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Prognosis after stroke in diabetic patients. A controlled prospective study

T. Olsson[1], M. Viitanen[2, 3], K. Asplund[1], S. Eriksson[2] and E. Hägg[1]

Departments of [1] Internal Medicine and [2] Geriatric Medicine, Umeå University Hospital, Umeå, and [3] Department of Geriatric Medicine, Karolinska Institute, Huddinge Hospital, Stockholm, Sweden

Summary. Cohorts of diabetic ($n = 121$) and non-diabetic ($n = 584$) patients were prospectively followed for up to ten years after having suffered from a stroke. All but six of the diabetic patients had Type 2 (non-insulin-dependent) diabetes mellitus. The diabetic patients had more risk factors associated with stroke: heart failure ($p < 0.001$) and angina pectoris ($p < 0.001$), than the non-diabetic patients. Neither body mass index nor blood pressure levels differed between the groups at admission. Haematocrit levels were higher in the diabetic group ($p < 0.01$). The diabetic patients were more commonly afflicted by cerebral embolism and to a lesser extent by transient ischaemic attacks than the non-diabetic patients. When calculated by log-rank tests, the diabetic group had an increased risk of death ($p < 0.001$), recurrent stroke ($p = 0.001$), and of myocardial infarction ($p = 0.001$) after the initial stroke. Autopsy-verified causes of death between the groups did not differ significantly, although half of all deaths during the period one to six months after stroke were caused by pulmonary embolism in the diabetic group. Thus, diabetes increases the risk of death after a stroke, and it also increases among stroke survivors the risk of recurrent stroke and myocardial infarction.

Key words: Diabetes mellitus, cerebrovascular disorders, mortality, recurrent stroke, myocardial infarction, causes of death.

Prospective epidemiological studies have established diabetes mellitus as an independent risk factor for thromboembolic stroke [1–5]. The relative risk for stroke in diabetic patients is about twice that for non-diabetic subjects, and stroke has been said to account for about 15% of deaths in Caucasians with Type 2 (non-insulin-dependent) diabetes mellitus [6]. In an earlier study we reported an increased fatality rate for diabetic patients during the acute phase of stroke [7]. The present study describes the prognosis after stroke for a prospectively studied cohort of diabetic patients as compared with a control group of non-diabetic stroke patients and characterizes the causes of death in these groups. An important goal was to study possible differences between the groups concerning recurrent stroke and myocardial infarction after the initial stroke. This was made possible through a prospective study with our closed cohort of well-defined stroke patients [8].

Subjects and methods

The patients in the study ($n = 705$) were all admitted to our stroke unit consecutively from January 1, 1978 to December 31, 1985. From this population, 121 diabetic patients were identified and compared with the non-diabetic group ($n = 584$). They have been shown to be a representative sample of all those admitted to hospital for acute stroke within the catchment area of our hospital [8]. The unit has been described previously in detail [8]. Briefly, all stroke patients were admitted directly from the emergency room if they had focal neurological signs of presumed vascular origin with a duration of less than one week. Diagnostic procedures for the stroke patients were performed in a standardised manner, with repeated clinical investigations, CT scan, cerebrospinal fluid analyses on two occasions including spectrophotometry, routine blood and urine testing including haematocrit and a fasting blood glucose level measured both on the day after admission and on discharge from our unit.

Diagnostic criteria were as follows: intracerebral haemorrhage – signs of intracerebral haematoma on CT scan, haemorrhagic pattern in spinal fluid analysis, or haemorrhage in brain at autopsy. Non-embolic cerebral infarction: neurological deficits persisting more than 24 h or until death with no signs of bleeding on CT scan, spinal fluid analysis or at autopsy and no potential source of emboli. Embolic cerebral infarction: as non-embolic cerebral infarction but with sudden onset and a potential cardiac source of an embolus. Transient ischaemic attack (TIA): focal neurological deficit of presumed ischaemic origin and of less than 24-h duration.

