Stroke in Patients With Diabetes

The Copenhagen Stroke Study

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Background and Purpose Although diabetes is a strong risk factor for stroke, it is still unsettled whether stroke is different in patients with and without diabetes. This is true for stroke type, stroke severity, the prognosis, and the relation between admission glucose levels and stroke severity/mortality.

Methods This community-based study included 1135 acute stroke patients (233 [20%] had diabetes). All patients were evaluated until the end of rehabilitation by weekly assessment of neurological deficits (Scandinavian Stroke Scale) and functional disabilities (Barthel Index). A computed tomographic scan was performed in 83%.

Results The diabetic stroke patient was 3.2 years younger than the nondiabetic stroke patient (P<.001) and had hypertension more frequently (48% versus 30%, P<.0001). Intracerebral hemorrhages were six times less frequent in diabetic patients (P=.002). Initial stroke severity, lesion size, and site were comparable between the two groups. However, mortality was higher in diabetic patients (24% versus 17%, P=.03), and diabetes independently increased the relative death risk by 1.8 (95% confidence interval [CI], 1.04 to 3.19). Outcome was comparable in surviving patients with and without diabetes, but patients with diabetes recovered more slowly. Mortality increased with increasing glucose levels on admission in nondiabetic patients independent of stroke severity (odds ratio, 1.2 per 1 mmol/L; CI, 1.01 to 1.42; P=.04). This was not the case in diabetic patients.

Conclusions Diabetes influences stroke in several aspects: in age, in subtype, in speed of recovery, and in mortality. Increased glucose levels on admission independently increase mortality from stroke in nondiabetic but not in diabetic patients. The effect of reducing high admission glucose levels in nondiabetic stroke patients should be examined in future trials. (Stroke. 1994;25:1977-1984.)

Key Words • diabetes mellitus • glucose • outcome • hyperglycemia • risk factors

The increased risk of stroke in the diabetic patient has been established in several studies.1-6 This increase has been connected to the pathophysiological changes seen in the cerebral vessels of patients with diabetes.7-8 The relative risk of stroke is approximately doubled compared with that in patients without diabetes.9

An increased mortality from stroke in the diabetic patient has been reported.10-18 The reason for this excess in mortality is unknown. Is it because diabetic patients have more severe strokes, is the recovery from stroke poorer, or is the higher mortality induced by an unfavorable effect of hyperglycemia on the ischemic brain tissue? Because the diabetic angiopathy is different from the atherosclerotic angiopathy, the diabetic stroke could well be different from stroke in nondiabetic patients. Little is known, however, about the characteristics of stroke in the diabetic patient, and no community-based study has been published.

Lithner et al13 and Toni et al16 reported that initial stroke severity was comparable in patients with and without diabetes, but Kiers et al17 found that diabetic patients had more severe strokes. Autopsy studies have indicated that diabetes may be a risk factor for lacunar infarction.19-22 This has not been confirmed in recent clinical studies,16,17 but the number of diabetic patients studied was small.

Pulsinelli et al11 reported in a retrospective study that neurological outcome of stroke was poorer in patients with versus without diabetes, whereas Toni et al16 found functional outcome comparable in patients with and without diabetes. The patients studied were selected and few in number. Furthermore, the time course of recovery from stroke in the diabetic patient has never been described.

It is unsettled if and how stroke severity and outcome are related to admission blood glucose levels. Increased mortality from stroke in nondiabetic patients with hyperglycemia on admission has been found in most studies16,17,23-25 but not in all26 compared with mortality in nondiabetic patients with normoglycemia. In patients with diabetes, Lithner et al13 found mortality increased in patients with high admission glucose; other studies16,17,25 found no such relation.

The aim of this study was to prospectively characterize stroke in the diabetic patients in a community-based stroke population and to determine the time course of recovery and the prognosis in stroke patients with diabetes. Furthermore, it was our purpose to describe the relation between admission blood glucose and stroke severity and outcome in patients with and without diabetes.

