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Impaired glucose metabolism in patients with acute stroke and no previous diagnosis of diabetes mellitus

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Summary

Background: About a third of patients with acute stroke and no prior diagnosis of diabetes have hyperglycaemia during the acute phase of stroke. Whether this is an acute stress response or a reflection of underlying diabetes is controversial.

Aim: To assess whether impaired glucose metabolism in patients with acute ischaemic stroke and no previous diagnosis of diabetes persists after 3 months, and whether such persistence can be predicted.

Design: Prospective observational study.

Methods: We enrolled 106 patients with acute ischaemic stroke and no history of diabetes. Fasting blood glucose, serum insulin and the insulin resistance index HOMA were recorded during hospital stay. A standard oral glucose tolerance test was performed at discharge and 3 months later.

Results: Ten patients did not complete the study. Eighty-one patients (84.4%) had abnormal glucose metabolism at discharge and 62 (64.6%) after 3 months. Thirty-seven (38.5%) had impaired glucose tolerance at discharge and 26 (27.1%) after 3 months. Forty-four (45.8%) had diabetes at discharge, and 36 (37.5%) at 3 months. Post-load hyperglycaemia at discharge was a predictor of diabetes after 3 months. A plasma glucose cut-off of 11.7 mmol/l (210 mg/dl) had a specificity of 90.0% and a positive predictive value of 81.3%. HOMA increased progressively from patients with normal glucose metabolism to those with newly diagnosed diabetes.

Discussion: Impaired glucose tolerance and previously unrecognized diabetes could be detected early in the stroke course, and persisted after 3 months in more than two-thirds of our patients. Post-load hyperglycaemia during the acute phase of stroke may be useful in identifying patients with abnormal glucose metabolism, which places them at risk for adverse outcomes, including cardiovascular disease.

Introduction

Diabetes doubles the risk of ischaemic stroke[1] and worsens survival of patients with acute stroke.[2,3] However, the onset of diabetes may occur several years before the clinical diagnosis, and its development is preceded by a prolonged period of insulin resistance. Furthermore, insulin resistance has been shown to be independently associated with increased risk of cerebrovascular events in non-diabetic subjects.[4] There is also a positive relation between mild plasma glucose elevations (even below the threshold for diabetes) and incident cardiovascular events.[5] Hyperglycaemia during the acute phase of stroke occurs in about one third of patients without a prior diagnosis of diabetes,[6,7]

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and is associated with worse neurological outcome and increased stroke mortality.[8–10] Whether this raised plasma glucose concentration in non-diabetic patients with acute stroke is a stress response to neurological insult, or a reflection of unrecognized diabetes, is controversial.[11–13] However, 3 months after an acute stroke, about two-thirds of patients without recognized diabetes have impaired glucose metabolism, using a standardized oral glucose tolerance test.[14,15] Moreover, ischaemic stroke shares many important risk factors with myocardial infarction.[16] In a recent study, one-third of patients with acute myocardial infarction, without a previous diagnosis of diabetes mellitus, were newly diagnosed with diabetes mellitus after an oral glucose tolerance test, and the same proportion could be detected 3 months after discharge.[17] This suggests that hyperglycaemia in these patients is not related to stress at the time of the acute ischaemic event. This observation could change the clinical management of these patients.

We therefore investigated the prevalence of undiagnosed impaired glucose metabolism in patients with acute stroke without a previous diagnosis of diabetes mellitus, and the possibility of predicting its persistence after the acute phase, to increase our understanding of the clinical implications of this potent and modifiable risk factor for stroke.