A four-point scale for consciousness was used. This was reduced into a two-point scale in the chi-square analysis due to a small number of observations in two of the groups for diabetic patients. The extent of paresis in the extremity most afflicted on admission was quantified using a four-point scale. Diabetes mellitus refers to the

Table 1. Concomitant stroke risk factors (%) for diabetic ($n = 121$) and non-diabetic patients ($n = 584$) on admission to hospital

Risk factor	Diabetic patients ($n = 121$)	Non-diabetic patients ($n = 584$)	P
Heart failure	54	30	< 0.001
Angina pectoris	45	26	< 0.001
Previous MI	24	14	0.005
Atrial fibrillation	26	17	0.03
Hypertension	57	50	0.16
Previous stroke	26	28	0.77
Previous TIA	17	19	0.74
Male sex	56	56	0.99
Advanced age			0.49

MI = Myocardial infarction; TIA = transient ischaemic attack

Table 2. Cerebrovascular diagnoses (%) in diabetic and non-diabetic patients

Diagnosis	Diabetic patients ($n = 121$)	Non-diabetic patients ($n = 584$)
Intracerebral haemorrhage	6	9
Non-embolic cerebral infarction	59	55
Embolic cerebral infarction	31	23
Transient cerebral ischaemia	4	13

classification by the World Health Organisation [6] and hypertension to a previously known and treated hypertensive disease. Atrial fibrillation was diagnosed on ECG. Congestive heart failure refers to heart insufficiency treated by a physician before stroke and angina pectoris to chest discomfort elicited by probable myocardial ischaemia. Acute myocardial infarction was defined by WHO criteria [9]. The clinical and autopsy criteria for causes of death have been described by Viitanen et al. [10]. Two separate reviews were obtained of the autopsy reports. The principles for treatment of the stroke patients at our unit have been described before [8].

Some changes of management have occurred through the years. Acetyl salicylic acid has been prescribed to an increasing number of patients as a prophylactic procedure after TIA or minor stroke. Low-dose heparin treatment is now used routinely at our stroke unit to prevent deep venous thrombosis and pulmonary embolism in immobilized patients with cerebral infarction and a moderate to severe leg paresis.

Patient follow-up

Each patient was followed to his/her death or until December 31, 1987 (from 0 to 10 years). No patient was lost during follow-up. The following registers were used: population registers with dates of death, registers of discharge diagnoses kept at the Departments of Internal Medicine and Geriatric Medicine at Umeå University Hospital, hospital records, medical records kept by general practitioners (in selected patients), and autopsy reports. A recurrent stroke was operationally defined as a recurrent stroke occuring more than one week after the index event. Only the first recurrent stroke was counted. Myocardial infarction was defined as above.

Statistical analysis

Two-tailed t-tests were used when appropriate for differences between means. Chi-square analysis and multiple linear regression analysis were used as specified in the text. Life table technique with Kaplan-Meier estimate was used to assess the risk of death, recurrent stroke and myocardial infarction [11]. Multivariate analysis for regression on the survival curves was done with Cox's proportional hazard model [12], which makes it possible to estimate the relative importance of different risk factors for mortality, recurrent stroke and myocardial infarction after the initial stroke.

Results

Baseline characteristics

The mean ages ± SD for diabetic patients and non-diabetic patients were 72.9 ± 9.7 and 72.2 ± 10.2 years respectively. In both groups there was a slight male preponderance (1.2:1 and 1.3:1, respectively). Out of the 121 diabetic patients all but six were considered to have Type 2 diabetes. The six patients with a probable Type 1 (insulin-dependent) diabetes mellitus had had their diabetes for 20 to 55 years with an age at onset of 7 to 30 years. Only one of these patients had known extensive vascular complications before the stroke. In two patients (2%) diabetes was diagnosed during the hospital stay. Risk factors associated with stroke for both groups are presented in Table 1. Possible differences were estimated by a multiple linear regression analysis with Bonferroni's adjustment for multiple testing of differences in means. This made a p-value of < 0.005 significant. Diabetic patients were clearly more afflicted by heart disease before the index event, indicated by significantly more heart failure and angina pectoris and a trend towards an increased proportion of previous myocardial infarction. Similar proportions of diabetic and non-diabetic stroke patients had a history of hypertension. Blood pressure on arrival and discharge (systolic/diastolic) did not differ between the groups (data not shown).