Subjects and Methods

Information from all patients admitted with an acute stroke to the Neurological Department of Bispebjerg Hospital, Copenhagen, has been collected prospectively and entered into a computerized data bank since September 1, 1991. The study population is community based, as (1) Bispebjerg Hospital
serves a well-defined community with 239,886 inhabitants within the City of Copenhagen, (2) hospital care is free, and a very high proportion of stroke patients are admitted to the hospital (in a neighboring area within Greater Copenhagen, it was recently shown that 88% of all stroke patients are hospitalized25), (3) Bispebjerg Hospital is the only hospital serving the region, and (4) all persons from the community who have an acute cerebrovascular disease that requires admission are referred to the neurological department. Not only initial diagnostic procedures and treatment take place here, but also all stages of rehabilitation. This is regardless of the age of the patient, the severity of the stroke, and the condition of the patient before the stroke.

Inclusion Criteria

Patients with an acute stroke admitted in the 2-year period from September 1, 1991, to August 31, 1993, were included. A total of 1169 acute stroke patients were admitted in the study period (536 men and 633 women; mean age, 74.4 years; standard deviation [SD], 11.1).

Exclusion Criteria

Reliable information about diabetes could not be obtained in 34 patients (2.9%); they had severe strokes, were unconscious on admission, and died before it could be established whether or not they had diabetes. Compared with the rest of the patients, they were significantly older (mean, 80.9 years; SD, 6.5 versus 74.2 years; SD, 11.2; P<.0005) and women predominated (7 men and 27 women versus 529 men and 606 women; P<.002).

Consequently, a total of 1135 acute stroke patients were included in the study. Time from stroke onset to admission was within 1 day in 70%, within 4 days in 86%, and within 1 week in 93% of the patients. These frequencies did not differ in patients with and without diabetes.

Definition of Acute Stroke

Stroke was defined according to World Health Organization (WHO) criteria: rapidly developed clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than vascular origin. Subarachnoidal bleeding was not included.28

Diagnosis of Diabetes

Patients were divided into three groups: (1) patients without diabetes, (2) patients with known diabetes (known diabetes before stroke), and (3) patients with diabetes diagnosed after stroke onset either because diabetes was diagnosed during the hospital stay or because admission plasma glucose level was >11 mmol/L in patients without known diabetes (in accordance with the WHO diagnostic criteria for diabetes). However, stroke may have preceded or even provoked diabetes in these patients. Furthermore, the specificity of the diagnosis of diabetes resting on an admission blood glucose level is not clear. The WHO diagnosis applies to nonstressed situations. As a consequence, the group of patients with diabetes diagnosed after stroke onset is not included in comparisons between patients with and without diabetes.

Clinical Assessment

The Scandinavian Stroke Scale (SSS) was used to assess neurological deficits.29,30 The SSS evaluates level of consciousness, eye movement, power in arm, hand, and leg, orientation, aphasia, facial paresis, and gait. The score ranges from 0 to 58 points. It was performed on admission, the day after admission, every week during the hospital stay, and at discharge. The weekly assessment was performed by the same neurologist (H.S.J.) in all patients.

The Barthel Index (BI) was used for the assessment of functional ability.31 It evaluates 10 different abilities and ranges in score from 0 to 100 points. It was measured by the nursing and training staffs once during the first week after admission, each week during hospital stay, and at discharge.

CT Measurements

A computed tomography (CT) scan was performed with a Siemens Somatom DR scanner. Contrast was not given routinely. The time from onset of stroke to CT examination was dependent on the accessibility of the scanner, which varied during the study period. Median time from stroke onset to CT was 8 days. All scans were described by the same radiologist (H.O.R.) with no knowledge of clinical data. Description included type, size, and region of lesion(s).

Size was defined as the largest visible diameter of the lesion on CT. Infarcts were divided according to whether cortical structures were involved or not. Data from the CT description were reviewed by a neurologist (H.S.J.) together with clinical data including symptoms from the present stroke and possible former strokes. Lesions were categorized as either the cause of the present stroke, a former stroke, or as a silent infarct. Leukoaraiosis was characterized by poorly delineated hypodense areas around the frontal horn and/or around the posterior part of the lateral ventricles.

Medical Condition Before Stroke

Information concerning comorbidity was obtained on admission and included other disabling disease apart from earlier stroke(s) (amputation, multiple sclerosis, severe dementia, heart failure, latent or persistent respiratory insufficiency, parkinsonism, and so forth).

