Mortality From Cerebrovascular Disease in a Cohort of 23 000 Patients With Insulin-Treated Diabetes

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Background and Purpose—Disease of the cardiovascular system is the main cause of long-term complications and mortality in patients with type I (insulin-dependent) and type II (non–insulin-dependent) diabetes. Cerebrovascular mortality rates have been shown to be raised in patients with type II diabetes but have not previously been reported by age and sex in patients with type I diabetes.

Methods—A cohort of 23 751 patients with insulin-treated diabetes, diagnosed under the age of 30 years from throughout the United Kingdom, was identified during 1972 to 1993 and followed up for mortality until the end of December 2000. Age- and sex-specific mortality rates and standardized mortality ratios (SMRs) were calculated.

Results—There were 1437 deaths during the follow-up, 80 due to cerebrovascular disease. Overall, the cerebrovascular mortality rates in the cohort were higher than the corresponding rates in the general population, and the SMRs were 3.1 (95% CI, 2.2 to 4.3) for men and 4.4 (95% CI, 3.1 to 6.0) for women. When stratified by age, the SMRs were highest in the 20- to 39-year-age group. After subdivision of cause of death into hemorrhagic and nonhemorrhagic origins, there remained a significant increase in mortality from stroke of nonhemorrhagic origin.

Conclusions—Analyses of mortality from this cohort, essentially one of patients with type I diabetes, has shown for the first time that cerebrovascular mortality is raised at all ages in these patients. Type I diabetes is at least as great a risk factor for cerebrovascular mortality as type II diabetes. (Stroke. 2003;34:418-421.)

Key Words: cerebrovascular disease ■ cohort study ■ type I diabetes mellitus

It has been recognized for many years that disease of the cardiovascular system is the predominant long-term cause of morbidity and mortality in patients with type I (insulin-dependent) and patients with type II (non–insulin-dependent) diabetes. In particular, these patients are at an increased risk of dying from heart disease.1

Mortality from cerebrovascular disease has been studied less frequently in patients with diabetes. Cerebrovascular mortality rates have been shown to be raised in patients with type II diabetes relative to the general population,2,3 but cerebrovascular disease is barely mentioned in studies of patients with type I diabetes, and there are no reports of cerebrovascular mortality rates by age in such patients.

The Diabetes UK (previously British Diabetic Association) Cohort has ≥23 000 patients with type I diabetes, is of sufficient size, and has sufficient follow-up to report cerebrovascular mortality rates by age and sex. The results are compared with rates in the general population and with previous data from studies of patients with type II diabetes.

Subjects and Methods

The Diabetes UK Cohort has been described in detail elsewhere.4,5 In total, 23 751 patients with insulin-treated diabetes, diagnosed under the age of 30 years, were recruited into the cohort from all parts of the United Kingdom between 1972 and 1993. Patients with diabetes secondary to other conditions were excluded from the cohort at the outset or, in a few cases, after notification of diagnosis from the death certificate. Although insulin treatment rather than evidence of absolute insulin dependency was the criterion for inclusion, this cohort was essentially one of patients with type I diabetes. The patients were all diagnosed before the age of 30, and from the age-specific percentages of diabetic patients with type I diabetes reported by Laakso and Pyorala,6 at least 94% will have had type I disease.

Identification details of the patients were sent to the National Health Service Central Registers for patients from England, Wales, and Scotland and to the Central Services Agency for patients from Northern Ireland, who notified us of all deaths and emigrations and supplied us with death certificates. The cause of death was coded to the relevant revision of the International Classification of Diseases (ICD)7 in force at the time of death. For overall cerebrovascular mortality, the ICD9 codes 430 to 438 were used, together with the
corresponding ICD8 and ICD10 codes where appropriate. Cerebrovascular mortality was further subdivided into hemorrhagic or nonhemorrhagic in origin by using ICD9 codes 4300 to 4329 for hemorrhagic causes of death and 4330 to 4371 for nonhemorrhagic causes.