Methods

Patients

We prospectively studied patients with acute ischaemic stroke, admitted to the Internal Medicine of the S. Elia Hospital, Caltanissetta, Sicily, from 1 January to 31 December 2003. There were no specific selection criteria for the admission of stroke patients. We excluded patients with previously diagnosed diabetes, those unable to perform an oral glucose tolerance test because of unconsciousness, and those with haemorrhagic stroke or atrial fibrillation, in which diabetes and atherothrombotic events cannot be considered a major causal factor.[1,18] The research protocol was approved by the local ethics committee, and informed consent was obtained from patients or relatives when patients had language or cognitive impairment. Acute stroke was defined according to World Health Organization criteria: rapidly developing clinical symptoms or signs of focal disturbance of cerebral function, lasting more than 24 h, with no apparent cause other than vascular origin.[19] The diagnosis of ischaemic stroke was established by neurological examination and confirmed by computed tomography. All patients had their stroke subtype categorized on the basis of clinical features according to the TOAST classification.[20] Stroke severity at admission was assessed using the National Institute of Health Stroke Scale (NIHSS).[21]

Protocol

We measured fasting plasma glucose concentration on the day of admission, and then overnight fasting plasma glucose concentration daily until hospital discharge. No patient received dextrose, insulin or drugs such beta-blockers, diuretics or glucocorticoids that could induce glucose intolerance during the hospitalization or after discharge. A standardized oral glucose tolerance test with 75 g of glucose dissolved in 200 ml of water was performed at discharge, when the patients had been on unrestricted diet for at least 3 days. Three months later, a second oral glucose tolerance test was taken after a overnight fast. Serum levels of insulin and HbA_{1c} were determined at discharge. Plasma glucose was measured by a hexokinase method. Insulin was determined by the electrochemiluminescence immunoassay (ECLIA). The percentage of HbA_{1c} was assessed by liquid chromatography, and its upper limit set at 5.7%. The degree of insulin resistance was estimated by the homeostasis model insulin resistance index (HOMA):[22] fasting glucose (mmol/l) × fasting insulin (mU/l), divided by 22.5. Higher HOMA values indicate higher insulin resistance, whereas lower values indicate insulin sensitivity. Impaired glucose tolerance and diabetes were defined according to the WHO definition[23] and the American Diabetes Association (ADA) criteria for fasting plasma glucose.[24] Thus normal glucose tolerance was defined as fasting glucose <6.1 mmol/l (110 mg/dl) and 2-h post-load glucose concentration <7.8 mmol/l (140 mg/dl); impaired glucose tolerance as fasting glucose 6.1–6.9 mmol/l (110–125 mg/dl) and 2-h glucose 7.8–11.0 mmol/l (140–199 mg/dl); diabetes mellitus as fasting glucose $\geqslant 7.0$ mmol/l (126 mg/dl), and/or 2-h post-load glucose concentration >11.1 mmol/l (200 mg/dl).

Statistical analysis

Summary measures for normally distributed variables are given as means (SD) and for others as medians (IQR). Insulin and HOMA appeared not to be normally distributed, so a logarithmic transformation was used. Categorical variables are presented as frequencies and percentages. The statistical significance of the differences among the three groups of patients with normal glucose tolerance, impaired glucose tolerance and diabetes

was tested with analysis of variance (ANOVA), χ^2 or the Kruskal–Wallis test. The relationships between 3 months post-load glucose and biochemical parameters as dependent variables were assessed using linear correlation and linear regression techniques. To find independent predictors of diabetes, we entered baseline parameters with $p \leqslant 0.2$ in a univariate logistic regression into a multiple logistic regression analysis. Linearity of the predictors was tested using quadratic and cubic terms. A Receiver Operating Characteristic (ROC) curve was plotted to show the trade-off between sensitivity and specificity, thus indicating the cut-points for diabetes predictors and their predictive values. We used Minitab (version 13) for statistical analysis.

Results

A total of 258 patients with acute ischaemic stroke were admitted in the study period (median age 69.6 years, IQR 63.2–76.7; 136 men). Patients with previously diagnosed diabetes ($n=76$), unconsciousness (defined as Glasgow Coma Scale $\leqslant 8$) ($n=26$), haemorrhagic stroke ($n=34$) or atrial fibrillation ($n=16$) were excluded. We therefore studied 106 patients (median age 71.0 years, IQR 63.2–77.0; 65 men) without a previous diagnosis of diabetes. None died during hospital admission. All had an oral glucose tolerance test before discharge, and 96 repeated the test 3 months later (90% of eligible participants). Baseline clinical and biochemical data are summarized in Table 1. Median time from clinical onset of symptoms and discharge oral glucose tolerance test was 7 days (range 4–13). The reasons for not doing the test after 3 months were: death after discharge ($n=2$); and unwillingness because of poor health at home ($n=8$). Five of the patients not studied at 3 months had normal glucose tolerance, and five impaired glucose tolerance at discharge.