Laboratory data showed that fasting blood glucose (FBG) the day after arrival was significantly higher in diabetic (mean ± SD: 11.2 ± 5.0 mmol/l) than in non-diabetic patients (6.1 ± 1.7). This difference persisted at discharge from hospital (FBG = 10.5 ± 4.6 and 5.8 ± 1.6, respectively). Haematocrit levels were also significantly higher in diabetic (43.7 ± 4.7%) than in non-diabetic patients (42.1 ± 4.7; $p < 0.01$). Body mass index, however, did not differ between the two groups (24.6 ± 4.1 and 24.7 ± 4.1, respectively).

Cerebrovascular diagnoses are summarized in Table 2. When calculated by a chi-square analysis there was a significant difference in diagnoses (chi-square-value 11.7, df = 3, $p = 0.008$). Diabetic patients were more commonly afflicted by cerebral embolism and less commonly by TIAs. Diabetic patients also tended to show a more severe neurological impairment at onset. Twenty-seven percent (33/121) of the diabetic patients showed decreased consciousness, whereas 21% of the non-diabetic patients showed decreased consciousness (chi-square value 2.1, df = 1, $p = 0.15$). Limb paresis was present in 74% (89/121) of the diabetic and 65% (378/584) of the non-diabetic patients (chi-square value 3.77, df = 3, $p = 0.29$).

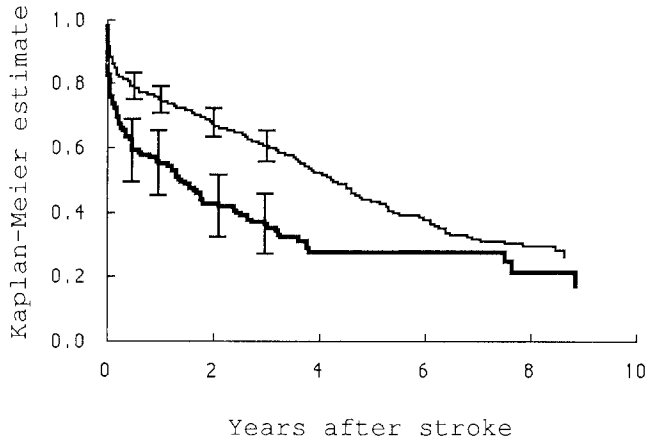

Fig. 1. Risk of death after stroke in diabetic (bold line) and non-diabetic (thin line) patients analysed by the life table technique. 95% confidence intervals are given at six months, one, two and three years after stroke

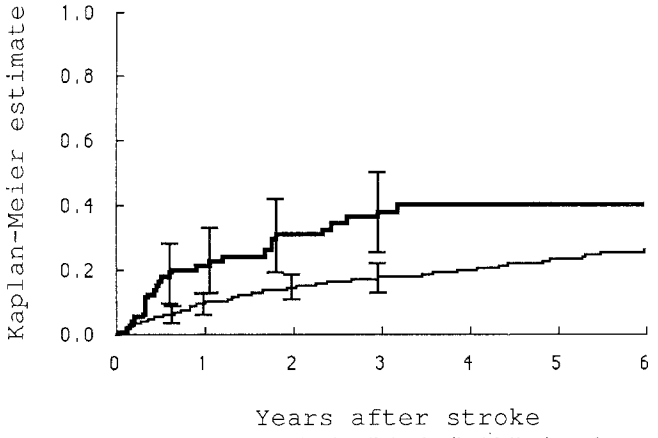

Fig. 2. Risk of recurrent stroke in diabetic (bold line) and non-diabetic (thin line) patients analysed by the life table technique. 95% confidence intervals are given at six months, one, two and three years after stroke