Risk Factors

The following risk factors were considered: age, sex, atrial fibrillation (if present on electrocardiography [ECG] on admission), a history of intermittent claudication, daily alcohol consumption (patients were divided into two groups: no daily alcohol consumption and daily alcohol consumption), daily smoking of any kind of tobacco, hypertension (in treatment with antihypertensive drugs at time of admission or hypertension diagnosed during hospital stay), diastolic and systolic blood pressures on admission, former myocardial infarction (MI) (a clinical event diagnosed as MI confirmed by hospital records and either ECG and/or enzymes), former stroke, and ischemic heart disease (IHD) (a history of IHD or IHD diagnosed during the hospital stay).

Causes of Death

The causes of death were, as suggested in the Oxfordshire Community Stroke Project,32 categorized into (1) death directly due to the stroke, (2) death directly due to a recurrent stroke in the period of rehabilitation, (3) death due to nonstroke cardiovascular reasons, (4) death due to the complications of immobility from stroke, for example, bronchopneumonia, pulmonary embolus, and sepsis, and (5) death unrelated to the stroke, eg, cancer or the cause of death unknown.

Statistics

Statistics were performed using the spss package (Windows version 5). In univariate analysis, the Student's t test was used for the comparison of continuous data between two groups. When more than two groups were compared, one-way analysis of variance (ANOVA) was performed. When the ANOVA showed significance, Duncan's multiple range test was used to seek out the significant groups. The χ² test was used for noncontinuous data. For dichotomous data, multiple logistic regression was used to test for independent variables. All variables of interest were tested using the backward procedure (ad modum Wald). For continuous data, multiple linear regression was used to test for independent variables. All variables of interest were tested using the backward procedure. The level of significance was chosen to be P<.05.
TABLE 1. Basic Characteristics of Patients in the Copenhagen Stroke Study

<table>
<thead>
<tr>
<th></th>
<th>Patients Without Diabetes</th>
<th>Known Diabetes Before Stroke</th>
<th>Diabetes Diagnosed After Stroke Onset</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>902 (80%)</td>
<td>176 (15%)</td>
<td>57 (5%)</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>74.7±11.2</td>
<td>71.5±10.5 (.001)</td>
<td>73.7±11.1</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>409 (49%)</td>
<td>97 (55%)</td>
<td>23 (40%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>189 (22%)</td>
<td>44 (25%)</td>
<td>26 (19%)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>78 (8%)</td>
<td>15 (8%)</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>367 (42%)</td>
<td>83 (48%)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Home care</td>
<td>314 (39%)</td>
<td>59 (40%)</td>
<td>.51</td>
<td></td>
</tr>
<tr>
<td>LOH, days</td>
<td>36.4±43.4</td>
<td>40.5±44.0 (.31)</td>
<td>36.0±40.3</td>
<td></td>
</tr>
</tbody>
</table>

Comorbidity includes other prestroke disabling disease; employed indicates still in the labor force; married, married or cohabitation; home care, receiving regular visits by the home helpers from the community; and LOH, length of hospital stay.

*Comparing patients with known diabetes before stroke and patients without diabetes.

Ethics

The study was approved by the Ethics Committee of Copenhagen, approval number V. 1002263/91.

Results

A total of 1135 acute stroke patients were included in the study. Diabetes was present in 233 (20.5%) of the patients. Thirty-four (15%) had type 1 diabetes (insulin-dependent), and 199 (85%) had type 2 diabetes (non-insulin-dependent).

In 176 (15.5%) patients, the diagnosis was known before the stroke, and in another 57 patients, diabetes was diagnosed after the stroke. Data for the latter group are included in Tables 1, 2, 3, and 4. As explained in "Methods," the group of patients with diabetes diagnosed after stroke onset is not included in the comparison between patients with and without diabetes. Hence, in the following, "diabetic patients" refers to patients with diabetes diagnosed before the stroke.

Associated Risk Factors

A comparison of the distribution of risk factors between patients with and without diabetes is given in Table 2.

Table 2. Only hypertension was significantly more common in the diabetic patients.

CT Characteristics

CT was performed in 83% of the patients. Intracerebral hemorrhage was significantly less common in patients with known diabetes (Table 3). Hypertension was present in the 2 diabetic patients with an intracerebral hemorrhage and in 20 of the 71 nondiabetic patients with an intracerebral hemorrhage (\(P=.04\)). CT findings were comparable between the two groups regarding lesion size and site and the frequency of cortical involvement, silent infarction, and leukoaraiosis.