As our purpose was to assess the prevalence of diabetes in patients with acute stroke and no history of diabetes, and then judge the extent of resolution vs. persistence of diabetes 3 months after hospital discharge, the comparison of glucose metabolism abnormalities at discharge vs after 3 months was restricted to those patients ($n=96$) in whom 3-month data were available.

Eighty-one patients (84.4%) had post-load abnormal glucose metabolism at discharge, and 62 (64.6%) after 3 months. Forty-four (45.8%) had diabetes at discharge, and 36 (37.5%) at 3 months (Table 2). The corresponding figures for impaired glucose tolerance were 37 (38.5%) and 26 (27.1%). However, using fasting plasma glucose criteria (fasting plasma glucose $\geqslant 7.0$ mmol/l), only 14 (14.6%) had admission hyperglycaemia. When their glucose metabolism was re-evaluated after 3 months, 12 (85.7%) had newly diagnosed diabetes.

Table 1 Baseline clinical and biochemical data for patients who completed the study ($n=96$)

Parameter	Value
Hypertension	66 (68.7%)
Previous stroke	17 (17.7%)
Subtypes of stroke	
Large-artery atherosclerosis	30 (31.2%)
Small-artery occlusion (lacunar)	59 (61.4%)
Undetermined aetiology	7 (7.3%)
Previous myocardial infarction	9 (8.5%)
Hyperlipidaemia	10 (9.4%)
Fasting hyperglycaemia ($\geqslant 7.0$ mmol/l) at admission	14 (14.6%)
Plasma glucose at admission (mmol/l)	5.9 ± 1.0
HbA_{1c} (%)	6.0 ± 1.8
Body mass index (kg/m^2)	25.9 ± 1.4
Serum insulin (mU/l)	9.0 (5.9–12.0)
HOMA	2.3 (1.5–3.3)

Data are numbers (%), means ± SD or medians (range), as appropriate. Hypertension, self-report of physician diagnosis of hypertension and current use of hypertension medications, or baseline blood pressure >160/100 mmHg; previous stroke, self-report of prior hospitalization for more than 1 day for stroke; previous myocardial infarction, self-report of prior hospitalization for more than 1 day for myocardial infarction; hyperlipidaemia, self-report of physician diagnosis of hyperlipidaemia or baseline total cholesterol $\geqslant 5.2$ mmol/l.

Differences in clinical and biochemical data in patients with normal and impaired glucose metabolism are shown in Table 3. Fasting and post-load glucose, fasting insulin and HOMA values at discharge were all significantly higher in patients newly diagnosed with diabetes mellitus than in those with normal glucose tolerance.

After 3 months, 86.6% of those with normal glucose tolerance at discharge were still normoglycaemic (Table 4). Of those with impaired glucose tolerance at discharge, 43.2% had impaired glucose tolerance, 37.8% showed normal glucose tolerance, and 19.0% had progressed to diabetes. Of those with diabetes at discharge, 63.7% were still diabetic at 3 months, 20.4% had impaired glucose tolerance, and 15.9% showed normal glucose tolerance.

We investigated the relationship between post-stroke abnormal glucose metabolism and average glucose concentrations in the preceding 3 months, as expressed by HbA_{1c}. Of 62 patients with

Table 2 Glucose metabolism abnormalities at discharge and at 3 months after discharge ($n=96$)

	Discharge		3 months	
	n (%)	95%CI	*n* (%)	95%CI
Normal glucose tolerance	15 (15.6)	10–24	34 (35.4)	27–45
Impaired glucose tolerance	37 (38.5)	29–48	26 (27.1)	19–37
Diabetes mellitus	44 (45.8)	36–56	36 (37.5)	28–47

Table 3 Clinical and biochemical data in patients with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and newly diagnosed diabetes mellitus 3 months after stroke ($n=96$)