Survival analysis

In all, 416 patients died during observation: 71% (86/121) of the diabetic and 57% (330/584) of the non-diabetic patients. Survival for the two groups is described by life table curves with 95% confidence intervals at selected time-points in Figure 1. Median survival time for diabetic patients was 513 days and for non-diabetic patients 1569 days. The risk of death after stroke was increased for the diabetic group mainly during the first six months after the index event. Thereafter, the survival curves run almost in parallel. Risk of death as calculated with a log-rank test was significantly higher for diabetic patients (chi-square value, 21.0 df = 1, $p < 0.001$). The uncertainty of the data rises with observation time because of the decreasing number of patients still at risk. Therefore, conclusions after three to four years of observation must be drawn with caution.

The risk for a recurrent stroke after the initial event is illustrated in Figure 2. Altogether, 130 patients suffered another stroke during the study: 24% (29/121) of the diabetic and 17% (101/584) of the non-diabetic patients. Diabetic patients were more prone to suffer a recurrent stroke (chi-square value 11.9, 1 df, $p = 0.001$). The curves for diabetic and non-diabetic patients run continuously apart until the number of events ceases in the diabetic group, after about three years of observation.

The life table curves for the risk for myocardial infarction after stroke are given in Figure 3. Twenty-one diabetic (17%) and 75 non-diabetic (13%) patients suffered a myocardial infarction after the index event. Diabetic patients showed a higher risk for myocardial infarction when calculated by a log-rank test (chi-square value 6.7, 1 df, $p = 0.001$), but the 95% confidence intervals were overlapping.

Data were analysed with the Cox proportional hazard model in an effort to determine the influence of the diabetic disease, irrespective of the increased proportion of cardiovascular risk factors in diabetic patients before stroke. The results are given in Table 3. Diabetes mellitus as such significantly influenced mortality and the risk of a recurrent stroke. Diabetes mellitus slightly increased the risk of myocardial infarction but this effect did not reach statistical significance. The strongest impact upon survival was from advanced age, followed by a lowered level of consciousness at arrival to the hospital. Heart failure and hypertension also influenced survival significantly. For recurrent stroke, the significant risk factors besides diabetes mellitus were heart failure and advanced age. The corresponding risk factors for myocardial infarction after stroke were angina pectoris, advanced age and heart failure. Finally, the haematocrit level on and the FBG at discharge from hospital were included in a separate statistical model for survival of diabetic patients but these two factors did not influence survival (data not shown).

Causes of death

Autopsy-verified primary causes of death at different times after stroke are illustrated in Figure 4. The frequency of autopsies for diabetic patients was 74% and

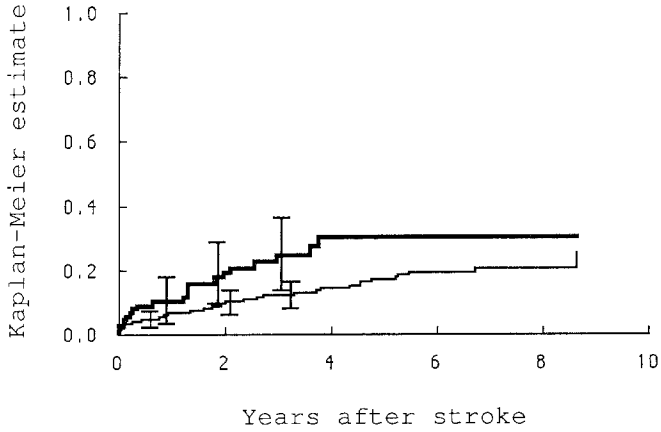

Fig. 3. Risk of a myocardial infarction after stroke in diabetic (bold line) and non-diabetic (thin line) patients analysed by the life table technique. 95% confidence intervals are given about six months, two and three years after stroke

Table 3. Results from a multivariate analysis with Cox's proportional hazard model for factors potentially influencing mortality, recurrent stroke and myocardial infarction after the initial stroke

