research that demonstrated the relationship between hyperglycaemia and poor patient outcomes post-stroke was published primarily in the mid-1980s through to the present day, clinicians caring for stroke patients in the late-1990s might have been less aware of the importance of hyperglycaemia than clinicians practicing today. Therefore, clinicians practicing today may be more likely to recognize or document hyperglycaemia, and our results may underestimate the current screening for undiagnosed diabetes.

A potential source of bias in this study involves patients with known diabetes being categorized as not having a prior diagnosis of diabetes. Our definition of diabetes was intentionally broad, and included having evidence of diabetic eye disease or neuropathy, or receiving insulin or an oral hypoglycaemic agent on admission. As a result, incorrect assignment should have been avoided.

We found that approximately one in ten stroke patients without a diagnosis of diabetes received insulin during their hospitalization. We do not know why these patients received insulin (i.e. for the treatment of hyperglycaemia, or as part of a glucose–insulin infusion for the acute therapy of stroke). A hyperglycaemic patient should be screened for diabetes, however, whether or not that patient received insulin.

The results of the current investigation are preliminary, and this topic requires further study. Our findings, however, are consistent with a previous report of hospitalized patients admitted for all diagnoses—not just stroke—in which 38% of medical patients and 33% of surgical patients with hyperglycaemia did not have a previous diagnosis of diabetes. In that study, only 7% of the progress notes stated that diabetes was a possible diagnosis, a result of a similar order of magnitude to our findings among stroke patients.

In conclusion, evidence exists to support the screening of patients at risk for diabetes. Stroke patients are particularly likely to benefit from screening, because hypertension is common in patients with stroke, and in patients with both hypertension and diabetes, more aggressive antihypertensive therapy is indicated. Given that diabetes is a risk factor for stroke, it is likely that stroke patients represent an enriched population for undiagnosed diabetes. Hyperglycaemia in the setting of stroke should prompt clinicians to screen patients for diabetes. Clinicians may not currently be using this opportunity to identify diabetes, a disease that may be an important aetiological contribution to their patients’ cerebrovascular disease, and that is likely to increase their patients’ long-term morbidity and mortality.

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