	NGT ($n=34$)	IGT ($n=26$)	Diabetes ($n=36$)	*p*
Age (years)	69.5 (63.7–76.2)	70.5 (63.0–81.0)	72.0 (66.0–76.7)	0.85
Men	20 (58.8%)	15 (57.7%)	22 (61.1%)	0.41
Hypertension	24 (70.6%)	18 (69.2%)	24 (66.7%)	0.90
Previous stroke	4 (11.8%)	6 (23.0%)	6 (16.7%)	0.51
Subtypes of stroke				
Large-artery atherosclerosis	9 (26.4%)	13 (50.0%)	9 (25.0%)	0.59
Small-artery occlusion (lacunar)	19 (55.9%)	12 (46.1%)	25 (69.4%)	0.22
Undetermined aetiology	6 (17.6%)	1 (3.8%)	2 (5.5%)	0.28
Previous myocardial infarction	1 (1.0%)	4 (4.2%)	3 (3.1%)	0.22
Hyperlipidaemia	3 (3.1%)	2 (2.1%)	5 (5.2%)	0.68
Hyperglycaemia at admission	2 (5.9%)	3 (11.5%)	9 (25.0%)	0.05
NIHSS score on admission				
0–6	12 (35.3%)	10 (38.5%)	11 (30.5%)	0.89
7–15	15 (44.1%)	9 (34.6%)	15 (41.7%)	0.88
$\geqslant$16	7 (20.6%)	7 (26.9%)	10 (27.8%)	0.84
Fasting plasma glucose (mmol/l)				
At discharge	5.6 ± 0.7	6.0 ± 0.9	6.4 ± 1.3	0.008
3 months after discharge	5.5 ± 0.5	6.1 ± 0.7	6.7 ± 0.9	<0.001
2-h plasma glucose (mmol/l)				
At discharge	8.6 ± 2.2	10.4 ± 1.4	12.4 ± 2.0	<0.001
3 months after discharge	6.8 ± 0.6	9.6 ± 1.1	14.0 ± 2.1	<0.001
HbA_{1c} (%)	5.8 ± 1.1	6.0 ± 1.7	6.2 ± 2.2	0.844
Body mass index (kg/m^2)	25.7 ± 1.4	25.7 ± 1.7	26.1 ± 1.3	0.434
Fasting serum insulin (mU/l)	7.7 (4.5–10.7)	8.9 (6.2–12.5)	10.7 (6.3–14.0)	0.021
HOMA	1.9 (1.0–2.5)	2.5 (1.8–3.3)	2.7 (1.8–4.2)	0.004

Data are means ± SD, number (percentage) or medians (IQR), as appropriate.

Table 4 Changing prevalence within each glucose metabolism pattern at discharge and 3 months after discharge

	At discharge ($n=96$)	3 months after discharge ($n=96$)		
		NGT (%)	IGT (%)	Diabetes (%)
NGT	15	13 (86.6)	1 (6.7)	1 (6.7)
IGT	37	14 (37.8)	16 (43.2)	7 (19.0)
Diabetes	44	7 (15.9)	9 (20.4)	28 (63.7)
Total		34 (35.4)	26 (27.1)	36 (37.5)

NGT, normal glucose tolerance; IGT, impaired glucose tolerance. The percentages for metabolic status 3 months after discharge are presented as row percentages.

Table 5 Multiple logistic regression analysis of predictors of diabetes mellitus at oral glucose tolerance test 3 months after discharge

Parameter	Unadjusted OR (95%CI)	*p*	Adjusted OR (95%CI)	*p*
Fasting plasma glucose at discharge*	1.75 (1.13–2.73)	0.013	1.38 (0.60–3.15)	0.450
Post-load glucose at discharge*	2.05 (1.52–2.76)	<0.001	1.77 (1.27–2.46)	0.001
Insulin**	1.14 (1.02–1.27)	0.019	1.09 (0.93–1.26)	0.289
HOMA***	1.69 (1.15–2.47)	0.007	1.18 (0.75–1.86)	0.484

OR, odds ratio. *OR for increase of 1 mmol/l in plasma glucose. **OR for increase of one unit in logarithm of serum insulin. ***OR for increase of one unit in logarithm of HOMA. Unadjusted OR, obtained from a univariate logistic regression; adjusted OR, obtained after adjusting for all the other predictors.