Patients Without CT Examination

Initial stroke severity (SSS on admission) was comparable in patients with and without diabetes in whom a CT examination was not performed; the SSS score on admission was 24.2 points (SD, 19.8) in diabetic patients versus 23.4 points (SD, 18.1) in nondiabetic patients (\(P=.81\)). Male/female ratio was 18/12 versus 59/85 (\(P=.06\)), and mean age was 73.1 years (SD, 9.7) versus 78.7 years (SD, 9.1; \(P=.003\)) in patients with and without diabetes.
The time course of neurological recovery in diabetic and nondiabetic patients is shown in Fig 1. SSS score on admission as well as SSS score at discharge were comparable between groups. However, recovery was slower in the patients with diabetes.

**Initial Stroke Severity and Outcome in Relation to Blood Glucose Levels on Admission**

Only patients admitted within 48 hours from stroke onset were included in this part of the study (133 with diabetes and 623 without diabetes).

In patients with diabetes, there was no relation between blood glucose levels (AGL) and initial stroke severity or mortality. A multiple regression analysis showed that AGL was not related to SSS on admission independent of age, sex, comorbidity, hemoglobin, hematocrit, and creatinine (P=.41). Similarly, a logistic regression analysis showed that AGL was not related to mortality in diabetic patients independent of comorbidity, sex, age, hemoglobin, creatinine, hematocrit, recurrent stroke during hospital stay, and SSS on admission (P=.16).

In nondiabetic patients, a multiple regression analysis showed that AGL was related to initial stroke severity (SSS on admission) independent of age, sex, comorbidity, hemoglobin, hematocrit, and creatinine (P<.0001).
TABLE 5. Causes of Death in Patients With and Without Diabetes

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patients Without Diabetes</th>
<th>Diabetes Known Before Stroke</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>65 (34%)</td>
<td>13 (31%)</td>
<td>.63</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>12 (8%)</td>
<td>5 (12%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>28 (19%)</td>
<td>7 (17%)</td>
<td></td>
</tr>
<tr>
<td>Secondary to immobility</td>
<td>40 (26%)</td>
<td>13 (31%)</td>
<td></td>
</tr>
<tr>
<td>Nonstroke/unknown</td>
<td>8 (5%)</td>
<td>4 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as number of patients and in %. See text for a more detailed definition of death causes.

An increase in AGL of 1 mmol/L corresponded to a decrease in SSS score on admission by 2.1 points (95% CI, 1.2 to 3.0 points). To visualize the relation between AGL and initial stroke severity, patients were grouped according to AGL as follows: group 1 (n=64): AGL <5 mmol/L; group 2 (n=177): 5 mmol/L<AGL≤6 mmol/L; group 3 (n=161): 6 mmol/L<AGL≤7 mmol/L; group 4 (n=119): 7 mmol/L<AGL≤8 mmol/L; group 5 (n=55): 8 mmol/L<AGL≤9 mmol/L; and group 6 (n=47): 9 mmol/L<AGL≤11 mmol/L. Neurological score on admission decreased significantly with increasing AGL levels (6 mmol/L (P<.0001) (Fig 2). Duncan’s multiple range test showed that SSS score in group 6 was significantly different from the scores in groups 1, 2, 3, and 4; the score in group 5 was significantly different from the score in groups 1 and 2; and the scores in groups 3 and 4 were significantly different from the scores in groups 1, 2, and 6.

Mortality increased significantly with increasing AGL >6 mmol/L in the nondiabetic patients (P<.0001) (Fig 3). A logistic regression analysis was then used to test if mortality was independently influenced by AGL using comorbidity, sex, age, hemoglobin, creatinine, hematocrit, and SSS on admission as independent variables. This model showed that increasing AGL independently increased mortality in the nondiabetic patient (OR, 1.2 per 1 mmol/L; 95% CI, 1.01 to 1.42; P=.04).

Discussion

In this community-based study of 1135 acute stroke patients, the prevalence of diabetes was 20%. In other studies, diabetes has been reported with a wide range between 13% and 36%, 10–18,25,33 This wide variation is probably caused by differences in selection because former studies have not been community based.

The patients with diabetes diagnosed after stroke onset were in most aspects similar to the patients without diabetes. This suggests that stroke might have preceded or even provoked diabetes in some of these patients. It is therefore reasonable not to include this group of patients in the assessment of the impact of diabetes on stroke.