Risk factor	Regression coefficient			*t*-value		
	Mortality	Recurrent stroke	MI	Mortality	Recurrent stroke	MI
Advanced age	0.05	0.03	0.04	8.28[c]	2.71[b]	2.97[b]
Lowered consciousness at admission	0.39	0.18	0.02	7.33[c]	−0.92	0.10
Heart failure	0.50	0.73	0.49	4.32[c]	3.56[c]	2.07[a]
Diabetes mellitus	0.32	0.59	0.40	2.50[a]	2.63[a]	1.56
Hypertension	0.25	0.26	0.05	2.40[a]	1.36	0.25
Male sex	0.23	0.05	0.44	0.28	1.36	1.94
Previous stroke	0.20	0.32	0.37	1.87	1.64	1.68
Previous TIA	−0.17	0.05	−0.11	−1.27	1.27	−0.40
Angina pectoris	0.19	0.08	0.69	1.69	0.39	3.02[b]
Atrial fibrillation	0.22	−0.48	−0.37	1.68	−1.71	−1.15
Previous MI	0.21	−0.27	0.37	0.48	−0.99	1.41

[a] = $p < 0.05$; [b] = $p < 0.01$; [c] = $p < 0.001$. TIA = transient ischaemic attack. MI = myocardial infarction

for non-diabetic patients 59%. Early after admission, the acute brain disease in itself causing cerebral oedema and coning was the major cause of death in both groups. Subsequently, secondary complications such as pulmonary embolism and pneumonia evolved as major causes of death in both groups. During the period from one week to one month after stroke, pulmonary embolism was the major cause of death in diabetic patients, causing more than half of the deaths i.e., five out of nine deaths.

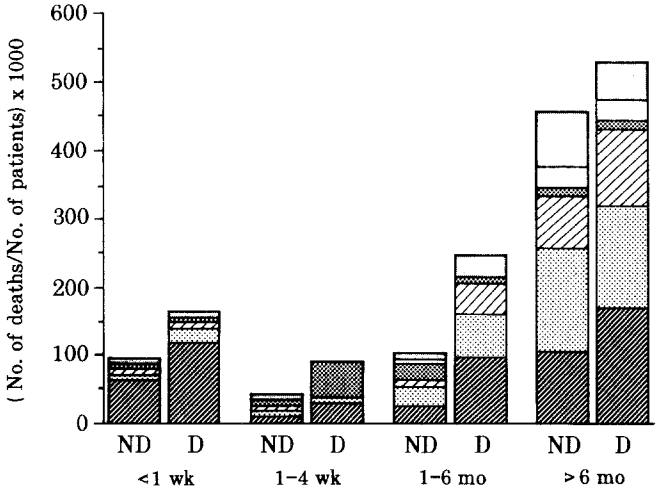

Fig. 4. Causes of death at various time-periods after stroke in diabetic and non-diabetic patients. ▨ = stroke, ▩ = cardiac disease, ▨ = bronchopneumonia, ▩ = pulmonary embolism, □ = malignancy, □ = other, e.g. sudden death, septicaemia. ND = Non-diabetic patients, D = Diabetic patients. Various time-periods after stroke are given, where < 1 wk = less than one week, 1–4 wk = one to four weeks, 1–6 mo = one to six months, and > 6 mo = more than six months after admission to the hospital

The proportion of cardiac deaths after the first six months of observation was 29 and 33% for diabetic patients and non-diabetic patients, respectively. The main reason for the excess mortality in the diabetic patients during the first six months appears to be the cerebrovascular lesion itself (Figure 4). When calculated by chi-square-analysis, the difference in the causes of death between diabetic and non-diabetic patients did not reach statistical significance. This was also true when data were analysed for the other time-periods used in the figure.