Table 6 Sensitivity, specificity and predictive values of post-load glucose at discharge for predicting diabetes 3 months after acute stroke

Post-load glucose at discharge (mmol/l) (mg/dl)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV %	NPV %
⩾6 (108)	100.0 (90.2–100.0)	6.7 (1.9–16.2)	39.1	100.0
⩾7 (126)	97.2 (85.4–99.5)	15.0 (7.1–26.6)	40.7	90.0
⩾8 (144)	97.2 (85.4–99.5)	28.3 (17.5–41.4)	44.9	94.4
⩾9 (162)	94.4 (81.3–99.2)	50.0 (30.6–56.8)	50.0	92.9
⩾10 (180)	83.3 (67.2–93.6)	61.7 (48.2–73.9)	56.6	86.0
⩾11 (198)	77.8 (60.8–89.9)	75.0 (62.1–85.3)	65.1	84.9
⩾12 (216)	63.9 (46.2–79.2)	91.7 (81.6–97.2)	82.1	80.9
⩾13 (234)	36.1 (20.8–53.8)	96.7 (88.4–99.5)	86.7	71.6
⩾14 (252)	16.7 (6.4–32.8)	98.3 (91.0–99.7)	85.7	66.3
⩾15 (270)	8.3 (1.8–22.5)	100.0 (94.0–100.0)	100.0	64.5

PPV, positive predictive value; NPV, negative predictive value.

abnormal glucose metabolism at 3 months, 27 (43.5%) had admission HbA_{1c} within normal limits.

Post-load plasma glucose at 3 months was significantly correlated to discharge fasting glucose ($r=0.29$, $p=0.004$), post-load glucose at discharge ($r=0.68$, $p<0.001$), insulin ($r=0.36$, $p=0.001$), HOMA ($r=0.408$, $p<0.001$) and 3-month fasting glucose ($r=0.58$, $p<0.001$). No statistically significant correlation was found with age, sex, BMI or HbA_{1c} concentrations. In a linear regression analysis, post-load glucose at discharge accounted for about half ($r^2=46.8\%$) of the variance in post-load glucose concentration after 3 months.

Using logistic regression analysis, predictors of newly detected diabetes after 3 months were fasting and post-load plasma glucose at discharge, fasting glucose at 3 months, insulin and HOMA (Table 5). Age, sex, subtype and severity of stroke were not confounders, as they were not significantly related to diabetes. After adjusting for all the predictors, only post-load glucose at discharge and fasting glucose at 3 months were predictors of diabetes at 3 months after stroke (Table 6). A cut-off value for post-load plasma glucose at discharge of 11.7 mmol/l (210 mg/dl) had the best combination of sensitivity and specificity, and was able to predict newly detected diabetes at 3 months with a sensitivity of 72.2% and a specificity of 90.0%. Positive and negative predictive values were 81.3% and 84.4%, respectively. The area under the ROC curve was 0.855 (95%CI 0.768–0.918, $p<0.0001$). Using this cut-off on our sample, 80/96 patients would have been correctly classified by the test (26/36 with diabetes and 54/60 without).

To investigate the relation between glucose metabolism and aetiology of ischaemic stroke, we divided patients according to subtype of acute stroke. Prevalences of impaired glucose metabolism were not significantly different within stroke subtypes. Dependency at discharge after stroke did not differ between patients with impaired and normal glucose metabolism.

Discussion

Our patients with acute ischaemic stroke, with no previous diagnosis of diabetes mellitus, had a high

prevalence of abnormal glucose metabolism and diabetes at discharge, and about two-thirds had the same glucose abnormalities after 3 months. Overall, one third of those with acute ischaemic stroke and no prior history of diabetes had a diabetic post-load level of plasma glucose 3 months after the acute event. This impaired glucose metabolism was recorded when the effects of the acute stress should have subsided, suggesting that in the majority of patients it is not caused by stress of the acute phase of stroke. This implies that the prevalence of unknown diabetes in patients with acute ischaemic stroke is much higher than previously reported. Since at admission 29% (76/258) of our stroke patients already had a diagnosis of diabetes (and were excluded from the study accordingly), the true prevalence of diabetes in these patients might be as high as 43% (76 + 36 of 258).