The present study shows that the diabetic patient is younger compared with the nondiabetic patient at the onset of stroke. This might be explained by a stronger disposition to stroke in the diabetic patient; apart from their diabetes, they more frequently suffer from hypertension, whereas other stroke risk factors are just as frequent as in the nondiabetic stroke patient.

Intracerebral hemorrhages were markedly less frequent in patients with diabetes. This is surprising,
considering the fact that hypertension, which in itself increases the risk of hemorrhage, was more frequent in the diabetic group. A lower frequency of intracerebral hemorrhages in diabetic patients has also been observed by Lithner et al\textsuperscript{15} (7\% versus 11\%) and by Kiers et al\textsuperscript{17} (13\% versus 22\%), but their findings were statistically insignificant because patient numbers were small. Lefkowitz et al\textsuperscript{18} found diabetes present in 18\% of patients with infarcts in the carotid territory but in only 10\% of patients with intracerebral hemorrhage, and Mohr et al reported similar results from the Harvard Stroke Registry\textsuperscript{24} (26\% versus 15\%). However, these studies did not report the frequency of intracerebral hemorrhage in patients with and without diabetes. The low frequency of hemorrhages in the patients with diabetes might be related to the specific angiopathy induced by diabetes in small vessels. It is characterized by a thickening of the basement membrane and proliferation of the endothelium.\textsuperscript{7,8} These changes might not favor hemorrhages. Moreover, the prostacyclin synthesis that increases platelet aggregability is impaired in the diabetic patient,\textsuperscript{30} coagulability is increased,\textsuperscript{36} fibrinolytic activity is decreased, and plasminogen activator inhibitor levels are increased.\textsuperscript{37}

The type and topography of diabetes-related cerebral infarction are believed to differ from brain infarcts in nondiabetic individuals. Fibrosis of the diabetic brain has been thought to be a risk factor for small and lacunar infarcts.\textsuperscript{10-13} The present study could not confirm this association. We found no significant differences between the groups regarding infarct size, site, and initial stroke severity. The symptomatic infarct seems therefore to be similar in patients with and without diabetes.

Asymptomatic or silent infarcts have been believed to occur more frequently in stroke patients with than without diabetes. Case et al in the Framingham Study\textsuperscript{39} suggested that diabetes could be a risk factor for silent infarction, but neither the present study nor other studies of risk factors for silent infarction have supported this.\textsuperscript{40-42} Furthermore, leukoaraiosis was not more frequent in diabetic patients. However, in the present study, asymptomatic or silent infarcts were associated with stroke severity. This is supported by animal studies showing a beneficial effect of insulin in acute cerebral and spinal chord ischemia.\textsuperscript{49-53}

Apart from the excess mortality, diabetes had no influence on the prognosis of stroke. Site and size of the lesions, initial stroke severity, and neurological and functional outcomes of stroke in survivors were identical in patients with and without diabetes. Previous studies considering these topics have not been community based, and their results are contradictory. One study\textsuperscript{47} reported more severe strokes in the diabetic patients, whereas three other studies\textsuperscript{13,16,48} found no such relation. Three studies\textsuperscript{11,14,25} found a poorer neurological/functional outcome, whereas one study\textsuperscript{66} found a similar outcome in patients with and without diabetes.

We found diabetic patients to recover more slowly than nondiabetic patients. This finding is supported by the study performed by Lithner et al,\textsuperscript{13} who reported that 4 days after admission, more stroke patients with than without diabetes were still confined to bed. The fact that the wound-healing process in the diabetic patient is often prolonged seems to be true also for the healing process from stroke. Various mechanisms could account for this. These include an alteration of post-ischemic cerebral blood flow related to an impaired autoregulation of cerebral blood flow,\textsuperscript{54} increased blood viscosity,\textsuperscript{55} and interference with collateral blood flow in the peri-ischemic zone due to proliferative angiopathy of small cerebral blood vessels.\textsuperscript{7}

**Conclusions**

Stroke in the diabetic patient is different from stroke in the nondiabetic patient in several aspects. The diabetic
stroke patient is younger. The frequency of intracerebral hemorrhage is markedly reduced in diabetic individuals. Recovery in patients with diabetes is slower, and mortality is increased. In survivors, however, outcome is similar to outcome in patients without diabetes. Admission glucose in diabetic patients does not affect either initial stroke severity or mortality. In contrast, admission glucose in patients without diabetes is independently related to initial stroke severity, and increased glucose levels independently increase mortality from stroke.

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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