For each cohort member, person-years at risk by age group, sex, calendar year, and country of residence were calculated, starting from the date of registration (or at age 1 year if registered younger than this) to either December 31, 2000, or the date of death, 85th birthday, emigration, or other loss to follow-up if earlier. Age-specific cerebrovascular mortality rates were calculated and compared with the relevant general population age-specific mortality rates. Expected mortality in the cohort was calculated by multiplying the age-, sex-, calendar-year-, and country-specific person-years at risk in the cohort by the corresponding mortality rates for the general population of England and Wales or Scotland, as appropriate. Scottish mortality rates were used to calculate the expected rates for the patients from Northern Ireland. Standardized mortality ratios (SMRs), reflecting the risk of cerebrovascular death in comparison with that in the general population, were calculated as the ratio of the number of observed deaths to the number of expected deaths. The absolute excess risk (AR), a measure of the excess mortality in the patients with diabetes, was calculated by subtracting the expected from the observed number of deaths and dividing by the person-years. Confidence intervals (95% CIs) and probability values were calculated by using the exact Poisson distribution.8

Results

The 23,751 patients contributed a total of 404,073 person-years of follow-up, an average of 17 years per person. During follow-up, there was a total of 14,37 death certificates, 536 of which were due to cardiovascular disease. Eighty of these deaths (40 in men, 40 in women) were due to cerebrovascular disease. As a proportion of mortality in the cohort, cerebrovascular disease constituted 4% of all deaths under the age of 40 years and 8% at ages older than this.

Cerebrovascular mortality rates, by age, in the cohort are shown in Table 1. The rates were comparable for men and women at all ages. Overall, the rates were significantly raised compared with the general population, though not significantly so at ages 1 to 19 years based on small numbers or in the men aged 60 to 84 years. In the 20- to 39-year-old group, the risk of cerebrovascular mortality was increased >5-fold in men and >7-fold in women. In both sexes, the AR increased with age.

We examined the death certificates further to determine whether the death had occurred as a result of hemorrhagic or nonhemorrhagic cerebrovascular disease. Of the 80 cerebrovascular deaths, 52 were classified as nonhemorrhagic and 18 as hemorrhagic, and the remaining 10 did not have sufficient information on the death certificate for classification and were therefore excluded. These groups have been analyzed separately, and the results are shown in Table 2. Mortality from stroke of nonhemorrhagic origin was raised compared with the general population in both sexes. This was especially notable in the group aged under 40 years: the SMR for females was 37.0 (95% CI, 18.5 to 66.3) and for males it was 18.6 (95% CI, 6.8 to 40.6).

Discussion

Cardiovascular disease is the predominant long-term complication and cause of death in patients with both type I and type II diabetes. Cerebrovascular disease contributed substantially to deaths in this study, accounting for 6% of all deaths overall and for 8% of deaths over the age of 40 years. A similar proportion, 7% of the total mortality, was reported by Deckert et al9 in a much smaller study of 307 patients diagnosed under the age of 31 years.

The Framingham Study1 was one of the earliest to demonstrate an increased morbidity and mortality from cerebrovascular disease in patients with diabetes. Similar conclusions have been drawn from most, though not all, subsequent studies of patients with type II diabetes.2,3,10 The results reported here indicate that overall cerebrovascular mortality is higher in patients with type I diabetes than in the general population and that this risk is especially high in young adults.

There are very few previous studies of patients with type I diabetes with which to compare the present results. The

| TABLE 1. Mortality Rates and SMRs From Cerebrovascular Disease in Cohort Members |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age at Death, y | No. of Deaths | Rate in Cohort (per 100 000 Person-Years) | SMR (95% CI) | AR |
| 1–19 | 2 | 2.3 | 4.6 (0.6–16.5) | 1.8 |
| 20–39 | 11 | 10.2 | 5.2 (2.6–9.2) | 8.2 |
| 40–59 | 15 | 100.3 | 4.6 (2.5–7.5) | 78.3 |
| 60–84 | 12 | 458.7 | 1.7 (0.9–3.0) | 194.8 |
| Total 1–84 | 40 | 18.7 | 3.1 (2.2–4.3) | 12.7 |

SMR indicates standardized mortality ratio; AR, absolute excess risk per 100 000 person-years.

| TABLE 2. Risks of Mortality From Hemorrhagic and Nonhemorrhagic Stroke in Cohort Members |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Sex, Age at Death (y) | No. of Deaths | Hemorrhagic | Nonhemorrhagic |
| 1–39 | 5 | 2.3 (0.7–5.3) | 6 | 18.6 (6.8–40.6) |
| 40–84 | 3 | 1.1 (0.2–3.2) | 20 | 3.1 (1.9–4.7) |
| 1–39 | 4 | 2.4 (0.6–6.0) | 11 | 37.0 (18.5–66.3) |
| 40–84 | 6 | 2.5 (0.9–5.4) | 15 | 3.6 (2.0–6.0) |