A population study using fasting or admission blood glucose to identify patients with diabetes reported that about 6% of patients with acute ischaemic stroke had undiagnosed diabetes.[25] Analysing our patients with the same diagnostic criteria for diabetes (fasting plasma glucose level >11 mmol/l), we found a similar percentage (4.8% with previously undiagnosed diabetes), so the increased prevalence of glucose metabolism abnormalities we observed is unlikely to result from differences in the population studied.

The oral glucose tolerance test we used to diagnose abnormal glucose metabolism is a better predictor of cardiovascular events and mortality than fasting plasma glucose levels are.[26–28] In the present study, a post-load glucose test at discharge was a strong predictor of diabetes 3 months after stroke. The diagnosis of diabetes would have been missed in two-thirds of our patients with ischaemic stroke and previously unknown diabetes if only tests of fasting glucose had been used. However, all predictive values depend on the prevalence of the disease in the population. The values we observed are based on this particular set of patients, and might vary for other populations where the prevalence is different.

The prevalence of fasting post-stroke hyperglycaemia we observed (14.6%) was similar to that seen in previous studies of stroke patients without a prior diagnosis of diabetes.[2] There is debate as to the significance of fasting hyperglycaemia in acute stroke patients: whether it is part of a stress response to cerebral ischaemia[29] or a marker of previously unrecognized diabetes[12,30] remains unclear. About half of our patients with admission hyperglycaemia had a normal HbA_{1c} concentration. As HbA_{1c} levels provide an indication of the average blood glucose concentration during the preceding 3 months, this observation would imply that fasting post stroke hyperglycaemia is a reflection of unrecognized diabetes in some patients, while in others it is a reflection of an acute stress response to cerebral damage. However, normal HbA_{1c} values do not preclude the existence of abnormal glucose metabolism. In healthy individuals, 37% of those with HbA_{1c} 5.0–5.4% had impaired glucose tolerance, impaired fasting glycaemia or diabetes.[31]

A large proportion of our patients with elevated 2-h post-load levels of plasma glucose at 3 months had fasting glucose concentration within normal range. This pattern of abnormal glucose metabolism identifies patients with isolated post-load hyperglycaemia (IPH). Although this condition becomes more common with age, it is not a benign phenomenon. Epidemiological studies demonstrate that subjects with IPH are at higher risk of all-cause and cardiovascular mortality, independent of other cardiovascular risk factors.[32–34]

In the present study, patients with previously undiagnosed impaired glucose tolerance and diabetes at 3 months were more insulin-resistant than patients with normal glucose metabolism. This result raises the possibility that the link between abnormal glucose metabolism and ischaemic stroke is insulin resistance. This cannot be explained by differences in body mass index. Although an association between insulin and atherosclerotic vascular disease has been hypothesized for more than 30 years,[35] and several lines of evidence have related insulin resistance and hyperinsulinaemia to coronary atherosclerosis,[36] their role in cerebrovascular atherosclerosis has received little attention.[37] In our patients, insulin resistance (expressed by HOMA) increased progressively with the impairment of glucose metabolism. Therefore, insulin resistance may be the underlying factor for abnormal glucose metabolism in patients without prior diagnosis of diabetes mellitus.

Our results may have clinical implications. Diabetic patients without cardiovascular disease have a risk of stroke mortality similar to that of non-diabetic subjects with a previous stroke.[38] Our findings indicate that stroke patients with the highest risk of diabetes at 3 months can be identified during the early course of acute stroke using the simple and inexpensive glucose tolerance test at discharge. Stroke patients without prior diagnosis of diabetes should be tested to identify those with abnormal glucose metabolism, which may justify aggressive treatment to prevent further cerebrovascular disease.

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