Discussion

We found diabetes mellitus to be a major determinant of mortality after stroke. An earlier retrospective study demonstrated a shortened life-span after stroke for diabetic patients, as compared with matched and randomly selected non-diabetic control patients [13]. The influence of diabetes upon short-term prognosis has been verified by some previous studies [7, 14–15], but in a Swedish community-based study, diabetes did not influence survival at a follow-up three months after the initial event [16]. When considering short- and long-term mortality after stroke, prognosis quo ad vitam has been influenced by diabetes in some studies [17–18], but not all [19–24]. Solzi et al. [25] found, with a multivariate survival analysis of patients admitted to a rehabilitation centre, an influence of diabetes upon survival of about five years after the cerebrovascular accident. In contrast, the present study suggests a greater influence upon mortality during the first months after stroke. Diabetic patients had an increased proportion of cardiovascular risk factors, especially heart failure and angina pectoris in our study. This could be a major reason for the increased risk of death after stroke for diabetic patients. However, with the use of the Cox proportional hazard model, we studied the influence of diabetes adjusted for the increment in cardiovascular risk factors in these patients. Clearly, diabetes influences mortality independently from an increased proportion of cardiac disease. The other risk factors for mortality emerging in this study, i.e., advanced age, decreased consciousness on admission and heart failure are well in line with most other investigations [26], although the case fatality rate after stroke for hypertensive patients has been the subject of some controversy [26].

We also found that diabetic patients tended to have a more pronounced neurological deficit at the time of arrival to hospital. A worse outcome has been documented in some studies of animals made hyperglycaemic and subjected to a global or transient focal ischaemia [27–28]. There are, however, contradictive findings suggesting that hyperglycaemia per se is not necessarily unfavourable in this situation [29]. Similar discrepencies as to prognosis after ischaemic damage are found in studies of animals made hyperglycaemic with an induced focal cerebral ischaemia [29]. An aggravated neurological outcome has been suggested in diabetic stroke patients, and in association with hyperglycaemia in patients without known

diabetes mellitus [30–31]. This has partly been attributed to the development of excessive lactic acidosis in the brain after an ischaemic insult in a hyperglycaemic state [32]. It has also been suggested that hyperglycaemia is associated with a more pronounced cerebral oedema in stroke patients [33]. Other factors might also contribute to the development of brain lesions in diabetic patients, such as an impaired autoregulation of cerebral flood flow, a decreased deformability of erythro- and leucocytes, hypercoagulability, hyperviscosity, a decreased synthesis of prostacyclin with an increased adhesivity of thrombocytes, and an increased adhesion of erythrocytes to endothelial cells [30].

As illustrated in Figure 4, a large proportion of autopsy-verified causes of deaths among the diabetic patients (albeit in a small number of patients) was due to pulmonary embolism during the period from one week to one month after admission. This might be linked to the higher degree of limb paresis in diabetic patients, as well as possible changes in blood and vessel walls in diabetic patients, leading to an increased risk of thromboembolic events.

The increased risk for diabetic patients to suffer from a recurrent stroke is also of considerable interest and importance. The risk factors for a recurrent stroke after the initial event have been sparsely studied. Diabetes seemed to be one of the factors associated with a higher mortality due to stroke following an initial stroke in a Russian study [14], but not in an American community hospital study [34]. The more widespread large-vessel atherosclerosis in the cerebral circulation and other abnormalities in vessel walls and blood components in diabetic patients [30] could probably contribute to this enhanced risk.

We found a tendency towards an increased risk for myocardial infarction in diabetic stroke patients. This is compatible with the well-known fact that diabetes is associated with an increased risk for myocardial infarction and a higher mortality rate, both during the acute phase and during follow-up [35, 36]. The mortality rate has been attributed to a high incidence of fatal reinfarction, perhaps related to a more widespread coronary atherosclerosis in diabetic patients [35, 37].

In conclusion, diabetes mellitus is an important risk factor for mortality after stroke, and for recurrent stroke and myocardial infarction after the initial stroke. We think that this is a subgroup of stroke patients who should be kept under especially close supervision, both during the acute phase after stroke and during follow-up, bearing in mind the increased risk of different complications such as venous thromboembolism. An aggressive attitude against other concomitant risk factors associated with cerebrovascular disease seems pertinent in these patients.

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Dr. T. Olsson
Department of Internal Medicine
Umeå University Hospital
S-901 85 Umeå
Sweden