SMR indicates Standardized mortality ratio.
World Health Organization multinational study of vascular disease in diabetes has indicated an overall raised cerebrovascular mortality in patients with type I diabetes but with considerable variation between countries.\footnote{1} Cerebrovascular mortality rates by age and sex have not been reported previously, probably because available studies have not been large enough or had sufficiently long follow-up. These studies have either grouped deaths from all cardiovascular causes together,\footnote{12} calculated risks of combined fatal and nonfatal cerebrovascular events,\footnote{13} or calculated risks of cerebrovascular mortality based on only a few deaths.\footnote{14}

Some comparisons can also be drawn with results from studies of patients with type II diabetes, although this must be approached with caution because these differ in country of origin and age structure. A number of studies of older patients with type II diabetes have reported SMRs similar to the SMRs of 1.7 in men and 2.8 in women in the 60- to 84-year age group reported here in our type I cohort. In particular, these studies have not demonstrated a significantly raised risk for men but have demonstrated a significantly raised risk for women. Kessler\footnote{10} from the Joslin Clinic reported SMRs for cerebrovascular mortality of 1.1 for men and 1.2 in women, with equivalent SMRs of 1.7 and 2.6 from the Rancho Bernardo Study\footnote{3} and 1.8 and 2.2 from the Wisconsin Study.\footnote{14} Results of studies that have included younger patients with type II diabetes have indicated higher risks, with a significant increase in risk for both men and women. The Nurses Health Study of women aged predominantly \( \leq 60 \) years at the end of follow-up reported an SMR for cerebrovascular mortality of 5.0,\footnote{13} and the MRFIT study of men of similar age reported an SMR of 2.7.\footnote{13} The result from the Nurses Health Study is comparable to the SMR of 5.1 in the 40- to 59-year age group for our patients with type I diabetes, whereas the result from the MRFIT study is lower than the SMR reported here of 4.6 in men aged 40 to 59 years.

The risk in patients with type II diabetes is only associated with ischemic, nonhemorrhagic stroke. From the MRFIT study in men, Neaton et al.\footnote{15} showed that diabetes was significantly associated with nonhemorrhagic stroke (relative risk, 3.8; 95% CI, 2.8 to 5.3) but that there was no association with either subarachnoid or intracranial hemorrhage. We have now shown similar findings for type I diabetes. The risk of death from nonhemorrhagic stroke was high, especially in the under-40 age group. The risk of mortality from hemorrhagic stroke, though higher than for the general population, was not significantly raised, but it should be emphasized that the numbers are too small in this group to draw any firm conclusions. Although it was not possible to be certain about the exact nature of the nonhemorrhagic strokes from the death certificates, it was likely that many were ischemic in origin.

Diabetes is a known risk factor for atherogenesis, and this may explain the specificity of the relation.

Risk factors for stroke have been studied in patients with type I and type II diabetes, and there appear to be many similarities. Blood pressure is a well-known risk factor for stroke in both types of diabetes,\footnote{16} and the UKPDS trial suggested that controlling blood pressure in patients with type II diabetes reduced the stroke risk, although this reduction did not reach statistical significance.\footnote{17} Nonetheless, Barrett-Connor and Khaw\footnote{3} in the Rancho Bernardo Study demonstrated that the raised risk of stroke in patients with type II diabetes persisted even after stratifying for blood pressure, suggesting that other diabetes-related variables might also be involved.

The World Health Organization multinational study of vascular disease in diabetes\footnote{16} has shown that proteinuria as well as raised blood pressure and serum cholesterol are predictors of mortality from stroke in patients with both types of diabetes, and it is known that the risk of stroke in patients with type I diabetes is 10-fold higher in those with diabetic nephropathy than in those without.\footnote{18} The study reported here has been based on the underlying cause of death as reported on the death certificate, and the full extent of additional diabetic nephropathy was not known.

Other risk factors do not appear to be equally important in the 2 types: for example, the duration of diabetes was only seen to increase the risk in patients with type II diabetes and did not appear to be relevant in patients with type I.\footnote{16} This may in part explain why the risks in older patients with type I diabetes were no greater than for the type II patients of comparable age who will have had diabetes incident at older ages and hence had diabetes of shorter duration.

The absolute numbers of persons dying from cerebrovascular disease as a consequence of type II diabetes are greater than for type I, because the former is the predominant type of diabetes among older people and cerebrovascular mortality is related to age. However, we have demonstrated that at younger ages, the relative risks of cerebrovascular mortality in patients with type I diabetes are very high, and although they are not so high for the older age groups, the results indicate that at these ages they are still comparable to those of similarly aged patients with type II diabetes.

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